International Journal of Neurology

ISSUE DEDICATED TO:

ENCEPHALITIS

VOLUME I JUNE 1960 NUMBER 3

INTERNATIONAL JOURNAL OF NEUROLOGY

CONTENTS OF VOLUME 3, JUNE 1960

EDITORIAL — Español 221

EDITORIAL — English 222

OCCLUSIVE DISEASE IN THE CAROTID ARTERIAL SYSTEM 223
Clark H. Millikan, M. D., Robert G. Siekert, M. D., Jack P. Whisnant, M. D.

THE CEREBRAL SOFTENING 242
Tronconi, V., Montanari, M., D'Agostini, N.

CENTRAL NERVOUS SYSTEM INVOLVEMENT BY VIRUSES 256
Knox H. Finley, M. D.

LES FORMES ENCEPHALITIQUES DE LA POLIOMYELITE 270
Stephane Thieffry.

ASPECTS E.E.G. DES ENCEPHALITES 277
P. Passouant.

PRESENT DAY ENCEPHALITIDES OF WESTERN AND CENTRAL EUROPE 285
Ludo van Bogaert.

JOHN F. FULTON (1899-1960) 300

NEWS 307

BOOK REVIEWS 308

The next issue will treat of: POLYMYOSITIS

Editorial

La "Revista Internacional de Neurología" dedica este número a la memoria de un muy querido amigo, a la vez que miembro de su Comité Consultivo, Prof. John F. Fulton.

Una nube de tristeza descendió sobre el mundo neurológico al saberse la noticia de la súbita desaparición de una de las personalidades contemporáneas más brillantes.

Aquellos quienes en vida conquistaron un lugar en el corazón de sus semejantes nunca mueren, sino que continúan viviendo en el recuerdo como estímulo e inspiración.

Por su etimología el término encefalitis indica inflamación del encéfalo.

Los agentes en condiciones de producirla son múltiples, tanto de naturaleza tóxica como infecciosa.

Si nos concretamos a los de naturaleza infecciosa su lista es numerosa y variada, yendo desde los virus de magnitud ultra microscópica a las parasitosis de organismos mayores. Y en la serie deben incluirse también las rickettsias, las bacterias, las espiroquetas (recordemos la sífilis) y los protozoarios.

En este número de la Revista Internacional de Neurología la atención de los autores está concentrada casi exclusivamente en las formas de etiología viral. El cerebro responde a los agentes que le son patógenos, cualquiera sea su naturaleza, por una reacción ecto y mesodérmica con variantes en la intensidad de los distintos elementos involucrados, pero sin especificidad. Agentes distintos pueden dar cuadros anatómicos similares. Los hallazgos patológicos muchas veces se hace difícil referirlos a determinada etiología y ciertos casos quizá sean debidos a una asociación de agentes virales.

La virología tiene en el capítulo de las encefalitis un amplio campo de estudio y de investigación y sus contribuciones son actualmente absolutamente necesarias en estas afecciones.

Enfocando el problema desde otro ángulo está el interesante proceso experimental conocido como encefalomielitis alérgica, donde la alergia es considerada como un mecanismo básico en su patogenia. Ultimamente las exploraciones con microscopía electrónica han puesto en evidencia cambios en la ultraestructura de las neuronas en distintas fases de la evolución de la enfermedad y se han hecho investigaciones en la química cerebral (lipoproteínas) relacionadas con este problema.

Esta línea de estudios a nuestro juicio es útil para intentar la comprensión de las encefalitis espontáneas de la clínica.

Figuras relevantes de la neurología en el escenario mundial han hecho el honor de contribuir con sus trabajos a darle jerarquía a este número de la Revista Internacional de Neurología, ellos son: Dr. K. H. Finley de San Francisco; Dr. S. Thieffry de París; Dr. P. Passouant de Montpellier y Dr. L. Van Bogaert de Amberes; a todos ellos nuestro reconocimiento por lo que significan sus aportes en este importante capítulo de la neurología.

VICTOR SORIANO

Editorial

The "International Journal of Neurology" dedicates this issue to the memory of a very dear friend and also a member of the Advisory Board, Prof. John F. Fulton.

A cloud of sadness descended over the neurological world upon the news of the sudden demise of one of the brightest contemporary personalities.

Those who in life have conquered a place in the heart of their fellow man, never die, but live on to encourage and inspire.

The etimology of the term encephalitis indicates brain inflamation.

There are multiple the agents able to cause it, either of a toxic or infectious nature.

If we limit ourselves to those of an infectious nature, we will see that there is a numerous and large variety of them, ranging from the ultra microscopic viruses to the large animal parasites. In this group are found rickettsias bacteria, spirochetes (syphilis) and the protozoa.

In this issue of the International Journal of Neurology the authors concentrate almost exclusively on the form of encephalitis of viral etiology.

The brain responds to the agents that are noxious to it, regardless of their nature, by an ecto and mesodermic reaction, variable in intensity of the different anatomical elements involved, but without being specific.

Different agents can give a similar anatomopathological picture.

Many times it is very difficult to relate pathological findings to a given etiology and in certain cases perhaps this is due to a combination of several viral agents.

Virology has an ample field of study and investigation in Encephalitis and its findings are at present very necessary in the understanding of this disease.

Looking at the problem from another angle there is a very interesting experimental process known as alergic encephalomyelitis where the alergy is considered as a basic mechanism in its pathogeny. Lately, ultra microscopic studies shown evidence of changes in the ultraestructures of the neurons in different stages of the evolution of the illness and investigations of the brain chemistry (lipoproteins) related to this problem have been conducted.

This line of investigation is in our opinion very useful in trying to understand spontaneous encephalitis in the clinic.

Oustanding specialits of world renown in this field have contributed papers that enhance the issue on Encephalitis.

Our warmest thanks to Dr. K. H. Finley (San Francisco); Dr. S. Thieffry (Paris); Dr. P. Passouant (Montpellier) and Dr. L. Van Bogaert (Anvers) for allowing us to ofter our readers the fruits of their investigation in this important chapter of Neurology.

VICTOR SORIANO

Occlusive Disease in the Carotid Arterial System

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For many years much study was directed toward the neuropathology of cerebral lesion associated with each infarct. Emphasis on the neuropathologic lesion was responsible in part for the relative lack of study of the common carotid arteries and the extracranial portion of the internal carotid arteries until the observations of Fisher(1). Now it has become commonplace to discuss occlusive disease of the carotid artery as an anatomically isolated process, in spite of the fact that the symptoms which commonly lead the clinician to suspect such a lesion are an expression of abnormal function of a portion of the brain or of the eye.

But as study of infarcts does not define the anatomic site of the vascular pathology in many instances, neither does gun-barrel vision of arterial stenosis or occlusion expressly describe the altered physiology in a region of brain supplied by a minor branch as well as the main stem of the carotid system. The pathologist who studies the infarct and the arterial lesion has no way to assess the temporary variations in circulatory sufficiency that may have occurred in the living state. The clinician can only infer such alteration in vascular sufficiency when there are symptoms or physical signs interpretable as evidence of focal brain dysfunction — for instance, trasient hemiparesis indicating that for some reason blood flow in a middle cerebral artery has been diminished for a few minutes. The physiologist currently has no satisfactory method for investigating such local changes in vascular sufficiency. The pathologist, were circumstances to pass the patient into his hands, frequently would be unable to demonstrate morbid change in either brain or vascular tissue. The clinician is faced with the responsibility of interdigitating available knowledge concerning physiology and pathology with phenomena observed in his scrutiny of patients, and from such interdigitation he constructs hypotheses about pathogenesis. From such speculations may come new treatment. Because of this key spot occupied by the clinical neurologist, our discussion will be oriented to his view of the patient appearing for diagnosis and treatment.

Although an elaborate classification(2) of cerebrovascular disorders exists, we have found a temporal clinical classification extremely useful in relation to treatment. The categories in this classification are defined in terms of an attempt to assess the current cerebrovascular pathologic physiology — in this instance in the carotid arterial system. These temporal categories are as follows: 1) incipient or impending stroke, 2) advancing stroke, 3) completed stroke, and 4) completed stroke with evidence of further activity of the cerebral ischemic proces.

Impending or Incipient Stroke in the Carotid System

This term indicates that at some future date a serious cerebral infarction in the ca-

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rotid system is likely or probable. The clinical entity which in certain instances warns that cerebral infarction may be in the offing is referred to as intermittent insufficiency in the carotid system.

Symptomatology and Diagnosis. — Johnson and Walker(3), reviewing 107 cases of thrombosis of the carotid arteries, described a type in which there were intermittent and immediately reversible symptoms. No attention was directed to the possibility that the physician might use such symptoms as warning phenomena. In that same year (1951) Denny-Brown(4) questioned the validity of "vasospasm" as the mechanism responsible for the clinical episodes which prior to that time had been called "attacks of cerebral vasospasm". He suggested that transient systemic hypotension associated with atherosclerotic narrowing of a cerebral vessel was the cause of the attacks. In 1955 Millikan and Siekert(5) described a group of specific patients, suggested that such phenomena constitute a definite clinical syndrome to be called "intermittent insufficiency in the carotid arterial system", and emphasized that many patients with the syndrome would subsequently suffer thrombosis in the carotid system. This latter observation has acquired primary clinical importance in the detection of carotid stenosis as well as disease located more distally in the system.

The designation "intermittent insufficiency in the carotid arterial system" is a clinical one. The syndrome is characterized by attacks composed of one or more neurologic phenomena that are determined by the region of the brain where the blood supply is insufficient. Such attacks begin quickly and often progress to maximal degree in a few seconds. Each attack can last for an hour or more, but the duration commonly is 5 to 20 minutes. The attacks terminate swiftly and the patient ordinarily is left in a normal state. After many attacks or a few severe or prolonged episodes, a minor or slight neurologic deficit may persist. In an individual case there usually is marked similarity between episodes, although deletions from or additions to the basic pattern may cause variation of the phenomenology in individual patients.

Weakness is the most common manifestation. It can involve half of the body or a minor portion such as a buccal angle. Ordinarily the weakness does not spread or march, and if multiple parts are affected the patient often is hard put to describe the mode of onset, save that it is very swift. Sensations of numbness, deadness, tingling, prickling, or other strange feelings may occur. These can occasion inaccuracy of movement or engender unwillingness of the patient to attempt movement. If the insufficiency is in the carotid supply to the dominant hemisphere, some degree of aphasia in global or fragmentary form is usual. The fragment can be minute —for instance, acalculia— implying that only a small portion of the carotid system is the locus of insufficiency. Aphasia is caused much more often by carotid-system insufficiency than by vertebral-basilar insufficiency. Some degree of dysarthria may be noted. Unilateral impairment of vision is the symptom most valuable in indicating that the intermittent insufficiency is in the carotid system. The impairment may be minor but can be complete. Positive phenomena such as bright lights and lines across the field are relatively uncommon. Diplopia, bilateral homonymous hemianopsia, dysphagia, vertigo, and bilateral impairment of motor or sensory function are not symptoms of carotid insufficiency unless there is some extreme congenital abnormality of the circle of Willis or bilateral disease of the carotid system.

There are three possible important abnormalities which may be detected on examination of a patient having intermittent insufficiency of the carotid system. First, pulsation of the cervical portion of the suspected carotid artery may be decreased. Pharyngeal palpation of the internal carotid as advocated by Dunning(6) is cumbersome and does not eliminate artifacts; its use has declined. When palpation of the neck surface discloses mild to moderate difference in the two carotids, little importance can be attached to such evidence, for some variation in these pulsations is not uncommon.

Second, a bruit over the appropriate carotid is important evidence of stenosis. Ordinarily such a sound can be distinguished from a transmitted cardiac sound, and

usually it indicates stenosis of the artery at the point of maximal intensity of the bruit. Rarely stenosis in the first few millimeters of the external carotid artery causes a bruit that cannot be distinguished from one originating from stenosis of the carotid bulb or internal carotid artery. A bruit over the ipsilateral or contralateral eye is of lesser significance.

Third, a relative decrease of pressure in the retinal artery on one side is substantial evidence of stenosis in the parent system. The significant finding is a definite difference between the pressures in the two eyes, since an absolute relationship does not exist between brachial blood pressure and retinal blood pressure. Hollenhorst(7) has suggested that a variation of 5 mm. to 10 mm. for pressures below 50 mm. Hg and a variation of 10 to 15 mm. for pressures above 50 be used as a measure of significant difference between the diastolic pressures on the two sides. If the diastolic pressures are within normal limits of similarity, the systolic pressures should be determined, for in rare instances an important difference may be detected. If the diastolic and systolic pressures are within the usual limits and have been obtained with the patient supine, a similar sequence of tests with the patient in a sitting position is probably wise. Retinal-artery pressures have been measured thousands of times at the Mayo Clinic without ill effect. Equal pressures on the two sides in the presence of carotid stenosis or occlusion can be called a false negative finding. This does rarely occur. False positive findings are so unusual as to be of little importance. O'Doherty and Green(8) have stressed the diagnostic value of Horner's syndrome in carotid thrombosis. When present this sign may be of assistance, but it is absent in most cases. The presence of diabetes, coronary-artery disease, peripheral vascular disease, or hypertension may serve to heighten the suspicion of the clinician that disease of the carotid arterial system is present also.

Differential diagnosis involves conditions such as a benign, malignant, or metastatic neoplasm, abscess, and scarring secondary to injury, all of which can produce episodes of focal neurologic deficit. In most cases the diagnosis is reasonably clear from the history alone. If the patient 1) does not have any clonic or other convulsive motor activity, 2) does not have a change in consciousness during any attacks, 3) is well between attacks, and 4) has a normal or near normal electroencephalogram, a mistake in diagnosis is rare indeed. However, if the physician is not willing to spend the time to obtain a meticulous history of several attacks the diagnosis remains very difficult. Probably in less than 10 per cent of uncertain cases is there need for arteriography, pneumoencephalography, or ventriculography.

The site in the carotid system of the stenosing or occluding lesion cannot be determined from history alone unless monocular involvement of vision is one of the episodic symptoms. Even this symptom does not preclude the existence of multiple segmental atherosclerotic lesions. The same comment pertains to a bruit or to significant lowering of the retinal-artery pressure on one side.

Mechanisms of Attacks of Insufficiency. — It must be repeated that the very nature of the syndrome of intermittent insufficiency of the carotid system is such as to emphasize the transient nature of the pathophysiology. One does not expect to demonstrate a pathologic change in one-to-one relationship to intermittent claudication. Yet association has linked certain lesions with the syndrome. Most important is the realization that thus far clinical-pathologic corelates only incompletely link the neurologic symptoms with any one site degree of occlusive disease. Segmental atherosclerotic stenosis in the common or internal carotid arteries is observed at times. However, we have noted the syndrome in instances where there was no arteriographic evidence of compromise of luminal integrity anywhere in the system. More important, considering the current popularity of reconstructive carotid surgery, is the study by Martin, Sayre, and Whisnant(9), wherein the four major extracranial cerebral vessels were studied routinely at necrospsy in 100 consecutive cases of patients older than 55 years. High-grade carotid stenosis was discovered in several instances where there had been free-

dom from all clinical evidence of cerebrovascular disease.

Occlusion in the carotid system can be present concomitanly with intermittent insufficiency in that system, although this situation is observed less commonly than stenosis. The site of occlusion can vary from the common carotid artery to the internal carotid to the middle cerebral. In such instances the coexistence of stenosis distal to the occlusion cannot be eliminated. Despite all of these variations, guilt by association implicates carotid atherosclerotic stenosis as the morbid change most often detected. Careful arteriographic study of 100 consecutive cases of intermittent carotid insufficiency would greatly clarify this point.

If atherosclerotic stenosis is the static pathologic matrix for intermittent carotid insufficiency, reason forces the conclusion that some additional *transient* factor must subtend to precipitate individual attacks. Possible factors include 1) transient systemic hypotension, 2) polycythemia, 3) external compression or kinking of the cervical portion of the carotid arterial system, 4) anemia, 5) multiple emboli, 6) vasospasm, and 7) incipient thrombosis.

Transient Systematic Hypotension. — Lowering of the arterial blood pressure can produce disproportionately greater decrease of blood flow distal to stenosis than it does in unobstructed comparable arteries. That this mechanism might induce focal neurologic phenomena was proposed by Fleming and Naffziger(10) in 1927. Corday and Rothenberg(11) believed that attacks of insufficiency were caused by transient systemic hypotension or decrease in cardiac output. Denny-Brown(12) repeatedly has emphasized the importance of this mechanism. Apparently it can have significant effect in producing attacks of intermittent insufficiency in the carotid system. Patients having the latter syndrome should be examined for evidence of hypersensitivity of the carotid sinus, orthostatic hypotension, aortic stenosis, and cardiac arrhythmias; and the clinician should be alert to the possible existence of obscure variations on this theme.

We recently observed a 60-year-old man who suffered attacks of intermittent insufficiency of the left carotid systems, which he said occurred only when he was standing. Auscultations over the left carotid bulb revealed a bruit of the kind so frequently associated with stenosis of the first portion of the internal carotid artery. When he stood, the blood pressure measured 110/70; and no attack occurred. Further interrogation elicited the suggestion that taking a deep breath might induce an episode. When the patient slowly inhaled deeply, the blood pressure fell to 30/? and a typical attack ensued.

The pertinent question, however, is how often this mechanism is the inciting one for such attacks. In five separate instances we have recorded blood pressures coincidentally with the onset of attacks. In no instance was there any change of the pressure from the level usual for each patient. Observations of hundreds of hypertensive patients being treated with antihypertensive drugs reveal that attacks of focal cerebrovascular insufficiency seldom occur. This is a situation where blood pressure often may drop suddenly below optimal levels, or particularly may drop too swiftly below optimal levels for that patient. Experience at the Mayo Clinic has shown, however, that such causes as this are found only in considerably less than five per cent of cases of such ischemic attacks. Therefore it appears that this mechanism is responsible for only a relative few of the attacks of intermittent insufficiency in the carotid system.

Polycythemia. — With such attacks we(13) have associated polycythemia of various types. In certain cases control of the polycythemia has been followed by cessation of the attacks, and in some of these the attacks recurred when the polycythemia was no longer controlled. Polycythemia causes an increase in the viscosity of the blood and marked decrease in cerebral blood flow. However, in the individual patient the polycythemia appears to be a relatively steady state. Without some further change in hemodynamics, polycythemia seems an unlikely cause for these dramatically sudden and temporally limited attacks.

Slowing of flow and increase of viscosity can increase the tendency to clot formation.

Early clot formation in the primary or collateral arterial channels to a focal area of brain could produce focal insufficiency. Segmental atherosclerotic narrowing in the primary channel could well provide the situation in which thrombosis would begin. Evidence is not at hand to explain the ultimate (and swift) fate of the thrombus in this hypothesis. Anyway, among patients having such attacks the incidence of discovered polycythemia is low — less than 5 per cent in our experience.

External Compression or Kinking. — Another mechanism for the production of intermittent carotid insufficiency is external compression or kinking. Although this phenomenon is possible in the absence of arterial disease, it is very rarely observed in the first three decades of life — a fact which implies that some primary arterial change must occur before such external factors can induce intermittent symptoms. Angulation of a tortuous vessel by turning of the head can interfere with flow and produce symptoms. (This we have observed, but the vessel was not a normal one). The tortuosity may be so great that a complete circle is produced. Compression of the vessel against a bony prominence or against some unusually rigid or abnormally placed structure in the neck can occur in association with certain positions of the head. Boldrey, Maass, and Miller(14) found instances in which turning of the head caused stretching of the carotid over the transverse process of a vertebra with compression of the vessel. For a number of years it has been our practice, when reviewing the problem of individual patients with carotid insufficiency, to question the patient about his position at the onset of attacks and then attempt to produce an episode by turning, extending, and flexing the neck. The yield of positive findings has been low: less than 2 per cent of patients have had any apparent relationship between neck movement and onset of symptoms. Instances where an operation is indicated to correct such a defect are rare indeed.

Anemia. — We(15) have observed and reported cessation of attacks of intermittent carotid insufficiency when severe anemia was corrected. In most of the patients who have such attacks severe anemia is uncommon. Addition of atherosclerosis to the alteration of oxygen-carrying capacity of the blood in anemia seems still not to provide sufficient cause for the episodes. Both anemia and atherosclerosis exist as steady states; some transitory phenomenon — sudden hypotension, vasospasm, initial thrombus formation, or embolism — must be superimposed to initiate the attacks. Hence the severe anemia should be only a part of the stage setting.

Multiple Emboli. — The occluding action of a tiny embolus would explain the sudden onset of each episode. To explain the short duration and rapid clearing of the attacks, such an embolus would have to cease its blocking or collaterals would have to open. Most of the patients observed by us have not had any of the commonly recognizable sources of origin for such emboly — that is, a cardiac lesion, arrhythmia, or pulmonary lesion. Likewise, such patients do not have repeated embolic phenomena elsewhere in the body — in lungs, spleen, skin, liver, or kidneys. To this negative evidence should be added the unlikelihood of a cardiac embolus repeatedly passing to the same distal part of the cerebral circulation.

But such arguments do not eliminate the possibility that a fragment of clot, formed in a region of atherosclerosis in a vessel, loosens and becomes an embolus. The fate of such embolic material remains a matter for speculation. Either it breaks into minute fragments very quickly, to explain the brief duration of most attacks, or effective collaterals to the ischemic region open with equal speed. If such an embolus causes an attack it ultimately must be cleared from the lumen to make possible the next episode.

In the monkey Denny-Brown and Meyer(16) observed, lodged in a small peripheral branch of a partially damaged middle cerebral artery, what they interpreted as a fibrin-platelet embolus from that artery. Later the embolus moved on, lodged again, only to move once more and disappear into the capillary vessels. Fisher(17) has observed a similar phenomenon in the retina of a patient. This same mechanism was suggested by Millikan, Siekert, and Shick(18) in discussion of the pathogene-

sis of attacks of intermittent carotid insufficiency. Such a mechanism would well explain the favorable effect of anticoagulation in these patients. However, this pathogenesis is not clearly established as the most important one in the human.

Vasospasm. — The term long applied to episodic focal cerebral phenomena not thought to be convulsive in nature was "vasospasm". De Takats and Gilbert(19) believed that vasospasm was the basic abnormal phenomenon in most cerebral infarctions. Constriction of the cervical portion of the carotids in association with stimulation at operation has been observed frequently, as has mild constriction of small arteries in the pia on the surface of the brain. Even so, there is no significant evidence that vasospasm of the main stem of the carotid or its peripheral portions is a paramount factor in triggering intermittent insufficiency.

There are a number of fragments of evidence which imply that vasospasm is not a factor. The age range of most of the affected patients is one in which progressive degenerative and atherosclerotic changes decrease the capacity of vessels for constriction by decreasing elasticity and thinning the muscularis. In migraine, where vasoconstriction and vasodilatation are thought to play significant roles, the frequency of the disorder decreases to almost zero in the very age range where insufficiency is most common.

Careful analysis of the histories of patients with attacks yields no evidence of an inciting phenomenon to trigger vasospasm. Conversely the administration of a powerful cerebrovasodilator, such as carbon dioxide, at the very onset of attacks does not appear to affect the course of attacks for that patient. Similarly, injections into the cervical sympathetic chain and operations to interrupt it have not influenced the attack pattern or significantly altered cerebral blood flow. Indeed, it is doubtful that pathways for the conduction of such impulses exist beyond the level of vessels to the surface of the brain. Experimentally Byrom(20) and Denny-Brown, Horenstein, and Fang(21) demonstrated that the most effective stimulus to effect some degree of vasoconstriction is an increase in intraluminal tension.

Finally, the low incidence of focal neurologic phenomena associated with carotid arteriography in relatively young patients, where such manipulation sometimes produces severe vasoconstriction, implies that vasoconstriction alone does not cause significant focal insufficiency. This entire pattern of evidence points away from vasospasm as an important factor in the pathogenesis of intermittent carotid insufficiency.

Incipient Thrombosis. — Perhaps the concept of beginning thrombosis as the cause of attacks should be discussed, with comments on the development of emboli from intracarotid sources. A number of years ago it was suggested that "a thrombus begins to form on an area of diseased endothelium. This soft material may reach a size sufficient to produce enough alteration in blood flow to cause symptoms, break from its source, fragment and be carried away"(18). To that concept should be added the possibility that lytic action dissolves the thrombus in situ. Hardly anything is known of how often thrombi begin to form in vivo only to be self-limited in development or actively lysed. Likewise, little is known about the possible effect of a minor impediment to flow in a major artery. Whether turbulence so developed could significantly change the flow through the orifice of a small right-angle branch is a matter for speculation — and study.

In any event a number of factors are known which may be a part of the disordered physiology of intermittent carotid insufficiency. In a single patient several of these may occur simultaneously. At present it continues to seem that atherosclerosis associated with beginning thrombosis or intracarotid embolus formation constitute the most important phenomena.

Treatment of Intermittent Carotid Insufficiency. Control of Pathogenetic Mechanisms. — Knowledge of the possible factors in the pathogenesis of in termittent carotid insufficiency is of paramonut importance to the physician dealing with it. Such knowledge leads to full study of each patient and the implementation of treatment designed as precisely as possible to correct

the abnormality of structure or physioiogy. In studyng such patients it has been our practice to review each of the possible mechanisms discussed above.

Thus we attempt to discover a possible cause for episodes of transitory systemic hypotension. Any remedial cardiac dysfunction should be corrected by appropriate methods. We search for evidence of orthostatic hypotension — a condiction sometimes associated with hypertension! If an orthostatic reaction is present it should be corrected. Many of the patients have some degree of hypertension. Cases in which treatment is being given for systemic hypertension are scrutinized for a possible relationship of such therapy to the episodes of carotid insufficiency. Unfortunately, in only a few cases has a definite cause for transitory systemic hypotension been discovered.

The hematocrit value often is obtained to screen for the presence of polycythemia. If polycythemia is discovered, more intensive study is indicated to ascertain the exact nature of the abnormality. Definitive treatment should be used to correct the polycythemia, as effective relief of symptoms may come from treatment of the blood alone. Here again, the yield of patients discovered to have polycythemia is low.

Each patient should be questioned about the position of the head at the onset of attacks. Further, an attempt should be made to produce an attack by turning, extending, and flexing the neck. Cautions palpation may reveal evidence of a structure which could compress a carotid in association with some specific position of the head. If evidence of compression or kinking is obtained, roentgenograms of the region may assist in defining the abnormality. In selected instances it may be prudent to examine the vessel by means of arteriography. An appropriately designed reconstructive surgical procedure may correct the abnormality and stop the attacks. Compression or kinking is indeed rare — the yield is exceedingly low!

The blood is examined for evidence of anemia. In those instances where an association of anemia with intermittent insufficiency has appeared, the anemia has been profound and for the most part self-evident. Sufficientstudy should be made to detect the cause of the anemia and indicate the proper corrective measures. Cessation of attacks may follow such treatment. Again, anemia of significant degree is rarely discovered.

Therapeutic efforts directed at relieving theoretic vasospasm have been unrewarding. Patients can be instructed to rebreathe to increase the carbon-dioxide concentration. Psychologic benefit may acrue, but the attacks usually go on unaltered. Surgical interruption of the cervical sympathetic chain is not recommended.

Multiple emboli from sources outside the carotid system seem unlikely to be a cause of intermittent carotid insufficiency. In the rare instance when such a mechanism appeared plausible, long term treatment with an anticoagulant drug would probably be the therapy of choice.

All of these factors account for less than 15 per cent of all cases of intermittent carotid insufficiency. For the majority of patients two basic methods of treatment are currently possible: 1) multiple-vessel arteriography followed by surgery to re-establish flow through a segmental stenosis or occlusion of the extracranial portion of the carotid system and 2) alteration of the coagulation mechanism to prevent thrombosis and prevent fragments of thrombus from becoming emboli. Firm indications for one or the other of these two methods of treatment must await further study of each. However, certain considerations can assist in establishing criteria for the selection of treatment to get investigation of the problem initiated.

If a patient has widespread clinically advancing atherosclerosis with involvement of the coronary circulation, extremities, and so forth, it does not seem wise to subject him to the hazards of *arteriography and surgery*. Likewise, coexistence of some rapidly lethal other disease effectively precludes the arteriographic-surgical approach. In cases where arteriography was performed by DeBakey, Crawford, and Fields(22), 60 per cent of the patients did not have lesions considered operable. Probably in the natural history of the disorder among unselected patients an even larger percentage do

not have operable lesions in the extracranial carotid system. Conversely, in the majority of instances the atherosclerotic lesion is intracranial and inaccessible to the surgeon. In others multiple stenoses occur on the same side, making surgical correction impossible. These and other considerations regarding surgical therapy we have discussed in another paper(23).

In most instances a significant segmental stenosis in the extracranial portion of the carotid system is associated with a bruit demonstrable over the lesion or with decrease in the retinal arterial pressure on the side of the lesion, or both. Such physical signs well may be of primary importance in selecting patients for multiple-vessel arteriography.

Once the physician elects to pursue this course and admits the patient to the surgical group for long-term study, a program of fairly routine arteriography must be undertaken. Introduction of the constrast medium into the right subclavian artery makes possible excellent visualization of the right vertebral, common carotid, and internal carotid arteries. Baker(24) recently described a method for this injection which is associated with a minimum of complications. In addition the left carotid system should be visualized, and in certain instances the left vertebral. Details concerning the complications associated with left carotid arteriography will be presented in another publication. The greater incidence of complications on the left, where the artery is needled directly, leads to the conjecture that the complications are related to manipulation of the vessel rather than to the passage of the contrast media through the vessel. In this group of cases there is likely to be a high incidence of atheromata of the vessel injected. On the right side the dye is injected into the subclavian artery, making manipulation of the carotid unnecessary. In order to assess the complications carefully it is necessary to observe the patients carefully for a number of hours after the procedure. If this precaution is omitted neurologic deficits can occur and never be linked to the arteriography.

Arteriography is used only to determine whether surgery is feasible, or for diagnostic help in those rare instances where diagnosis is not possible from the history and examination. If arteriography reveals evidence of segmental stenosis, an appropiate surgical procedure can be undertaken. Since the classic case reported by Eastcott, Pickering, and Rob(25) there has not been a report dealing with long-term follow-up after surgical therapy in a group of patients specifically having intermittent carotid insufficiency. The morbidity and mortality of this method of treatment remain to be determined. In addition all such patients thus treated must have follow-up assessment to collect information concerning recurrence of symptoms, subsequent cerebral infarction, and duration of patency of the vessel operated upon. Hence practically the whole status of such surgery is a matter for the future!

The other potential treatment method available is *alteration of the coagulation mechanism.* Millikan, Siekert, and Shick first reported using anticoagulant treatment in a group of patients. The attacks ceased. Later we(26) found that attacks stopped in 82 of 85 patients treated. Then, Fisher(27) reported treatment of 14 patients whose attacks stopped 1 to 10 days after effective anticoagulant levels had been reached. Still, key questions remained unanswered. In how many such patients would the attacks have stopped spontaneously? In how many would significant cerebral infarction develop? Would long-term anticoagulative treatment prevent cerebral infarction in a significant number of patients? It has been our impression that anticoagulants do influence favorably the natural history of the disorder without an inordinate incidence of serious complications. Only recently, however, have data concerning long-term follow-up of treated and untreated patients become available. We(28) found that in a follow-up period of 3 to 5 years the incidence of cerebral infarction was significantly greater in a group of untreated patients than in a group of similar patients receiving anticoagulants continuously. The incidence of intracerebral hemorrhage was essentially the same in the two groups.

It is emphasized that feasibility of the administration of anticoagulants over a long

period is determined by the cooperation of the patient, the experience of the local physician with the use of such drugs, and the availability of suitable laboratory assistance. It is our practice to keep the prothrombin time at about twice normal for the laboratory in which the test is performed or to maintain a prothrombin activity of 15 to 25 per cent. Current experience suggests that treatment should be continued indefinitely.

Actively Advancing Thrombosis in the Carotid System

The second major category of occiusive disease in the carotid system is actively advancing thrombosis. Such an attack mav begin exactly as does an attack of intermittent carotid insufficiency. In attaks of this type, however, the ischemia is of such duration and severity that relatively permanent to very serious damage is produced. Instead of abating in a few minutes, as in intermittent insufficiency, the condition generally worsens —often in steps— until the neurologic deficit is severe and extensive, indicating that significant infarction has taken place. The diagnosis of this type of occlusive carotid disease is dependent upon close attention to the history and precise observation of the patient in the first few hours after onset. During an attack of intermittent insufficiency it is not usually possible to determine the moment when the process will become irreversible; but when the duration or severity of the neurologic phenomena differs decidedly from the pattern of previous attacks suffered by that patient, it is likely that a more serious process is under way. The term "actively advancing thrombosis" is a speculative clinical one in which the physician caring for a patient attempts to explain an extension of the process at work in intermittent insufficiency. Such a process may not actually be present in all instances. It may be that 1) stenosis —probably due to advancing thrombosis— is present, or 2) collateral supply has failed to provide the blood needed, or 3) prolonged inadequacy of supply produces defective function in more and more brain cells, or 4) a combination of these factorsis existent. Until there is better understanding of the mechanism this term is a tenable one, and it may lead to a rational therapeutic approach. If thrombosis is progressing and causing infarction, worsening may continue by steps for a good many hours. In contrast, an infarct secondary to embolism attains full, or almost full, pathophysiologic development in seconds to a few minutes. General diagnostic criteria which aid the physician are 1) a history of warning attacks of intermittent insufficiency, 2) steplike progression over many minutes or a few hours, 3) a rather minimal amount of pain in the head, 4) preservation of consciousness — usually — and 5) clear cerebrospinal fluid. Often other evidence of atherosclerosis in heart, kidneys, or extremities is present. In addition to the general points there are certain anatomically determined neurologic signs. These include monoparesis to hemiplegia, hemianesthesia, homonymous visual-field defect or impaired vision in the eye on the side of the lesion, and some disturbance of language function (aphasia, agraphia, alexia, or the like) if the dominant hemisphere is involved. Under "Symptomatology and Diagnosis" of "Impeding or Incipient Stroke", certain physical signs referable to the patency of the appropriate carotid were described. The same signs may be present in progressing thrombosis in the carotid system. For instance, measurement of both retinal arterial pressures may assist greatly in localizing the site of the arterial lesion. Unless some such signs exist the physician can only speculate as to whether thrombosis is going on in the intracranial or extracranial portion of the system.

Contrasting with the abrupt temporal profile described above, in a small number of patients the clinical pattern forms gradually or progressively over many days to a few weeks. The progression of neurologic phenomena in such instances is like that caused by a metastasis to the brain or a rapidly growing glioma. Unless these is a definite decrease in retinal arterial pressures, absence of carotid pulse, or a bruit —each on the appropriate side— a firm clinical diagnosis is dificult indeed. Carotidarteriography is ordinarily advised.

It is true, of course, that carotid thrombosis can become manifest by the very rapid onset (minutes) of a maximal neurologic deficit; but the clinician seldom sees such a patient until the stroke is completed. Therefore the discussion of the problem will be later in this paper.

As in intermittent carotid insufficiency, so in actively advancing thrombosis in the carotid system, the diagnosis is a clinical one. It can be established with great accuracy by prudent assessment of a detailed history, precise examination, and hour-to-hour observation of the patient. In this category of occlusive cerebrovascular disease the electroencephalogram is of little diagnostic value. Carotid arteriography rarely is necessary for primary diagnosis if the physician has the time and skill to obtain the data mentioned above. Arteriography preliminary to carotid surgery will be discussed under "Treatment".

Pathogenesis of Actively Advancing Carotid Thrombosis. — The influence of extracranial carotid atherosclerosis on the pathogenesis of intermittent carotid insufficiency is far from clear, but a more direct relationship to actively advancing thrombosis apears likely. In the few instances where there has been careful inspections of the cervical portion of the carotid arteries, thrombosis without atherosclerosis has not been found. However, in the study by Martin, Sayre, and Whisnant(9), occlusion or severe compromise of at least one carotid or vertebral artery or of its ostia at the aorta was discovered in 40 per cent of the cases. Most of these were carotid involvements. It seems logical that in each instance a significant degree of stenosis had been present for months or years. Yet in most instances thrombosis had not occurred and the patients had had no clinical evidence of cerebrovascular disease. In most cases of actual occlusion there was no associated cerebral infarct.

These observations stimulate investigators to ask several questions. Why does thrombosis occur at a specific time and not at all others, in that patient? Why can gradual or swift occlusion take place without producing clinical phenomena? Why can massive infarction happen with atherosclerotic stenosis but no thrombosis? What factor must be added to occlusion —whether resulting from atherosclerosis or from atherosclerosis plus thrombosis— to produce infarction?

