

International Journal of Neurology



ISSUE DEDICATED TO:

COMA

VOLUME 2

1961

NUMBER 4

INTERNATIONAL JOURNAL OF NEUROLOGY

CONTENTS OF NUMBER 4 — 1961

EDITORIAL — Español	277
EDITORIAL — English	279
PATHOGENESIS OF COMA. CLINICAL AND METABOLIC CONSIDERATIONS	281
John Stirling Meyer, M. D. and Fumio Gotoh, M. D.	
CEREBRAL ENERGETICS IN COMA	299
Joseph F. Fazekas, M. D. and Ralph W. Alman, M. D.	
ELECTROENCEPHALOGRAPHIC FINDINGS DURING COMA	311
Carlo Loeb.	
REACTIVITE DU TRACE E.E.G. DANS LE COMA	323
Dr. Fischgold.	
INSULIN COMA	339
Víctor Soriano, Ovidio H. Cerviño and Héctor Puppo.	
COMA DUE TO CEREBRAL TRAUMA	352
W. Ritchie Russell.	
COMA PRODUCED BY EXPANSIVE INTRACRANIAL PROCESSES	358
Edwin Boldrey, M. D.	
COMA HEPATIQUE DES CIRRHOSSES	364
G. Boudin et R. Labet.	
VASCULAR COMA	375
Raymond Hierons, M. B. B.Sc. M. R. C. P.	
TREATMENT OF PROLONGED COMA	385
P. C. Gautier-Smith, M. D.	
PERSONALITY	393

Editorial

Los estados de coma hasta no hace más de tres décadas merecían solamente un interés asistencial por la gravedad que representaban y por la importancia de llegar a un diagnóstico etiológico, dado que para algunos casos (coma diabético, ciertas intoxicaciones) se contaba con recursos terapéuticos adecuados que aplicados correctamente y a tiempo, podían restaurar al paciente a su estado normal. La prolongación de un coma por más de cinco días implicaba en la práctica un pronóstico fatal.

Un progreso se realizó en este aspecto cuando se comprendió la importancia de la hidratación y del aporte de material nutritivo a los pacientes, y se pudo prolongar su sobrevivencia, con lo cual muchas veces se conseguía en los casos en que no existía un tratamiento específico, que el organismo resistiera y se obtuviera su recuperación.

Con el advenimiento de los antibióticos y las sulfas pudieron tratarse con éxito ciertos comas de origen infeccioso al mismo tiempo que podían controlarse las complicaciones infecciosas de los comas de otro origen.

En los últimos años este problema se ha actualizado por varias razones importantes que mencionaremos:

El renovado interés por el conocimiento de los mecanismos nerviosos responsables del sueño (inconciencia) y de la vigilia, resultante de las investigaciones sobre la Formación Reticular y de las funciones en que ésta estaría implicada.

La electroencefalografía aportó nuevos elementos al problema y permitió transportar a la clínica las ideas elaboradas en la experimentación animal. Resulta de valor para reconocer la existencia de una lesión y establecer su localización. Se ha estudiado una posible correlación con el coma y con su profundidad y es útil para apreciar su evolución. Se observa la reactividad del trazado a los estímulos aplicados al paciente, en cierto modo intentando un paralelismo con lo que evidencia el sueño (con un supuesto parentesco fisiopatológico con el coma) y la vigilia y con lo que el neurofisiólogo comprueba como respuestas inespecíficas en la actividad eléctrica cortical con las estimulaciones periféricas y las modificaciones de las respuestas cuando se lesiona la Formación Reticular.

Ultimamente se ha conseguido estudiar el metabolismo cerebral en el hombre. En el estado de coma se evidencian perturbaciones en la química cerebral dignas de señalarse por su importancia y por lo que significan para la comprensión fisiopatológica del síndrome y en cierto grado para la terapéutica. Estos cambios en gran parte están en relación con la producción de energía

por el tejido cerebral. El cerebro obtiene su energía principalmente de la oxidación de glucosa. La disminución del consumo de oxígeno se comprueba en el coma de cualquier origen. En el coma por hipoglicemia, la falta es del otro elemento energético fundamental, la glucosa. Pero la química cerebral se altera mucho más allá de lo que está involucrado en la simple combustión de la glucosa; en el coma hepático es importante la acumulación de amonio; las enzimas y coenzimas cerebrales pueden deprimirse por factores endógenos como en los comas hepático, diabético o urémico o por inhibidores de origen exógeno, tales ciertos tóxicos.

Con la técnica de Sackel del shock insulínico, el coma provocado con una finalidad terapéutica, brindó un recurso con casi el alcance de un experimento para estudiar este problema en el hombre.

La neurocirugía al tomar a su cargo algunos casos especiales de accidentes vasculares cerebrales y los traumatismos craneoencefálicos, con el aporte invaluable de las técnicas neurorradiológicas particularmente la arteriografía, y con los recursos de la hipotermia también ha contribuido a acrecentar el interés en las investigaciones acerca del coma.

Todo esto se ha capitalizado en términos de mejor y más profundo conocimiento de sus mecanismos, de diagnósticos más precisos, de tratamientos más decididos y de un perfeccionamiento en los cuidados del enfermo comatoso, tanto en la fase aguda, como cuando el estado se prolonga.

Estamos seguros que este número dedicado al coma tendrá la misma aceptación que los anteriores, teniendo en cuenta la jerarquía de los autores invitados que en él participan, a quienes agradecemos por la valiosa cooperación prestada.

VICTOR SORIANO.

Editorial

Until nearly three decades ago, coma was merely a serious and urgent clinical problem. It was important to reach an early diagnosis of its etiology because, in certain cases, i.e., (diabetic coma, some intoxications), it was possible to apply therapeutical means that, when employed correctly and in time, might restore the patient's health to normal. A prolonged coma of more than five days had, almost invariably, a fatal prognosis.

Progress was made in this respect when the importance of hydration and nourishment of the patient was understood and it thus became possible to prolong his life. This allowed, in those cases for which a specific treatment was not available, to give the organism a chance to fight its way back to health.

With the advent of antibiotics and sulfas it became possible to treat with success certain infectious comas and at the same time feasible to control the infectious complications in comas of different origins.

Recently, this problem has been studied for several important reasons, some of which we will mention:

The growing desire for knowledge about the nervous mechanism responsible for sleep (unconsciousness) and wakefulness, derived from investigation performed upon the Reticular Formation, and its functional meaning.

The EEG rendered other elements of study to this problem and allowed new ideas to be transferred to the clinic after they had been tested in the experimental animal. It is of great value to recognize the existence of a lesion and to establish its position. A possible correlation has been studied with coma and with the degree of its depth. It has been used to study its evolution, to observe the reaction of the patient to the different stimulations, and in a certain way to compare these findings with what is observed during sleep (which is in some aspects physiopathologically related to coma) and wakefulness, and with which the neurophysiologists proved through its investigation to be unspecific responses of corticalelectrical activity to peripheral stimulation and its modification when the Reticular Formation is lesioned.

Recently it has been possible to study the brain metabolism in man. The findings during state of coma have shown certain alterations in the cerebral chemistry worthy to be emphasized because of their importance and meaning in understanding the physiopathological syndrome of coma and in a certain degree its therapeutics. These changes are very much related to the production of energy of the brain tissue. The brain obtains its energy principally as a result of the oxidation of glucose. The diminishing of oxygen consumption has been proven in coma regardless of the coma's origin. In hypoglycemic coma there is a lack of another fundamental energetic element, the glucose. But the

disturbances of brain chemistry go beyond the mere diminishing of the combustion of glucose; in the hepatic coma the accumulation of ammonia is of great importance; the brain enzymes and coenzymes may be depressed by endogenous factors, as in hepatic, diabetic or uremic coma, or by exogenous factors such as certain toxics.

With Sackel's technique of insuline shock, coma, produced with a therapeutic aim, gave a resource for its study, which was nearly as valuable as an experimental situation.

Neurosurgery performed to treat certain cases of coma due to trauma and cerebro-vascular disease, with the aid of invaluable neuroradiologic techniques, particularly arteriography, and with the resources of hypothermia, have contributed to the increasing interest in the problem.

All this has created a better and more profound knowledge of the mechanism involved, and a more precise diagnosis, and thus a more energetic treatment and better care of the patient in coma has been established, when in its acute phase, as well as when it is prolonged.

This has contributed to the understanding of the problem of coma in these last few years and has led to investigations in several directions.

Taking into consideration the outstanding competency of the authors, we are sure that the issue devoted to coma will find the same favorable acceptance as the former issues. We herewith wish to express to them our sincere recognition for their valued cooperation.

VICTOR SORIANO.

Pathogenesis of Coma.

Clinical and Metabolic Considerations

JOHN STIRLING MEYER, M. D. and FUMIO GOTOH, M. D. *

From the Departments of Neurology, Wayne State University, College of Medicine, the Harper Hospital, and the Wayne Center for Cerebrovascular Research.

The purpose of this communication is to define coma, to outline its causes, to discuss briefly clinical considerations and to offer an hypothesis concerning the biochemical and metabolic basis for different types of coma in the light of presently available clinical and experimental data.

Definition.

The neurologist can only define states of impaired consciousness in terms of the reaction of the patient to the environment. If a painful stimulus produces only a primitive movement of defense (corneal reflex or reflex withdrawal of a limb) or none at all, this impaired state of consciousness is extremely severe and is referred to as coma⁽¹⁾. Another definition of coma, according to Dorland's Medical Dictionary, is "an abnormal state of depressed responsiveness, with absence of adaptive response to tactile, thermal, proprioceptive, visual, auditory, olfactory or verbal stimuli." In other words, coma is a state of diffuse impairment of cerebral neuronal function with accompanying alteration of cerebral electrical activity.

* This work was supported by grants from the Receiving Hospital Research Corporation and the U. S. Public Health Service.

Electroencephalogram in Coma.

The electroencephalogram (EEG) in coma shows high voltage, usually symmetrical slow waves in the delta range, severe depression or complete absence of electrical activity. We do not know of a normal EEG being recorded in coma except in hysterical states. Absence of EEG activity indicates a poor prognosis since it is usually seen when permanent, irreversible brain damage is present. Asymmetrical or focal abnormalities imply local structural injury to the brain. Spike activity in addition to slow waves raises the question of coma following an epileptic seizure (post-epileptic or post-ictal coma).

History and Examination.

The history of onset of coma is important in assessing the cause. Ingestion of drugs must always be considered. A sudden apoplectic onset implies a circulatory cause. The general medical examination must never be omitted since the cause of the coma is often revealed thereby. A complete neurological examination is performed with particular search for signs of trauma to the head, stiffness of the neck, inequality of the pupils, papilledema, abnormalities of respiration, and signs indicating focal damage to the brain⁽²⁾.

Lumbar Puncture and Diagnostic Tests.

