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CONTENTS OF VOL. 9 — NUMBER 1

EDITORIAL — Español	7
EDITORIAL — English	9
TREATMENT OF HEADACHE	11
Arnold P. Friedman.	
MODALITES DE LA THERAPEUTIQUE DU SYNDROME PARKINSONIEN PAR LA L-DOPA	23
G. Yanniotis, J. J. Eisenring, G. Gauthier, R. Tissot, J. de Ajuriaguerra.	
TREATMENT OF CEREBROVASCULAR DISORDERS	33
Arthur C. Klassen.	
TREATMENT OF PERIODIC DISTURBANCE OF CONSCIOUSNESS IN THE SPECIFIC TYPE OF HEPATOCEREBRAL DEGENERATION (INOSE TYPE) A TRIAL WITH GOBAB	43
Takeo Takahashi, Takashi Miyakoshi and Toyoji Wada.	
TREATMENT OF NEUROMUSCULAR DISORDERS	54
Eijiro Satoyoshi and Masao Kinoshita.	
LA MALADIE DES SPASMES EN FLEXION DE LA PREMIERE ENFANCE A SYMPTOMATOLOGIE TYPIQUE ET ATYPIQUE ET SON TRAITEMENT	61
L. Sorel et M. Rucquoy-Ponsar.	
THE CLASSIFICATION AND CONDITIONING TREATMENT OF THE REFLEX EPILEPSIES	73
Francis M. Forster.	
PROF. RAYMOND GARCIN	87
BOOK REVIEWS	90
NEWS	91

Editorial

En la clínica neurológica en las múltiples circunstancias en que se engendran sus cuadros mórbidos, si intentamos una visión panorámica de los tratamientos médicos actualmente vigentes, seremos impresionados por los positivos y espectaculares adelantos logrados en los últimos años.

Con el advenimiento de los antibióticos y otras sustancias útiles en la contienda antibacteriana, se cuenta con recursos terapéuticos decisivos en la lucha contra las infecciones del sistema nervioso central, de sus vasos y envolturas.

En las afecciones vasculares constituyen un arsenal terapéutico los vasodilatadores, los agentes fibrinolíticos, los anticoagulantes, que imponen la necesidad de un criterio para su uso y oportunidad.

En el amplio campo de las perturbaciones metabólicas reconocidas, se han hecho ingentes progresos. En la enfermedad de Wilson donde se debe favorecer la eliminación del cobre se cuenta ahora con la Penicilamina o dimetilcisteína que es un agente sumamente eficaz por cuanto asegura una remoción progresiva del metal en exceso.

Las encefalopatías pancreáticas, que aparecen después de intervenciones quirúrgicas por pancreatitis agudas, cuyas lesiones asientan particularmente en el tronco cerebral, cerebelo, y tálamo, y su síntoma esencial es la amilasemia, se tratan con inhibidores de enzima de origen pancreático o parotídeo.

Los epilépticos tratados pueden presentar una anemia megaloblástica. Su diagnóstico exige a veces una punción de médula ósea. Se cura con ácido fólico y de este modo se mejora también la bradipsiquia y la apatía que se suele ver en el epiléptico medicado.

Hiperbaria en las enfermedades neurológicas. Este recurso es señalado sobre todo en accidentes vasculares cerebrales, edema cerebral, anoxia cerebral, accidentes de decompresión, embolias gaseosas, intoxicaciones con C O.

La esclerosis múltiple, pone en evidencia en el líquido cefalorraquídeo un aumento de las gamas globulinas en relación con un acrecentamiento de los linfocitos; la cual está vinculada a un proceso inmunológico, que estaría condicionado a una infección viral (virus lento) contraída en la infancia o la adolescencia y que años más tarde daría lugar a los signos clínicos de la esclerosis múltiple. En el tratamiento de esta afección tienen ahora amplia vigencia el ACTH, los corticoides, el suero antilinfocitario y los antimetabólicos.

El ACTH se emplea preferentemente en perfusiones intravenosas, una diaria de 25 a 30 unidades en 250 cm³ de suero glucosado isotónico, se hacen curas de 15 a 20 perfusiones. Según la evolución de la enfermedad pueden repetirse. Los corticoides se emplean en dosis progresivas, la dosis máxima es de 30 a 40 mg. por día que se puede mantener de 1 a 2 meses. Después progresivamente se eleva a 10 o 15 mg. por día y se continúa así durante 5 o 6 meses.

Una vez por semana después cada quince días, el ACTH por vía intramuscular permitirá la prosecución de la corticoterapia.

El suero antilinfocitario (globulinas antilinfocitarias) puede ser empleado en la esclerosis múltiple severa, de evolución muy desfavorable.

Los antimitóticos más empleados son el Endoxan, de 100 a 200 mg. por día, no pasar en el tratamiento en total los 4 a 8 gr. Se usa también el Imuran. Estas sustancias tienen como fin bloquear el proceso inmunitario.

La encefalitis herpética, se presenta con signos de meningo encefalitis, epilepsia, trastornos de la conciencia, síntomas de lóbulo temporal, alucinaciones auditivas y olfatorias, trastornos de la memoria de tipo Korsakoff, etc.

El líquido céfalo raquídeo señala un aumento de la gama globulina. El tratamiento que resulta efectivo empleado temprano es idoxiridina.

Una conquista resonante en la terapéutica neurológica es sin lugar a dudas la que se ha logrado en el parkinsonismo con las nuevas drogas, que brindan al clínico optimismo aún para aquellas enfermedades de prolongada y progresiva evolución cuyas lesiones anatómicas parecen incompatibles con una apreciable recuperación funcional.

Muy complacidos damos la bienvenida a nuestro Consejo Consultivo a un distinguido neurólogo reputado en el mundo entero, el Prof. Dr. Paul Castaigne, de París, quien brindará su asesoramiento a esta publicación en los tópicos de su especialidad..

Deseamos agradecer al grupo brillante de autores quienes colaboran en este número que será sin duda, altamente apreciado por sus lectores.

VICTOR SORIANO

Editorial

Casting a panoramic look on the medical treatments presently employed in the numerous circumstances that clinical Neurology offers in the multiplicity of its morbid pictures, we would feel highly impressed by the positive and spectacular advances achieved in the last decades.

With the arrival of antibiotics and other substances useful in the struggle against bacteriums, it was possible to count with therapeutic resources of prime importance in dealing with infectious diseases of the central nervous system, and of its vessels and meninges.

Concerning to vascular diseases, we can mention as therapeutic weapons, the vasodilating and fibronilific agents and the anticoagulants. They demand careful judgement in their use and opportunity.

In the large field of the metabolic disturbances already known, great progresses has been obtained. In the Wilson disease where must be facilitated the cooper elimination, we can count with the aid of the Penicilamine or dimetil-citéine, which is a very effective agent because it assures a progresive removal of the metal in excess.

The pancreatic encephalopathy, that appears after the surgical procedure due to acute pancreatitis, whose lesions are particularly stressed in the brain stem, cerebellum and thalamus, and its essential symptom is the amylasemia; is treated with enzymatic inhibitors of pancreatic or parotidic origin.

The epileptic patient treated with Dilantin may show a megaloblastic anemia. Its diagnosis sometimes exiges a punction of the bone marrow. It can be cured with folic acid an thus is obtained also an improvement of the bradypsyché and the apathy which can be also seen in the epileptic under this treatment.

Hyperbaria in neurological diseases. This method is aplied with success in vascular strokes, brain edema, cerebral anoxia, accident by decompression, air embolism, and intoxication with C O

In multiple sclerosis, is evident that in the spinal fluid exists an increase of the gamma globulines related to an increase of the lynfocytes, which it is linked to an immunologic process, that may be conditionned to an infection (slow virus) adquired during the infancy or adolescence and that in years later would produce the multiple sclerosis's clinical symptomatology.

The ACTH is employed preferently in intravenous perfussion, one dayly of 25 to 50 units on 250 cm³ of isotonic glucosed serum, the treatment involves 15 to 20 perfussions. According to the illness's evolution they can be repeated.

The corticoids are employed in progressive dosis, being the maximun of 30 to 40 mgr. per day and it is continued during for 2 months. Progressively later can be attained 10 to 15 mgrs. a day during fice or six months.

Once a week, after every fifteen days, the ACTH by intramuscular way will allow the prosecution of the corticotherapy.

The antilymphocytarium serum may be used in multiple sclerosis severe.

The antimytotic more employed is the Endoxan, 100 to 200 mgr. per day avoiding to give during the treatment more than 4 to 5 grs. Imuran is also employed.

These substances have aim at blocking the immunitary process.

The herpetic encephalitis shows signs of meningoencephalitis, epilepsy, consciousness disturbances, tempora lobe symptomatology, auditive and olfactive allucinations memory impairment of the Korsakoww's type, etc.

The spinal fluid shows increased gamma globulins. The more efective treatment employed early is idoxiridine.

A remarkable conquest in neurological therapy is, there is no doubt, the one obtained with the new drugs in Parkinson Disease, that gave to the clinician an optimistic outlook even in he case of prolonged illness of progressive evolution whose anatomical lesions seems to make impossible an important functional recovery.

We are very glad to welcome in our Advisory Board one of the most distinguished neurologists of a worldwide reputation Prof. Dr. Paul Castaigne of París, who will enrich our Journal with his kind advise in topics of our speciality.

We want to thank the brilliant host of authors who collaborate in this issue which we have no doubt will be highly appreciated by our readers.

VICTOR SORIANO

Treatment of Headache

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Every sentient being knows what is meant by pain but the true significance of pain eludes the most sapient. For philosophers, pain is a problem of metaphysics, and exercise for stoics; for mystics it is an ecstasy, for the religious, a travail meekly to be borne, for clinicians a symptom to be understood and an ill to be relieved.

Charles F. W. Illingworth.

The current treatment of headache is in part empiric and in part based on our knowledge of the underlying mechanism that produces the symptoms. Common to all problems of treatment, diagnosis is the first step in management. Headache as a troublesome complaint in the course of an already recognized disease poses no problem in management. In the study and care of patients with headache, the physician needs more than routine skill and interest. He must carefully evaluate what the patient reports, treat rationally, and never lose sight of the person behind the disease.

The whole patient not the symptom is the single most important factor in the treatment of headache. Next in importance is awareness that psychophysiological disorders may have both periods of remission and of greatly increased activity and may respond to a variety of treatment for short periods of time. The evidence lies in the often efficacious effect of placebo therapy and the success of a physician in whom the patient has confidence.

The success of the pharmacologic treatment of headache will be determined within the framework of the functional

and structural changes present in the patient; the psychology of the patient's personality; the nature of his environmental stresses and the course of the patient-physician relationship.

VASCULAR HEADACHES

The term "vascular headache" is comprehensive and includes two main categories: (1) migraine and (2) the nonmigrainous vascular headaches. The latter include headache associated with hypertension, infection and inflammation, disorders of body chemistry and metabolism, and reactions to chemical agents and foods. Our discussion will be confined mainly to the management of migraine and several specific types of nonmigrainous vascular headache.

In general, the treatment of migraine as in most headache syndromes is treatment of an attack of headache and prophylaxis. The objectives are to diminish the intensity of the headache and to shorten its duration. In addition, prophylaxis intends to decrease headache frequency.

MANAGEMENT OF THE ATTACK

The treatment of an attack of migraine is similar whether the type is classic, common, or cluster migraine. The most effective chemical agent in the management of the migraine attack is ergotamine tartrate (Gynergen). Although oral administration of ergonovine maleate (Ergotrate) and methylergonovine (Methergine) provides more reliable absorption, they have not been as effective in our hands as ergotamine tartrate.

This derivative of ergot is important both in the pharmacologic clarification of the mechanism of the migraine attack and as a diagnostic test. Ergotamine tartrate has neither a sedative nor an analgesic effect, and it does not relieve other types of head pain. The beneficial effect of ergotamine administration on migraine attacks is probably related to its vasoconstrictive action on the smooth muscles of the cranial blood vessels⁶. This peripheral vasoconstriction is as effective in patients with sympathectomized extracranial arteries as in those with intact arteries. The agent's ability to decrease the amplitude of pulsations of the cranial arteries is paralleled by the diminishing headache, as demonstrated by recording the extracranial pulse waves in patients with vascular headaches. Ergotamine can be given by inhalation, sublingually, orally, rectally, or parenterally.

Ergotamine derivatives, in various combinations with caffeine, antispasmodics, sedatives, and antiemetics, have been introduced for the treatment of migraine. Caffeine acts synergistically with the ergot alkaloids; since it also constricts the cerebral blood vessels and reduces blood flow⁵, it may reduce the total dosage of ergotamine needed. In our experience, combinations of ergotamine, caffeine, sedative, anti-nauseant, or antispasmodic have been the most effective. The rectal route has proved empirically to be most efficacious, especially when vomiting prevents retention of oral medication. The importance of administering adequate doses of medication early in the course of an attack cannot be overemphasized. Errors in therapy result

from improper use of the drug and range from inadequate dosage to recklessness in administration as well as failure to prevent undue side effects such as vomiting.

In certain patients, the taking of ergotamine becomes a daily ritual which may persist for many years. We have observed a number of patients who have taken ergotamine tartrate in daily dosages of 2 to 2 mg. for 15 to 20 years. They complain of daily headaches, and in some instances, they have had to increase their daily dosage to secure relief from attacks. It has been suggested that the drug relieves the headache for which it is administered and, at the same time, alters the physiologic state of the blood vessels, this produces a rebound reaction of constriction, followed by dilatation and headache.

Ergotamine dependency, accompanied by withdrawal manifestations, may also occur in patients who use the drug daily, usually with increasing dosage, for long periods of time. Recognition of this type of patient is essential. The symptoms are often greater frequency of headache, loss of feeling of well-being, fatigue, and depression. These patients report the occurrence of headache without the medication, but a careful investigation reveals that the use of ergotamine bears little relation to the relief of their headache. Most of these patients wear the mask of migraine but suffer from an underlying depression. The question arises whether the excessive use of ergotamine, which has a significant effect on the central nervous system, contributes to their depression. Withdrawal of the drug and management of the underlying depression form the basis of treatment.

Although certain persons may take ergotamine tartrate excessively without apparent harm, untoward effects associated with the use of ergot preparations do occur: they include nausea, vomiting, epigastric discomfort, leg cramps, transient tachycardia or bradycardia, and localized edema. Severe vasoconstriction, endarteritis or even gangrene may result from long term use of this agent or its derivatives. Discontinuing the drug usually causes all these reactions to disappear. Since all ergot

preparations have oxytatic properties, their use should be avoided during pregnancy. Their use is also contraindicated with peripheral vascular disease, severe hypertension, thrombophlebitis, peptic ulcer, renal disease, liver disease, and sepsis.

Other vasoconstrictive agents, such as ergonovine maleate, caffeine, amphetamine, ephedrine, vasopressin, cortisone, and ACTH alleviate the headache only in those patients in whom the amplitude of the arterial pulse wave is decreased by 40 to 50 per cent, i. e., the same as that produced by ergotamine tartrate⁹. Of the agents studied thus far, ergotamine tartrate has had the most constant and lasting effect on the migraine attack.

In an occasional patient, inhalation of 100 per cent oxygen relieves an acute attack. The cerebral blood flow is reduced after inhalation of oxygen, and this may be the basis for the relief obtained by inhaling oxygen.

In the late stages of the migraine attack, analgesics combined with sedatives or tranquilizers may be helpful, particularly if the headache has persisted long enough for the blood vessels to become firm and tortuous or when a muscle-contraction headache occurs.

Attempts to interrupt the migraine attack in the prodromal state (cerebral anoxia stage) by administration of intracranial vasodilating agents, such as the nitrites, or inhalation or 10 per cent carbon dioxide in oxygen, have seldom proved effective.

PROPHYLAXIS

Any appraisal of chemoprophylaxis must take into account the natural history of migraine with its unpredictable remissions for months or even years. Many of the preventive measures introduced in the past have been based on unsubstantiated concepts of the nature of migraine headache. Management of classic and common migraine is essentially the same. Cluster headache presents special problems because of the nature of the disorder, and interim treatment between bouts of the closely packed clusters is not indicated.

Of the pharmacologic agents used in the prophylactic treatment of migraine, methysergide maleate, a serotonin and histamine antagonist, has proven to be the most effective prophylactic agent (60 %) ⁴. Like serotonin and ergotamine this compound contains an indole nucleus and is chemically related to methylergonovine. The way in which methysergide prevents the occurrence of migraine has not yet been fully established.

Patients should be seen frequently during methysergide therapy, and they should be instructed to report symptoms such as leg or chest pains, paresthesias in the extremities, changes in color of extremities, or edema. Careful follow-up of the patient is also indicated to evaluate possible psychic effects which can produce depression, restlessness, insomnia, anxiety states, feelings of unreality, etc. A vasospastic reaction simulating the Leriche syndrome also may occur when taking the drug.

Because a syndrome resembling retroperitoneal fibrosis has been found in patients taking methysergide for more than 6 months, drug withdrawal for 60 days after each 6 months of therapy is advisable⁶. This syndrome regresses markedly when medication is stopped. A related condition, pleural pulmonary fibrosis, manifested by chest pain or dyspnea and such signs as pleural friction rub and effusion, cardiac murmurs or vascular bruits also has been noted. This syndrome can develop silently in patients as shown by our study where we performed intravenous urography in 114 consecutive migraine patients without either clinical or laboratory symptoms of retroperitoneal fibrosis but who had been on methysergide from 6 months to 3 years. Of the 114 urograms, three had abnormal characteristics, and the tests were diagnostic of retroperitoneal fibrosis. In these 3 patients, the urograms reverted to normal within 3 months after discontinuing the drug¹. The same 3 patients were also studied by Dr. Bianchine at Johns Hopkins Medical School who, using labelled methysergide, could find no difference in the way these patients metabolized the agent from the control group of migraine patients on

methysergide. In patients taking the drug for 6 months or longer kidney studies, urogram, BUN, and cardiac studies including EKG and sedimentation rates are indicated before continuing the therapy. It is clear that methysergide must be used only in those patients who are refractory to other types of treatment and must be used with vigilance and caution on the part of the patient and the physician.

In general, daily use of ergotamine for migraine prophylaxis is not advisable, as shown by reports of the undesirable side effects. Although helpful in ending individual attacks, the agent is not to be used in treating the migraine syndrome. However, for patients suffering from nocturnal attacks of headache (cluster headache), 1 to 2 mg. of ergotamine by mouth taken nightly before retiring for 10 to 14 days may help to terminate the series of headaches. Ergotamine may be combined with cyproheptadine HCl (an antihistamine and antiserotonin agent) which may help to keep the daily intake of ergotamine to a minimum.

Barbiturates, phenothiazines, propane-diols, and benzodiazepine may be beneficial in migraine prophylaxis by reducing anxiety and temporarily improving the patient's ability to handle stressful situations.

Another drug suggested for prophylactic use in migraine is cyproheptadine HCl (Periactin HCl, Merck). Its structure somewhat resembles that of phenothiazine and an antihistamine, and it is a mild CNS depressant. It is unusual in being an antagonist both of histamine and 5-HT. Cyproheptadine HCl (Periactin HCl, Merck) has only occasionally proved effective in migraine prophylaxis, because the therapeutically effective dosages of 16-20 mg. a day cannot be used, since in many patients even 4-8 mg. per day causes drowsiness. The drug may also cause dryness of the mouth, anorexia, nausea, dizziness, and ataxia.

A combination of a belladonna alkaloid, a barbiturate, and ergotamine (Bellergal), has also been used as a prophylactic agent. Neither of these or similar agents are as

effective as methysergide in the prevention of migraine headache.

For migraine patients subject to depression, the antidepressants are more effective than the anxiety-reducing drugs. The dibenzazepine derivatives, imipramine HCl (Tofranil) and amitriptyline HCl (Elavil), are the most effective antidepressants. Their cholinergic-blocking properties cause dryness of the mouth, palpitation, blurred vision, urinary retention, and, paradoxically, excessive sweating. It is, therefore, essential that any patient taking these drugs be seen frequently so that dosage can be properly adjusted after clinical evaluation.

Beneficial effects of hormone preparations in the prophylactic treatment of migraine have been reported over the past three decades. Recently, Lundberg reported that a synthetic steroid, progesterone, was effective in preventing migraine. This agent does not contain any estrogen, which is present in the currently available contraceptive preparations. Our personal experience with this agent does not concur with Lundberg⁷, and we have not found this to be an effective prophylactic agent. On the other hand, the occurrence of severe unrelenting headache in patients taking oral contraceptives and the exacerbation of migraine during such therapy has been noted. This paradox may possibly be explained by the presence of estrogens in the oral contraceptives which, in themselves, may trigger an attack of migraine. In general, we do not advise the use of the contraceptive pill in migraine patients because of possible side effects - phlebitis, neurological complications, and the frequent increase of migraine attacks.

In patients with migraine, the presence of edema and electrolyte changes, particularly premenstrually, has led to the use of diuretics in the treatment of migraine. Usually, drug-induced diuresis during a period of fluid retention or during a headache attack neither prevents nor affects the headache. Occasionally, the response to diuresis is favorable, and in selected cases, the diuretics are worth a trial. Nevertheless, no close correlation has been found be-

tween water retention and an attack of migraine headache.

Anticonvulsants have not prevented migraine headaches except in the small number of patients whose family history is heavily weighted with migraine, epilepsy, or both, whose personal history reveals aphasia, hemiplegia, or paresthesias before or during the headache attack, and whose EEG is abnormal, with spiked patterns. In some of these patients, the hydantoins may be combined with caffeine for more effective results.

Treatment of migraine is rarely successful unless a thorough investigation of the personality factors involved are discussed with the patient. Therapeutic approach to the symptomatic manifestation of the headache requires an understanding of the patient's life experiences as they are reflected in the development of his personality. This approach will provide the physician with an understanding and knowledge of the anxiety-producing situations which precipitate the headache attacks. Most patients with migraine follow rigid norms of behavior which deny the expression of aggressive or demonstrative feelings. As a broad generalization, the migraine patient has a compulsive, rigid, or perfectionistic nature. Feelings of resentment or hostility toward a parent or other respected or loved person tends to be deeply rejected or repressed by such patients. Thus, a conflict emerges with associated anxiety, over inevitably emerging hostilities, accompanied by a need to maintain family standards in order to continue desired relationships; these feelings when activated can form the basis which triggers the headache³.

If one looks at the situations in which headaches occur and recur, and their psychological significance to the patient, it is usually apparent that these are the times of emotional stress. While the personality features of the migraine patient are important psychologically, it should be emphasized that a large number of persons have this type of personality structure without suffering migraine headache.

On a more difficult level, the patient's conflicts must be ventilated. Often these

are wholly or partly unconscious; the patient is not aware that his tension and anxiety are engendered by, for example, ambivalent feelings of combined admiration and hostility toward a boss, spouse, parent, or child. Therapy should include reassurance, suggestion, psychic catharsis, and re-education.

Unless the physician is trained for more intensive psychotherapy, he should not attempt to probe deeply into subconscious emotional conflicts. Some cases will require intensive psychiatric treatment to effect any improvement in the patient's condition.

INDICATIONS FOR SURGERY

In general, the surgical treatment of migraine is contraindicated except in selected cases, and in these, only patients suffering from unilateral hemicranial headaches which have always affected the same side. Surgery is directed toward interruption of the various extracranial and middle meningeal arteries, and their accompanying nerves, and alcohol injection into, or section of, branches of the trigeminal nerve.

TREATMENT OF NONMIGRAINOUS VASCULAR HEADACHE

The treatment of this group of headaches, which are due to excessive cranial vasodilatation, generally consists of recognition and correction of the specific underlying cause. Once the underlying cause has been determined and treatment started, the headache itself usually requires only the selection of an appropriate combination of an analgesic and a sedative.

HEADACHES ASSOCIATED WITH ESSENTIAL HYPERTENSION

Management of hypertension has the aim of decreasing the blood pressure and protecting the patient from vascular insults.

Our study of patients with headache and hypertension did not clearly indicate a definite type of headache⁸. Frontal or occipital early morning headache occurred

most frequently. Although in many patients given antihypertensive therapy, the blood pressure decreased or the headache was relieved, only 25 per cent experienced definite freedom from headache with a fall in blood pressure. Headaches in patients with severe hypertension and in men with an elevated diastolic blood pressure respond most satisfactorily to specific therapy, i. e., an antihypertensive agent. Since there is a greatly variable response of hypertensive headache to nonspecific therapy such as analgesics or tranquilizers, the use of this symptom as a guide for treatment or for the success of a particular chemical agent for the treatment of hypertension is hazardous. For the "wake-up" hypertensive headache, the non-narcotic analgesics with a mild sedative were effective. Treatment of the headache of hypertensive encephalopathy, seen in malignant hypertension, consists of measures to lower the increased blood pressure and to reduce the edema.

HEADACHE DUE TO CRANIAL ARTERITIS

The pain of cranial arteritis and systemic disorders (fatigue, anemia, weakness) require early and vigorous treatment. Early recognition and treatment of cranial arteritis (temporal arteritis), not a common disorder, is important because it can cause blindness. Corticosteroids in the treatment of this condition usually relieves pain and prevents blindness far more effectively than any previously used remedy, but they do not cure the arteritis. If visual disturbances occur, the use of anticoagulants should be considered for the first 10 days of treatment.

VASCULAR HEADACHE ASSOCIATED WITH DISORDERED BODY CHEMISTRY AND METABOLISM

Headache due to cranial vasodilatation may accompany conditions in which hydration, electrolyte balance, and body chemistry are disturbed. The dehydration associated with febrile illness and electrolyte loss due to vomiting and diarrhea may

prolong and accentuate vascular headache until the dehydration is corrected. Replacement therapy and the more specific measures dictated by the etiology of the original headache form part of the treatment plan.

Hypercapnia and anoxia most commonly occur in patients with severe pulmonary disease. They may cause severe headache due to cranial vasodilatation, at times associated with increased intracranial pressure and papilledema. Headache in such patients is an important and serious symptom, calling for immediate attention. The treatment is usually based upon measures for proper ventilation of the patient. Due to the risk of paralysis of the respiratory center by high carbon dioxide concentrations, the use of high oxygen concentrations to ventilate the patient are inadvisable, for the respiratory center may be depending on a certain degree of anoxemia as the sole remaining stimulus to respiration. Digitalis and diuretics may be required, if there is right-sided heart failure, with increased venous (hence intracranial) pressure.

Vascular headache is usually one of the symptoms of hypoglycemia from any cause. It may also occur as a symptom of hyperparathyroidism, hyper- and hypothyroidism, and hyperadrenal function.

Vascular headaches may be produced by chemicals prescribed by the physician as treatment for headache. Reactions to many drugs and chemical agents can cause a vascular headache. However, the headache may occur not only as a result of the drugs given the patient but also from the anxiety produced by the words and actions of the physician. He must therefore carefully review with each new or old headache patient the types of drugs the patient has been taking, either as therapy for headache or for some other condition.

Drugs capable of producing headache include reserpine, nitroglycerine, hydralazine hydrochloride, antipyrine and its congeners, phenacetin and its congeners, caffeine, corticosteroids, sedatives in large doses, and hypoglycemic agents, such as insulin and the sulfonylureas (tolbutamide and chlorpropamide). Ingestion of alcohol is also a factor.

In recent years, the monoamine oxidase (MAO) inhibitors have sometimes dramatically produced headaches. At present, the MAO inhibitors are widely used for the treatment of depression; they include isocarboxazid, nialamide, phenelzine sulfate, and tranylcypromine. The first three are hydrazine derivatives; the fourth is a non-hydrazine drug; the pharmacologic effects of all four are similar.

TREATMENT OF MUSCLE-CONTRACTION HEADACHE

Muscle-contraction headache frequently referred to as tension headache but also described as psychogenic headache, myalgic headache, rheumatic headache, etc. is the most frequently occurring chronic headache. Many have a combined muscle-contraction and vascular element in their mechanism. Regardless of the cause, reaction to life stress, discogenic disease, trauma, or forms of noxious stimulation from any portion of the head, the clinical picture is similar. Management of headache from sustained muscle-contraction is directed toward lessening both muscle and emotional tension. For treatment of an attack, the pain threshold can be raised and anxiety reduced by use of a non-narcotic analgesic-sedative or tranquilizer drug combination². Narcotics should be avoided.

The prophylactic treatment of muscle-contraction headaches include the appropriate use of sedatives, tranquilizers, antidepressants, and muscle relaxant agents. Although drugs cannot replace insight or help the patient in understanding his emotional problems, they do reduce his reaction to stress and enable him to handle his life situations more effectively. Physical dependency on these agents may develop, and their misuse may be accompanied by undesirable side effects, masking of the underlying anxiety state and risk of habituation. The side effects of the newer sedative drugs include states of intoxication, dependence, resembling that on barbiturates, and withdrawal symptoms. Patients with headache are not all exactly

alike in the nature of their illness or in their reaction to a given therapeutic agent. It is, therefore, essential that patients being treated with these agents be closely followed.

Physical therapy including gentle massage, hot packs, cervical traction, and cervical collars should be considered. Injections of local anesthetics into trigger areas or spastic muscles can bring dramatic but usually temporary relief. Correcting faulty posture may prevent recurrence, but this requires a great deal of time and effort. One must approach with caution the use of energetic manipulative measures to the cervical spine, especially if there is reason to suspect atherosclerotic changes in the vertebral artery. The successful treatment of the patient with muscle-contraction headache, as in all chronic headache syndromes, can be summed up in one phrase: treat the whole patient and not the symptom. In the patient with muscle-contraction headache due to an anxiety and/or depressive state, psychotherapy is an important part of therapy.

POSTTRAUMATIC HEADACHE - MANAGEMENT

In discussing the management of chronic posttraumatic headache patients, only certain guidelines will be brought out for the physician: cases in which other major injuries predominate are not included.