Referring to the first problem, knowledge concerning the fundamental mechanisms involved in the initial phases of thrombosis is fragmentary. It may be presumed that the degree of roughness of intima involved by atherosclerosis will remain relatively constant from hour to hour. How variations of flow, including slowing or turbulence, will influence platelet deposition on this surface is not known. Details of the natural variations in coagulation tendencies are not understood. There is still debate concerning the acute affect of a high-fat meal on coagulation. There is no knowledge concerning the possible existence of hour-to-hour variations in blood viscosity. Just now attention is being directed toward study of the variable dynamic equilibrium which must exist between forces of coagulation and lysis, as well as of factors which may precipitate imbalance in this system. The probability that temporary distortions of atherosclerotic patches could be effected by transient changes in position of the head has not been investigated even in models. It is apparent that extensive long-term studies must be implemented for discovery of even partial answers to explain the varying relationship between atherosclerosis and thrombosis.

Equally elusive is the variable relationship between occlusion and infarction. To what degree the speed of occlusion affects this process is a matter for speculation. Millikan and Moersch(29) pointed out that when a neurologic defect caused by infarction comes on quickly and persists, the prognosis for recovery is poorer than when the same quantity of impaired function appears slowly. While this observation suggests that speed of occlusion may be related to severity of infarction, this point is not proved.

A standard explanation for the wide spectrum —from normal brain to massive infarction —of phenomena associated with carotid occlusion is that the collateral circulation is adequate or has failed to supply sufficient blood. This is almost as extreme

an oversimplification of the problem as to say, "There is not enough blood because there is not enough blood!" Quite obviously, if infarction follows carotid occlusion, the collateral supply is insufficient.

However, a wide variety of pathologic relationships between primary and collateral blood supply to a given area of brain do potentially exist, any one of which could cause infarction. In considering such theoretic relationship it is well to remember that there are two well-known collateral sources of supply in carotid mainstem disease: supply through the circle of Willis, and distal collaterals to areas supplied by small subdivisions of the carotid system. Some potential variations which could produce infarction are:

Carotid stenosis.
- Affecting supply to whole region of distribution.
  - Flow suddenly becomes less sufficient; collateral remains inactive.
- Affecting only part of supply to a focal area.
  - Suddenly becomes less sufficient; collateral does not increase.
  - Suddenly becomes less sufficient; collateral decreases.
  - Remains constant; collateral fails.

Carotid occlusion.
- Collateral is insufficient or is sufficient for a time, then fails.

Carotid open but significant portion of supply to area is through other channels.
- Collateral fails.

If "Mechanisms of Attacks of Insufficiency" in the discussion of "Impending or Incipient Stroke" is reviewed with the understanding that one or several of those mechanisms also may enter into relationships listed above, it is apparent that the pathogenesis of actively advancing thrombosis (infarction) is potentially complex indeed.

In those instances where arteriography or pathologic study indicates that occlusion took place days or months prior to infarction, one can supplement his speculation about mechanism by experience with a model handily provided by the neurosurgeon. Infarction of the brain has occurred or a few days after the carotid was surgically occluded in the treatment of intracranial aneurysm. This has taken place in young patients without evidence of any cardiac abnormality that might produce transitory systemic hypotension. The onset of neurologic phenomena in these postoperative situations is often very sudden, similar to that observed with cerebral embolism. It may well be, in selected instances, that a fragment of thrombus, formed just distal to the surgical occlusion, breaks free and becomes an embolus. A similar mechanism may account for infarction which appears long after atherosclerotic occlusion.

Elucidation of the pathogenesis of this phase of carotid disease will assist greatly in constructing logical programs of treatment.

Treatment of Actively Advancing Carotid Thrombosis. — During the last two decades one of the principal methods of treatment of all types of cerebral infarction has been "vasodilator" therapy in one form or another. Various drugs or procedures have been reported as efficacious. We(30) have summarized the pertinent data as well as our own experience and concluded that none of the therapeutic methods which attempted to produce vasodilatation has fundamentally changed the natural history of cerebral infarction due to thrombosis.

If actively advancing thrombosis is a fact in addition to being a clinical concept, it is natural to speculate concerning treatment with a thrombolytic agent. We(31) have pointed out that the time required for lysis by an agent administered intravenously is probably too long for optimal benefit. As the degree of oxygen sufficiency is far from static in actively advancing thrombosis, lysis might be of great benefit. In certain instances introduction of the thrombolytic agent directly adjacent to the lesion may be feasible. At the present time several factors suggest that much more study will be needed before a thrombolytic agent can be used with assurance. The thrombolytic agents available appear to need standardization for degree of activity, and certainly it will be helpful when some more practical laboratory method is available for measuring the activity of the lytic system after a thrombolytic agent is administered. Whether concomitant administration of an-

ticoagulant will be necessary is not known. Existing agents can produce untoward side reactions. The variability of the clinical course of actively advancing thrombosis makes indispensable the observation of a group of untreated patients for comparison of results before final evaluation of such treatment. All of these problems are important; together they indicate that it will likely be several years before a practical thrombolytic agent is available for widespread use in this disorder.

Study of the natural history of actively advancing thrombosis in the carotid system shows that mortality is approximately 14 per cent. Our early experience as well as that of Fisher suggested that after emergency administration of anticoagulants the progression of the neurologic deficit was halted in enough cases of this kind to indicate a significant beneficial effect of treatment. Meyer and associates(32) and Carter(33) found similar encouraging results. Our subsequent experience has continued to confirm the initial impression. In continuing study of this application of anticoagulant therapy our practice has been to institute anticoagulation immediately after clinical diagnosis by administering heparin intravenously every 4 hours and concurrently giving an orally ingested anticoagulant. The important matter of the need for long-term anticoagulation in actively advancing thrombosis has not been settled. Perhaps the treatment should be continued for a month or two and then gradually tapered off. If evidence of activity appears later in the form of attacks of intermittent insufficiency, it probably would be prudent to recommend long-term anticoagulation.

Many points concerning the value of treatment with anticoagulants in this situation remain to be clarified.

While anticoagulations can prevent an increase in thrombosis, it apparently effects very little destruction of the thrombus and that action is probably slow. Fibrinolysin or activated plasminogen is capable of digesting fibrin and can dissolve fresh clots. Pilot studies indicate that in vivo dissolution of thrombus can be attained in thrombophlebitis. Even in this disorder, however, many problems must be solved before the treatment can be widely applied with safety.

Sussman and Fitch(34) and Moser(35) have reported initial experience concerning the treatment of cerebral thrombosis with fibrinolysin, but the efficacy of the therapy could not be assessed. The time required for lysis of an arterial clot by fibrinolytic agents administered intravenously is probably too long for optimal benefit in actively advancing thrombosis. Direct injection of a fibrinolytic substance into an occluded artery may produce more certain lysis of the thrombus. However, if the thrombus produces occlusion the time element is so crucial that the lytic agent must work very swiftly to prevent infarction. The main application of this treatment will probably be where thrombosis has not progressed to the stage of occlusion.

Another method of lysing thrombus is to administer an agent, such as purified streptokinase, which will enter a thrombus and activate the plasminogen naturally present, thus dissolving the clot from within. As yet this method has not been tried. As more effective lytic agents become available, it will be necessary to design methods for testing their effectiveness in clinical situations. We(31) have suggested that this could be done by comparison of the patient's clinical course after treatment with the course of a control group and by serial arteriographic determination of the patency of the arteries to the suspected area of brain before and after treatment. The latter measure will demonstrate whether occlusion has been relieved but will not indicate whether the patient has benefited from the treatment. The role of lytic agents in treatment of actively advancing thrombosis in the carotid system is still in the phase of investigation.

Surgical treatment of actively advancing thrombosis in the cervical portion of the carotid system has not yet been carefully evaluated. A number of factors contribute to the complexity of this problem. In a majority of cases the thrombotic process is in the intracranial portion of the carotid system, thus definitely precluding surgery. The risks of carotid arteriography in this specific category have never been assessed realistically and may well be considerable.

Our initial experience suggests there may be greater risk in arteriography of the left carotid, into which the dye is injected directly, than in such study of the right, for which the injection is made into the right subclavian artery as described by Baker(24). In the latter procedure, manipulation of the carotid itself is not necessary. The manipulation can fracture a thrombus or atheroma, releasing an embolus, or incite thrombosis on a plaque; the needle can traumatize the vessel, causing a dissecting aneurysm. The very need to do arteriography is to be questioned, as the procedure may use up many minutes to several hours of time, which need not be lost if anticoagulation or fibrinolytic treatment is effective.

This same consideration applies to the surgery, for as much time may be lost in readying the operating room staff, and so forth. The morbidity and mortality from surgery are not known. If occlusion has occurred already, although the progression of symptoms is continuing, it is often impossible to re-establish blood flow; and in some instances there is danger of dislodging material from the distal portion of the thrombus with disastrous results. If the actively advancing thrombosis has proceeded only to the point of causing stenosis, however, it appears feasible to correct the defect by surgery. Because of the variable natural history of the disorder and these other considerations, it is unlikely that surgery ever will become the optimal treatment for actively advancing carotid thrombosis. Control studies comparing treated and untreated patients must be undertaken.

Completed Stroke in the Carotid System

The completed stroke is that subdivision in the dynamic temporal classification in which there is no further progression. This is detected by frequent meticulous examinations. If such an examination reveals an increase in the severity or extent of the neurologic deficit, it indicates that the stroke is progressing or is not completed. Precise definition of the point where the process changes from active progression to completion cannot be obtained unless the patient can give an accurate history or be observed by a knowledgeable person.

This clinical designation is accompanied by the presumptions that the thrombosis is no longer extending anatomically and that infarction has reached maximal involvement for that stroke. In cases of thrombosis in the carotid system, lack of progression for a few hours generally indicates that the incident is complete — that is, there will be no worsening of weakness, sensory defect, aphasia, or other abnormality. After cessation of progression there may be a number of hours when the patient's condition changes little. Then, unless damage has been extraordinarily severe, improvement begins. This phase of modest improvement is particularly characteristic of infarcts produced by thrombosis. The early and continuing improvement so common in cerebral thrombosis may be of importance in establishing the diagnosis, particularly when there has been some reason to suspect the presence of a brain tumor or abscess.

These comments describe the temporal profile of a completed stroke in the carotid system. There may be wide variation in the character and severity of the neurologic defect, depending on the portion of the carotid system involved and the effectiveness of the collateral circulation. Occlusion of the internal carotid artery may not be associated with any clinical phenomena or the neurologic deficit can be massive, similar to that often observed with thrombosis of the main stem of the middle cerebral artery. Characteristic neurologic deficits commonly observed with thrombosis in individual vessel are described in standard text books of neurology. Detection of a neurologic problem may imply thrombosis in a specific distal branch of the system but does not eliminate the possibility that atherosclerosis with or without thrombosis has stenosed or occluded the parent internal or common carotid artery. Therefore it is important to assess the patency of these vessels by palpation, and ophthalmodynometry. Rare, indeed, is acute extracranial carotid occlusion without concomitant reduction in the retinal arterial pressure on the side of the lesion.

Pathogenesis of Completed Stroke in Carotid System. — It is obvious that all the factors entering into the pathogenesis of intermittent insufficiency and actively advancing thrombosis can enter into the pathogenesis of the completed stroke, since the latter is the temporal end-point of the former. It is likewise obvious that collateral blood flow is not adequate — or infarction would not occur.

Physicians who have viewed the rapid improvement of the neurologic deficit in some cases, contrasting it with the slow and minimal improvement in others, have been led to postulate a marginal zone. This theoretic marginal zone is a region at the periphery of the zone of maximal ischemia where function is deranged because of insufficiency of blood supply but the gradient of oxygen deprivation is not so steep as to extinguish the life of the neural elements. Subsequent increase of flow to this marginal zone is attended by return of active function of cells and decrease in the neurologic manifestations.

This explanation of improvement is a plausible one. Although often ignored, the variable natural history of completed infarcts in the carotid system is well known. The sequence of pathophysiologic events in the marginal zone of surface infarcts has been studied carefully by Meyer and Denny-Brown(36) but leaves unexplained the fundamental disparity between the effective generation of adequate collateral in some instances and the inadequate collateral in others. Whether the occluding agent becomes a permanent block to flow either in primary or collateral channels probably depends on the nature of the agent — whether it is lysible or friable or firm.

Treatment of the Completed Stroke in the Carotid System. — In attempting to design efficacious treatment for this category certain theoretic considerations are of importance. Neural elements anoxic for 6 to 10 minutes are permanently damaged or killed. Practically, if this were the sole consideration effective therapy would be impossible. It has been pointed out, however, that this all-or-none concept is operative only in part. Cells whose function is deranged by hypoxia may return to normality. This introduces the element of variability in the clinical pattern. No way is known of promoting regrowth of infarcted brain, but attempts have been made to stimulate the opening of adequate primary or collateral blood vessels to protect tissues in the region of marginal damage.

We(30) have summarized elsewhere the many therapeutic technics to produce a hypothetic increase in blood flow to cerebral infarcts. These methods include stellate ganglion block, inhalation of carbon dioxide, and administration of histamine, papaverine hydrochloride, tolazoline hydrochloride (priscoline), nicotinic acid, alcohol, and aminophylline. It is apparent that none of these therapeutic methods has fundamentally changed the natural history of completed strokes in the carotid system.

From a theoretic standpoint we consider that anticoagulant therapy would be of no benefit when the neurologic lesion is complete. Moyes and associates(37) reported that experimental canine cerebral infarcts were more hemorrhagic when anticoagulants were administered than were those in a similar experiment without anticoagulants. Reports by Vastola and Frugh(38) and Ushiro and Schaller(39) suggest that in this category of cerebrovascular disease anticoagulants are of no benefit and may be harmful. Preliminary reports of the participants in the cooperative clinical study of anticoagulants in cerebrovascular disease confirm our original impression. Therefore it appears wise to continue advising against the administration of anticoagulants in this type of stroke soon after its occurrence. It is possible that subsequent long-term administration of anticoagulants may decrease the incidence of "recurring" strokes; however, this has never been fully investigated.

Probably the only circumstances justifying exception to this rule are 1) the presence of some complication such as thrombophlebitis and 2) when the completed stroke was caused by an embolus which is evidence to indicate that embolism could recur. The reports of Carter(33, 40) suggested that improvement may be associated with anticoagulation in complete strokes which required several hours to develop. There was little effect in patients who had

acute onset of non-embolic strokes. Likewise Carter(41) found significant benefit when patients with cerebral embolus received anticoagulants, beginning as soon after the stroke as possible. We have not treated such a group of patients by this means, as there appeared to be added risk of bleeding in experimental infarction due to embolism when anticoagulation was initiated within 3 days after embolization. These problems need further investigation.

If thrombolytic agents are to dissolve an occluding thrombus, the agents must be administered a few hours after the thrombosis. Hence the potential use of these agents is limited to the acute phase of the completed stroke. The observations of Howard(42) suggest that the lytic agents do not damage freshly infarcted brain. However, it is not known whether suddenly flooding a recent cerebral infarct with blood by removing the occlusion would be beneficial or detrimental to recovery. At any rate there appears to be little theoretic reason for presuming that thrombolytic agents will materially benefit many patients in this category. Ambrus(43) comments that there was no change in a number of patients treated by him. At present our knowledge concerning thrombolytic agents is so limited that it appears prudent to consider their use in cerebrovascular disease still in the experimental phase.

Surgical technics for re-establishing blood flow in the extracranial portion of the carotid system are subject to theoretic problems similar to those existing with other methods of treatment. In the immediate interval following a completed stroke increasing blood flow can aid recovery only in marginally oxgenated regions where permanent ramage has not yet occurred. The reason for re-establishing a normal pattern of flow some time after thrombotic occlusion would be to obtain hypothetic protection against subsequent occlusion in some other vessel or simply to get as much blood going to the brain as possible.

Experience at the Mayo Clinic(44), as well as elsewhere reveals a disappointingly low incidence of cases in which patency can be produced surgically when occlusion is due to thrombosis. The thrombus often extends for some distance, and there is even danger of dislodging a fragment from the distal end if a vigorous attempt is made to remove the clot. In those instances where occlusion is due to atherosclerosis, without recent thrombosis, the occlusion is commonly segmental and hence more easily corrected by surgery. However, it appears that occlusion due to atherosclerosis without thrombosis is less commonly encountered in direct relationship to cerebral infarction than is occlusion due to the combination of atherosclerosis and thrombosis.

Since it is usual for the patient's condition to improve after infarction in the carotid system is complete, investigators must contrast treated and untreated patients in order to assess the treatment. If surgery is to be used some time after infarction, simply to give theoretic protection in the future, assessment of the result will be tedious indeed, requering several years' follow-up observation of both treated and untreated patients. If surgeons wish to operate for atherosclerotic occlusion without reference to attaining any certain objective, there will be ample opportunity as revealed in the study of Martin, Sayre, and Whisnant (9). Thus far there is no satisfactory evidence in the literature that vascular surgery is of clear-cut benefit in completed infarction in the carotid system.

Rehabilitation continues as the mainstay for inducing simptomatic improvement after completed stroke. The many methods for encouraging and facilitating improvement in language and motor function will not be reviewed here.

Completed Stroke With Evidence of Continuingly Active Pathophysiology

More a combination of categories than a separate one, completed stroke with evidence of continuingly active pathophysiology is often enough encountered in practice. It is exemplified by the patient who has had a completed stroke with appropriate neurologic abnormalities and then begins to have attacks of intermittent insufficiency in the same or opposite carotid system or vertebral-basilar system. Criteria for diagnosis are indentical to those reviewed under

"Impending or Incipient Stroke" and "Completed Stroke", but simply are present in the same patient at different points in time. Another combination of categories is presented by the patient who has had a completed stroke in the carotid system and then exhibits the clinical phenomena characteristic of actively advancing thrombosis in the same or opposite carotid systems or vertebral-basilar system.

While the clinical designation of these combinations is relatively straightforward, the pathophysiology probably is complex and —broadly speaking— has not been studied. One begins with the assumption that the completed-stroke portion of the combinations is the clinical counterpart of focal brain damage due to ischemia. All of the variables in pathogenesis may be present, as in any completed stroke. To explain the new activity, new elements of dynamic pathophysiology must be added to this state. It is easy to presume that collateral circulation is inadequate, intermittently or continuosly; this is obvious. But is the inadequacy related to atherosclerosis in the arterial system of the completed stroke or in some portion of another system? Is there a complex interrelationship between multiple zones of stenosis in two or more systems? What part is played by transient systemic hypotension, emboli, anemia, polycythemia, or altered clotting mechanisms? Plainly, a variety of possible explanations must be investigated before the pathophysiology of these clinical combinations can be defined.

Treatment of these complex problems has been developed on the basis of trying to limit the progression of the active portion of the combination. Accordingly, if in a case of completed stroke in the carotid system, intermittent insufficiency develops in that or another arterial system, study and treatment are instituted as though there had been no antecedent completed stroke—assuming, necessarily, that the completed stroke did not leave the patient completely invalided. This approach provides the physician with a working plan for therapy in such complex problems. Methods of treatment have been discussed under "Impending or Incipient Stroke" and "Advancing Stroke".

SUMMARY

It has become popular to presume that a segmental atheromatous lesion in the proximal portion of the carotid system is responsible for all pathophysiology observed in the distal reaches of the system—neglecting to integrate into a logical pattern the many lesions which are not associated with pathophysiology. It is now important for us as clinicians to interrelate what appears to be insufficiency of blood flow with stenosis or occlusion in some portion of the system (as demonstrated by arteriography, surgery, nor necropsy) and infarction of the brain as interpreted through the persistence of a focal neurologic dificit as well as through gross and histologic study of the brain. Only when the investigator considers the entire carotid system as well as each of the parts can he begin to postulate explanations for absence of clinical phenomena in the presence of occlusion of the internal carotid artery and to construct a possible explanation for the pathogenesis of massive infarction when the primary channels are wide open.

In developing the concept of clinical consideration of the total carotid system, we have introduced a temporal classification of occlusive disease to assist the clinician in the diagnosis and the selection of treatment. The temporal categories are: (1) incipient or impending stroke, (2) advancing stroke, (3) completed stroke, and (4) completed stroke with evidence of further activity of the cerebral ischemic process. The clinical pattern, pathogenesis, and various methods of treatment of each category are discussed.

RESUMEN

Se ha hecho popular presumir que una lesión ateromatosa segmental en la parte proximal del sistema carotidio es responsable por toda la fisiopatología observada en la parte distal del sistema, descuidando integrar en un esquema lógico las múltiples lesiones que no están asociadas con fisiopatología.

Es ahora importante para nosotros clínicos relacionar lo que aparece ser insuficiencia de flujo sanguíneo con estenosis u oclusión en alguna parte del sistema (demostrados ellos por arteriografía, cirugía, o autopsia) y el infarto del cerebro tal como se interpreta a través de la persistencia de un foco neurológico deficitario así como a través de un estudio macroscópico e histológico del cerebro.

Solamente cuando el investigador tenga en consideración todo el sistema carotidio tanto como cada una de sus partes puede él comenzar a postular explicaciones acerca de la ausencia de fenómenos clínicos en presencia de oclusión de la arteria carótida interna y a construir una explicación posible para la patogénesis del infarto masivo cuando los canales primarios están ampliamente abiertos.

Desarrollando el concepto de la consideración clínica de todo el sistema carotidio, hemos introducido una clasificación temporal de enfermedad oclusiva para ayudar al clínico en el diagnóstico y en la selección del tratamiento. Las categorías temporales son: (1) ataque incipiente o amenazante, (2) ataque en progreso, (3) ataque completo, (4) ataque completado con evidencia de actividad ulterior del proceso isquémico cerebral. Son discutidos el esquema clínico, la patogenia y varios métodos de tratamiento en cada categoría.

RESUME

C'est populaire de supposer qu'une lésion atheromateuse segmental dans la partie proximal du système carotidiene est responsable pour toute la physiopathologie observée dans la partie distal du système, négligeant intégrer dans le schéma logique les multiples lésions qui ne sont pas asociées avec physiopathologie.

C'est maintenant important pour nous les cliniciens relationner ce quì parait être insuffisance de flux sanguin avec stenoses ou occlusion dans quelque partie du système (ils demontré par arteriographie chirurgie on autopsie) et l'infarctus du cerveau tel comme on l'interprete au travers de la persistance d'un foyer neurologique deficitaire ainsi qu' au travers d'une étude macroscopique et histologique du cerveau.

Seulement quand l'investigateur a en consideration tout le système carotidien de même que chacune de ses parties, il peut comencer à considérer des explications au sujet de l'absence de phénomènes cliniques en présence d'occlusion de l'artère carotide interne et a penser à une explication possible pour la pathogenie de l'infarctus massif quand les voies principales sont amplement ouverts.

Devellopant le concept de la considération clinique de tout le système carotidien, nous avons introduit une classification temporelle des maladies oclusives pour aider le clinicien dans le diagnostique et la sélection du traîtement. Les catégories temporelles sont:

(1) attaque initiale ou menaçante
(2) attaque en progrès
(3) attaque complète
(4) attaque complétée avec évidence d'activité ultérieure dans le procès ischemique cérebral.

Les schemas cliniques sont discutés ainsi que la pathogenie et plusiers traîtements dans chaque catégorie.

ZUSAMMENFASSUNG

Es ist Gewohnheit geworden, anzunehmen, dass eine segmentaere atheromatoese Laesion im proximalen Teil des Carotis-Systems fuer all die beobachtete Pathophysiologie der distalen Teile des Systems verantwortlich sei, wobei vergessen wird, die vielen Laesionen, die nicht mit der Physiopathologie verbunden sind, in eine logische Form einzufuegen.

Es ist nun fuer uns als Kliniker wichtig, das was uns als Insuffizienz der Blutzirkulation erscheint, in Beziehung zu setzen mit einer Stenose oder Occlusion in irgend einem Teile des Systems (wie man es durch die Arteriographie, Chirurgie oder Autopsie demonstrieren kann) oder einem Infarkte des Gehirns, wie er interpretiert wird durch die Persistenz eines neurologischen Herddefektes sowohl als auch mittels der mikro-und makroskopischen Untersuchung des Gehirns. Nur wenn der Forscher das gesammte Carotis-System sowie auch jedes seiner Teile in Betracht zieht, kann er beginnen Erklaereungen fuer die Abwesenheit klinischer Erscheinungen zu geben, wenn eine Occlusion der art. Carotis interna besteht und eine moegliche Erklaerung fuer die Pathogenese des massiven Infarktes aufstellen, wenn die primaeren Blutwege durchgaengig sind.

Bei der Entwicklung des Konzeptes der klinischen Betrachtung des gesammten Carotis-Systems, haben wir eine chronologische Klassifizierung der occlusiven Erkrankung eingefuehrt, um dem Kliniker bei der Diagnose und Wahl der Behandlung behilflich zu sein. Die chronologischen Kategorien sind:

1. Der beginnende oder unmittelbar bevorstehende Schlaganfall
2. der progerdiente Schlaganfall
3. der vollendete Schlaganfall
4. der vollendete Schalaganfall mit den Symptomen einer weiterbestehenden Aktivitaet des ischaemischen Hirnprozesses. Es werden die klinischen Formen, die Pathgenese und die verschiedenen Behandlungsmethoden einer jeden Kategorie besprochen.

REFERENCES

(1) *Fisher, Miller*: "Occlusion of the Internal Carotid Artery". A.M.A. Arch. Neurol. & Psychiat. *65*:346-377 (Mar.) 1951.

(2) Report by an ad hoc Committee, Advisory Council for the National Institute of Neurological Diseases and Blindness, Public Health Service: A Classification and Outline of Cerebrovascular Diseases. Neurology. *8*:405-434 (May) 1958.

(3) *Johnson, H. C. and Walker, A. E.*: "The Angiographic Diagnosis of Spontaneous Thrombosis of the Internal and Common Carotid Arteries". J. Neurosurg. *8*:631-659 (Nov.) 1951.

(4) *Denny-Brown, D.*: "Symposium on Specific Methods of Treatment: Treatment of Recurrent Cerebrovascular Symptoms and the Questions of «Vasospasm»". M. Clin. North America, September, 1951, pp. 1457-1474.

(5) *Millikan, C. H. and Siekert, R. G.*: "Studies in Cerebrovascular Disease. IV. The Syndrome of Intermittent Insufficiency of the Carotid Arterial System". Proc. Staff Meet., Mayo Clin. *30*:186-191 (May 4) 1955.

(6) *Dunning, H. S.*: "Detection of Occlusion of the Internal Carotid Artery by Pharyngeal Palpation". J.A.M.A. *152*:321 (May 23) 1953.

(7) *Hollenhorst, R. W.*: "Ocular Manifestations of Insufficiency or Thrombosis of the Internal Carotid Artery". Am. J. Ophth. *47*: 753-767 (June) 1959.

(8) *O'Doherty, D. S. and Green, J. B.*: "Diagnostic Value of Horner's Syndrome in Thrombosis of the Carotid Artery". Neurology. *8*:842-845 (Nov.) 1958.

(9) *Martin, M. J., Sayre, G. and Whisnant, J. P.*: "Incidence of Occlusive Vascular Disease in the Extracranial Arteries Contributing to the Cerebral Circulation". Read at the meeting of the American Neurological Association, Boston, Massachusetts, June 13 to 15, 1960.

(10) *Fleming, H. W. and Naffziger, H. C.*: "Physiology and Treatment of Transient Hemiplegia". J.A.M.A. *89*:1484-1487 (Oct. 29) 1927.

(11) *Corday, Eliot and Rothenberg, S. F.*: "The Clinical Aspects of Cerebral Vascular Insufficiency". Ann. Int. Med. *47*:626-639 (Oct.) 1957.

(12) *Denny-Brown, D.*: "Recurrent Cerebrovascular Episodes". A.M.A. Arch. Neurol. *2*:194-210 (Feb.) 1960.

(13) *Millikan, C. H., Siekert, R. G. and Whisnant, J. P.*: "Intermittent Carotid and Vertebral-Basilar Insufficiency Associated

With Polycythemia". Neurology. *10*:188-196 (Feb.) 1960.

(14) *Boldrey, Edwin, Maass, Lyman and Miller, Earl*: "The Role of Atlantoid Compression in the Etiology of Internal Carotid Thrombosis". J. Neurosurg. *13*:127-139 (Mar.) 1956.

(15) *Siekert, R. G., Whisnant, J. P. and Millikan, C. H.*: "Anemia and Intermittent Focal Cerebral Arterial Insufficiency". A.M.A. Arch. Neurol. (In press.).

(16) *Denny-Brown, D. and Meyer, J. W.*: "The Cerebral Collateral Circulation. 2. Production of Cerebral Infarction by Ischemic Anoxia and Its Reversibility in Early Stages". Neurology. *7*:567-579 (Aug.) 1957.

(17) *Fisher, C. M.*: "Observations of the Fundus Oculi in Transient Monocular Blindness". Neurology. *9*:333-347 (May) 1959.

(18) *Mallikan, C. H., Sienkert, R. G. and Shick, R. M.*: "Studies in Cerebrovascular Disease. V. The Use of Anticoagulant Drugs in the Treatment of Intermittent Insufficiency of the Internal Carotid Arterial System". Proc. Staff Meet., Mayo Clin. *30*:578-586 (Nov. 30) 1955.

(19) *de Takats, Geza and Gilbert, N. C.*: "The immediate Treatment of Cerebrovascular Accidents". Am. Pract. & Digest Treat. *2*:287-290 (Jan.) 1948.

(20) *Byrom, F. B.*: "The Pathogenesis of Hypertensive Encephalopathy and Its Relation to the Malignant Phase of Hypertension: Experimental Evidence From Hypertensive Rat". Lancet. *2*:201-211 (July 31) 1954.

(21) *Denny-Brown, D., Horenstein, S. and Fang, H. C. H.*: "Cerebral Infarction Produced by Venous Distention". J. Neuropath. & Exper. Neurol. *15*:146-180 (Apr.) 1956.

(22) *DeBakey, M. E., Crawford, E. S. and Fields, W. S.*: "Surgical Treatment of Lesions Producing Arterial Insufficiency of the Internal Carotid, Common Carotid, Vertebral, Innominate and Subclavian Arteries". Ann. Int. Med. *51*:436-448 (Sept.) 1959.

(23) *Whisnant, J. P., Siekert, R. G. and Millikan, C. H.*: "Appraisal of the Current Trend Toward Surgical Treatment of Occlusive Cerebrovascular Disease". M. Clin. North America. July, 1960, pp. 875-886.

(24) *Baker, H. L., Jr.*: "A New Approach to Percutaneous Subclavian Angiography". Proc. Staff Meet., Mayo Clin. *35*:169-174 (Mar. 30) 1960.

(25) *Eastcott, H. H. G., Pickering, G. W. and Rob, C. G.*: "Reconstruction of Internal Carotid Artery in Patient With Intermittent Attacks of Hemiplegia". Lancet. *2*:994-996 (Nov. 13) 1954.

(26) *Millikan, C. H., Siekert, R. G. and Whisnant, J. P.*: "Anticoagulant Therapy in Cerebral Vascular Disease — Current Status". J.A.M.A. *166*:587-592 (Feb. 8) 1958.

(27) *Fisher, C. M.*: "The Use of Anticoagulants in Cerebral Thrombosis". Neurology. *8*:311-332 (May) 1958.

(28) *Siekert, R. G., Millikan, C. H. and Whisnant, J. P.*: "Anticoagulant Therapy in Intermittent Cerebrovascular Insufficiency: Follow-up Data". J.A.M.A. (In press.).

(29) *Millikan, C. H. and Moersch, F. P.*: "Factors That Influence Prognosis in Acute Focal Cerebrovascular Lesions". A.M.A. Arch. Neurol. & Psychiat. *70*:558-562 (Nov.) 1953.

(30) *Millikan, C. H., Siekert, R. G. and Whisnant, J. P.*: "The Medical Therapy of Occlusive Cerebrovascular Disease". M. Clin. North America, July, 1960, pp. 861-873.

(31) *Whisnant, J. P., Millikan, C. H. and Siekert, R. G.*: "Cerebral Infarction and Fibrinolytic Agents". Minnesota Med. *43*:594-595 (Sept.) 1960.

(32) *Meyer, J. S., Wegner, Walter, Kane, C. A. and Reinmuth, O. M.*: "Electroencephalographic Evaluation of Treatment in obstructive Disease of the Basilar and Carotid Arteries". Neurology. *7*:765-776 (Nov.) 1957.

(33) *Carter, A. B.*: Immediate Treatment of Cerebral Infarction: Seven Years' Personal Experience". Lancet. *1*:345-351 (Feb. 13) 1960.

(34) *Sussman, B. J. and Fitch, T. S. P.*: "Thrombolysis With Fibrinolysin in Cerebral Arterial Occlusion". J.A.M.A. *167*:1705-1709 (Aug. 2) 1958.

(35) *Moser, K. M.*: "Thrombolysis With Fibrinolysin (Plasmin) — New Therapeutic Approach to Thromboembolism". J.A.M.A. *167*:1695-1704 (Aug. 2) 1958.

(36) *Meyer, J. S. and Denny-Brown, D.*: "The Cerebral Collateral Circulation. 1. Factors Influencing Collateral Blood Flow". Neurology. *7*:447-458 (July) 1958.

(37) *Moyes, P. D., Millikan, C. H., Wakim, K. G., Sayre, G. P. and Whisnant, J. P.*: "Influence of Anticoagulants on Experimental Canine Cerebral Infarcts". Proc. Staff Meet., Mayo Clin. *32*:124-130 (Mar. 20) 1957.

(38) *Vastola, E. F. and Frugh, A.*: "Anticoagulants for Occlusive Cerebrovascular Lesions". Neurology. *9*:143-148 (Mar.) 1959.

(39) *Ushiro, C. S. and Schaller, W. F.*: "Anticoagulation Therapy in Cerebral Thrombosis and Embolism". Neurology. *7*:253-258 (Apr.) 1957.

(40) *Carter, A. B.*: "The Immediate Treatment of Non-embolic Hemiplegic Cerebral Infarction". Quart. J. Med. *28*:125-140 (Jan.) 1959.

(41) *Carter, A. B.*: "The Immediate Treatment of Cerebral Embolism". Quart. J. Med. *26*:335-348 (July) 1957.

(42) *Howard, F. P.*: Personal communication to the authors.

(43) *Ambrus, Julian*: Personal communication to the authors.

(44) *Siekert, R. G., Whisnant, J. P. Baker, H. L. Jr., Bernatz, P. E., Ellis, F. H. Jr., and Millikan, C. H.*: "Symposium on Surgical Treatment of Extracranial Occlusive Cerebrovascular Disease". Proc. Staff Meet., Mayo Clin. *35*:473-499 (Aug. 17) 1960.

The Cerebral Softening

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In 1934 O. Rossi wrote: "As far the nerve centers are concerned, the closure of a cerebral vessel does not represent the only cause, the essential and sufficient cause of the softening".

"This statement, based on the critical analysis of the foremost theories at that time, has been corroborated by further research" (Berlucchi).

If it is true, that the cerebral blood circulation is a part of the general circulation, and that on the regular functioning of the latter, the former also depends; it is also true, that some conditions correspond to the brain, and generally speaking, to the nerve tissue.

It is, in fact, sufficient to thing that alterations, even only transitory in the oxygen supply or in the supply of the elements for the tissular nutrition, may create in the brain, preparatory or present conditions conducive to a malacic process, even very circumscribed.

It is also justified to think that, in turn, the softening, because of a phenomenon of pathological resonance, may produce alterations in contiguous parts.

Many other physiological aspects, besides the pathological, biochemical and even anatomical ones play a role in the determinism of the clinical pictures caused by cerebral softening.

During recent years this subject has become very discussed with many new and interesting contributions being made.

Leaving aside every theoretical debate and confining ourselves to the bibliographical quotations, we want to give a concise and complete view of the whole problem, beginning with a short anatomical description; since we are sure that an exact knowledge of the topography of the blood supply is the first condition necessary to establish an exact diagnosis of localization.

A brief note concerning the physiopathology of the cerebral circulation and the pathological anatomy will follow.

The blood of the encephalon, is supplied by some arterial branches coming from both the internal carotids and the basilar one, tied together at the base of the brain by an anastomotic system the "Willis circle". This arterial hexagon establishes an important intracranial anastomosis between the internal carotids and the basilar one, giving the possibility of a mutual reinforcement in the blood-supply.

In the human body, however, the larger contribution is provided by the internal carotids.