A lumbar puncture is performed and the initial and final pressure noted. The appearance of the fluid is recorded together with total and differential counting of the cells, Pandy test for gamma globulin, serological test for syphilis, glucose content and colloidal gold. If the fluid is bloody, it should be centrifuged, the hematocrit recorded and the supernatant examined for xanthochromia. Where indicated, the fluid is cultured for bacteria. The following laboratory procedures are recommended in cases of coma of unknown cause; roentgenograms of skull and chest, electrocardiogram, electroencephalogram, urinalysis, complete blood count, blood urea nitrogen, sugar, sodium, potassium, carbon dioxide and pH, bilirubin, fibrinogen, bromide and barbiturate level. If subdural hematoma, tumor, or occlusion of a large vessel is suspected, arteriograms should be performed since cerebral hemodynamics are less altered by this procedure than pneumoencephalogram.

Etiological Classification.

The common causes of coma are listed in Table 1. In general, *the infections of the central nervous system* (CNS) and its coverings which may produce coma are associated with stiff neck and pleocytosis of the cerebrospinal fluid (c. s. f.). The majority of bacterial infections are curable by appropriate antibiotic therapy. If coma is deep the spinal reflexes producing nuchal rigidity may be depressed so that neck stiffness is no longer present. This is rare. In order to establish the diagnosis and isolate any identifiable organism, lumbar puncture with culture of the c. s. f. is essential. Rarely in some cases of encephalitis pleocytosis is not present in the c. s. f. In paretic and meningovascular neurosyphilis the precipitin and complement fixation tests for syphilis are positive in blood or cerebrospinal fluid or both.

Pneumonic and systemic infections may cause coma by c. n. s. hypoxia or poisoning of c. n. s. enzymes (Figure 1). In either event, it is our view that the energy

TABLE 1**Etiological Classification of Coma**

Infections Bacterial Meningitis: Meningococcal, pneumococci, staphylococci, tuberculous, syphilitic, toxoplasma and yeast infections, Waterhouse-Friederickson's syndrome etc. Viral Encephalitis: Eastern, Western, equine, Japanese B, poliomyelitis, Echo, etc. Pneumonia and other systemic infections. Trauma Subdural, epidural, and intracerebral hematoma. Concussion, contusion and brain laceration. Brain stem injury. Systemic Disorders Anoxia, uremia, metabolic acidosis, diabetic ketosis, respiratory acidosis,	cirrhosis (hepatic coma), water intoxication, hyponatremia, hypokalemia, Addisonian crisis, heart failure, hypoglycemia, post-epileptic (post-ictal coma). Wernicke's encephalopathy, pellagra encephalopathy, heavy metal intoxication, barbiturate poisoning, Bromison, coma due to sedatives, hypnotics, alcoholism and opiates, hyperthermia, hypothermia. Circulatory Cardiac arrest, circulatory shock, cerebral vascular thrombosis, cerebral hemorrhage, hypertensive encephalopathy, eclampsia, cortical venous thrombosis and sagittal sinus thrombosis. Neoplastic Primary and secondary large brain tumors and small tumors of the brain stem.
--	---

necessary to maintain cerebral ionic homeostasis and hence normal electrical activity of the brain is lost and coma ensues with EEG slowing. This concept of coma mechanisms will be discussed in detail

bral cortical neurones (electrotonus) or from a diffuse neuronal paralysis resulting from less localized injury. In either event, cerebral oxygen utilization is decreased⁽³⁾. Cerebral contusion, laceration, and sub-

HYPOTHESIS OF COMA MECHANISMS

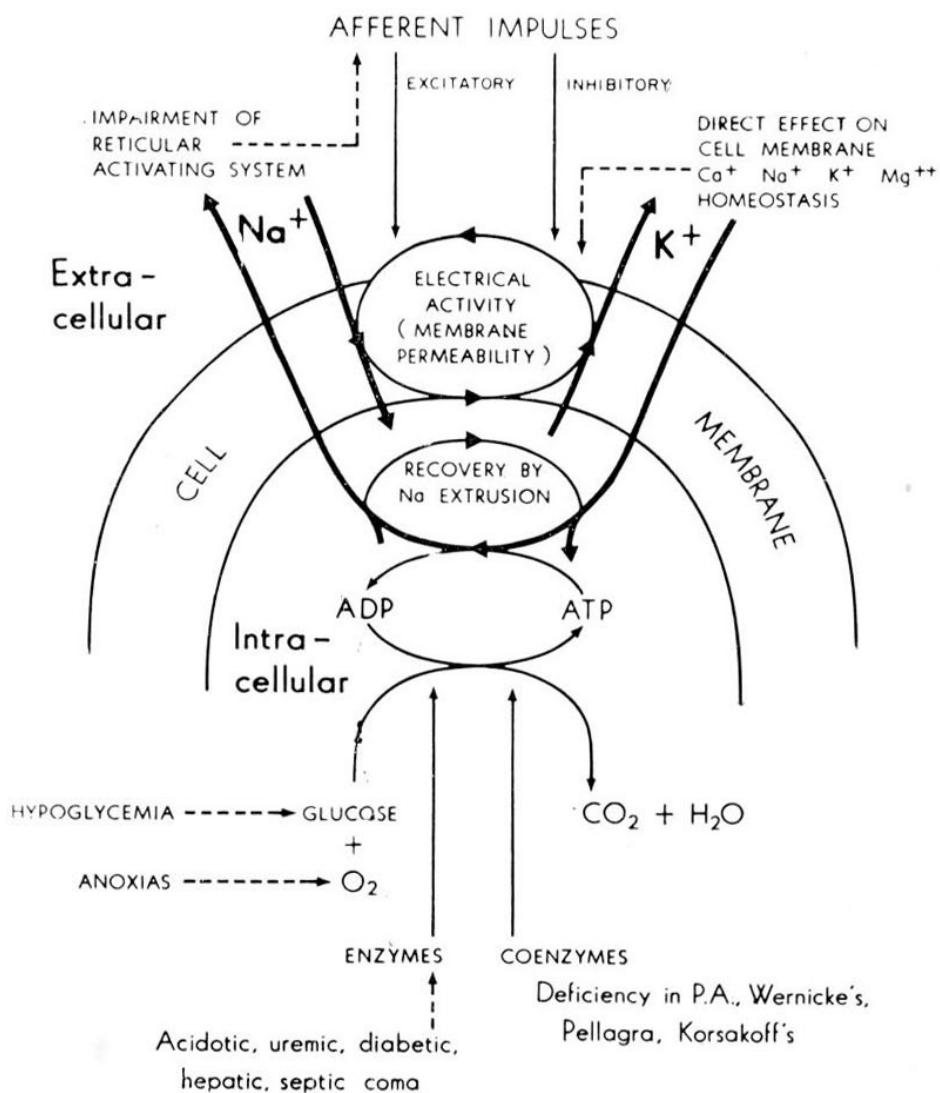


Figure 1

later. In coma from any cause, cerebral oxidative metabolism is usually depressed; important exceptions will be discussed later.

Traumatic causes of coma may result from direct injury to the reticular activating system of the brain stem with a decreased excitatory afferent drive on cere-

and epidural hematomata cause coma not only by direct traumatic injury to nerve cells but more commonly by cerebral compression and ischemic anoxia^(4, 5). In establishing such a diagnosis, evidence of trauma to the head, skull fracture by roentgenogram, waxing and waning of consciousness (in sub-dural hematoma),

and the lucid interval (in epidural hematoma) are helpful. Carotid arteriograms will establish the presence and localization of large hematoma.

In acidosis from any cause (uremic, diabetic, metabolic, respiratory and cirrhotic) the nerve cell becomes paralyzed when the extracellular pH falls below approximately 6.8 pH units^(6, 7). The neuronal intracellular pH is probably lower than the extracellular pH since CO₂ travels across the nerve cell membrane readily and intracellular metabolites are acid. Preliminary data in our laboratory in man where pH of the jugular venous blood has been measured and in other laboratories where intracellular muscle pH of man has been measured would support this view^(8, 9). Hence coma may be of sudden onset in the respiratory insufficiencies of emphysema, pneumopathies and severe obesity. In such patients the anoxic drive to the respiratory center replaces the normal CO₂ drive, since the respiratory neurones become refractory to PCO₂ stimulation at high partial pressures. Oxygen therapy should be administered to such patients with extreme caution since it may prove fatal. Mechanical respiration is the most effective treatment.

In metabolic acidosis, such as diabetic acidosis, correction of the underlying metabolic disorder is the key to treatment. Kussmaul breathing and dilatation of skin vessels is characteristic of metabolic acidosis. In some cases of hepatic and most cases of uremic coma, acidosis exists but circulating toxins such as ammonia, bilirubin and angiotoxins (in uremia) probably also play a part.

Water intoxication is characterized by coma and seizures. It is a condition seen in infants and children following prolonged gastric washing during and after surgery of the gastro-intestinal tract or irrigation of the bladder during and after prostatic operations in the adult male. Withdrawal of water, and replacement therapy by hypertonic infusions of saline and potassium is the treatment of choice. Hyponatremic coma occurs following vomiting, diarrhea, surgery, Addisonian cri-

sis, and prolonged illness. Hypokalemic coma is usually encountered following treatment of diabetic acidosis and responds rapidly to infusion of potassium.

In congestive heart failure coma is occasionally encountered and is due to diffuse cerebral anoxia. Treatment with oxygen, digitalis, and correction of cardiac dysrhythmias with quinidine usually provides dramatic relief of the cerebral signs.

Post-epileptic paralysis with coma is commonly encountered in neurological practice and results from an inability of the cerebral circulation to supply the increased metabolic demand accompanying the seizure, despite the fact that cerebral circulation is increased during the seizure. Failure of nerve cell function (exhaustion paralysis) may result from such factors as insufficient cerebral glucose and oxygen, metabolic acidosis of the brain and inability to maintain the normal ratio of extra- and intracellular electrolytes within cerebral neurones⁽¹⁰⁾. The basic importance of ionic homeostasis within the cellular components of the central nervous system will be discussed in detail in the second half of this paper dealing with biochemical and metabolic considerations in coma and related disturbances.

Hypoglycemic coma is associated with insulin secreting tumors, overdosage with insulin in diabetics, functional hyperinsulinism and leucinesensitive hypoglycemia. If local cerebral circulatory insufficiency is present, focal signs may appear simulating stroke⁽¹¹⁾. In hypoglycemia, insufficient glucose is available to the cerebral neurones to maintain the energy requirements necessary for cerebral ionic homeostasis and normal neuronal activity⁽¹²⁾.

More common in clinical practice than absence of glucose substrate is oxygen lack (anoxia) which may be due to circulatory or respiratory insufficiency or due to chemical (enzymatic) poisoning such as occurs in cyanide intoxication. Treatment is directed toward restoring cerebral oxygen delivery as rapidly as possible since the brain cannot tolerate anoxia for longer than 4-8 minutes. Coma may occur in

Wernicke's encephalopathy where there is a lack of thiamine (Vitamin B₁; cocarboxylase) which is essential to the metabolism of nerve cells.

Heavy metal intoxication (lead, arsenic) leads to cerebral vascular damage, cerebral edema and consequent coma. Anesthetic agents such as nitrous oxide, ether and barbiturates are used for their coma producing properties. Barbiturate poisoning is the most common cause of suicide in the United States. Acetyl salicylic acid ingestion causes a severe metabolic acidosis with coma in infants and children. Other sedative and narcotic drugs in overdosage also cause coma.