More specifically, the usual posttraumatic patient is an anxious patient. Acceleration of the patient's convalescence reduces the usual sequence of symptoms, including headache, by minimizing the patient's anxiety about the seriousness of his injury. The management of a patient with posttraumatic headache should involve the use of pharmacological agents, psychotherapy, and physical medicine or a combination of these therapies.

The nonaddictive analgesics are recommended in the symptomatic treatment of chronic headache of moderate intensity, although these chemical agents are inferior

to the addictive drugs, such as codeine and meperidine, in their analgesic potency. The latter group should be used with extreme caution because of the hazard of addiction.

For treatment of an attack of vascular headache, ergotamine tartrate, which may be combined with caffeine, sedatives, and/or analgesics, is recommended.

Prophylactic drug therapy for posttraumatic headaches is valuable because the sedating and tranquilizing drugs act to reduce emotional stress, anxiety, and depression; they allow the patient to handle his life situation more effectively.

For patients subject to depression, antidepressants are more effective than anxiety-reducing drugs.

Physical medicine has a useful but limited role in the treatment of chronic posttraumatic headache patients. Over-treatment which builds anxiety may do more to increase the chronicity of the problem than to relieve it.

There is little or no disagreement as to the importance of psychogenic factors in chronic posttraumatic headache. It is not possible to fit all posttraumatic headaches into the same pattern, because there are many kinds of emotional concomitants to headache. It is necessary that the physician understand not only the nature of the headache but also the role the symptom plays in relation to the patient's personality and environment.

S U M M A R Y

When a physician undertakes the management of a patient with headache, there are three major questions that must be answered. First, what type or types of headache does the patient truly have. Second, what is the mechanism or mechanisms involved. Finally, what causes this headache. Common to all problems of treatment, diagnosis is the first step in management. Having established the diagnosis, specific therapy can be instituted. The management of the headache patient starts with treatment of the whole patient and removal of causative factors when they are known. This may entail operative therapy of remediable lesions, chemotherapy of infectious processes, treatment of metabolic disturbances, or removal of any allergic factors. However, in most chronic headache patients no structural lesion is found.

The current treatment of migraine is in part empiric and in part based on what we know of the underlying mechanisms. Drugs and psychotherapy are the principal forms of therapy. The single and most important factor in the treatment of migraine is that the whole patient rather than the symptom must be treated.

No important discovery in the last ten years has been noted in the pharmacologi-

cal treatment of headache. A critical review of the many agents introduced for the treatment of headache reveals that no specific chemotherapy has been wholly effective. After the initial wave of enthusiasm for most of these therapeutic agents subsides, their lack of effectiveness becomes apparent.

The pharmacological treatment of an attack of migraine is most effective when ergotamine is used alone or in combination with other drugs as indicated at the beginning of an attack and in an appropriate dosage which varies with the individual patient. In the prevention of migraine, methysergide (Sansert) is an effective agent in a limited number of patients who have frequent incapacitating attacks and respond to no other form of therapy. Careful screening and followup of patients on this agent are necessary because of possible side effects.

When treating an attack of muscle-contraction headache, analgesics with sedatives or tranquilizers are the most effective combination. Tranquilizers and sedatives have limited value in reducing anxiety and temporarily improving the patient's ability to handle stressful situations.

Since emotional factors appear to be the

most frequent precipitants of chronic recurring headache, treatment of the psychological problems is paramount. Psychotherapy, like all medical therapy may range from supportive to long-term treatment.

Physiotherapy has limited value but serves as an useful adjunct in treating headaches originating from the structures of the cervical spine.

R E S U M E N

Cuando un médico inicia el tratamiento de un paciente con cefalalgia debe resolver tres cuestiones fundamentales.

En primer lugar debe determinar de que tipo o tipos de cefalalgia sufre el paciente en realidad, luego cual o cuales son los mecanismos implicados y finalmente cual es la causa de la misma. Como en todos los problemas de tratamiento, el diagnóstico es lo primero a considerar.

Una vez determinado éste, puede indicarse la terapéutica específica. Debe comenzarse por el tratamiento del paciente en su totalidad y por la eliminación de factores causales cuando estos son conocidos. Esto puede traer aparejado una terapéutica activa de lesiones curables, la quimioterapia de procesos infecciosos, el tratamiento de trastornos metabólicos o la eliminación de factores alérgicos. Sin embargo la mayoría de los pacientes con cefalalgia crónica no presenta lesiones estructurales.

El tratamiento corriente de la jaqueca es en parte empírico y en parte se basa en lo que sabemos acerca de los mecanismos subyacentes. Las drogas y la psicoterapia constituyen las principales formas de terapéutica. El único y más importante factor en el tratamiento de la jaqueca es que más que el síntoma se debe tratar al paciente.

No han surgido descubrimientos importantes en el tratamiento farmacológico de la jaqueca en los últimos diez años. Una reseña crítica de los diversos agentes introducidos para el tratamiento de la cefalalgia revela que ninguna quimioterapia específica se ha mostrado totalmente

The meaning of headache can be considered only in relation to the individual patient and his environment. Selection of suitable treatment depends on a correct diagnosis which, in turn, depends on a carefully taken and detailed history, and correct medical, neurological, and psychological assessment of the patient.

eficaz. Aunque subsiste algo del entusiasmo inicial despertado por la mayoría de estos agentes terapéuticos, su falta de eficacia se hace evidente.

El tratamiento farmacológico de un ataque de jaqueca tiene el máximo de eficacia cuando se aplica la ergotamina sola o combinada con otras drogas de acuerdo a lo indicado al comienzo del ataque y en una dosis adecuada, lo cual varía de paciente a paciente. En la prevención del ataque de jaqueca la metisergida (Sansert) es un agente eficaz en un número limitado de pacientes que tienen ataques incapacitantes con frecuencia y responden a otro tipo de terapia. Debe seleccionarse y vigilarse cuidadosamente a los pacientes que reciben esta medicación porque pueden presentarse efectos secundarios.

Cuando se trata de un ataque de cefalalgia por contracción muscular los analgésicos combinados con sedantes o tranquilizantes resultan lo más eficaz. Los tranquilizantes y sedantes tienen un valor limitado para reducir la ansiedad y para mejorar transitoriamente la capacidad del paciente para resolver situaciones de "stress".

Dado que los factores emocionales parecen ser los que más frecuentemente precipitan la cefalalgia crónica recurrente, es fundamental el tratamiento de los problemas psicológicos. Como toda terapéutica, la psicoterapia puede oscilar entre una acción de sostén y un tratamiento a largo plazo.

La fisioterapia tiene un valor limitado pero es útil como complemento al tratar cefalalgias cuyo origen está en las estructuras de la columna cervical.

El significado de la cefalalgia sólo puede ser considerado en relación con el paciente individual y su ambiente. La selección de un tratamiento adecuado depende de un diagnóstico correcto que a su vez

depende de la cuidadosa y detallada realización de la historia y de la correcta valoración médica, neurológica y psicológica del paciente.

R É S U M É

Quand un médecin commence le traitement d'un patient souffrant de céphalalgie il doit résoudre trois problèmes extrêmement importants.

Il doit d'abord déterminer de quel genre de céphalalgie il s'agit, puis découvrir quels sont les mécanismes en jeu et finalement préciser la cause de cette céphalalgie. De même que dans tous les problèmes concernant le traitement, le diagnostic est la première des choses à considérer. Une fois le diagnostic établi, on peut passer à l'indication de la thérapeutique spécifique. On doit commencer par le traitement du patient dans sa totalité et par l'élimination des facteurs qui causent la céphalalgie lorsqu'ils sont connus. Ceci peut amener à une thérapeutique active des lésions guérissables, à la chimiothérapie des processus infectieux, au traitement des dérèglements métaboliques ou à l'élimination des facteurs allergiques. Cependant la plupart des patients souffrant de céphalalgie chronique ne présente pas des lésions structurales.

Le traitement courant de la migraine est partiellement empirique mais il est fondé aussi sur ce qui est connu quant aux mécanismes sous-jacents. Les médicaments et la psychothérapie constituent les principales formes de thérapeutique. Le facteur le plus important, donc le seul à considérer dans le traitement de la migraine est le fait qu'au delà du symptôme en soi on doit traiter le patient.

Il n'y a pas eu de découvertes importantes dans le domaine du traitement pharmacologique de la migraine pendant les derniers dix ans. Une approche critique des différents éléments introduits pour le traitement de la céphalalgie révèle qu'aucune chimiothérapie spécifique ne s'est montrée totalement efficace. Il subsiste des vestiges

de l'enthousiasme initial éveillé par la plupart de ces substances thérapeutiques, mais cependant leur manque d'efficacité est évident. Le traitement pharmacologique d'une crise de migraine a un maximum d'efficacité lorsqu'on ordonne l'ergotamine seule ou combinée avec d'autres médicaments au début de la crise et convenablement dosifiée; la dose varie d'un patient à l'autre. Dans la prévention de la crise de migraine la metisergide (Sansert) est souvent un agent efficace dans un nombre limité de patients qui souffrent de crises incapacitantes; ces malades répondent à un autre genre de thérapie. Il faut choisir et surveiller soigneusement les patients soumis à ce genre de traitement parce qu'ils peuvent présenter des effets secondaires.

Quand il s'agit d'une crise de céphalalgie due à la contraction musculaire les analgésiques combinés avec des sédants ou des tranquillisants sont les agents les plus efficaces. Ces tranquillisants et ces sédants ont une valeur limitée quant à la réduction de l'anxiété et à l'amélioration passagère de la capacité du patient pour résoudre des situations de "stress".

Etant donné qu'apparemment les facteurs émotionnels sont ceux qui le plus fréquemment précipitent la céphalalgie chronique, le traitement des problèmes psychologiques est fondamental. Comme dans toute autre thérapeutique, la psychothérapie peut jouer des rôles très différents allant d'une action de support jusqu'au traitement à longue échéance.

La physiothérapie a une valeur limitée mais elle est utile comme complément lorsqu'on traite des céphalalgies qui proviennent des structures de la colonne cervicale.

La signification de la céphalalgie peut

être considérée uniquement en rapport avec le patient individuellement et avec son milieu. La sélection d'un traitement convenable dépend d'un diagnostic correct,

qui dépend à son tour d'une élaboration soigneuse et détaillée du rapport clinique et de la valoration médicale, neurologique et psychologique du patient.

ZUSAMMENFASSUNG

Wenn ein Arzt die Behandlung eines Patienten mit Kopfschmerzen beginnt, muss er drei grundlegende Probleme loesen.

Zunaechst muss er feststellen welcher Art die Kopfschmerzen sind, sodann welche die beteiligten Mechanismen sind und schliesslich die Ursache derselben. Wie alle Behandlungsprobleme, muss zuerst die Diagnose in Betracht gezogen werden. Ist sie einmal gestellt, kann man die spezifische Therapie indizieren. Man muss mit der Behandlung des Patienten in seiner Ganzheit beginnen und auch mit der Beseitigung der Kausalfaktoren, wenn diese bekannt sind. Dieses kann gleichzeitig mit einer aktiven Therapie heilbarer Laesionen einher gehen, der Chemotherapie der infektiösen Prozesse, die Behandlung von Stoffwechselstörungen oder die Eliminierung allergischer Faktoren. -Immerhin, die meisten Patienten mit chronischen Kopfschmerzen haben keine Strukturveraenderungen. Die gewoehnliche Behandlung der Migräne ist teils empirisch und teils beruhend auf dem, was wir ueber die zugrunde liegenden Mechanismen wissen. Medikamente und Psychotherapie sind die hauptsaechlichen Behandlungsformen. Der einzige und wichtigste Faktor einer Behandlung der Migräne besteht darin, dass man mehr den Patienten als solchen, als das Symptom behandeln muss.

In den letzten zehn Jahren sind keine neuen und wichtigen Entdeckungen auf dem Gebiete der pharmakologischen Behandlung der Migräne erschienen. Eine Kritische Uebersicht ueber die verschiedenen Medikamente gegen die Kopfschmerzen zeigt, dass keine spezifische Chemotherapie sich vollkommen erfolgreich erwiesen hat. Obwohl noch die anfaengliche Begeisterung, die durch die meisten dieser Medikamente hervorgerufen worden war, weiter

besteht, ist ihre Wirkungslosigkeit evident.

Die pharmakologische Behandlung eines Migränefalls hat ihre maximale Wirkung wenn man Ergotamin allein oder in Kombination mit anderen Medikamenten anwendet, bei Beginn des Anfalls und in der wirkungsvollen Dosis, die von Patient zu Patient variiert. Bei der Verhuetung des Anfalls hat sich als wirkungsvoll Metiser-gida (Sancert) bei einer beschraenkten Anzahl von Patienten erwiesen, die oft an invalidierender Anfaellen gelitten hatten und auf keine andere Art von Behandlung ansprachen. Man muss die Patienten sorgfaeltig auswaehlen und ueberwachen, die diese Art von Behandlung erfahren, weil sich Nebenerscheinungen bemerkbar machen koennen. Wenn es sich um einen Anfall von Kopfschmerz durch Muskelkontraktur handelt, sind am wirksamsten die Analgesica kombiniert mit Sedativa und Tranquillizern. Die Tranquillizer und Sedativa haben beschraenkten Wert um die Angustia zu mindern und um voruebergehend die Faehigkeit des Patienten zu bessern, um "Stress"-Situationen loesen zu koennen. Da die emotionellen Faktoren die sind die am meisten die chronischen Kopfschmerzen hervorrufen, ist die Behandlung der psychologischen Probleme von grundlegender Wichtigkeit. Wie jede Behandlung, kann die Psychotherapie sich bewegen zwischen einer Unterstuetzungstherapie und einer langdauernden Therapie. Die Physiotherapie hat beschraenkten Wert, ist jedoch nuetzlich, um die Behandlung derjenigen Kopfschmerzen zu vervollstaendigen, die ihren Ursprung in der Halswirbelsaeule haben. Die Bedeutung der Kopfschmerzen kann nur im Zusammenhang mit den individuellen Patienten und seinem Milieu betrachtet werden. Die Auswahl der geeig-

neten Behandlung haengt von der korrekten Diagnose ab, die ihrerseits abhaengt von einer detaillierten Krankengeschichte und

der korrekten, medizinischen, neurologischen und psychologischen Bewertung des Patienten.

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Modalités de la Thérapeutique du Syndrome Parkinsonien par la L-Dopa

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Introduction: physiopathologie

Depuis les travaux classiques de Carlsson^{11,12,13} chez l'animal et de Hornykiewicz²⁶ chez l'homme, on sait que les régions du système nerveux central les plus riches en dopamine comprennent essentiellement le striatum et le locus niger: noyau caudé et putamen 2-4 µg/g de tissu frais, substantia nigra 0,8 µg/g, globus pallidus 0,1-0,3 µg/g. L'existence d'une voie nigro striatale dopaminergique est définitivement établie. D'ailleurs la visualisation des catécholamines par la méthode d'histofluorescence de Falk et Hillarp permet de constater qu'au niveau du locus niger la dopamine a une localisation pericaryonale alors qu'au niveau du noyau caudé, elle a une répartition diffuse correspondant vraisemblablement aux terminaisons presynaptiques. Le métabolite principal de la dopamine l'acide homovalinique (HVA) a une distribution grossièrement parallèle à celle de la Dopamine. Il en est de même de l'enzyme limitante de la synthèse de la Dopamine, la thyroxine hydroxylase. La decarboxylase qui intervient aussi bien dans la decarboxylation de la Dopa en dopamine que dans la transformation du 5 hydroxytryptophane (5 HTP) en serotine (5HT) a une répartition plus ubiquitaire, encore qu'elle soit nettement plus active dans les régions riches en monoamines. Très abondante, elle ne joue pas le rôle d'étape limitante de la

synthèse de la Dopamine. Elle a encore une autre fonction au niveau du SNC. En effet, les capillaires cérébraux partagent avec quelques capillaires de la médullaire rénale la propriété d'être riches en decarboxylase (DC). Une bonne partie de la Dopa, qui passe du courant sanguin dans l'endothelium des capillaires cérébraux, est transformée en dopamine qui du fait de la barrière hémato-encéphalique pour les amines ne passe pas dans le parenchyme cérébral. La DC des capillaires cérébraux constitue donc une barrière enzymatique diminuant le passage de la Dopa dans le parenchyme cérébral. L'intensité de cette barrière n'est pas la même pour tous les capillaires du SNC: à quelques exceptions près, elle est de plus faible intensité au niveau des structures riches en catécholamines (striatum, locus niger, hypothalamus inférieur) qu'au niveau des structures qui en contiennent peu (cortex cérébral, cervelet). Il semble donc exister une double barrière hémato-encéphalique pour les catéchols, l'une probablement de nature physique anciennement connue qui empêche la pénétration des amines, l'autre enzymatique due à la DC et relativement et topologiquement sélective qui diminue le passage des précurseurs et en particulier de la Dopa.

Dans la maladie de Parkinson, on sait depuis les travaux d'Hornykiewicz²⁶ que la teneur des noyaux gris centraux en dopamine est diminuée. Ceci ne paraît pas résul-

ter d'un déficit de la thyroxine hydroxylase, donc d'une diminution de la synthèse de la Dopa à partir de la thyroxine. D'ailleurs, l'administration de cette dernière n'a pas d'efficacité thérapeutique.

L'experimentation animale semble démontrer qu'après lésion de la voie nigro-striatale, qui est compromise dans la maladie de Parkinson, le striatum perd en partie sa capacité d'effectuer la synthèse de la dopamine à partir de la Dopa. Chez le Parkinsonien on doit donc admettre, soit qu'il reste suffisamment de fibres nigro-striatales pour assurer en présence d'une surcharge de Dopa une synthèse compensatrice de dopamine, soit que la DC d'autres substrats cellulaires, serotoninergique par exemple, se substitue à celle des fibres dopaminergiques. Force est de constater que si un maillon du métabolisme de la dopamine fait défaut dans le parkinson, on n'a pas réussi à l'identifier. Par ailleurs, l'étude attentive du métabolisme de la Dopa chez ces malades, parle plutôt en faveur d'une perte du pouvoir de fixer la dopamine que d'une faille dans son métabolisme.

Traitement des syndromes parkinsoniens par la L-Dopa (L-dihydroxyphénylalanine)

C'est peu après la découverte par Hornykiewicz d'une insuffisance du taux de dopamine cérébrale, que les premiers essais de l'administration de Dopa par voie veineuse chez les parkinsoniens ont été tentés par Birkmayer^{7, 9} et Barbeau², il y a plus de 10 ans. Jusqu'à l'administration de la Dopa à fortes doses par voie orale due à Cotzias, leurs résultats positifs avaient été contestés. Actuellement, les effets favorables de la L-Dopa sur les syndromes parkinsoniens ne font plus de doute et tous les auteurs viennent le confirmer. La plupart d'entre eux considèrent que 75 % des patients bénéficient nettement de cette thérapeutique.

Lorsque la L-Dopa est utilisée seule, elle est en général administrée à des doses qui

en moyenne se situent aux environs de 5 g par jour. Une dose optimum doit être recherchée pour chaque cas. On commence le traitement avec 0,5 à 1g/jour et la dose optimum est atteinte au bout de quelques semaines ou mois. Avec cette méthode, Yahr^{37,38} trouve une amélioration de 50 % de la gravité du syndrome chez 60 % de ses patients après 6 mois de thérapeutique. Après 18 mois, ce taux s'élève à 75 % des patients et se maintient. Boudin, Castaigne, Lhermitte et coll¹⁰ observent une amélioration qui dépasse 50 % chez 132 patients sur 171 étudiés. Les résultats obtenus par d'autres auteurs sont à peu près identiques. Chacun s'accorde pour constater que même chez les patients qui ont présenté une réponse favorable et rapide, la progression sans augmentation de doses peut se poursuivre durant 6 mois et même une année ou plus. Ceci pose le problème du temps limite pour décider de l'efficacité du traitement et de la posologie optimum. Tous les symptômes de la maladie sont modifiés mais à des degrés variables. L'akinésie, la bradyphrénie et la rigidité répondent généralement mieux, plus rapidement, que le tremblement. C'est surtout pour ce dernier que les délais d'amélioration peuvent être longs. En principe la réponse thérapeutique dépend de la dose totale de L-Dopa par jour, et de la durée du traitement. Les effets secondaires dans ce mode d'administration sont souvent impressionnants. Parfois, ils imposent l'arrêt du traitement avant d'atteindre les doses thérapeutiques. Il en est ainsi pour les nausées, les vomissements, les variations de la TAH ou les dysfonctions cardiaques non tolérées. Ces effets secondaires sont généralement précoces. Par contre, les mouvements anormaux, qui peuvent survenir dès le début du traitement, en particulier si l'augmentation des doses de Dopa est trop rapide, peuvent également apparaître tardivement. En effet, on constate qu'avec le temps, un nombre de plus en plus élevé de patients, sans modification de doses, sont atteints de ces mouvements anormaux.

Traitement du parkinsonisme à la L-Dopa combinée à un inhibiteur de la décarboxylase (IDC)

Dès les premiers essais cliniques, on s'est rendu compte que, du fait du métabolisme rapide de la Dopa, cette dernière ne pourrait que difficilement constituer une thérapeutique optimum à moins qu'on parvienne à prolonger son action et à diminuer au minimum ou à faire disparaître les effets secondaires. Les premières tentatives dans ce sens ont consisté à combiner à la L-Dopa des inhibiteurs de la monoamino-oxydase et des médicaments antidépresseurs, sans résultats très convaincants. Après la découverte par Pletcher et Bartholini⁴ de l'effet des inhibiteurs de la décarboxylase (IDC) sur la concentration des catécholamines cérébrales chez l'animal. Birkmayer^{7,8,9}, J. Siegfried³⁰ et nous-même avons effectué les premiers essais cliniques de cette combinaison. Si l'administration orale de Dopa seule à doses très élevées préconisée par Cotzias^{17,18,19} a constitué la pierre de touche de l'avènement de la thérapeutique du Parkinson par la L-Dopa, la combinaison L-Dopa + IDC représente une nouvelle étape intéressante. Les IDC à dose adéquate inhibent la décarboxylase extracérébrale, y compris celle de l'endothélium des capillaires cérébraux, mais ils n'agissent pas sur la DC du parenchyme nerveux. Cette inhibition a comme conséquence une bonne résorption intestinale de la L-Dopa tout en limitant la métabolisation périphérique. Elle facilite le passage de la "barrière enzymatique" des capillaires cérébraux sans entraver la formation des catécholamines cérébrales. Sur le plan clinique, il en résulte une réduction importante des doses de L-Dopa nécessaires, une diminution, voire une abolition des effets secondaires périphériques, et une augmentation de l'efficacité de la L-Dopa.

Les IDC que nous utilisons sont des dérivés des dydrazines, le RO-46.02 et le RO-17.56. Il en existe d'autres dont nous n'avons pas l'expérience. Dans une étude portant sur 209 patients dont 100 recevaient la combinaison de L-Dopa + RO—46.02 et

109 la combinaison L-Dopa + RO—17.56, nous avons pu objectiver les avantages de ce traitement. Les résultats globaux sont supérieurs à ceux dont il est fait état dans la littérature avec la Dopa seule (coefficient d'amélioration égal ou supérieur à 60 % dans environ 75 % des cas et cela malgré les doses inférieures de Dopa). Le seuil d'action thérapeutique est en moyenne de 450 mg de Dopa et le délai d'action de 8 jours environ. La dose moyenne de Dopa par jour est de 800 mg environ, c'est-à-dire 5 à 10 fois inférieure à celle qui est nécessaire lorsqu'elle est utilisée seule. Comme avec la Dopa seule, le traitement est instauré lentement pour arriver à une dose maximum au bout de quelques semaines (4 à 6). Sur le plan pratique, la protection contre les effets secondaires est meilleure, elle dépend directement de la dose d'IDC. La diminution de la fréquence et de l'intensité des mouvements anormaux qu'entraîne une bonne inhibition de la décarboxylase extracérébrale est difficile à expliquer. Toutefois, les expériences chez l'animal ont montré que les IDC entraînent une distribution plus spécifique dans le S. N. C. de la Dopaamine synthétisée qu'avec la Dopa seule.

Cependant, bien que la Dopa soit la médication de choix parmi toutes les autres dans le parkinsonisme, bien que son administration en association avec un IDC présente des avantages évidents, tous les auteurs constatent qu'elle ne conduit qu'exceptionnellement à une guérison complète de la maladie. Il ne s'agit pas d'une thérapeutique de couverture comme celle des anticholinergiques. Comme le laissait prévoir les données physiopathologiques, la L-Dopa corrige certainement un trouble métabolique spécifique. Mais cela ne suffit pas dans la plupart des cas pour maîtriser complètement les syndromes parkinsoniens; tout se passe comme si un autre trouble métabolique existait à côté de celui de la dopamine.

Les effets secondaires

Ils sont nombreux et posent des problèmes sérieux surtout quand la L-Dopa est

administrée seule. Pour Yahr^{37,38}, la cause d'échec la plus fréquente dans le traitement de ses malades reste la non tolérance de la L-Dopa.

Les mouvements anormaux. Cliniquement on peut en distinguer deux types. Les mouvements stéréotypés et ceux qui rappellent les mouvements des chorées. Dans les premiers, on peut décrire des mouvements de mastication, mâchonnement, grimaces faciales, rotation de la tête, une élévation des épaules ou du tronc, un pseudo-clonus du pied avec appui sur la pointe, le piano-tage sur la table. Ces mouvements sont toujours annoncés par une gêne dans le territoire musculaire où ils vont survenir et qui n'est pas grossièrement hypotonique. Cette gêne est ressentie par le malade comme une contraction, une raideur, une crampe ou une douleur. Ces mouvements stéréotypés peuvent alterner avec des contractions dystoniques: flexion, extension du gros orteil qui peut faire place à une extension permanente: rotation interne et adduction du pied. Tous ces phénomènes sont généralement conscients et rappellent de très près le syndrome excito-moteur décrit par LEVY après la grande épidémie d'encéphalite léthargique. A ces stéréotypies motrices s'opposent les mouvements rappelant ceux de la chorée. Ils surviennent sur fond d'hypotonie durable ou momentanée. Ils sont brusques et rapides et leur intensité varie de l'hypermimie grimaçante aux mouvements explosifs, désinsérés, très mal supportés par l'entourage. Plus rarement ont été décrits une contracture des masseters, des crises oculogyres, un blépharospasme, des accès de blocage respiratoire.

Chez les patients traités à la Dopa seule, on constate que dans un groupe traité, la dose qui produit les mouvements anormaux est en moyenne la même que celle de tout le groupe. D'autre part, on a l'impression que la dose thérapeutique optimum et la dose qui déclenche les mouvements anormaux son très voisines. Chez les patients recevant de la L-Dopa associée à un IDC, l'apparition des mouvements anormaux dépend du rapport Dopa-inhibiteur et de la dose de Dopa. Il est de plus en plus évi-

dent que le développement des mouvements anormaux est plus fréquent quand l'augmentation de la posologie de la L-Dopa se fait trop rapidement.

En général, l'arrêt du traitement ou la réduction de la dose font disparaître ces mouvements anormaux, que la Dopa ait été administrée seule ou qu'ils soient apparus malgré l'association Dopa-IDC. Mais parfois cela ne suffit pas. Les symptômes parkinsoniens réapparaissent sans que disparaissent les mouvements anormaux. Il est alors indiqué d'arrêter le traitement pendant 2 à 3 semaines et de le reprendre sous de fortes doses d'IDC en augmentant la L-Dopa très progressivement. A notre connaissance tous les traitements adjuvants visant à faire disparaître les mouvements anormaux sans diminuer les doses de Dopa se son révélés décevants. Les neurolyptiques, la pyridoxine peuvent faire disparaître les mouvements anormaux mais ils entraînent une réapparition de la symptomatologie du parkinson. Seuls les dérivés de la benzodiazépine bien qu'ayant une activité faible sur ces mouvements anormaux n'entraînent pas une aggravation des signes parkinsoniens.

Effets cardio-vasculaires: La L-Dopa peut produire des effets cardio-vasculaires par deux mécanismes différents; d'abord la production de dopamine à la périphérie en grande quantité agissant sur les récepteurs catécholaminergiques; d'autre part, mais ce mécanisme est encore contesté, le système vasculaire pourrait être affecté par une dysrégulation à point de départ du système nerveux central. Les travaux de ces dernières années ont établi que la dopamine exerce des effets bêta-adrénergiques sur le coeur, des effets alpha-adrénergiques typiques sur la plupart des lits vasculaires et une vasodilatation rénale et mésentérique qui semblent être dus à l'action sur un récepteur dopaminergique spécifique. L'injection iv de L-Dopa donne des effets qualitativement semblables à ceux de la dopamine mais pour produire les mêmes résultats il faut donner une dose de L-Dopa 300 à 400 fois supérieure à celle de dopamine. Par contre, l'effet de la L-Dopa dure 10 fois plus longtemps que celui de la dopamine.

Action sur le coeur: Elle résulterait de l'effet bêta-adrénergique de la dopamine et des autres catécholamines favorisant les arythmies ectopiques mais aussi une contraction accrue, une accélération du rythme cardiaque et une diminution du temps de conduction auriculo-ventriculaire. Lors de l'administration orale de la L-Dopa, la quantité de dopamine déversée dans le sang dépend de plusieurs facteurs y compris la dose, l'absorption, la vitesse de décarboxylation, le stockage dans les tissus et le métabolisme. Il est donc très difficile d'évaluer quelle quantité d'amine exercera un effet bêta-récepteur et encore plus difficile d'évaluer la dose susceptible d'entraîner une arythmie chez un Parkinsonien qui présente une insuffisance coronarienne.