The Basilar Artery, formed by the convergence of the two vertebral arteries at the level of the posterior margin of the protuberance turns upward and continues along the middle line of the basilar pontine furrow.

Reaching its forward limit, the basilar artery bifurcates into the two posterior cerebral arteries. These after a few millimeters from their origin, receive the posterior communicating arteries from the internal carotids.

The Internal carotid arteries, enter into the cranium through the carotid canal, run along the carotic furrow of the body of the sphenoid, and going below the anterior process, describe in this tract a double S-shaped curve included in the vertical plane.

Then they turn backwards and upwards, perforating the dura and afterwards fur-

nishing the ophthalmic arteries and their terminal branches close to the anterior perforated substance, beside the optic chiasm.

In their next to last tract they run along the cavernous sinus. Their terminal branches are: the posterior communicating arteries, the anterior choroid arteries, the middle cerebral and anterior cerebral arteries.

The Posterior cerebral artery, after receiving the posterior communicating, sorrounds the cerebral peduncle as far as the "tubercula quadrigemina", it goes under the "corpus callosum" and arriving over the occipital lobe it penetrates into the calcarine fissure.

It provides branches to the interior part of the cerebral peduncle, to the wall and to the choroid plexus of the third ventricle, to the tubercula quadrigemina, to the posterior and dorsal parts of the optic thalamus, to the geniculate bodies, to the fornix, to the lateral choroid plexus, to the convolution of the hippocampus to the lingual lobule and to the fusiform lobule, to the inferior temporal convolution, to the cuneus, to the lingual gyrus and to the inferior and lateral face of the occipital lobe.

The Posterior Communicating Artery, which joins the internal carotid to the posterior cerebral one, provides along its length small branches for the optic tract, the chiasm, the "tuber cinereum", the hypophysis, the mamillary body, the mesencephalon and the middle part of the optic thalamus.

The Anterior Choroid Artery, is mainly a tributary to the lateral choroid plexus, but sends branches to the posterior portion of the internal capsule and to the internal segment of the lenticular nucleus.

The Middle Cerebral Artery, placed in the lateral fissure of Sylvius, emits in its beginning the important collateral lenticulocaudate and lenticulothalamic arteries of a terminal type which irrigate the lenticular nucleus, the external capsule, the internal capsule, the nucleus caudatus and the thalamus. One of these arteries, which irrigates the anterior part of the internal capsule, has been called by Charcot "The artery of cerebral hemorrhage", because more often than the others it is liable to break.

The middle cerebral artery suplies lateral surface of hemisphere with exception of part supplied by anterior cerebral artery and inferior temporal and occipital gzri which are supplied by posterior cerebral artery. With long branches it irrigates the semioval center.

The Anterior Cerebral Artery, runs forward and medially above optic nerve and before introducing itself into the longitudinal fissure of the brain, emits the anterior communicating artery which anastomoses itself to fellow of the opposite side closing in front the "Willis' circle".

It passes upwards and then backwards above genu and body of corpus callosum to end above splenium. It feeds the corpus callosum itself; the orbital surface of hemisphere; medial surface of hemisphere as far back as parietooccipital fissure; and a strip on superolateral surface, adjoining superomedial border.

With long branches it reaches the semioval center.

The Cerebral Venous Bood flowing back from the cortex of the hemispheres and some of that flowing back from the white substance of the oval center, flows into a venous network located superficially within the pia.

From this network, some veins branch off and converging together gradually, form many tributary trunks of the sinus durae matris. The blood flowing from the central gray nuclei, from the wall of the ventricles and from a large part of the oval center through the internal cerebral veins and through Galeno's great cerebral vein, flows into the "sinus rectus".

The internal jugular vein is the final pathway of the cerebral venous confluence.

The abundant blood vascularization here described, is justified by the high quantity of oxygen which the nerve central system needs for its normal activity.

We calculate that, in order to supply the normal necessities, 100cc./minute of blood circulates in the brain for every 100 gr. of nervous substance. This exceptional blood contribution, which becomes possible because of a rich capillary network, is proportional to the difference of the pressure

between the afferent and the efferent cerebral vessels: the bigger the difference, the higher is the speed of circulation (the average of the carotid-jugular circulation is 3 seconds).

We must remember, by the way, that the encephalon cannot supply functional emergency requests with a sufficient and quick vasodilatation because it is enclosed in a stiff shell. Therefore it cannot expand as other organs and no timely dynamic adaptations of the cerebrospinal fluid seems to be possible.

We obviate these inconveniences by increasing the speed of the circulation.

The cerebral circulation besides is not completely conditioned to that of the other arterial districts.

The cerebral vessels, within certain limits, may change their capacity and the speed of the blood they carry, independently of the pressure of the major circle.

All this in order to maintain, just in case, the blood supply necessary to the brain and to the vital centers which are here located.

These short notes explain why, such vascular alterations, unable to produce substantial modification in other organs, may on the contrary, cause serious damage in the encephalon.

The nervous cells, in fact, because of brief periods of lack of oxygen, may be liable to irreversible alterations and produce considerable symptoms when a yhole nervous center happens to be damaged.

The necrosis, which happens due to an insufficient or complete lack of blood supply is called "The cerebral softening".

Accordingly to the classic way of thinking, the cerebral softening may be caused either by a thrombosis of an arterial branch or by an occluding embolus starting usually from the left heart.

The pathologic anatomy however demonstrates that it is possible to find softenings without thrombosis and rarely, thrombosis without softenings.

As a result of these considerations, many hypotheses, more or less documented, have been made about the non-embolic softening.

So therefore, the cerebral angiospasm has been cited in order to explain certain transitory paresis, or even a definite paralysis, in case of protracted ischemia. On the contrary, but with the same consequences, we spoke of a local circulatory stasis produced by a vasoparalitic atonia of the arterial walls.

We consider this as possible that, the arteriosclerosis, even without causing thromboses, may hinder the exchanges of oxygen between blood and nervous tissue, producing distrophic alterations, which will lead to the softening, as soon as any cause worsens the local situation. It is possible that, every time all these factors, be they alone or together interfere in the pathogenesis of this morbid form; as also Fazio has pointed out in some recent publications.

Classic pathological anatomy describes three evolutive phases of the softening: a first phase, during which the phenomena of anemia, edema and necrosis prevail; a second phase of colliquation and swallowing clearance and finally, as a last phase there is or cyst or a cicatrix. In case of an erythrocytic diapedesis of the capillary walls, with the formation of small red clusters which afterwards converge, occurs, what we speak of as hemorrhagic or red softening.

The clinical pictures of the cerebral softening are numerous, either because of the different etiology, or because of the variety of the injured parts. The most frequent causes of the cerebral softening are the thrombosis, the embole and the vasospasm.

Arterial thrombosis constitutes the most favorable condition for the softening and relatively it is one of the most frequently reported in the alteration of cerebral vessels, even if at present in the long process of revising the chapter of the cerebral apoplexia (Delisi et al.) the old pathogenetic conceptions have evidently been changed. Besides it has been noted that in more than half the cerebral softenings it is impossible to find organic occlusion of the vessels; the process of softening, in these cases, is probably due to some disparities in the circulatory dynamics. The most frequent cause of arterial thrombosis is arteriosclerosis. The cerebral vessels, in fact, take part in the vascular alterations peculiar to arteriosclerosis, which is a very widespread disease

in the most propitious age for cerebral softenings. Sometimes, the arteriosclerotic process does not start directly in the vessels in question, but it may be a development, starting from the carotids. Sometimes the arteriosclerotic process starts from the aneurism of a cerebral vessel.

Other cases are: the thromboangiitis obliterans called also Winiwarter-Beurger's disease, which preferably attacks, after the carotid, the middle cerebral artery (Lipmann); the syphilis, especially in young people; the rheumatic disease in the picture of a more diffused panvasculitis; infectious diseases peculiar to infancy and adolescence (as typhus, scarlet fever, etc.); direct and indirect traumas, hematic dyscrasias such as polycythemia vera and the leukemias. Degenerations of the arterial vessels, with a consequent thrombosis, are not unusual in diabetes which is often accompanied by arteriosclerosis, and in chronic nephritis. Even the congenital cardiopathies in young patients with polycythemia secondary to the chronic cyanosis and affected by sincopal crisis, may be predisposed to cerebral arterial thrombosis (Ford). Excess in the use of tobacco and alcoholic drinks, but mainly, dietetic may foment thrombotic softening.

The artery, where more frequently the thrombosis takes place, is the middle cerebral one (in 75 % of the cases), while the posterior cerebral and the basilar ones are injured in 10 % of cases; the anterior cerebral only in 5 %.

The age bracket during which cerebral thrombosis most often occurs, is from sixty to seventy, unless under special circumstances in which even younger people may be attacked. Men suffer from thrombosis twice or three times more often than women. According to some authors a third of the affected people had previously had other cerebral vasculopatic phenomena. The seasonable incidence should be at its maximun during the cold months and mainly in January. In about the 10 % of the cases the patient feels premonitory symptoms: headache, vertigo and disesthesias. Usually the ictus is less dangerous and imposing than that caused by a cerebral hemorrhage. The starting is often slow and the symptomatology may take place for an hour or, rarely, for some days. In the majority of cases (about 2/3 rds.) consciousness is always so present that, it is usually said, the patient watches the developing of the symptomatology. Mainly, if the syphilis shows itself or if the injury is near the motor cortex, even convulsive manifestations may appear. Vomiting is rare. The arterial pressure generally stays normal, or rarely, dicreases. With a ophthalmoscopic examination, sometimes a papillary edema is found, with retinal hemorrhages, but the more frequent finding is the sclerotic aspect of the retinal vessels.

Recent statistics (Montanari and Romerio) show that in almost half of the thrombotic softenings there is a progressive improvement in the symptomatology, which only in exceptional cases attains a complete "restitutio ad integrum"; in the remaning half the symptomatology is stationary or worsens. Death occurs in from 10 to 12 % of the cases.

Cerebral embolia forms about the 5 % of the principal cerebral vascular syndromes. Statistically it happens to be more frequent in middle age, but not rare in young people affected by rheumatism.

Cerebral embolia is a frequent complication of cardiopathies. The most responsible cardiopathies are the rheumatic endocarditis in an active phase, the bacterial endocarditis, the cardiac infarct and the congenital cardiopathy. The cerebral embolia having a cardiac origin usually attacks the right hemisphere an mainly the part supplied with blood by the middle cerebral artery. In the field of the cerebellar blood-supply the superior cerebellar artery is generally attacked. Other sources of embolia are the atheromatous ulcerations of the carotid and the thrombi which form after the ligature of the carotid itself. Gaseous emboli may be produced by operations on the chest, by traumas at the jugulars or at the epidural vertebral veins, by pneumothorax, by pneumoencephalography, by the perirenal insufflation of the cavity of the jaw and of the Eustachian tubes, by the catheterization of the right side of the heart.

Skeletal fractures and wide contusions of the adipose tissue, surgical operations on the whole, anesthesia, electroshock, rare

poisoning and injections of oily substances for a diagnostic or therapeutic aim, may be the cause of fat emboli. Rarer are the emboli of neoplastic tissue, of parasites and of amniotic liquid. Besides arterial embolia we must remember the venous one, which may be provoked by a quick change in the intravenous pressure and mainly by phlebites mostly of a puerperal origin.

The cerebral embolia in cardiopathies almost always shows itself suddenly. With a certain frequency (32 % of the cases, according to Merritt and Aring) preceding cases of embolia may result from anamnesis, in almost a third of the patients headaches and vomiting may appear, from the beginning. Consciousness is generally maintained, unless there are very wide embolic softenings. In the carriers of the endocarditis we may see signs of multiple peripheral embolism at the same time. The lack of and or irritative symptomatology of focus of course depends on the site of the softening. If the embolus was infected, a manifestation of a progressive intracranial hypertension with signs of irritation indicates the presence of a developing abscess. The gaseous embolism starts often with headache, nausea and vertigo, which may be followed by a reduction of the vision, a collapse, convulsions and coma. In case of gaseous embolism, there may be a free interval followed by hyperpirexia, tachycardia and by more serious signs of cerebral involvement, as rigidity of decerebration. The clinical manifestations for venous, neoplastic and parasitic emboli, manifest themselves tardily and they are often misleading. The neurologic deficiency may be associated with the signs of an increased intracranial pressure.

Cerebral angiospasm, has been, before a clinical observation, a experimental acquisition (Villaret and Cachera, Echlin). The spastic contraction of the arteries may be directly observed during neurosurgical operations (Bassett) and, is is well known how it is a frequent angiographic finding distinguishable from the straitenings and vascular organic occlusions; and for the peculiar aspects which the vessels at the site of the spasm assume, and the certitude, therapeutically and experimentally observable, with the use of procaine. As it is well known, many cerebral-vascular troubles are ascribed to the spasm which, if too prolonged and particularly serious, may lead to a dilatation and stasis of the capillary network with diapedesis of plasma and of figured elements, and to a prolonged arteriolar constraint.

Cerebral angiospastic phenomena very often accompany Raynaud's disease, headache, arterial hypertension, arteriosclerosis and cerebral embolism, some poisonings (the ergotism) and even multiple sclerosis. It has been noted that vasospastic phenomena in the site of an old cerebral cicatrix may cause epileptic attacks (Penfield). The cases of cerebral vasospasm often announce themselves with dizziness, vertigo, headache and confusional states. If the patient does not lose consciousness, as often happens, and if he has previously suffered from other attacks, he experiences a strong state of anxiety. Neurologic symptomatology is determined by the site of the spasm. Independently of the presence of cerebral scar tissue, the cerebral angiospasm may be the determinant cause of convulsive manifestations. The prognostic on the spasm of the cerebral vessels depends on the particular pathological conditions. If it is a question of serious hipertension caused by nephrosclerosis, the mortality rate will be very high. In case of arteriosclerosis at the angiospasm, thrombosis may follow. Even the exact position of the injury plays a role of much importance in the study of cerebral softening. There are many syndromes of localisation which we now are going to review.

Syndrome of the anterior Cerebral Artery

Studied mainly by Foix and Hillemand, Critchley, Ethelberg and Chavany it is relatively rare, less rare than the complete occlusion of the artery is the occlusion of the single branches. We may distinguish a total syndrome and some partial ones.

The total syndrome is determined by the obliteration of the artery at its beginning, and it concerns, therefore, either the cortical territory or the central one. The beginning is often brutal and is accompanied

by coma. When this ends, there is often the loss of motor initiative, troubles of emotivity characterized by laughing and crying without any reason and temporo-spatial confusion.

Counterlaterally we have a hemiplegia involving mainly the lower limb. Light disorders in the superficial and deep sensibilities may accompany the hemiplegia. Sometimes the "grasping reflex" appears. In the case in which the injury involves the dominant hemisphere, we have a motor aphasia, often transitory.

Some authors have observed out of the aphasia, some dysarthric disorders, aphemia and kinetic mutism. Foix has pointed out the frequence of ideo-motrice left apraxia. The psychic troubles and the aphasia are not constant. The occlusion of Heubner's recurrent artery manifests itself with a motor deficiency of the counter-lateral upper limb, a light facial paralysis, a paralysis of the veil and of the tongue and an aphasia, if the injury involves the dominant hemispere.

The occlusion of the internal frontal branches, of the posterior and middle ones, is exceptional. The occlusion of the paracentral artery causes an inferior monoplegia at distal predominance. The bilateral occlusion of the anterior cerebral which, however, is very rare, is to be considered incompatible with life.

Syndrome of the Anterior Choroid Artery

The vessel, as is well known, irrigates a part of the posterior arm of the capsule and the mesencephalon.

The clinical picture is caracterized by:

—a serious spastic hemiplegia at crural predominance,

—total hemianesthesia,

—homonym lateral hemianopsia often total sometimes involving only the superior quadrant.

Syndrome of the middle cerebral artery and its branches

These are without question the most frequent syndromes particularly studied by Foix and Levy.

The etiology of these softenings is not fundamentally different from that of the other syndromes; however, we must emphasize the frequence, in this site, of the embolism, which, not always, is of a cardiac source but which may even be caused at the level of the carotid bifurcation.

In the total sylvian softening, as it is called, we have a complete obliteration of the sylvian artery at its beginning often extended for many centimeters. The territory-site of the softening is that of the middle cerebral artery along all its extension.

The clinical symptomatology is produced by coma with a dangerous hemiplegia and hemianesthesia.

When the examination of the patient is possible, which rarely happens, because of the gravity of the disorders, we may observe an aphasia (in cases involving the dominant hemisphere) and a homonym lateral hemianopsia. In the deep sylvian softening we have a more or less complete occlusion at the beginning of the sylvian artery. Damage in the superficial territory often accompanies the softening of the deep territory.

The clinical picture is characterized by a hemiplegia of a capsular type, eventually accompanied by a motor aphasia.

This hemiplegia, often not very serious, differentiates itself from the hemiplegia caused by superficial softening because of the following data:

A lack of hemianopsia and sensitive disorders, a simultaneous involvement of the limbs and of the face on the side of the paralysis; an absence of the distal character of motor deficiency.

When the deep softening is combined with foci of cortical softening, the hemiplegia becomes so complete that it simulates the picture of the total softening.

When the injury involves the dominant hemisphere we have an aphasia of motor type.

Usually the intelligence is not impaired.

In the superficial sylvian softening of anterior type, the occlusion concerns the sylvian trunk of the beginning of the common trunk of the ascending arteries. If the injury is widespread or lacks an efficient collateral circle we have a softening of the

whole superficial cortical-undercortical territory of the sylvian artery, the hemiplegia predominantes over the upper limb and the face, where also disorders in the sensibilities prevail.

We have no hemianopsia; the aphasia in case of an injury in the dominant hemisphere, is of a mixed type.

If the occlusion occurs after the branching out of the ascending arteries the softening involves the territory of the posterior arteries (parietal artery and posterior temporal one, and the artery of the gyrus angularis) and we have the so-called posterior sylvian softening which causes an homonym lateral hemianopsia.

In case of a damage in the dominant hemisphere we have an aphasia of sensorial type.

There are often some difficulties in understanding orders, in naming objects, in reading, writing and calculating.

Among the localized superficial softenings we must remember these caused by the following arteries:

1) The artery of the prerolandic fissure which causes a facial-lingual-masticatory paralysis,

2) The artery of the interparietal sulcus which accompanies a pseudo-thalamic clinical syndrome,

3) The posterior temporal artery and the artery of the gyrus angularis which, in case of an injury on the left side leads to a hemianopsia, to a sensorial aphasia and ideational apraxia; posterior parietal artery and artery of the gyrus angularis with hemianopsia, sensorial aphasia and in case of am injury in the dominant hemisphere, bilatepanied by aphasia and apraxia.

The bilateral deep sylvian softening causes a clinical picture of a "pseudo bulbar" type in which, to the real pseudo bulbar symptoms, some disorders of the deambulation, of the sphincters and a certain intellectual deficiency coincide.

The bilateral superficial softenings are often asymetric and may determine the so-called "prerolandic" picture, with a facial diplegia of a cortical origin and the "posterior" one with double hemianopsia accompained by aphasia and apraxia.

Syndrome of the Posterior cerebral artery

The total occlusion of the posterior cerebral artery is rare. It causes homonym lateral hemianopsia with preservation, however, of the macular vision; and hemiparesis which may be accompanied by dyskynesias, hemianesthesia and pains.

In case of an involvement of the dominant hemisphere we have sensorial aphasia, alexia and visual agnosia. If the injury on the contrary, involves the counter-lateral hemisphere an anosognosic disorder may appear.

Among the partial syndromes of the posterior cerebral artery we must remember: the occlusion of the cortical branches and of the intracerebral ones. It is very difficult to give a detailed picture of the clinical syndromes caused by occlusion of the cortical branches which produce central visual disorders, disorders of the praxis and gnosis, alterations in the body scheme, difficulty in reading, etc.

The occlusion of the calcarine artery causes homonym lateral hemianopsia with persistence of macular vision; if the lower branch alone is involved, we have a hemianopsia upper quadrant; if, on the contrary, the upper branch is involved, we have a hemianopsia at the lower quadrant.

The hemianopsic trouble is often ignored by patients.

Partial injuries produce some hemiachromotopsias. The bilateral damage of the calcarine artery may cause a bilateral hemianopsia, but more often we have a cortical blindness which may accompany a visual anosognosia.

Among the occlusions of the intracerebral branches, we must remember those which involve the thalamo-geniculate artery, which are the most frequent cause of Dejerine and Roussy's thalamic syndrome and the thalamo-perforated artery, with the following Chiray, Foix and Nicolesco's syndrome.

The contemporaneous involvement of the two thalamo-geniculate and thalamo-perforated arterial trunks causes a cerebellar-thalamic syndrome with homonym lateral hemianopsia, hemiparesis and trophic disorders with thalamic hand.

ELECTROENCEPHALOGRAPHY

The E.E.G. modifications of the cerebral softening may depend on many factors such as:

The modality of the beginning,

The site and the gravity of the injury,

The age of the subject,

The collateral phenomena and the development of the symptoms,

The cerebral softening therefore, furnishes very variable bioelectric pictures.

Not always the E. E. G. tracings are pathological.

They have been noted to be normal in percentages which go from 55 % (Passouant and coll.) to 11 % (Loeb); other authors (Cohn and Coll. Abbott and Bautista, Gastaldi and Masciocchi), on the contrary, have never observed completely normal tracings.

The E. E. G. answer is related, first of all, to the initiation of the softening. In accordance with Strauss and Greenstein, van Buskirk and Zarling, the E. E. G does not furnish, even at its best, sure elements for diagnosis.

However, slow waves may appear, since the beginning in regions distant from the injured one or in the place of focus (Jones and Bagghi). The E. E. G. valuation of the softening, at its acute phase, is almost always hindered by the presence of vasospastic or edematous phenomena, and by alteration of consciousness.

The site of the injury may be E. E. G. graphically identified. The delta activity in the focus is, for some authors a steady index of superficial injury (Cohn and Coll., Jones and Bagghi, Roseman and Coll.). In accordance with others, even the deep foci may project biolectric alterations (Gozzano e Colombati, van Buskirk and Zarling), at a slower rhythm, or diffused in both the hemispheres (Montanari and Romerio).

In accordance with Rivolta and Migliore the frequence of normal reports in cases of deep lesions, should be due to technical difficulties; Rohmer and Coll. suggest the derivations from a long interelectrodic distance or the registration while sleeping.

In the softenings of the anterior cerebral artery the bioelectric alterations project mainly on the frontal regions. In those of the middle cerebral artery the focus of slow waves appear mostly in the temporal projections.

If the alteration is in the territory of the posterior cerebral artery, we normally observe slow and very wide waves from the posterior derivations.

Cicatrical foci located deep in the temporal and occipital lobe may suppress, because of an interruption of the optic radiations, the reaction of arrest to the visual stimuli.

Between the gravity of the clinical symptomatology and E. E. G. abnormality no connection is found (Strauss and Coll., Passouant and Coll., van Buskirk and Zarling). Sometimes, though the entity of the E.E.G. alterations is proportional to the clinical gravity, (Maleci and Montanari) but this may not be assumed as a constant rule.

We must bear in mind *the age* of the subject, as long as in young patients the more efficient circulatory conditions may bring about a better and quicker restoration of bioelectric activity (Strauss and Greenstein, Cohn and Coll., Abbott and Bautista, Gastaldi and Masciocchi, Carreras and Coll.).

Collateral factors to the softening such as arterial spasms, the cerebral edema and the alterations of the conscience may remarkably affect the tracings.

According to Roseman and Coll. the vascular spasm is sufficient to produce delta waves which may regress in a few days. The cerebral edema causes slow waves of a delta type usually diffused and indicating the sufering of a whole hemisphere or of the whole brain (Gozzano and Colombati).

The alterations of consciousness accompany modifications of the cerebral electric activity, (Davis and Davis, Gibbs and Gibbs, Fischgold and Bounes) which consist, in the most serious cases, of a slow activity at high voltage (Hill).

Even in the simple obnubilations, we may observe volleys of delta monomorphic waves, which are bilateral and synchronous in the frontal and center-temporal regions (Rohmer and Coll.).

Many authors assert that: the more recent the softening, the clearer the E. E. G. alterations. We think that it is not possible to fix a constant rule and that we must bear in mind the following points:

1) the E. E. G. registration soon after the softening indicates an activity, which due to the said transitory phenomena, more or less rapidly mitigates itself.

2) In some cases the abnormalities completely disappear. In other cases in which the injuries are larger and more serious, the opposite occurs and the E.E.G. alterations aim to localize themselves in the most injuried territory. The E. E. G., at least, may furnish some useful prognostic elements.

Some authors have observed that a few abnormalities of the E. E. G. at the beginning of a serious clinical picture are often a sign of a favorable development, while conspicously pathologic tracings of patients with a scanty symptomatology, are elements of an unfavorable prognosis (van Buskirk and Zarling, Martelli and Coll., Bossi and Pini, Montanari and Romerio). It is useful, in these cases, to follow up with repeated controls. From what we said it is difficult to establish the E. E. G. picture of the cerebral softening.

Premising that such a picture is very variable in relation with many factors and that, with a different frequence, it may be even normal, we may conclude that its characteristics are the following: lateral asymmetries of the alpha rhythm, voltages usually low and only rarely increased, the presence of slow waves (delta and theta) varying in place and in time but prevailingly having a focus, not transmitted at a distance and to the opopsite hemisphere; the said rhythms in the focus often do not mitigate towards the central-outskirts. The alterations of epileptic type are rare. The bioelectric picture of the cerebral softening is often less serious than what the symptomatology would make one believe and it has a clear tendency to improvement in time.

NEURORADIOLOGIC DIAGNOSIS

The neuroradiologic diagnosis of the cerebral softenings uses the direct radiography of the cranium, the examination by means of gaseous contrast (as the pneumoencephalography, the pneumoventriculography, the pneumocisternography) or an opaque contrast (as the angiography). The direct radiography may point out arteriosclerotic calcifications with the aspect of small spots and rings, not always visible through radiography, they may look like dural or ligamentous calcifications.

It is only the case of indicating the so-called: "thecal signs" of the cerebral atrophias generally speaking, and also the following cerebral softenings. It is a question of sphenoidal alar asymmetry, of asymmetries of the cranial fossae, circumscribed parietal dips to which we may give a certain value only if they are of a certain dimension (Lenzi).

The examination, by means of gaseous contrast (air, oxygen or other gaseous mixtures) in accordance with the numerous techniques which are in use may be done only under the conditions of a stabilized process, not before 10-15 days after the acute episode. If the research is well conducted it is possible to document some variations, be they even modest in their form and volume, of the preformed cavities of the endocranial nervous system.

In the cerebral softenings the variations of the form are tightly bound to those of the volume, which consist of an increase caused by parenchymal atrophy. Reductions of the ventricular and subarachnoid cavities may be found in case of edema which may even give a "pseudo-tumor cerebri" picture.

The examination by gaseous means may reveal the post softening atrophy, even precociously (Toti) and indicate more than the nature, the site, even when because of its limitation it escapes the angiographic ascertainement. The angiography is, without doubt, the most useful investigation in order to find the site of the softening and the conditions of the collateral circulation, but it may cause aggravations of the clinical syndrome or accidents of more importance. For this reason it must be executed with particular caution. When there is an involvement of the arteries of small calibre, when revascularisation of the periphery of the injuried territory and also in other cases, the angiographic picture may seem to be normal.

When a clear perifocal edematous reaction sets in, the softening reveals itself angiographically as an expansive process. The typical report is the lack or non-opacification of an arterial trunk and of its branches ("vide vasculaire").

The observation of interrupted arteries, incompletely or irregularly filled reveals however only a vasal occlusion which may have a completely different nature. A total and sudden stop of the injection usually indicates an embolic or spastic occlusion; otherwise we observe, for a certain tract, a progresive reduction of the tonality of shade, of the opaque means which produce a pale, shaded and often irregular vessel.

The angiographic diagnosis of occlusion is easy if it involves a vessel of a certain calibre and if irregularities of opacifications of the vessel itself coexist. In the partial occlusions the report must result constant and the branches in the valley of the site of the injury must appear to be normal.

We must bear in mind the necessity of excluding with the careful use of procaine, occasional spasms and the possibility of finding ourselves in the presence of anatomic variations. We must remember, at the end, the large utility of the angiography in studying the collateral blood-supply of the parts, site of softening.

SUMMARY

It has been noted that in more than half the cerebral softenings it is impossible to find organic occlusion of the vessels; the process of softening, in these cases, is probably due to some disparities in the circulatory dynamics.

The artery where more frequently the thrombosis takes place is the middle cerebral one (in 75% of the cases), while the posterior cerebral and the basilar ones are injured in 10% of cases; the anterior cerebral only in 5%.

In about 10% of the cases the patient feels premonitory symptoms: headache, vertigo and disesthesias.

Usually the ictus is less dangerous and imposing than than caused by a cerebral hemorrhage.

In the majority of cases (about 2/3 rds.) consciousness is always so present that, it is usually said, the patient watches the developing of the symptomatology.

Vomiting is rare, The arterial pressure generally stays normal or rarely decreases.

Cerebral embolia, forms about the 5% of the principal cerebral vascular syndromes. Statistically it happens to be more frequent in middle age, but not rare in young people affected by rheumatism.

The most responsible cardiopathies are the rheumatic endocarditis in an active phase, the bacterial endocarditis, the cardiac infarct and the congenital cardiopathy.

The cerebral embolia in cardiopathies almost always shows itself suddenly. With a certain frequency (32% of the cases, according to Merritt and Aring) preceding cases of embolia may result from anamnesis. In almost a third of the patients headaches and vomiting may appear from the begining. Consciousness is generally maintained unless there are very wide embolic softenings.

The cases of cerebral vasospasm often announce themselves with dizziness vertigo, headache and confusional states. If the patient does not lose consciousness, as often happens, and if he has previously suffered from other attacks he experiences a strong state of anxiety.

Are described:

Syndrome of the anterior Cerebral Artery.

Syndrome of the anterior Choroid artery.

Syndrome of the middle cerebral artery and its branches.

Syndrome of the Posterior cerebral artery.

The E. E. G. modifications of the cerebral softening may depend on many factors such as:

The modality of the rising.

The site and the gravity of the injury.

The age of the subject.

The collateral phenomena and the development of the symptoms.

The cerebral softening therefore, furnishes very variable bioelectric pictures.

Not always the E. E. G. tracings are pathological.

The neuroradiologic diagnosis of the cerebral softenings uses the direct radiography of the cranium, the examination by means of gaseous contrast (as the pneumoencephalography, the pneumoventricolography, the peneumocisternography) or an opaque contrast (as the angiography).

The examination by means of gaseous contrast (air, oxygen or other gaseous mixtures) in accordance with the numerous techniques which are in use may be done only under the conditions of a stabilized process, not before 10-15 days after the acute episode.

The angiographic diagnosis of occlusion is easy if it involves a vessel of a certain calibre and if irregularities of opacifications of the vessel itself coexist.

RESUMEN

Se puntualizan algunos datos anatómicos y fisiopatológicos de la circulación cerebral. Se ha comprobado que en más de la mitad de los reblandecimientos cerebrales, es imposible encontrar una oclusión de los vasos; el proceso de reblandecimiento en estos casos, es probablemente debido a algunos desequilibrios en la dinámica circulatoria.

La arteria, donde se produce con más frecuencia la trombosis, es la cerebral media (75% de los casos); la cerebral posterior y la basilar están lesionadas en el 10% de los casos; la cerebral anterior sólo en el 5%.

En más o menos el 10% de los casos el paciente experimenta síntomas premonitorios: cefalgias, vértigo y disestesias.

En las dos terceras partes la conciencia está presente; el paciente asiste al desarrollo de la sintomatología.

Los vómitos son raros. La presión arterial generalmente se mantiene normal, o raramente decrece.

La embolia cerebral constituye alrededor del 5% de los síndromes vasculares cerebrales.

Las cardiopatías que con más frecuencia dan embolia, son las endocarditis reumática en una fase de actividad, la endocarditis bacteriana, el infarto del miocardio y la cardiopatía congénita.

En el 32% de los casos existe en los antecedentes datos de otras embolias.

En angioespasmo cerebral fue considerado por los experimentadores, mucho antes de que los clínicos le dieran confirmación.

Los casos de vasoespasmo cerebral se anuncian, con mareos, cefalalgia y estados confusionales. Si el paciente no pierde la conciencia como ocurre a menudo, y si sufrió previamente de otros ataques experimenta un fuerte estado de ansiedad.

Se describen síndromes de:

Arteria cerebral anterior

Arteria coroidea anterior

Arteria cerebral media y sus ramas

Arteria cerebral posterior.

Las modificaciones electroencefalográficas en el reblandecimiento cerebral pueden depender de varios factores tales como: La modalidad del comienzo. El sitio y la gravedad de la lesión. La edad del sujeto. El fenómeno colateral y el desarrollo de los síntomas. En esta forma el reblandecimiento cerebral, suministra cuadros bioeléctricos muy variables.

El diagnóstico neuroradiológico se vale de la radiografía simple de cráneo; del examen con medios de contraste gaseoso u opaco (angiografía).

El examen por contraste gaseoso (aire, oxígeno, u otras mezclas) puede ser hecho solamente cuando el proceso esté estabilizado, no antes de los 10-15 días después del episodio agudo.

El diagnóstico angiográfico de oclusión es fácil si afecta un vaso de un cierto calibre y si coexisten irregularidades en la opacificación del mismo vaso. En las oclusiones parciales el relleno debe resultar constante y las ramas arteriales del foco lesional aparecen normales.

RESUME

On a remarqué quelques informations anatomiques et physiopathologiques de la circulation cérébrale.

On a prouvé que dans plus de la moitié des ramollissements cérébraux c'est impossible de trouver une occlusion des vaisseaux; le procès du ramollissement dans ce cas est probablement dû à quelques manque d'équilibre dans la dinamique circulatoire.

L'artere où se produit avec plus de fréquence la thrombose est la cérébrale moyenne (75% des cas). La cérébrale postérieure et la basilar sont lésionées dans le 10% des cas; la cérébrale anterieure seulement 5%.

Dans plus on moins le 10% des cas les malades sentent les symptômes prémonitoire cephalalgie, vertiges et dysestesies.

Dans le deux tiers la couscience est présente; le malade assiste au développement de la sympthomatologie.

Les vomissements sont rares, la tension arterielle généralement reste normale, rarement elle diminue.

L'embolie cérébrale constitue presque le 5% des syndromes vasculaires cérébrales.

Les cardiopathies que le plus souvent provoquent l'embolie sont les endocardites rhumatiques dans une phase d'activité, les endocardites bacterian, l'infarctus du coeur et les cardiopathies congenitales.

Dans le 32% des cas il existe dans les antécedents des indices d'autres embolies.

L'angiospasme cérébral fut consideré par les investigateurs bien avant que les cliniciens leur donne la confirmation.

Les cas de vasospame cérébral s'annoncent avec des vertiges, maux de tête et un etat de confussion. Si le malade ne perd pas la conscience comme il arrive souvent et s'il a eu avant d'autre attaques il experimente un fort etat d'anxiété.

On décrit syndromes de:

Artère cérébrale anterieure.

Artère cérébrale moyenne et ses branches.

Artère choroidien anterieure.

Artère cérébrale posterieure.

Les modifications electroencephalographiques dans le ramollisement cérébral peuvent dépendre de plusieurs facteurs tels comme: la forme du commencement. L'endroit et la gravité de la lésion. L'âge du patient. Le phénomène colateral et le dévellopement des symptòmes.

De cette façon le ramollimement cérébral présente des cadres byoélectriques très variables.

Le diagnostic neuroradiologique se sert de la radiographie simple du crâne, de l'examen avec moyen de contraste gazeux ou opaques (angiografia).

L'examen par contraste gazeux (air, oxigène au autres mélanges) peut être fait seulement quand le procès est stabilisé, pas avant de 10 à 15 jours après l'épisode aigu.

Le diagnostique angiographique d'occlusion est facile, s'il obstrue un vaisseau d'un certain calibre et si coexiste des irregularités dans l'opacité du même vaisseau.

ZUSAMMENFASSUNG

Es werden einige anatomische und physiopathologische Eigenschaften der Gehirnzirkulation beschrieben.

Man hat festgestellt, dass bei mahr als der Haelfte der Faelle von Ictus es unmoeglich ist einen Gefaessverschluss zu finden: der Ictus ist in diesen Faellen wahrscheinlich zureuckzufuehren auf eine Gleichgewichtsstoerung der Gefaessdynamik.