Circulatory disorders ultimately cause coma by cerebral ischemic anoxia. This occurs late in circulatory shock since cerebral vessels are dilated while the peripheral vessels are constricted⁽¹⁰⁾. In cerebral hemorrhage ischemia is caused by cerebral compression and occasionally by cerebral arterial spasm accompanying rupture of a cerebral arterial saccular aneurysm. Coma may occur following thrombosis or embolism of a carotid artery, the basilar or vertebral arteries and more rarely, following left (dominant) middle cerebral artery thrombosis. In sagittal and cortical venous thrombosis, coma may result usually accompanied by seizures. Diffuse cerebrovascular spasm accompanies severe hypertension and this, together with cerebral edema, may result in sufficient ischemic anoxia to cause coma⁽¹⁴⁾. Brain tumor may also cause sufficient cerebral compression and intracranial hypertension to cause cerebral ischemia and coma while in other instances direct involvement or compression of the reticular activating system in the brain stem may cause coma.

Metabolic Classification of Coma.

In order for neurones to maintain functional and structural integrity, a well regulated supply of energy is essential. The source of energy for the brain is primarily the oxidation of glucose⁽¹⁵⁾. Although there is still some debate, it is generally

accepted that glucose in the brain is oxidized by glycolysis through the Embden-Meyerhof pathway followed by the TCA cycle^(16, 17). These cycles are coupled with phosphorylation, which produces high energy phosphate bonds such as adenosine-triphosphate or phosphocreatine. A considerable part of the energy is utilized to maintain the extracellular versus intracellular electrolyte distribution, which is important in relation to normal membrane permeability and function of neurones^(18, 19, 20).

If impairment of the above mentioned metabolic process is of sufficient magnitude and duration, regardless of the site of action, cerebral functional disorder and coma will result.

On the basis of the biochemical and metabolic disorder, coma and related disturbances can be conveniently divided into two groups consisting of eight classes as follows:

A. IMPAIRMENT OF ENERGY METABOLISM

I. Disturbances of substrate supply

1. Hypoglycemia
(insulin coma, pancreatic islet cell tumor, leucine sensitivity etc.)
2. Decreased cerebral blood flow
(cardiac arrest, shock, severe cerebrovascular disease)

II. Impairment of enzyme

1. Exogenous intoxication
(barbiturate? alcohol? opiates? heavy metal?)
2. Endogenous intoxication
(diabetic coma, hepatic coma, uremic coma, CO₂ narcosis, eclampsia, severe systemic infections)
3. Infection
(encephalitis, neurosyphilis, meningitis)
4. Abnormal temperature
(hyperthermia, hypothermia)

III. Lack of co-enzyme

1. Thiamine deficiency - Wernicke's encephalopathy
2. Niacin deficiency - Pellagra encephalopathy
3. Vitamin B₁₂ deficiency - Pernicious anemia

IV. Disturbances of oxidative phosphorylation

Barbiturate? Alcohol?

V. Disturbances of oxygen supply

1. Decreased arterial oxygen content
(anoxemia, CO poisoning, cyanide poisoning)
2. Decreased cerebral blood flow
(cerebrovascular disease, circulatory collapse, cardiac arrest and decompensation)

B. IMPAIRMENT OF PERMEABILITY OF NEURONAL CELL MEMBRANE

I. Epilepsy

II. Impairment of the activating system

1. Brain stem lesion
(trauma, tumor, vascular accident)
2. Tentorial pressure cone

III. Disturbances of fluid and electrolyte balance

IV. Electroshock and lightning stroke.

Cerebral circulation and metabolism in coma and related disturbances.

As far as human cerebral circulation and metabolism in coma is concerned, the only published data at present is the data obtained from the whole brain using the nitrous oxide method⁽²⁶⁾. In the following discussion, most of these reports will be reviewed and the data is summarized in Table 2.

Under normal conditions glucose is the main source of energy for other organs as

well as the brain; but the brain is unique in its dependence on glucose. If the blood sugar level falls, organs other than the brain oxidize other substrates⁽¹⁷⁾ and continue functioning for a considerable length of time. This is the reason cerebral activity is the first to fail in hypoglycemia. Kety et al.,⁽²¹⁾ noted a progressive fall in both oxygen and blood glucose utilization by the brain as hypoglycemia and coma developed. Cerebral blood flow and arterial blood pressure were not significantly affected. The cerebral RQ was not significantly changed, which confirmed the dependency of the brain on glucose. Aizawa⁽²²⁾ found the same results in man but also demonstrated that the decrease of oxygen consumption and glycogen was marked in animal cerebral cortex while metabolic changes in the medulla were minimal. This data correlates well with clinical observations in hypoglycemia⁽²³⁾ and indicates the important role of cerebral cortex in coma mechanisms. Fazekas⁽³⁶⁾ et al., studied cerebral circulation and metabolism in prolonged, intense, post-hypoglycemic coma. In such cases cerebral oxygen consumption remained depressed until death despite restoration of blood sugar to normal levels. In post-hypoglycemic coma, the metabolic disturbance which was originally due to lack of substrate then becomes due to irreversible impairment of enzyme systems. It should be recalled that delivery of glucose to the brain is the product of blood glucose and cerebral blood flow. Thus, lack of glucose may result from reduction of cerebral blood flow. Under normal conditions, however, reserves of glucose in blood and brain are far higher than that of oxygen. In cases of impairment of cerebral blood flow without hypoglycemia, the effects of anoxia are prominent but in localized impairment of cerebral blood flow with hypoglycemia the hypoglycemic effects predominate⁽¹¹⁾.

Enzymatic Impairment.

There are many kinds of noxious factors, exogenous or endogenous, which impair the enzymatic activity of the brain and

produce coma. Although the exact sites of action of most of these factors are still obscure, the following disorders with coma appear to be due to disturbance of enzyme.

Kety and co-workers⁽²⁴⁾ studied the blood flow and oxygen consumption of the human brain in diabetic acidosis with coma and found a most significant difference in cerebral oxygen uptake between the comatose and non-comatose patients. They concluded that "coma was associated with and probably the result of a 40% reduction in cerebral utilization of oxygen which occurred in spite of a generally augmented cerebral blood flow and a normal arterial oxygen saturation." A critical level for cerebral oxygen consumption at or below which consciousness disappears was 2./cc/100 g/min. Aizawa and Kitamura⁽⁶¹⁾ found the same results, the only difference from Kety's data being a slight reduction in cerebral blood flow. The responsible factor for the depression of oxygen consumption is still unproven but the acidosis and ketosis⁽²⁴⁾ or a hexokinase inhibitor⁽²⁵⁾ have been suggested.

Wechsler and co-workers⁽²⁷⁾ measured cerebral blood flow (CBF) and oxygen consumption (CMRO₂) in hepatic coma. They found alkalosis and significant decrease in CBF and CMRO₂ in spite of constant cerebral vascular resistance. There was a greater depression of cerebral metabolism than CBF or hemoglobin, indicating a greater supply of O₂ to the brain than it was able to utilize. This suggested an intracellular enzyme impairment in the brain as the cause for the suppression of CMRO₂ and production of coma. Bessman and Bessman⁽²⁸⁾ measured the elevated blood level of ammonia and the cerebral uptake of ammonia which was roughly proportional to the depth of coma. From these results they postulated that increased synthesis of glutamate from alpha ketoglutarate and ammonia was the cause for the diminution of cerebral oxygen consumption and coma. Fazekas and collaborators⁽²⁹⁾ however denied any satisfactory correlation between arterial blood ammonia levels and cerebral oxygen utilization or the clinical neurologic state. They also

noted the depression of cerebral oxygen utilization even in those subjects with no clinically evident neurologic disturbances. In contrast to Fazekas' result, Aizawa⁽²²⁾ showed no reduction of cerebral oxygen uptake in the precoma stage but marked decrease in coma. Posner and Plum⁽³⁰⁾ and Scheinberg⁽³¹⁾ also failed to demonstrate a reduction of cerebral metabolism in patients with hepatic insufficiency but no evidence of neurologic disorder. Posner and Plum concluded that the clinical estimate of grade of encephalopathy and the mean CMRO₂ reduction correlated directly and quantitatively. Their conclusion is compatible with Kety's observation in insulin and diabetic coma. The existence of reduced cerebral metabolism in hepatic insufficiency without coma is still in dispute. However, there is no question that there is marked depression of cerebral oxygen consumption in hepatic coma.

Heyman and co-workers⁽³²⁾ found similar results in uremia. According to their data, cerebral blood flow and cerebral oxygen uptake decreased in uremia with hypertensive vascular disease but cerebral blood flow remained normal in uremia without vascular disease. They did not find any definite correlation between the CMRO₂ reduction and disturbance of consciousness. Aizawa⁽³³⁾ has shown marked depression of cerebral metabolism and slight decrease of cerebral blood flow in uremic coma and suggested the probable intracellular enzymic impairment in the brain as well as electrolyte imbalance as the cause of uremic coma. So far as the reduction of CMRO₂ is concerned, the two studies showed complete agreement.

McCall⁽³⁴⁾ investigated the effect of the toxemia of pregnancy on cerebral function and found that, contrary to expectation, cerebral blood flow was not affected by this disease, although cerebral vascular resistance was significantly increased. Cerebral oxygen metabolism was normal in nonconvulsive toxemia, but was significantly depressed during the coma of eclampsia. The reduced oxygen consumption by the brain despite normal oxygen delivery suggested a histotoxic anoxia. Further in-

vestigation is required to decide whether the impaired oxygen metabolism is the cause of the coma or the result of the convulsions, but the former seems likely.

Aizawa⁽²²⁾ noted that cerebral blood flow was maintained normal in virus encephalitis and yet cerebral oxygen consumption and cerebral glucose utilization were markedly depressed. This indicates the inhibition of intracellular enzymatic activity.

In general, as far as comatose states due to endogenous toxic factors are concerned, it is universally agreed that there are intracellular enzymatic impairments which result in reduction of oxygen consumption in the brain. As yet there is no information concerning the exact etiologic factors or the specific enzymes inhibited.

The mechanism of action of general anesthetics or hypnotic and depressant drugs on the central nervous system are as yet unknown. Whether their effect on cerebral metabolism is due to primary action on intracellular enzymatic systems or to the secondary effect of the depression of neuronal function is undetermined. For convenience, however, the data concerning barbiturates and alcohol will be discussed in the section concerning the disturbances of oxidative phosphorylation.

Lack of coenzyme.

The oxidation of glucose is catalyzed by many enzymes, which require additional help from coenzymes so that they may function effectively. Therefore, lack of coenzyme may disturb the glucose oxidation in the brain, which in turn results in depression of neuronal function and coma. Thiamine, niacin and Vitamin B₁₂ are coenzymes which, if absent or decreased, cause mental dysfunction and eventually coma.