La dopamine augmente la contractibilité myocardique entraînant une augmentation du débit cardiaque. Cet effet inotrope positif ne serait pas défavorable aux patients ayant un coeur normal et pourrait être même bénéfique aux insuffisants cardiaques. Par contre, elle entraîne une consommation d'oxygène plus grande d'où le danger de produire une ischémie myocardique chez les patients à coronaires hypotéquées. La dopamine et la L-Dopa diminuant le temps de la conduction auriculo-ventriculaire, les patients souffrant de fibrillation auriculaire ou flutter peuvent présenter une augmentation d'extrasystole ventriculaire après administration de L-Dopa. Cet effet est inhibé par les bêta-bloqueurs et est moins susceptible de se produire, semble-t-il, chez les patients digitalisés.

Effets sur la tension artérielle: Expérimentalement la L-Dopa a la capacité d'augmenter et de diminuer la TA. Il semble que l'administration iv de fortes doses de L-Dopa ou dopamine détermine une augmentation de la TA par stimulation des bêta-récepteurs. Cet effet ne s'observe pratiquement pas après administration orale. On observe au contraire des chutes de la TA. Elles semblent liées à deux phénomènes, une vasodilatation par action sur les récepteurs dopaminergiques des vaisseaux rénaux et mésentériques et une vasodilatation consécutive à un effet neurogène sur les autres

lits vasculaires périphériques. L'origine centrale ou périphérique de ce phénomène est sujet à controverse. Ainsi Barbeau et coll.³ ont montré que l'activité de la rénine plasmatique est très diminuée par la L-Dopa et suggère une action centrale de la L-Dopa sur les mécanismes de feed-back de la régulation de la TA.

Enfin, dopamine et L-Dopa augmentent l'excrétion du Na et pourraient produire de l'orthostatisme par diminution du volume plasmatique. Aussi l'augmentation prudente de la consommation de sel peut être utile chez certains patients présentant de l'hypotension orthostatique. En conclusion, le danger le plus important de la L-Dopa est l'arythmie ventriculaire qui serait exceptionnelle chez le normal mais susceptible d'apparaître en cas d'irritabilité myocardique et d'ischémie. On observe ces effets cardiovasculaires plutôt au début du traitement. L'emploi d'IDC empêchant la formation de grandes quantités de dopamine à la périphérie est manifestement utile, même si certains de ces effets secondaires ont une composante centrale. En effet, pour les auteurs utilisant la L-Dopa seule, l'hypotension et les troubles cardiaques conduisent assez fréquemment à des arrêts de traitement. Par contre, sur 209 cas traités avec IDC, nous n'avons jamais dû interrompre, même momentanément, la thérapeutique pour hypotension et dans cette série les complications cardiaques sont restées très rares et ne sont probablement pas dues à la L-Dopa.

Effets digestifs: Les troubles digestifs observés sont surtout des nausées, des vomissements et moins souvent une anorexie avec pesanteur gastrique et pyrosis. Gênant mais sans grande conséquence, habituellement ils vont en s'atténuant et ne motivent qu'exceptionnellement l'arrêt de la thérapeutique. L'administration d'un IDC supprime pratiquement toujours les vomissements et les nausées. Le pyrosis peut être corrigé par un alcalinisant. La constipation habituelle chez le parkinsonien est souvent augmentée, que la Dopa soit administrée seule ou avec un IDC.

Fatigue et somnolence: Elles sont obser-

vées surtout au début du traitement et disparaissent par la suite. Lorsqu'on associe un IDC à la Dopa ces effets sont souvent aggravés surtout si l'IDC est administré à relativement fortes doses.

Autres effets secondaires somatiques: Dans les premières observations de Cotzias qui utilisait de la DL-Dopa des atteintes graves de l'hématopoïèse mais cédant à l'arrêt de la thérapeutique ont été observées. Depuis que l'on utilise de la L-Dopa purifiée, quelques perturbations biologiques sans conséquence ont été rapportées. Elles sont transitoires, portant sur la formule sanguine (réticulocytose, plaquettopénie), les transaminases, la créatinine, la bilirubinémie. Des rétentions urinaires aiguës sur adénome prostatique sont également signalées. Si les IDC présentent une certaine toxicité chez l'animal et d'ailleurs seulement dans certaines espèces depuis 3 ans que nous les utilisons chez l'homme, nous n'avons jamais observé de signes biologiques ou cliniques de toxicité en dépit des nombreux contrôles biologiques que nous avons pratiqués.

Modifications psychiatriques et effets secondaires psychiatriques

Deux types de complications psychiatriques provoquées par la L-Dopa ont été décrits. Les premières complications apparaissent sous des doses élevées ou relativement élevées. Elles prennent la forme de syndromes confusionnels toxiques. Le deuxième type de réponse se développerait indépendamment de la dose de L-Dopa et ne serait que l'exacerbation ou la réapparition de troubles psychiatriques antérieurs. Avec la combinaison L-Dopa/IDC nous n'avons jamais observé ce type de réaction.

Les syndromes hallucinosiques décrits surtout chez les parkinsoniens post-encéphaliques, même en l'absence de toute thérapeutique, sont souvent déclenchés ou renforcés par les anticholinergiques à fortes doses. Le passage à la L-Dopa est souvent bénéfique et nous n'avons pas observé, sous L-Dopa, d'apparition de tels syndromes. Par contre, les malades font fréquem-

ment état d'une augmentation des rêves dont ils se souviennent au matin.

Chez beaucoup de malades le traitement à la L-Dopa entraîne une amélioration nette de l'humeur. On voit rarement apparaître de petits syndromes hypomaniaques. Mais curieusement chez d'autres sujets, au contraire, après quelques mois de traitement, on voit leur humeur dépressive s'accroître et même se développer de véritables syndromes mélancoliques. Ces derniers réagissent, dans la règle, rapidement et bien à l'administration d'antidépresseurs tricycliques.

Les effets aphrodisiaques de la L-Dopa nous paraissent avoir été considérablement exagérés. On observe assez fréquemment une reprise de l'activité sexuelle des malades sans qu'on puisse faire la part de ce qui revient à la correction du syndrome de parkinson ou à un éventuel effet spécifique.

Thérapeutique adjuvante par la 3-O-Méthyl-Dopa

Il s'agit d'un métabolite méthylé physiologique de la Dopa qui possède la propriété de passer à travers toutes les barrières cellulaires sans difficulté. Par conséquent, son absorption intestinale est facile ainsi que son accumulation au niveau des organes et du cerveau en particulier. Un autre avantage par rapport à la Dopa est que la 3-OMD a une demi-vie beaucoup plus longue - 12 heures - alors que celle de la L-Dopa est d'une demi-heure. Son métabolisme est en partie réversible, c'est-à-dire que la 3-OMD se transforme partiellement en L-Dopa. A la dose de 4g/jour le taux de la L-Dopa circulante des patients s'élève jusqu'aux environs de 800 à 1000 µg/ml. Il est remarquablement constant dans la journée, au contraire de ce que l'on observe après la L-Dopa même si les prises journalières sont nombreuses. Malheureusement aux doses employées jusqu'ici, le taux de la L-Dopa circulante après 3-OMD est insuffisant. Aussi les premiers essais cliniques faits avec la 3-OMD seule, aux doses indiquées ne sont pas concluants. Cependant on aurait tort de ne pas tenir compte des pro-

priétés intéressantes de ce produit. De nombreux patients traités à la L-Dopa seule ou à la L-Dopa + IDC présentent des fluctuations de leur état dans le nycthémère. La reprise de la symptomatologie parkinsonnienne se produit au moment où le taux circulant de L-Dopa s'abaisse fortement. L'ad-

jonction de 3-OMD à la dose de 1,5 à 2 g diminue significativement ces fluctuations de la Dopa circulante et chez un certain nombre de patients corrige ou diminue parallèlement les fluctuations de l'amélioration clinique.

R É S U M É

La thérapeutique du syndrome parkinsonnien par la L-Dopa seule à la dose moyenne de 5 g/jour bien que grevée de beaucoup d'effets secondaires donne des résultats spectaculaires comportant une amélioration de l'ordre de 60 % des signes parkinsonien chez 75 à 80 % des patients. L'association à la L-Dopa d'un IDC conduit à des résultats encore plus favorables. L'inhibition de la DC extra-cérébrale a comme conséquence une bonne résorption de la L-Dopa au niveau intestinal tout en limitant sa métabolisation périphérique. Elle facilite le passage de la barrière hémato-encéphalique enzymatique. Sur le plan clinique, il en résulte une réduction des doses de L-Dopa journalière nécessaire, une diminution, voire une abolition des effets secondaires cardiovasculaires et digestifs, une augmentation de l'efficacité de la L-Dopa. Parmi les effets secondaires, ceux qui compromettent le plus la réussite du traitement sont les mouvements anormaux; ils sont de deux types: mouvements stéréotypés et mouve-

ments rappelant ceux de la chorée; ils sont moins graves et significativement moins fréquents quand la L-Dopa est associée à un IDC à doses suffisantes. Toutefois, la L-Dopa seule ou associée à un IDC malgré ses effets spectaculaires ne constitue pas une thérapeutique radicale du syndrome de Parkinson. Il ne s'agit pas d'une thérapeutique de couverture; elle corrige certainement un trouble métabolique spécifique mais il existe probablement d'autres troubles métaboliques encore inconnus dans le syndrome de Parkinson, qui offre par ailleurs un polymorphisme de symptômes beaucoup plus riches que cela n'est admis actuellement. La 3-OMD, métabolite de la Dopa jouit de propriétés intéressantes. Ne constituant pas à elle seule une thérapeutique du syndrome de Parkinson, en combinaison avec la L-Dopa + IDC, c'est un adjuvant très utile pour diminuer ou faire disparaître les fluctuations nycthémérales de l'action de la Dopa.

R E S U M E N

El empleo de la L-Dopa sola en una dosis promedio de 5 gm. diarios, al tratamiento del síndrome parkinsoniano, a pesar de implicar la aparición de numerosos efectos secundarios, da resultados espectaculares que se traducen en una mejoría del orden del 60 % de los signos parkinsonianos, en el 75 al 80 % de los pacientes. La asociación de un IDC a la L-Dopa conduce a resultados aún más favorables. La inhibición de la DC extracerebral da lugar a una buena absorción de la L-Dopa a nivel intesti-

nal limitando su metabolización periférica. Facilita el pasaje de la barrera hematoencefálica enzimática. En el plano clínico, permite la reducción de la dosis diaria de L-Dopa necesaria, y se produce la disminución o abolición de los efectos secundarios cardiovasculares y digestivos, el aumento de la eficacia de la L-Dopa. Entre los efectos secundarios los que más comprometen el éxito del tratamiento son los movimientos anormales que son de dos tipos: movimientos estereotipados y movimientos similares a

los de la corea; estos son menos graves y considerablemente menos frecuentes cuando la L-Dopa está asociada a un IDC en dosis suficientes. Sin embargo la L-Dopa sola o combinada con un IDC a pesar de sus efectos espectaculares no constituye una terapéutica radical del síndrome de Parkinson. No se trata de una terapéutica que compense todas las deficiencias; si bien indudablemente corrige un trastorno metabólico específico, probablemente existan otros trastornos metabólicos aún desconocidos en

el síndrome de Parkinson, que ofrece un polimorfismo de síntomas mucho más variado que el que se admite actualmente. La 3-OMD, metabolito de la Dopa tiene propiedades interesantes. No constituye por si misma una terapéutica del síndrome de Parkinson pero combinada con la L-Dopa y un IDC es un elemento coadyuvante sumamente útil para disminuir o hacer desaparecer las fluctuaciones nictemerales de la acción de la Dopa.

S U M M A R Y

L-Dopa administered alone in an average dosis of 5 gm. a day constitutes an effective therapy of parkinsonian syndrome leading to spectacular results in spite of its numerous secondary effects; it allows a 60 % improvement of parkinsonian signs 75 to 80% of the patients. Association of L-Dopa to an IDC leads to even more favourable results. Inhibition of extracerebral DC allows a good resorption of L-Dopa at the intestinal level while it limitates peripheral metabolism. This inhibition facilitates the passage of the hematoencephalic enzymatic barrier. In the clinical aspect, this results in a reduction of the necessary daily L-Dopa doses, in a diminution or abolition of cardio-vascular and digestive secondary effects, in an increase of L-Dopa efficacy. Among secondary effects those most endanger the success of treatment are abnormal movements, which are of two ty-

pes: stereotyped movements and movements similar to those of chorea; these are not so serious and significantly less frequent when L-Dopa is associated to sufficient doses of an IDC. Anyway, L-Dopa alone or associated to an IDC is not, in spite of its spectacular effects, a radical therapy of Parkinson syndrome. It is not a therapy for all the deficiencies it certainly corrects a specific metabolic disturbance but there are probably other metabolic disturbances still unknown in the Parkinson syndrome, which presents much richer polymorphysm of symptoms than the one admitted now. 3-OMD is a Dopa metabolite presenting interesting properties. It does not constitute in itself a therapy of the Parkinson syndrome, but combined with L-Dopa and IDC it is a useful adjuvant to diminish or abolish nictemeral fluctuations of Dopa.

Z U S A M M E N F A S S U N G

Die Behandlung des Parkinsonsyndroms mit L-Dopa allein zu 5 gr. pro Tag gibt, trotz der vielen Nebenerscheinungen dramatische Resultate mit einer Besserung Parkinsonsymptome um 60 % bei 75-80 % der Patienten. Die Kombination von L-Dopa mit einem IDC gibt sogar noch bessere Ergebnisse. Die Inhibition der extrazerebralen DC hat als Folge eine gute intestinale Resorption der L-Dopa, indem die pe-

ripherische Metabolisierung begrenzt wird. Sie erleichtert die Passage der enzymatischen hemato-zerebralen Barriere. Auf klinischem Gebiet ergibt sich daraus eine Verminderung der Dosen von L-Dopa und eine Verminderung der tagelichen Dosis bedeutet die Vermeidung der kardiovaskulären und digestiven Seiteneffekte und eine Vermehrung der Wirksamkeit der L-Dopa. Unter den Nebenerscheinungen sind es die

anormales Bewegungen, die am meisten den Behandlungserfolg in Frage stellen koennen. Es gibt zwei Arten: stereotype Bewegungen und Chorea aehnliche Bewegungen; sie sind weniger heftig und sind weniger haeufig, wenn man mit L-Dopa ein IDC in genuegender Dosis gibt. Jedenfalls, die L-Dopa allein oder zusammen mit IDC stellen keine radikale Therapie des Parkinsonsyndroms dar, trotz ihres dramatischen Erfolges. Es handelt sich nicht um eine etiologische Therapie; gewiss korrigiert sie eine spezifische Stoffwechselstoe- rung, aber es gibt wahrscheinlich noch an-

dere Stoffwechselstoerungen beim Parkin- sonsyndrom, die bisher unbekannt geblie- ben sind, ein Syndrom der uebrigens einen Polymorphismus an Symptomen aufweist, der viel reicher ist als man zur Zeit annimmt. Die 3-OMD, Metabolit der Dopa hat interessante Eigenschaften. Da sie allein kein therapeutisches Mittel beim Parkin- sonsyndrom ist, stellt sie in Kombination mit L-Dopa und IDC eine sehr nuetzliche Adjuvanz dar, um die nycthemerale Schwankungen des Dopa-Effektes zu ver- mindern oder zum verschwinden zu brin- gen.

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Treatment of Cerebrovascular Disorders

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In the past few decades we have witnessed a striking increase in knowledge regarding the pathogenesis of cerebrovascular disorders. Unfortunately, this has not been accompanied by a corresponding degree of improvement in the prevention and treatment of these disorders. This paper will briefly review some of the evidences regarding current modes of therapy.

PREVENTION

Significant reduction of mortality and morbidity due to cerebrovascular disorders must ultimately depend on effective preventative measures.

Attempts to identify "stroke prone" individuals prior to the development of symptomatic states have been largely unrewarding¹¹. As might be expected, those conditions known to be associated with an increased incidence of coronary artery disease, that is, hypertension, peripheral vascular disease, diabetes mellitus, hypercholesterolemia and possibly smoking, are also associated with an increased incidence of cerebrovascular disorders³⁶. The presence of clinical ischemic cardiac disease or even EKG changes suggesting ischemic cardiac disease are also associated with an increased susceptibility of "stroke". At the present time, however, there is little evidence that effective treatment of ischemic cardiac disease, diabetes mellitus or the

various hyperlipidemic states will in any way influence the subsequent development of cerebrovascular disorders.

On the other hand, effective treatment of hypertension has apparently resulted in reducing the incidence of cerebrovascular disorders in such individuals^{28, 63}. The lowering of blood pressure in hypertensive patients who have had "strokes" has also resulted in apparent decreases in mortality and recurrence rates of "stroke"⁴⁰. It should be noted, however, that in the only available controlled study on the effect of treatment of hypertension, no demonstrable difference was observed between treated subjects and controls with regard to the development of cerebrovascular disease³⁴.

A recent study of cerebrovascular disease mortality rates in the U.S.A. showed marked variations in reported rates in various geographic locations³⁹. It would thus appear that pathological studies and other investigations of possible risk factors in selected populations may eventually prove valuable in the determination of etiological factors.

NATURAL HISTORY OF "STROKE"

Accurate knowledge of the natural history of cerebrovascular disorders is of course essential to the evaluation of any therapeutic measure. The available studies on the prognosis after "stroke", most recently reviewed by Ford and Katz²⁴, show rather remarkable variations among different series of patients. For example, early mortality (in the first week after the

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TABLE
VASCULAR CAUSES OF THE STROKE
SYNDROME

- A. Ischemia and Infarction**
1. Atherosclerosis in neck vessels and intracranial arteries:
 - a. with thrombosis
 - b. without thrombosis
 2. Thrombosis without atherosclerosis:
 - a. arteritis — collagen disorders — syphilis, etc.
 - b. trauma to neck arteries
 - c. hematologic disorders — polycythemia — sickle cell anemia
 - d. "hypercoagulable" states — pregnancy — contraceptive medication (?)
 3. Embolism:
 - a. cardiac — atrial fibrillation — mural thrombus — endocarditis (septic and marantic)
 - b. atherosclerotic — from neck arteries
 - c. paradoxical
 4. Systemic Hypotension:
 - a. cardiogenic
 - b. hypovolemic
 - c. drug induced
 - d. idiopathic postural
- B. Intracerebral Hemorrhage**
1. Hypertensive
 2. Rupture of congenital aneurysm or vascular malformation
 3. Bleeding disorder
- C. Venous Sinus Thrombosis**
- associated with — infection — dehydration — "hypercoagulable" states (postpartum, postoperative)

onset) varied from 14 to 58 per cent in different series. Long term studies of survivors of the initial "stroke" showed similar variability, with the two-year mortality rates ranging from 17 to 43 per cent and five-year mortality rates ranging from 38 to 60 per cent. The recurrence rate of "stroke" in survivors of the first "stroke" varied from 13 to 30 per cent while estimates of eventual death due to cerebrovascular disease in survivors ranged from 17 to 53 per cent. It has even been suggested that after the first month, survivors of "strokes" of all types show three and five-

year mortality rates similar to those of the general population²⁰. Other studies, however, indicate a marked reduction in life expectancy for survivors of "strokes" as compared to the general population². Long-term studies on the eventual prognosis of patients with cerebrovascular insufficiency (or transient ischemic episodes) give similarly conflicting results^{3, 16, 41}.

It is against this background of rather wide variation in the reported mortality and recurrence rates of "stroke" that one must attempt to evaluate the results of specific therapeutic measures. The difficulties in comparing the results of such therapeutic efforts in different institutions and different patient populations are obvious. It is only in recent years that adequately controlled therapeutic trials have been undertaken.

DIAGNOSIS

Absolutely basic to the question of therapy is the problem of accurate clinical and pathological diagnosis. The largest contribution to our knowledge of cerebrovascular disorders in recent years has been the recognition of the multiplicity of responsible pathogenetic mechanisms⁴². Perhaps outstanding in this regard have been studies related to occlusive disease of the extracranial cerebral arteries, vertebral-basilar occlusive syndromes, cerebrovascular pathology due to hypertension, and the concept of cerebrovascular insufficiency.

The major vascular causes of the stroke syndrome are listed in the accompanying table. In many patients with stroke syndromes, the onset and subsequent course of the illness, and the associated medical findings will provide sufficient evidence to establish a reasonably accurate etiological diagnosis. However, it has become increasingly clear that the clinical profiles traditionally used to separate patients within these major categories are not always reliable^{14, 95}. For example, intracerebral hemorrhage does not necessarily occur only in hypertensive individuals during periods of activity, and may not

be accompanied by headache, loss of consciousness and bloody cerebro-spinal fluid, and is not necessarily fatal. A large cerebral infarct may behave like a hemorrhage, and a small hemorrhage may mimic the classical clinical picture of cerebral thrombosis. Even some cases of cerebral embolism have been reported to have a subacute onset²³. Cerebral ischemia and infarction due to extracranial vascular disease can frequently not be differentiated by simple clinical means from the clinical picture produced by intracranial vascular occlusions. Of considerable significance is the fact that in many large series of patients admitted to hospitals with the diagnosis of "stroke", approximately 5 to 10 per cent of such patients have been found to be suffering from non-vascular cerebral lesions, especially intracranial mass lesions.

It is primarily because of these diagnostic problems that cerebral angiography has found such extensive application in the diagnosis and management of cerebrovascular disorders and stroke syndromes. Indeed, in some centers, cerebral angiography is apparently performed in virtually all patients with stroke syndromes. The use of cerebral angiography should rather be limited to those patients in whom the information so obtained is necessary not merely for anatomical diagnosis, but for the institution of the most appropriate therapy.

The subsequent discussion will be limited to specific therapeutic measures which have been advocated for those conditions which may result in cerebrovascular insufficiency (or transient ischemic episodes), cerebral infarction and intracerebral hemorrhage. The problem of intracranial aneurysms and subarachnoid hemorrhage will not be considered.

ACUTE MEDICAL CARE

The acute medical care of the patient who has just suffered a "stroke" due to cerebral infarction or stable non-fatal cerebral hemorrhage will, of course, depend on the degree of neurological dysfunction. The patient with minor or even major

hemiparesis without impairment of consciousness usually presents a relatively simple nursing problem. On the other hand, in severely obtunded or comatose patients, or those with significant brain stem dysfunction, survival itself is often dependent on the excellence of the general nursing and medical care.

Proper positioning and suctioning will insure adequate ventilation in the majority of patients. Intermittent assisted ventilation (e. g. intermittent positive pressure breathing) may prevent atelectasis and pneumonia. Oxygen therapy is not usually necessary unless decreased arterial PO_2 or O_2 saturation are demonstrated, or obvious cyanosis is present. If cardiac failure is present, oxygen may be a helpful adjunct to therapy.

Antibiotics are not indicated for the prevention of pulmonary infection. Adequate nursing care is a much more effective prophylactic measure. If pneumonia occurs, adequate attempts should be made to isolate the organism and the infection should be treated vigorously with the appropriate antibiotic. Tracheostomy is rarely indicated and its use should be limited to those patients in whom significant neurological recovery appears possible.

Proper positioning and frequent turning are essential for the prevention of the pulmonary complications and skin breakdown. The comatose or severely obtunded or hemiplegic patient should be turned at least every two hours. The use of foot boards and hand-roll splints and passive range of motion exercises should be instituted immediately for the prevention of unnecessary and disabling contractures.

If the blood pressure is elevated, it is frequently due to pre-existing hypertension. In some patients, however, the blood pressure elevation may be a result of the cerebral lesion, usually on the basis of increased intracranial pressure. In other cases, a recent severe rise in blood pressure may have preceded the "stroke", thus raising the question of "hypertensive encephalopathy". It is often not possible to differentiate these causes of increased blood pressure in a patient with a "completed

stroke" and thus the blood pressure should be controlled. This may require the use of parenteral reserpine, hydralazine or methyl-dopa. In general, diastolic blood pressure need not be lowered below 100 mm. of mercury. Some hypertensive patients with strokes respond to even small doses of reserpine with precipitous drops in the blood pressure. Marked increases or decreases in blood pressure during this immediate postinfarction stage may be associated with increased symptomatology and should be avoided. Persistent hypotension may occur terminally in patients with extensive cerebral or brain-stem lesions. In less severely involved patients, persistent hypotension is often secondary to underlying cardiac dysfunction, electrolyte imbalance, hypovolemia or other general systemic factors.

Cardiac status should be carefully evaluated in all patients presenting with a stroke syndrome. Approximately 20 per cent of elderly patients with cerebral infarction are found to have electrocardiographic and/or serum enzyme changes characteristic of recent or acute myocardial infarction. In such cases it is assumed that the "stroke" is probably due to embolism from a mural thrombus. Cerebral emboli may also be related to atrial fibrillation or endocarditis. Intermittent cerebrovascular insufficiency can be due to decreased cardiac output caused by arrhythmias or myocardial ischemia. Congestive heart failure, if present, should be treated with appropriate use of diuretics and digitalization.

Bladder care is often necessary because of incontinence. If possible, catheterization should be avoided. In males, an external condom-type drainage may be suitable. In females, disposable diapers may be adequate but more often indwelling catheterization is necessary. This leads, almost invariably, to some degree of urinary tract infection. Fecal impaction should also be avoided.

While these measures can be applied in any general medical ward, it has been our experience that they can be performed most effectively in an intensive care unit setting. In our institution, a three bed neurological intensive care unit designed

primarily for the care of patients with acute stroke syndromes is available. The quality of the care which can be obtained in such a setting, staffed by adequate numbers of experienced well-trained nurses, far exceeds that usually available.

In addition to general medical care, a wide variety of specific medical and surgical approaches have been proposed and utilized. The rationale for such forms of treatment will be briefly reviewed and commented upon.

ANTICOAGULANTS

At the present time, valid use of anticoagulants in cerebrovascular disorders appears to be limited to selected patients in three categories, namely: multiple cerebral embolism, transient ischemic episodes and "progressive strokes". The eventual role of anticoagulants in the management of each of these conditions is, however, by no means settled and the controversy over anticoagulant therapy may well rage on for many years.

Approximately 75 per cent of proven cases of cerebral embolism are related to atrial fibrillation, most often associated with rheumatic mitral stenosis. Other frequent causes of embolism include myocardial infarction with mural thrombus formation and subacute bacterial endocarditis⁸. Recurrent embolism can apparently be reduced in frequency by anticoagulation¹⁰. No adequately controlled study, however, of the use of anticoagulants in recurrent cerebral embolism has been performed as yet. In view of the tendency of embolic cerebral infarcts to be quite hemorrhagic, there is some theoretical rationale for waiting at least several days or even weeks following the embolism before instituting anticoagulation. The actual risk of hemorrhage into a hemorrhagic infarct is unknown but may be considerable. Such treatment is obviously aimed at prevention of recurrent embolism and not at restoration of function in the infarcted area.

Transient ischemic episodes (or cerebrovascular insufficiency) in either the carotid

or vertebral-basilar distribution constitute the most widely accepted reason for anticoagulant therapy in cerebrovascular disease. The ultimate prognosis of patients with transient ischemic episodes is still unknown. The incidence of subsequent "completed strokes" in patients with transient ischemic episodes may be as high as 20 per cent but has also been reported to be as low as 1 to 5 per cent. Initial reports suggested a marked reduction in the frequency of transient ischemic episodes in patients who were placed on anticoagulants⁶¹. The only well controlled study⁴ also suggested that anticoagulation was probably of value in the treatment of these transient ischemic episodes although ultimate mortality was identical in the treated and control groups.

In patients with "progressive stroke" syndromes, anticoagulant therapy has been claimed to result in reduction of mortality and morbidity^{9, 62}. However, the real incidence of this form of stroke is still unknown with estimates of frequency ranging from 1 to 40 per cent of stroke patients. Apparent progression of symptoms may be due to progressive thrombosis in some cases, but may also be due to other factors such as cerebral edema, hemorrhage or multiple embolism. Therefore, anticoagulation cannot be recommended for all "stroke" patients in whom signs and symptoms progress after the initial acute onset. Patients with apparent progressive basilar artery thrombosis should probably receive the somewhat questionable benefit of anticoagulants, however.

In patients with completed stroke syndromes of the athero-sclerotic-thrombotic variety, anticoagulant therapy appears to have little benefit to offer^{21, 33}. It is our practice not to use anticoagulants in patients with completed stroke syndromes. There are, however, several reports suggesting that the use of anticoagulants following a thrombotic stroke may result in a reduction of subsequent thromboembolic complications^{27, 43, 44}.

Lumbar puncture should be performed prior to instituting anticoagulant therapy in patients with recent symptoms. This

will be of some aid in ruling out the presence of subarachnoid and intracerebral hemorrhage. The presence of hypertension should probably be considered an absolute contraindication to the use of anticoagulants. For those conditions in which anticoagulants may be useful, the duration of therapy for optimal results is unknown, although it appears likely that maximal benefit is obtained in the initial six to twelve months of therapy.

OTHER MEDICAL MEASURES

Patients with postural hypotension may experience focal as well as diffuse cerebrovascular insufficiency on assuming the erect position. It has also been suggested that nocturnal hypotension may be responsible for the increased incidence of onset of cerebral infarction during the night⁷¹. Despite this, transient nocturnal or postural hypotension is probably not a frequent cause of transient ischemic episodes or of cerebral infarction³⁷. If postural hypotension can be demonstrated and is apparently temporally related to symptoms of cerebrovascular insufficiency, it should be treated. A variety of methods including elastic leg bandages, increased salt intake, and mineralocorticoids may be used.

Vasodilator drugs have been widely advertised and prescribed on the assumption that cerebral circulation and function will thereby be improved^{5, 17, 38, 53, 68}. Inhaled CO₂ is still the most potent cerebral vasodilator available⁶⁴. It should be emphasized that there is virtually no evidence that the use of vasodilator drugs or inhaled CO₂ is associated with therapeutic benefit to patients with cerebrovascular disorders. One study, however, suggested that "stroke" patients treated with intravenous papaverine showed a greater degree of improvement than did control subjects not receiving this drug⁴⁸. This unusual and possibly significant finding requires verification by other studies.