Die Arterie, die am haeufigsten Thrombose zeigt, ist die a. Cerebralis media (75% der Faelle); die a. cerebralis anterior und die a. basilaris sind nur in 10% del Faelle beteiligt und die a. cerebralis anterior nur in 5%.

In ungefaehr 10% der Faelle versouert der Patient Fruehsymptome wie z. B. Kopfschmerzen, Schwindel und Dysaesthesien.

Bei zwei Drittel der Faelle ist das Bewusstsein erhalten; der Patient beobachtet die Entwicklung der Symptomatolgie.

Erbrechen ist selten. Der Blutdruck ist im allgemeinen normal, selten nimmt er ab.

Bei ungefaehr 5% der Gefaessyndrome des Gehirns liegen Gehirnembolien vor.

Die Herzkrankheiten, die am meisten Embolien verursachen, sind die rheumatische Endokarditis in Aktivitaetsphase, die bakterielle Endokarditis, der Herzinfarkt und die angeborenen Herzfehler.

Bei 32% der Faelle existieren in der Anamnese Zeichen von frueheren Embolien.

Das Bestehen von Gefaesspasmen wurde von den Experimentatoren viel frueher vermutet als es von den Klinikern bestaetigt gefunden wurde.

Bei den Faellen von Gefaesspasmen existieren Schwindel, Kopfschmerzen und Verwirrthetszustaende. Wenn der Patient nicht das Bewusstsein verliert, was oft der Fall ist und wenn er schon frueher an aehnlichen Anfaellen litt, so zeigt er einen starken Angstzustand.

Es werden folgende Syndrome beschrieben:

A. cerebralis anterior.

A. coroidea anterior.

A. cerebralis media und ihre Aeste.

A. cerebralis posterior.

Die elektroenzephalographischen Veraenderungen beim Ictus haegen von verschiedenen Faktoren ab: von der Art des Beginns, vom Sitz der Laesion und deren Schwere, vom Alter des Patienten, vom Kollateralkreislauf und der Entwicklung der Symptome. Diese Form von Ictus gibt sehr verschiedene bioelektrische Veraenderungen.

Die neuroradiologische Diagnose stuetzt sich auf das Roentgenbild des Schaedels mit und ohne Kontrastmittel (Angiographie).

Die Untersuchung mittels gashaltiger Substanzen (Luft, Sauerstoff oder andere Mischungen) kann nur gemacht werden wenn der Prozess stabilisiert ist und nie frueher als 10-15 Tage nach der akuten Phase.

Die angiographische D i a g n o s e des Verschlusses ist leicht, wenn ein Gefaess von einem gewissen Kaliber beteiligt ist oder wenn Unregelmaessigkeiten in der Opzifizierung des Gefaesses bestehen. Bei partiellen Verschluessen muss die Fuellung konstant sein und Gefaessaeste der Laesion erscheinen normal.

BIBLIOGRAPHY

Abbott J. A., Bautista P. C.: E. E. Gic findings in various types of intracerebral accidents. "E. E. G. Clin. Neurophysiologica", 1, 254, 1948.

Ambrosetto C.: Sulla forma cerebrale della malattia di Winiwarter-Buerger. "Atti 1° Congresso Internazionale Istopatol. Sist. Nerv.", Roma, settembre 1952.

Basset R. C.: Multiple cerebral aneurysms: Report of a case. "J. Neurosurg.", 8, 132, 1951.

Berlucchi C.: Osservazioni cliniche ed anatomo-patologiche sulla emorragia cerebrale. "Riv. Pat. Nerv. e Ment.", 48, 301, 1936.

Bossi R., Pisani C.: Trombosi e spasmi delle carotidi e loro diramazioni. "Giorn. Psich. Neuropat.", 82, 413, 1954.

Buskirk (van) C., Zarling V. R.: E. E. G. prognosis in vascular hemiplegia rehabilitation. "Arch. Neur. Psych.", 65. 372, 1951.

Carreras M., Angeleri F., Urbani M.: L'elettroencefalografia nella diagnosi differenziale delle malattie cerebrovascolari occlusive. "Riv. Neurobiol.", 1. 213, 1955.

Chavany J. A., Messimy R., Pertruiset B., Hagenmuller: Les fonctions du territoire cortical de l'artère cérèbrale antérieure. "Presse Méd.", 63, 512, 1955.

Cohn R., Raines G. N., Mulder D. W., Neumann M. A.: Cerebral vascular lesions. Electroencephalographic and neuropathologic correlation. "Arch. Neurol. Psychiat.", 60, 165, 1948.

Critchley N. D.: Syndrome de l'artère cérèbrale antérieure. "Brain", 53, 12, 1930.

Davis P. A., Davis H.: Electrical activity of the brain. Its relation to physiological states and to states of impaired consciousness. "Res. Pubbl. Ass. Nerv. Ment. Dis.", 19, 50, 1939.

De Lisi L.: Il problema dell'apoplessia cerebrale. "Relaz. allo XI Congr. Soc. It. Neurol.", Napoli, 1952.

Echlin F. A.: Vasoplasm and focal cerebral ischemia: an experimental study. "Arch. Neurol. Psychiat.", 47, 77, 1942.

Ethelberg S.: Des modifications dans la circulation de l'artère cérèbrale antérieure. Une étude clinico-angiographique. "Acta Psychiat. Neurol. Scand.", 75, 211, 1951.

Fazio C.: Red softening of the brain. "J. Neuropath. Exp. Neur.", 8. 43. 1949.

Fazio C.: Il problema dell'apoplessia cerebrale. "Relaz. all'XI Congr. Soc. It. Neurol.", Napoli 1952.

Fischgold H., Bounes G.: Exploration élec-

troencéphalographique des états comateux. "Sem. Hop.", 22, 1245, 1946.
Foix C. H., Hillemand P.: La syndrome de l'artère cérèbrale antérieure. "Encéphale", 20, 209, 1925.
Ford F. R.: Diseases of the Nervous System in Infancy, Childhood and Adolescence. Charles C. Thomas, Publisher Springfield, III., 1937.
Gastaldi G., Masciocchi A.: Osservazioni elettroencefalografiche nelle encefalopatie vascolari a focolaio. "Sist. Nerv.", 4, 461, 1952.
Gibbs F. A., Gibbs E. L.: Atlas of E. E. G. - Cumming, Cambridge, Mass., 1941.
Gozzano M., Colombati S.: Elettroencefalografia clinica, Rosemberg e Sellier, Torino, 1951.
Hill D.: cit. da Loeb.
Jones E. V., Bagghi B. K.: E. E. G. in verified thrombosis of major cerebral arteries. "E. E. G. Clin. Neurophys.", 3, 374, 1951.
Kernohan J. W., Woltman H. W., Barnes A. R.: Involvement of the nervous system associated with endocarditis. "Arch. Neurol. Psychiat.", 42, 789, 1942.
Lenzi M.: Semeiotica e diagnostica Röntgen. Vol. III, A. Wassermann & C., Milano, 1956.
Lippmann H. I.: Cerebrovascular thrombosis in patients with Buerger's disease. "Circulation", 5, 680, 1952.
Loeb C.: Apoplessia cerebrale e attività elettrica corticale. "Sist. Nerv.", 4, 408, 1952.
Lunedei, Maleci O., Montanari M.: L'elettroencefalogramma nelle lesioni vascolari acute a focolaio dell'encefalo. "Sist. Nerv.", 4, 472, 1952.
Martelli F., Canali C., Pisani C.: Considerazioni su alcuni casi di apoplessia cerebrale seguiti con l'arteriografia carotidea, coll' elettro-e pneumoencefalografia. "Sist. Nerv.", 4, 479, 1952.
Merrit H. H., Aring C. D.: Differential diagnosis of cerebral vascular lesions. "A Res. Nerv. Ment. Dis.", 18, 682, 1938.
Montanari M., Romeiro C.: Contributo clinico-statistico allo studio delle sindromi vasali intracraniche. "Rass. Neuropsich.", 9, 346, 1955.
Montanari M., Romerio C.: Considerazioni su alcuni aspetti elettroencefalografici nelle sindromi vasali acute intracraniche. "Rass. Studi Psich.", 44, fasc. 6, 1955.
Penfield W.: The circulation of the epileptic brain. "A. Res. Nerv. Ment. Dis.", 18, 605, 1938.
Rohmer F., Gastaut Y., Dell M. B.: L'E E.G. dans la pathologie vasculaire du cerveau. "Rev. Neurol.", 87, 93, 1952.
Roseman E., Schmidt R. P., Foltz E. L.: Seriel electroencephalography in vascular lesions of the brain. "Neurol.", 2, 311, 1952.
Rossi O.: Aspetti moderni di problemi antichi. "Riv. Pat. Nerv. Ment.", 43, 946, 1934.
Strauss H., Greenstein L.: The electroencephalogram in cerebrovascular disease. "Arch. Neurol. Psych.", 59, 395, 1943.
Villaret M., Cachera R.: Les embolies cerebrales. Masson & C., Paris, 1939.

Central Nervous System Involvement by Viruses

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Research in virology is rapidly increasing the number of known viruses and is adding to the knowledge of the relationship of viruses to human disease.(1) An increasing number of both "old" and "new" viruses are being implicated in central nervous system diseases. Some viruses, which were formerly thought to infect organs other than the nervous system, are now believed to involve either directly or indirectly the central nervous system. For example, a number of cases of encephalitis** have been reported following Asian influenza.(2, 3) The viruses of the Coxsackie and Echo groups, previously identified more in relation to non-central nervous system diseases, have now been found to be the etiologic agents in some cases of meningoencephalitis.(4) Since the development of a reliable laboratory diagnostic method for mumps virus, it has been possible to establish the diagnostic of mumps meningitis or meningoencephalitis in cases in which the usual glandular manifestations were not present.(5) Several recently discovered viruses in the arthropod-borne group have serologic properties similar to viruses know to be neurotropic and further investigations may show they are related to human encephalitis.(6)

There is, as yet, no completely satisfactory classification of the viral encephalomyelitides, although attempts have been made to classify them according to epidemiology, etiology, clinical patterns, pathologic characteristics, or combinations of categories. Peters and Struck,(7) reporting recently on a group of 13 cases in which the specific etiology was unknown, classified their cases into two main groups based on the clinical picture and the neuropathologic findings. Brewis,(8) whose group consisted of 28 cases with known and 65 cases with unknown etiologies, classified his cases according to four main patterns of illness. The classification used in this present paper is centered around etiology and possible pathogenic mechanisms. On the basis of what is known today, the classification outlined in Table I. may aid in extending knowledge and serve as a clue for further investigative approaches.

Viral encephalomyelitides are here considered "primary" when the virus attacks initially the neuron and/or glial cells of the central nervous system. Viral encephalomyelitides are classified as "secondary" if the virus first invades and produces lesions in organs other than the central nervous system and the encephalitis which follows is an end result or incidental event of the viral illness. Often the pathogenic process in secondary encephalitis is not clear but, in some instances, it may be an immunologic mechanism.(9, 10) The pathologic picture varies.(7, 11) One type of anatomic

** Although "encephalomyelitis" describes more correctly the widespread distribution of the lesions in all levels of the neuraxis, "encephalitis" is used interchangeably for brevity.

TABLE I

TYPES OF VIRAL ENCEPHALOMYELITIDES

A. PRIMARY

1. Enteric
   a. Poliomyelitis
   b. Coxsackie
   c. ECHO
2. Arthropod-borne *
   a. Eastern equine
   b. Western equine
   c. St. Louis
   d. Japanese B
   e. Russian tick-borne
   f. Murray Valley (Australian X)
   g. Louping-ill
   h. West Nile
3. Rabies
4. Von Economo's (Included here only because of its historical importance. Virus etiology, while suspected, has never been proved)

B. SECONDARY

1. Postexanthematous
   a. Rubeola
   b. Rubella
   c. Varicella
   d. Variola
2. Postvaccinal
   a. Pertussis
   b. Rabies
   c. Variola
3. Postinfectious
4. Herpes simplex
5. Herpes zoster
6. Salivary gland (Cytomegalic inclusion disease)
7. Dengue *
8. Yellow fever *
9. Psittacosis
10. Mumps
11. Influenza
12. Inclusion (Dawson's) (Possible viral origin)

* *The viruses of dengue and yellow fever are arthropod-borne but produce encephalitis through secondary rather than primary pathogenic mechanisms.*

sian tick-borne, West Nile, St. Louis (Missouri, U.S.A.), Eastern equine (Eastern part of U.S.A. and Canada), Western equine (Western part of U.S.A. and Canada).

By definition, the viruses included in the arthropod-borne group all have insect vectors - usually mosquitoes, ticks, or mites. Some require an intermediate host. The hosts for Eastern equine encephalomyelitis (EEE), Western equine encephalomyelitis (WEE), and St. Louis encephalitis (SLE) are birds, domestic fowl, and some mammals.(18) The blood-sucking arthropod becomes infected by feeding on the host and, in turn, transmits the virus to humans or other animals. Being dependent on a vector, the seasonal occurrence of disease (usually summer-fall) and the geographic distribution (rural more than urban areas) correspond other location and life cycle of the vector.(19) Although most of these viruses cause central nervous system illness in persons of all ages, some of them, such as EEE and WEE, have a predilection for and result in more severe illness in the very young. Several instances of transplacental transmission of the WEE virus have been reported(20) in which the infant became severely ill while the mother showed no clinical signs of the infection. SLE rarely occurs in patients less than one year of age.

In the arthropod-borne viral encephalitides, the clinical illnes in adults is characterized by fever, eadache, stiff neck, and tremors. Convulsions are rare except in the more severely ill. Adults are likely to be ill only a few days to a week and usually recover without permanent residuals. These

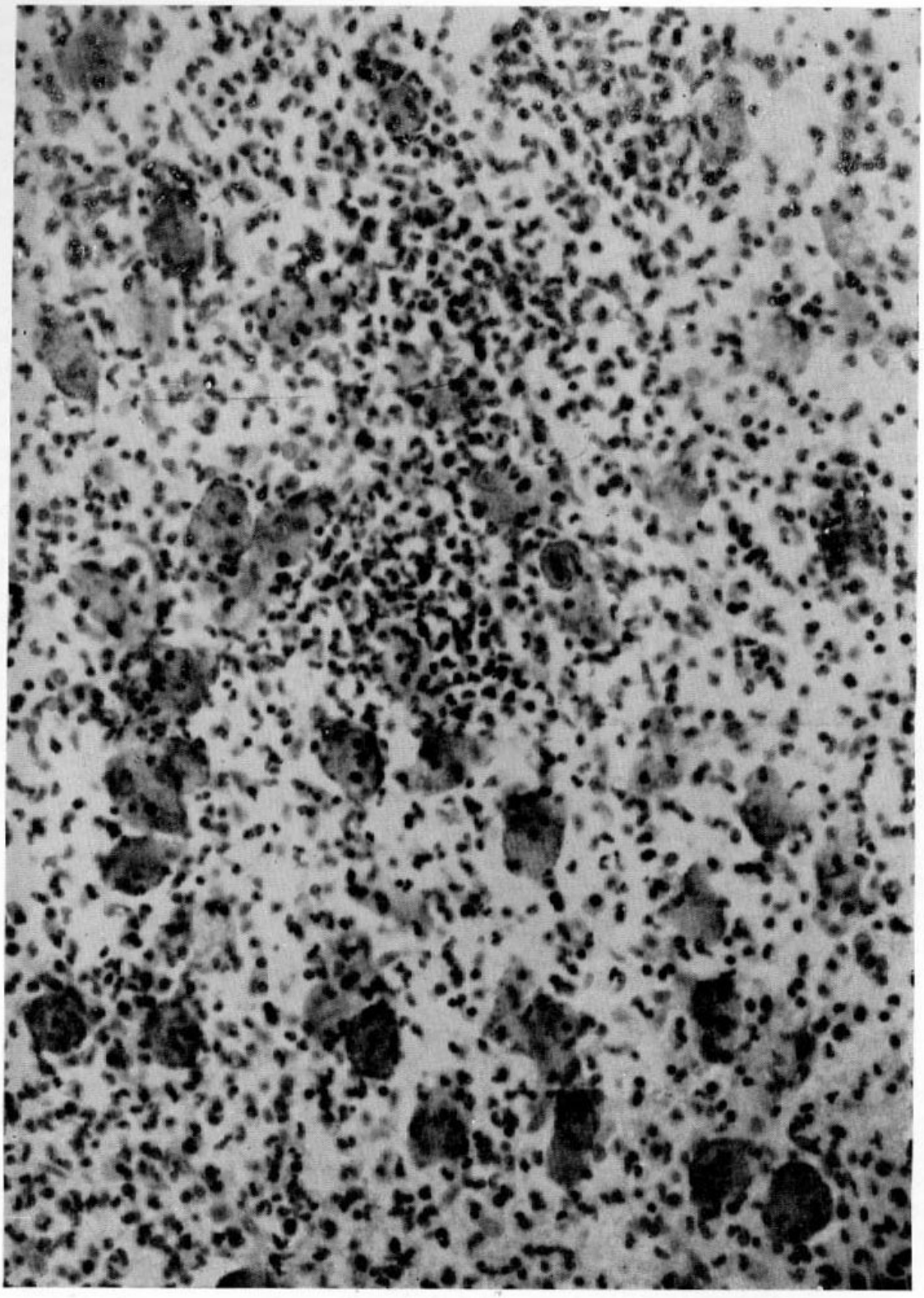

Figure 1. — *Neuronaphagia of nerve cells in the thalamus from a case of Western equine encephalitis. Nissl stain - X40.*

viruses cause more severe illness in infants, particularly very young infants. The symptoms and signs are fever, irritability, drowsiness, and lethargy. Paralysis is of the upper motor neuron type and may be severe. Convulsions are particularly common in very young infants — one study reported that 90 per cent of all patients who became ill before the age of one year had convulsions.(21) The duration of illness in in-

fants and young children is usually one to two weeks, or longer in the more severely ill. Severe and permanent motor and intellectual sequelae are frequent when the illnes occurs in early infancy.(21)

Similarity in symptomatology and neurological findings and variability from patient in the intensity of the illnes makes it difficult to differentiate not only the arthropod-borne viral encephalitides from one another but also from encephalitides due to other viruses. Complement fixation, neutralization, and hemagglutination inhibition serologic tests are used to establish etiology. Efforts to isolate the virus are seldom rewarding, although in rare instances the virus has been demonstrated in the blood and spiral fluid. In fatal cases, the virus may be isolated from the brain.(22)

Spinal fluid findings are not specifically diagnostic but help to establish a clinical diagnosis of encephalitis. White cell counts range up to 500, occasionally higher. Polymorphonuclear cells predominate early in the illness but after a few days lymphocytes predominate. Protein is usually normal in the acute stage of the illness and becomes moderately elevated later.

The neuropathology in the various types of neurotropic arthropod-borne encephalitides is basically the same. The primary histologic lesion is neuronaphagia of the nerve cells (occasionally glia) by microglia (gitter cells) and macrophages (Figure 1.). All levels of the central nervous system are involved but lesions occur primarily in the basal ganglia, brain stem, and cerebellum. Scattered lesions may be found throughout the cerebral cortex and spinal cord. The secondary finding is lymphocytic perivascular cuffing in the later acute or subacute stage. This is followed by gliosis and/or necrosis with cystic formation.

Rabies

Rabies is an acute and almost invariably fatal infection of the central nervous system caused by the specific virus of rabies. The virus is transmitted to humans through the bite of an infected wild or domestic animal, including the bat. Animals, without manifest signs of illness, may excrete the rabies virus in their saliva for prolonged periods of time.(23) The diagnosis of rabies is based on a history of exposure, although it can only be confirmed on necropsy through the observation of diagnostically significant Negri bodies, which are viral inclusion bodies in the cytoplasm of nerve cells. The ultimate proof that the agent isolated in test animals is the rabies virus is through neutralization tests in mice. The clinical picture has been well described by Johnson.(24) There is no known treatment once rabies becomes manifest. Prophylactic measures only are effective. These consist of local treatment of the wound, vaccine and/or hyperimmune antirabies serum. Reference should be made to statements outlining the indications for postexposure treatment of persons exposed to rabies which have been published by the World Health Organization and by national and local public health officials.(25, 26) Severe neurologic complications may follow rabies vaccination (variously reported as from 1:1,200 to 1:18,000 persons vaccinated) and therefore, vaccine should be used only when there is good evidence of exposure to rabies.

SECONDARY VIRAL ENCEPHALOMYELITIDES

Postexanthematous, Postvaccinal, Postinfectious

The encephalomyelitides in this interesting and important group have a common denominator in the anatomical change which occurs. This change is demyelinization about blood vessels (mostly veins) in all levels of the neuraxis. As a secondary histopathologic change, phagocytosis of the injured myelin in the parenchyma about the blood vessels by microglia (gitter cells) occurs, followed by lymphocytic cuffing in the perivascular spaces within or in the neighborhood of the demyelinization.(10, 12) (Figure 2.) Viruses known to produce this type of encephalomyelitis are the exanthemas (measles, variola, and varicella.(9) The phenomenon also occurs occasionally following smallpox vaccination and rabies vaccination.(27) This encephalitic anatomic entity is also known to oc-

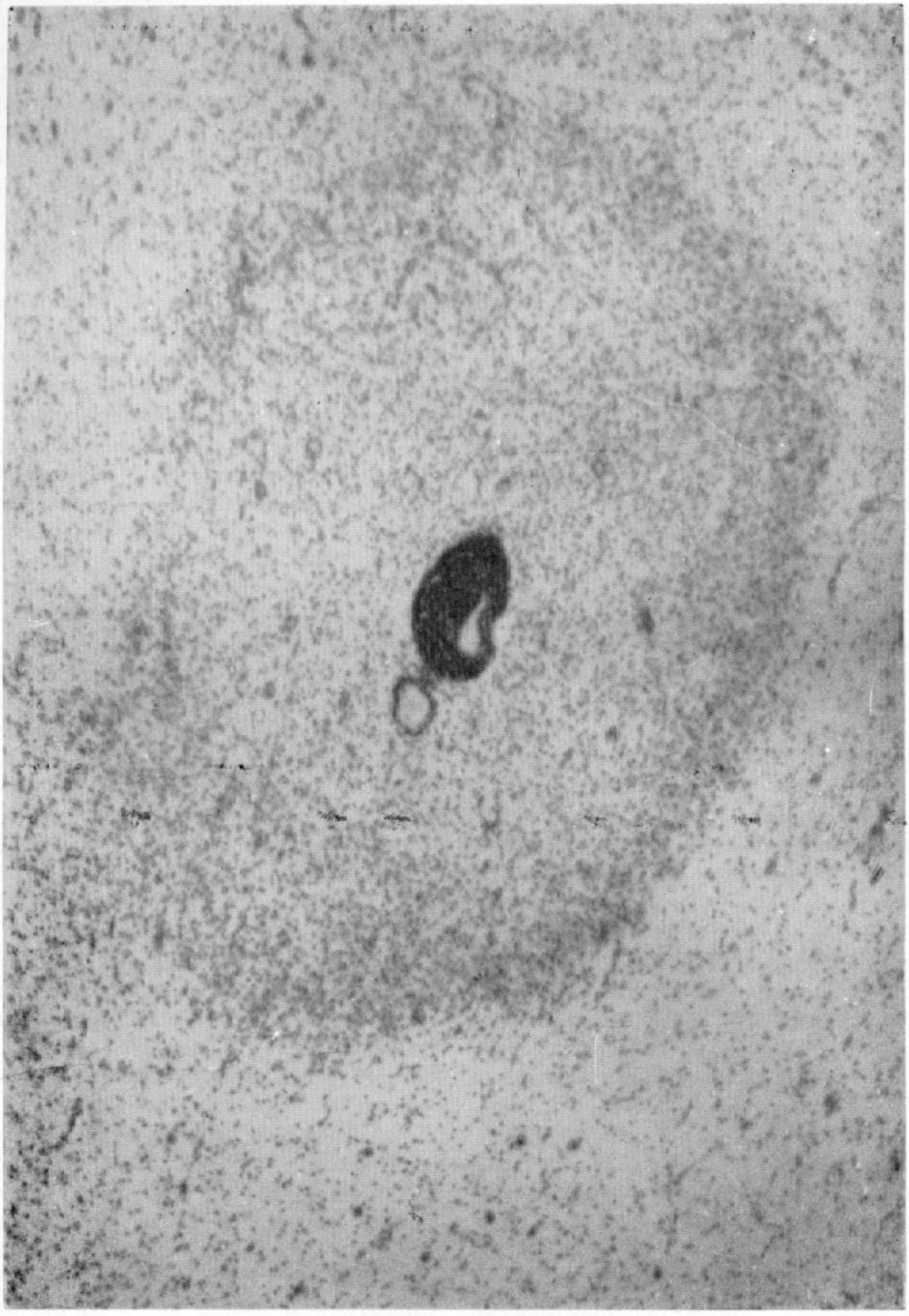

Figure 2. — *Perivenous microglial (gitter cell) reaction to injured myelin in the deep white matter of the cerebral hemisphere. Note the increased activity of microglia at the border of demyelinization. The perivascular Case of postinfectious encephalitis. Nissl stain - X40.*

cur without a known exanthematous viral infection or vaccination, usually clinically diagnosed as a postinfectious type because it not infrequently follows an upper respiratory infection.(7) It is possible that some cases of postinfectious encephalitis are a complication of the exanthematous viruses without a clinically recognizable skin eruption.

Perivascular demyelinating encephalomyelitides occur at all ages, although they are most common in childhood because of the prevalence of exanthematous viral infections in this age group.

There are no specific neurologic clinical characteristics or laboratory procedures to establish the diagnosis. The presumptive diagnosis depends on the time relationship between the exanthematous skin eruption or vaccination and the onset of the encephalomyelitic symptoms or signs. The time interval between the skin eruption or height of the vaccination wound and the onset of central nervous system symptoms and signs is usually between two and eight days.

The clinical neurologic feature are similar to those of the primary viral encephalitides except the acute illness is usually longer. The acute illness is more severe in infants and young children than in adults. In encephalitis following veccination, recovery more often is complete, while infants and children who recover from postexanthematous encephalitis may have sequelae such as spastic paralysis, tremors, athetosis, and mental disturbances.

Miscellaneous Secondary Viral Encephalomyelitides

Included in this group are encephalitides or meningoencephalitides associated with the viruses of herpes simplex, herpes zoster, salivary gland, dengue, yellow fever, psittacosis, mumps, and influenza and one other, inclusion (Dawson's) encephalitis, which is possibly of viral origin. Except for mumps and herpes simplex, encephalitides caused by these etiologic agents are rare. These encephalitides have differing pathogenic, pathologic, and epidemiologic patterns and also the diseases often differ clinically from patient to patient within the same diagnostic category.

The herpes simplex virus is one of the commonest infectious agents of man. It may account for from 5 to 7 per cent of the meningoencephalitides.(28) It is most frequently associated with encephalitides in premature infants but may be the etiologic agent in encephalitis in persons of all ages. The central nervous system infection may range from a meningitis to an acute encephalitis with coma, convulsions, ocular palsies, paresis, and sensory changes. The mechanism of spread to the nervous system is not clear. A definitive diagnosis can be made only by laboratory means.

Encephalitis is an uncommon complication of herpes zoster,(29) but when it occurs, it follows the signs of nerve root involvement within a few weeks. The clinical picture and pathology are similar to that seen in postinfectious encephalitis.(30)

Salivary gland virus is one of the recently identified viruses, althoug the clinical picture of the illness was described many years ago.(31) The disease is often fatal in very young infants. It is less severe in older children and is rarely seen in adults. Central nervous system disease is one of several forms of illness the virus produces.

Dengue and yellow fever viruses are arthropod-borne but are not included in the "arthropod-borne encephalitides" because encephalitis occurs secondarily to the systemic illness. In dengue, if neurologic complications occur, all levels of the neuraxis, including the peripheral nerves, may be involved. In encephalitis complicating yellow fever, signs of cranial nerve involvement may be prominent.

In psittacosis, there are almost always some neurologic symptoms ranging in severity from insomnia, restlessness, disorientation to mental depression, irrationality and delirium. Death may occur or the patient may recover without permanent residuals. Characteristic lesions are petechial hemorrhages, softening associated with neuronaphagia, and microglial rosettes. Pathology occurs primarily in the cerebral (including claustrum) and cerebellar cortices.(32)

The intracranial complications of mumps are usually meningeal. If the meningitis is

accompanied by encephalitic signs, which are usually mild, the clinical picture cannot be distinguished from many other types of viral encephalitides which are associated with mild meningeal irritation. Lenette et al(33) has recently reportted 11 cases of mumps virus infection simulating paralytic poliomyelitis. Although it has long been recognized that mumps meningoencephalitis can occur without parotid swelling, recent technics for laboratory detection of the virus have made it possible to confirm the diagnosis. Furthermore, mumps meningitis or meningoencephalitis is now being diagnosed by laboratory methods in cases which otherwise would not be etiologically diagnosed.

The concurrent epidemics of influenza and Von Economo's encephalitis during the late teens and early twenties of this century led some investigators to believe that the influenza virus was the etiology for Von Economo's encephalitis but this was never established.(34) Recently, there has been laboratory evidence that meningitis or encephalitis may be asssociated with influenza.(2, 3) Further study is needed to clarify this relationship.

Inclusion encephalitis is the name applied to a group of encephalitides which have in common a characteristic anatomic finding of intranuclear inclusions in neurons and oligodendroglia. These inclusions are distributed in both the ganglion cells and glial elements throughout all levels of the central nervous system.(35) Inclusions have been found in encephalitis associated with herpes simplex, herpes zoster, and salivary gland viruses and with encephalitides of undetermined etiology.

The subacute inclusion encephalitis described by Dawson,(36) for which no etiology has been determined, has an insidious onset. Mental deterioration is progressive. Motor signs and convulsions may appear at any time during the chronic course of the illness.(37)

DIFFERENTIAL DIAGNOSIS

Although improved technical methods in virology during recent years have added immeasurably to the possibility of diagnosing encephalitides etiologically, present knowledge, technics, and laboratory facilities still limit the number of cases in which the etiologic agent can be established.

There are, however, many time-honored methods upon which clinicians can rely. Awareness of epidemiologic factors such as geographic and seasonal distribution of specific infections, presence or absence of vectors, age and sex most likely to be affected are important leads to possible diagnoses. Has the patient traveled beyond his usual surroundings? Does is occupation place him in contact with vectors of infection? Has he been exposed to other ill persons? Does he give a history of rash, recent illnes, exposure to noxious substances, or has he been vaccinated recently?

The clinician relies most heavily on the patient's symptoms and signs and on laboratory aids for diagnosis. Convulsions are frequently an early indication of central nervous system involvement, particularly in infants, and suggest encephalitis. Prominent meningeal signs in the early phase of illness favor a diagnosis of primary bacterial meningitis, while milder meningeal symptoms favor a diagnosis of a meningitis secondary to an encephalitis. Involvement of the lower motor neurons point to poliomyelitis and generally rule out other encephalitides such as the arthropod-borne, which characteristically show signs of involvement of higher levels of the neuraxis. Since toxic or chemical agents usually produce peripheral nerve radicular signs in addition to signs of central nervous system involvement, the peripheral distribution of sensory and motor disturbances will help in making a diagnosis.

The spinal fluid examination is useful but will not establish the viral etiology. Low sugar content, for example, tends to exclude a viral etiology and favors tuberculous or parasitic meningitis. The cell count helps to differentiate between an acute primary meningitis of bacterial origin and a viral encephalitis. Protein of over 75 mg. % is uncommon in viral encephalitis.

More and more laboratories are offering viral diagnostic services and it is recommended that physicians familiarize them-

selves with viral laboratories in their vicinities. Specific instructions for securing, preserving, and transporting blood, feces, tissue and other specimens should be secured from the laboratory. Because of the large number of viruses, it is imposible for any laboratory to tests for all of the routinely. The physician should accompany each laboratory specimen with clinical data in sufficient detail to aid the laboratory in determining which tests to perform.

TREATMENT

Only a few salient points regarding treatment will be covered in this paper. For a fuller discussion, reference may be made to an appropriate text.(38) Specific treatment is available for only two of the viral encephalitides - hyperimmune serum and vaccine for the prophylactic treatment of rabies and antibiotics for psittacosis.

At the present time, there is no evidence that the antibiotics or sulfonamides benefit the course of the other known viral encephalitides. Their use is discouraged because of the possibility of toxic and immunologic complications from the drugs themselves. Antibiotics and sulfonamides are recommended only in instances of secondary infection in which these drugs are specific.

Treatment is symptomatic and much depends on good nursing care. Hospitalization should be considered to appropriately handle critical symptoms and signs. Convulsions, headache, and chills may be treated by appropriate methods for controlling these disturbing symptoms. Fluid losses and electrolyte imbalance may result from diarrhea, vomiting, fever, and perspiration and fluids must be replaced and the electrolyte balance restored. To maintain adequate nutrition, parenteral fluids or tube feeding may be necessary. Skin care is important, Every effort should be made to keep the patient as comfortable as possible and to avoid debilitating complications.

SEQUELAE

Much has been written about the sequelae of Von Economo's encephalitis, particularly Parkinsonism which appeared either immediately or sometimes after many years. This type of encephalitis, which was of suspected viral etiology, is seldom, if ever, seen today. The literature dealing with the viral encephalitides which are now occurring rarely report Parkinsonism as a sequela.

During the past seven years the author has been associated with a follow-up study of Western equine encephalitis and St. Louis encephalitis in California. The following data are taken from reports of this study.(21, 39, 40, 41) Permanent sequelae occurred in less than 5 per cent of 306 adults who were examined. Several older patients had mild Parkinsonism associated with cerebrovascular disease; in three patients, the possibility was equivocal that WEE and not other pathology was responsible for the Parkinson-like symptoms.

In this study, permanent and often severe sequelae occurred in almost half the patients who had WEE during the early months of life. (Figure 3.) (SLE rarely occurs in infants.) Sequelae occurred less often and were less severe in children who were beyond infancy when they became ill.

Convulsions recurred in about 25 per cent of the patients who had convulsions during their acute illness but convulsions had not occurred following recovery unless convulsions had occurred during the acute illness. This observation is important to the clinician in making his prognosis for continuing convulsions. Most of the patients who had recurrent convulsions had had WEE and had been less than one year of age when they became ill.

There has been no evidence in the California study that the encephalitic disease process continued after the acute phase subsided. Several children who were ill in infancy had what might be interpreted as a chronic progression of the encephalitis but it is believed that what appeared to be progression actually was a result of damage to maturational potentialities of the immature brain at the time of the acute attack. Clinically, some of these children seemed to have recovered but later showed evidence of brain damage.

Karl L. illustrates this phenomenon. In July, 1950, at the age of 13 months, he

Figure 3. — *Rudy, a premature infant, developed fever, lethargy, twitchings, and convulsions at the age of 26 days. Diagnosis of WEE confirmed by complement fixation tests. At the age of 6½ years (above) he was microcephalic, had severe spasticity, intellectual impairment, and recurrent convulsions.*

became severely ill with fever, vomiting, lethargy, stiff back, and convulsions. On the ninth day he still had a peculiar vacant stare, was disinterested in his surroundings, and had intermittent mild internal strabismus. The virus laboratory reported a complement fixation titer rise from less than 1:8 to 1:2048 for WEE. He left the hospital in good condition 15 days after the onset of his illness. The pediatrician who had cared for Karl during his acute illness saw him again two years later and commented that the boy had made an excellent recovery. Karl's complaint that his "leg fell asleep" and his slowness in acquiring speech were then discounted as sequelae of his encephalitis. At the age of five years, when Karl was first seen in the encephalitis study, there was turning-in of the left foot, indicative of pyramidal tract damage. Two years later, Karl was failing in the first grade in school because of poor memory and short attention span. He had had two convulsions. An EEG was borderline. When last seen at the age of 11, Karl was in an ungraded class in school, doing first and second grade work. Mild left hemiparesis was evident on neurologic examination. Convulsions had not recurred and he was not on anticonvulsant medication. His social behavior was good.

In these children who were in infancy and whose impairment of intellect and behavior did not become apparent until several years later, the logical inference pathologically is that the maturational potentialities (the organization) of the brain were curtailed by damage to the higher, nonfunctioning levels of the cerebral hemispheres at the time of the encephalitis. This damage could not become clinically apparent until the child reached the age when these levels of the cerebral hemispheres normally begin to influence behavior. How often this occurs in other types of viral encephalitis and in clinically unrecognized encephalitis in infancy is a worthy subject of future observation.