Thiamine is a catalytic agent for the oxidative decarboxylation of ketoglutaric acid. The actual coenzyme is believed to be a compound of thiamine pyrophosphate (co-carboxylase) and lipoic acid. This is called lipothiamide pyrophosphate⁽¹⁶⁾. Hu-

man diseases due to lack of lipoic acid are not known, but it has been suggested that the mechanism of encephalopathy due to heavy metal poisoning may be a deficiency of lipoic acid⁽³⁶⁾. Lack of thiamine may inhibit both the Embden-Meyerhof pathway and the TCA-cycle, since pyruvic acid and α -Ketoglutaric acid are essential members of these metabolic processes. Clinical manifestations of thiamine deficiency in the C.N.S. are seen in Wernicke's encephalopathy where coma may supervene. Fazekas and Bessman⁽³⁶⁾ demonstrated a reduction of cerebral oxygen consumption and slight fall of cerebral blood flow in Wernicke's encephalopathy. A restoration of cerebral metabolic rate toward normal following the administration of Vitamin B₁ was also noted. Nicotinic acid deficiency has been regarded as the cause of an encephalopathy leading to coma occurring alone or associated with pellagra, but there is no data available concerning cerebral circulation and metabolism in this condition.

It is well known that deficiency of Vitamin B₁₂ causes not only pernicious anemia but also disturbances in the central nervous system. However, the role of Vitamin B₁₂ in cerebral metabolism is unknown and this vitamin has not actually been identified as a co-factor in any known enzymatic system, although relationships to transmethylation or nucleic acid synthesis have been suggested. Scheinberg⁽³⁷⁾ has demonstrated that in pernicious anemia, cerebral oxygen and glucose consumption were decreased and that there was good correlation between the defect in mental status and cerebral oxygen consumption or the severity of neurologic involvement and CMRO₂. There was no correlation between the degree of anemia and cerebral oxygen consumption. This data indicates that Vitamin B₁₂ participates in cerebral oxidative metabolism.

Disturbances of oxidative phosphorylation.

The true pharmacological mechanism of barbiturates or alcohol is still obscure des-

pite numerous experimental studies and theoretical assumptions. Recent studies *in vitro*⁽³⁸⁾, however, favor the Brody and Bain⁽³⁹⁾ "uncoupling" theory. For this reason effects of barbiturate and alcohol on cerebral circulation and metabolism in man will be discussed under the title of "disturbances of oxidative phosphorylation".

Kety and co-workers⁽²¹⁾ have shown there was no significant change in cerebral blood flow or cerebral metabolic rate during the semianarcotic state produced by the intravenous administration of sodium pentothal or sodium amytal. Schieve and Wilson⁽⁴⁰⁾ noted marked depression of cerebral oxygen consumption and cerebrovascular reactivity to CO_2 during thiopental anesthesia. Pierce and coworkers⁽⁴¹⁾ also noted the significant and nearly proportional reductions in CMRO_2 and CBF during thiopental, but the reactivity of cerebral vessels to carbon dioxide was preserved. Aizawa⁽²¹⁾ has shown during deep coma due to hypnotic drugs there was reduced CBF, elevation of CVR and decrease CMRO_2 , in spite of elevated arterial PCO_2 and reduced oxygen tension. The grade of reduction of CMRO_2 , however, was not so severe as seen in coma caused by other diseases. Bernsmeier and Gottstein⁽⁴²⁾ have also noted the marked depression of CMRO_2 and CBF in deep coma due to veronal, luminal or phanodorm-intoxication and its recovery after neurological improvement. In conclusion, barbiturates in large doses depress cerebral metabolism and cerebral blood flow but in semianarcotic doses they do not necessarily depress the CMRO_2 and CBF. These results coincide with *in vitro* data⁽²⁷⁾ and suggest that reduction of cerebral oxygen consumption is not necessarily essential to depress consciousness. This could be explained either by Brody and Bain's⁽⁴²⁾ "uncoupling of phosphorylation from oxidative processes" or by Larrabee's⁽⁴³⁾ "primary inhibition of synaptic transmission and neuronal interaction". Our own hypothesis will be discussed later.

Studies of the effect of alcohol in man employing nitrous oxide methods have revealed similar findings to those found due

to barbiturates. According to Battey and coworkers⁽⁴⁴⁾, low concentrations of ethyl alcohol in the blood sufficient to produce mild inebriation have little or no measurable effect on cerebral circulation, while high levels, sufficient to cause severe intoxication, produce a pronounced depression in cerebral oxygen consumption; despite an increase in cerebral blood flow. In delirium tremens⁽⁴⁵⁾ there is a definite reduction of cerebral blood flow and oxygen consumption. Fazekas and Bessman⁽³⁶⁾ demonstrated the same results. In coma due to methanol ingestion, Battey and co-workers⁽⁴⁵⁾ found marked suppression in both cerebral blood flow and oxygen uptake.

Disturbances of oxygen supply.

Since oxygen reserves in the brain and blood are to all purposes non-existent when compared to glucose, any kind of disturbance in cerebral oxygen supply will produce severe functional impairment to the brain which leads to coma within short periods of time. If anoxia is prolonged, irreversible damage results in 4-8 minutes. There are two ways to induce disturbance of oxygen supply to the brain: (1) Impairment of oxygen availability from erythrocytes (2) Decrease of cerebral blood flow. The former includes anoxemia, CO-poisoning, cyanide poisoning, etc. Unfortunately, there is no available quantitative data concerning human cerebral blood flow and metabolism in coma due to these factors, although one may assume marked depression of cerebral oxygen consumption. Fazekas and Bessman⁽³⁶⁾ studied a case of coma after strangulation which showed decreased CMRO_2 but a normal CBF. In this case, however, many other factors were involved. The latter included associated cerebral vascular disease and systemic circulatory failure. Fazekas and co-workers⁽⁴⁶⁾ noted that in subjects with cerebral vascular disease and depressed consciousness, cerebral blood flow, cerebral oxygen delivery and cerebral oxygen consumption were all depressed and cerebral vascular resistance was elevated.

These mean cerebral values, however, did not differ significantly from those of another older age group with vascular disease but normal mental status. It is surprising that they observed cerebral metabolic rates as low as 1.3 cc/100 G./min. in the absence of recognizable mental deterioration. Their observations indicated a lack of correlation between cerebral function and measurable cerebral oxygen utilization and blood flow.

Heyman and co-workers⁽⁴⁷⁾ also demonstrated that in acute "cerebrovascular accidents" there was a significant reduction of cerebral blood flow, slight depression of cerebral oxygen consumption, an elevation of cerebrovascular resistance, and the mean values for CMRO₂ were practically the same regardless of whether they were alert, confused or stuporous. Linden's⁽⁴⁸⁾ data presents a striking contrast to the above two reports. He found that in "cerebrovascular accident" oxygen consumption and cerebral blood flow decreased in proportion to the mental changes. Aizawa and associates⁽⁴⁹⁾ noted that in cerebral hemorrhage, reductions of cerebral blood flow and cerebral oxygen consumption were more marked in comatose patients than in conscious patients. The discrepancy of results among the four studies appear to be due to the differences of cases, diagnostic classification, the time of the study in relation to the ictus and the extensiveness of the neurological evaluation. They all agree that both CBF and CMRO₂ are depressed in coma due to cerebrovascular accidents, although the reduction of CMRO₂ does not necessarily reflect the disturbance of consciousness.

Regarding coma due to systemic circulatory failure, the only available quantitative data in man is the result of a case of cardiac arrest which was described by Fazekas and Bessman⁽³³⁾. They showed marked reduction of CBF and CMRO₂ which persisted after restoration of normal oxygen delivery. Finerty and co-workers⁽⁵⁰⁾ and McHenry and co-workers⁽⁵¹⁾ studied the cerebral hemodynamics during syncope and revealed that the critical level at which unconsciousness started was approximately 25 to 30 cc/100 gm. brain/min. and that cerebral oxygen consumption did not undergo a demon-

strable reduction during unconsciousness due to induced hypotension. This is another example of a reported dissociation between CMRO₂ and consciousness, but this may have been due to technical limitations of the nitrous oxide method.

Impairment of Permeability of Neuronal Cell Membrane.

It is generally assumed that the electrical activity of the nerve cell depends on the ionic movement across the cell membrane, which in turn is controlled by the energy metabolism and the membrane permeability of the cell. If this assumption is correct, impairment of membrane permeability as well as impairment of energy metabolism may result in functional disorder of nerve cells and coma.

There is no available knowledge concerning human cerebral hemodynamics and metabolism during epileptic seizures. It is not unreasonable, however, to assume on the basis of animal experiments^(52, 53) that cerebral blood flow and metabolism are both increased during seizures.

Grant and co-workers⁽⁵⁴⁾ have found that there was no significant difference in CBF and CMRO₂ between the values obtained from epileptics during the interseizure period and the normal values, but after metrazol convulsion, the CBF and CMRO₂ were significantly increased. According to Kennedy and co-workers⁽⁵⁵⁾ in epileptic children, unlike the results obtained in adult epileptics, cerebral blood flow during the interseizure period is significantly reduced. Kety and co-workers⁽²¹⁾ and Tazaki and co-workers⁽⁵³⁾ have shown a severe acidosis, a moderate fall in CMRO₂ and a marked decrease in CBF after a generalized convulsion by electroshock. The fall in CMRO₂, however, is not sufficient to explain post-convulsive unconsciousness. Wilson and co-workers⁽⁵⁶⁾ noted no significant change in CBF or CMRO₂ after repeated electric shock treatments. The actual mechanism of epilepsy is as yet unknown. There is no evidence of impairment of energy metabolism as a primary factor but there is some evidence

suggesting a change in the membrane permeability of nerve cells during the seizure. This is indicated by the change in EEG activity and increased sodium influx during the seizure⁽⁵³⁾.

Kety and co-workers⁽⁵⁷⁾ investigated the hemodynamics and metabolism in brain tumor and found that cerebral blood flow was markedly diminished in cases where cerebrospinal fluid pressure was above 450 mm. Hg. They noted that there was a good correlation between the mental state and cerebral oxygen consumption as was reported in other clinical conditions. In contrast to Kety et al., Yoshino⁽⁵⁶⁾ noted that in the patients with brain tumor, cerebral blood flow and oxygen consumption were markedly depressed in spite of normal consciousness. It is our belief that coma mechanisms in brain tumor can be complicated. Lack of oxygen due to the decreased cerebral blood flow, at least in part, may be responsible for unconsciousness in many cases. However, the reduction of CMRO₂ in coma due to brain tumor is not always as low as in other forms of coma. Therefore, we postulate that damage to localized areas responsible for consciousness, such as the reticular activating system of the brain stem, may account for unconsciousness in some cases. Impairment of the activating system may result in a primary change of cell permeability due to decreased afferent impulses to the cortex.

Coma mechanisms — Our Hypothesis.