Cervical sympathectomy and stellate ganglion block or removal have been utilized in attempts to improve the cerebral circu-

lation, but no definite therapeutic benefit of these procedures has been demonstrated^{8, 25, 60}.

Available reports on the use of hyperbaric oxygen therapy in patients with acute stroke syndromes suggest that some patients will show clinical improvement while receiving hyperbaric oxygen, but that such improvement is not maintained when the treatment is discontinued^{31, 35}.

In patients with recent thrombotic strokes, blood viscosity and fibrinogen levels may be increased¹⁹. These changes in turn may adversely affect the cerebral microcirculation. The use of low molecular weight dextran in experimental cerebral infarction in animals has resulted in improvement of the cerebral microcirculation and in decreased size of cerebral infarction^{7, 13, 65}. No data on the use of low molecular weight dextran in humans with cerebral infarction is available as yet, but this method is being currently investigated in a large joint project in the U.S.A.

Attempts to prevent possible thrombus formation in patients with transient ischemic episodes by the use of drugs which reduce platelet "stickiness" have shown no beneficial effect^{1, 49}.

The use of thrombolytic agents in the treatment of acute cerebral thrombosis has also not met with measurable success and may be hazardous⁴⁷. However, adequate clinical trials at controlled blood levels of thrombolytic activity have not been reported. Recent successful use of such agents in the management of peripheral vascular disease⁵⁵ suggests that such trials may be useful.

Stroke patients treated with estrogenic substances do not experience decreased recurrence of stroke or reduction of subsequent mortality rates⁵⁶.

In patients with extensive acute cerebral infarction, the use of adrenocortical steroids, especially dexamethasone, has been advocated for the reduction of accompanying cerebral edema⁵⁷. The results of these studies are inconclusive, but do suggest that, in some cases, the use of steroids may prevent and decrease cerebral edema and result in clinical improvement.

SURGICAL MANAGEMENT

The role of surgery in the management of patients with cerebrovascular disorders has been largely directed towards the restoration of normal blood flow in atherosclerotic extracranial cerebral arteries, especially the proximal internal carotid artery^{12, 15, 50, 70}. Endarterectomy may prevent the progression of a stenotic atherosclerotic lesion to a complete occlusion of the vessel. Removal of ulcerated atheromatous plaques in the neck vessels may also remove the source of microemboli to the cerebral vessels. Approximately 75 per cent of patients with stroke syndromes subjected to angiography will have atherosclerotic occlusive lesions in surgically accessible neck vessels^{22, 30}. However, the relationship between a demonstrated stenotic lesion in the neck arteries and the clinical stroke syndrome is often far from clear.

Carotid endarterectomy has been claimed to result in clinical improvement or improved long-term prognosis^{18, 32, 52}. However, preliminary results of the only controlled study of such therapy indicate that surgical treatment is possibly beneficial only in patients with unilateral carotid artery stenosis who have experienced transient ischemic episodes, or have suffered mild neurological deficit⁶. There is no evidence that endarterectomy in severe completed or progressive stroke syndrome is of benefit to the patient.

The natural history of the so-called "subclavian steal syndrome" is as yet unknown, but surgical therapy is probably indicated if symptoms of vertebral-basilar insufficiency are present⁵⁴.

Cervical spondylosis may cause compression of the vertebral arteries because of osteophyte formation. This may result in symptoms of vertebral-basilar insufficiency especially on rotatory movements of the neck²⁹. Decompressive surgery may be indicated in selected cases if vascular compression can be identified by angiography. A trial of cervical immobilization should be attempted before resorting to surgery.

Similar compression and even thrombosis of the vertebral artery has occurred in

patients with rheumatoid arthritis of the cervical spine. Posterior occipito-axial fusion has been suggested for such cases⁶⁷.

Fibromuscular disease of the extracranial internal carotid artery has been recently implicated as a cause of obstructive cerebrovascular disease and has been treated with internal dilatation⁵¹. The significance of this angiographic finding and the need for such therapy is still unknown.

Surgical evacuation of an intracerebral hematoma may occasionally be beneficial to the patient⁵⁸. However, the only large controlled study suggests that such treatment does not really improve the ultimate prognosis⁴⁵. Patients with spontaneous cerebellar hemorrhage should receive the potential benefit of surgery if the diagnosis of this otherwise fatal condition can be established soon enough⁴⁶.

In some patients with massive cerebral infarction accompanied by cerebral edema, decompressive craniotomy may prevent transtentorial herniation and thus be life-saving²⁶. This possible benefit must be of course be weighed against the extensive neurological deficit usually present in survivors of such a lesion.

REHABILITATION

Efforts at rehabilitation of the stroke patient should begin virtually on admission to the hospital⁶⁶. The basic aims of these efforts are that the patient should eventually be able to walk and sit, to dress and feed himself to get in and out of bed and to attend to toilet functions unaided. These aims are best accomplished by utilizing a team effort of the physician, nursing staff, physiotherapist, speech and occupational therapists and social workers. The early nursing care is of extreme importance in the prevention of bed sores and unnecessary contractures which may prolong hospitalization and result in increased disability. The effective application of such a team approach appears to have resulted in an increased percentage of patients regaining their independence after a stroke. There is, however, a serious lack of knowledge about the response of stroke patients to rehabilitative care⁶⁹. No strictly controlled studies on the value of rehabilitative care in stroke victims have yet been reported.

S U M M A R Y

Current modes of therapy of cerebrovascular disorders have been reviewed. New and effective therapeutic and preventative measures are urgently needed. Adequate therapy is largely dependent on accuracy of diagnosis. The general medical care required for patients with acute stroke syndromes can best be provided in a neurological intensive care unit.

Anticoagulant therapy is probably useful in the management of multiple cerebral embolism and transient ischemic episodes. Endarterectomy appears to be a useful procedure only in patients with unilateral carotid stenosis associated with transient ischemic episodes or mild neurological deficit.

R E S U M E N

Se ha pasado revista a los recursos corrientes de terapéutica de los trastornos cerebro vasculares. Se hacen con urgencia necesarias nuevas y efectivas medidas de prevención y tratamiento.

Una terapéutica adecuada depende en alto grado de la precisión en el diagnósti-

co. El mejor cuidado de los pacientes afectados de un accidente vascular cerebral agudo se puede realizar en una unidad de tratamiento neurológico intensivo.

La terapéutica con anticoagulantes es útil probablemente en la atención de múltiples embolias cerebrales y de episodios

isquémicos transitorios. La endarterectomía parece mostrarse como un recurso positivo sólo en pacientes que padecen de esteno-

sis carotídea unilateral asociadas a episodios isquémicos transitorios o a defectos neurológicos leves.

R É S U M É

Des modes courants de thérapeutique des désordres vasculaires cérébraux ont été exposés. Un grand besoin existe de nouvelles et efficaces mesures thérapeutiques et préventives. Une thérapeutique appropriée dépend en large mesure d'un diagnostic précis. Le meilleur soin médical des malades avec un accident vasculaire cérébral peut être fourni dans une unité neurologi-

que de soins intensifs. Une thérapeutique anticoagulante n'est probablement indiquée que dans le traitement des embolies multiples et des accidents ischémiques transitoires. L'endartériectomie semble être indiquée seulement dans des cas de sténoses carotidiennes unilatérales associées avec des accidents ischémiques transitoires ou avec des déficits neurologique légers.

Z U S A M M E N F A S S U N G

Gegenwärtige Behandlungsweisen der Zirkulationsstörungen des Gehirns wurden kritisch betrachtet. Neue und wirksame therapeutische und preventive Methoden sind dringend erforderlich. Eine angemessene Therapie hängt zum grossen Teil von der Richtigkeit der Diagnose ab. Die allgemeine ärztliche Betreuung von Kranken mit akutem Hirnschlag kann am besten in einer "intensive care unit" gewährleistet

werden. Antigoagulationstherapie ist wahrscheinlich angebracht in der Behandlung von mehrfacher Hirnembolie und intermittierender Ischämie. Thrombendarteriektomie scheint eine erfolgreiche Massnahme zu sein nur bei Patienten mit einseitiger Carotisstenosis verbunden mit intermittierender Ischämie oder leichtem neurologischem Ausfall.

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Treatment of Periodic Disturbance of Consciousness in the Specific Type of Hepatocerebral Degeneration (inose type) a Trial with Gobab

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INTRODUCTION

Inose² first described from the histopathological point of view a specific type of hepatocerebral degeneration, which can be differentiated from Wilson's disease. Since that time, numerous reports concerning this disease have appeared^{3, 1}, and it is now considered that the portal systemic encephalopathy described by Sherlock et al.⁷ is identical with it.

The mechanism of the periodic disturbance of consciousness characteristic of this disease is as yet unknown, so that treatment has not been fully established. As a therapeutic trial, we have administered a new drug, GOBAB (γ -hydroxy- β -aminobutyric acid [DL form]), continuously or intermittently to four cases of this disease for a long period. A decrease or disappearance of the disturbance of consciousness was observed. The experiences are summarized in this paper.

SUBJECTS

Table 1 summarizes clinical symptoms of the four cases treated with GOBAB and Table 2 summarizes results of liver func-

tion tests, blood ammonia and citrulline in the body fluid for these cases.

CASE I. 31-year-old male: Factory worker.

Family history: Non-contributory.

Past history: Since childhood, the patient had been taking a one-sided diet, particularly liked beans and he was the smallest of the siblings.

Present illness: In August 1966, while he was hospitalized with the diagnosis of gastric ulcer, the first disturbance of consciousness from twilight state to coma was experienced. In the same month, he was admitted to this hospital.

His height was 158 cm and body weight 47 kg. Development and nutritional state was slightly below average. No jaundice, venous dilatation of the abdominal wall or hepatosplenomegaly were noted.

During hospitalization, he frequently complained of headache and insomnia. Episodes of disturbance of consciousness lasting from several hours to one day (mostly twilight state) occurred once to twice a week until the beginning of December of the same year. Thereafter he fell into coma several times. Most of these disturbances of consciousness occurred at

TABLE 1
Summary of Clinical Symptoms

	Case 1	Case 2	Case 3	Case 4
Age	31-year-old	41-year-old	31-year-old	52-year-old
Sex	Male	Male	Female	Male
Past history	Gastric ulcer at age 28	Pancreatic necrosis at age 38	Jaundice at age 16	High fever at age 5
Duration of disease	3 years	2 years	11 years	2 years
General emaciation	(+)	(+++)	(+++)	(++)
Liver symptoms	(—)	(+)	(++)	()
Flapping tremor	(—)	(—)	(+++)	(+)
Exaggerated tendon reflexes	(—)	(++)	(—)	(—)
Dementia	(±)	(++)	(±)	(+)

Note: Signs of (—), (±), (+), (++) and (+++) indicate no symptom, suspicious symptom, slight symptom, moderate symptom, and advanced symptom respectively.

night. In accordance with the intensity of the attacks, extrapyramidal signs such as excessive movement, fine tremor of the fingers, and an increase of muscle tone appeared together with exaggerated tendon reflexes and pathologic reflexes.

Results of tests: Liver function tests stayed normal throughout the course. Blood ammonia examined 54 times revealed a minimum value of 89 γ /dl and a maximum value of 639 γ /dl, with higher values always encountered during attacks. However, abnormally high values were also frequently noted during clear consciousness. Blood ammonia increased from evening to night. Abnormally high values of citrulline in the body fluid also showed parallel fluctuations. EEGs were recorded a total of 67 times at various states of consciousness. Typical triphasic waves were recorded mostly in the twilight state (Fig. 1).

CASE 2. 41-year-old male: Fish-dealer.

Family history: Non-contributory.

Past history: Although the patient had been small since birth, no remarkable disease was experienced. The diet mainly consisted of raw fish and beans (especially soyabeans) due to food preference.

Present illness: In March 1966, acute abdominal pains were experienced, and laparotomy was performed under the diagnosis of pancreas necrosis. Postoperatively, emaciation became even more pronounced, but he again started his normal business. However, his physical strength turned out to be not sufficient and he had to stop for rest. From February 1967, episodes of disturbance of consciousness reaching the degree of coma occurred repeatedly once or twice a week from late night to the next morning. In April of the same year, he was admitted to this hospital.

TABLE 2

Results of liver function test, blood ammonia and citrulline in the body fluid

Item of tests	Normal value	Case 1		Case 2		Case 3		Case 4
		At admission	At present	At admission	At present	At admission	At present	
Icterus index	2-8	4.1	6	6	5	7.4	7	5
CCFT	—~+	—	—	++	++	++	—	—
ZTT	less than 12	2.6	2.5	7.2	6.4	4.0	3.3	4.6
T'TT	less than 4	1.4	1.2	4.0	2.9	1.2	1.8	0.5
GOT	less than 40	19	13	45	30	16	16	15
GPT	less than 35	32	19	30	19	10	8	15
Alkaline phosphatase	less than 10	5.8	5.8	9.1	8.9	7.5	8.9	8.2
BSP 30'	—	20	—	28	25.6	—	14	—
45'	0.5 %	12	—	12	16	6	5.8	—
Serum total protein	6.5-8.3	6	6.9	5.8	5.8	7.2	6.2	6.9
Serum al.	62.8±1.4 %	66.6	57.2	43.9	45.4	64.1	66.8	64.9
α 1	3.2±1.2 %	3.4	5.2	4.9	7.1	3.0	5.1	4.8
α 2	8.6±1.0 %	10.2	12.5	11.4	12.1	9.0	6.8	9.1
β	10.1±0.4 %	8.8	9.9	7.3	9.2	9.0	8.5	8.5
γ	15.3±1.1 %	11.0	15.2	32.5	26.2	14.9	12.8	12.7
Blood ammonia (γ/dl)	less than 100	89-639		53-250		136-1230		100-222
Citrulline Serum	less than 30	70-745		77-538		168-752		212
(μmoles/l) Urine*	±	82-1566		186-295		17-152		
CSF	1.7	41-45		45-73		32-177		

* μmoles/day.

His height was 154 cm and body weight 39 kg, with marked emaciation. The hair was light brown and the skin lacked lustrous tone, without jaundice. Neither venous engorgement of the abdominal wall nor hepatosplenomegaly were noted. He was euphoric, and carefree with definite change in personality compared to previous times. Neurologically, no abnormality was noted except for exaggerated tendon reflexes.

After hospitalization, the attacks occurred

almost every night (Fig. 3), lasting from several hours to one, and occasionally two days. During an attack, muscle tone was increased, tendon reflexes were markedly exaggerated, and pathologic reflexes appeared. However, neither tremor of fingers nor flapping tremor were noted at any time.

Results of tests: Moderate functional disturbance of the liver was noted and a liver cirrhosis was confirmed by liver biopsy. In the test for liver circulation,

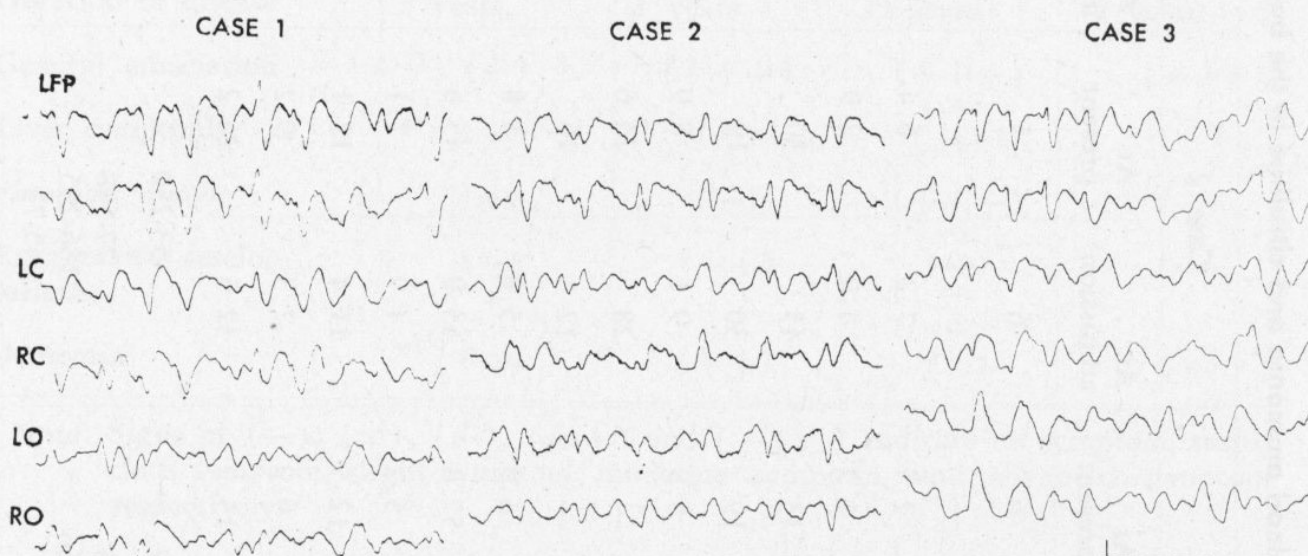


Fig. 1. — Triphasic wave in three cases. EEG was recorded by monopolar lead using the ipsilateral ear lobe as indifferent electrode. The mark represents 50 μ V, 1 second.

hepatic blood flow was as low as 383 ml/m²/min (normal value 800). However, an intra- or extrahepatic shunt was not evident. Blood ammonia examined 37 times so far revealed values ranging from 53 to 250 γ /dl. Citrulline in body fluid reached high values parallel with the blood ammonia. EEGs recorded 38 times in total revealed similar triphasic waves in the twilight state (Fig. 1).

CASE 3. 31-year-old female: Company employee.

Family history: Non-contributory.

Past history: At the age of two, the patient suffered a long lasting high fever and was in a considerably serious condition. She had preferred fat containing foods

from childhood, and had an episode of jaundice at the age of 16.

Present illness: Onset was presumably around the age of 19 years. Since that time, two to three attacks were experienced each year. At night, she would suddenly start singing or crying without reason. On the next day, she remembered nothing of the attack. Occasionally the state of excitation lasted two to three days and she would be unable to recall the attack. She had sometimes been treated by internists for a short time, and a disturbance of the liver function was pointed out once. The attacks gradually occurred also during the day and she repeated meaningless acts in a twilight state. In March 1967, she was

admitted to a psychiatric hospital under the suspected diagnosis of schizophrenia. Attacks of disturbance of consciousness from twilight state to coma occurred once a week. Tremor of fingers intensified in the twilight state and exaggerated tendon reflexes supervened in coma, together with pathologic reflexes. In May of the same year, she was admitted to this hospital under suspicion of the specific type of hepatocerebral degeneration.

Her height was 148 cm and body weight

44 kg. Development and nutritional state were somewhat below average. Mild bilateral exophthalmos was noted. Vascular spiders were prominent in the face. However, venous dilatation on the abdominal wall and hepatosplenomegaly were not observed. Since hospitalization, attacks of disturbance of consciousness ranging from twilight state and/or delirium to coma were frequently noted (Fig. 4). Aggravation of the symptoms were noted similarly at night. In the twilight state, flapping

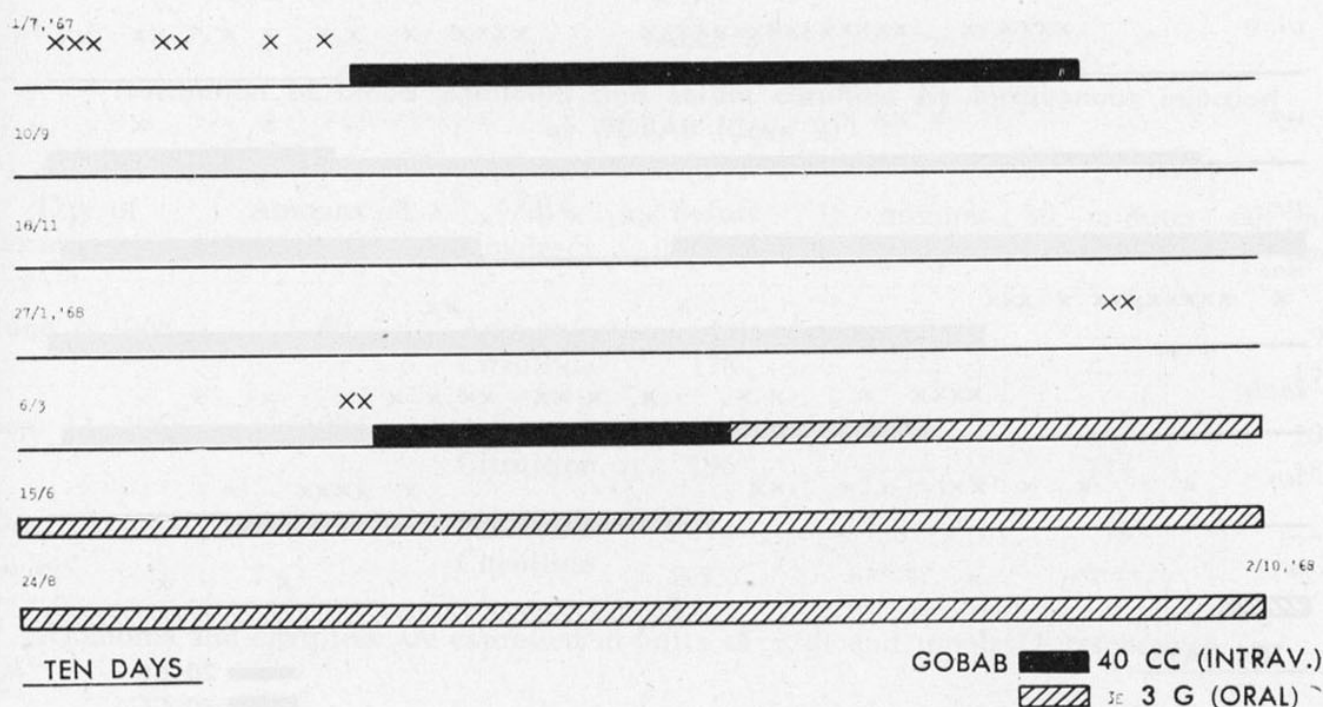


Fig. 2. — Changes in frequency of the bouts the use of GOBAB (Case 1).
Mark x indicates a bout of disturbed consciousness.

tremor of both upper extremities appeared with marked hypersalivation.

Results of tests: The patient revealed mild disturbance of the liver function. Tests of hepatic circulation revealed 40 % intrahepatic shunt (less than 15 % in normal subjects). Hepatic blood flow was as low as 600 ml/m²/min. Celiac arteriography revealed scanty hepatic arteries with narrowing, and no splenomegaly was confirmed. Blood ammonia examined 33 times ranged from 136 to 1230 γ /dl, suggesting continuous hyperammonemia. Citrulline in the body fluid was also high in parallel

with this. EEGs recorded 54 times showed frequent appearance of typical triphasic waves (Fig. 1).

CASE 4. 52-year-old male: Fish-dealer.

Family history: Non-contributory.

Past history: Body build was small from birth. At the age five, a high fever occurred and typhoid fever was suspected. Since childhood, the patient especially liked beans and raw fish.

Present illness: He had been rather short-tempered, but became more passive since a few years ago, with a tendency towards forgetfulness. Since that time in-

somnia and anorexia were noted, and more recently hypersalivation and emaciation became conspicuous. In June 1969, general malaise was experienced during the day and he became dazed at night, staying in the same state until morning. Hypersalivation and flapping tremor of both upper extremities were noted at that time. Similar attacks occurred twice with an interval of one week and he was admitted to the department of internal medicine of a hospital. Soon after admission, the fourth

attack occurred, lasting until the next day. EEG recorded during the attack revealed triphasic waves. He was then admitted to this department under the diagnosis of the specific type of hepatocerebral degeneration.

His height was 154 cm, body weight 40 kg. Growth and nutritional state were somewhat below average. There was no jaundice, venous dilatation of the abdominal wall or hepatosplenomegaly. His mental state was rather euphoric with a defi-

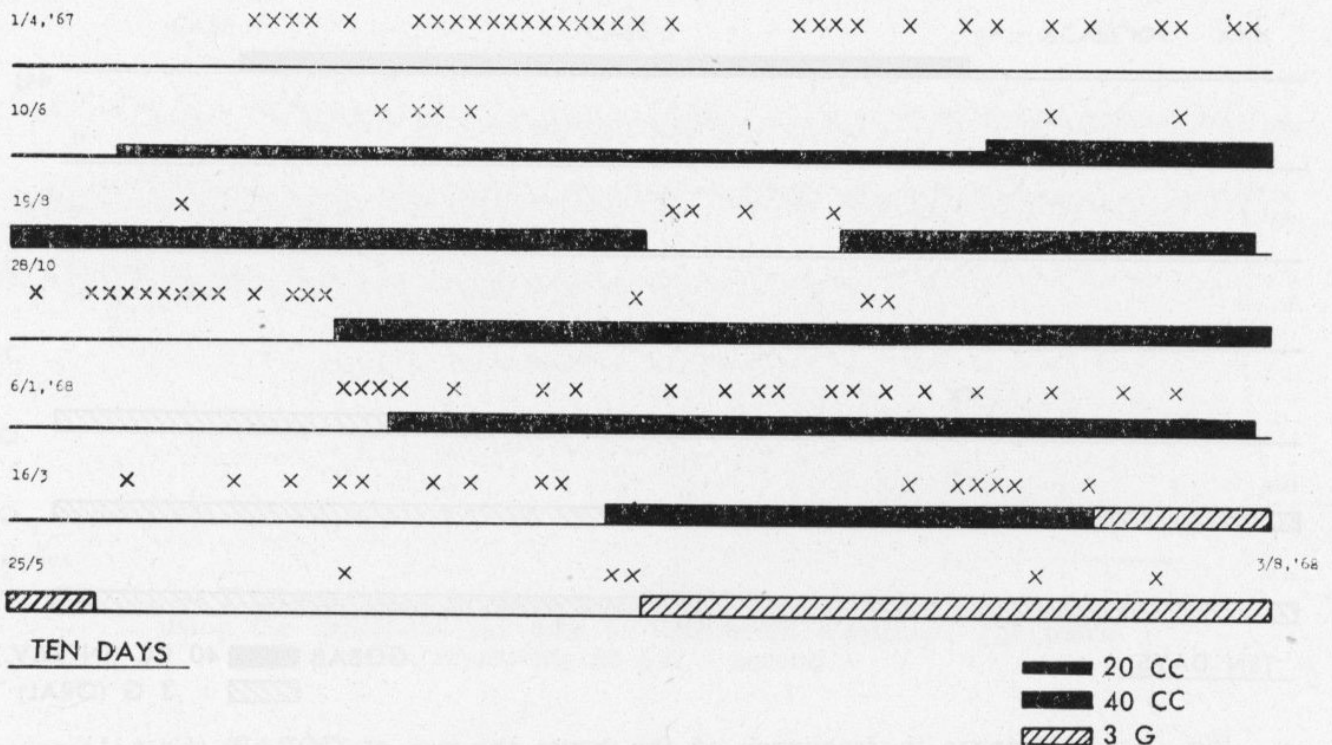


Fig. 3. — Changes in frequency of the bouts by the use of GOBAB (Case 2).

nite personality change. Neurological examination was negative except for lack of abdominal reflexes.

Results of test: General liver function tests were normal. Tests for hepatic circulation revealed slightly low hepatic blood flow, 624 ml/m²/min with elevated rate of intrahepatic shunt, 29.3 %. Celiac arteriography revealed narrowing of the branches of the hepatic arteries and widening of the branching angle of the hepatic veins. Blood ammonia examined for two days revealed 100 and 222 γ /dl, and blood citrulline showed a parallel elevation.

Results of blood sugar, serum electrolytes, and non-protein nitrogen gave values within normal limits in all four cases.

ADMINISTRATION OF GOBAB; METHOD AND RESULTS

In these four cases, GOBAB was administered orally or intravenously (5 % solution). In oral administration, 3-6 g of GOBAB was administered, while 20 (1 g)-40 (2 g) ml was daily injected intravenously. In these cases, the total period

of administration was 19, 22, 16 and 3 months respectively. The influence of treatment on the appearance of attacks of disturbance of consciousness is summarized in Fig. 2, 3 and 4.

In Case 1 (Fig. 2), frequently occurring attacks disappeared in response to intravenous injection of GOBAB but reappeared upon discontinuation of treatment. Readministration of this drug (intravenously, then orally) resulted in a complete disappearance of attacks until October 1969. Frequent

nocturnal headache and insomnia, encountered during hospitalization also disappeared and the patient is at present normally working at home.

In Case 2 (Fig. 3), frequently occurring attacks markedly decreased after the use of GOBAB intravenously and reappeared frequently upon discontinuation, as is clearly seen in Fig. 2. This tendency was especially evident during the initial period of the treatment. Interruption of the treatment always caused frequent attacks.

TABLE 3

Fluctuation of blood ammonia and serum citrulline by intravenous injection of GOBAB (Case 2)

Day of examination	Amount of injection (cc)	γ /dl* μ moles/l	Before injection	15 minutes later	30 minutes later	60 minutes later
June 2, 1968	80	Ammonia	190	—	—	90
		Citrulline	178	—	—	152
Sep. 11, 1968	100	Ammonia	219	—	147	204
		Citrulline	196	—	174	186
Dec. 18, 1968	100	Ammonia	210	87	79	—
		Citrulline	—	—	—	—

* Ammonia and citrulline are expressed in units of γ /dl and μ moles/l respectively.