SUMMARY

In this paper, a classification of viral encephalomyelitis based on etiology and pathogenic mechanisms is given as a contemporary baseline for extending knowledge and as a clue for further investigative approaches. The clinical manifestations of the diseases caused by viruses which produce central nervous system involvement either by primary or secondary pathogenic processes are discussed. Brief sections on differential diagnosis, treatment, and sequelae are included.

Two particularly interesting findings of a seven-year follow-up study of WEE and SLE are reported: (1) Convulsions as a sequela of these two types of viral encephalitis have not occurred unless convulsions occurred during the acute illness. (2) Several children in the study, who had WEE in infancy and clinically recovered, developed intellectual and behavioral deficiencies several years later. This is interpreted not as evidence of progression of the primary disease process; rather it is due to damage to the maturation potentialities of the nonfunctioning portions of the brain at the time of the encephalitis in infancy. This interference with cerebral maturation may not become apparent until months or years later when the intellectual and behavioral functions normally become apparent.

RESUMEN

En este trabajo, con el fin de difundir los conocimientos y dar una guía para ulteriores investigaciones, se exponen conceptos básicos modernos con una clasificación de las encefalomielitis virósicas, basadas en la etiología y en mecanismos patogénicos. Se discuten las manifestaciones clínicas de las enfermedades causadas por virus que producen compromisos del sistema nervioso central por procesos patogénicos pri-

marios o secundarios. Se incluyen breves secciones sobre diagnóstico diferencial, tratamiento y secuelas.

Se refieren dos hallazgos particularmente interesantes de estudios prolongados por siete años de la WEE y de SLE: 1) Las convulsiones no se producen como secuela de estos dos tipos de encefalitis, a menos que ocurran convulsiones en la fase aguda. 2) Varios niños que tuvieron WEE en la infancia y se recobraron clínicamente desarrollaron deficiencia intelectual y de la conducta varios años más tarde. Esto no es interpretado como una evidencia de progresión del proceso primario; más bien es debido al daño de los potencialidades de maduración de sectores no funcionantes del cerebro en la época en que ocurrió la encefalitis en la infancia. Esta interferencia con la maduración cerebral puede no ser aparente hasta meses o años más tarde cuando las funciones intelectuales y de la conducta se hacen normalmente aparentes.

RESUME

Dans ce travail afin de propager les connaissances et de donner un guide pour de futures investigations on expose des concepts basiques modernes avec une classification des encephalomyelites virals basée dans l'etiologie et le mécanisme pathogénique. On descute les manifestations cliniques des malades causées par le virus que produisent des compromis du système nerveux central par des procédés patogéniqués primaires ou secondaires. On inclus de brèves sections sur des dianostiques différentiels, traitements et conséquences.

On décrit deux decouverts particulierèments interessantes d'études prolongées pour sept ans de la WEE et de SLE: 1) Les convulsions ne se produisent pas comme conséquences des ces deux types d'éncéphalitis à moins qu'il arrive des convulsions dans le phase aigue. 2) Plusieurs enfants que ont en WEE dans l'enfance et qui se sont remis cliniquement, dévellopèrent des defauts intelectuels et du comportement plusieurs années plus tard. Cela n'est pas interpreté comme une évidence de progression du procès morbide primaire, pluôt il est dû au dommage des potentialilées de la maturation des portions du cervau qui ne fonctionnent pas dans l'epoque où est apparue l'encephalite dans l'enfance.

Cette intromission en la maturation cérébrale peut ne pas être apparente jusqu a des mois ou des années plus tarde quand les fonctions intelectuelles et de la conduite se font normalement apparent.

ZUSAMMENFASSUNG

Um die Kenntniss der Virusencephalitis zu verbreiten und weitere Untersuchungen anzuregen, werden die modernen Grundlagen dieser Krankheiten und ihre Klassifizierung beschrieben, ausgehend von der Aetiologie und der Pathogenese. Die klinischen Symptome der durch Virus verursachten Krankheiten werden diskutiert, welche das Zentralnervensystem angreifen durch primaere oder sekundaere Prozesse. Es werden kurze Abschnitte ueber Differentialdiagnose, Behandlung und Folgeerscheinungen eingeschoben. Zwei besonders interessante Befunde, basiert auf Untersuchungen ueber die WEE und die SLE waehrend 7 Jahren werden beschrieben: 1. Die Konvulsionen sind nicht Folgeerscheinungen dieser beiden Formen von Enzephalitis, es sei denn, dass sie waehrend der akuten Phase auftreten. 2. Mehrere Kinder, welche an WEE litten und klinisch geheilt wurden, zeigten mehrere Jahre spaeter Stoerungen der intellektuellen Entwicklung und des Betragens. Dies wird nicht als Fortschreiten des primaeren Krankheitsgeschehens interpretiert; es ist vielmehr zurueckzufuehren auf die Schaedigung der Reifungsmoeglich-

keit des nicht funktionierenden Sektors des Gehirns waehrend der Zeit, in der die Enzephalitis aufgetreten war. Diese Stoerung der Reifung des Gehirns kann latent bleiben waehrend mehrerer Monate oder Jahre und sich erst dann manifestieren, wenn die intellektuellen Funktionen und das Betragen apparent werden.

REFERENCES

(1) *Rhodes, A. J.*: "Recent Advances in Virus Infections: The New Era in Virology". Brit. M. J. 5179:1071 (April 9) 1960.

(2) *Olivarius, B. de F., and Fog, M.*: Neuroinfections in Asian Influenza". Danish Med. Bull. 6:248 (Nov.) 1959.

(3) *Bennett, A. E., and Turk, R. E.*: "Acute Encephalitis and Death Following Asian Influenza". California Med. 87:411 (Dec.) 1957.

(4) *Lennette, E. H.; Magoffin, R. L.; Schmidt, N. J., and Hollister, A. C., Jr.*: "Viral Disease of the Central Nervous System — Influence of Poliomyelitis Vaccination on Etiology". J.A.M.A. 171:1456 (Nov.) 1959.

(5) *Kravis, L. P.*: "Mumps Meningoencephalitis with Special Reference to Use of Complement Fixation Test in Diagnosis". Pediatrics 8:204, 1951.

(6) *Rivers, T. M., and Horsfall, F. L., Jr. (editors)*: "Viral and Rickettsial infections of Man, ed. 3". Philadelphia, J. B. Lippincott Company, 1959.

(7) *Peters, G. und Struck, G.*: "Zur Klinik und Pathomorphologie Sporadisch Auftretender Spontaner Encephalitiden". Psychiatria Et Neurologia Japonica 61:343 1959.

(8) *Brewis, E. G.*: "Recent Experience of Encephalitis in Childhood". Brit. M. J. June 5, 1954, p. 1298.

(9) *Finley, K. H.*: "Pathogenesis of Encephalitis Occurring with Vaccination, Variola, and Measles". Arch. Neurol. & Psychiat. 39:1047, 1938.

(10) *Roizin, L., and Kolb, L. C.*: "Neuropathologic Relationship of Multiple Sclerosis to the Experimental Allergic Encephalomyelitides. Comparative Histologic and Some Histochemical Studies". Psychiatria Et Neurologia Japonica 61:483, 1959.

(11) *Jacob, H.*: "Sporadische, atypische "primäre" Encephalitiden, Encephalitis Japonica B und Parainfektiöse Encephalitiden". Psychiatria Et Neurologia Japonica 61:311, 1959.

(12) *Finley, K. H.*: "Perivenous Changes in Acute Encephalitis Associated with Vaccination, Variola, and Measles". Arch. Neurol. & Psychiat. 37:505 (March) 1937.

(13) *Hammon, W. McD., and Reeves, W. C.*: "Recent Advances in the Epidemiology of the Arthropod-borne Virus Encephalitides Including Certain Exotic Types". Am. J. Pub. Health 35:994, 1945.

(14) *Dalldorf, G.*: "The Enteric Viruses'.' Kaiser Foundation Medical Bulletin 7:36 (January-March) 1959.

(15) *Finley, K. H.*: "Viral Encephalomyelitis, in M. Clin. of North America". W. B. Saunders Company, Philadelphia & London, 43:1465 (September) 1959.

(16) *Francis, T., Jr. (editor)*: "Diagnostic Procedures for Virus and Rickettsial Diseases". New York, Am. Pub. Health Assoc., 1956.

(17) *Robbins, F. C.*: "The Clicinal Laboratory Diagnosis of Viral Infections of the Central Nervous System, in Viral Encephalitis". Springfield, Ill., Charles C. Thomas, Publisher, 1958, p. 46.

(18) *Reeves, W. C.*: "The Knowns and the Unknowns in the Natural History of Encephalitis". Proceedings and Papers of the 21st Annual Conference of the California Mosquito Control Association, February, 1953.

(19) *Longshore, W. A., Jr.; Stevens, I. M.; Hollister, A. C., Jr.; Gittelsohn, A., and Lennette, E. H.*s "Epidemiologic Observations on Acute Infectious Encephalitis in California, with Special Reference to the 1952 Outbreak". Am. J. Hyg. 63:69, 1956.

(20) *Shinefield, H. R., and Townsend, T. E.*: "Transplacental Transmission of Western Equine Encephalomyelitis". J. Pediat. 43:21, 1953.

(21) *Finley, K. H.*: "Postencephalitis Manifestations of Viral Encephalitides, in Viral Encephalitis". Charles C. Thomas, Publisher, Springfield, Illinois, 1958, p. 69.

(22) *Lennette, E. H.; Nyberg, M. C.; Barghausen, D. M.; Chin, R.; Fujimoto, A. B., and Itatani, M. D.*: "The 1952 Outbreak of Encephalitis in California — Laboratory Methods for Etiologic Diagnosis". California Med. 79:78 (August) 1953.

(23) *Pawan, J. L.*: "Rabies in the Vampire Bat of Trinidad, with Special Reference to the Clinical Course and Latency of Infection". Ann. Trop. Med. 30:401, 1936.

(24) *Johnson, H. N.*; Rabies, *In Rivers, T. M. and Horsfall, F. L., Jr. (editors)*: "Viral and Rickettsial Infections of Man". Ed. 3, Philadelphia, 1959, J. B. Lippincott Co., chap. 21.

(25) *Anonymous*: "World Health Organization Expert Committee on Rabies: Third Report. Technical Report Series N° 121". Geneva, 1957.

(26) *Anonymous*: "Rabies — Suggested Indications for Treatment of Persons After

Exposure to Infection". California Med. 93: 148 (Sept.) 1960.

(27) *Uchimura, I., and Shiraki, H.*: "A Contribution to the Classification and the Pathogenesis of Demyelinating Encephalomyelitis; with Special Reference to the Central Nervous System Lesions Caused by Preventive Inoculation Against Rabies". J. Neuropath. & Exper. Neurol. 16:203 (April) 1957.

(28) *Afzelius-Alm, L.*: "Aseptic Encephalomeningitides in Gothenburg, 1932-1948. Clinical and Experimental Investigation with Special Reference to the Viruses of Herpes, Influenza, Mumps and Lymphocytic Choriomeningitis". Acta Med. Scandinav. (Supp. 263) 140:1, 1951.

(29) *McCormick, G. W.*: "Encephalitis Associated with Herpes Zoster,". J. Pediat. 30:473, 1947.

(30) *Dekaban, A.*: "Neurology of Infancy". Baltimore, Williams and Wilkins, 1959.

(31) *Warren, J.*: "Infections of Minor Importance". *In Rivers, T. M. and Horsfall, F. L., Jr. (editors)*: "Viral and Rickettsial Infections of Man". Ed. 3, Philadelphia, 1959, J. B. Lippincott Col, chap. 46.

(32) *Scholz, W.*: "Nervensystem, p. 1297 in Handbuch der Speziellen Pathologischen Anatomie und Histologie". Vol. XIII, part 2, Springer. Berlin, 1958.

(33) *Lennette, E. H.; Caplan, G. E., and Magoffin, R. L.*: "Mumps Virus Infection Simulating Paralytic Poliomyelitis. A Report of 11 Cases". Pediatrics 25:788 (May) 1960.

(34) *Neal, J. B.*: "Encephalitis; A Clinical Study". Grune & Stratton, New York, 1942.

(35) *Haymaker, W.; Smith, M. G.; Van Bogaert, L., and De Chenar, C.*: "Pathology of Viral Disease in Man Characterized by Intranuclear Inclusions, in Viral Encephalitis". Charles C. Thomas, Publisher, Springfield, Illinois, 1958.

(36) *Dawson, J. R., Jr.*: "Cellular Inclusions in Cerebral Lesions of Epidemic Encephalitis". Arch. Neurol. & Psychiat. 31: 685, 1934.

(37) *Malamud, N.; Haymaker, W., and Pinkerton, H.*: "Inclusion Encephalitis with Clinicopathologic Report of 3 Cases". Am. J. Path. 26:133, 1950.

(38) *Finley, K. H.*: "Treatment of the Encephalomyelitides", in *Forster, F. M. (editor)*: "Modern Therapy in Neurology". C. V. Mosby Co., St. Louis, 1957, Chap. 1.

(39) *Finley, K. H.; Longshore, W. A., Jr.; Palmer, R. J.; Cook, R. E., and Riggs, N.*: "Western Equine and St. Louis Encephalitis — Preliminary Report of a Clinical Follow-up Study in California". Neurology 5:223 (April) 1955.

(40) *Palmer, R. J., and Finley, K. H.*: "Sequelae of Encephalitis: Report of a Study After the California Epidemic". California Med. 84:98 (Feb.) 1956.

(41) *Riggs, N., and Finley, K. H.*: "Sequelae of Western Encephalitis and St. Louis Encephalitis". California Vector Views 7:35 (June) 1960.

Les Formes Encéphalitiques de la Poliomyèlite

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L'epithète de poliomyèlite antérieure aigue proposée pour qualifier la paralysie infantile est une des plus heureuses du langage médical.

Dans la grande majorité des cas, en effet, rique, et l'anatomiste ne constate qu'une paralysie par atteinte du neurone périphérique, et l'anatomiste ne constate qu'une atteinte élective et primordiale des cellules motrices de la colonne grise antérieure de la moelle et du tronc cérébral.

Réduire à une simple poliomyèlite antérieure aigue la lésion provoquée par les virus poliomyèlitiques serait cependant inexact. Le clinicien qui a eu l'occasion d'examiner un grand nombre de malades, dès la période initiale, est familiarisé avec une riche sémiologie qui implique d'autres localisations virales, sur le système nerveux suprasegmentaire. Nous ne citerons, en exemple, que les troubles de la vigilance si fréquents à la phase initiale de beaucoup de poliomyèlites communes.

De leur côté, les pathologistes ont depuis longtemps insisté sur l'extrême diffusion des lésions inflammatoires et même neuronales bien au-delà des territoires de prédilection.

Ainsi, beaucoup de poliomyèlites, par ailleurs communes, possèdent transitoirement pour le clinicien un aspect encéphalitique. Et, pour le pathologiste la notion d'encephalite poliomyèlitique est un fait acquis.

Ces remarques, pour capitales qu'elles soient en pathologie générale, n'ont en pratique qu'un intérêt limité. Les nuances sont habituellement insuffisantes pour détourner l'attention du clinicien de la sémiologie fondamentale de la paralysie infantile qui va très rapidement s'isoler et se confirmer. Si tout en restait là, l'isolement des formes encéphalitiques de la maladie de Heine-Médin ne serait pas justifié.

Mais depuis longtemps déjà, l'attention des cliniciens a été retenue par des maladies aigues du système nerveux comportant une riche sémiologie cérébrale, justifiant le diagnostic d'encéphalite, donc très différentes de la poliomyèlite commune et qui cependant doivent y être rattachées. L'intégration de formes si anormales à la poliomyèlite a été proposé sur la base d'arguments épidémiologiques (survenue au milieu d'une épidémie, coïncidence avec des cas familiaux); cliniques (association à des paralysies périphériques typiques); évolutifs (disparition des signes encéphalitiques, guérison complète avec comme seules séquelles celles des paralysies classiques).

A vrai dire, cette accumlation d'arguments aboutissait à une conviction et non à une certitude. La réponse précise à la question posée n'a pu être apportée que tout récement avec l'avènement des procédés de diagnostic virologique applicables à la clinique. Indiquons dès maintenant que la réalité des formes encéphalitiques de la poliomyèlite ne peut, à l'heure actuelle, être mise en doute.

Notre expérience personnelle concernant les formes encéphalitiques repose actuellement sur onze observations — recueillies parmi 1.500 cas de poliomyèlite — qui ont été étudiées à l'Hôpital des Enfants-Malades. C'est dire que la fréquence de ces formes est très faible. Aussi, faut-il d'emblée poser la question de l'authenticité de ces formes anormales. Leur réalité ne nous paraît pas discutable, car pour toutes nos observations nous possèdons le contrôle

virologique et sérologique établi suivant une méthode très sûre et très fidèle. (13) (14)

La plus caractéristique est la *forme ataxique de la poliomyèlite* (6 cas).

Elle a été décrite de façon parfaite dès 1898 par Médin, qui n'hésita pas à rattacher à la poliomyèlite cette "ataxie aigue transitoire" de la convalescence. Médin insistait sur le bon pronostic. Il faut méditer cette remarque: "certains cas d'ataxie n'auraient pu être rapportés à la paralysie infantile s'ils avaient été isolés, mais ils étaient observés pêle-mêle avec la poliomyèlite et le doute n'était pas permis". (1)

Ces constatations sont confirmées par de nombreux auteurs. (2) (3) Wickman (4), dans sa célèbre étude sur la poliomyèlite, fait une large place à cette forme. Milbank la signale au cours des épidémies de New-York, en 1916 et 1931 (5) Howe en 1919 (6). Plus récemment, cette *forme rare* de poliomyèlite a été observée au cours de l'épidémie de Stockholm en 1953 par Berglund (3 cas) (8) et Rydenstam. (7).

De la comparaison des cas mentionnés et de nos cas personnels se dégage un tableau d'esemble d'une très grande originalité. L'âge de nos malades est de 2 à 13 ans.

Le début est souvent brusque, marqué presque toujours par un syndrome infectieux qui ne se distingue en rien de celui de la poliomyèlite commune. Cependant, il nous a paru souvent moins intense. La fièvre est alors modérée ne dépassant pas 38c. Les douleurs peuvent manquer à ce stade. *Les signes neurologiques* apparaissent toujours *brusquement* et sont maximun soit d'emblée, soit au bout de 2 ou 3 jours.

C'est presque toujours *le tremblement qui est le signe majeur.* (7) Il existait dans la plupart de nos cas, dominait le tableau dans 3 cas. Il intéresse tout le corps: membres, tronc, tête. Il est à certains moments d'une intensité telle qu'il rend la marche impossible ainsi que la station assise. Il disparaît au repos complet et pendant le sommeil. Il s'exagère à l'examen, avec les émotions et au cours du mouvement. S'il est discret, on met facilement en évidence son caractère intentionnel. La *marche* est souvent impossible, du moins au début. Si elle est réalisable, on observe une ataxie statique et cinétique. Debout, le corps peut être animé d'oscillations antéro-postérieures qui intéressent les membres et le tronc. Les tendons du jambier antérieur saillent â chaque oscillation: c'est la "danse des tendons", signe précieux à cet âge de la vie. A la marche l'enfant titube, oscille: sa marche est ébrieuse et non aggravée par la fermeture des yeux. Souvent il lui est impossible d'avancer seul: alors il oscille et tombe. Il est assez rare que l'on puisse mettre en évidence, du moins au début, une dysmétrie, une hypermétrie. Il en est de même pour l'asynergie. En effet, chez ces enfants qui tremblent de façon si impressionnante, l'examen est rendu difficile. Néanmoins, une de nos observations est intéressante à ce sujet puisqu'il existait d'un seul côte: tremblement, hypermétrie à l'épreuve du doigt sur le nez, du talon sur le genou, exagération de la passivité, signe de Stewart Holmes. La parole est parfois saccadée. Devant une telle sémiologie, on comprend que l'on parle de formes cérebelleuses de poliomyèlite (5) (7) (8). Certaines de nos observations en sont un exemple. Mais très souvent il existe d'autres signes sur lesquels nous voulons maintenant insister et qui donnent à ces formes un relief très spécial.

Le tonus segmentaire est normal ou simplement légèrement diminué. Les réflexes tendineux sont toujours très facilement retrouvés et en règle vifs. Mais surtout, il *s'associe* fréquemment *au tremblement des mouvements anormaux très particuliers au niveau des membres, des globes oculaires et même des paupières.* Il s'agit, au niveau des membres, d'indiscutables *mouvements involontaires.* Sur le tremblement de fond qui est permanent à l'état de veille, se greffent de véritables décharges de mouvements anormaux. Ils apparaissent avec une grande brusquerie et sont provoqués par la moindre excitation. A certains moments, c'est presque un *"mouvement chréique".* La constatation de *mouvements anormaux au niveaux des globes oculaires* donne enfin à cette forme une allure saisissante. Ils sont signalés par Berglund (8) et Rydenstam (7). Ils étaient d'une intensité extrême dans 2

cas. Il s'agit d'un véritable *"tremblement oculaire"* caractérisé par un rythme assez lent, une égalité des secousses, d'amplitude assez grande. Il aparaît uniquement au moment de la fixation du regard sur la ligne médiane. Il s'y associait dans un cas une composante rotatoire.

Les paralysies manquent ou sont discrètes et régresives (racines des membres — paralysie faciale).

A ce syndrome neurologique si riche s'associe un *syndrome infectieux* dont l'intensité est variable. Quant aux *syndromes douloreux et méningé,* ils restent discrets comparativement aux formes communes de poliomyèlites et manquent assez souvent. La ponction lombaire fournit de précieux renseignements orientant le diagnostic par la constatation des anomalies cytochimiques habituelles dans la poliomyèlite antérieure aigüe. Dans tous les cas, nous avons isolé dès le début *dans les selles un virus de poliomyèlite.* Il s'agissait du type I et, une seule fois, du type III. Chaque fois que nous avons pu le vérifier, il existait dès le premier prélèvement des anticorps neutralisants pour le type correspondant.

Le *pronostic* de ces formes est excellent (7) (8). Tous nos enfants ont guéri complètement et sans séquelles, dans un délai qui n'excède pas un mois. Il arrive très exceptionnellement que cette ataxie soit transitoire, marquant alors le début de la maladie qui, ensuite, fait place à des paralysies évidentes. Mais, même dans ces cas, il est curieux de constater qu'il s'agit habituellement de formes bénignes, avec des paralysies peu étendues et nettement régressives.

Il n'est pas aussi singulier qu'on pourrait le croire au premier abord d'observer de tels faits au cours de la poliomyèlite, puisqu'on connait la fréquence des lésions au niveau du cervelet(9) (11). On peut même s'étonner de leur relative rareté. Baker, dans une étude des lésions du cervelet dans 75 cas de poliomyèlite mortelle, trouve dans 77 % des cas au moins des lésions inflammatoires et des altérations neuronales. Les localisations les plus communes se font au niveau du noyau dentelé (57 %), des noyaux du toit (19 %) et dans le cortex du vermis. Ces lésions inflammatoires sont régressives et expliquent probablement la guérison de tous nos enfants. Ce n'est qu' une hypothèse puisqu'il n'existe aucune autopsie de forme ataxique de poliomyèlite. L'analyse clinique de nos cas suggère que le noyau rouge, ainsi que le locus niger, soient englobés par un processus inflammatoire (de telles constatations ont d'ailleurs été classiques au cours de la poliomyèlite). En effet, l'intensité du tremblement et des mouvements anormaux évoque ce que l'on voit dans le syndrome de Benedikt.

La description de Médin reste encore, aujourd'hui si juste que nous devons conserver le terme de *"forme ataxique de poliomyèlite"*, bien qu'il n'évoque qu'une partie des faits observés. L'important est de rappeler au clinicien qu'un syndrome ataxique aigu, installé dans un cortège fébrile éventuellement accompagné de paralysies périphériques coïncidant avec une modification du liquide rachidien, doit faire envisager, en première hypothèse et avec peu de chance d'erreur, la poliomyèlite. C'est avec ce rappel de ses circonstances d'installation et d'accompagnement, que cette forme clinique si spéciale de la maladie de Heine-Médin peut être nettement différenciée, par la simple clinique, des autres ataxies aigües que l'on peut observer chez l'enfant et, en particulier, d'une entité morbide que nous avons proposé d'appeler: *"l'ataxie cérebelleuse aigüe solitaire et curable de l'enfant"*.(10)

Si, dans une certaine mesure, on peut quand on en a l'expérience évoquer d'emblée la poliomyèlite devant un tableau aussi particulier que celui de l'ataxie aigüe de Médin, il n'en est plus de même avec les accidents neurologiques dont nous allons parler.

A vrai dire, ils sont encore rares et nous n'en avons trouvé que de rares mentions.(7) (12) (15) (16). Aussi, aurions-nous hésité à les rattacher à la poliomyèlite si nous n'avions eu la preuve formelle de cette étiologie par les examens virologique et sérologique. Cette sémiologie extraordinaire ne s'observe qu'à la phase initiale de la maladie. Elle domine tellement le tableau que le clinicien ne donne pas toute leur valeur aux autres signes bien plus communs au cours de la poliomyèlite commune:

somnolence, torpeur, paralysies périphériques habituelles, syndrome infectieux, syndrome méningé, modifications du liquide rachidien. A l'heure actuelle, nous avons pu isoler trois ordres de manifestations encéphalitiques dans la poliomyèlite: crises de contracture tonique, clonies, syndrome parkinsonien.

Les crises de contracture tonique ne s'accompagnent pas de perte de conscience. Elles sont parfois entrecoupées d'*accès de tremblement.* Au cours de la crise, la tête est rejetée en arrière et sur le côte, le membre non paralysé est en hyperextension. Les mâchoires sont serrées et simulent un trismus mais il est réductible. Fait très particulier, la volonté parvenait à les contrôler dans une certaine mesure, et surtout un ordre impératif permettait d'obtenir une diminution de la contracture. Ainsi cette enfant arrivait à ouvrir la bouche à cette seule condition, alors qu'elle était incapable de le faire si on lui présentait simplement à manger. On douta même de l'organicité de ces manifestations spectaculaires. Ces accès toniques évoquent ceux que l'on observe au cours de l'intoxication par la Prochlorpémazine. Ils ont complètement disparu en 2 jours.

Parfois, on peut voir des *clonies.* Elles son intermittentes, intéressent les membres, la face et surviennent sans rythme particulier, ne sont pas synchrones et entraînent souvent des clignements des paupières. Elles n'ont pas forcèment une signification fâcheuse, et finissent par disparaître en 4 à 5 jours. On les observe dans les *formes avec coma.* Ce fut le cas d'un de nos enfants qui y resta pendant 3 semaines et finit par guérir au prix d'une séquelle de type périphérique au niveau du membre supérieur gauche. Elles existaient chez un autre enfant dans le coma qui mourut de poliomyèlite respiratoire, après 16 jours de maladie. Ces secousses étaient si intenses à certains moments qu'elles évoquaient un *mouvement choréique* (obs. 8).

Les 4 observations de *syndrome parkinsonien* au cours de la poliomyèlite sont, croyons-nous, les premières où la preuve virologique ait été apportée. Chez notre malade, le tableau était saisissant à plus d'un titre. Il existait en effet une hypertonie plastique avec exagération des réflxes de posture, un phénomène de la roue dentée et une persévération des attitudes. La face était figée, la voix monotone et saccadée. Il y avait une hypersialorrhé ainsi qu'un état d'hyperémotivité particulière. L'enfant pleurait sans raison, ce qui n'etait pas dans son caractère antérieur. Le réflexe naso-palpébral était exagéré et tous les gestes dans les territoires non paralysés étaient exécutés avec une extrême lenteur. Cet état parkinsonien fut amélioré assez rapidement par un traitment par l'artane et finit par disparaître complètement et définitivement en 3 semaines.

Ainsi, il est démontré que la sémiologie peut parfois être dominée, à la période initiale, par des manifestations extra-pyramidales. Ces accidents viennent s'ajouter au tableau habituel de la maladie. Autant qu'on puisse le dire sur un nombre aussi restreint de malades, ils ne témoignent pas obligatoirement d'une forme particulièrement sévère. Le sort des malades a été réglé par l'étendue et la localisation des paralysies. La mort, dans une observation, est la conséquence d'une faillite respiratoire. Tout au contraire, les accidents encéphalitiques initiaux disparaissent en quelques jours ou quelques semaines, sans laisser de séquelles qui leur soient propres. L'existence dans une poliomyèlite paralytique de manifestations extra-pyramidales transitoires ne peut être mise en doute.

Mais notre expérience personelle nous permet de franchir une étape de plus et d'affirmer que le syndrome parkinsonien peut persister à titre de *séquelle.* Nous pouvons ainsi répondre affirmativement à la question posée en 1939 par le Prof. Alajouanine(17): "Un syndrome parkinsonien peut-il reconnaître la maladie de Heine-Médin comme étiologie?"

Nous avons assisté à l'apparition chez trois enfants d'une famille d'une maladie provoquant, chez l'un, un simple état fébrile et, chez les deux autres, des signes remarquablement semblables se reproduisant avec une telle similitude que l'on pouvait prévoir l'évolution de l'un en examinant l'autre: fièvre, signes méningés, accès de somnolence, algies, crises de contracture tonique avec spasme d'ouverture

de la bouche, clonies et grands mouvements choréiformes, installation d'un syndrome parkinsonien très complet, mutisme akinétique, paralysies discrètes, localisées, d'un membre inférieur. Le syndrome parkinsonien devait, chez d'un des enfants, disparaître en quelques semaines; il persiste, au contraire, chez l'autre et, un an après le début de la maladie, sans tendance régressive, il est tellement intense qu'il rend difficile l'appréciation exacte du déficit musculaire d'origine périphérique qui est certainement discret.

Des recherches très complètes de laboratoire, pratiquées dans d'excellentes conditions, ont permis de découvrir le virus en cause (type II) et d'assister par des épreuves en série à la montée significative des anticorps correspondants, à des taux d'ailleurs exceptionnellement élevés.

Ces résultats du laboratoire — d'après une étude personnelle concernant plus de 750 observations(18) — nous autorisent à affirmer la réalité d'une infection poliomyèlitique chez deux malades, présentant un syndrome parkinsonien: transitoire et curable chez l'un, durable et non amélioré chez l'autre. Sans une telle coïncidence et sans de telles possibilités d'étude, il est très probable que le diagnostic envisagé avec le plus de faveur eut été celui d'une maladie aujourd'hui disparue: l'encéphalite de Von Economo.

RESUME

Dans un certain nombre de paralysis infantiles communes, on peut observer des symptômes qui ne trouvent leur explication que par l'atteinte virale des formations suprasegmentaires de l'encéphale. Les contrôles anatomiques ont montré la fréquence des altérations débordant largement la zone des neurones moteurs périphériques, vers une série de centres en rapport avec les fonctions musculaires: calotte pédonculaire, locus niger, étage sous-optique et cortex moteur.

Dans ces cas exceptionnels, les localisations du virus sur ces formations cérébrales créent une sémiologie neurologique tellement inhabituelle que le diagnostic de poliomyèlite risque d'être méconnu. Les formes encéphalitiques de la poliomyèlite avaient été admises pour diverses raisons, surtout épidémiologiques. La réalité peut en être aujourd'hui affirmée par les recherches virologiques et sérologiques en cours de maladie.

L'auteur, à propos de 12 observations d'encéphalite poliomyèlitique (confirmées par le laboratoire) passe en revue les principaux aspects:

1) Forme ataxique, décrite par Médin en 1898, comportant: tremblement, signes cérebelleux, agitation choréique et, notamment, des mouvements oculaires d'un type très particulier.
2) Crises de contracture tonique avec spasmes de la bouche.
3) Clonies et *secousses,* mouvements choréiques.
4) Syndrome parkinsonien.

Dans onze cas, sur douze, ces signes encéphalitiques ont disparu après quelques jours ou quelques semaines, sans séquelles. Dans la forme ataxique, la discrétion des paralysies associées est trè remarquable.

A ces syndromes encéphalitiques transitoires, régressifs et curables, s'oppose une observation qui apporte les preuves de l'étiologie poliomyèlitique d'un syndrome parkinsonien permanent.

SUMMARY

In a certain number of common types of Infatile Paralysis, symptoms are observed with the only explainable cause of a virus attack of the suprasegmentary formations of encephalo. Anatomical studies have shown the frequency of alterations that amply lap over the peripheral motor neuron zone toward several centers related to muscle functions: tectum of the midbrain, susbstantia Nigra, subthalamus and motor cortex. In these exceptional cases the localization of virus on cerebral formations produces a

neurological semiology in such an unusual way that the diagnosis of poliomyelitis runs the risk of not being recognized. The encephalitic forms of polio have been admitted for several reasons, specially during epidemics. At present reality can be confirmed by virus investigations during the illness. The author reviews the principal aspects of polio encephalitis with 12 observations (confirmed by laboratory studies).

1. Ataxique form, described by Medin in 1898, which consists of tremor, cerebellar signs, choreic agitation, and notably ocular movements of a very peculiar type.
2. Crises of tonic contraction with mouth spasms.
3. Clonic jerks, choreic movements.
4. Parkinsonian syndrome.

In eleven out of twelve cases these encephalitic signs disappeared after some days or weeks without, sequelae.

It is very remarkable the slight paralysis in the ataxic form.

The author presents the proof of a case of the polioetiology of a permanent Parkinsonia syndrome, to show the possibility of exceptions to the usual, transitory and curable encephalitic syndrome.

RESUMEN

En un cierto número de parálisis infantiles comunes, se pueden observar síntomas que no encuentran su explicación más que por el ataque viral de las formaciones suprasegmentarias del encéfalo. Los controles anatómicos mostraron la frecuencia de las alteraciones que desbordan ampliamente la zona de las neuronas motoras periféricas, hacia una serie de centros en relación con las funciones musculares: casquete peduncular, locus niger, piso subóptico y corteza motora.

En estos casos excepcionales, las localizaciones del virus sobre estas formaciones cerebrales crean una semiología neurológica tan poco habitual que el diagnóstico de poliomielitis riesga de no ser reconocido. Las formas encefalíticas de la poliomielitis habían sido admitidas por diversas razones, sobretodo epidemiológicas.

La realidad puede ser hoy afirmada por las investigaciones virológicas y serológicas en el curso de la enfermedad.

El autor a propósito de 12 observaciones de encefalitis poliomelítica confirmadas por el laboratorio pasa en revista los principales aspectos:

1) Forma atáxica, descrita por Medin en 1898, que comporta: temblor, signos cerebelosos, agitación coreica y, principalmente, movimientos oculares de un tipo muy particular.
2) Crisis de contractura tónica con espasmos de la boca.
3) Clonias y sacudidas, movimientos coreicos.
4) Sindrome Parkinsoniano.

En once casos, sobre doce, estos signos encefálicos han desaparecido después de algunos días o algunas semanas sin secuela. En la forma atáxica es muy notable lo leve de las parálisis asociadas.

A estos síndromes encefálicos transitorios, regresivos y curables, se opone una observación que aporta las pruebas de la etiología poliomielítica de un síndrome parkinsoniano permanente.

ZUSAMMENFASSUNG

Bei einer gewissen Anzahl von Faellen von gewoehnlicher Kinderlaehmung kan man Symptome beoachten, die sich nur durch die Laesion der suprasegmentaeren Abschnitte des Gehirn durch das Virus erklaeren lassen. Die antamomischen Kontrolluntersuchungen haben gezeigt, wie haeufig die krankhaften Veraenderungen die Zone der peripheren motororischen Neuronen weit ueberschreiten und sich in Richtung auf eine Reihe von Zentren, die mit der Muskelfunktionen zu tun haben, ausbreiten: dem Tegmentum pedunculi cerebri dem locus niger, der zona suboptica und der motorischen Hirnrinde.

Ausnahmsweise verursacht die Lokalisation des Virus in diesen Gerirnzentren eine so ungewoehnliche neurologische Symptoma-

tologie, dass die Gefahr besteht, die Diagnose einer Poliomyelitis zu verkennen.

Man hat das Vorhandensein enzephalitischer Former der Poliomyelitis aus verschiedenen Gruenden angenommen, vor allem epidemiologischer Art. Diese Tatsache kann heute durch die virologischen und serologischen Untersuchungen im Verlauf der Krankheit bestaetigt werden. Der Autor beschreibt an Hand von 12 eigenen Faellen von poliomyelitischer Enzephalitis (die durch das Laboratorium vestaetigt worden sind) ihre hauptsaechlichen Aspekte:

1. Die von Medin im Jahre 1898 beschriebene ataxische Form, bei der man Zittern, zerebellaere Symptome, choreiforme Bewegungen und bezeichnenderweise Augengewegungen ganz eigentuemlicher Art beobachtet.
2. Krisen von tonischen Kontrakturen und Spasms des Mundes.
3. Klonische Bewegungen und Klonische Kraempfe; choreiforme Bewegungen.
4. Das parkinsonsche Syndrom.