Table 2 summarizes presently available data concerning human cerebral blood flow and metabolism in coma and related disturbances. Its details have already been discussed in the previous section. A glance at the table shows that the most common change in all kinds of coma is depression of cerebral oxygen consumption. Kety⁽⁵⁹⁾ said, "In all of our studies we have been impressed with the close correlation between the level of consciousness and the rate of oxygen consumption by the brain. In patients who are comatose for whatever reason, cerebral oxygen consumption falls to a value of less

than 2.0 ss. per 100 gm. per minute, while in those who are semistuporous or confused, the value lies between 2.5 and 3.0". If the reduction of cerebral metabolism is the final common path to coma, all comatose patients should have marked depression of CMRO₂ and vice versa. Yet this is not the case. For example, in Fazeka's data⁽⁴⁶⁾ there were many conscious patients with cerebrovascular disease in spite of marked depressed CMRO₂. Heyman et al.⁽⁴⁷⁾, also have shown that in acute cerebrovascular accident, CMRO₂ was the same, regardless of the state of consciousness. In Yoshino's data⁽⁵⁸⁾ a case of brain tumor was conscious in spite of depressed CMRO₂ as low as 0.83 cc/100 Mg./min. Conversely, in acute induced hypotension⁽⁵⁰⁾ the patients were unconscious despite normal CMRO₂. Light narcosis produces a similar condition. It may be possible that the nitrous oxide technic is not accurate enough to demonstrate minor changes of oxygen consumption in a localized area of the brain which is responsible for consciousness. But still this does not explain the mechanism of unconsciousness in epilepsy during which CMRO₂ is increased, particularly since it is unlikely that CMRO₂ in one area of the brain is depressed and that in the rest is increased.

In peripheral nerve, close relationship exists between electrical activity and ionic movement⁽¹⁸⁾. If the same mechanism exists also in the central nervous system, any functional change of the brain should be associated with sodium and potassium movements between extracellular and intracellular space. Recent studies in our laboratory have supported this view^(19, 20, 53, 60). We have been impressed with the close correlation between the electrical activity and metabolic activity and the sodium movement. At the beginning of this communication it was emphasized that in coma, the EEG is abnormal. In the monkey cortex, EEG slowing or suppression, regardless of reason, was closely associated with a marked decrease in extracellular sodium. Presumably there is an accompanying intracellular accumulation of sodium and loss of potassium. Any factor which suppressed energy metabolism such as anoxia^(19, 20),

TABLE 2

Disease	Mental State	Cerebral Blood Flow cc/100 g brain/ min.	Mean Arterial Blood Pressure (mm. Hg.)	Cerebral Vascular Resistance (mm. Hg./cc blood/100 g brain/min.	Cerebral Oxygen Consumption (cc/100 g brain/min.	Author
IMPAIRMENT OF ENERGY METABOLISM						
Insulin coma	Comatose	62.5	93	—	1.9	Kety - 1948
Post-hypogly- cemic coma	"	52.2	99	2.1	1.5	Fazekas - 1951
Insulin coma	"	61.8	95	1.66	1.68	Aizawa - 1957
IMPAIRMENT OF ENZYME						
Diabetic coma	Confused	45	86	2.1	2.7	Kety - 1948
"	Unconscious	65	66	1.1	1.7	Kety - 1948
"	Comatose	42.0	84	2.00	1.36	Aizawa - 1957
Hepatic coma	"	33	78	2.4	1.7	Wechsler - 1954
"	"	39.6	65	1.7	1.6	Fazekas - 1956
"	Precoma	50.2	95	1.94	3.61	Aizawa - 1957
"	Comatose	32.6	85	2.68	1.93	Aizawa - 1957
"	"	22			1.2	Posner - 1960
Uremic coma & Hypertensive vascular disease		45.0			2.1	Heyman - 1951
Non-hypertensive vascular disease		57.0			2.2	Heyman - 1951
Uremic coma	"	49.0			1.2	Aizawa - 1956
Eclampsia	"	51	124	2.5	1.06	McCall - 1953
Encephalitis	"	63.3	77	1.14	1.80	Aizawa - 1957
Wernicke's encephalopathy		41.2			2.2	Fazekas - 1953
Pernicious anemia		96	69	0.83	2.0	Scheinberg - 1951
semi-narcosis	state	53			3.3	Kety - 1948

LACK OF
COENZYME

Disturbance	Anesthesia	46	2.2	Schieve-Wilson 1953
Barbiturate coma	Comatose	51.0	2.3	Fazekas - 1953
Hypnotic intoxication	"	36.1	1.3	Bodechtel - 1954
Veronal intoxication	"	28.0	1.1	Bernsmeier - 1956
Luminal intoxication	"	44.3	1.5	Bernsmeier - 1956
Phenodorm intoxication	"	28.0	1.8	Bernsmeier - 1956
Hypnotic Drug intoxication	"	43.2	2.66	Aizawa - 1957
Thiopental anesthesia	Anesthesia	27.6	1.5	Pierce - 1962
Methanol ingestion	Confused comatose	36	2.0	Batley - 1952
Delirium tremens	Delirious	34	2.4	Batley - 1952
Acute alcoholic intoxication	Intoxication	67	2.2	Batley - 1953
Alcoholism	"	68.0	2.7	Fazekas - 1953

Disturbance	Depressed consciousness	112	4.1	2.1	Fazekas - 1952
Vascular disease	Depressed consciousness	33.5			
Acute vascular disease	Stupor, lethargic, confused, comatose	40	3.1	2.7	Heyman - 1953
Central vascular accident	Restless, comatose	32.8	3.99	2.47	Linden - 1955
Cerebral hemorrhage	Comatose	35.7	3.88	2.27	Aizawa - 1961
Hypertensive encephalopathy	Moderate encephalopathy	51	3.6	3.0	Moyer - 1953
Cardiac arrest	Comatose	28.0		1.8	Fazekas - 1953
Strangulation	"	36.0		1.7	Fazekas - 1953

IMPAIRMENT OF PERMEABILITY OF NORMAL CELL MEMBRANE

Disturbance	Comatose	35	2.4	Grandt - 1947
Epilepsy	Comatose	35		
Electric shock	Post-convulsion	37	3.1	Kety - 1947
"	"	38.8	2.48	Tazaki - 1959
Tumor	Comatose	33.8	2.5	Kety - 1948

ischemia⁽²⁰⁾, hypoglycemia⁽²⁰⁾, high CO_2 ^(6, 53) and barbiturates⁽⁴⁹⁾ impaired the active sodium extrusion mechanism, which in turn resulted in an intracellular sodium debt. All of these factors may produce coma in man with EEG changes similar to those noted in the monkey. Recently, we have made preliminary determinations of cerebral circulation and metabolism in man by the application of flow meters to the jugular veins and by determinations of arterial and jugular PO_2 , PCO_2 , pH, Na, K, Cl, NH_3 and glucose. This preliminary data confirms extensive studies in the monkey where cerebral blood flow, metabolism and ionic activity of the brain were closely correlated with EEG activity^(6-8, 10-14, 19, 20, 52, 53, 60). On the basis of the above data, although it is admittedly incomplete, it seems reasonable to assume that the final common pathway for production of coma is an impairment of ionic homeostasis within and without the nerve cell membrane. This is shown schematically in Figure 1.

The ionic distribution across neuronal cell membrane is controlled by two systems:

1. the permeability of the cell membrane

2. the sodium extrusion mechanism

The former is closely associated with electrical activity and controlled by impulse from other neurones.

If the permeability increases, sodium influx and potassium efflux result, followed in turn by increase of electrical activity. Intracellular sodium debt due to increased functional activity must be repaid and this can only be done by the sodium extrusion mechanism. Since this restoring movement is an uphill motion, it requires energy. The energy is supplied from high energy phosphate bonds which are reformed by oxidation of glucose. A disturbance of this system, the energy metabolism or the permeability, regardless of the site, results in an impairment of the ionic distribution. In our view, this is probably the final common pathway of the mechanisms of coma.

Acknowledgement

We wish to acknowledge the kind assistance of Dr. S. Ebihara with the review of the literature.

S U M M A R Y

Definition, classification and clinical considerations of coma were discussed briefly and the literature concerning human cerebral circulation and metabolism in coma was reviewed extensively. An hypothesis concerning the biochemical and metabolic basis for different types of coma was offered in the light of presently available clinical and experimental data.

The most common change in all kinds of coma was depression of cerebral oxygen consumption as indicated by Kety. Yet it was pointed out that there were considerable exceptions and that the reduction of CMRO_2 was not always the pathogenetic factor for the production of coma contrary to a generally accepted view. Furthermore,

CMRO_2 is greatly depressed in some cases in the absence of coma.

It was assumed that the final common pathway for production of coma was an impairment of ionic homeostasis within and without the nerve cell membrane.

The ionic distribution across neuronal cell membrane is controlled by (1) the permeability of the cell membrane and (2) the sodium extrusion mechanism. The former is closely associated with electrical activity and the latter with metabolic activity. A disturbance of this system, the energy metabolism or the permeability, regardless of the site, results in an impairment of the ionic distribution, which is the postulated final common pathway of the mechanisms of the coma.

RESUMEN

Fueron consideradas en forma breve, la definición, clasificación y los aspectos clínicos de los comas y se hizo extensamente la revisión de la literatura referente a la circulación y el metabolismo cerebral del hombre en el estado de coma. En base a los datos clínicos y experimentales con que contamos actualmente, se expone una hipótesis acerca de la bioquímica y los mecanismos metabólicos de los diferentes tipos de coma. En todos los tipos de coma el trastorno metabólico hallado con más frecuencia, ha sido tal como lo indicó Kety una depresión en el consumo de oxígeno cerebral. Sin embargo, se ha señalado que numerosas excepciones escapan a esta regla y que en contra de la opinión general la reducción del CMRO_2 (consumo de oxígeno) no es siempre el factor patogenético en la producción del coma.

Por otra parte existen casos de gran depresión en el consumo de oxígeno por el cerebro, sin que aparezca el coma.

Se presume que el factor común en la producción del coma es un trastorno de la homeostasis iónica dentro y fuera de la membrana de la célula nerviosa. La distribución iónica a través de la membrana de la célula nerviosa se controla por 1) la permeabilidad de la membrana celular y 2) el mecanismo de la bomba de sodio. La primera está en estrecha relación con la actividad eléctrica y el último con la actividad metabólica. Una perturbación de este sistema, la energética metabólica o la permeabilidad, sin tener en cuenta su asiento, trae como resultado dificultades en la distribución iónica, la cual es el factor común postulado de los mecanismos del coma.

RÉSUMÉ

Les auteurs discutent brièvement la définition, la classification et la clinique du coma et revoient de manière exhaustive la littérature se rapportant à la circulation et au métabolisme cérébral dans le coma. A la lumière des données actuellement fournies par la clinique et l'expérimentation, ils avancent une hypothèse concernant la biochimie et les mécanismes métaboliques des différents types de coma.

Dans tous les types de coma le trouble métabolique le plus fréquemment rencontré est une dépression de la consommation cérébrale d'oxygène comme Kety l'a montré. Cependant il a été souligné que de nombreuses exceptions échappent à cette règle et que contrairement à l'opinion générale, la réduction du CMRO_2 n'est ni nécessaire

ni suffisante dans l'état de coma.

Il a été suggéré que la voie finale commune dans la production du coma est un trouble de l'homéostasie ionique de part et d'autre de la membrane de la cellule nerveuse.

La distribution ionique de part et d'autre de la membrane du neurone est contrôlée par 1) la perméabilité de la membrane cellulaire 2) le mécanisme de la pompe sodée. La première est intimement liée à l'activité électrique, et le dernier à l'activité métabolique. Une altération de ce système, à savoir l'énergie métabolique ou la perméabilité, quel que soit le siège entraîne un trouble de la distribution ionique qui est proposée comme voie finale commune des mécanismes du coma.