In order to confirm further the effect of GOBAB, a large dose of this drug, 80-100 cc, was injected intravenously in Case 2, for observation of changes of clinical symptoms, blood ammonia and serum citrulline, along with recordings of EEG and visual evoked potential (VEP). As shown in Table 3, such tests were carried out three times. During each of these tests, the patient was undergoing an attack and was disoriented. EEG revealed some diffuse medium voltage 0-waves. Intravenous injection of GOBAB seemed to improve the clinical symptoms, and to decrease blood ammonia and serum citrulline. Although the changes in EEG were indistinct, VEP revealed a transient decrease of amplitude as shown in Fig. 5.

In Case 3, a decrease of the frequency of attacks was confirmed after initial treatment with intravenous injection of GOBAB (Fig. 4), but the effect became gradually indistinct. At 10 a. m. October 29, 1968, when the patient was in a dazed state, triphasic waves were recorded on EEG and blood ammonia reached the maximum value of 1230 γ /dl. Intravenous injection of 10- ml of GOBAB caused a fall of ammonia to 1170 γ /dl 15 minutes after administration. Citrulline also fell from 271 to 255 μ moles/l. However, no significant clinical or EEG changes were confirmed.

In Case 4, oral administration of 6 g GOBAB was started after hospitalization

and no attacks have been experienced since.

In Cases 1, 2 and 4, the patient himself recognized the effect of this drug.

In all the cases, various kinds of treatment were tried before and during the use of GOBAB. Restriction of protein diet, administration of antibiotics, various vitamins often in combination with glucose, arginine-glutamate and other drugs,

including prednisolone, CDP-choline, GABOB (γ -amino- β -hydroxybutyric acid) and meclofenoxate hydrochloride, failed to show significant effects. However, in Case 1 cytochrome-C appeared to be effective during the attack.

Intravenous administration of a large dose of GOBAB or long term oral administration did not show any side effects at all in any of the four cases.

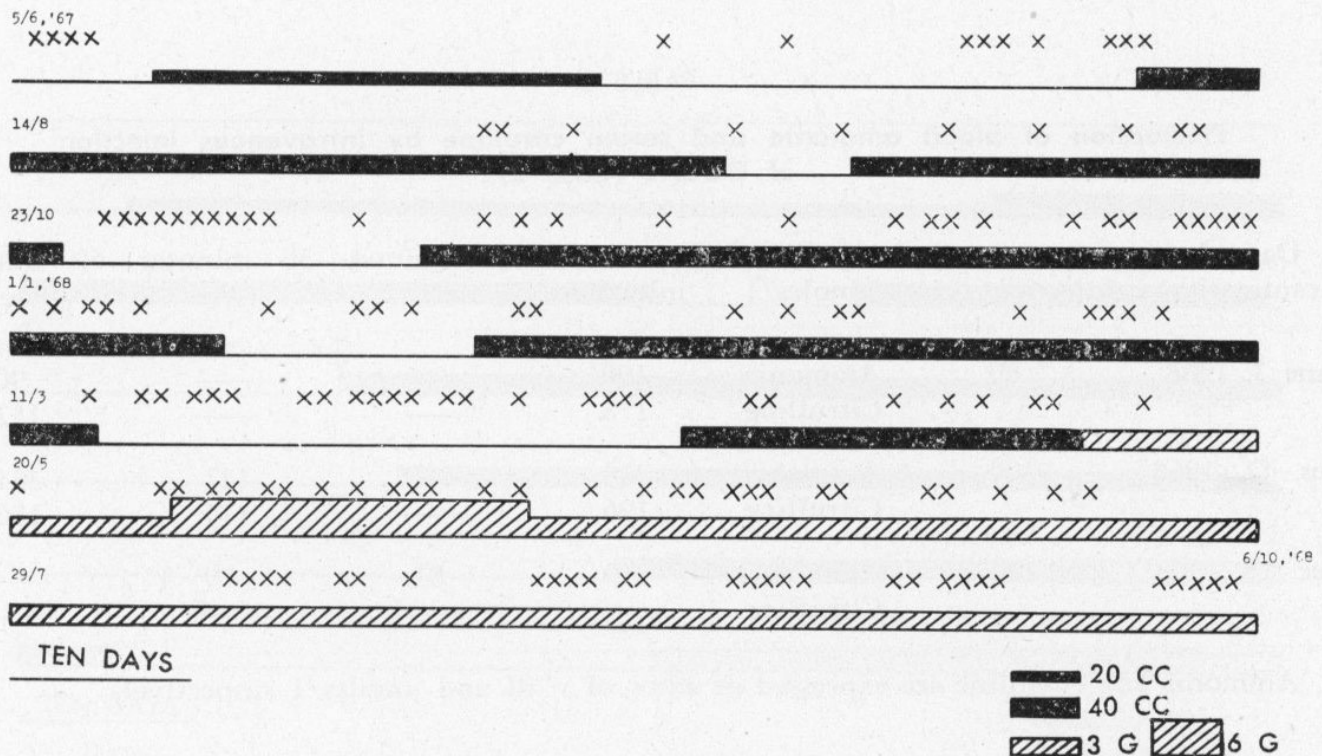


Fig. 4. — Changes in frequency of the bouts by the use of GOBAB (Case 3).

DISCUSSION

In all the four cases, the diagnosis of the specific type of hepatocerebral degeneration (Inose type) is probably justified, though a possibility of pseudoulegyria type by Shiraki et al.⁸, especially in Cases 1 and 3, can not be excluded without the knowledge of pathological findings.

One of the authors, Wada et al.¹¹ studied the clinical effects of GABOB on epilepsy and proved its positive effect. Following this, GOBAB was also tried to treat patients with various neurological disorders,

such as sequela of head trauma, cerebral arteriosclerosis and peripheral nervous diseases, and GOBAB also showed its positive effects¹².

Concerning the four cases described in this paper, it had been shown that various therapeutical efforts produced no positive results, except cytochrome-C in Case 1. Therefore GOBAB was tried first with Case 2, in an effort to eliminate repeated bouts of disturbed consciousness. A positive effect was obtained as expected, and subsequent use in Case 3, 1 and 4 gave results as described above.

It is rather difficult to evaluate the effect of GOBAB only from the clinical point of view, so it therefore seems necessary to add some objective measurements. During a biochemical investigation of this disease, we have found a marked and specific elevation of citrulline in the body fluid, as apart from other liver diseases⁵. EEG is indispensable for the objective expression of the level of consciousness, but a precise change is not always detected by routine recordings. However, it is assumed that the change of the VEP

reflects the change of level of consciousness rather accurately and it is not difficult to calculate the averaged VEP with a computer. Especially with this disease, amplitude of the VEP becomes larger than average in accordance with the intensity of the disturbance of consciousness, and the latent period of each type of wave of the VEP is prolonged¹⁰.

In Case 2, GOBAB was intravenously injected during a state of mild disturbance of consciousness, to compare clinical findings with the determination of blood ammonia, serum citrulline, and VEP, which were used as objective indices of the effectiveness of the drug. Consistent results obtained in all three examinations especially in Case 2 might serve to confirm the clinical experience of a positive effect of this drug during a disturbance of consciousness.

GOBAB was obtained accidentally during the process of synthesis of GABOB, which has been widely used clinically as a regulator of metabolic function of the brain in recent years in Japan. Although GOBAB is an isomer of GABOB, it has not been detected in vivo, and many things have remained unknown concerning its metabolic pathway. However, it was observed that this drug like GABOB⁶ exerts an inhibitory action on the central nervous system. As for the influence on the peripheral circulatory dynamics, this drug was reported to stimulate the parasympathetic nervous system to dilate blood vessels⁹. The use of this drug therefore probably exerts an inhibitory action on the stimulatory symptoms of the limbic system of the cerebrum secondary to hyperammonemia⁴. In both Cases 2 and 3, a decrease of the hepatic blood flow was confirmed. However, a secondary effect due to the vasodilating action of GOBAB cannot be excluded. During a disturbance of consciousness due to liver disease, intravenous injection of substance related to the urea cycle such as aspartic acid, glutamic acid, arginine and ornithine is known to produce positive effects^{1, 3, 14}. The use of GOBAB, which belongs to a similar amino-group also

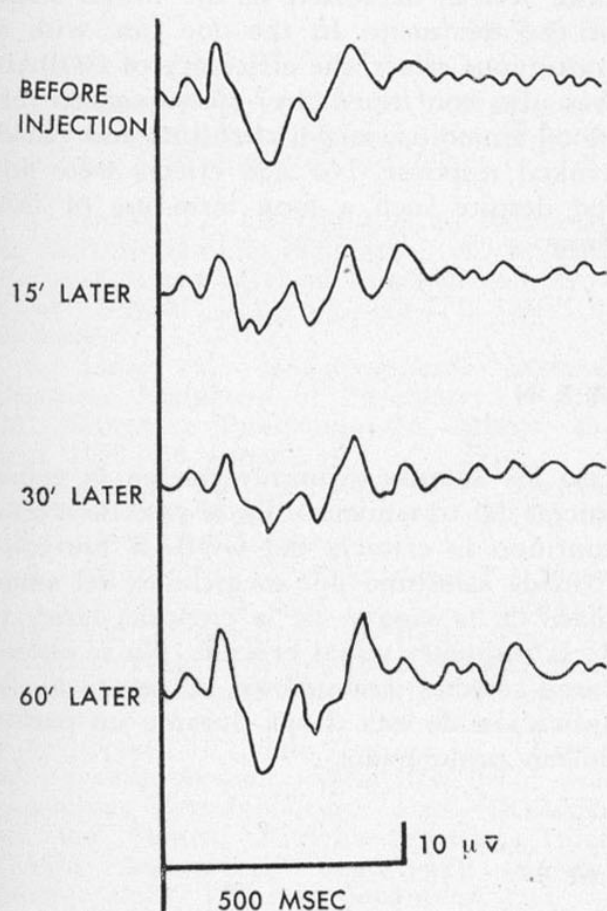


Fig. 5. — Changes in VEP in response to intravenous injection of GOBAB (Case 2). VEP was recorded from the occipital region; the responses to single flash stimulus repeated 20 times with more than one second interval were accumulated. Summation was carried out with a computer (ATAC-401, Nihon Kodan), making the left ear lobe indifferent electrode. This was recorded on September 11, 1968.

decreases blood ammonia and citrulline, possibly resulting in the clinical improvement. It might therefore be said that GOBAB has a similar mechanism of action such as aspartic acid.

GOBAB appears to have a positive effect on the occurrence of disturbance of consciousness in the specific type of hepatocerebral degeneration (Inose type). This not only helps serve the analysis of the pharma-

cological action of GOBAB but also may be useful as a step toward elucidation of the pathogenesis of this disease.

ACKNOWLEDGMENTS

Courtesy of Kaken Kagaku Company, Tokyo, for supplying GOBAB is deeply appreciated.

S U M M A R Y

In four cases of the specific type of hepatocerebral degeneration (Inose type) with frequent episodes of disturbance of consciousness, GOBAB (γ -hydroxy- β -aminobutyric acid [DL-form]) was administered in the dose of 3-6 g orally or 1-2 g intravenously for 3-22 months. Attacks disappeared in two cases and a continuous effect was observed in one case. In another

case, attacks decreased in the initial stage of the treatment. In the one case with a continuous effect, the efficiency of GOBAB was also confirmed by measurements of blood ammonia, serum citrulline and visual evoked response. No side effects were noted despite such a long term use of this drug.

R E S U M E N

En cuatro casos de degeneración hepatocerebral de tipo específico (tipo Inose) con frecuentes episodios de trastorno de la conciencia se suministró GOBAB (ácido gamma-hidroxi-B-aminobutírico [forma DL]) en dosis de 3-6 gm por vía oral o 1-2 gm por vía intravenosa durante 3-22 meses. Los ataques desaparecieron en dos casos y en un caso se observó un efecto continuo. En otro

caso los ataques disminuyeron en la etapa inicial del tratamiento. En el caso de efecto continuo la eficacia del GOBAB fue confirmada asimismo por mediciones del amoníaco de la sangre, de la citrulina sérica y de la respuesta visual evocada. No se observaron efectos secundarios a pesar de la aplicación de esta droga durante un período tan prolongado.

R É S U M É

GOBAB (γ -hydroxy- β -aminobutyrique acide) à la dose de 3 à 6 g par route buccale ou à la dose de 1 à 2 g par route intraveineuse fut administré pendant 3 à 22 mois dans 4 cas de la dégénération hépato-cérébrale du type spécifique (Type Inose) avec des épisodes fréquents du trouble de la conscience. Dans deux cas les attaques ont disparu. Dans un cas l'effet continuuel a été observé et dans un cas les attaques ont di-

minué à la phase initiale du traitement. Dans les cas pour lesquels l'effet continuuel a été observé, l'effet du GOBAB fut constaté par la détermination de l'ammoniaque du sang, du la citrulline du sérum et par l'enregistrement du potentiel visuel évoqué. On n'observe pas d'effet secondaire bien que le GOBAB soit administré pendant longtemps.

ZUSAMMENFASSUNG

In vier Fällen einer Sonderform der Hepato-Cerebral Degeneration (Inose-Typ) mit häufigen Anfällen von Bewußtseinstörungen wurde GOBAB (γ -Hydroxy- β -Amino-Buttersäure [DL-Form]) während einer Zeit von 3 bis 22 Monaten oral in Dosen von 3-6 g oder intravenös in Dosen von 1-2 g verabreicht. Die Anfälle verschwanden in 2 Fällen, und in einem Fall wurde eine anhaltende Wirkung beobachtet. In einem

Fall liessen die Anfälle nur im Anfangsstadium der Behandlung nach. In dem Fall, der eine anhaltende Wirkung zeigte, wurde der Effekt der Droge durch Bestimmung von Blutammniak, Serum-Citrulline und die Aufzeichnung des visueller Reaktionspotentials bestätigt. Trotz der langzeitigen Verabreichung des Mittels wurden keine Nebenwirkungen festgestellt.

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Treatment of Neuromuscular Disorders

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In the past two decades remarkable progress has been made in the field of neuromuscular disorders. Consequently, at present, early detection or diagnosis of pre-clinical stage or even carrier state of various muscle diseases have become possible by means of supplemental laboratory studies such as serum enzyme detection, electromyogram, or histological or histochemical observation in biopsied specimens. The development of these new techniques, on the other hand, led to the discovery of several new diseases and required new classification of the disorders.

In spite of the tremendous clinical as well as fundamental progress in this field, the treatment of these disorders was somewhat limited. Actually, in the majority of the patients, no satisfactory treatment for complete recovery has been reported. In certain diseases, however, some of the therapeutic trials are of value for the purpose of relieving or controlling symptoms or of prolonging the course of the disease, and considerable remission may even occur.

1. MUSCULAR DYSTROPHY

Muscular dystrophy, defined as genetically determined primary degenerative myopathy, is a disorder for which no appropriate medical treatment is known at present. Many remedies have been tried in the past. Formerly, the use of glycine and glyocol which are known as precursors of creatine, or creatine itself has been attempted because of marked creatinuria in this disease. Wheat germ oil, alphatocopherol, adrenaline or pilocarpine which

were once believed effective, failed to show any definite effect finally. Vitamin E has been considered effective because muscular involvement in vitamin E deficiency in animal resembles muscular dystrophy in humans. However, in 1960, Berneske et al.² confirmed the ineffectiveness of this treatment in 33 cases of muscular dystrophy. Multiple, amino-acid therapy, isoniazid, adenosinetriphosphate, leucine and pachycarpine, or high dosage of multiple vitamins were also once believed to be effective³⁴. Dowben⁵ reported that anabolic steroids prolonged the life of dystrophic mice, and de Toni³⁰ gave this steroid to 18 children with muscular dystrophy and found improvement of muscular strength in 8 of them. However, the effect of this drug was later doubted by Barwick and Walton¹. Corticosteroids were also tried, and more recently it was found that this drug lowered the serum level of creatine-phosphokinase activity, though this effect is only temporary. More recently a mixture of nucleotides and nucleosides was introduced as effective²⁸. With tentative trial this treatment also failed to reveal any definite improvement.

In contrast to unsatisfactory effect of these remedies, appropriate physical therapy, no doubt, prolongs the course of this disease. Walking, swimming and other exercise should be continued in a suitable manner. Inactivity always facilitates the deterioration in the disease and ends in contracture of limbs. Patients with muscular dystrophy, of course, should be satisfactorily nourished, but they should avoid gaining excessive weight. Obesity facilita-

tes a tendency toward inactivity and may cause fracture of limbs.

One of the most important considerations in managing the patients with this disorder is a careful attention to the occurrence of complications, especially of respiratory ones which are most often fatal in these patients.

2. MYOTONIA

Diseases accompanied by the myotonic phenomenon are myotonia congenita, dystrophia myotonica, paramyotonia congenita and so-called myotonia acquisita. Myotonic phenomenon is caused by a failure in immediate relaxation of voluntary contraction of striated muscles due to continued after-discharge which has been clearly demonstrated with electromyography. It has long been known that quinine^{10, 35} and quinidine can relieve this phenomenon, and more recently procain amide⁷ was found to be more effective. Quinine in dosage of 1 to 2 gm or procain amide in the dosage of 4 to 6 gm daily will reduce or abolish myotonia. ACTH⁹ or cortisone²⁰, or prednisone have also been reported to be effective. In our experience, 10 to 20 mg of prednisone, 12 to 24 mg of triamcinolone or 25 mg of ACTH were effective in some cases, though steroid treatment over a long period is not completely satisfactory. Ion exchange resins were once reported to reduce myotonia by the action of lowering the serum potassium level,¹³ though this therapy by itself was found to be ineffective¹¹. Epinephrine or insulin may also have a mild effect and intravenous injections of calcium may also help the symptom, and diphenyl hydantoin is also said to relieve symptom.

All these medications, particularly quinine and procain amide, are beneficial in relieving the symptom of myotonia over a long period and are most useful in patients with myotonia congenita, because they mainly suffer from this phenomenon without any muscular wasting or marked weakness. In cases of myotonic dystrophy, the medication is also effective to some

extent if muscular weakness is not prominent. However, in later stages muscular wasting and weakness become apparent so that the medication is not significantly helpful. Appropriate physical therapy is required as in muscular dystrophy, and there is no known effective medical treatment for progressive muscular atrophy. In addition, there are several associated symptoms such as cataract, alopecia and other endocrine disorders which may require appropriate treatment individually.

Paramyotonia congenita, described by Eulenburg, is now thought to be identical to adynamia episodica hereditaria of Gams-torp⁶ and hyperkalemic periodic paralysis. The treatment for this condition will be described elsewhere.

3. PRIMARY MUSCLE DISEASES OTHER THAN MUSCULAR DYSTROPHY

Certain disorders other than muscular dystrophy are considered to be primary muscle diseases due to either genetic or metabolic etiologies. Several types of glycogen storage disease predominantly involving striated muscles, paroxysmal myoglobinuria, and familial periodic paralysis belong to this category. The last one will be discussed in the next section.

Several newly established diseases such as central core disease²¹, nemaline myopathy²², myotubular²⁵ (centronuclear¹⁹ or pericentronuclear⁴) myopathy, and well known diseases such as myositis ossificans and arthrogryposis multiplex congenita also belong to this group. No medical treatment for these diseases has been found and physical therapy similar to that for muscular dystrophy is recommended.

In 1951 McArdle¹² first described a syndrome presenting muscle stiffness or contracture associated with pain following exercise. Accumulation of glycogen was found in the muscle fibers and later this was proved to be due to absence of amylophosphorylase in the muscle^{18, 14}. Since then, similar conditions have been reported in different enzymic levels of glycolytic

pathway. These were reported by Thompson (abnormality in phosphoglucomutase level?)²⁹, Tarui et al (phosphofructokinase deficiency)²⁷, and by Satoyoshi et al (phosphohexoisomerase?)¹⁶. The treatment of these conditions is, first of all, to limit exertion. Intake of glucose or fructose, especially 100 to 200 gm of fructose prior to exertion has been reported to be of benefit. A significant increase in the tolerance of the exercise may occur. Satoyoshi observed that the administration of 30 to 50 gm of fructose improves the symptom and produces a postexertional elevation of blood lactic acid, absence of which was a feature in his cases.

Paroxysmal myoglobinuria is characterized by an attack of muscle pain and cramps followed by myoglobinuria within a few hours. Several types have been reported in this disease and one of these is associated with exertion. In this condition rest is essentially required and exercise should always be limited.

4. PERIODIC PARALYSIS

Periodic paralysis is a disease or a condition characterized by intermittent paralytic attack of the limbs which may vary in frequency and in severity. Paralysis subsides completely after a few hours, days or even weeks. Periodic paralysis is classified into two groups, one of which has been considered to be genetic in origin and the other is a condition associated with various disorders such as hyperthyroidism, aldosteronism, diabetes mellitus, renal tubular acidosis or severe renal insufficiency. Familial periodic paralysis may be classified by the serum potassium level during paralytic stage into three categories: hypokalemic periodic paralysis, hyperkalemic periodic paralysis³² (adynamia episodica hereditaria, paramyotonia congenita?) and normokalemic periodic paralysis¹⁵. The last may be a variant of the hyperkalemic type.

As far as treatment is concerned, the serum potassium level during paralysis is a

guide for therapeutic trials. In hypokalemic type, during paralytic attack oral administration of 10 gm of KCl is recommended and, if paralysis still continues, additional KCl in the dosage of 5 gm should be followed. In a severe attack, intravenous injections of KCl may be beneficial, though the potassium in a concentration of less than 15 mEq/L should be dripped into the vein slowly and carefully. Between attacks, precipitating factors of paralysis such as heavy exercise, excessive carbohydrate or alcohol intake should be avoided. Daily administration of 1 to 3 gm of KCl orally associated with spironolactone in doses of 50 to 100 mg or with triamterene in doses of 100 to 200 mg daily may prevent considerably or lessen paralytic attack.

Hyperkalemic periodic paralysis, on the other hand, responds to intravenous injections of calcium gluconate in the dose of 1 to 2 gm. Diuretics such as acetazolamide, hydrochlorothiazide, and dichlorophenamide may prevent the attack by increasing urinary excretion of potassium. But acetazolamide and carbonic anhydrase inhibitor in doses of 50 to 200 mg daily seems to be most effective. Potassium intake should be restricted because it precipitates the paralytic attack. Similar treatment is applicable to normokalemic periodic paralysis. In some cases of normokalemic paralysis, however, large doses of NaCl may relieve an attack in contrast to potassium which will worsen the paralysis. In pleoconical myopathy²³, salt craving symptom is a prominent feature of the disease.

In symptomatic periodic paralysis, various disorders such as hyperthyroidism, primary aldosteronism, steroid administration, diabetes mellitus under insulin therapy, and renal tubular acidosis are the causes of hypokalemic attacks and renal insufficiency or adrenal insufficiency may precipitate the hyperkalemic attack. Among them, thyrotoxic periodic paralysis is well known. The treatment for these basic disorders reduces or prevents the paralytic attacks completely. However, during paralytic attack appropriate treatment for hypo or hyperkalemic paralytic attacks should be undertaken in every case.

5. INFLAMMATORY MYOPATHY AND RELATED CONDITIONS

Diseases belonging to this group demonstrate various types of inflammatory changes in the muscle tissue which can be detected by histological examinations. This group includes polymyositis, dermatomyositis, myopathy in other collagen diseases, myopathy in Sjogren's syndrome and in macroglobulinemia, myopathy in sarcoidosis, myopathy due to remote effect of malignancy and various infectious myositis.

It is most important to distinguish these conditions from progressive muscular dystrophy because these inflammatory conditions may be curable by medication.

For polymyositis in a wide sense, which may include dermatomyositis, myopathy in other collagen diseases and in Sjogren's syndrome, adrenocortic steroid therapy usually shows excellent results. An initial dosage of 40 to 60 mg of prednisone daily is recommended. In accordance with improvement of clinical symptoms, the dosage can be gradually decreased. Successive determination of serum creatinephosphokinase activity will give useful information for the reduction of the dosage, and 5 to 20 mg is given as a maintenance dosage after the disease reaches a static condition. When exacerbation or relapse occurs during the treatment, switching from one steroid to another steroid such as dexamethasone or fluorohydrocortisone may be helpful. In the acute or subacute stage, or even in a chronic condition, if the serum enzyme activity shows remarkable elevation, absolute rest is necessary. Otherwise, appropriate physical therapy should be continued. As a supplemental treatment, small dosage of KCl may be helpful for maintaining muscle strength, and salicylic acids are also of benefit for relieving muscle pain. Anabolic steroids may also have some effects on muscular wasting and weakness.

In other types of the disease basic disorders should be primarily treated properly, though combined therapy with corticosteroids is of some benefit in recovery from the disease.

As a remote effect of malignancy various types of neuromuscular disorders have been described which may be called carcinomatous neuromyopathy³. Among these, myositis or dermatomyositis and myasthenic syndrome often precede the onset of the symptoms of carcinom. Therefore, if an inflammatory myopathy of unknown cause is observed, an effort to seek for underlying malignancy should always be made before corticosteroid therapy is started, especially in patients of middle or older age. Removal of the cancer may or may not have an effect on the symptoms except for the myasthenic syndrome, which often shows a tendency toward recovery after surgical treatment of cancer.

6. MYASTHENIA GRAVIS

Myasthenia gravis is a disease in which the neuromuscular junction is considered to be a site of the lesion. The treatment of this disorder started in 1929 when an epinephrine preparation was coincidentally found to be effective on this condition²⁶. In 1934 physostigmine was discovered³³ and since then various kinds of anticholinesterase drugs such as pyridostigmine bromide, ambenonium chloride, edrophonium chloride, and BC-51 (ubretid) have been found.

Neostigmine bromide (prostigmin) is used most frequently. The dose of the drug varies from patient to patient and the average dose is 30 to 150 mg daily. Subcutaneous injections of neostigmine methylsulphate is also in wide usage. Injection of 1 mg corresponds to 15 mg of oral administration. Neostigmine has a rapid anticholinesterase activity, though the duration of its effect is rather short. Moreover, required maintained dosage tends to increase gradually after the treatment is started. As dosage is increased, muscarinic side-effects become more apparent.

Pyridostigmine bromide (mestinone) is preferable in practice to neostigmine because of longer duration of effects with fewer side effects. Sixty milligrams of

pyridostigmine has an effect almost equal to 15 mg of neostigmine.

Ambenonium chloride (mysuran, mytelase) is also very effective and the duration of the action is longer than that of the previous two drugs. Twenty to 35 mg have been used.

BC-51 (ubretid) has been found to have a relatively long acting anti-cholinesterase activity with mild side-effects which are close to that of mestinone. Some cases with ocular myasthenia respond better to BC-51 than to other drugs. An average dose is 5 to 30 mg.

Edrophonium chloride (tensilon) is a short acting anti-cholinesterase drug and its maximum effect is completed within 5 minutes after intravenous injection. This drug, therefore, is of value in diagnostic procedure rather than for therapeutic trials.

Choice of these various anti-cholinesterase drugs should be based on the clinical state and severity. Besides these drugs, aldosterone inhibitors, such as 400 mg of spironolactone⁸ or 100 to 200 mg of triamterene¹⁷, have been used to potentiate the anti-cholinesterase activity. Potassium chloride showed similar action. Guanidine hydrochloride has a limited anti-myasthenic action to sensitization of chemoreceptor to acetylcholine but is rarely used because of its side-effects.

Recently myasthenia gravis has been postulated to be a kind of autoimmune disorder because of the frequent association with thymoma or thymic abnormalities. Various attempts to prove the autoimmune reactions have been reported. However, no convincing result has yet been obtained. But, as treatments to suppress the autoimmune process in this disease, massive dosage of ACTH or corticosteroids³¹ have been administered. Torda et al described the remission of the symptoms following administration of 60 mg of corticotropin or 120 to 160 mg of cortisone daily. However, a temporary exacerbation of the symptoms is very common during the treatment. Intensive respiratory care is necessary during the administration. A complete remission or remarkable improvement of the symptoms may occur.

When the presence of thymoma is proved, surgical treatment is seriously considered. However, concerning the value of the thymectomy there are several opinions. Recently Simpson²⁴ recommended the operation in patients with a duration of illness less than 5 years because of the high percentage of complete remission following surgical procedures. Radiation therapy has also been applied on thymoma or even in the absence of apparent tumor, though the effect is not conclusive.

Myasthenic crisis is frequently precipitated by an infection, emotional stress, physical exertion, or by careless usage of curare, ether, quinine, quinidine, morphine, ACTH, corticosteroids, thyroxine, sedatives, or certain antibiotics such as streptomycin, neomycin or kanamycin or by enema. When patients respond to edrophonium during crisis, the dosage of anti-cholinesterase drugs should be increased immediately. Parenteral administration of neostigmine is suitable in these cases. Careful control of respiration and in the majority of patients tracheotomy is required.

Cholinergic crisis may occur occasionally by the overdosage of anti-cholinesterase drugs. Paralysis of the muscle occurs due to depolarization block and respiratory control and tracheotomy are frequently required as in myasthenic crisis. Various muscarinic signs may be seen in this condition. Vomiting, hypersalivation, sweating or fasciculation may be present. Myosis is of value to distinguish this condition from the myasthenic crisis. Edrophonium is not effective. Intravenous injection of 1 to 2 mg of atropine sulphate is of benefit. This can be repeated every hour until the side-effect of atropine appears. A few specific treatments for cholinergic crisis have been reported. Pyridine-2-aldoxime (2-PAM), methane sulphate (P2S) or d-tubocurarine are helpful in some cases. But there are some difficulties in using these drugs and often the result is unsatisfactory. Careful control of respiration and atropine administration should be continued until an apparent response to edrophonium reappears.

SUMMARY

Treatments of neuromuscular diseases have been described briefly. In spite of remarkable progress in the study of neuromuscular diseases, the treatment is still limited to some extent. However, therapeutic

trials should be proposed tentatively and repeated, particularly in the genetically determined muscle diseases because of their poor prognosis.

RESUMEN

Se describen brevemente los tratamientos de enfermedades neuromusculares. A pesar del notable progreso alcanzado en el estudio de estas enfermedades, las posibilidades de tratamiento son hasta cierto punto limitadas.