In 11 von den 12 Faellen verschwanden diese enzephalischen Symptome nach einigen Tagen oder wenigen Wochen, ohne Spuren zu hinterlassen. Bei der ataxischen Form ist die Mildheit der beigeodneten Paralysen sehr bemerkenswert.

Diesen voruebergenenden, regressiven und heilbaren enzephalitischen Syndromen steht ein Fall eines permananten parkinsonschen Syndromes gegenueber, bei dem der Nachweis der poliomyelitischen Aetiologie durch die Laboratoriumsuntersuchungen erbracht ist.

BIBLIOGRAPHIE

(1) *Medin, O.*: "L'état aigu de la paralysie infantile". Arch. Med. Enf. 1898, 5:257-279 et 6:321-343.

(2) *Zappert, J.*: "Kliniche Studien über Poliomyelitis". Jahrb. Kinderkh., 1901, 53: 125.

(3) *Linder E., Mally A.*: "Zur Poliomyelitis Epidemie in Oberrösterreich". D. Zeitsch Nervenh., 1918, 38:343.

(4) *Wickman, I.*: "Studien über Poliomyelitis acuta". S. Krager verl., Berlin, 1905; Acuta Poliomyelitis; Heine-Medin's disease. Nerv. a Mental Dis. monographs, 1913:16: 402.

(5) *Noel, G.*: "A propos des formes cérebelleuses de la poliomyèlite aigue". Bul. Soc. Clin. Hôp. Civil de Charleroi, 1955, VI, 3:158-167.

(6) *Howe, H. S.*: "The pathological changes in the cerebellum in the acute ant. polio". Neurol. Bul., 1919 - II:261.

(7) *Rydenstam, B.*: "Some atypical cases of polioencephalitis". Acta Med. Scandinav., 1956, 154 suppl. 316:50-55.

(8) *Berglund G., Mossberg H. O. et Rydenstam, B.*: "Acute cerebellar ataxia in children". Acta Paediat., 1955, 44:254-262.

(9) *Baker A. B., Cornwell S.*: "Poliomyelitis cerebellum". Arch. of Neur. a Psychiatr., 1954, 71:455-465.

(10) *Thieffry S., Mme. Martin Ch. et Arthuis M.*: "L'ataxie cérebelleuse aigüe solitaire et curable de l'enfant". Rev. Neur., 1958, 98, 6:669-673.

(11) *Angela G. C., Galli Della Loggia D.*: "Lesioni cerebellari in corso di poliomielite anteriore acuta". Annali di Laringologia, Otologia, Rinologia, Faringologia, 1958, XXXII, 2:129-139.

(12) *Marinesco, Draganesco et Grigoresco*: "Sur un cas de parkinsonisme post-encéphalitique survenu chez un ancien poliomyèlitique". Rev. Neur., 1929, 2:102.

(13) *Drouhet V.*: "Diagnostic virologique et sérologique de la poliomyèlite — Méthodes et Techniques". Sem. Hôp. Paris 1959, XVIII — 4:1333-1342.

(14) *Thieffry S. et coll.*: "Apport du labaratoire pour le diagnostic de la poliomyèlite". — Sem. Hôp. Paris, 1959, XVIII — 4: 1343-1349.

(15) *Altenbruger, E.*: "Kasuistischer Beitrag zur Klinik der Polio". ant. acuta — Klin. Woch. 1940, XIX:423-426.

(16) *Vujic V., Ristic V.*: "Le syndrome parkinsonien comme complication de la maladie de Heine-Médin" — Presse méd., 1938, XLVI:901-902.

(17) *Alajouanine T., Mignot H., Mozziconacci P.*: "Un syndrome parkinsonien peut-il reconnaître la maladie de Heine-Médin comme étiologie?" — Revue Neur., 1939, LXXII:66-69.

(18) *Thieffry S., Arthuis M., Lyon G.*: "Intérêt et valeur des recherches virologiques en pratique neurologique" — (Sous presse in Revue Neurologique).

Aspects E.E.G. des Encéphalites

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L'électroencéphalographie a apporté des indications diagnostiques et surtout pronostiques aux problèmes posés par les encéphalites. Les premières concernent certaines images électriques tels les paroxysmes des leucoencéphalites subaigües, les secondes correspondent aux modifications du tracé E.E.G. durant l'évolution de la maladie. Les recherches centrées sur les relations éventuelles entre les anomalies E.E.G. et les constatations anatomiques sont à la base des indications les plus précises sur cette question.

Les premiers travaux de Lindsley et Cutts (1941), de F. Gibbs et E. Gibbs (1947), de Shinners et coll. (1949), ont été électrocliniques et ont porté sur des encéphalites de nature diverse. L'étude systématique de la méningo-encéphalite tuberculeuse faite en France et en particulier à Montpellier (1948-1954), a souligné d'après des corrélations cliniques, radiographiques et anatomiques la valeur des données E.E.G. pour le pronostic de cette affection.

Radermecker a fait le point actuel de cette question dans son importante monographie de 1956 et a précisé l'aspect E.E.G. des encéphalites en recherchant les relations des anomalies électriques avec les lésions anatomiques.

Au cours de ce travail, deux types de renseignements apportés par l'E.E.G. seront envisagés. L'un concerne l'évolution des encéphalites, le second correspond à des aspects E.E.G. propres à certains types d'encéphalite. Ces deux indications peuvent préciser un pronostic ou orienter un diagnostic.

E.E.G. ET EVOLUTION DES ENCEPHALITES

Les anomalies E.E.G. dues aux encéphalites son diffuses avec parfois une majoration sur une partie du scalp.

Les anomalies sont d'autant plus importantes que l'état clinique est sévère. A la période d'état des encéphalites, leur aspect varie plus d'après la topographie des lésions, l'intensité de l'atteinte cérébrale et l'âge du sujet que d'après la nature même de l'encéphalite.

Avec l'évolution de l'encéphalite, on observe une modification des anomalies électriques. Leur aggravation est de pronostic réservé, leur persistance fait redouter des séquelles soit épileptiques, soit psychiques, leur atténuation va généralement de pair avec l'amélioration clinique.

Pour illustrer ce cycle évolutif des encéphalites, la *méningo-encéphalite tuberculeuse* sera prise en exemple et étudiée à la période de début, à la période d'état et à la période de séquelles (fig. 1).

a) *Période de début.* Les anomalies E.E.G. sont variables selon la gravité des signes cliniques et surtout selon l'âge. C'est en effet à ce stade que les modifications électriques sont particulièrement plus précises chez l'enfant que chez l'adulte. Comme au cours de toutes les aggressions cérébrales, la désorganisation du tracé électrique est plus marquée chez l'enfant.

Chez l'enfant, les modifications E.E.G. sont pratiquement constantes, au cours de la méningite tuberculeuse. Elles correspondent selon leur intensité:

(1) à des ondes lentes sinusoïdales à localisation pariéto-occipitale, constatation banale retrouvée au cours d'encéphalites de natures diverses, en particulier, post-infectieuses,

(2) à des ondes lentes sinusoïdales intéressant globalement les deux hémisphères,

(3) à un tracé anarchique avec ondes lentes irrégulières et sinusoïdales. Ce dernier type correspond aux méningites tuberculeuses débutant par un coma, formes particu-

lièrement graves en particulier chez les très jeunes enfants.

Chez l'adulte, le tracé peut être normal avec un rythme alpha conservé dans 20% des cas (Janbon, Passouant et coll., 1952). Les tracés moyennement perturbés sont les plus communs avec ondes ralenties (5 à 6 c/s), des rythmes rapides supérieurs à 12 c/s.

b) *Période d'état.* A ce stade, l'E.E.G. apporte des indications sur la *topographie des lésions soit corticale soit sous corticale.*

Les *anomalies localisées corticales* sont d'expression diverse: foyer d'ondes lentes, décharges épileptiques, bas voltage localisé. Ces anomalies correspondent à une réaction d'œdème, elles sont en général fugaces et disparaissent en quelques jours (fig. 2).

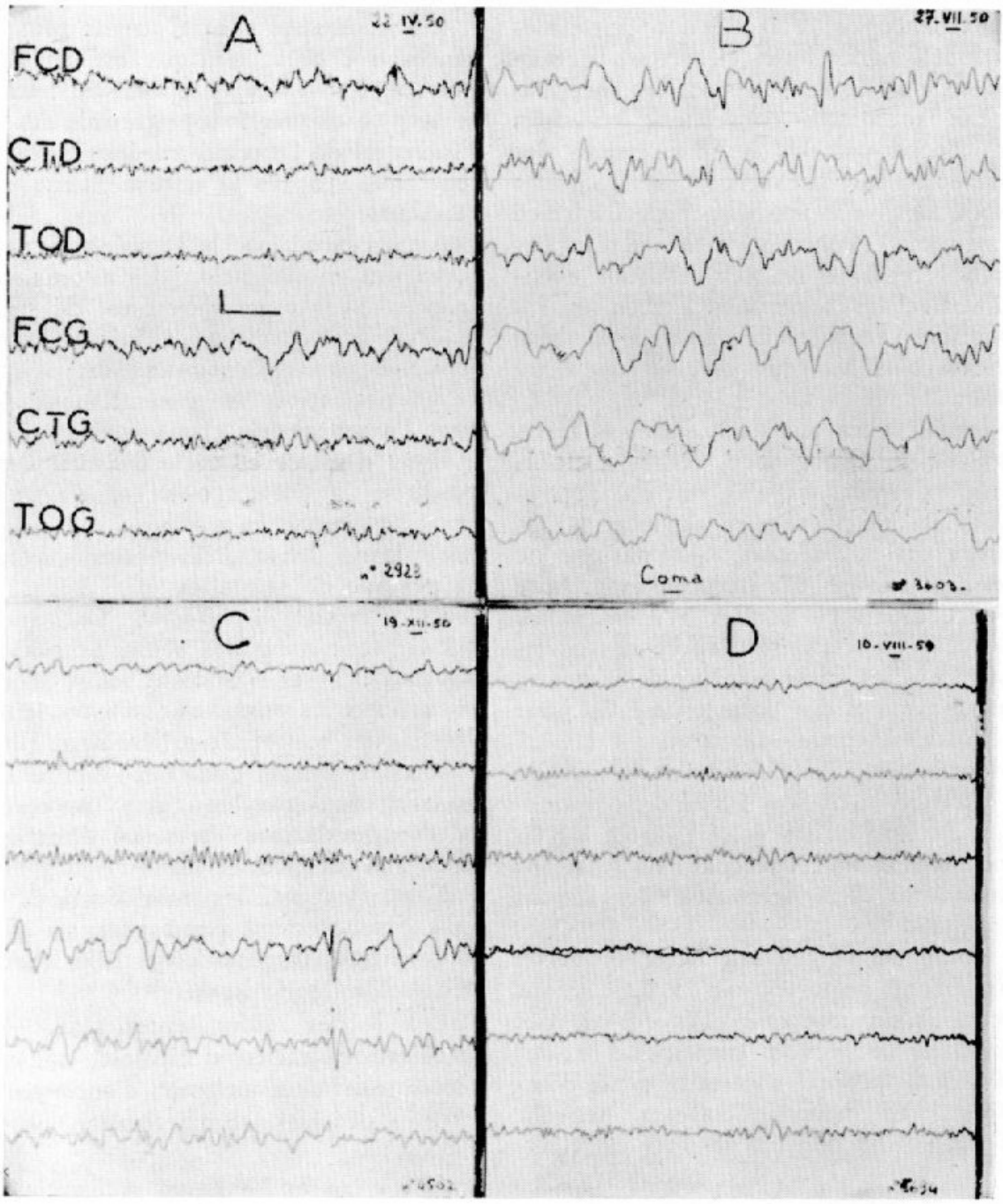

Fig. 1. — *Evolution d'une méningo-encéphalite tuberculeuse chez un enfant de 10 ans. A.* - Début: *ondes lentes frontales majorées pour l'hémisphère gauche. B.* - Rechute: *ondes lentes diffuses. C et D.* - Séquelles: *Foyer épileptique fronto-central gauche puis dysrythmie mineure intéressant les deux hémisphères.*

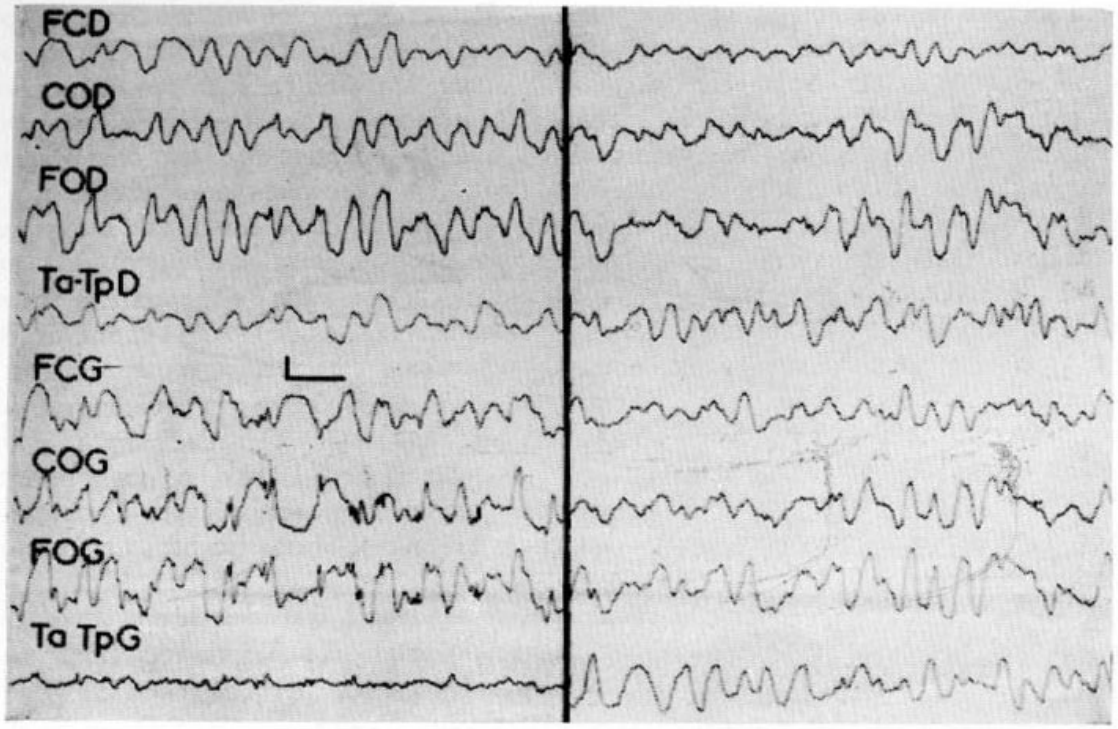

Fig. 2. — *Méningoencéphalite tuberculeuse chez un enfant de 5 ans. I. - Foyer épileptique occipital gauche avec ondes lentes diffuses et bas voltage temporal gauche. II. 24 heures après: ondes lentes diffuses, disparition du foyer.*

Plus rarement, ces anomalies persistent et peuvent être à l'origine de séquelles neurologiques (hémiplégie), ou épileptiques. Elles peuvent alors dépendre d'une atteinte vasculaire (thrombose artérielle ou veineuse).

Les *anomalies bilatérales* correspondent aux rythmes delta bifrontaux isolés au cours de la méningite tuberculeuse sous le nom de *"tracé de souffrance basale"* (fig. 3). Ces rythmes s'inscrivent en bouffées rythmiques séparées par des périodes d'ondes lentes irrégulières de tracé bas volté. Ces rythmes frontaux observés par ailleurs au cours d'atteintes cérébrales de nature diverse (tumeurs, arachnoïdites opto-chromatiques), ont été rapportés à une atteinte hypothalamique et thalamique. Au cours de la méningite tuberculeuse, ils sont observés dans les formes diencéphaliques traduits du point de vue clinique par une obnubilation, un amaigrissement et un dérèglement végétatif, du point de vue radiographique par une hydrocéphalie quadriventriculaire sans déplacement, du point de vue anatomique par une arachnoïdite basale engainant le chiasma s'infiltrant dans le plancher du troisième ventricule et l'hypothalamus.

Ce tracé de souffrance basale indiquait un très mauvais pronostic lorsque le traitment de la méningite tuberculeuse était limité à la streptomycine. Au cours de l'étude de cette question, nous avions constaté que ce type de tracé était suivi de décès dans 90% des cas chez l'adulte et 97% des cas chez l'enfant. Avec l'élargissement du traitement aux isionazides et du P.A.S., ce type de tracé n'a plus de valeur pronostique, sauf chez l'enfant très jeune.

b) Période de guérisons et de séquelles. C'est à cette période que la discordance entre le tracé E.E.G. et la clinique peut être précise et rendre difficile l'interprétation des données E.E.G.

Des anomalies électriques peuvent coïncider soit avec des séquelles cliniques, soit avec un état normal. Une dysrythmie électrique peut en effet persister après la guérison apparente et plus fréquemment chez l'enfant que chez l'adulte. Les tracés de type épileptique sont particulièrement fréquents chez l'enfant (10% de notre statistique de

1955), alors que l'épilepsie séquelle est rare (1% de notre statistique de 1955).

D'n autre côté, si la normalisation du tracé a pu être considérée comme un test de guérison, par contre, un tracé normal n'écarte pas la possibilité d'une rechute et a pu être obtenu chez des sujets présentant des séquelles. Aussi, au cours d'une étude faite avec J. Chaptal (1954), concernant les séquelles de la méningite tuberculeuse de l'enfant, des tracés normaux ont été constatés chez des enfants présentant des séquelles encéphalopathiques et des séquelles sensorielles (surdité, cécité).

LES ACTIVITES PAROXYSTIQUES

Au cours d'encéphalites de nature diverse, des paroxysmes électriques peuvent être identifiés. Ces paroxysmes peuvent correspondre à des décharges épileptiques ordinaires et traduire, soit une épilepsie localisée en foyer, soit une épilepsie sous corticale. De telles décharges, expression d'une complication épileptique peuvent survenir au cours de la plupart des encéphalites et ne seront pas envisagés ici.

Par contre, certains paroxysmes particuliers à certains types d'encéphalite ont une valeur soit diagnostique soit pronostique. Ces paroxysmes correspondent aux décharges myocloniques des leucoencéphalites, aux pointes rythmiques des encéphalites nécrosantes subaigües à localisation temporo hippocampique, aux décharges hypsarythmiques de certains encéphalites post-infectieuses. Ce sont ces trois types d'activité paroxystique qui seront étudiés.

a) Les décharges myocloniques des leuco-encéphalites. Ces décharges isolées par Radermecker (1949), correspondent à des paroxysmes généralisés aux deux hémisphères et faits d'ondes pointues suivies d'ondes lentes survoltées (fig. 4). Ces complexes, de morphologie identique, au cours d'un même tracé se répètent régulièrement selon une fréquence qui varie de 4 à 8 par minute. Ils s'inscrivent sur un rythme de fond ralenti et désorganisé. Leur durée est de une à trois secondes, leur amplitude varie entre 200 et 400 HV. Les ondes aigües sont en général synchrones des myoclonies lorsque celles-ci surviennent.

De telles décharges ont été rapprochées

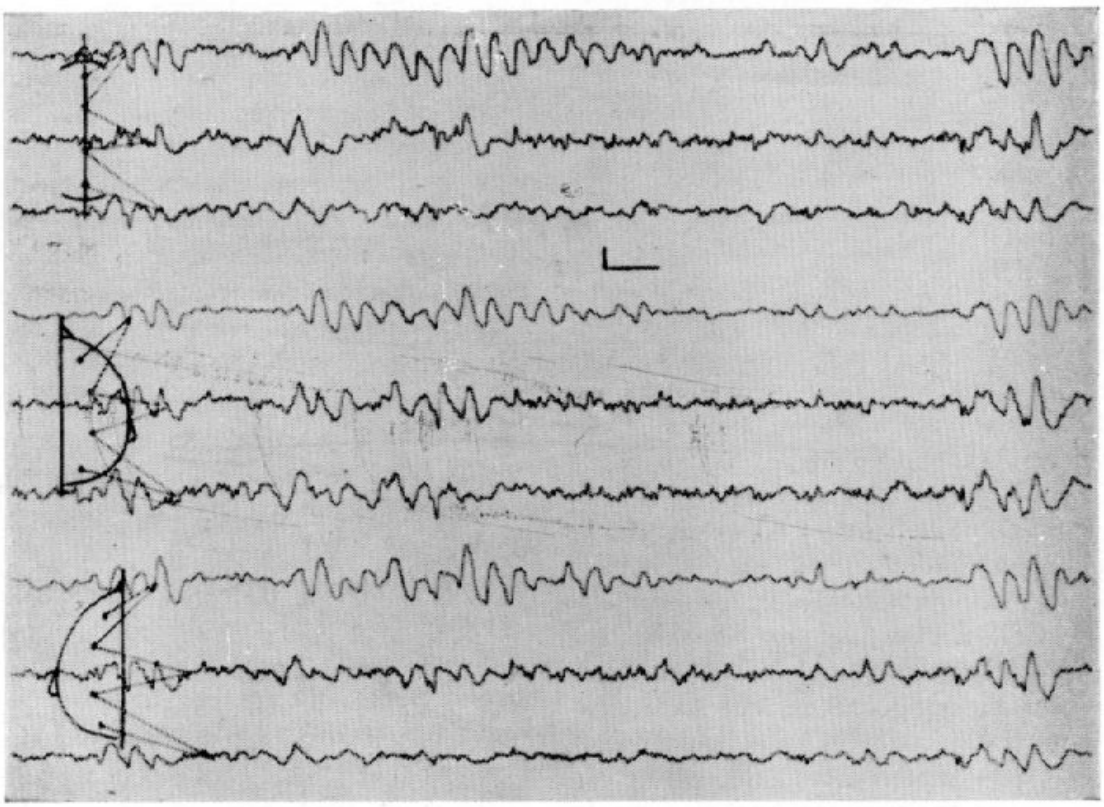

Fig. 3. — *Tracé de souffrance basale: ondes lentes bifrontales.*

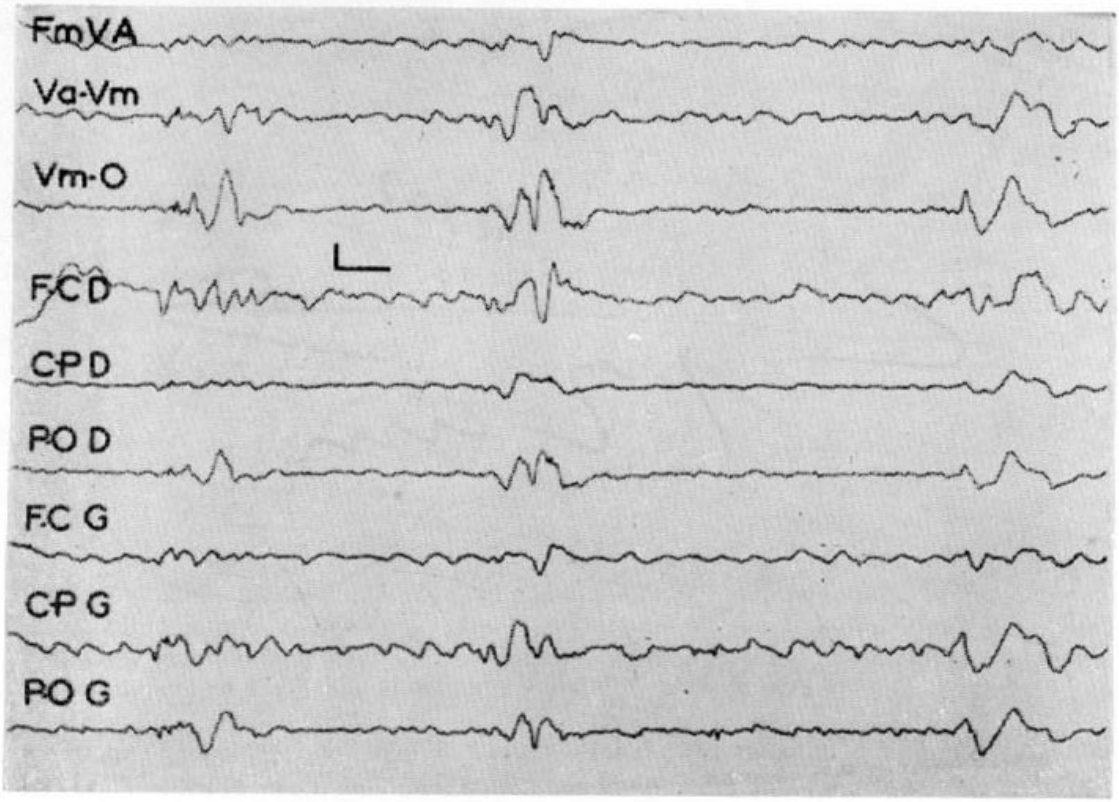

Fig. 4. — *Leucoencéphalite subaigüe. Paroxysmes lents d'inscription rythmique généralisés aux deux hémisphères.*

des "complexes K" enregistrés en cours de sommeil. Leur morphologie et leur rythmicité sont partiellement comparables. D'autre part, les lésions anatomiques propres aux leucoencéphalites prédominent à l'étage thalamo-sous thalamique et s'étendent au mésencéphale. Ces lésions intéressent les formations réticulaires du tronc cérébral dont on connaît le rôle dans la régulation de la vigilance. Aussi, à l'image des complexes K du sommeil, ces paroxysmes ont ils été rapportés par Radermecker (1956), à une libération des "automatismes neuroniques diencéphalo-corticaux". Ces complexes très particuliers sont enregistrés au cours de la leuco-encéphalite sclérosante subaigüe de Van Bogaert et ont été observées au cours de l'encéphalite subaigüe à inclusion de Dawson et de la panencéphalite type Pette. Ces trois types d'encéphalites forment en fait un groupe unique du point de vue clinique et anatomique. Les paroxysmes électriques de type très particulier constatés dans ces trois types ont incontestablement une réelle valeur diagnostique.

b) Les pointes rythmiques des encéphalites nécrosantes subaigües. Elles correspondent à des pointes lentes répétitives d'allure diphasique séparées par un tracé plat (fig. 5). Ces pointes peuvent prédominer sur un hémisphère et une région temporale, ou intéresser tout le cortex. Avec l'évolution de la maladie, les pointes deviennent plus lentes, plus rares, et le tracé de fond plus plat.

Cet aspect E.E.G. peut être comparé à celui que l'on obtient chez l'animal au cours de l'épilepsie hippocampique expérimentale provoquée par l'injection d'alumine dans le Corne d'Ammon (Passouant et coll., 1957). Aussi, ce type de tracé est-il évocateur d'une lésion temporo-hippocampique.

C'est, en effect, au cours des encéphalites nécrosantes subaigües à localisation temporo-hippocampique que ce type de tracé a été décrit par Radermecker (1956). Ces encéphalites sont représentées par l'encéphalite herpétique et par des encéphalites d'étiologie virale non encore précisées. Leur évolution, quelqu'en soit l'origine, est assez stéréotypée. Après un début infectieux de type grippal accompagné ou non d'herpès, des crises soit jacksoniennnes soit tempora-

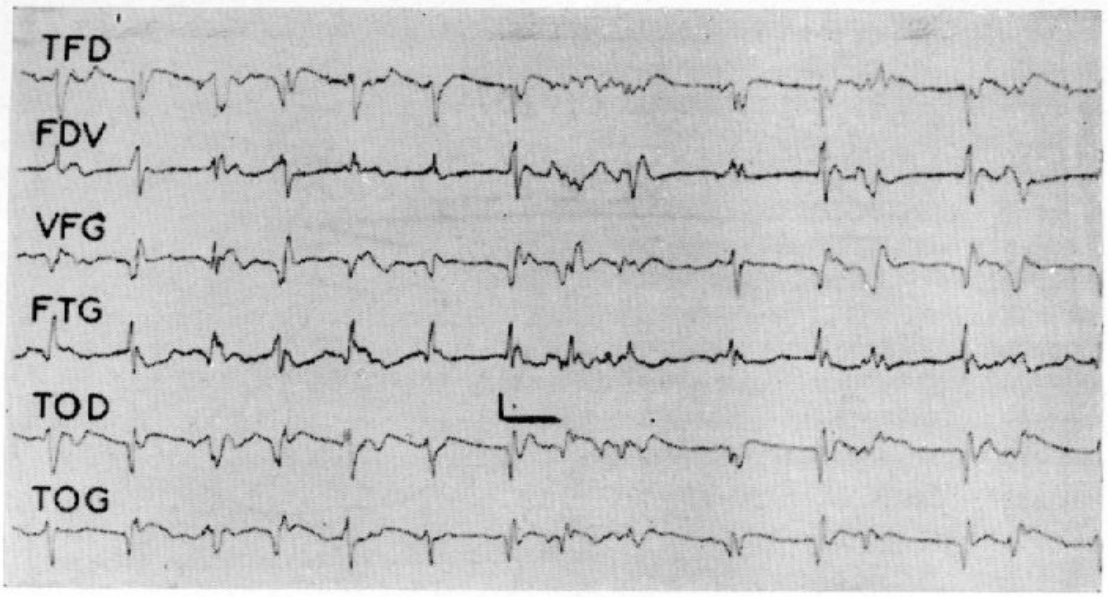

Fig. 5. — *Encéphalite nécrosante subaigüe à localisation temporo-basale. Période terminale. Pointes rythmiques, tracé de fond très plat.*

les avec hallucinations olfactives ou visuelles, se produisent associées ou non à des troubles moteurs de type hémiplégique ou de type de rigidité catatonique. Des manifestations mentales se précisent: état de confusion avec ou sans délire, auquel fait suite un état de torpeur puis de coma. Sur cette évolution clinique, est calquée une évolution de tracé E.E.G. dont les points rythmiques sont l'élément le plus constant.

c) Les tracés hypsarythmiques. La désorganisation majeure du tracé E.E.G. correspondant à l'hypsarythmie associée ou non à des spasmes toniques axiaux peut être ob-

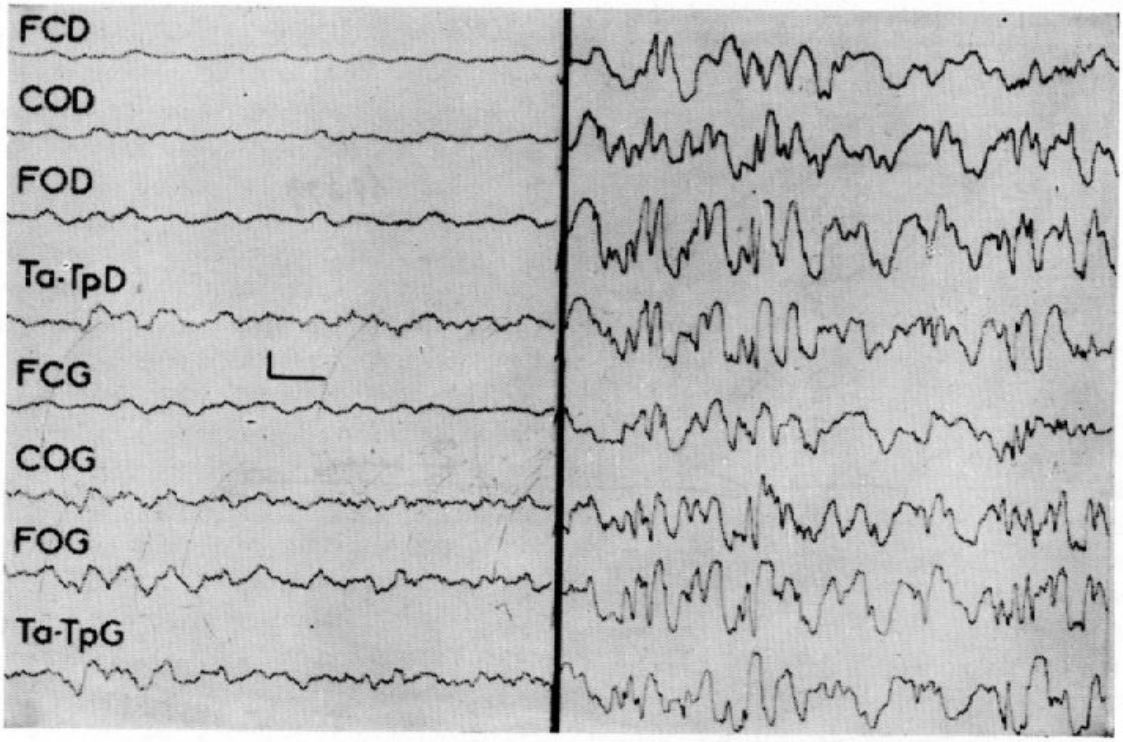

Fig. 6. — *Evolution d'une encéphalite post-infectieuse grave. 1) Début: tracé peu volté avec ondes lentes prédominant pour l'hémisphère gauche. 2) Période d'état: tracé désorganisé type hypsarythmique.*

servée au cours d'encéphalites post-infectieuses graves de l'enfant (fig. 6).

Des encéphalites de type séro-hémmoragiques produisent des lésions importantes avec larges foyers de nécrose associés à des altérations vasculaires provoquent cette désorganisation globale du tracé. Ces encéphalites observées au cours de la coqueluche, de la grippe, succèdent parfois à des troubles digestifs et catarrhaux.

Les tracés de dysrythmie majeure sont parfois associés à de larges foyers de souffrance (ondes subdelta localisées), qui peuvent avoir une expression hémiplégique. Les décharges myocloniques sont fréquentes, les spasmes toniques possibles. La détérioration mentale est importante et les séquelles psychiques, épileptiques et motrices graves.

RESUME

L'apport de l'E.E.G. au problème des encéphalites est indiqué d'après les modifications E.E.G. qui se produisent durant l'évolution des encéphalites et d'après certains paroxysmes électriques propres à certains types d'encéphalites.

L'aspect évolutif E.E.G. est illustré par l'exemple de la méningo-encéphalite tuberculeuse. En complément des données pronostiques tirées de cette étude, certaines indications concernant la topographie corticale et sous-corticale des lésions sont retenues. Le rôle du terrain et surtout de l'âge est indiqué. Enfin, la discordance électroclinique de la période de guérison ou de séquelles est signalée.

Parmi les paroxysmes propres à certains types d'encéphalites, trois sont retenus: les myoclonies lentes des leuco-encéphalites subaigües, les décharges épileptiques continues des encéphalites nécrosantes subaigues à localisation temporo-hippocampique, les désorganisations de tracé de type hypsarythmique de certaines encéphalites post-infectieuses. Ces anomalies peuvent orienter un diagnostic ou préciser un pronostic.

SUMMARY

The importance of the EEG findings in encephalitis is due to the modifications that are produced in the record during the evolution of this illness and also through certain electrical paroxisms belonging to some types of encephalitis. The evolutive aspect in this ailment is significatively illustrated in the course of the tuberculous meningo-encephalitis. In order to complement the prognostic data of these studies certain indications concerning cortical and subcortical topography of the lesions are brought to mind.

The role of the physical condition especially the age are emphasized. It is pointed out that the electroclinical findings during the period of recovering and sequele don't always jib with the patients true condition.

Among the paroxisms typical of certain types of encephalitis three are chosen: the slow myoclonus of the subacute leuco encephalitis the continual epileptic discharges of the subacute nechrotic encephalitis localizing in temporo hippocampic region, the desorganization of the record and hypsarhitmic type in certain postinfectious encephalitis.

These anomalies may orient a diagnosis or fix a prognosis.

RESUMEN

El aporte de la E. E. G. al problema de las encefalitis está indicado por las modificaciones E. E. G. que se producen durante la evolución de las encefalitis y por ciertos paroxismos eléctricos propios de ciertos tipos de encefalitis.

El aspecto evolutivo E. E. G. está ilustrado por el ejemplo de la meningo encefalitis tuberculosa. En complemento a los datos de valor pronóstico que salen de este estudio, se afirman ciertas indicaciones que conciernen a la topografía cortical y subcortical

de las lesiones. Se indica el valor del terreno y sobretodo el de la edad. Se señala en fin, la discordancia electroclínica del período de curación o de secuela.

Se remarcan tres tipos de paroxismos propios de ciertos tipos de encefalitis: las mioclonias lentas de las leucoencefalitis subagudas, las descargas epilépticas continuas de las encefalitis necrosantes subagudas de localización témporo hipocámpica, las desorganizaciones del trazado de tipo hipsarrítmico de ciertas encefalitis post - infecciosas.