ZUSAMMENFASSUNG

Das Koma wird hinsichtlich seiner Definition, seiner Einteilung und hinsichtlich klinischer Überlegungen diskutiert. Es wird eine Literaturübersicht bezüglich der Durch-

blutung und des Stoffwechsels des menschlichen Gehirns im Koma gegeben. Im Hinblick auf gegenwärtig vorhandene klinische und experimentelle Daten wird eine Hypo-

these aufgestellt, die die biochemische und metabolische Grundlage für verschiedene Typen des Komas darstellt.

Die häufigste Veränderung in allen Arten von Koma soll eine Herabsetzung des cerebralen Sauerstoffverbrauchs sein, wie von Kety ausgeführt wurde. Wir fanden jedoch im Gegensatz zur allgemein üblichen Annahme, dass es beträchtliche Ausnahmen gibt und dass die Herabsetzung der $CMRO_2$ ein weder notwendiger noch genügender Faktor für das Koma darstellt.

Es wird angenommen, dass eine Beeinträchtigung der Ionendurchwanderung in-

nerhalb und ausserhalb der Nervenzellmembran der übliche Entstehungsmechanismus für das Koma ist.

Die Verteilung der Ionen an Nervenzellmembranen wird (1) von der Durchlässigkeit der Zellmembranen und (2) vom Natriumaustrittsmechanismus kontrolliert. Erstere ist eng mit der elektrischen Aktivität, letztere mit Stoffwechselvorgängen verknüpft. Eine Störung in diesem System, dem Energiestoffwechsel und der Permeabilität, führt, unabhängig von der Lokalisation, zu einer Beeinträchtigung der Ionenverteilung, die als auslösende Ursache des Komas gefordert wird.

REFERENCES

- (1) Denny - Brown, D.: Handbook of neurological examination and case recording. Harvard University Press, Cambridge, Mass., 1949.
- (2) Meyer, J. S.: Neurological approach to the comatose patient. Med. Record and Annals, Houston, Texas, 14, 249, 1961.
- (3) Meyer, J. S. and Denny-Brown, D.: Studies of cerebral circulation in brain injury. 2. Cerebral concussion. EEG Clin. Neurophysiol. 7, 529-544, 1955.
- (4) Meyer, J. S.: Studies of cerebral circulation in brain injury. 3. Cerebral contusion, laceration and brain stem injury. EEG Clin. Neurophysiol., 8, 107-116, 1956.
- (5) Meyer, J. S. and Hunter, J.: Polarographic study of cortical blood flow in man. J. Neurosurg., 14, 382-399, 1957.
- (6) Meyer, J. S., Gotoh, F., and Tazaki, Y.: CO_2 , Narcosis. An experimental study. Neurol., 11, 524-535, 1961.
- (7) Meyer, J. S., Gotham J., Tazaki, Y., and Gotoh, F.: Cardiorespiratory syndrome of extreme obesity with papilledema. Report of a fatal case with EEG, metabolic and necropsy studies. Neurol. 11, 950-958, 1961.
- (8) Meyer, J. S., and Gotoh, F.: Measurement of jugular PO_2 , PCO_2 , pH, Na and K activity with the EEG in Man. Unpublished data.
- (9) Bihar, E. E., Watt, M. F., Pateras, V. R., and Parrish, A. E.: The pH of muscle in Laennec's cirrhosis and uremia. Clin. Sci., 23, 265-276, 1962.
- (10) Meyer, J. S. and Portnoy, H.: Post-epileptic paralysis. A clinical and experimental study. Brain, 82, 162-185, 1959.
- (11) Meyer, J. S. and Portnoy, H.: Localized cerebral hypoglycemia simulating stroke. A clinical and experimental study. Neurol. 8, 601-614, 1958.
- (12) Gomez, M. R., Gotham, J. F., and Meyer, J. S.: The effect of sodium glutamate on leucine-induced hypoglycemia. Clin. and Electroencephalographic Study. Pediatrics, 28, 935-942, 1961.
- (13) Lavy, S., Ishikawa, S., Symon, L., and Meyer, J. S.: Electromagnetic flow meter studies of cerebral blood flow. Am. J. Physiol. In Press, 1963.
- (14) Meyer, J. S., Waltz, A. G., and Gotoh, F.: Pathogenesis of cerebral vasospasm in hypertensive encephalopathy. 1. Effects of acute increase in blood pressure on pial blood flow. Neurol. 10, 735-744, 1960.
- (15) Himwich, H. E. and Nahum, L. H.: Respiratory quotient of the brain. Am. J. Physiol., 101, 446-453, 1932.
- (16) Elliott, K. A. C., Page, H. H., and Quastel, J. H.: Neurochemistry, Springfield, Ill. Chas. C. Thomas, publisher, 1955.
- (17) McIlwain, H.: Biochemistry and the central nervous system, London. J. A. Churchill, Ltd., 1955.
- (18) Hodgkin, A. L.: Ionic movements and electrical activity in giant nerve fibers. Proc. Roy. Soc., 148, 1-37, 1958.
- (19) Gotoh, F., Tazaki, Y., Hamaguchi, K., and Meyer, J. S.: Continuous recording of sodium and potassium ionic activity of blood and brain in situ. J. Neurochem., 9, 81-97, 1962.
- (20) Meyer, J. S., Ishikawa, S., Hamaguchi, K., Gotoh, F., Tazaki, Y., Nouailhat, F., and Symon, L.: Effects of anoxia, hypoglycemia, ischemia, acidosis, alkalosis and alterations of blood PCO_2 on regional cerebral blood flow and metabolism in vivo. Arch. of Neurol. In Press, 1963.
- (21) Kety, S. S., Woodford, R. B., Harmel, M. H., Freyhan, F. A., Appel, K. E., and Schmidt, C. F.: Cerebral blood flow and metabolism in schizophrenia. Am. J. Psychiat., 104, 765-770, 1948.

- (22) Aizawa, T.: Cerebral circulation and metabolism in coma. *Psychiat. Neurol.*, Jap., 59, 943-948, 1957.
- (23) Himwich, H. E., Frostig, J. P., Fazekas, J. F., and Hadidian, F.: Mechanism of symptoms of insulin hypoglycemia. *Am. J. Psychiat.*, 96, 371-385, 1939.
- (24) Kety, S. S., Polis, B. D., Nadler, C. S., and Schmidt, C. F.: The blood flow and oxygen consumption of the human brain in diabetic acidosis and coma. *J. Clin. Invest.*, 27, 500-510, 1948.
- (25) Weil-Malherbe, H.: Inhibitor of hexokinase in plasma of diabetics. *Nature*, 165, 155, 1950.
- (26) Kety, S. S. and Schmidt, C. F.: The determination of cerebral blood flow in man by the use of nitrous oxide in low concentrations. *Am. J. Physiol.*, 143, 53, 1945.
- (27) Wechsler, R. L., Crum, W., and Roth, J. L. A.: The blood flow and O₂ consumption of the human brain in hepatic coma. *Clin. Research Proc.*, 2, 74, 1954.
- (28) Bessman, S. P. and Bessman, A. L.: The cerebral and peripheral uptake of ammonia in liver disease with an hypothesis for the mechanism of hepatic coma. *J. Clin. Invest.*, 34, 622-627, 1955.
- (29) Fazekas, J. F., Ticktin, H. E., Ehrmantrent, W. R., and Almen, R. W.: Cerebral metabolism in hepatic insufficiency. *Am. J. Med.*, 21, 843-849, 1956.
- (30) Posner, J. B. and Plum, F.: The toxic effect of carbon dioxide and acetazolamide in hepatic encephalopathy. *J. Clin. Invest.*, 38, 1246-1258, 1960.
- (31) Scheinberg, P.: Brain metabolism in liver disease. *World Neurol.*, 2, 288-295, 1962.
- (32) Heuman, A., Paterson, J. L. Jr., and Jones, R. W. Jr.: Cerebral circulation and metabolism in uremia. *Circulation* 3, 558-563, 1951.
- (33) Aizawa, T.: Problems of cerebral circulation. P. 168, Tokyo, Kanehara, 1956.
- (34) McCall, M. L.: Cerebral circulation and metabolism in toxemia of pregnancy. Observations on the effects of veratrum oxide and apresoline. *Am. J. Obst. and Gynecol.*, 66, 1015-1030, 1953.
- (35) Reed, L. J., Debusk, B. G., Gunsalus, I. C., and Schnakberg, G. H. F.: Chemical nature of alpha-lipoic acid. *J. Am. Chem. Soc.*, 73, 5920, 1951.
- (36) Fazekas, J. F. and Bessman, A. N.: Coma mechanism. *Am. J. Med.* 15, 804-812, 1953.
- (37) Scheinberg, P.: Cerebral blood flow and Metabolism in pernicious anemia. *Blood* 6, 213-227, 1951.
- (38) Quastel, J. H. and Quastel, D. M. J.: The chemistry of brain metabolism in health and disease. P 104, Springfield, Ill. C. C. Thomas, publisher, 1961.
- (39) Brody, T. M. and Bain, J. A.: Effect of barbiturates on oxidative phosphorylation. *Proc. Soc. Exper. Biol. and Med.*, 77, 50-53, 1951.
- (40) Schieve, J. F. and Wilson, W. P.: The influence of age, anesthesia and cerebral arteriosclerosis on cerebral vascular activity to CO₂. *Am. J. Med.*, 15, 171-174, 1953.
- (41) Pierce, E. C., Lambertsen, C. J., Deutsch, S., Chase, P. E., Linde, H. W., Dripps, R. D., and Price, H. L.: Cerebral circulation and metabolism during thiopental anesthesia in hyperventilation in man. *J. Clin. Invest.*, 41, 1664-1671, 1962.
- (42) Bernsmeier, A. and Gottstein, U.: Die Sauerstoffaufnahme des menschlichen Gehirns unter Phenothiacinen, Barbituraten und in der Ischämie. *Pflüg. Arch.*, 263, 102-108, 1956.
- (43) Larrabee, M. G., Ramos, J. F., and Bülbring, E.: Effects of anesthetics on oxygen consumption and on synaptic transmission in sympathetic ganglia. *J. Cell. Comp. Physiol.*, 40, 461-494, 1952.
- (44) Battey, L. L., Heyman, A., and Patterson, J. L.: Effects of ethyl alcohol on CBF and metabolism. *JAMA* 152, 6-10, 1953.
- (45) Battey, L. L., Patterson, J. L., and Heyman, A.: Effect of methyl and ethyl alcohol on cerebral blood flow and oxygen consumption. *Am. J. Med.*, 13, 105, 1952.
- (46) Fazekas, J. F., Almen, R. W., and Bessman, A. N.: Cerebral physiology of the aged. *Am. J. Med. Sci.*, 223, 245-257, 1952.
- (47) Heyman, A., Patterson, J. L., Duke, T. W., and Battey, L. L.: The cerebral circulation and metabolism in arteriosclerotic and hypertensive cerebrovascular disease. *New England J. M.*, 249, 223-229, 1953.
- (48) Linden, L.: The effect of stellate ganglion block on cerebral circulation in cerebrovascular accidents. *Acta medica Scand. Suppl.*, 301, 7-110, 1955.
- (49) Aizawa, T., Tazaki, Y., and Gotoh, F.: Cerebral circulation in cerebrovascular disease. *World Neurol.*, 2, 635-648, 1961.
- (50) Finnerty, F. A., Jr., Witkin, L., and Fazekas, J. F.: Cerebral hemodynamics during cerebral ischemia induced by acute hypotension. *J. Clin. Invest.*, 33, 1227-1232, 1954.
- (51) McHenry, L. C., Jr., and Fazekas, J. F.: Cerebral hemodynamics of syncope. *Am. J. Med. Sci.*, 241, 173-178, 1961.
- (52) Meyer, J. S. and Gotoh, F.: Interaction of cerebral hemodynamics and metabolism. *Neurol. II (Part. II)*, 46-65, 1961.
- (53) Meyer, J. S., Gotoh, F., and Tazaki, Y.: Inhibitory action of carbon dioxide and acetazoleamide in seizure activity. *EEG. Clin. Neurophysiol.*, 13, 762-775, 1961.
- (54) Grant, F. C., Spitz, E. B., Shenkin, H. A., Schmidt, C. F., and Kety, S. S.: The cerebral blood flow and metabolism in idiopathic epilepsy. *Trans. Am. Neurol. Assoc.*, 72, 82-86, 1947.