Sin embargo, deben proponerse y reiterarse intentos terapéuticos, especialmente en los casos de enfermedades musculares de origen genético debido a su mal pronóstico.

RÉSUMÉ

On décrit brièvement les traitements des maladies neuromusculaires. Malgré le remarquable progrès atteint dans l'étude de ces maladies, les possibilités de traitement sont jusqu'à un certain point limitées.

Cependant, des essais thérapeutiques devraient être proposés et répétés, surtout dans les cas des maladies musculaires d'origine génétique à cause de leur mauvais pronostic.

ZUSAMMENFASSUNG

Die Behandlung der Krankheiten der Muskeln ist kurz beschrieben worden. Trotz beachtenswerter Fortschritte auf dem Gebiet der Erforschung der neuromuskulären Krankheiten, ist die Behandlung noch in bestimmten Grade beschränkt.

Jedoch, die therapeutischen Versuche sollten vorgenommen werden und wiederholt werden, besonders bei den Muskelkrankheiten genetischen Ursprungs, wegen ihrer schlechten Prognose.

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La Maladie des Spasmes en Flexion de la Première Enfance à Symptomatologie Typique et Atypique et son Traitement

A PROPOS DE 192 OBSERVATIONS

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INTRODUCTION

Les premiers cas de maladie de spasmes en flexion de la première enfance appelés encéphalopathies myocloniques infantiles avec hypsarythmie (E.M.I.H.) que nous avons eu l'occasion de traiter datent de 1955. Nos résultats ont été exposés au Congrès International de Neurologie à Bruxelles en 1957 et publiés en 1958 dans les "Acta Neurologica Belgica" ⁸¹. Depuis, en dehors de quelques publications parcellaires ^{82, 83} nous n'avons pas exécuté de travail d'ensemble au sujet du traitement de cette affection et de ses conséquences lointaines.

Nous voudrions, dans le présent travail, développer 3 ordres de faits:

1^o l'avenir lointain des cas traités.

2^o notre conception de la maladie, ce qui nous permet de décrire des cas typiques et atypiques, justifiables d'ailleurs de la même thérapeutique avec les mêmes résultats.

3^o la technique que nous utilisons actuellement pour traiter des cas semblables, technique fort différente de celle relatée dans nos premières observations. Elle nous permet en effet d'utiliser les doses les plus faibles possibles tout en évitant cependant les récurrences anciennement fréquentes.

DONNEES DE LA LITERATURE

Nous mentionnerons en fin de cet article, les différents travaux qui ont été publiés à notre connaissance depuis la parution du livre "L'encéphalopathie myoclonique infantile avec hypsarythmie", qui résume les interventions présentées au 9^e colloque international de Marseille en 1960, sans reprendre cependant le contenu de la majorité d'entr'eux. ^{1, 2, 3, 6, 9, 11, 12, 14, 17, 18, 19, 20, 22, 24, 25, 26, 29, 30, 35, 38, 40, 41, 42, 43, 45, 47, 48, 52, 53, 55, 57, 58, 59, 61, 62, 64, 67, 70, 72, 73, 76, 79, 81, 82, 85, 91, 92, 95, 97, 98, 99.}

Néanmoins soulignons que les résultats thérapeutiques relatés dans la littérature sont souvent médiocres et parfois même nuls, contrastant ainsi avec les résultats observés et vérifiés par toute notre équipe médicale. ^{4, 5, 7, 8, 10, 13, 16, 21, 23, 27, 28, 31, 32, 33, 34, 36, 37, 39, 44, 46, 49, 50, 51, 54, 56, 60, 63, 65, 66, 68, 69, 71, 74, 75, 77, 78, 80, 86, 87, 88, 89, 90, 93, 94, 96, 100 et 15.}

Les causes en sont toujours les mêmes: les auteurs se refusent:

1^o à dissocier au départ les formes d'E.M.I.H. apparues sur cerveau sain et celles se greffant sur un cerveau préalablement lésé;

2° à attacher une importance capitale au moment auquel le traitement a pu être instauré;

3° à appliquer un traitement valable quant au produit à utiliser, aux doses à prescrire et à la durée d'application de la médication.

Or, de ces trois éléments dépendent en fait tous les résultats thérapeutiques.

I. CONSIDERATIONS AU SUJET DU DEVENIR DE 50 CAS OBSERVÉS DE 1955 A 1959

A. Le diagnostic de l'affection

1° Au début de notre étude, nous n'avons retenu le diagnostic de maladie des spasmes en flexion de la première enfance que chez les enfants qui présentaient suivant les données de la littérature une triade symptomatique qui s'était installée dans son entièreté en l'espace de 2 à 3 semaines maximum: arrêt ou retard du développement psycho-moteur, crises myocloniques ou akinétiques le plus souvent en salves, image typique d'hypsarythmie à l'E.E.G.

37 enfants présentant ce syndrome ont été observés et traités par l'A.C.T.H. retard de 1955 à 1959.

Chez 15 de ces 37 enfants, la triade symptomatique s'est installée alors que le développement psycho-moteur de l'enfant était jusqu'à ce moment en tous points normal. Chez les 17 autres, divers signes neurologiques ou psychiatriques confirmés ou non par des anomalies radiologiques montraient que nous avions affaire à des cerveaux déjà lésés par une encéphalopathie préalable.

Dans tous nos cas cependant, l'âge du début de l'affection se situait avant l'âge de un an.

2° Etant donné les observations qui nous ont été données de faire ces dernières années, nous avons rétrospectivement repris 13 cas que nous avons eu l'occasion de voir durant la même période et que nous n'avions pas à ce moment considérés comme pouvant relever de la même affection. De ce fait ils n'ont pas été traités par l'A.C.T.H.

Il s'agit d'enfants présentant également une symptomatologie ayant débuté avant l'âge de un an, mais chez lesquels, certains éléments de la triade symptomatique manquaient ou chez qui certains symptômes étaient atypiques.

Dans 9 cas sur 13 ces symptomatologies étaient apparues chez des enfants jusqu'alors exempts de tous troubles neuropsychiques.

Voici le résumé de la symptomatologie de ces cas:

a) crises myocloniques ou akinétiques isolées ou en salves, sans retard intellectuel. Tracé normal ou légèrement pathologique sans image d'hypsarythmie. Ces enfants ont développé l'affection sur un cerveau préalablement sain. (6 cas).

b) crises myocloniques en salves avec retard intellectuel. Tracé normal ou peu altéré. Dans 2 cas, l'affection survient sur un cerveau préalablement sain, dans 2 cas, des signes d'encéphalopathie préalable pouvaient être décelés.

c) deux enfants présentaient non pas des crises myocloniques ou akinétiques en salves, mais bien des crises grand mal apparaissant isolément à des fréquences variables, sans que le tracé E.E.G. ne soit typique d'hypsarythmie. Dans un cas l'intellect était normal; l'affection semblait se développer sur un cerveau préalablement sain. Dans l'autre cas, il existait un retard intellectuel: il s'agissait d'un cerveau préalablement lésé.

d) il nous a été donné d'examiner un enfant présentant un retard intellectuel, semblait-il depuis la naissance et qui au moment de l'examen, qui se situait à l'âge de 6 mois présentait au tracé E.E.G. une image d'hypsarythmie. Cet enfant n'avait jamais présenté de crise.

B. Evolution

1° Evolution des 37 cas typiques d'E.M.I.H.

Le traitement que nous avons appliqué de 1955 à 1959 varie considérablement d'avec notre technique actuelle. Il consistait en l'application journalière de doses faibles d'A.C.T.H. retard pendant 15 jours à 3 semaines en moyenne. Le flacon à ce

moment, qui contenait 2cm³ de solution, avait un pouvoir d'action correspondant à 40 unités internationales. Comme on le sait depuis, les 40 u. anciennes correspondent à 120 u. actuelles. Le traitement appliqué ultérieurement correspondait donc à l'injection quotidienne d'environ 15 à 40 u. actuelles de Cortrophine Z Organon.

De 1955 à 1959, de nombreuses récides furent à déplorer. Elles ne purent pas toujours être jugulées par une nouvelle cure d'A.C.T.H.

Comme nous y avons toujours insisté, le moment d'application du traitement conditionne de façon formelle l'évolution de l'affection.

Le pronostic futur dépendra de plus de l'état du cerveau avant le début de la maladie. Dans les cas de cerveaux préalablement lésés, si la thérapeutique agit, elle n'aura évidemment comme effet que de supprimer la complication hypsarythmique sans modifier l'évolution de l'encéphalopathie préexistante.

Nous distinguerons dans l'exposé de nos résultats 4 groupes de malades:

1er. groupe: affection sur cerveau sain, traitement entrepris au cours des 6 premières semaines de l'évolution (dernière limite 2 mois): 7 cas.

5 enfants sur les 7 qui constituent ce groupe sont actuellement encore normaux à tous points de vue. Ils ont suivi un écolage ordinaire à partir de la première année d'étude et notamment l'enfant⁸¹ de J. Ju. dith, dont l'image E.E.G. illustre notre première publication entreprend cette année le début de ses études universitaires. Les 4 autres enfants suivent toujours un écolage sans difficulté dans des écoles ordinaires. Remarquons cependant que si la cure d'A.C.T.H. permet assez rapidement la réapparition du sourire, et que le comportement s'améliore peu à peu, il arrive fréquemment que vers l'âge de 2 à 3 ans, l'on constate encore un retard intellectuel qui inquiète parfois l'entourage.

Cependant, dans les 5 cas cités, le retard intellectuel s'est complètement comblé, vers l'âge de 5 ans, ce qui a permis d'emblée l'intégration de ces enfants dans l'écolage

ordinaire. Nous avons observé dans 3 cas, une instabilité psychomotrice anormale pendant une durée de 3 à 4 ans, ces troubles comportementaux, peut-être en partie d'origine éducative, ont disparu entre l'âge de 7 à 10 ans.

Signalons qu'il n'est jamais apparu de récive plus de un an après la fin du traitement. De plus, chez les enfants dont la réponse au traitement a été complète, nous n'avons jamais constaté de séquelle épileptique ultérieure.

Dans 1 cas sur 7, l'amélioration reste incomplète sur le plan intellectuel.

Chez le 7ème enfant, les crises se sont arrêtées, le tracé s'est normalisé, mais le développement psychomoteur est resté ralenti. Trois ans après la fin du traitement sont apparues des crises grand mal à prédominance gauche et des anomalies électriques latéralisées.

2ème groupe: affection sur cerveau sain. Traitement entrepris après le 2ème mois d'évolution: 8 cas.

Du point de vue psychique: 6 cas n'ont montré aucune amélioration et l'évolution démentielle s'est poursuivie. Un cas a montré une amélioration certaine et un autre, contre toute attente, s'est développé au point de vue intellectuel pour n'atteindre cependant actuellement que le quotient de 80.

Pour ce qui est des crises, 3 malades, ont été débarrassés définitivement de celles-ci. Trois après une disparition momentanée des crises ont vu apparaître des manifestations soit grand mal, soit psychomotrices. Deux ont évolués vers un syndrome de petit mal variant avec crises toniques axiales.

Le tracé E.E.G. s'est normalisé dans deux cas. Chez un enfant, il persiste une dysrythmie diffuse modérée. Chez les autres, le tracé est resté nettement pathologique, quoique présentant parfois des améliorations transitoires.

Sur ces 8 enfants, 5 sont morts aux âges suivants: 4, 6, 11, 12 et 14 ans.

3ème groupe: affection survenue sur cerveau encéphalopathe. Traitement entrepris au cours des 6 premières semaines d'évolution (maximum 2 mois): 6 cas.

Notons que 2 enfants présentaient une cécité accompagnant un important retard intellectuel. Bien que le traitement fut entrepris rapidement, aucune amélioration durable n'a pu être obtenue et ces deux enfants sont morts, l'un à 6 ans, l'autre à 12 ans.

Dans 3 cas, une amélioration immédiate s'est produite qui supprima les crises, améliora le tracé dans de très importantes proportions et permit un développement intellectuel appréciable, le Q.I. actuel se situant entre 70 et 90.

Le dernier cas a récidivé sans qu'une nouvelle cure ne puisse améliorer la situation. L'enfant est mort à 11 ans, dans un état de démence totale.

Prenons parmi les enfants de ce groupe le cas du petit Jean-Pierre F. qui nous paraît consituer un exemple démonstratif. Nous avons en traitement cet enfant depuis l'âge de 3 mois pour séquelles hémiparétiques d'origine obstétricale. Il présentait de plus moyenne une fois par mois, des convulsions latéralisées. Brusquement à l'âge de 9 mois, les parents constatent un changement dans l'attitude de l'enfant et dans l'aspect des crises qui deviennent bilatérales symétriques et revêtent le caractère de spasmes en flexion apparaissant en salves. Le tracé que nous avons coutume d'enregistrer montrait une légère asymétrie du rythme de fond. Le tracé prélevé lors de l'apparition des crises en salves avait un aspect tout à fait différent et caractéristique de l'hypsarythmie. Quinze jours après le début de l'évolution, le traitement fut entrepris au moyen d'A.C.T.H. retard. Les crises s'arrêtèrent, le tracé redevint semblable à celui que l'on enregistrait avant la complication hypsarythmique, mais l'enfant gardait un niveau intellectuel nettement plus inférieur à ce qu'il était avant l'apparition des chocs en salves. Ce retard intellectuel s'est cependant progressivement comblé et actuellement âgé de 10 ans, cet enfant suit l'enseignement ordinaire aidé par des cours particuliers. Il présente encore en moyenne 3 fois par an des convulsions latéralisées. L'amélioration de son trouble moteur se poursuit régulièrement. Tout porte à croi-

re, que l'enfant se trouve actuellement dans l'état neuropsychique où il aurait été de par sa lésion encéphalopathique obstétricale. La complication sous forme de maladie de spasmes en flexion de la première enfance paraît avoir été complètement jugulée sans séquelle.

4ème groupe: affection survenue sur cerveau encéphalopathe. Traitement entrepris après 2 mois d'évolution: 11 cas.

Les résultats obtenus dans ce groupe sont particulièrement catastrophiques. 9 enfants n'ont réagi que de façon momentanée ou n'ont pas réagi du tout, 5 sont morts respectivement à 4, 5, 7, et 12 ans.

Chez deux malades cependant, les traitements furent entrepris respectivement 3 et 11 mois après le début de l'affection. Dans ces cas l'A.C.T.H. semble avoir apporté néanmoins une amélioration nette en supprimant définitivement les crises et en améliorant le Q.I. qui reste cependant voisin de 50.

2° *Evolution des 13 cas atypiques.*

Nous avons décrit 13 cas d'enfants présentant une symptomatologie incomplète (un des éléments de la triade symptomatique de l'E.M.I.H. manquant) ou atypique (existence de crises grand mal isolées au lieu de crises à composantes myocloniques ou en salves.)

C'est dans ce groupe que nous avons rencontré deux malades qui ont guéri spontanément, il s'agissait d'enfants sans atteinte intellectuelle et présentant des crises en salves. Dans un cas, le tracé était normal, dans l'autre, modérément et globalement perturbé. Les spasmes ont duré chez un enfant 15 jours, chez l'autre 6 semaines.

Tous les autres enfants ont, au cours des mois ou années qui suivirent le début de l'apparition des premiers symptômes, vu apparaître le ou les symptômes qui manquaient au départ, pour constituer finalement la triade symptomatique dans les cas à symptomatologie incomplète. Dans les cas atypiques, les crises en salves ont fait leur apparition plusieurs mois ou années après les crises grand mal qui avaient été le premier signe de l'affection.

II. CONSIDERATIONS AU SUJET DE LA CONCEPTION DE L'E.M.I.H.

Ces constatations nous ont fait repenser non seulement nos critères diagnostiques, mais encore et surtout notre conception de cette affection. Nous ne pensons pas que le diagnostic doive exiger l'existence d'une triade symptomatique constituant un syndrome bien strict. Il faut introduire une notion évolutive bien particulière qui fait de l'E.M.I.H. ou du Syndrome de West une véritable maladie. C'est pourquoi, nous préférons la terminologie de maladie des spasmes en flexion de la première enfance. Dans notre optique, il s'agit d'une entité bien définie, relevant sans doute de causes multiples, mais ayant toutes entraîné un même dysfonctionnement physiopathogénique d'évolution identique. C'est pourquoi, dans notre esprit l'âge de début (toujours avant un an) est extrêmement important. De plus traitée de façon précise, dans un délai

bien établi, cette affection évoluera toujours de la même façon dans à peu près le même laps de temps.

Cette notion d'entité épileptique, qui se distingue nettement du syndrome épileptique de par son caractère évolutif propre et particulier, entraîne des conséquences capitales pour la conduite pratique à tenir en face de ces malades.

En effet, s'il est parfaitement justifié de n'admettre l'existence d'un syndrome que si les différents éléments qui le composent sont tous présents, il en est tout autrement d'une entité ou d'une maladie. En effet, dans ces cas, chacun peut, pour une cause morbide identique, faire "sa maladie à sa façon". C'est pourquoi, nous avons, depuis 1965, systématiquement traité toutes ces formes atypiques ou incomplètes de la même façon que les cas typiques, car nous avons acquis la certitude que toutes ces formes relevaient du même désordre physiopathogénique.

III. ETUDE DE 142 NOUVELLES OBSERVATIONS

A. Répartition des cas en fonction des particularités diagnostiques

Formes de maladie de spasmes en flexion de la première enfance.			Affection survenue sur cerveau préalablement		
	crise	état mental	tracé EEG	sain	lésé
Typique	{ chocs en salves	déficit	Hypsarythmie	38	46
atypique	{ chocs en salves chocs en salves chocs en salves pas de crise grand mal grand mal grand mal	déficit	limite normale ou dysrythmie	1	1
		normal	hypsarythmie	8	0
		normal	limite normale ou dysrythmie	18	2
		déficit	hypsarythmie	5	1
		déficit	limite normale ou dysrythmie	3	6
		déficit	hypsarythmie	6	3
		normal	hypsarythmie	4	0

B. Traitement

1° Modalité thérapeutiques

Dans tous les cas, qu'il s'agisse d'une forme typique ou atypique, une thérapeutique précise a été systématiquement instaurée suivant un schéma bien défini. Jusqu'à ces dernières années, les récurrences étaient fréquentes. Le schéma thérapeutique proposé présentement nous a permis d'éviter, dans presque tous les cas, cet inconvénient.

Nous croyons que les modalités thérapeutiques sont extrêmement importantes, tant pour le type de corticoides utilisés que pour les doses et la durée du traitement.

Le traitement proposé a été mis au point après de longs tâtonnements, et est maintenant inchangé dans notre laboratoire depuis ces 6 dernières années.

La substance utilisée est l'A.C.T.H. retard sous forme de Cortrophine Z Organon ou Corticotrophine gel Wilson. On pratique des injections quotidiennes, en une fois, par voie intra-musculaire. Les traitements sont effectués de préférence dans le milieu familial afin d'éviter les réactions psychiques d'hospitalisme qui sont particulièrement prononcées chez ce genre d'enfant.

Les doses sont à instaurer progressivement. Pour un enfant de six mois voici la progression que nous suivons: 20 u. par jour pendant 4 jours, 30 u. par jour pendant 4 jours, 40 u. par jour pendant 4 jours, 60 u. par jour pendant 6 jours, 90 u. par jour pendant 10 jours.

Pendant l'exécution de ce schéma nous observons les crises. Si celles-ci cessent, la progression est arrêtée et l'on continue pendant un mois à injecter quotidiennement la dose d'A.C.T.H. retard qui a été nécessaire pour enrayer les crises. On envisage ensuite une réduction progressive pour cesser toutes injections après un total de trois mois d'injections quotidiennes ininterrompues.

Dans l'exemple cité de l'enfant de six mois, si les crises s'arrêtent après deux injections de 40 u. Le schéma thérapeutique total aura été le suivant: 20 u. pendant 4 jours, 30 u. pendant 4 jours, 40 u. pendant 2 jours, plus 30 jours soit pendant 32 jours, 30 u. pendant 10 jours, 20 u. pendant 10

jours, 10 u. pendant 10 jours, 5 u. pendant 10 jours.

Nous joignons toujours à cette thérapeutique par voie intra-musculaire, une médication per os à base de deux fois par jour: $\frac{1}{4}$ de Mysoline et 3 à 5 gouttes de Largactil. On y adjoint également deux cuillères à café de Potassium. On recommande un régime sans sel. Le Largactil peut être augmenté ou diminué suivant la nervosité de l'enfant.

Au cours du traitement on portera spécialement son attention sur l'évolution des crises et du tracé électroencéphalographique. Si l'état mental venait à s'altérer davantage, spécialement pendant les injections des fortes doses d'A.C.T.H. retard, il n'y aura nullement lieu de s'en inquiéter. L'amélioration mentale n'apparaîtra qu'au moment où les doses seront réduites à 20 ou 10 u. Cette altération de l'état mental ne doit en rien décourager le thérapeute et ne justifie pas une réduction des doses d'A.C.T.H.

La médication prise per os est poursuivie pendant plusieurs mois après la fin de la cure par voie parentérale. Depuis 6 mois la substance utilisée est le Cortrosyn dépôt OR Organon avec les memes résultats thérapeutiques.

2° Résultats.

Les résultats obtenus sont qualitativement du même ordre que ceux décrits plus haut. Les récurrences étant cependant tout à fait exceptionnelles, les enfants améliorés sont quantitativement plus nombreux. Il nous semble fastidieux de rapporter en détail les différentes observations.

Nous aimerions plutôt souligner quelques faits:

a) Le traitement a été appliqué au cours des 2 premiers mois d'évolution chez 15 enfants ayant présenté l'affection typique survenue sur cerveau préalablement sain. 13 d'entre eux sont entièrement guéris sans séquelle d'aucune sorte. Ils sont ou seront capables de suivre un enseignement absolument normal.

b) Dans les autres cas typiques, l'évolution est fonction du moment d'instaura-

tion du traitement et de l'état cérébral préalable à l'affection.

c) Dans les cas atypiques, les enfants se sont améliorés en fonction des mêmes éléments qui conditionnent l'amélioration des cas typiques, c'est-à-dire, moment d'instauration de traitement et état du cerveau avant le début de l'affection. 9 enfants ont ainsi été débarrassés des symptômes qu'ils présentaient et n'ont pas vu apparaître ultérieurement de nouveaux signes. Nous les considérons comme entièrement guéris. Le moment d'instauration du traitement est moins urgent si le déficit intellectuel n'est pas encore présent.

d) 4 enfants ont présenté des spasmes en flexion qui ont guéri spontanément, aucun d'eux n'avait de troubles intellectuels, ni d'altérations importantes du tracé EEG. La durée d'évolution des spasmes a été respectivement de 15 jours, 20 jours, 1 1/2 mois, 2 1/2 ans.

e) Il est apparu chez 4 malades dont l'évolution clinique sur les plans critique et psychique avait été tout à fait favorable, des anomalies E.E.G. ultérieures qui ont subsisté pendant 3 à 24 mois. Cette pathologie EEG est caractérisée soit par des poin-

tes ératiques, soit par des pointe-ondes atypiques sans aucune pathologie clinique concomitante. Dans ces cas, les anomalies E.E.G. sont exactement semblables à celles que nous avons décrites dans les épilepsies fonctionnelles de maturation, ⁸⁴a: en montage vertical référentiel au cou, toutes ces activités paroxystiques ont une polarité simultanément positive dans les régions antérieures et négative dans les régions moyennes et postérieures. Ces anomalies d'aspect souvent spectaculaire paraissent ne pas être l'image de séquelles organiques et évoluent d'ailleurs toujours favorablement.

f) La médication dans l'ensemble a été bien tolérée. Nous demandons systématiquement à la famille que la température soit régulièrement prise tous les jours et qu'un traitement antibiotique énergique soit instauré immédiatement si une poussée thermique venait à apparaître. L'œdème des téguments est extrêmement fréquent pour ne pas dire constant. Dans deux cas, des enfants ont présenté à une reprise des hématuries. Celles-ci ne se sont plus reproduites malgré la poursuite inchangée du traitement. Deux enfants sont décédés en cours de cure, d'infection gastro-intestinale suraiguë.

CONCLUSION GENERALE ET RESUME

Les spasmes en flexion de la première enfance doivent être envisagés comme une entité morbide propre à évolution bien définie.

Il ne faut poser ce diagnostic ni sur un aspect bien précis de crise (Blitz, Nick und Salaamkrämpfen, épilepsie généralisée en flexion, épilepsie salutatoire), ni sur une image EEG absolument typique (hypsarythmie), mais sur tout un ensemble évolutif atteignant les enfants à un âge bien déterminé, toujours avant l'âge de un an, et ayant une évolution bien particulière. Il ne faut donc pas limiter ce diagnostic aux enfants qui présentent uniquement la triade symptomatique bien typique décrite classiquement dans le syndrome de West ou dans l'E.M.I.H.

De ce fait, le diagnostic doit être posé et un traitement bien défini instauré de toute urgence dans toute une série de formes électrocliniques à symptomatologie typique, atypique ou incomplète.

Le traitement proposé décrit est le résultat de nombreuses années d'expériences et de recherche, et permet, lorsqu'il est appliqué avec régularité et méticulosité, en tenant compte du produit, des doses et des modalités d'applications d'avoir des résultats extrêmement constants. Ceux-ci seront toujours fonction de l'état du cerveau avant l'éclosion de l'affection et du moment de l'instauration du traitement. Des guérisons totales et définitives sont régulièrement obtenues chez les enfants présentant la maladie de spasme en flexion sur un cerveau préalablement sain et traité précocement.

RESUMEN

Los espasmos en flexión que aparecen en la infancia corresponden a una entidad clínica muy particular y tienen una evolución bien definida. No se puede hacer el diagnóstico sobre la base de determinado tipo de ataques (Blitz—, Nick— und Salaamkrämpfe, epilepsia generalizada en flexión, epilepsia salutaria) ni tampoco sobre la base de un trazado electroencefalográfico totalmente típico (hipsarritmia), sino que éste surge del desarrollo de un síndrome evolutivo que se presenta en niños de determinada edad (siempre menores de un año) y que tiene una evolución particular. Sin embargo el diagnóstico no debe limitarse a los niños que presentan solamente la triple sintomatología descrita en la encefalopatía mioclónica con hipsarritmia de la infancia o en el síndrome de West. Por lo tanto debe hacerse el diagnóstico en todo

un grupo de formas electroclínicas con sintomatología típica, atípica o incompleta y en esos casos se requiere la institución inmediata de un tratamiento bien definido.

Varios años de experiencia e investigación nos permiten proponer un tratamiento que conduce a resultados terapéuticos constantes, si se instituye regularmente y con precisión y si se tiene en cuenta el tipo de droga usado, su dosis y su forma de aplicación. El resultado terapéutico siempre depende de las condiciones en que esté el cerebro antes de comenzar la enfermedad y a partir de la iniciación del tratamiento. Se puede obtener una recuperación completa y definitiva en pacientes cuyo cerebro haya sido sano antes de aparecer la afección de espasmos en flexión y en quienes el tratamiento haya sido iniciado durante las primeras fases de la enfermedad.

SUMMARY

The flexion spasms occurring in infancy correspond to a particular clinical entity with a well defined evolution. The diagnosis cannot be made either on the basis of a given type of fits (Blitz—, Nick— und Salaamkrämpfe, generalized epilepsy in flexion, salutatory epilepsy), nor on the basis of a completely typical EEG record (hypsarhythmia), but rests on the occurrence of a whole evolutive syndrome appearing in children of a given age (always less than one year), and with a particular evolution. The diagnosis should thus not be limited to children presenting only the typical symptomatic triad described in the myoclonic encephalopathy with hypsarhythmia of childhood, or West syndrome. Accordingly, the diagnosis must be made in a whole group of electroclinical forms with typical, atypical or incomplete

symptomatology, and in those cases the immediate application of a well defined treatment is required.

Several years of experience and research allow us to propose a treatment leading to extremely constant therapeutical results, when given regularly and with precision, and if due allowance is made to the kind of drug which is used, its dosis and its mode of application. The therapeutical result depends always from the condition of the brain before the start of the disease and from the moment of initiation of the treatment. Complete and definitive recovery can consistently be obtained in patients developing the disease of flexions spasms on a previously healthy brain and when the treatment has been initiated in the early stages of the disease.

ZUSAMMENFASSUNG

Die Blitz-, Nick- und Salaamkrämpfe müssen als ein besonderes Krankheitsbild erkannt werden, deren Verlauf gut bekannt ist. Diese Diagnose darf nicht nach einem besonderen Anfallstyp (z. B. Blitz-, Nick- und Salaamkrämpfe, generalisierte Flexions-Krampfanfälle, propulsiv Epilepsie) gestellt werden, noch nach einem typisch reinem EEG Bild (Hypsarrhythmia), jedoch bei einer sich fortentwickelnden Einheit bei Kindern eines gewissen Alters (bis zu einem Jahr) und eines eigentümlichen Verlaufes. Die Diagnose darf also nicht bei Kindern die nur ein typische symptomatisches Trias aufweisen, beschränkt bleiben, sowie sie in der myoclonischen Encephalopathie der Kindheit mit Hypsarrhythmia oder West Krankheit beschrieben wird. Folglich muss die Diagnose in einer Reihe von elektroklinischen Formen

mit typischen, atypischen und unvollständigen Symptomenkreis gemacht werden. In diesem Falle ist dringend eine gut festgelegte Behandlung erforderlich. Jahre Erfahrungen und Untersuchungen erlauben uns eine Behandlung vorzuschlagen, die standhafte therapeutische Erfolge erzielen lässt, wenn regelmässig gegeben und genau Rechnung mit den Medikamenten, der Dosis und der Anwendungsweise getragen wird. Die therapeutische Erfolge hängen immer von dem Zustand des Gehirns vor Beginn der Krankheit und von der Zeit, wenn die Behandlung eingesetzt wird, ab. Vollständige und endgültige Heilung kann regelmässig bei Kindern mit einer Propulsiv Petit Mal Erscheinung auf ein gesundes Gehirn erreicht werden, wenn die Behandlung frühzeitig gestartet wird.