Estas anomalías pueden orientar un diagnóstico o precisar un pronóstico.

ZUSAMMENFASSUNG

Der Beitrag des Elektroenzephalogramms zum Problem der Enzephalitis ist gekennzeichnet durch die Veraenderungen, welche im Verlauf der Enzephalitis auftreten und durch gewisse elektrische Paroxysmen, die charakteristich sind fuer gewisse Typen dieser Krankheit. Der evolutive Aspekt des Elektroenzephalogramms kann am Beispiel der tuberkuloesen Meningoenzephalitis illustriert werden. Ausser dem prognostischen Wert der elektroenzephalographischen Veraenderungen kann man auch gewisse Rueckschluesse auf die kortikale und subkortikale Topographie der Laesionen ziehen. Es wird die Wichtigkeit der Konstitution und vor allem des Alters unterstrichen. Es besteht ein elektroklinische Diskordanz in der Heilungsperiode und den Folgeerscheinungen.

Man unterscheidet drei Typen von Anfaellen bei gewissen Arten von Enzephalitis: die langsamen Myoklonien der subakuten Leukoenzephalitis, die dauernden elektrischen Entladungen der subakuten nekrotisierenden Enzephalitis mit temporo-hypokampischer Lokalisation, die Desorganisationen des EEG vom hypsarrhythmischen Typ bei gewissen postinfektioesen Enzephalitiden. Diese Veraenderungen koennen wertvoll sein sowohl fuer die Diagnose als auch fuer die Prognose.

BIBLIOGRAPHIE

Chaptal J., et Passouant, P.: Electroencéphalographie et méningite tuberculeuse chez l'enfant. in Traitment par la streptomycine des tuberculoses aigües de l'enfant. Comptes Rendus de la réunion d'experts organisée par le F.I.S.E. et l'O.M.S.". Paris, février 1950, pp. 60-64.

Chaptal, J. Passouant P., Jean R., Cadilhac J., et Minvielle J.: "Signes E.E.G. des séquelles de méningite tuberculeuse". Rev. Neur., 1954, 90, nº 6, 830-834.

Euziere J., Chaptal J., et Passouant P.: "Méningite tuberculeuse et streptomycémie. Contrôle électroencéphalographique". Rev. Neur., 1948, 80, nº 8, 589-595.

Euzière J., Passouant P., et Latour H.: "La souffrance basale de la méningite tuberculeuse". Rev. Neur., 1950, 82, nº 6, 566-567.

Gibbs F. A., et Gibbs E. I.: "The electroencephalogram in encephalitis". Arch. Neurol. Psych., 1947, 58, nº 2, pp. 184-192.

Janbon M., Passouant P., Bertrand L., Latour H., et Salvaing J.: "Etude électroencéphalographique de la tuberculose méningée de l'adulte. Confrontations anatomiques et radiologiques". Semaine Hôpitaux de Paris, 1952, nº 51-52.

Lindsley D. B., et Cutts K. K.: "Clinical and E.E.G. changes in child during recovery from encephalitis". Arch. Neurol. Psych., 1941, 45, pp. 156-161.

Passouant P., Passouant-Fontaine Th., et Cadilhac J.: "Etude de la réaction d'éveil au cours de l'épilepsie hippocampique expérimentale". Proceedings of the first International Congress of Neurological Sciences. Vol. III, 579-593. Pergamon Press, 1959.

Radermecker J.: "Aspects électroencéphalographiques dans trois cas d'encéphalites subaigues". Acta Neurol. Psychiat. Bel., 1949, 49, 222-232.

Radermecker J.: "Systématique et électroencéphalographie des encéphalites et encéphalopathies". 1956, Masson, édit., Paris, 239 pp.

Radermecker J.: "Diagnostic clinique et électroencéphalographique de l'encéphalite et encéphalopathies". 1956, Masson, édit., Paris, 239 pp.

Radermecker J.: "Diagnostic clinique et électroencéphalographique de l'encéphalite nécrosante aigüe. Son intérêt comme détermination inflammatoire sur les formations rhinencéphaliques". Rev. Neur., 1956, 95, nº 6, 576.

Shinners B. M., Krauss R. F., et Rochester B.: "Encephalitis in children with E.E.G. changes". New York State Journal of Medicine. Easton, 1949, 49, pp. 2140-2144.

Present Day Encephalitides of Western and Central Europe

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Acute encephalitides of type A of Von Economo which were epidemic in 1921 and 1925 are seen today only in the most exceptional circumstances. I myself have not seen a single verified case of this disease since 1925.

This infectious disease continues to exist among us in the endemic state and produces parkinsonian sequelae. Parkinson's disease, occurring both in young and middle aged adults, is still seen frequently and case histories reveal its fairly recent onset. Detailed histories of certain patients with Parkinson's disease have indicated that these patients had had suspicious "influenza" infections although few of them were aware of having had any disease of this type.

The onset of this parkinsonian syndrome may be explained either by the hypothesis that the "influenzas" really are unrecognized forms of Von Economo's disease, or that other neurotropic diseases may also result in a parkinsonian syndrome which has the appearance of the post-encephalitic type. Theoretically the latter cannot be excluded, since cases of Parkinson's disease have been seen following poliomyelitis, although this is extremely rare.

The disappearance of epidemic encephalitis type A in our part of the world and the appearance of other forms of both acute and subacute types of encephalitides brings up the interesting question of the mutation of the overall aspect of epidemics; that is the etiological relationship that exists between the various clinical pictures assumed by the neurotropic infectious diseases.

It would be most attractive indeed —and perhaps too easy— to think that the same epidemic circumstances that led to encephalitis A in 1916-1917, 1921-1922 and 1925 would be responsible for the subacute and acute encephalitides that we see today. The difference in the symptomatology and the general epidemic characteristics might be accounted for by either a mutation of the viral agents themselves or by a modification of the substratum of the host. There are, however, two large voids in our present knowledge which force us to discard these hypotheses. These are that the etiological agents (probably viruses) of encephalitis type A and subacute encephalitis have not yet been isolated, and that in many cases of acute encephalitis we are not sure what is the etiological agent at all. The pathology of the disease is helpful only to a point.

We know to-day that a lesion in the substancia nigra is the most constant characteristic of Von Economo's disease. What is not as well known (and this is because the typical cases are less frequent with this particular type of localisation), is that the same characteristic lesion may be seen in rabies and poliomyelitis. What does distinguish the two latter diseases from Von Economo's disease however, is that, in addition to the substancia nigra involvement, there are other well localized lesions which easily permit the differenciation.

It is thus in the overall localisation of the lesions that one must look for a clue to the diagnosis in addition to the quality and type of the neuronal alterations and the inflammatory infiltrations. There was a time, a very short one however, during which many general pathologists felt that the presence of a few perivascular cuffs in a mesencephalon justified to their eyes a diagnosis of lethargic encephalitis. Howe-

ver, one accepts the characteristic topography and the qualitative aspects of Von Economo's disease as it existed in the cases seen between 1917 and 1925, then we must admit that this disease is no longer seen for practical purposes to-day.

It took a long time for the epidemic encephalitis of Von Economo to be recognized as an entity from among the confused group of so-called "influenza encephalitides" that were prevalent between 1915 and 1925. There was a chronological coincidence between the of these two different types of encephalitis.

It seems that the present day recurrence of subacute encephalitides in some parts of Western Europe is also contemporaneous with the appearance of severe epidemics of influenza, among which a certain number of cases can be shown to affect the entire nervous system. There may be a parallel evolution or fluctuation for a hole series of viruses, in terms of the fragility of the human substratum to the neuro-aggressivity of the different morbid agents. Many years ago the pediatricians noted that certain epidemics of measles were frequently associated with acute poliomyelitis. None the less, this accordance complicates, even more than we are willing to realize, the task of the virologist, upon whom rests the responsibility for defining the etiological agent.

Since 1938 my collaborators and I have observed a certain number of encephalitides which we have been able to verify anatomically and which we had never seen between 1923 and 1938. We last saw an acute case of Von Economo's encephalitis between 1924 and 1925. On the other hand, the percentage of acute poliomyelitis, except for a slight recurrence during 1929, remained approximately constant during these years in the province of Antwerp.

I have been able to study a certain number of a typical encephalomyelitides during the last 36 years, but I will discuss only those that fall into the three following large groups: that of the influenzal encephalitides of types A and B, that of the acute necrotizing encephalitides, and that of the subacute sclerosing encephalitides.

The so-called arthopod-borne encephalitides are only rarely seen in Western Europe except for Austria. I have often wondered however, if some of the atypical encephalomyelitides that have been reported in Western Europe are not virologically related to this group.

Influenzal Encephalitides: Types A and B

The clinical observations during the influenza epidemics of 1890 and 1891, and of 1918-1919, consist primarily in signs of coma with or without meningismus, convulsions, a few discreet focal signs and severe pulmonary involvement. There were no viral studies on these cases. The sporadic cases that were observed between 1919 and 1952 are also for the most part rather poor in symptoms and in general have the same clinical picture. From the histopathological point of view, the large majority of these cases presented a diffuse lymphocitic meningo-encephalitis, with an oedematous component which was more or less severe, or, occasionally, a hemorrhagic encephalitis and, in exceptional circumstances, a glio-perivenous type of involvement.

The histologic picture described by Hurst under the name of "acute hemorrhagic leucoencephalitis" had all the pathologic manifestations in a single case with a subacute clinical course, but it is impossible to name the specific virus that caused the disease. It was only around 1950, that the epidemics of virus A and B began to be separated from each other and that certain authors even suggested that influenza type B was more neurotropic than type A.

The meager information which is all that can be gleaned concerning past epidemics contrasts sharply with the tremendous interest that at first was focused on the epidemic of Asian influenza of 1956-1958 which was observed with all the apparatus of modern viral-research available. This epidemic, oddly enough, little material of value to neurologists. I was able to see only four cases with severe neurologic involvement, of which one was verified by histologic examination.

The literature concerning the central nervous system involvement of Asian in-

fluenza was reviewed by Furtado (1958) and by Battaglia and his co-workers in 1959.

The following are the three fatal cases of Asian influenza which we observed but on which we could get no autopsy.

Case I

Anne G., aged 18 years, began to cough and had a fever of 40,1° two days after her mother had a benign attack of grippe. On March 9, 1958 her tracheo-bronchitis became worse and she seemed somewhat cyanotic. She wheezed and had some blood-tinged sputum. She was somewhat less alert than usual.

On March 10, she sweated profusely and her respiration was rapid. She had two attacks of generalized convulsions as well as two right-sided jacksonian seizures. Her optic fundi remained normal.

On March 11, her temperature was 40,2° and she had slight nuchal rigidity. She had a left-side jacksonian seizure which was followed by coma.

A lumbar puncture revealed 12 cells, almost all lymphocytes, 0,40 of protein. No organisms could be found on smear.

Examination of the serum reveals a +++ serological reaction for virus type A.

Case II

Henri R., aged 27, with a completely negative history.

On December 26, 1957 he complained of very severe generalized muscle pains with nuchal rigidity, slight sleepiness, nausea and temperature of 39,7°.

The next day, his sputum was blood-tinged and his respiration was rapid. He had a pulse of 120, a beginning right-sided bronchopneumonia and his extremities were pale and cyanotic.

He had several generalized convulsions, a slight papiloedema, a few myoclonic jerks of the extremities and the thorax, and a complete loss of deep tendon reflexes on December 1928.

Spinal fluid examination reevals 22 cells, almost all lymphocytes, and a protein of 0,40.

The patient became comatose December 28 and died the following day.

A serum examination revealed a positive serological reaction ++ for virus type A.

Case III

Marcelle D., aged 22, with a completely negative past history. The patient was 1 ½ months post-partum.

On April 18, 1957, she had a temperature of 38°, and complained of generalized aches, especially in the back, the lumbar region, and the shoulders. She had severe headaches, fainted and was found to have a pulse rate of 128.

Examination of the spinal fluid showed 8 cells with a total protein of 0,30.

On April 19, her extremities were cyanotic; she had some condensation of both pulmonary bases and some râles. Her sputum was tinged with blood and her temperature had risen to 40,2°. The deep tendon reflexes were hypo-active and the patient was rather somnolent. A new spinal fluid examination showed 12 cells with a total protein of 0,30.

On April 22, the fever diminished, but the pulmonary involvement became more marked. The patient had two minor convulsive episodes. Her pulse became more and more difficult to record. Examination of the abdomen and of the genitalia remained negative. The patient became comatose and died in hypothermia. Serological examination reveals a +++ reaction for virus type A.

In these three cases the clinical picture was the same: somnolence, cyanosis, profuse sweating, a few epileptic attacks, and coma followed by death. The spinal fluid showed little alteration and the evolution of the disease terminated in death in about four days. The disease was constantly associated with a fulminating tracheo-bronchopneumonia with several episodes of hemorrhagic sputum.

In addition, however, we have been able to study a child with a much more varied and extensive neurological picture.

Carlo Del..., aged 10 years, had had an encephalopathy, probably post-pneumonic, during his infancy. On October 18, 1957 he had a severe grippe with a toxic reaction, rapid loss of weight and total loss of consciousness.

A neurological examination revealed an expressionless facies. The patient cried out rhytmically. There were isolated occasion-

ally symmetrical clonic jerks of the pectoral muscles; contorsion movements of the trunk; and occasional flexion movements of the forearm, less often on the left side, which appeared to occur with a certain periodicity. From time to time there was an episode of contracture in extension. There were uncoordinated movements of the eyes to the right and to the left. This state persisted for approximately two days. Then the mental status became better, the patient started to speak again and the convalescence thereafter was rapid. At the end of fifteen days the patient was completely well.

In another case which terminated in death, the neurologic picture revealed in a fully conscious patient the same local torsion movements with a few clonic movements of the upper extremities and the neck.

This child, V. Ist..., aged 12 years, was seen en October 17, 1957 in a state of somnolence with occasional absences. The coma rapidly deepened and the temperature remained at 38,5°. A spinal puncture performed by Dr. Lowenthal revealed 9 cells. The muscular hypotonia became severe rapidly and the child grew comatose soon after the onset of the disease. The optic fundi remained normal. The child died ten days after the disease started and the cerebral lesions consisted only of a diffuse oedema with a few extravasations of red blood cells.

We were fortunate enough to be able to study the 14 cases that were published by Macchi, Battaglia, Guazzi, and Masini in 1959. Dr. Macchi has worked at the Institut Bunge and he was kind enough to allow me to study his material. Relatively few deaths occurred during the recent epidemic of Asian influenza and thus the cases that he and his co-workers collected present a great deal of interest.

These 14 patients became sick at the height of the epidemic. In 11 cases the diagnosis of virus type A Singapore was merited. The authors have noted that in the catarrhal diseases of the so-called influenzal type, the actual influenza viruses can be discovered in only a very small percentage of cases. (14 % as reported by Dascomb and Hilleman in 1956). This serves to strengthen the concept of an etiological relationship between the influenzal encephalitides and the type A virus.

The fourteen cases are divided into three groups on the basis of their clinical symptomatology. The first group consists of only one case: A myoclonic encephalitis which involved primarily the cephalic portion of the body with severe respiratory difficulties, difficulty with speech and swallowing, a few involuntary movements, and death following respiratory paralysis.

The second group was characterized by a hypoacute ascending paralysis with respiratory death and was found in four cases.

The third group, which consists of 6 cases, is rather reminiscent from the clinical point of view of the older types of influenzal encephalitides. The symptoms were sommolence going on to coma, convulsions, agitation with occasional involuntary movements, severe generalized intoxication occurring rather early in the disease and that due to cardiac collapse or bronchopulmonary involvement. One of the cases which evolved in two phases showed a necrotizing keratitis and a labial herpes during the first part of the disease.

The pulmonary involvement noted clinically was found at autopsy to consist of lesions of bronchitis and of hemorrhagic bronchopneumonia, either unilateral or bilateral. The other viscera showed inflammatory alterations with no hemorrhagic component.

The difference in these three clinical pictures would indicate that the pathologic picture in this group of cases also show some differences. In fact, the second group of cases was found to resemble poliomyelitis with the exception that the dentate nuclei were also involved and that in one of the cases there were even some nodules in the cortex. One case in group three, in which there were no alterations of consciousness, and in which the clinical involvement consisted of dyspnea and cardiac difficulties, might seem more properly to belong to the second group. This might be true if the importance of the lesions in the nuclei of the brain stem is noted. Here,

however, as in a case found in the second group, there was an extension of the lesions to the telencephalon, a localisation which is usually not seen in acute poliomyelitis.

The only case in the first group had lesions that are reminiscent of the perinous encephalitides and of the acute plurifocal poliencephalitis. It evolved in two phases and lasted little more than three weeks.

A case very similar to this one evolving in the manner of an ascending paralysis of Landry in but a few days, was published by Dr. Radermecker. These two cases are, as far as the histological picture is concerned, primarily "panencephalitides".

The lesions in a third group are reminiscent of those seen in the classical influenzal encephalitis.

Because of the polymorphism that is apparent in groups 1 and 2 both from a clinical and pathological point of view, the authors have raised the question of the etiologic relationship between these clinical and pathological states and the type A Singapore virus. This polymorphism in lesions is even more disturbing in view of the fact that it is not observed at the level of the other organs.

It is also a question whether these cases are not manifestations of more than one virus or if they have not been activated by a latent infection by another virus. Another possibility is that a single virus may have different manifestations both from the pathological and clinical point of view, depending upon the nature of the "terrain" upon which it is implanted.

Neither the clinician nor the morphologist can find a solution to this question. What can, however, be derived from the work of the Italian workers, from our own very rare personal cases and the study of literature concerning this disease, is that the neurologic picture of influenza is dominated from the clinical point of view by somnolence with a severe vegetative involvement, a few meningeal signs, a very slight pleocytosis of the spinal fluid, few local signs, occasional epileptic manifestations, and a rapid evolution toward a terminal collapse and death. The clinical picture in this way resembles very much and is quite indistinguishable from the hypertoxic forms of post-infectious encephalitis.

The influenzal encephalitides that we have just discussed are part and parcel of a severe diffuse involvement of the entire body in which the pulmonary involvement appears to be the dominant clinical point. Of secondary importance are involvement of the kidneys and the liver and intestins. These visceral lesions often have a hemorrhagic tendency and occasionally one can see an exanthem as was seen in one of the Italian cases. This, however, is exceptional. The collapse of the autonomic system is the most striking feature in addition to the somnolence.

Acute necrotizing encephalitides

There is another group of encephalitides which very often starts with the same clinical signs: intense malaise and elevated temperature, altough the tracheo-bronchopneumonia and the hepatic or intestinal manifestations are rare and more vague and less apparent. There is also a free interval between general and neurological symptoms. Thus the clinical picture is much less severe to the eyes of a physician. It is the mental confusion and disorientation which are most striking. The meningeal reaction occurs early and is very definite. The alterations in the spinal fluid, when present, are more pronounced. In the adult, the cutaneous or mucous herpetic lesions are as a rule unnoticed or inexistent.

In the adult it is the acute meningoencephalitis which is noted at first. It is of extreme gravity and most often fatal. A vesicular eruption was seen in only 2 of our 37 cases reported with Haymaker, Smith and de Chenar in 1958 and there again this eruption was not recognized as being of the herpes simplex type. In our 37 cases, the herpetic origin of the disease could be demonstrated by biological tests in only 7 instances.

The clinical pathologic picture of these encephalitides is sufficiently characteristic that they may be recognized with ease. Since in most instances the herpetic etiology cannot be demonstrated in spite of the similarity between the two clinical

entities, we characterized them in an article written in 1955 with Drs. Radermecker and Devos, as "acute necrotising encephalitides", a term which certainly leaves much to be derived from the standpoint of etiology. There seems to be no point in reviewing all the literature on this entity, but we will mention however the reports of Dr. Radermecker in 1956, Dr. Van Gehuchten and his co-workers in 1958, Dr. Haymaker and his co-workers in 1958 and the monograph of Dr. Brihaye in 1958.

The clinical and pathological details of this encephalitis should be better known, since it is only in cases in which the diagnosis is made during the patient's life that will lend themselves to fruitful viral investigation.

It is true that the visceral signs (acute respiratory or intestinal involvement of a rather diffused type) are often the first manifestation of the disease, although they are not present in every case. Following this, the neuropsychiatric component of the disease is immediately surimposed and frequently presents itself in the form of a convulsive episode. This initial phase is dominated by a picture of disorientation with anxiety and hallucinatory agitation. This was well described by Dr. Radermecker in the following terms: "At the beginning of the disease the patient may have fugue states, and stereotyped actions which may or may not be related to his usual occupations. He may be disoriented, may confabulate, may not be able to recognize his environment. In certain cases one may even notice episodes of confusion and oneirophrenia with occasional depressive psychotic episodes, refusal of food and suicidal attemps". Olfactory hallucinations are frequent (odors of foliage, of paint, of incense, etc.) while auditory hallucinations (music) or complex visual ones (finding himselft in a wood in springtime) are more rare.

Jacksonian or generalized convulsive seizures occur shortly thereafter and may be associated with focal signs consisting of hemiplegia or aphasia. Other neurological signs such as temporary paralysis of the cranial nerves, involuntary movements, etc. may also be superimposed, but these are quite rare and in a way appear to be secondary. The patient rapidly passes from somnolence to lethargy or coma, he is either flaccid or rigid, and in a certain number of cases there is a meningeal reaction noted in the spinal fluid. The latter, however, may be absent, and the spinal fluid may be completely normal, although in most of the cases there is a rather marked pleocytis consisting of both poly- and lymphocytes alone (500 to 1000 cells with an elevation of the spinal fluid protein which is proportionate to the number of cells). Disturbance of respiration and deglutition appear quite rapidly, and death due to cardiac collapse with or without bronchopneumonia usually follows in 5 to 15 days following the onset of the disease.

In short, this type of encephalitis differs from the influenzal type by the superposition of a psychiatric symptomatology, where in addition to lethargy or somnolence there are active elements such as hallucinations, refusal of food, suicidal tendency, fugues, etc. The early apparition of focal signs, the intensity in a fairly large number of cases in which there is a spinal fluid cellular reaction, the absence of an autonomic component which gives to the influenzal type its appearance of severe intoxication, and the absence in most cases of acute signs of respiratory involvement with hemorrhagic tendency, are other clinical signs that aid in recognizing the necrotizing type of enceplalitis. The influenza encephalitis more characteristically evolves towards respiratory paralysis and circulatory collapse, while the necrotizing type is more characterized by epileptic episodes.

In the necrotizing encephalitides there is a predominant corticobasal involvement with special localization to the temporo-hippocampal region. The diagnosis can be made from the microscopic appearance of brain as it can be made in the true herpetic encephalitis. The necrotic softening, occasionally accompanied by a few hemorrhages in the temporo-hippocampal regions on both sides, or more predominantly on one side, is characteristic. Coronal sections of brain immediately reveal the extension

of the necrosis: the lesions involve the tips of the temporal lobes and the posterior parts of tne orbital brain, the rhinencephalon, the hippocampus, and the callosomarginal gyrus. Starting from these different areas, necrotic alterations may be followed into the hypothalamic regions and especially the subependymal regions. The insula is always involved. A similar process may be seen in the convexity of the hemispheres, although with less regularity for instance, in the area of F 1 near the interhemispheric fissure, in the temporal gyri of T 2 and T 3, and occasionally in the parieto-angular region. In contrast with these large necrotic areas which begin in the subpial regions and involve either the superior layers or the entirety of cortex, one may also observe small disseminated lesions, consisting of glial and perivascular infiltrations in the hypothalamic regions, in the brain stem, and occasionally even in the medulla. These latter areas, however, are minimal in comparison with the necrotic ones.

The acute necrotic encephalitides thus present a pathologic and clinical picture which is very similar to that in encephalitides of the adult in which the herpetic origin can be demonstrated, and certain so-called "polioclastic" encephalitides of Greenfield with negative viral studies. In Greenfield's cases type A inclusions have not been recorded, although the are present in the cases of herpetic encephalitides of the adult and in all but two of our cases of acute necrotizing encephalitis.

The reason why we persist in calling them "acute necrotic encephalitis" without, however, denying the possibility of a herpetic etiology is that there is almost no biologic demonstration of the presence of a virus.

The number of cases of acute necrotizing encephalitis is constantly increasing now that its clinical and pathological picture is better known. I know this from personal experience in studying cases from different countries in order to present them at the Symposium on Encephalitides which was held in Antwerp in May 1959.

To be complete, I will mention only briefly the acute forms of herpetic encephalitis noted in the infant and the premature child and the septicemic form both cerebral and visceral which I discussed in Birmingham in 1958. Also of note is the recurrent form of herpetic encephalitis which is characterized by a polioencephalitic involvement of the brain stem, a case of which is described by Brihaye in his thesis (1958). There probably also exist allergic forms which masquerade as glioperivenous encephalitides, as I demonstrated in 1956.

All the typical cases of necrotizing encephalitis in our series were fatal. Of course this is not always so; as a matter of fact, it is conceivable that certain other acute encephalitides (reported by Drs. Radermecker, Lowenthal, Macken and Meulders in 1957) do not actually belong to the same disease group.

The cases that these latter authors reported presented during a rather long period some psychic difficulties (mental confusion, psychopatic manifestations and hysterical signs) with amnesia which might last for several months, such psychiatric difficulties occurring only in very short episodes. These signs of organic mental involvement were accompanied by electroencephalographic manifestations and humoral disturbances which, in certain aspects, were reminiscent of the necrotizing encephalitides. The clinical course of these patients is still under observation and is not yet complete. What is disturbing in terms of the possible etiology of these diseases is that these cases coincided in Belgium with the existence of a severe epidemic of viral lymphocytic meningitis.

Subacute Sclerosing Encephalitis

There is still another type of encephalitis which I named "subacute sclerosing leucoencephalitis" in 1945. The literature concerning this type was reviewed by Brucher and Dechef in 1957. Their description of the clinical picture is quite complete and may be summed up as follows:

The disease is seen primarily in children between the ages of 2 and 18 years. It has a progressive subacute course with a mean duration of between 3 and 10 months,

although it will occasionally go as long as 27 months. The beginning of the disease is characterized by progressive deterioration of the entire intellectual functions, a definite worsening of school performance, a severe and rapid involvement of psychic functions, and more or less severe manifestation of agnosia, apraxia, and aphasia. Following this initial phase there are epileptiform seizures, associated with complex and varied hyperkinesias (consisting of myoclonic, choreoathetotic, ballistic or tremulous movements). The neurologic signs are in most cases poorly defined but may consist of uni- or bilateral pyramidal tract signs; rarely are ocular paralysis seen, but there is a constant hypertonicity which is more or less pronounced but which evolves finally to a complete hypertonicity of decortication. There are few important alterations of the biological fluids and fever is present only in rare cases. A pneumoencephalogram is almost always completely normal.

The typical electroencephalographic picture reveals the presence of periodic complexes consisting of high voltage spikes followed by slow waves superimposed on a basic tracing which is more or less altered. These complexes have an identical morphological appearance in the same leads in one patient. The paroxisms have a variable interval from one record to the other and on certain days might not even be present. They are frequently in chronological relation to the myoclonic jerks or may coincide with the momentary suppression of the voluntary psychic activity.

The etiology of the disease is unknown. The course of disease leads to cachexia. These children die in a state of hyperthermia and of extreme marasmus.

The histologic picture is characterized by an infiltrative glial, and lymphoplasmocytic process, which is reinforced by an edema of the central nerve system axis, predominantly in the white matter, although there is certainly involvement of the cortical and subcortical grey masses. The glial reaction is important and consists of both micro- and macroglia forming a diffuse although lacunal gliosis. A secondary disintegrated process taking the form of a demyelination with disintegration into fatty substances, as well as necrotic areas and cellular disintegration, is also visible. Intranuclear inclusions are present in some of the cases.

The most recent and the most complete study of this disease was done by Macchi (1958) and consists of an analysis of 110 cases which appeared in literature. A few observations of this disease process were published before we reported ours. A review of such cases can be found in the extensive article published by Macken and Lhermitte in 1950. The case of "panencephalitis of Pette and Döring" that I was able to study at that time reveals that in those cases the white matter is also severely involved in certain instances (Lhermitte, 1950).

In evaluating my experience over the last 20 years, and considering the disease process in its entire evolution as well as its structural and topographic component, it seems to me that the three tpyes of subacute encephalitis, the Pette-Döring type, the Dawson type and the one I myself described, are simply variants of one another. The research work and the electroencephalographic evidence brought forth by Dr. Radermecker from 1949 to 1955 is in accordance with this conclusion. It remains then to see if these variants represent different modalities of a reaction of the central nervous system to a single viral agent, or if the three slightly different reactions suggest the existence of different etiological agents. To answer this question is impossible at the present time with the clinical and morphological means in our possession. Regardless of the name that is given to these entities, there can be no question about the fact that the evolution of these forms of encephalitis is so similar that they should be considered as part of a single clinical entity.

The first question that must be asked is: Do these different types of encephalitis not represent different forms of the same disease process of which the etiological agent is the herpes simplex virus? One may indeed see in the leuco-encephalitides necrotic areas, and they should not surprise

us in view of the importance of the serous and perivascular inflammatory reaction. Those cases with necrotic areas are, however, rather rare; and the necroses that can be seen in them are of a different localization and a different quality than those characterizing acute necrotizing encephalitides. The cases of leucoencephalitides in which these are found have all the other characteristics of the disease, including the axial sclerosis, and it is for this reason that we think that it is pointless to distinguish a particular form as "leuco-necrotizing" as was done by Alajouanine, Gruner, Coulon, Nélille and Guyot in 1956. The histopathologic spectrum and the EEG picture of subacute sclerosing leucoencephalitis is sufficiently broad to include those cases to which we have just alluded.

It has been suggested by some such as Krucke in 1957 and Haymaker in 1958 that acute necrotizing leucoencephalitis and subacute sclerosing leucoencephalitis, as well as the subacute inclusion encephalitis of Dawson represent simply different reactional modalities of the neuraxis toward a single agent (or, in my opinion, toward several different etiologic agents). I indicated the possibility of the plurality of reaction types to a single fundamental disease in terms of infectious encephalitis in 1950. Dr. Radermecker also introduced this concept in the field of the anatomic and electro-encephalographic considerations of encephalitides in 1958.

As a matter of fact, Hans Jacob was able to demonstrate in 1948 that certain reaction types might vary, either being of the hemorrhagic type or of a completely different type, and this of course in of extreme interest to us when applied to the necrotizing encephalitides. If these different anatomo-clinical manifestations simply represent the manner in which a central nervous system responds to the invasion of a viral agent, it is then understandable that certain morphologic pictures might overlap and represent possibly different basic lesions.

Influenzal encephalitis can be diagnosed clinically in the midst of an epidemic on the basis of its diffuse toxic appearance, (for instance with somnolence, epilepsy, and accompanying pulmonary involvement); acute necrotizing encephalitis is easily recognized by its picture of mental confusion associated with hallucinations, delirium, psychomotor agitation, frequently accompanied by severe focal signs which are most frequently cerebral in origin, and a slower evolution towards terminal coma. It is important to consider this diagnosis in order not to refer patients with these diseases to the neurosurgeon with a diagnosis of abcess as well as to furnish the virologist with cerebrospinal fluid and cerebral tissue for his study. There is no other way in which the discovery of an etiological agent or specific treatment could be hastened.

A subacute sclerosing leucoencephalitis should not be confused with a left-sided temporo-parieto-angular gliomatosis (especially since there might be papilledema present) and here again one should not neglect the opportunity of sending to the virologist the material that might enable him to discover the causal agent.

Unclassified meningo-encephalitides

In addition to these diseases some meningoencephalitides are occasionally seen in the Western European countries which usually appear in small groups or as sporadic cases, which closely resemble the Spring-Summer meningoencephalitides and other types that are recognized in Central Europe. The viral agent is already known in some of those and a serological identification is possible in such cases. These cases usually present very similar clinical characteristics which were delineated in 1956. My personal experience consists of 12 cases that we collected between 1938 and 1952 and two other groups of cases that were observed during the war, one consisting of 22 cases in 1942 in the Stuyvenberg Hospital in Antwerp in the medical service and the other one of 11 cases observed in 1943 in the isolation hospital for Jews in Antwerp under German occupation. As the clinical picture of these diseases has been reported previously, I will only discuss their histopathologic aspect.

With few exceptions, this pathologic picture was deceiving because of the simplicity and apparent lack of severity of

the lesions, by the fact that the lesions were less severe than one would have been led to expect from the clinical picture, and by the absence of systematic topography of their distribution. A large number of these cases had a favourable outcome, provided that the patients had not been previously in poor health.

After 1947-1948 a type of meningoencephalitis appeared in sporadic cases in Belgium which was characterized by a definite "biphasic" evolution. Two of these cases occurred in men who had returned from Bohemia and one in a man returning from the Palatinate, where they had been sent under extremely poor hygienic conditions. A few other cases have been observed in people who never left Belgium but who were very poorly nourished and lived in wooded areas of the Campine. These cases also occurred during the summer. They all recovered without any sequela. Clinically they showed actually no difference with the cases described in Czechoslovakia. Unfortunately, in none of these cases were we able to pursue any virological investigation. It is therefore impossible to come to any conclusion concerning their identity with the arthropod-borne encephalitides described in Eastern Europe.

The differential diagnosis from a preparalytic phase of poliomyelitis was extremely difficult in some of these cases. However, the presence of encephalitic involvement, of pyramidal signs, the acuity of the febrile reaction, the latency time between the two phases of the infection, are arguments that are in favour of a viral etiology of the meningo-encephalitis and against the preparalytic meningeal phase of poliomyelitis. These differencial signs were only relative ones. The high early pleocytosis of over 300 lymphocytes, the rapidity of an initial peripheral leucocytosis were much more interesting, as was the sedimentation rate.

The arthropod- or tickborne encephalitides of Czechoslovakia more closely resemble the Russian spring-summer encephalitides than they do the louping-ill. They were first observed in Bohemia and Moravia and then in the entire country, but more particularly in the region of Roznava. The natural host of the virus are small rodents, the vector is the tick, and the virus is transmitted by the eggs from one generation to the next. Transmission to man and animal is made by tick bite, by swallowing infected ticks, or by ingestion of non-pasteurized goat milk.

The semiology of this particular type of encephalitis has been well described in a review by Henner and Hanzal in 1958 and in a critical study by Pearce Bailey, also in 1958.

It is a disease in which a biphasic evolution is seen in about three-quarters of the cases. The initial period of viremia, which lasts from 4 to 15 days, after a period of incubation varying from 3 days to 3 weeks, is followed by a neurologic phase. The first phase in characterized primarily by systematic manifestations (fever, headaches, digestive difficulties, back, muscle, and joint pains) occasionally associated with hepatosplenomegaly, nasal-pharingeal catarrh, albuminuria, and slight leucocytosis. The spinal fluid remains normal during this period. The second phase usually appears at the end of a few days. It begins with a recrudescence of headache and fever and the appearance of chills, vertigo, diplopia, and occasionally delirium and coma. The mental disturbances consist mainly of confusion with memory disturbance and somnolence; a tremor of the hand and of the chin is frequently seen and these interfere with the gait, speech and drinking. Meningeal, encephalitic, and encephalomyelitic forms have been described on the basis of the symptomatic localization. In the encephalitic form there is in addition to wholly localized hemispheric focal manifestation an involvement of the III, VII and VIII cranial nerves, less frequently and less severe of the IX, X, XI and XII cranial nerves, and also of the supernuclear tracks with paralysis of convergence. Vertigo is very severe as well as extrapyramidal signs with modification of muscle tone and occasional dissociated cerebellar signs.

The encephalomyelitic form includes a frequent involvement of the anterior horns of the cervical spinal cord resulting in a flasque paralysis of the upper limb, especially on the right side, and suggesting a cervicoscapular or cervico-scapulobrachial

localization with a Claude-Bernard-Horner syndrome. When the lower limbs are involved, paralysis is also usually proximal in type. The paralyses are frequently seen early in the course of the disease and are accompanied by subjective signs such as pain and paresthesias. Convalescence lasts between 15 days and one month, and a loss of hair and persistence of psychic and autonomic difficulties frequently disappear rapidly, but atrophy may persist. The disease is particularly dangerous at both extremes of life.

In the Roznava epidemic the lesions were found most frequently in the substancia nigra and in the extrapyramidal centers of the diencephalon and the periventricular areas. The sequelae usually involve the extrapyramidal system. It seems that the typical extrapyramidal form as described in Roznava was mainly the result of infection by the elementary track following ingestion of goat's milk.