(55) Tazaki, Y., Nakazato, T., Aoki, T., Makino, K., Hamaya, S., Okada, T., Yoshino, R., Umehara, M., Obayashi, H., Tsukabe, S., Hashimura, A., and Tomita, M.: Cerebral circulation and metabolism. *Sashin Igaku*, 14, 2259-2263, 1959.

(56) Wilson, W. P., Schieve, J. F., and Scheinberg, P.: Effect of series of electric shock treatments on cerebral blood flow and metabolism. *Arch. Neurol. and Psychiat.*, 68, 651-654, 1952.

(57) Kety, S. S., Shenkin, H. A., and Schmidt, C. F.: The effects of increased intracranial pressure on cerebral circulatory functions in man. *J. Clin. Invest.*, 27, 493-499, 1948.

(58) Yoshino, R.: The effect of increased cerebrospinal pressure on the cerebral circulation. *Psychiat. Neurol. Jap.*, 58, 721-727, 1956.

(59) Kety, S. S.: The physiology of the human cerebral circulation. *Anesthesiology*, 10, 610-614, 1949.

(60) Meyer, J. S., Gotoh, F., Tazaki, Y., and Hamaguchi, K.: Sodium and potassium activity of living brain. Relation to EEG and active sodium transport. *Trans. Am. Neurol. Assoc.*, P. 17, 1961.

(61) Kitamura, S.: Cerebral circulation and metabolism in diabetics. *Nippon Naibun-pi Gakkai Zasshi* 34, 1198-1208, 1959.

Cerebral Energetics in Coma

JOSEPH F. FAZEKAS, M. D., and RALPH W. ALMAN, M. D. *

Department of Neurology and Neurological Surgery,
The George Washington University School of Medicine,
Washington, D. C.

The readiness of the brain to perceive and react to external and internal stimuli is a primary requisite for consciousness. Such readiness is embodied in the condition of wakefulness, the increasing depression of which is associated with clinical states ranging from sleep to coma. During sleep, one finds a characteristic synchronous pattern of cerebral electrical activity⁽¹⁾, no demonstrable change in overall cerebral oxygen consumption, and a slight increase in rate of cerebral blood flow⁽²⁾. The failure to observe a significant change in overall cerebral oxygen consumption may indicate only that metabolic alterations (presumably occurring chiefly in the reticular formation) may be of such slight magnitude that they are not measurable by procedures presently available. In contrast to sleep, stupor and coma may not only be due to pathochemical impairment of those brain areas upon which wakefulness depends but may also be associated with disturbances in energy production or utilization throughout the entire central nervous system, and gross impairment of cerebral metabolic activity may often be demonstrable. The ensuing discussion will be concerned with

the biochemical and physiological alterations associated with those comatose states more frequently encountered in clinical practice and classified according to their metabolic origins (Table 1).

TABLE 1

Metabolic Origins of Coma

- I. *Coma due to Oxygen Insufficiency*
 - A. Hypoxemic
 - B. Hemodynamic (generalized or localized)
- II. *Coma due to Substrate Insufficiency*
 - A. Hypoglycemia
- III. *Coma due to Enzymatic Disturbances*
 - A. Inhibition
 1. Endogenous
 2. Exogenous
 - B. Co-factor deficiency
- IV. *Coma due to Multiple Etiologies*

I. Coma due to Oxygen Insufficiency

Probably the most common cause of coma is the failure of the brain to receive sufficient oxygen to maintain its functional activity. Not only may oxygen insufficiency be primarily etiologic, but not infrequently it may complicate all forms of coma and render irreversible an otherwise less serious cerebral disorder.

* Parts of this manuscript have been abstracted from "Coma: Biochemistry, Physiology and Therapeutic Principles," by Fazekas, J. F., and Alman, R. W.; published by Charles C. Thomas, Springfield, Ill., 1962.

The unusual sensitivity of the brain to oxygen lack is due to its high oxygen requirements, related to the fact that only relatively small amounts of energy result from cerebral glycolytic processes⁽³⁾. The magnitude of the oxygen consumption of the adult brain is such that it consumes 20 per cent of the total body oxygen utilization although it constitutes only 2 per cent of the total body weight. It has been estimated that at any moment the brain tissue and the blood circulating through it contain about 7 cc. of oxygen, an amount sufficient to supply the needs of the brain for only a few seconds. Experimentally, consciousness is lost within 7 seconds after sudden arrest of cerebral circulation, and, clinically, irreversible brain damage occurs after 4 to 6 minutes of cerebral ischemia, as in cardiac arrest⁽⁴⁾.

The primary factors governing oxygen delivery to cerebral tissues are the oxygen content of the arterial blood and the rate of cerebral blood flow. A classification of the clinical causes of impairment of cerebral oxygen delivery is presented in Table 2. Cerebral hypoxia frequently occurs in these disorders if homeostatic mechanisms become inadequate. For example, studies with different atmospheric concentrations of oxygen at sea level indicate that with inhalation of 10 per cent oxygen there is an increase in rate of total cerebral blood flow of approximately 50 per cent in the course of a 10-to-20-minute period, the reduction of arterial oxygen saturation being largely compensated by the increased rate of cerebral blood flow, so that there is no change in cerebral oxygen utilization⁽⁵⁾. However, upon inhalation of 7 per cent atmospheric oxygen, the decrease in arterial oxygen saturation is so marked that the reactive increase in cerebral blood flow is not sufficient to maintain adequate cerebral oxygen delivery for even 5 minutes and is quickly associated with evident cerebral dysfunction⁽⁶⁾.

The rate of cerebral blood flow is dependent upon the head of pressure and the cerebral vascular resistance. The former is regulated, for the most part, by the arterial pressure which is influenced by a large number of extracranial factors. The

TABLE 2

Causes of Impaired Cerebral Oxygen Delivery

- I. *Reduced Arterial Oxygen Content*
 - A. Hypoxemia
 1. Decreased atmospheric oxygen tension
 2. Cardiorespiratory disease
 3. Reduced oxygen-carrying capacity of blood
- II. *Reduced Cerebral Blood Flow*
 - A. Extracerebral
 1. Decreased cardiac output
 - a. Decreased venous return
 - b. Arrhythmias
 - c. Myocardial insufficiency
 - d. Valvular disease (e. g., aortic stenosis)
 2. Aortocranial arterial stenosis
 3. Hypotension
 - a. Carotid sinus or aortic arch reflexes
 - b. Drug-induced vasodilatation
 - c. Hypovolemic shock
 4. Increased blood viscosity (polycythemia, lipemia)
 - B. Intracerebral
 1. Cerebral vascular disease
 2. Cerebral vasoconstriction
- III. *Various Combinations of the Above*

latter, i.e., cerebral vascular resistance, is principally dependent upon the caliber of the cerebral vessels and upon the viscosity of the blood. Cerebral ischemia sufficient to induce coma may result from systemic circulatory changes associated with reduction of mean arterial pressure, due to diminished cardiac output or to a marked reduction in peripheral vascular resistance.

The normal rate of total cerebral blood flow is approximately 800 cc. per minute, representing 15 to 20 per cent of the total cardiac output. An acute reduction in the rate of cerebral blood flow sufficient to bring oxygen delivery below critical levels results in syncope and, if severe and not immediately corrected, in coma and irreversible brain damage. Table 3 presents cerebral hemodynamic observations in subjects

TABLE 3
Cerebral Hemodynamics in Induced Syncope

	CBF	CVR	MAP
Normal subjects	55.0	1.7	90 to 100
Orthostatic hypotension	27.9	1.0	26
Drug-induced hypotension:			
In normotensive subjects	31.3	1.2	35
In malignant hypertension	30.0	3.5	100
<i>In this and other tables, CBF signifies cerebral blood flow in cc./min./100 g. brain; CVR, cerebral vascular resistance in mm. Hg/cc. blood/min./100 g. brain; and MAP, mean arterial blood pressure in mm. Hg.</i>			

in whom syncope resulted from acute reduction in cerebral oxygen delivery due to hypotension, orthostatic or pharmacologically-induced.

Regardless of the manner of induction of acute generalized cerebral ischemia, the critical rate of overall cerebral blood flow in the presence of normal arterial oxygen content is usually about 30 cc. of blood per 100 gms. of brain per minute, indicating that cerebral oxygen delivery can be acutely reduced to about 50 to 60 per cent of normal before unconsciousness supervenes⁽⁷⁾. It is important to point out, however, that the mean arterial pressure at which consciousness is lost may vary considerably and is related to the capacity of the cerebral vessels to dilate in the face of an acute reduction of pressure. As indicated in Table 3, in those subjects with malignant hypertension and an initially high cerebral vascular resistance, critical rates of cerebral blood flow may occur with a normal mean arterial pressure because of the persisting high cerebral vascular resistance.

Coma from focal cerebral ischemia, as occurs upon the development of stenosis or occlusion of intracranial vessels, probably results principally from disturbance of blood supply to the brain-stem region⁽⁸⁾.

II. Coma due to Substrate Insufficiency

The brain derives the energy to support its functional activities and to maintain its

structural integrity almost exclusively from the catalytic degradation of glucose, as is evident from the almost equivalent quantities of oxygen consumed and carbon dioxide produced (R. O. of unity)⁽⁹⁾. Since cerebral glycogen stores are quantitatively negligible, the brain is dependent upon the circulating blood for its glucose supplies⁽¹⁰⁾. It should be apparent that hypoglycemia, however induced, if of sufficient intensity will curtail cerebral energy production and eventuate in coma^(11, 12).