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The Classification and Conditioning Treatment of the Reflex Epilepsies

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Reflex or sensory evoked epilepsy constitutes a unique group of patients. Their seizures are induced by the presentation of physiological stimuli. These physiological stimuli are innocuous for all but the relatively few patients with reflex epilepsy. Unfortunately of all the forms of epilepsy, patients with sensory evoked or reflex epilepsy are among the most difficult to treat medically. In many of the patients centroparietal discharges are the chief components of their seizure discharges and when ablation is possible there is often greater risk of permanent deficit. This is particularly applicable to those with musicogenic or voice induced epilepsy who have aphasic components in their seizures and discharging foci in the temporal lobe of the dominant hemisphere. In these patients surgical ablations could lead to permanent language dysfunction. The possibility of behavioral type of therapy is therefore particularly welcome in the group of patients with reflex epilepsy.

There has often been speculation that these types of epilepsy might be a form of conditional reflex^{1, 2, 3}. Indeed this hypothesis originally led my colleagues and myself to study this group of epilepsies. We are certain now that the seizures are not due to a conditional reflex. The reasons for this conclusion are stated elsewhere⁴. However the pursuit of the hypothesis led to the discovery of a behavioral or conditioning type of therapy. In the course of our studies we first considered the suc-

cessful therapeutic results to be an extinction of a conditioned reflex^{5, 6, 7}, but subsequent observations led us to believe that we had encountered a conditioning type of therapy⁴. The classification of these types of reflex epilepsy is essential for the choice of behavioral therapy. This paper therefore deals with the classification as well as the techniques of behavioral therapy in reflex epilepsy.

TYPES OF REFLEX EPILEPSY

Table I presents the types of reflex epilepsy studied in the Epilepsy Center at the University of Wisconsin Medical Center at the time of this writing. The number of cases studied is as follows. photic 25 patients; pattern 4; eye closure 3; color induced 1; startle or acoustico-motor 4; specific sound induced 2; musicogenic 4; voice induced 1; somato-sensory (A) 2; (B) 1; reading epilepsy 4; and swallowing epilepsy 1. These studies are therefore based upon the careful and detailed observations of 52 patients.

CLASSIFICATION OF REFLEX EPILEPSIES

The various types of seizures presented in the aforementioned section can be reclassi-

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TABLE I
Types of Reflex Epilepsy

	Evoking stimulus	Clinical seizure type	EEG changes evoked
Visually Induced			
Photic	Flashing light	Minor motor rarely major motor	Gen. dys. atypical wave and spike
Pattern	Visual patterns	Minor motor	Gen. dys. atypical wave and spike
Eye closure	Closing eyes in bright light	Minor motor	Gen. dys. atypical wave and spike
Color	Specific colors specially red	Tonic, gen.	Gen. Suppression followed by spiking
Auditory Induced			
Acoustico - motor (startle)	(A) Sudden unexpected nonspecific noise	Minor motor or focal motor to gen.	O or gen. dys. Focal dys. proceeding to gen. dys.
	(B) Specific sounds	Major motor	Probably focal to gen. dys.
Music induced	Specific types of music	T. L. seizure	T. L. spiking proceeding to gen. dys.
Voice induced	Specific type of Voice	T. L. seizure	T. L. spiking proceeding to gen. dys.
Somate - sensory			
Tactile stimulus to a particular part of the body			
	(A) Brisk, sudden unexpected tap	Akinetic seizure	Spike and slow wave in the contralateral sensory motor areas
	(B) Prolonged tactile stimulation	T. L. type seizure	?
Language			
Reading	Reading words or numbers with or without comprehension	Myoclonic jerk of the jaw progressing to major motor seizure	T. L. focus may spread centrencephalically
Seizures with eating	Not related to texture, temperature, food, taste or phase of deglutition	T. L. seizure with apraxia of tongue and pharynx	Suppression followed by spiking discharges in T. L.
T. L.: Temporal lobe Gen: Generalized Dys.: Dysrhythmia			

fied. The purpose of this classification is to allow a better understanding of the mechanisms involved and therefore of the possible modes of therapy. Table II presents the classification of the reflex epilepsies.

The contrast between the types of noxious stimuli evoking the simple and complex types of reflex epilepsy is best demonstrated by the difference between the stimuli in startle epilepsy and in musicogenic epilepsy. In startle epilepsy the particular sound need not be specific for example any sudden, loud noise as the dropping of a dish, a sudden rap on a

door is sufficient to evoke a seizure. In musicogenic epilepsy the stimulus is not related to any particular note or chord or instrumentation and exists rather in the theme of the music. The patient described by Poskanzer et al.⁸ in whom the seizure could be evoked by a particular note is not a complex type of reflex epilepsy but rather a simple type. This illustrates the importance of the classification for the method of behavioral treatment would be entirely different in Poskanzer's case than was employed in our four patients.

TABLE II
Classifications of Reflex Epilepsies

Types	Simple	Complex
Noxious stimulus	Simple and easily definable	Complex and difficult to define
Appearance of abnormal responses	Immediate	Delayed
EEG dysrhythmia	Primarily generalized	Primarily focal cortical
Mixed seizure types	Within group	Within group
Unilateral presentation	Usually innocuous	Noxious
Presentation during sleep	Usually ineffective	Effective when applicable
Repeated presentation during and after seizure	Noxious	Innocuous
Effect of conditioning on evoked dysrhythmia	Decrease of generalized dysrhythmia	Restriction to focal cortical area followed by disappearance
Examples of Types		
Visual	Photic, pattern, eye closure	Color
Auditory	Acousticomotor A	Acousticomotor B, musicogenic and voice induced
Somato-sensory	Type A	Type B
Language	—	Reading
Seizures with eating	—	+

Usually in the simple type the abnormal responses, after presentation of the stimulus occur very abruptly and a few flashes delivered by the stroboscope are sufficient to induce a seizure in a photosensitive patient. A loud noise immediately evokes an acoustico-motor seizure but in reading epilepsy it may be necessary to read five or ten minutes or as in one patient personally observed it required four hours of reading before dysrhythmia occurred. The EEG dysrhythmia in the simple type is primarily generalized, usually of the secondary bisynchrony type and of the atypical wave and spike dysrhythmia type. By contrast in the complex type the dysrhythmia is primarily focal cortical. This may not always be immediately apparent, for example in reading epilepsy the dysrhythmia may appear to be generalized and only after conditioning treatment is underway does the focus become primarily limited to the one temporal lobe. However unilateral temporal lobe dysrhythmia in reading epilepsy has been reported without introduction of conditioning.

It has been noted by us that unilateral photic stimulation is often times innocuous in the photosensitive patient⁷. This is not always true of course and occurs perhaps in about two-thirds of the patients. Likewise in startle or acoustico-motor epilepsy if the sound is administered unilaterally by stereophonic earphones and below the level of 60 decibels to prevent bone conduction to the opposite ear no seizure dysrhythmia occurs^{6, 9}. In musicogenic epilepsy monaural presentation of the appropriate music evokes a seizure. Patients with reading epilepsy still have seizures when reading with the vision of one eye completely occluded.¹⁰

The generalized dysrhythmia evoked by photosensitivity becomes decreased during conditioning therapy and this necessitates a change in sensitivity levels of the computer during the process of computer automation. In the complex types of reflex epilepsy however if there is a secondary bisynchrony this disappears with conditioning and only focal cortical dysrhythmia

remains and this itself is degraded so it eventually disappears in the conditioning process (Fig. 1)¹¹.

It is not uncommon to find mixtures of reflex epilepsy in the same patient. This is particularly true in the visually induced types of patients. For example, the combination of photosensitivity and pattern epilepsy or photosensitivity and eye closure seizures occur. Also combinations of reading epilepsy occur and involve other types of language epilepsy. However there have been no mixed seizure types between the two groups, that is simple and complex, e. g. one does not find a musicogenic patient who is also photosensitive.

DIFFERENTIAL DIAGNOSIS FROM OTHER ENTITIES

Certain entities can be confused with the reflex epilepsies and these are often referred to the Epilepsy Center with the diagnosis of sensory evoked seizures. Careful study has found that they either have a different type of sensory evoked seizures than those for which they were referred or they have another neurologic or medical entity. An example, of the occurrence of a different type of sensory evoked seizure is exemplified by the young man who was referred to the Epilepsy Center for seizures on looking at bright lights. With careful audio-visual tape recording using a split screen technique, recording his brain waves on one-half of the screen and the image of the patient on the other half it became immediately apparent that when he was looking at a bright light the seizure dysrhythmia was evoked not by looking at the light but upon closing his eyes. He therefore had an eye closure type of seizure. Two patients referred for musicogenic epilepsy were especially interesting. Again using the split screen technique and this time including autonomic recordings one patient was demonstrated to have a hyperventilation syndrome elicited by playing certain music. It developed that this patient was

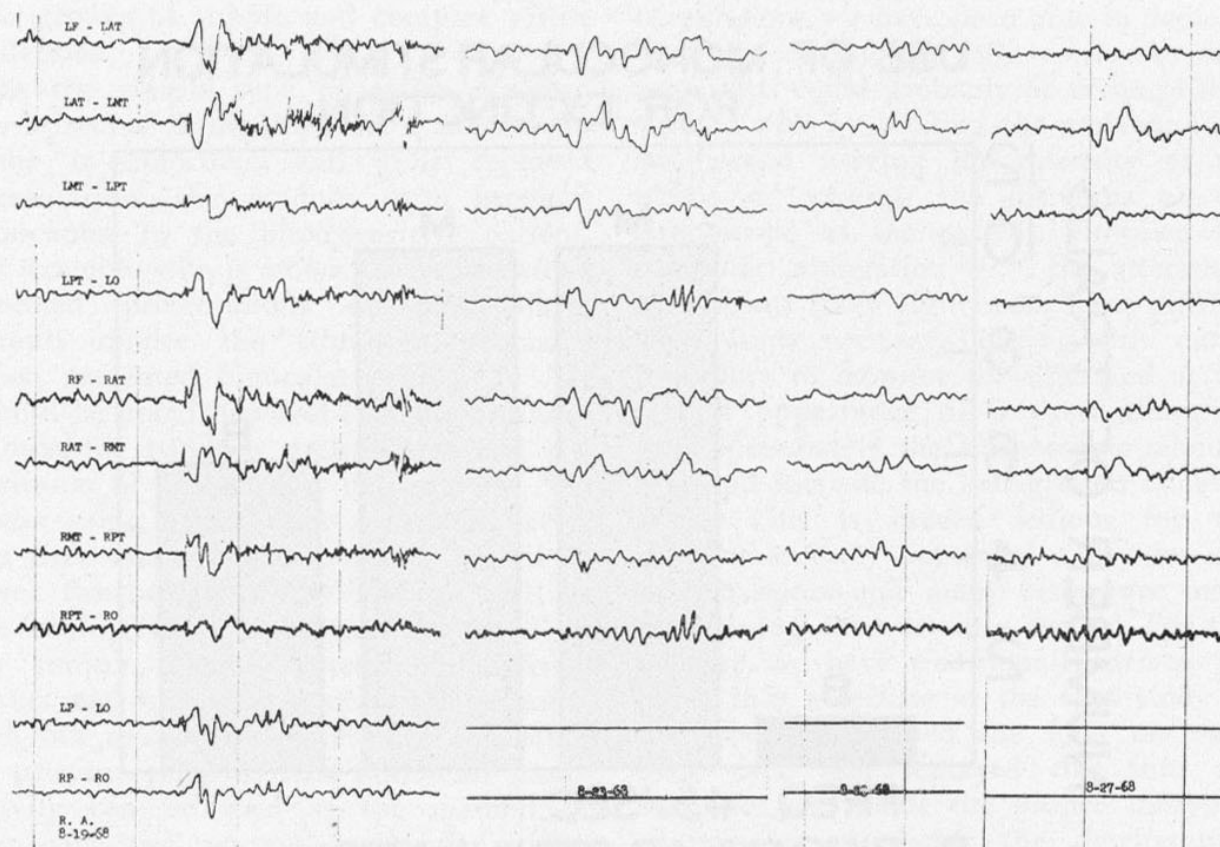


Fig. 1. — EEG changes in patient with reading epilepsy and undergoing conditioning therapy. Prior to the institution of treatment on 8/19/68 the dysrhythmia appears generalized. As the conditioning process was underway the evoked spike remained limited to the left temporal leads and diminished in sharpness and in amplitude at the site of evocation. This demonstrates not only the failure to spread but also the degradation of the spike evoked.

having attacks while helping her husband in the management of his music store and she was quite unhappy in this situation. The other patient thought to have musico-genic epilepsy was an accomplished musician and suffered a ruptured aneurysm of the right middle cerebral artery. Following this he had a depressed reaction while listening to music which formerly had been most pleasing. Electroencephalographically there were no alterations during the playing of this music but upon studying his autonomic responses it was found he had lost the normal autonomic responses to music. This lack of autonomic reaction gave rise to his affective alteration while listening to music.

In the realm of reading epilepsy, patients with dyslexia and narcolepsy have been referred for study. The audio visual tape

recording technique described above sufficed to make the correct diagnosis in these patients. One most unusual patient was a young student nurse referred for reading or language epilepsy because during classes she had long periods of three to five minutes of loss of attention. Her resting EEGs have shown 14 and 6 per second dysrhythmia. She had been treated with anticonvulsant medication without effect. In our laboratory of the Epilepsy Center the lecture environment was reconstructed and during the AV tape monitoring while she took notes from lectures presented to her it was noted that she would stop taking notes for a period of three to five minutes, stare ahead, with a rather blank facial expression, would come out of the situation rather abruptly and would return to taking notes. There

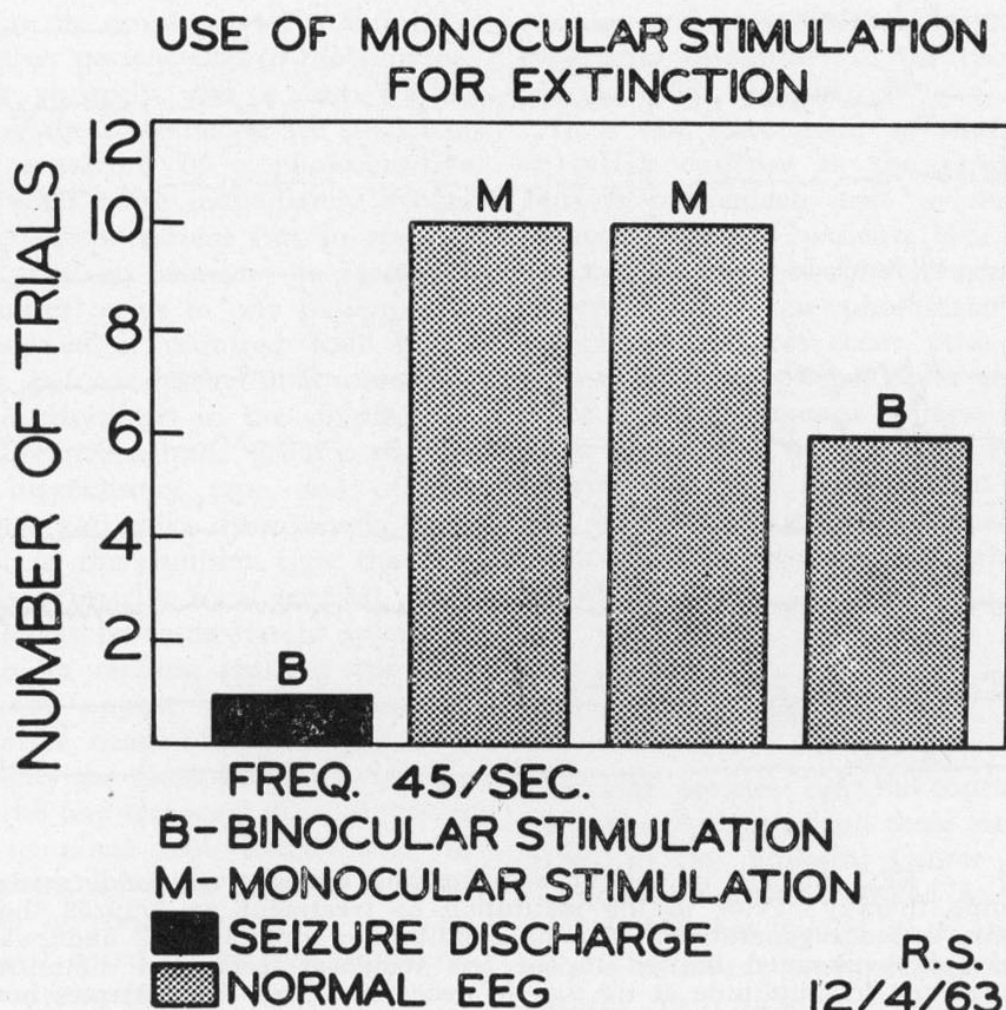


Fig. 2. — Nomogram showing the efficacy of monocular stimulation in milder cases of photosensitivity. With binocular stimulations a seizure could readily be elicited but careful monocular presentations did not evoke a seizure or seizure discharge. After ten repeated and consecutive monocular stimulations first to one eye and then to the other eye no seizures could be elicited by binocular stimulations.

was no significant EEG dysrhythmia during this time. When the anticonvulsant medication was stopped these episodes were not more frequent or worse. The use of amphetamines did not alter the situation. This was neither narcolepsy nor epilepsy and this patient responded to avoidance conditioning therapy. This last patient especially stresses the importance in arriving at the diagnosis of reflex epilepsy. The patient not only must have a proper clinical seizure picture but if dysrhythmia is present it should be established as occurring during the evoked seizure. In

evoked epilepsy it is relatively easy to reproduce the situation in the laboratory.

TREATMENT OF REFLEX EPILEPSIES

Clinical therapeutic conditioning is a form of therapy devised by us in the treatment of the reflex epilepsies¹¹. This consists of controlled careful presentations of the noxious stimulus with the aim and goal of rendering the stimulus innocuous in the future. The type or mechanism of treatment differs radically between the

two groups of simple and complex reflex epilepsies.

In the simple type of reflex epilepsy the stimulus is modified in a manner to make it innocuous and after repeated presentations the noxious form becomes innocuous. In the photosensitive patient, for example who is monocularly insensitive repeated presentations of monocularly stimuli render the stimulus innocuous when presented binocularly (Fig. 2)⁷. It should be noted however that the ordinary ophthalmic patch is useless here and the occlusion of vision must be complete. We prefer using a soft black swatch of velvet put over one eye and carefully placed to cover the bridge of the nose as well as the orbit. This can be held in place by the subject. This unilateral insensitivity occurs not only with stroboscopic stimulation but usually in eye closure and often in pattern epilepsy. This unilateral insensitivity can be used as the method of treatment and repeated monocular stimulations are administered first to one eye and then to the other. In the laboratory we have used this method and have given repeated stimulations for several hours morning and afternoon for several days and had the patient between laboratory sessions wear some type of patching device as well designed as possible.

Monocular stimulations require a great deal of cooperation on the part of the patient. It is particularly important to realize that if the patch is allowed to slip and some slight visual stimulus is put into the visually occluded eye the patients become monocularly sensitive. For this reason another technique has been employed for altering the noxious stimulus. This we have defined as the Relative Differential Light Intensity technique¹². This consists of holding the stroboscopic stimulus at a constant intensity but varying the background lights. Stroboscopic stimulation is at first relatively less conspicuous. We have arbitrarily chosen an illumination of 600 foot candles at the bridge of the patient's nose and by gradually diminishing the ambient light during the stroboscopic

stimulations we have been able to decrease the room or ambient light to zero or near zero. This could probably be accomplished equally well by holding the ambient light steady and varying the intensity of the strobe or varying the distances of the stroboscope to the patient. However for computer automation^{13, 14} the alterations of ambient room light seem most satisfactory. It is necessary during this entire procedure to monitor the EEG and at the earliest appearance of a dysrhythmia to stop immediately the stroboscopic stimulation and increase the background illumination. This is indeed tedious for the scientist to carry out twice a day for one to two hours and many errors are made and seizures inadvertently evoked. For this purpose we have traditionally driven patients into a seizure at the first study in the laboratory, taped the EEG on magnetic tape and replayed this into the computer and made the proper computer adjustments to detect the dysrhythmia. Only after this are the patient's brain waves fed directly into the computer and stimulations begun under the automation control of the computer. (Fig. 3).

The stroboscopic stimulations can be rendered innocuous using this technique. However the sensitivity for the entire range will not disappear. If the patient, for example is sensitive from 15 to 30 cycles per second and the therapy is administered at 22 cycles per second the resultant insensitivity will extend for a slight distance on each side of this frequency say from 20 to 24 cycles per second. It is therefore necessary to clear the entire range of sensitivity. It is usually better to start in the middle of the sensitive range rather than at either end for it is less time consuming.

What has been said regarding the use of unilateral stimulation or differential light intensity in the stroboscopic stimulation applies equally well to pattern and eye closure seizures¹⁵. Eye closure seizures are visual and are not related to the proprioceptive input for when the patients close their eyes in the dark, there is no

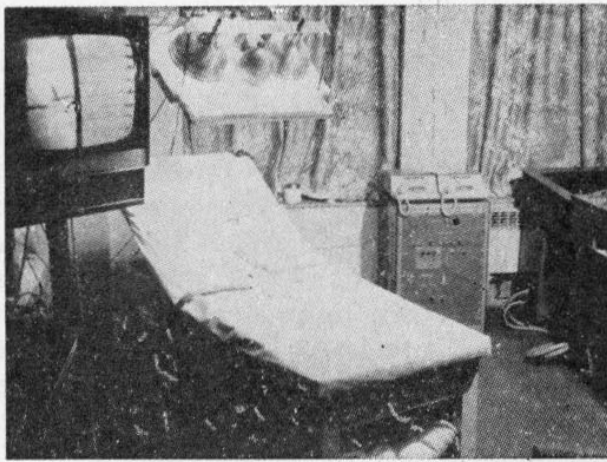


Fig. 3. — Equipment used in computer automation in the differential Light Intensity technique. On the left is the couch upon which the patient reclines. The unit with an opaque screen contains the stroboscope flanked by photoflood lights. It is ready to be lowered to one meter distance from the patient's nose. The EEG machine is on the mid-right and on the far left is the A-V monitoring split screen. The patient is observed and taped on the left half of the screen and the EEG'S simultaneously on the right half. In the center is the panel with controls for manual or automation control of both stroboscope and ambient room light. Once the parameters have been determined the control panels are set for computer automation and this is accomplished by means of the telephones. One line carries the brain waves to the U. W. Computer Center for monitoring while the other telephone line controls the presentation of stroboscopic stimuli and the background or ambient light.

dysrhythmia. Eye closure seizures therefore are dependent upon a certain amount of light being filtered through the eyelids. If these patients are monocularly insensitive they can be conditioned by blinking their eyes with one eye patched or again blinking their eyes in the dark and gradually increasing the ambient light. The same applies to the pattern sensitivity.

The conditioning of pattern sensitivity can be automated using a Super 8 movie projector with a Cassette movie film of the particular patient's sensitive patterns presented for 3 to 5 minutes beginning in the

dark and out of focus and gradually approaching focus and bright light. This can also be accomplished by the automated technique, the pattern being presented on a projection screen in front of the ambient light source. In the bright light the pattern is barely perceptible and as the ambient light is decreased the pattern becomes more and more obvious. By computer automation the steps in room light can be increased if any sensitivity occurs.

These same techniques can be employed in startle epilepsy. Stereo earphones can be employed playing the sound in one ear only and at a level below 60 decibels so it is not conducted by bone to become binaural⁶. In somato-sensory epilepsy the unilateral technique of course is not available since this type of seizure is evoked from only one part of the patient's body, for example by tapping of the left shoulder or of the right thigh. However generally the same techniques can be employed by administering very gentle taps below the threshold level, and gradually increasing in strength or beginning outside of the sensitive zone, for example below the knee and gradually approaching the thigh¹⁶. In the complex types of reflex epilepsies it is possible to use the same methods¹⁷. This however is extremely laborious for the specific stimulus is vague. For example in our first musico-genic epilepsy patient a particular song (Star Dust) played in full orchestration or vocal and instrumentation consistently evoked seizures but this did not occur with presentation of the same musical number as recorded from an electric organ or computer. By careful introduction of only a few bars appropriately placed of orchestration music into the organ music as presented to him and gradually increasing the orchestrated music it was possible to render the orchestrations innocuous. This then had to be followed by the same technique for the introduction of male and female voices and certain particular instruments. This obviously is a tremendously laborious and time consuming operation.

Fortunately in the complex types a more simple technique is available^{18, 19}. The stimulus is presented and when a seizure occurs, the stimulus is repeatedly presented during the seizure, during the postictal confused period and for 10 or 15 times after the patient has regained consciousness and the EEGs have become normal. In the event that only a dysrhythmia occurs and there is no seizure but only a sub-clinical seizure, repeated presentations of the same stimulus will bring about the disappearance of the dysrhythmia. This is usually more laborious, and requires longer periods of time of presentation than takes place if a seizure has been induced. Musicogenic and voice induced epilepsy are readily amenable to this form of treatment.

MAINTENANCE OR REINFORCEMENT OF THE CONDITIONING EFFECT

Unfortunately the results in the laboratory do not persist and some day-to-day protection in the environment is required. The patients with auditory induced seizures for example, musicogenic and voice induced epilepsies listen daily to audio tapes which summarize the conditioning process in the laboratory. This has proven successful.

In the photic induced seizures the problem is somewhat more complex. In the less severely involved patients with monocular insensitivity, conditioning using monocular stimulations was employed in the laboratory and the patients were given a relatively inexpensive stroboscope to take home. Twice a day they spend a half hour with the vision of one eye completely occluded and administering stroboscopic stimulations to themselves. This of course requires a great deal of cooperation and ability on the part of the patients so as to not to render them monocularly sensitive.

Most of the photosensitive patients have been treated with the use of specially designed eye glasses (Fig. 4) with a photo electric cell over the bridge of the nose activating a hearing aid device over

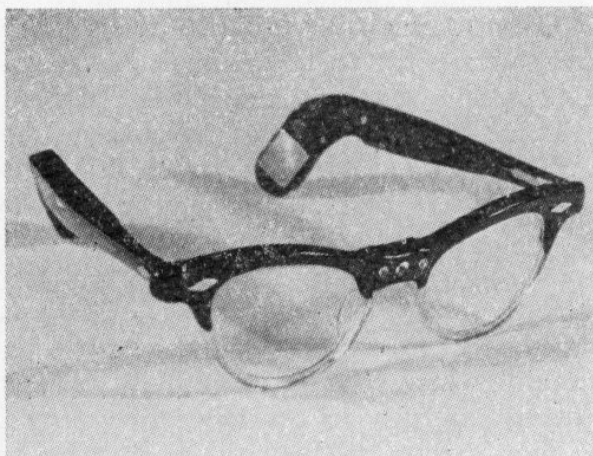


Fig. 4. — The specially designed eye glasses for reinforcement or maintenance of the conditioning effect in photosensitivity. The ornament over the bridge of the nose includes a photoelectric cell which is activated by light changes in the patient's milieu. The photoelectric cell activates the hearing aid device over the mastoid process. Each sudden change in room or outdoor light induces a click. The patients are conditioned in the laboratory wearing these glasses so the innocuousness of the clicks presented in the laboratory is coupled with the auditory clicks, thus serving to set up "second signal system".

the mastoid so that at each flash of light they receive an audible click⁵.

Reinforcement or maintenance of the therapeutic effect is not necessary in the patients who can control the noxious environment. Most of the reflex epilepsy patients have no control over the inadvertent administration in their day-to-day milieu of the noxious stimulus. It is impossible for the musicogenic epileptic to avoid music completely or for the pattern epileptic's parents to screen their child completely from the possibility of grids patterns or other patterns which may be noxious. Reading epilepsy however is different. These patients do not have seizures on merely reading several words such as on a billboard or on the title of a book. They usually have to read several minutes before having their first seizure. They therefore are in control of the situation since the evoking stimulus cannot be presented to them without their consent.

In reading epilepsy vigilance trials have proven successful in aborting the seizures. This consists of asking the patient to read while pressing his fingers together at the occurrence of a certain letter. For this purpose letters that are frequently occurring in the text, for example a, e, o, s, and t are employed rather than rarely appearing letters such as q and v. The patient indicates the occurrence of the letter by squeezing his fingers together and is observed carefully in the laboratory, using AV monitoring, to be certain that he is not careless in using this technique. With a little experience this technique does not interfere with the learning techniques as was determined informally by giving the patient a selected article to read for the first time and testing him afterwards on detailed as well as on general information derived from the article. Also a more sophisticated memory recall test was performed and demonstrated that the patients can readily acquire the ability to read while carrying out vigilance trials and without impairment of their learning functions.

Swallowing epilepsy is in part a controlled environment in the sense that the patient is well aware of swallowing when eating or drinking. Unfortunately however the patients also swallow unconsciously many times during the course of the day. In our patient the vigilance trials have been of some value in decreasing the number of seizures at mealtime.

SELECTION OF CASES

Intelligence in itself is not an important criteria in the selection of patients. An extremely retarded child was successfully conditioned in the laboratory. However sufficient intelligence by the patient or family are necessary to carry out the maintenance process and the behavioral activity of the patient must be adequate to assure success of conditioning in the laboratory. An extremely overactive child who will not look at the stroboscope and remains quiet for the periods of time

necessary is of course not amenable to this type of therapy. Also patients with numerous spontaneous seizures are not amenable to this therapy since the computer cannot distinguish between spontaneous and induced dysrhythmia.