The lesions found in the anterior and posterior horns of the bulbar nuclei are almost identical to those seen in poliomyelitis, with the difference, however, that the glionodules, the diffused areas of gliosis, and the perivascular infiltrations were also seen in the olives, the dentate nuclei and the cerebellum.

The basal nuclei were also seen to show diffuse glial infiltrations and perivascular reactions, but they are usually rarer and less severe. Hemorrhagic areas were exceptional. The Czech neurologists were correct in stressing the importance of the lesions of the olives, of the dentate nuclei and of the cerebral cortex as a means of differentiating these infections from poliomyelitis.

An epidemic appeared in 1953 in Styria, which was thoroughly studied and reported by Richling and also by Gringschl. The latter author stressed the fact that Fanconi's specific morbid phase was better defined and more frequently seen in the Austrian viral meningo-encephalitides than in poliomyelitis. He noted also the appearance of a poorly defined first phase in the viral meningo-encephalitis, characterized by fever, anorexia, fatigue, headaches, and lumbar pains, which are quite analogous with what one can usually describe as a grippe. The first phase is more definite in the meningeal forms and also includes digestive troubles or a pharyngeal catarrh.

In the Austrian cases these phenomena disappeared rapidly and fatigue, pains and headaches quickly diminished. The symptomless interval occasionally lasted as long as three weeks but usually did not go beyond 12 days. Following that, the second phase appeared, during which a meningeal reaction with a gliocytosis of the spinal fluid and neurologic signs were noted. The Austrian authors also described rare cases of ascending radiculitis which began in the lower limbs and ended with a respiratory paralysis; cases with a transverse myelitic form; paralytic types, indistinguishable from poliomyelitis, ascending spinal and bulbospinal forms, cranialforms with involvement primarily of nerves III-VII-IX and XII and finally encephalitic forms chracterized by mental confusion, which might be either paranoid or with a great deal of anxiety on an apathetic substratum. The neurologic signs of the encephalitic form included dysarthria, tremor, choreiform movements, and cerebellar signs. Pyramidal signs were not unusual.

This short clinical review serves to emphasize the fact that many of the different types described in the Austrian epidemic are similar to those described in the Czech epidemic as well as those seen in Russian spring-summer encephalitis, where paralyses involved the proximal points of the upper limbs and the shoulders.

Cases with anatomic confirmation of the Austrian epidemic are rare. Gringschl's description includes lesions which are more severe in the cervical spinal cord than in the lumbar cord. These lesions are similar to those seen in certain cases of poliomyelitis, but here again there is also involvement of the posterior horns, of the bulbar nuclei, and of the Purkinjé cells. He saw few isolated cellular lesions in the meso- and the diencephalon and he also described some diffuse and nodular leptomeningeal infiltrations, a few perivascular cuffs, and a few diffuse glionodular reactions. In his most recent report Gringschl mentioned massive cerebellar lesions with almost complete disappearance of the Purkinjé cells in many areas and a glial reaction most frequently in the form of nodules.

SUMMARY

A few general principles can be derived from a general survey of the sporadic or epidemic encephalitides that we see to-day in Werstern Europe:

1. The influenzal viral encephalitides, type A or B, do not differ markedly from the clinical standpoint from those that were described between 1919 and 1950. In most of these cases the pathologic picture is that of hemorrhagic oedematous encephalitis or diffuse lymphocytic encephalitis. In both forms there are occasional cases with glial mobilizations, nodular or diffuse in type. The classic glioperivenous forms are rare.

2. The cases observed during the epidemic of Asian influenza are characterized by histologic lesions which are reminiscent of acute poliomyelitis or of panencephalitis and are difficult to interpret from the etiologic point of view since the question always arises whether they are not caused by a mixture of diseases or by an associated disease.

3. The acute necrotizing encephalitides present a uniform clinical picture, regardless of their etiology. They are present in the same manner, whether they are caused by the herpes simplex virus, the virus of lymphocytic chorio-meningitis, or even in the event that no virus or no indication of other etiology can be obtained.

4. An identical clinical picture is also presented by the subacute sclerosing leucoencephalitides, with or without inclusion bodies, and regardless of the variant type by which they are designated.

5. The arthopod-borne encephalitides with primary cerebral involvement have a uniform clinical and pathological picture. Cases similar to those observed in Czechoslovakia and in Austria have been recorded elsewhere. The bulbar forms are almost impossible to distinguish from acute poliomyelitis. It is probable that certain epidemics or certain series of cases described in Western Europe as "acute poliomyelitis" may belong to this group of arthopodborne viral diseases, the question naturally should be raised for all cases of poliomyelitis where lesions of the olivo-dentate-cerebellar systems are noted. However, here again it is possible that there is an associated complicating viral disease.

6. While the clinical neurologist may attemp to classify the disease on the basis of the clinical picture, the examination of spinal fluid, and the clinical course of the disease, and the pathologist may attempt to do the same on the basis of the histologic alterations that he observes, it is up to the virologist to solve the question of etiologic classification.

Virology will only be able to make progress in this direction if the clinician and the pathologist provide him with the necessary material to work with as early as possible during the course of the disease. Public health all over the world depends upon such team work.

RESUMEN

Algunos principios generales pueden deducirse de una consideración general de las encefalitis esporádicas o epidémicas que vemos hoy en Europa.

1. Las Encefalitis virales de tipo influenza A o B, no difieren en forma neta del punto de vista clínico de aquellas que fueron descritas entre 1919 y 1950. En la mayoría de los casos el cuadro patológico es el de la encefalitis edematosa hemorrágica o encefalitis difusa linfocítica. En ambas formas hay casos ocasionales con movilizaciones gliales, de tipo nodular o difuso, las formas clásicas glioperivenosas son raras.

2. Los casos observados durante la epidemia de influenza asiática están caracterizados por lesiones histológicas que recuerdan a la poliomielitis aguda o a la panencefalitis y son difíciles de interpretar desde el punto de vista etiológico desde que la cuestión siempre se plantea de si ellas son o no causadas por una mezcla de enfermedades o por una enfermedad asociada.

3. La encefalitis necrotizante aguda presenta un cuadro clínico uniforme, cualquiera que sea su etiología. Se presenta en la

misma forma si son causadas por el virus del herpes simplex; el virus de la coriomeningitis linfocitaria; mismo en el caso de que no se obtengan ni virus ni indicación de otra etiología.

4. Un cuadro clínico idéntico es también presentado por la leucoencefalitis esclerosante subaguda, con o sin cuerpos de inclusión y sin tener en cuenta el tipo de variante con el cual ellas son designadas.

5. Las encefalitis producidas por artrópodos con compromiso cerebral primario tienen un cuadro clínico y patológico uniforme.

Casos similares a aquellos observados en Checoeslovaquia y en Austria han sido registrados en otras partes. Las formas bulbares han sido casi imposible de distinguir de la poliomielitis aguda. Es probable que ciertas epidemias o ciertas series de casos descritos en Europa occidental como "poliomielitis aguda" puedan corresponder a este grupo de enfermedades virales originadas por artropodos. La cuestión indudablemente debería plantearse en todos los casos de poliomielitis donde se notan lesiones de los sistemas olivo-dentado-cerebelosos.

No obstante aquí otra vez es posible que exista una enfermedad viral asociada complicante.

6. Mientras el neurólogo clínico puede intentar clasificar la enfermedad sobre la base del cuadro clínico, el examen del líquido céfaloraquídeo y el curso clínico de la enfermedad y el anatomopatólogo puede intentar hacer lo mismo sobre la base de las alteraciones histológicas que él observa, corresponde al virólogo resolver la cuestión de la clasificación etiológica.

La virología podrá solamente hacer progresos en esta dirección si el clínico y el anátomo patólogo le proveen con el material necesario para trabajar lo antes posible durante el curso de la enfermedad. La Salud pública en todo el mundo depende sobre el trabajo realizado en equipo.

RESUME

Quelques principes généraux peuvent se deduire d'une consideration générale des encéphalites sporadiques ou épidemiques que nous voyons aujuord'hui en Europe.

1. Les encéphalites virales du type influenza A ou B ne se differencient pas en forme nette du point de vue clinique de celles que furent décrites entre 1919 et 1950. Dans la plupart des cas le cadre pathologique est celui d el'encéphalite edemateuse hémorragique ou encéphalite diffuse linfocitaire. Dans les deux formes il y a quelques cas avec des mobilisations gliales du type nodulaire ou diffuse.

Les formes clasiques glioperiveneuses sont rares.

2. Les cas observés pendant l'épidemie d'influenza asiatique sont caracterises par des lésions histologiques que rappelent la poliomyèlite aigüe ou à panencefalites et sont difficiles d'interpreter au point de une étiologique.

3. L'encephalites necrosante aigue présente un cadre clinique uniforme, quelque que soit son étiologie. Elles se présentent de la même manière si elles sont causées par le virus du herpes simplex, le virus de la coriomeningitis linfocitaire; de même dans le cas qu'on n'obtiene pas ni virus ni indication d'une autre etiológie.

4. Un cadre clinique identique est aussi présenté par la leucoencéphalite sclerosante subaigue, avec ou sans corps d'inclusion sans tenir compte le type de variante avec lequel elles sont désignées.

5. Les encephalites produites par arthropodes avec des complications cérébrales primaires, ont un cadre clinique et pathologique uniforme.

Des cas semblables à ceux la, observés en Checoslovaquie, en Autriche ont été enrégistrés dans d'autres endroits. Les formes bulbaires ont été presque impossible de distinguer de la poliomyèlite aigües. Il est probable que certaines épidémies ou certaines séries de cas décrits en Europe occidentale comme poliomyèlite aigües peuvent correspondre à ces groupes de maladies

virales occasionées par des arthropodes. La question naturellement doit être posée dans tous les cas de poliomielites où se trouve des lésions des systèmes olivo-dentée cervelleuse.

Cependant il est possible une fois de plus que se trouve associé une maladie virale complicante.

6. Pendant que le neurologist clinique tente de classer la maladie sur la base du cadre clinique l'examen du liquide cefalorachidien et le cours clinique de la maladie. L'anatomo pathologist peut tenter de faire la même chose sur la base des altérations histologiques qu'il observe, il correspond au virologist résoudre la question de la classification étiologique.

La virologie pourra seulement faire des progrés dans cette direction si le clinicien et l'anatomo patologist lui donne le matériel nécessaire pour travailler le plus tôt possible pendant le cours de la maladie. La Santé Publique dans le monde entier dépend du travail réalisé en équipe.

ZUSAMMENFASSUNG

Von dem allgemeinen Ueberblick der sporadischen oder epide mischen Enzephalitiden, wie wir sie heutigentages in Westeuropa beobachten, koennen einige allgemoine Grundtatsachen festgestellt werden.

1. Die influenzaartigen Virusenzephalitiden, Typ A und B, unterscheiden sich nicht verklich vom klinischen Standpunkt aus gesehen von denen, die zwischen 1919 und 1950 beschrieben worden sind. In den meisten dieser Faelle ist das pathologische Bild das einer diffusen lymphozytaeren Enzephalitis. Oder haemorrhagisch oedematoesen Enzephalitis. Beibeiden Formen gibt es gelegentliche Faelle mit Mobilisierung der Glia, in nodulaerer oder diffuser Form. Die klassischen glioperivenoesen Formen sind selten.

2. Die waehrend der asiatischen Influenzaepidemie beobachteten Faelle zeilchnen sich durch histologische Laesionen aus, die an die akute Poliomyelitis oder an die Panenzephalitis erinnern und vom aetiologischen Standpunkt aus schwer zu interpretieren sind, weil immer die Frage entsteht ob sie nicht durch eine Vielheit von Krankheiten oder durch eine beigeordnete Krankheit verursacht worden sind.

3. Die akuten nekrotisierenden Enzephalitiden stellen ein leinheitliches klinisches Bild dar, ohne Ruecksicht auf ihre Aetiologie. Sie praesentieren sich auf die gleiche Weise, ob sie nun durch einen Virus des Herpes simplex oder lymphozytaeren Choriomeningitis verursacht worden sind oder gar wenn kein Virus isoliert werden kann noch eine sonstige Information ueber eine andere Aetiologie besteht.

4. Ein identisches klinisches Bild stellen auch die subakuten sklerosierenden Leukoenzephalitiden, mit oder ohne Einschlusskoerperchen, dar un ohne Ruecksicht au die Variante, durch die sie ihre Benennung erhalten haben.

5. Die durch Arthropoden verursachten Enzephalitiden mit primaerer zerebraler Erkrankung haben ein einheitliches klinisches und pathologisches Bild. Aehnlich wie die in der Tschechoslovakei und Oestreich beobachteten Faelle sind auch anderswo in Erscheinung getreten. Es ist fast unmoeglich, die bulbaeren Formen von der akuten Poliomyelitis zu unterscheiden. Wahrscheinlich gehoeren gewisse Epidemien oder gewisse Serien von in Westeuropa als "akute Poliomyelitis" beschriebene Faelle zu dieser Gruppe von durch Arthropoden verursachten Virurskrankheiten. Die Frage sollte natuerlich immer bei allen Faellen von Poliomyelitis, bei denen man Laesionen des olivo-dentaeren-zerebelloesen Systems bemerkt, gestellt werden. Jedoch ist es auch hier moeglich, dass es sich um eine beigeordnete komplizierende Viruskrankheit handelt.

6. Waehrend der klinische Neurologe versuchen mag, die Krankheit auf Grund des klinischen Bildes, des Examens der Spinalfluessigkeit und des klinischen Verlaufs der Krankheit zu klassifizieren, und der Pathologe versuchen wird, dasselbe auf Grund der histologischen Veraenderungen,

die er beobachtet, zu tun, liegt es am Virologen, die Frage der aetiologischen Klassifizierung zu loesen.

Die Virologie wird nur dann in der Lage sein, in dieser Richtung Fortschritte zu verzeichnen, wenn Kliniker und Pathologe sie mit dem noetigen Material versehen, um so fruehzeitig wie moeglich damit im Verlaufe der Krankheit arbeiten zu koennen. Die Oeffentliche Gesundheit in der ganzen Welt haengt von derartiger Gemeinschaftsarbeit ab.

BIBLIOGRAPHIE

Battaglia S., Guazzi G. C., Macchi G., et Masini T.: "Les encéphalomyélites observées pendant la dernière épidémie grippale". Acta Neurol. Psych. Belgica 59, 2, 123-162, 1959.

Furtado D.: "Encéphalite par grippa asiatique". Rev. Neurol. 98, 192-205, 1958 (litt.).

Haymaker W., Smith M. G., van Bogaert L., et de Chennar C.: "Pathology of viral disease in man characterized by nuclear inclusions with herpes simplex and subacute inclusion encephalitis — dans Viral Encephalitides". Edit. Charles C. Thomas, Springfield Ill. USA 1958, pp. 118-145.

Henner G., et Hanzal F.: "Encéphalite tchécoslovaque à tiques. Tableau clinique, diagnostic et traitement". Revue Neurol. 96, nº 5, 384-408, 1957.

Russell D. S.: "The nosological unity of acute haemorrhagic leucoencephalitis and acute disseminated encephalomyelitis Brain 78 nº 3, 369-376.

Smadel J. E. & Bailey P. & Baker A. B.: "Sequelae in the arthropod-borne encephalitides". Neurology 8, 873-896, 1958.

van Bogaert L.: "Aspects cliniques des méningo-encéphalites actuelles d'origine inconnue mais dites virales en Europe Occidentale". L'Encéphale nº 5, 1267-1293, 1956.

JOHN F. FULTON
(1899-1960)

You in others — this is what you are. Your soul, your immortality, your life in others. And what now? You have always been in others. This will be you — the you that enter the future and becomes a part of it.

BORIS PASTERNAK
(From "Doctor Zhivago")

How can man be measured? What is his true dimension? Physically men differ little one from the other, mentally, who can dare to say how far he reaches?

As the tree expands its branches in the air, man grows in other peoples' souls. His actions and deeds are recorded in others' minds. His influence is felt sometimes as an unwanted, guest, like an invader who disturbs our peace and then man is unhappy because of man. Sometimes his presence in our soul helps to live and stir the best of our mind.

Interwoven with daily events this fact passes unnoticed by most of us. Suddenly a man disappears from our midst, the impact of death evokes a reaction. Like the sun in the twilight before going into the shadows brightens the skies

with its best colours, a man's departure from life brings to light all of his goodness still dwelling in the memory of his fellows.

A pattern can be drawn. How far has he reached in the pursuit of knowledge? How deep has he etched in others' sensibilities his deeds? How many has he helped to climb up the painful road to perfection?

And that will give us the man's true dimension.

Time and again, throughout the centuries of human experiences, this final judgment is made of man by his fellows man.

When the announcement, that Prof. Fulton had left life's stage deeply saddened his numerous friends, we proposed to create a Fulton Society to maintain his ideals alive in scientific circles, and to build a bond of cooperation among those who had worked with him and enjoyed his warm friendship.

Mary Wheeler, as a "Labor of Love" so she states, took the task to search and to provide us with a long list of his former Staff Members and Collaborators.

To as far as India, Italy, Brasil, Belgium, England, France, Spain, Canada, Australia, China, Russia, Holland, Sweden, Norway, Turkey, Mexico, and all throughout the United States, invitations were sent to join thes Society.

What a rewarding experience to open the answer: Physiologists, neurologists, neurosurgeons, psychiatrists, psycologists, historians, sent words of warm remembrance toward the teacher, friend and for many of them a source of inspiration that was John Fulton.

Being not possible to reproduce all of them we just extract a few sentences in which the fascinating personality of John F. Fulton will be reflected as in a mirror.

"All of us who had the previlege of working in his laboratory will carry with us for all of our lives his influence, not only in Science, but in the Humanities".

Francis M. Forster M. D.
Chairman Dept. of Neurology.
University of Wisconsin.

"...and the one thing that I should like to point out at this time is that I felt John Fulton imparted something of himself to each and everyone of us and thus his spirit lives on. While the spirit may never be lost among our generation, I like the idea of a Fulton Society because it will help to preserve this great man's spirit among succeding generations".

L. M. Davey (Neurosurgeon).
New Haven Conn. U.S.A.

"He was one of the most striking and impresive and stimulating personalities *that I have ever met in my life".*

Pietro de Franciscis
(Physiologist) Naple Italy.

"I am very much in favor of creating a Fulton Society and I would be extremely happy to have my name included among the long list of members of this new Society, I spent some of the best days of my life in Fulton's laboratory".

Birger Kaada.
Anatomical Institute University of Oslo.
Oslo.

"The year I spent in the Physiology Lab. at Yale under Dr. Fulton will remain one of the highlights of my life. I shall be most happy to do anything to perpetuate his memory and the spirit with which he conducted his life".

C. G. Drake M. D.
London-Canada.

"I shall consider it the greatest honor to be enrolled among the membership of the Fulton Society, and to share with his friends the bonds of amity which he did so much to foster".

Hubert R. Catchpole.
University of Illinois. U.S.A.

"This is certainly a wonderful and inspiring tribute to a man, who has devoted his entire life to science. I fell honored that I was able to work with him. I assure you he was a great inspiration to me, and also a very personal friend".

Joseph A. Epstein M. D. F.A.C.S.
Hempstead Medical Center
Hempstead, L. I. New York.

"The thought of creating a Fulton Society was a most pleasing one and I am sure that all those who had the privilege of working with John at one time or another during his career will be happy thus to signalize the pleasure it was to be with him".

Joseph P. Evans M. D.
Neurosurgeon
University of Chicago.

"I find it a wonderful idea to create a society bearing the name of Dr. Fulton, with whom I was connected in esteem and friendship for more than 20 years".

Bruno Kisch M. D.
New York.

"I have always had a deep affection for Dr. Fulton and will be glad to join any venture that will do him honor".

Morris Kessler M. D.
Cleveland.
Ohio.

"This evokes a favorable response in me, and I shall be glad to cooperate in the plan to preserve J F F's name and ideals, particulary his unique spirit of enthusiasm and friendliness".

Edwin A. Weinsten M. D.
Neuropsychiatry Division.
Washington D. C.

"John Fulton's death deprived us all of a gay, gallant, generous friend. I personally miss him very much, for he was always interested in one so much and quickened one's own zest for living. He more than anyone I knew took pleasure from success of friends and he had a boyish delight in announcing any new honor that came to him. Now it remains with us who knew and loved him to keep his memory green and your suggestion that a Fulton Society be created to aid in that purpose is an attractive one and I'm most grateful for your invitation to join with you and others in its establishment".

Donald H. Barron.
Department of Physiology.
Yale University
New Haven - Conn.

"With him and his wife and at his laboratory I have had the priviledge to spend such a happy time and I am grateful that you have thought of my name in connection with the proposition of a Fulton Society".

Barbro Hydén.
Histologiska Institutionen
Universitetet I Göteborg Göteborg C.

"He did a great deal for me during the two years I worked with him".

Donald Sheehan M. D. Chairman
Department of Anatomy
New York University School of Medicine
New York.

"Although Professor Fulton will always live in everyone of us both as the great and inspiring scientist and the unusually warm, altruistic and enthusiastic human being foundation of the Society in his name, with the purpose you have in mind, would, I feel sure, meet with Professor Fulton's whole hearted approval".

Walter S. Boernstein.
Research Center for Mental Health.
New York University.
New York.

"I therefore join the Fulton Society with the greatest enthusiasm because of my gratitude to John Fulton. Although I am a clinical neurosurgeon, I had the privilege of spending a year in his laboratory as a Rockefeller Research Fellow".

James B. Cambell M. D.
Neurological Surgery.
Columbia-Presbyterian Medical Cen'er.
New York.

"I have the most pleassant memories of the time I worked in Fulton's laboratory, and it has been of much use to me in my later activities".

W. J. C. Vehaart.
Rukinisersiteit Leiden.
Wassenaarseweg.
Holland.

"I noticed at the last Congress in Buenos Aires, that in spite of his apparent ill health, he still radiated the same charm, friendliness and sincerity to all those around him. For years in my lectures, I have often mentioned his work and of his personality to my students and colleagues in Turkey. I would also like to add that, from now on. I will consider all members of the future Fulton Society among my very best friends, who are united in memory of a person whom I have esteemed very highly and who has been a constant source of inspiration to me in my academic life".

Meliha Terzioglu.
Professor of Physiology.
University of Istanbul.

"We have all been sick at heart from this loss, and I am grateful of the thoughts that a bond of friendship can be preserved among those of us who were his friends and students".

John F. Marchand M. D.
New York.

"An International Society such as you suggest seems to me to be particularly appropiate not only because the people with whom Fulton worked are in so many places over the world, but because he was truly an Internationalist at heart".

H. Enger Rosvold.
Chief Section of Animal Behavior
Nat'l Institute of Mental Health.
Bethesda - Maryland.

"I shall be glad to join the Fulton Society and help to perpetuate the memory of one of "the greats" in Physiology and Medical Bibliography. I knew John in Oxford and Harvard and taught under him at Yale at 1931-34 I miss him greatly".

John Fergusson.
Prof. of Physiology.
University of North Carolina.

"Naturally I think it is most fitting that you should seek to honor the name of John Fulton and to keep it alive in scientific circles, and I should be most happy to have you include my name as a member of the Fulton Society".

Paul C. Bucy, M. D.
Professor of Neurosurgery
Northwestern University Medical School
Chicago.

"Many thanks for your letter and your invitation to join the newly created Fulton Society. I think this is a wonderful idea and I will be proud and happy to be a member of this Society. I have been very attached to John Fulton and considered him as one of my most faithful and best friends".

David Nachmansohn, M. D.
Professor of Biochemistry.
Columbia University.

"Man is above all a leader charged with survival of the «values which are in his keeping»" says Sir Charles Sherrington, and adds "With the «values» his leadership must be some form of fellowship. The pivot of fellowship is altruism".

This generous soul who has also expressed "The loveliest friend of man is man", was a fitting leader for young John Fulton, near him he learned to experiment and watch nature disclose her misteries.

Sherrington's taste for letters, art, history of medicine and rare old books deepened John Fulton's early interest in these subjects, and in many instances Sherrington gave to this brilliant American student many bibliographical trophies of his own collection.

Testimony of the beneficial effect of being under the utmost authority in physiology of the nervous system were the number of papers he wrote during his stay in England.

Cushing was, along with Sherrington, the main source of inspiration for further activity. This noted neurosurgeon was of prime importance in his life. As the years passed Fulton was going to build in his honour a rotonda in one of the most important historical libraries of the world, containing Cushing's library, Kleb's and his own.

Besides he wrote a highly praised biography about his friend and mentor, the father of neurosurgery.

John F. Fulton's boundless energy, the creative force of his active mind, were the appropriate crucible to intermingle the messages that these two outstanding lives gave to him.

The "values" that Sherrington refers to, found an original response in his bright intellect. Sherrington, and Cushing were fused in Fulton. And neurosurgery entered the neuro physiological laboratory. This, along with the passionate love for books that both masters of medicine professed, was going to flourish in many ways.

From a long time, clinician and research man considered themselves belonging to quite different discipline, and their activities circumscribed to their special field.

Bringing to the research laboratory the techniques of neurosurgery, Fulton was the first to introduce primates becauses of his similarity with man in his performing of his investigations. Operations on the animals were performed under the identical conditions as if they were human patients. The same operating room, the same care during and after the operation and the same chart record.

The protocols of the Yale Lab. were a source of inspiration for every new comer that arrived there.

Many branches of medicine were going to receive the fruits of his inspiring leadership.

Psychology received great benefits due to the research performed on chimpanzees, and his investigation associated with Jacobsen gave the clues and means by which Psychiatry initiated a chapter of surgical treatment, a wohle new branch.

Neurology owes to him the complete revision of the Pyramidal Syndrome, and it proved of immediate value to Neurosurgery, supplying the data that it was possible to stop in monkeys an abnormal movement by the ablation of the motor cortex. Many studies were performed on the basis of Dr. Fulton's work on this subject.

By means of stimulation and ablation of the cortex, its influence was established upon the autonomic system and this gave experimental and physiological fundamentals to the Psychosomatic Medicine.

Great indeed has been the impact of Dr. Fulton's achievements in the Neurological Sciences. In many instances like in prefrontal lobotomy his studies culminated in the opening of a new road to investigation. Others, he revised well known problems like those of Piramidal Symdrome, and so theoretical speculation, gave way to experimental physiological proofs by which many specialties were benefited.

From his laboratory, papers have come that always interested both neurophysiologists, and clinicians.

Being a physiologist he was at home at Neurology and Neurosurgery meetings to the point that sometimes he was named by the clinicians to organize some meetings in which he was particurlaly interested, it was a task that he always took upon his shoulder with his characteristic enthusiasm and organizing hability.

But if you happen to go a meeting of the History of Medicine or of Neurophysiology or of Neurology or of Neurosurgery, you could be sure that John Fulton would be one of the highlights and be greeted with warm affection by everyone there.

Dr. Fulton has exercised a fundamental influence in the last decades upon the clinicians and surgeons of the nervous system, making them to give preferential attention in their training to neurophysiological studies and his laboratory methods.

What was the magic formula by which Dr. Fulton conquered in everyone of his fellows an everlasting friend?

The brilliant student that won the highest laurels in his field, the outstanding investigator that made many important contributions to science, and the gifted author of widely known books had a warm and understanding human heart.

His home for many of us was a place of joy and relaxation. At Chrismas an illuminated angel showed the way to John Fulton's home. Who was the foreigner that far from home will not admit the elating experience it was meeting Mrs. Fulton with her smiling friendly face at the door step of her house at Mill Rock? This gracious lady along with her husband instantly won everybody's affection.

The young scientist struggling to get started, the fellow who needed support for his studies, the old research man bittered by misunderstanding and pressed by the anguish of daily living, found a friendly ear for their troubles, and everyone had their problems resolved one way or another.

No matter how he hid these deeds, all his good actions leaked out somehow.

No matter how far a man has reached in knowledge, how many distinctions

or decorations he has received from different countries, good actions and a place in the heart of his fellow man will remain his best harvest.

He didn't spare any effort to reach the human core of the people of another lands. This anecdote will illustrate this fact.

In 1953 we went to London to attend the meeting on World Education.

Dr. Fulton was also in London, and invited us to his hotel. After dinner he expressed his wishes that we hear a paper he was going to read in spanish at a homage to Cajal in Madrid.

He lead us to his room, and after hearing him strugle with our language, we searched desperately for a solution, when our eyes discovered in a corner of the room the companion of his voyages, a dictaphone.

We proposed to him that I dictate the speech in his machine and in this way he could hear it as many times as he wanted in order to improve his pronunciation.

His eyes brighten at the idea. Inmediatly he fixed everything and we read it the speech with our clearest vocalization.

A few days after, I had a telphone call. In the other end of the line Dr. Fulton was asking us if we could possible go to his hotel to dictate the speech again , because the record was orn out.

Dr. Fulton's tremendous energy and zest for living easily overcame and surpassed his physical handicap. The initial sentences of his Chritsmas letter of 1959 reveals how much he loved life and activity.

"The year 1959 started with fresh energy, a healed myocardium and new zest for work, year most rewarding on many counts: books gathered in six countries, travel and congresses, and many new developments inthe Library Department".

At nearly the end of the letter "I cant possibly tell you how much this trip has meant to me spiritually and otherwise, for it proves that I am able to circulate once again in the wide world. Fresh contacts are proving infinitely valuable professionally, especially since I was able to meet a number of young and lively minds proposing to go into the history of medicine and science on a full time basis".

Physician, Neurophisiologist, Historian, Man of letters, Dr. Fulton has lived in one many lives, and even though he reached only his sixtieth year we can affirm along with Leonardo da Vinci "A life well spend is always a long life".

VICTOR SORIANO

• News

FEDERAL GRANT TO AID TAY-SACHS' DISEASE RESEARCH

Isaac Albert Research Institute Receives U$S 153,890 In Federal Funds.

A five-year grant in the amount of U$S 153,890 has been made by the National Institutes of Health to Drs. Bruno W. Volk, director, and Sydney S. Lazarus, assistant director, Isaac Albert Research Institute of the Jewish Chronic Disease Hospital, Brooklyn, N. Y. The grant is being made for studies into Tay-Sachs' disease and allied fatal degenerative diseases of the nervous system occuring in infancy and childhood. Specifically, the study is on "enzymatic histochemistry of the central nervous system of the sphingolipidoses".

At the present time the institute is conducting a full-time laboratory research project on the Tay-Sachs group of diseases which has been supported since 1958 by the National Tay-Sachs Association. In conjuction with the laboratory project, the association sponsors a 17-bed special pediatric ward at the hospital for the care and study of afflicted infants and children.

Though each disease in the Tay-Sachs group has its own set of symptoms, they are all, basically, genetic metabolic disorders of the central nervous system affecting infants and children. They are all invariably fatal. The 16 diseases in the group are: Infantile Tay-Sachs' disease; Schilder's disease; Balo's disease; Krabbe's disease; Polizaeus-Merzbacher disease; Infantile Gaucher's disease; Hurler's disease; Amyotonia Congenita; Alper's disease; Heller's Dementia; Friedrich's Ataxia; Hereditary Myoclonic Epilepsies; Dystonia Musculorum; Wilson's disease; and Arthrogryposis.

Most of the diseases in the Tay-Sachs group have been known to the medical world for many years — Tay-Sachs' disease was originally identified by Dr. Warren Tay, an English ophthalmologist, in 1881; its nature was first described in detail in 1887 by Dr. Bernard Sachs of New York, a leader in American neurology. It has only been in recent years that effective techniques and equipment for the investigation of these diseases have been developed. The increased activity in medical research into biochemical disorders of the human body, particularly in the chemistry of the nervous system, and the field of genetics has given added emphasis to the program originally begun by the Isaac Albert Research Institute, and aided by the National Tay-Sachs Association.

The federal grant comes at an auspicious time, as final plans for an international Symposium on The Sphingolipidoses are being completed by the three co-sponsoring organizations: Isaac Albert Research Institute of the Jewish Chronic Disease Hospital, Brooklyn, N. Y.; State University of New York, Downstate Medical Center, Brooklyn, N. Y.; and National Tay-Sachs Association, New York. N. Y. Representatives from leading universities and research centers in the United States and Western Europe will be meeting March 29-30, 1961, to discuss their mutual efforts into the investigation of the Tay-Sachs group of fatal diseases.

COURSE IN ELECTROENCEPHALOGRAPHY

Preceding the International Congress of Electroencephalography in Rome an advanced course in electroencephalography will be given in Marseille, August 28-September 2, 1961 under the auspices of the International Federation of Societies for Electroencephalography and Clinical Neurophysiology and the Council for International Organizations of Medical Sciences.

This course is intented primarily for experienced electroencephalographers, particularly for those responsible for training others in the field. Electroencephalographers who have completed their training and who already have had some experience in clinical electroencephalography will also be welcome, as will be experienced technicians. The course is not intented to be a short training course for those who are not familiar with the basic principles and practice of electroencephalography.

Three main topies will be considered: I. Principles underlying methods of recording and interpretation of electroencephalograms. II. Pathophysiological significance of various phenomena observed in electroencephalograms. III. Borderlines of normality in electroencephalography.

The course will be opened by the 3 distinguished officiers of the International Federation who are Doctor honoris causa of the University of Aix-Marseille: Prof. F. Bremer, Prof. H. Jasper and Dr. W. Grey Walter. They will be joined by the Dean, Prof. G. Morin, and by Prof. H. Gastaut.

Each day 3 lectures will be given, followed by discussions. The afternoon session will be devoted to interpretation of electroence-

phalograms by panels of experienced electroencephalographers. In view of the season, afternoon session will end at about 3:30 P.M. Thursday afternoon will be reserved for an excursion.

Admission fee will be U$S 25.00 (technicians U$S 10.00). Participants will receive a certificate from the International Federation testifying that they have attended the course.

Applications should be addressed to: Dr. O. Magnus, St. Ursula Clinic, Wassenaar, Holland.

CONGRESS OF NEUROLOGICAL SURGEONS

The Survey Commitee of the Congress of Neurological Surgeons continues to maintain a Placement Service in order to facilitate the discovery of available positions by those residents who are seeking an association. The Commitee maintains two listings, one furnishing the names of those men who are offering a position, and another listing those physicians who are looking for an association. This service has been of special value to men completing their training; however, numerous associations have also been formed by other men who have been in practice for some period of time.

The listing themselves are revised frequently and are sent on request to any neurosurgeon in practice, or to those individuals who have completed residency training, or have started their final year of neurosurgical residency. Contact between individual neurological surgeons may, therefore, be initiated either by those seeking the position, or by the man offering the association. The Survey Committee does not participate in individual contacts and arrangements, and cannot be responsible for unsatisfactory placements. No charge is made for this service. All inquiries should be directed to the Chairman of the Survey Committee, Dr. Karl L. Manders, 3400 N. Meridian Street, Indianapolis 7, Indiana.

• Book Reviews

"Atrofia Cerebral y Demencia" por A. Delmar, A. Mosovich y E. A. Pedace. 166 páginas. 60 ilustraciones. Editorial Atlas. - Buenos Aires.

Esta es una monografía muy bien realizada por los distinguidos neurólogos argentinos. Abarca en forma completa todos los aspectos del problema involucrado en el título.

Estudian en distintos capítulos: Factores etiológicos; Anatomía patológica; Fisiopatología cerebral en relación con la atrofia; Sintomatología; Síntomas focales; Formas clínicas; Diagnóstico positivo; Diagnóstico diferencial y Tratamiento.

Los autores expresan que entre los tres tipos de atrofia que determinan la demencia senil y las demencias preseniles, la enfermedad de Pick ofrece una mayor perspectiva para la investigación del problema en su totalidad.

Definen su posición frente a estos procesos en esta forma: "...se trata de una entidad anatomo clínica diferenciada con un síndrome neuropsíquico progresivo y complejo que puede alternar con transtornos focales y cuya causa es la atrofia cerebral simétrica de las distintas regiones corticales que lesiona electivamente las capas receptoras y las vías de asociación".

Además de resumir experiencia de otros autores presentan 17 observaciones con estudio clínico y anatómico (biopsias y autopsias de casi todos los casos), algunos de ellos con neumoencefalografía y electroencefalografía.

Describen un nuevo capítulo donde el proceso atrófico se estudia a través del daño de las vías asociativas y de su repercusión fisiopatológica cerebral.

La presentación del libro es muy buena. Es una obra sumamente útil para neurólogos psiquiatras y patólogos en la cual en forma clara y concisa está tratado con brillantez este importante tema.