Also we have found little or no success in dealing with a progressive degenerative disease, for example the progressive cerebellar degeneration with photosensitivity. The downward course of the patient renders the conditioning of little or no value.

ANTICONVULSANT MEDICATION

Almost all of the patients studied in this series had been on anticonvulsant medication and on adequate dosages. The medication which the patient was taking at the time of admission to the program was kept constant. This had not been sufficient to control the patient's seizures and indeed this was the reason why they were referred. No alterations in medication were allowed during the course of the conditioning therapy. Two patients with photosensitivity had had no prior anticonvulsant medication and these patients were treated exclusively by the conditioning technique.

RESULTS OF BEHAVIORAL THERAPY

In the photosensitivity group three patients were treated with monocular stimulations and maintenance of monocular presentations at home. Since the institution of therapy they have remained seizure free from three to seven years. Eight patients are wearing the specially designed glasses. One patient has ceased wearing them after having been seizure free for three years. Two of the patients have been seizure free for three years and are continuing to wear their glasses. One patient with both mixed seizure and pattern epilepsy was conditioned against both types of reflex epilepsy and has worn her glasses for five years and has a very occasional seizure. This

child when taken to school had to wear a magazine over her face so as not to have a seizure while being driven in the family car. On a recent family trip her parents deliberately tested the therapeutic efficacy by walking her along the "strip" at Las Vegas, Nevada at night with all of its glaring, flashing lights. No seizure occurred.

The two original eye closure seizure patients could not be followed because of other medical and emotional problems. A third has not been followed for a sufficient period of time to determine the efficacy of the conditioning. The patient with color induced seizures was not amenable to prolonged conditioning because he is a mute, hyperactive, mentally retarded child totally unable to cooperate.

The four musicogenic epileptic patients are able to listen to their master tapes which daily reviews the conditioning process and they do this without having seizures. They listen to a wide gammut of music and very occasionally will find a number which will induce a seizure. They have learned to tape and replay these numbers the same way as was done in the laboratory. The patient with voice induced epilepsy has gone 3 1/2 years without a seizure and prefers to continue listening to her conditioning tapes rather than make the attempt to decrease the listening time. Two of the reading epilepsy patients were not available for continuing study. The other two who were placed in the treatment program have both returned to the pursuit of their educational goals.

S U M M A R Y

This paper presents the types of sensory evoked or reflex epilepsy studied at the Epilepsy Center, University of Wisconsin. These include photic, pattern, eye closure, color induced, acousticomotor, music, voice induced, somato-sensory, language epilepsies, and seizures while eating. These types of reflex epilepsy have been classified into a simple and complex type depending upon the criteria of the stimulus and the clinical and EEG responses of the patient. The importance is stressed of audio-visual recording, preferably using a split screen technique with visualization of both the patient and the brain waves. Certain patients referred as having reflex epilepsy upon careful laboratory scrutiny are found either not to be reflex epilepsy at all, for example narcolepsy rather than reading epilepsy or found to be a different type of reflex epilepsy, for example eye closure rather than bright light induced.

Clinical therapeutic conditioning or behavioral therapy is described. This differs in the simple and complex types of reflex epilepsy. In the simple types, therapy consist of the presentation of the noxious stimulus altered so as not to be innocuous and after repeated presentation the original stimulus becomes innocuous. In the complex type the stimulus is presented in the noxious form to induce a seizure and during the ictal and post-ictal periods the stimulus is repeatedly presented. This noxious stimulus then becomes innocuous. Regardless of the technique and in both types of reflex epilepsy reinforcement or maintenance of the conditioning process is necessary on a day-to-day basis. The exception to this is reading epilepsy where the patient is in control of the presentation of his stimulus so that reinforcement in the usual sense is not necessary.

RESUMEN

Este trabajo presenta los tipos de epilepsia refleja o sensorialmente provocada estudiados en el Centro de Investigación de la Epilepsia de la Universidad de Wisconsin. Entre los casos estudiados se han encontrado los siguientes tipos de epilepsia: las provocadas por la luz, o los dibujos geométricos, el cierre de los ojos, los colores, los fenómenos acústico-motores, la música, la voz, los efectos sensoriales somáticos así como también las epilepsias provocadas por el lenguaje y la acción de comer. Estos tipos de epilepsia han sido clasificados en simples y complejos, de acuerdo a los criterios de estímulo y de examen clínico y electroencefalográfico del paciente.

Se destaca la importancia de los resultados audiovisuales, obtenidos sobre todo mediante la técnica de la doble pantalla, que permite observar simultáneamente al enfermo y la proyección del electroencefalograma.

Luego de un minucioso examen, ciertos enfermos considerados como casos de epilepsia refleja, demostraron no presentar esta dolencia. Así por ejemplo algunos son narcolépticos y no casos de epilepsia re-

fleja a la lectura o bien son casos de epilepsia diferentes: son inducidos por el cierre de los ojos y no por la luz intensa.

Se describen un tratamiento clínico condicionante y un tratamiento orientado hacia el comportamiento del enfermo. Estos tratamientos difieren según se trate de tipos simples o complejos de epilepsia refleja. En los tipos simples el tratamiento consiste en la presentación de un estímulo patógeno ajustado para que sea efectivo. Después de reiteradas presentaciones, el estímulo se hace ineficaz. En los casos complejos el estímulo es presentado en su forma patógena a los efectos de inducir la crisis y durante los períodos ictal y post-ictal el estímulo es presentado varias veces. El estímulo patógeno queda entonces sin efecto. Cualquiera sea la técnica empleada en ambos casos de epilepsia refleja, es necesario mantener o intensificar el condicionamiento diario del enfermo. El caso de la epilepsia inducida por la lectura constituye sin embargo una excepción, en que el enfermo controla la presentación del estímulo y el refuerzo en el sentido habitual es innecesario.

R É S U M É

Ce travail présente tous les types d'épilepsie d'origine sensitive ou reflexe étudiés au Centre d'Epilepsie de l'Université de Wisconsin.

Ceci comprend les crises photiques, provoquées par la clôture des yeux, par la couleur, acoustico-motrices, provoquées par la musique, par la voix, somato-sensitives, épilepsies du langage et crises apparues pendant l'action de manger. Ces différents types d'épilepsie reflexe ont été classifiés en simple ou complexe d'après les critères du stimulus et d'après les réponses cliniques et électroencéphalographiques du patient. On signale l'importance de l'enregistrement audio-visuel en employant de préférence une technique double éventail

(split-screen) permettant de voir le patient et les ondes cérébrales.

Certains patients étudiés comme des cas d'épilepsie reflexe démontrent après une soigneuse étude faite au laboratoire qu'ils n'ont pas du tout ce genre d'épilepsie, par exemple ils souffrent de narcolepsie au lieu d'avoir une épilepsie de lecture, ou bien on découvre qu'ils ont un autre genre d'épilepsie reflexe; par exemple que l'épilepsie est due à la clôture des yeux mais qu'elle n'est pas provoquée par la lumière forte.

On décrit une thérapie de conditionnement clinique ou de comportement. Ceci diffère selon qu'il s'agisse d'un type simple ou complexe d'épilepsie reflexe. Dans

les types simples la thérapie consiste à présenter un stimulus nocif modifié; après la présentation successive le stimulus original devient inoffensif. Dans les types complexes le stimulus est présenté sous sa forme nocive pour provoquer une crise; se stimulus est présenté plusieurs fois pendant la période ictale et postictale. De cette façon le stimulus devient inoffensif.

Indépendamment de la technique employée et dans les deux types d'épilepsie réflexe le renforcement ou la prolongation du processus de conditionnement est nécessaire d'une façon continue. L'épilepsie de lecture constitue une exception puisque le patient contrôle la présentation de son stimulus de façon que le renforcement dans le sens courant n'est pas nécessaire.

ZUSAMMENFASSUNG

Die Formen (Anfallstypen) der sensorisch bedingten oder die Reflex-Epilepsien sind die Unterlagen der Studien der Epilepsie Research Zentrale der University Wisconsin.

Das Material umfasst photische, Augenschließen, farbige Reizungen; Akustischmotor, "musical", "vocal", somatische-sensorische bedingt, Sprachkrampfarten und Anfälle während des Essens.

Die Sonderformen im Gebiet der Reflex-Epilepsien sind aufgeteilt in eine Einfache und die Komplizierte Form in Abhängigkeit des kausativen Reizes und des klinischen Status sowie der EEG Befunde. Die Wichtigkeit dieser Forderung im "Audio-visual Rekord" ist der Grund zu einer Bild — EEG Film Technik, die eine lange klinische mit graphischer Beobachtung ermöglicht.

Gewisse Patienten, die als Reflex Epilepsie eingewiesen waren, zeigten nach der obigen exakten Untersuchung, dass sie nicht Reflex Epilepsien waren. Zum Beispiel, Narcolepsy mehr als Lesenepilepsy

sind andere Typen von Reflex Epilepsien.

Die therapeutischen Behandlungen als "Conditioning oder Behavior" werden kurz umzeichnet. Sie sind anders in den einfachen und den komplexen Anfallstypen der Reflex Epilepsien. In der einfachen (simple) Form muss die "Noxious" Reizung geändert werden bis sie nach wiederholter Applikation des Originalstimulus nicht mehr "innocuous" ist. In dem komplex Typus muss der Stimulus zu einer epileptische Entladung (seizure) führen. Während der ictalen und postictalen Zeitspanne muss dieser Reiz häufig wiederholt werden bis keine Irritationen statt finden, i.e., Innocuous zu dem Stimulus. Die Technik in beiden Formen von Reflex Epilepsie benötigt Unterstützung und Erhaltung bis zur gänzlichen Ausschaltung weiterer epileptische Anfälle. Tägliche Stimulierung ist oft notwendig oder ratsam. Eine Ausnahme ist die Lesebedingte Epilepsy wo der Patient Kontrolle über den kausativen Stimulus hat und eine "Stärkung" ist nicht nötig.

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Prof. Raymond Garcin

(1897 - 1971)

March 29, 1971. The last page of the book of life was written about Dr. Raymond Garcin. The book that is written by itself turning its pages, from one day to the next, is now closed. Nothing would be added, nothing could be taken from it. We have witnessed a large part of it.



It was beautifully written by a clean sensitive soul, manifesting itself in every act, in every gesture, disclosing the inner beauty of intelligence coupled with generosity and kindness.

"What time destroys memory restores", as Proust affirmed.

And Raymond Garcin remains alive in our memory. Turning back many pages I find the moment when we first met.

Montevideo, 1951. We were at the Airport waiting for the arrival of Prof. Garcin from Paris.

He was coming to deliver some lectures in our country. From the stairway, we saw a short man with a round face in which beamed a kind smile. We immediately guessed that he was the

person we were awaiting. He had a little stooped shoulders due to the peering into books excessively or bending over the patient, searching for reflexes and signals which might give a hint of his illness.

A hearty handshake sealed a life-long friendship. All I might say about his wonderful contributions to sciences is already known by every specialist of neurology who loves his trade. His name is forever linked to the bibliography to which the student of every epoch will return from time to time to seek inspiration for new conquests, affirming the permanent influence of the past over the future.

We want to stress in this homage to his memory, that nobody but his contemporaries could attest, the wonderful person that Raymond Garcin was in the flesh.

Born in the beautiful island of "La Martinique", where he spent his infancy and adolescence, it seems that this colorful environment shed in his sensibility a love for the aesthetic values of Nature.

I remember that during his stay in Montevideo he used to pause so often to admire a sunset, which are particularly beautiful in our country. He would stay for several minutes absorbing the entrancing shades of bright orange, fading into deep red and violet surrounded by rosy nacreous clouds that heralded the coming night. Later we learned that he used to paint, may be he was framing in his mind this nature's colorful display in some of his watercolours.

He was very fond of family life, a devoted husband and parent; he often referred to his family in his conversation, and when we met he often talked about his younger son then a child as "le petit agneau" because of his curly hair, and his "walking stick who would assist him in old age".

This affectionate nature was also enjoyed by his numerous pupils and friends. I remember in his well-known rounds in his Service at La Salpêtrière that he cast a vigilant look on his young collaborators to see if they were in good shape, taking paternal care if they seemed too pale or showing some symptoms of fatigue or ill health. This was particularly emphasized if they happened to be far from home alone in Paris on scholarships.

He used to address his patients by their names as a good friend in misfortune. No matter how ill they were, they looked comforted and confident under his supervision.

Dr. Garcin was an example of all that made French Neurology one of the most praised in the world. He had many visitors from all over the world enjoying his way of studying his patients.

He was an artist at work, the nervous system was wisely explored with hammer, tuningfork, tubes and cottons, eliciting with remarkable finesse all the reflexes, and responses which he was happy to show to his audience, discarding, sorting the elements of judgement and arriving to the right diagnosis. Many important contributions came from this center of Neurological studies at La Salpêtrière. A room with the proper lighting was always fixed to record in pictures whatever was important to keep for illustrations.

His love for knowledge was equal to his love for teaching, so many were the pupils benefited by this gifted personality which made justice to the philosopher who said. "Teaching is the highest form of love". For only those who bestow on others whom they regard in high esteem know the real meaning of this noble word.

The many friends who enjoyed Dr. Garcin and Madame Ivonne's warm hospitality know how particularly enjoyable it was to share the wonderful atmosphere in his home. They formed a lovely couple and

their memories are for us linked to many wonderful moments. For example when they took us, many years ago, to visit Versailles on a day when the marvellous fountains were displaying all their beauty at work. They shared with joy the enthusiastic admiration that the sumptuous castles and gardens aroused in us.

Later, in Congresses in Paris, and in different countries, we were always happy in their company.

But lately, Dr. Garcin's soft and kind smile was clouded with a silent sadness. Madame Ivonne was cruelly separated from him by an unfortunate accident. Now both remain as a sweet memory of the past, which is brought back in the many details that linked our lives. The Advisory and Editorial Board of the International Journal of Neurology particularly regrets the departure of one of its founding members. For more than a decade this publication benefited from his wise advice and clear vision of the most tangling problems in clinical Neurology.

His international personality based on a world wide reputation as a specialist of exceptional value and as a human being enhanced with the best attributes that make a man be truly loved by his kind, caused this loss to be felt as a personal one in the many countries in which his name is highly revered.

VICTOR SORIANO.

Book Reviews

NEUROLOGY OF EARLY CHILDHOOD. —

By Anatole Dekaban, M. D. Ph. D. — The William Wilkins Co. — 1970 — 488 pp.

This book of well defined and ordered chapters, written concisely and clearly and with an evident purpose of offering the necessary knowledge, to get the reader acquainted with the fundamental of each of the neurological pictures belonging to early childhood can be very useful for the clinical practice.

The didactical value of the book is increased with numerous illustrations. Emphasis is pointed out on the study of metabolic disorders affecting the nervous system, epilepsy, degenerative disorders, mental retardation, that constitute very frequently pathological processes in the first years.

Any perturbation concerning the brain of a child, may produce varied clinical manifestations in close relation with the period of maturity of neural mechanisms.

In the newborns, the expression of life are under control of the spinal cord, brain stem and basal ganglia mechanisms. Later in the following months and in the first years of life, the cerebral cortex starts the control of the above mentioned centers progressively. Brain cortex is the foundation for the learning from experience, future planification, abstract thought, intellectual accomplishments and controlled emotions.

The first years of life are concerned with gradual acquisitions of these functions. The book consists of several and important chapters.

Anatomical evolution of the nervous system. Electroencephalographic changes.

The way of studying the child. The physical, neuropsychical examination, movements, perception, adaptational integration, specific reflex reactions, etc.

Possible lesions in intracranial formations, in the cranial bones, spinal cord, brachial plexus and peripheral nerves.

Meningitis, *Listeria Monocytogenes*, *Coccidioides*, Tuberculous, Acute viral meningitis, suppurative lesions about the meninges.

Encephalitis and Encephalomyelitis, bacterial, fungus, syphilis, virus and encephalitis or Encephalomyelitis of obscure etiology.

Dysraphic states and various abnormalities of the skull and spine. A pathological factor or a genetic lesion damage a segment of the central nervous system, or of primitive mesenchymal tissue; in the rachis as well as in the skull.

Hydrocephalus. Its most important mechanism is the obstruction of the pathways of circulation of the cerebro spinal fluid. Most frequent lesions are congenital malformations, inflammatory processes, expanding intracranial lesions.

Vascular disorders affecting the Central Nervous System, hemorrhage, thrombosis and embolism. Sturge Weber, arteriovenous angiomas, primary diseases of the blood vessels.

Cerebral Palsy. Chronic nonprogressive diseases which affect the central nervous system and involve predominantly motor functions. The lesion can be prenatal, intranatal or postnatal. Its nature: traumatism, malformations, infections, intoxications, vascular abnormalities and genetic-metabolic aberrations.

Mental deficiency and certain disorders leading to retardation of Development.

Neurocutaneous Dysgenesis. Sturge-Weber Disease, Tuberous Sclerosis, Von Hippel Lindau Disease, Neurofibromatosis (Von Recklinhausen's Disease).

Exogenous and Endogenous Intoxications affecting the Nervous System. Damage of the Nervous System in Certain Metabolic and Endocrine disorders.

Selected Syndromes with Neurological abnormalities, Syndromes with Chromosomal Anomalies and Neurological Involvement.

Primary diseases of the muscular System.

We tried to point out to the reader the variety of subjects that are developed in this book. We are not going to repeat what we said at the beginning of this review, about the impression we are having about it.

We believe that for all that are dedicated to the study of Nervous System, as for the Pediatricians this book deserves to be read and consulted, it encompasses all modern knowledge on the subject.

VICTOR SORIANO

A MANUAL OF ECHOENCEPHALOGRAPHY. — By Sumio Uematsu, M. D. and Earl Walker, M. D. — The Williams & Wilkins Company. — Baltimore, pp. 150. — 1971.

This interesting book gives a round idea about the possibilities and limitations of a technique that is becoming very popular nowadays.

It is a method harmless to the patient, does not require special preparation and can be repeated giving valuable information.

It takes only fifteen minutes to make an examination, which may demonstrate if the midline is displaced by a lesion, and if dilatation of the ventricles exists. It can

not make a pathological diagnosis, but it can demonstrate the location of certain intracranial structures. The following examinations of a midline shift are of great prognostic and clinical importance.

Karl Dussik suggested in 1942 that ultrasonics might be used to localize lesions in the brain. Lecksell in 1955 developed ultrasonic equipment to get information about the midline intracranial structures. He named the technique Echoencephalography "the process of examining through the intact skull discrete ultrasonic pulses reflected back to their remitting sources from intracranial structures."

Ultrasonic waves are produced applying briefly, moderate electrical energy of high voltage and low power to the surface of a piezoelectric crystal, the most used, is barium titanate.

For echoencephalography 2 megacycles (Mc)/sec is the best frequency. For more penetration a 1 Mc/sec transducer may be occasionally necessary.

Instruments and techniques for recording the echogram are described.

The different locations for making the exploration: 1) Temporal echograms, are used to determine the location of the 3rd. ventricle, septum pellucidum or fornix, 2) Parietal echogram, is reflexed in posterior part of 3rd. ventricle and the pineal gland., 3) Occipito Parietal echogram, a bearing may be made on the falx by applying the transducer above the mastoid process., 4) Precentral echograms, reflecting from frontal falx, walls of the third ventricle. Other locations are considered.

Interpretation of Normal and abnormal Echograms., Brain Tumor. If the tumor is supratentorial there is deviation of the midline. If infratentorial an enlargement of third ventricle will be recognized.

It is very useful to study the deteriorated patients after operation. Absence of midline displacement makes possible brain edema; midline displacement indicates hematoma.

Midline shift. The maximum is seen in temporal lobe lesions. Next in tumors of the occipital lobe. Minimal shift in frontal lobe tumors. A large shift with no abnormal reflexion favors low grade astrocytoma, unilateral edema, metastasis or abscess.

Supratentorial tumors. Three types of echoencephalographic abnormalities. 1- Midline displacement, 2- Complex of abnormal echoes., 3- Displaced lateral echoes indicative of ventricular dilatation.

Different types of tumors are considered. Infratentorial tumors. Patterns suggestive of a posterior fossa mass consist of lateral displacement of the lateral echo and abnormal separation of the 3rd. ventricle echoes.

Ultrasonic determination of the size of

the cerebral ventricular system. The determination of the size of the lateral ventricle is of more clinical value than that of the third ventricle.

Echoencephalography is one of the most effective diagnostic procedures in Head Trauma. Extradural and subdural hemorrhages, intracerebral hemorrhage, edema and cerebral contusion may be diagnosed by this technique.

In Cerebral vascular accidents echoencephalography will allow to recognize an intracerebral hematoma from non-expanding encephalomalacia.

In Epilepsy is useful to rule out the possibility of an expanding lesion or suggest further diagnostic procedure.

Return of a midline shift is studied in Subdural Hematoma, Tumor, Intracerebral Hemorrhage., Carotid Artery Occlusion and Brain Abscess.

Dural Echography is a technique that allows to localize precisely a lesion and give information of its nature.

In chapter: Future of Echoencephalography three major methods for ultrasonic tomography are studied. Contact linear Scanning, Contact Sector Scanning, Compound Scanning.

The Book is profusely illustrated with very well made pictures of echograms compared with brain arteriographies, and neuroencephalographies of the same patients, referred to the numerous examples mentioned in the text.

It is a very interesting book, clear and objective, for everybody interested in nervous system.

VICTOR SORIANO.

News

HEALTH CARE SYSTEMS DESIGN TRAINING PROGRAM.

The National Center for Health Services Research and Development of the Department of Health, Education, and Welfare has recently awarded the Department of Industrial Engineering at the University of Missouri - Columbia a training grant to support a Ph. D program in Health Care Systems Design. This grant provides additional resources to support the Department's extensive current commitment in this area. A vital feature of the program is the unique collaboration between the University School of Medicine and the College of Engineering. The program emphasizes industrial engineering analysis tools, as well as medical diagnosis and treatment

practice, health care organization, and methods of health care systems evaluation. These areas of emphasis are applied in a series of design experiences. The program culminates in an original research dissertation.

A limited number of openings for admission and financial support are available to highly qualified persons with medical, paramedical, engineering, and science backgrounds, who have a professional commitment to research, design, or management of health care systems. Persons with a strong quantitative background who are interested in the program may write for more information to H. Allan Knappenberger, Ph. D.; Professor and Director of Graduate Studies; Department of Industrial Engineering; University of Missouri; Columbia, MO 65201.

SIR JOHN C. ECCLES

Sir John C. Eccles, Nobel Laureate and experimental brain researcher, was a guest on **The David Frost Show**, scheduled Wednesday, December 22, 1971.

Sir John has explored the physical brain for a half century and refuses to accept the notion held by many of his colleagues that the brain and the mind are one. "I have much knowledge of the way the brain works", he says, "but I can not explain my own existence. What makes me a unique being with my own conscious self?" He examines this and other questions in his book, **FACING REALITY Philosophical Adventures by a Brain Scientist** (Springer-Verlag New York Inc., 1970, \$ 6.50).

As a neurophysiologist, Sir John has a specialist's knowledge of the brain which is alone concerned in the whole life-long interplay between the conscious self and the external world, including other selves. **FACING REALITY** is a critical account of the way in which the brain receives every kind of information from the world through the senses and the way in which the brain initiates action into the world. But more importantly, the book is a philosophical treatment of the age-old problems of the liaison between the brain and the conscious self, as uniquely known directly to each one of us, with its amazing continuity and unity.

Sir John takes issue with certain reductionary tendencies in behavioristic psychology to reject from its subject matter all conscious experience, which he asserts to be the primary reality. Regarding evolutionary biology:

I readily accept all that (biologists) postulate in respect of my brain, yet I find my own consciously experiencing self not satisfactorily accounted

for. ...the further we progress in research, the more each of us will realize the tremendous mystery of our personal existence, as a consciously experiencing being with imagination and a sense of values and a systemization of knowledge. (**FACING REALITY**, page 6).

In a review of **FACING REALITY** (September 17, 1971), the **London Times Literary Supplement** stated:

...its message is urgent, and cogent. It is that in our day science, and especially the science of man, is in danger of a misinterpretation as inimical as any totalitarian tyranny to the values that give human life its meaning. The remedy urged is not to turn away from science, but rather to turn to face and welcome all facts, those of science as well as those of other phases of conscious experience and to do proper justice to each category in the context of the whole... For the health of the next generation, we need more, much more of such positive yet sane and humble realism....

Among the honors accorded Sir John are: Knight Bachelor (Kt.) Queen's Birthday Honours; Fellow, Royal Society, London; Royal Medal, Royal Society, London; Foreign Associate, U. S. National Academy of Sciences; and Foreign Member of several other National Academies. In 1963 he was a recipient of the Nobel Prize in Physiology and Medicine for his work on the transmission of impulses between neurons in the central nervous system. The research work for which he was awarded the Nobel Prize is the subject of **THE PHYSIOLOGY OF SYNAPSES** (Springer-Verlag New York Inc., 1964). Other books written or edited by Sir John C. Eccles and published by Springer-Verlag New York Inc. are: **BRAIN AND CONSCIOUS EXPERIENCE** edited by Eccles (1966), **THE CEREBELLUM AS A NEURONAL MACHINE** by Eccles/Ito/Szentagothai (1967), and **STUDIES IN PHYSIOLOGY** edited by Curtis/McIntyre (1965). A new book, **BRAIN AND HUMAN BEHAVIOR** edited by Karczmar/Eccles will soon be published.

HEAD-PAIN ASSOCIATION RE-ELECTS Mac NEAL, PRESIDENT; GRATER, VICE-PRESIDENT

CHICAGO. — The American Association for the Study of Headache, having successfully concluded the first International Headache Symposium—in Elsinore, Denmark, May 16-18, with the Danish Migraine Society as cohost—set a second precedent by conducting its annual business meeting in the air.

The meeting was held high over the North Atlantic on May 29 in the chartered plane which carried American Symposium participants and guests from London to New York City.

Its members re-elected Perry S. MacNeal, M. D., Associate Professor of Clinical Medicine, University of Pennsylvania Medical School, Philadelphia, to a second term. Others elected were:

Vice-President, William G. Grater, M. D., Clinical Assistant Professor of Medicine (Allergy), Southwestern Medical School, Dallas, Texas (re-elected);

Recording Secretary, Averill Stowell, M. D., Consulting Neurosurgeon at the VA Hospitals, Fayetteville, Ark., and Muskogee, Okla., Attending Neurosurgeon, St. Francis, St. Johns Hospital and Hill-Crest Medical Center, Tulsa, Okla. (re-elected);

Treasurer Robert G. Sherrill, Jr., M. D., Medical Director, Hillsborough County Hospital; President, Drs. Sherrill, Smith and Associates, Pa., Tampa, Fla. (re-elected);

Executive Secretary (a new office), Seymour Diamond, M. D., Clinical Assistant Professor in Neurology, The Chicago Medical School, Co-Director, Headache Clinic, Mt. Sinai Hospital Medical Center, Chicago;

Program Chairman (made a two-person office), Dr. Diamond was chosen to continue as Program Chairman; John R. Graham, M. D., Lecturer in Medicine, Harvard Medical School, Chief of Medical Service, Faulkner Hospital, Boston, Co-Chairman.

The Association set its next scientific meeting for June 17, 1972, in San Francisco.

"PROGRAM NOTICE — AMERICAN NEUROLOGICAL ASSOCIATION NINETY-SEVENTH ANNUAL MEETING"

"The Annual Meeting of the American Neurological Association will be held June 12-13-14, 1972 at the Palmer House, Chicago, Illinois".

"Special forms and instructions will be provided for use in submitting abstracts for consideration by the Program Committee. These will be mailed automatically to all members. Non-members requesting a place on the program should promptly request forms and instructions from the Secretary, Dr. Samuel A. Trufant, Cincinnati General Hospital, Cincinnati, Ohio 45229".

"The deadline for receipt of abstracts is February 1, 1972".

"Space is available for Scientific Exhibits. Those interested should submit to Dr. Kenneth R. Magee, Department of Neurology, University Hospital, Ann Arbor, Michigan in triplicate the title of the exhibit, a 200-word description, and indicate the amount

of space required. These should be received by February 1, 1972".

4th EUROPEAN SYMPOSIUM ON EPILEPSY

Place and date

The 4th European Symposium on Epilepsy was held at the Royal Tropical Institute (Koninklijk Instituut voor de Tropen), Mauritskade 63, Amsterdam, The Netherlands on 6, 7, and 8 September 1971.

Languages

The official languages of the Symposium were English, French and German. Simultaneous interpretation was provided.

Themes

- I Social Aspects of Epilepsy
(Training; Occupation; Social Adjustment)
- II Epilepsy in Developing Countries
- III Medical and Social Prognosis in Epilepsy
- IV The Need for Special Centres.

COMMITTEE TO COMBAT HUNTINGTON'S DISEASE Inc.

The World Federation of Neurology's Research Group on Huntington's Chorea is planning a Centennial Symposium on Huntington's Chorea to be held March 26-29, 1972, in Columbus, Ohio, in the state where George Huntington gave his historic lecture to the local Medical Society. The program will include sessions on History Early Detection, Epidemiology and Genetics, Pathology and Experimental Models, Clinical Aspects and Variants, Mental Functions, Biochemistry, and Management. There will also be a Round Table discussion on "unexplored areas and basic science developments of possible related interest". Short communications directly concerned with the above topics will be accepted. Abstracts in English, not to exceed 300 words, are to be sent, to:

Dr. Andre Barbeau
Secretary General
Department of Neurobiology
Clinical Research Institute of Montreal
110 Pine Avenue West
Montreal (130), Quebec, Canada

Inquiries regarding accommodations and registration should be sent to:

Dr. George W. Paulson
3957 Lytham Court
Columbus, Ohio 43220