Table 4 presents typical results of cerebral studies in patients in whom coma was therapeutically induced by the administration of insulin and subsequently terminated by intravenous glucose. It may be noted that in acute hypoglycemic coma there is a normal rate of cerebral blood flow and oxygen delivery but a significant decrease in cerebral oxygen utilization. As one might expect, because of the unchanged blood flow and diminished cerebral oxygen consumption, there is a higher than usual oxygen content in the cerebral venous blood and related narrowing of the cerebral arteriovenous oxygen difference. The rapid return to normal of cerebral oxygen consumption upon administration of glucose substantiates the thesis that the basic disturbance in uncomplicated hypoglycemic coma is one of substrate unavailability rather than enzymatic inhibition.

If hypoglycemia is sufficiently intense and prolonged, irreversible coma may result⁽¹³⁾. In Table 5 are presented metabolic

TABLE 4

Cerebral Values in Acute Hypoglycemic Coma

	CBF	CMRO ₂	CAVO ₂	Blood Sugar
Control	59	3.1	5.25	96
Hypoglycemia	56	2.6	4.64	48
Coma	57	1.9	3.33	27
Post-coma	56	3.0	5.36	190

CBF signifies cerebral blood flow in cc./min./100 g. brain; CMRO₂, cerebral oxygen consumption in cc./min./100 g. brain; CAVO₂, cerebral arteriovenous oxygen difference in volumes per cent; and blood sugar in mgs. per cent.

TABLE 5

Cerebral Findings in Irreversible Post-Hypoglycemic Coma

Days in Coma	Blood Sugar	CBF	CMRO ₂	MAP
3	385	62	2.8	105
9	150	56	2.0	100
11	312	41	0.5	113

See Tables 3 and 4 for explanation of abbreviations.

data from a subject with irreversible post-hypoglycemic coma. In such cases, the cerebral oxygen consumption remains depressed despite restoration of even more than adequate cerebral delivery of glucose and, in fact, continues to fall over a prolonged period, possibly because of superimposed hypoxic cerebral damage such as often complicates profound coma of whatever origin. The gradual decrease in cerebral blood flow probably is related causally to the chronically-diminished cerebral oxygen requirements.

III. Coma due to Enzymatic Disturbances

Numerous enzymes are required to catalyze glucose degradation at body temperature⁽¹⁴⁾. Interference with their activity or lack of necessary co-factors will impair

glucose and oxygen utilization, resulting in decreased energy formation and cerebral dysfunction. Figures 1 and 2 present an abbreviated schematic representation of the generally-accepted pathways involved in the catalytic degradation of glucose. The first stage (Embden-Meyerhof cycle, Fig. 1) is comprised of the breakdown of glucose to pyruvic acid; the second (Krebs cycle, Fig. 2), the condensation of active acetyl with oxalacetate to form citrate, which undergoes a series of reactions (tricarboxylic acid cycle) involving dehydrogenation and decarboxylation and addition of water or phosphate. As a result of these reactions, energy is released to various hydrogen acceptors (electron-transfer system, Fig. 3), the hydrogen ultimately combining with oxygen to form water. Energy yielded by these reactions is finally transferred to form high-energy phosphate compounds (ATP),

EMBDEN-MEYERHOF PATHWAY

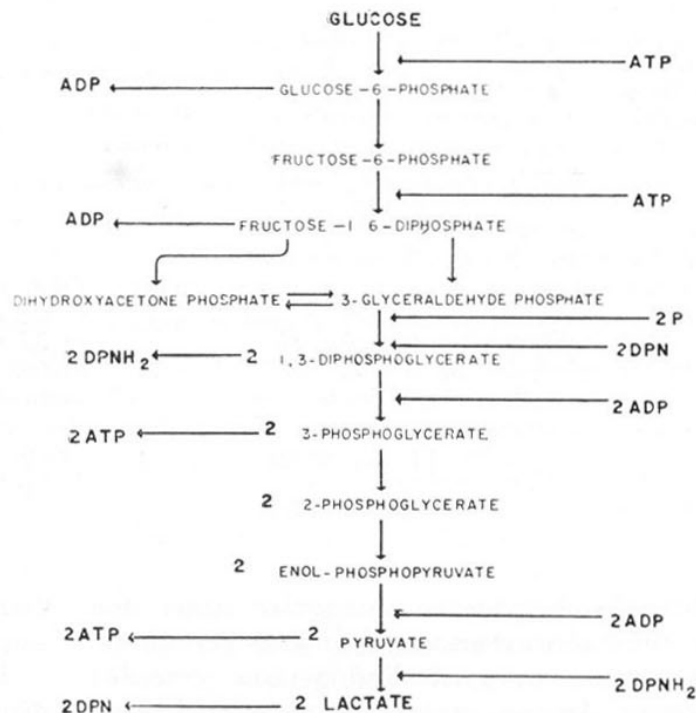


Fig. 1. — Glycolysis is the first step in energy recovery from glucose. Six-carbon glucose is broken down into two molecules of three-carbon lactate (or lactic acid; the ionic rather than the acid form of the intermediate compounds is shown in the diagrams). Two molecules of ATP are used up in glycolysis but four are formed, for a net gain of two molecules of ATP. (Reprinted with permission from Lehninger, A. L.: *Scientific American*, 205:63, 1961.)

KREBS "CITRIC ACID" CYCLE

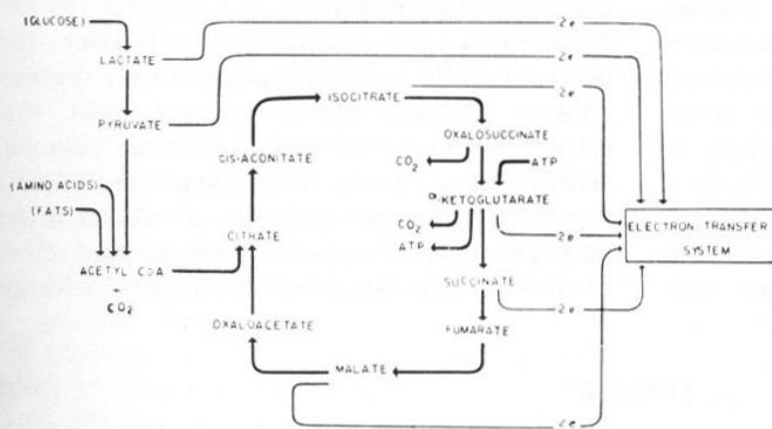


Fig. 2. — Krebs "Citric Acid" Cycle finally oxidizes the products of glycolysis to carbon dioxide and water. Lactate is first converted to pyruvate, which in turn goes to acetyl coenzyme A. (Here fat and protein join carbohydrate in the metabolic process.) There follows a cycle of reactions, involving the regeneration of oxaloacetate, in which carbon compounds are broken down to carbon dioxide. (Reprinted with permission from Lehninger, A. L.: *Scientific American*, 205:63, 1961.)

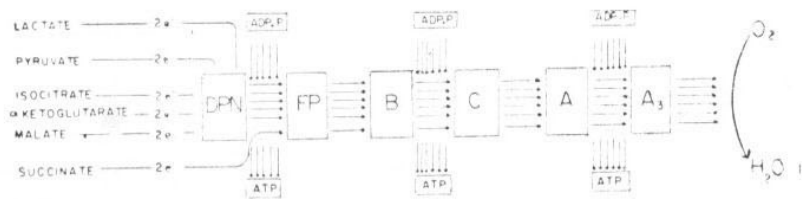
oxidative phosphorylation being nearly eighteen times as productive of ATP as aerobic glycolysis (2 mols ATP gained in Embden-Meyerhof cycle; 36 mols ATP gained in Krebs cycle). ATP is the specific operative substance constantly formed and utilized by the brain in order to transfer energy derived from substrate metabolism to the various neurobiosynthetic reactions (membrane permeability maintenance, synthesis of organic compounds, transmission

of neuronal impulses). Specificity of reactions is achieved by transferral of the phosphate group of the ATP moiety to specific acceptor molecules; the energy-rich ATP is broken down to energy-poor ADP, which is again resynthesized to ATP.

Although in many cases, there is poor understanding of the precise nature of the biochemical disorders by which the various enzymes concerned with cerebral metabolic processes are inhibited or inactivated, it is

ELECTRON TRANSFER SYSTEM

Fig. 3. — Electrons removed at various stages of the Krebs "Citric Acid" Cycle are passed down a "respiratory chain" of electron carriers: diphosphopyridine nucleotide (DPN), a flavo-protein enzyme (FP) and a series of iron-containing enzymes: cytochromes B, C, A, and A_3 . As the electrons pass down the chain, ultimately to reduce oxygen to water, they drive the phosphorylations in which ATP is formed. Each molecule of lactate contributes six pairs of electrons; five of these charge up three ATP molecules each and the sixth makes two ATP's.



One more ATP is formed in the citric acid "mill" itself, so a total of 36 molecules of ATP are produced by the two molecules of lactate that were formed from the original glucose molecule. (Reprinted with permission from Lehninger, A. L.: Scientific American, 205:63, 1961.)

clinically helpful to categorize coma due to these disturbances as of endogenous or exogenous origin. Endogenous cerebral enzyme depression may be associated with visceral decompensation as manifested in hepatic, diabetic, or uremic coma. The enzymatic inhibition responsible for coma in each of these clinical disorders is most likely of the competitive type, enzyme surfaces being occluded by abnormally accumulated metabolites. In the comatose states of endogenous origin, there is no primary reduction in cerebral oxygen or glucose availability, although there is a marked diminution of cerebral oxygen consumption as indicated in Table 6. The characteristic biochemical aberrations asso-

ciated with the various endogenous comatose states may be reviewed briefly:

Diabetic coma cannot be attributed directly to a deficiency of insulin since it has been repeatedly demonstrated that the brain does not require this hormone for the metabolism of carbohydrate, both glycolysis and pyruvate oxidation proceeding in the absence of insulin^(15, 16). Apparently the blood brain barrier and cerebral cells are inherently freely permeable to glucose. Diabetic coma must, therefore, be due to those disturbances (ketosis, acidosis, and water and electrolyte losses) resulting from the inability of tissues other than the brain (muscle, liver, kidney, etc.) to metabolize glucose adequately without

TABLE 6
Cerebral Values in Visceral Decompensation Coma

	CBF	CDO ₂	Blood Sugar	CMRO ₂
Normal	55	Normal	Normal	3.5
Diabetic	65	Normal	Elevated	1.7
Hepatic	42	Normal	Normal	1.6
Uremic	45	Normal	Normal	2.1

See Table 4 for explanation of abbreviations; CDO₂ signifies cerebral oxygen delivery in cc O₂/min./100 g. brain.

insulin. Despite our rather good understanding of the various biochemical changes resulting from insulin deficiency, the precise cause of the reduction in cerebral oxygen consumption and the loss of consciousness in diabetic coma remains obscure ⁽¹⁷⁾.

Decompensation of renal function is associated with urinary loss of substances normally conserved by the kidneys and retention in excessive quantities of material normally excreted, resulting in a profound disturbance of electrolyte and fluid balance. As in diabetic coma, the reason for the associated cerebral oxidative depression is unknown ⁽¹⁸⁾. Experimental administration of individual metabolites retained in the disorder have failed to demonstrate specific comatogenic properties. All that can be stated with certainty is that hemodialysis presumably eliminates some unidentified etiologic substance or substances, since the procedure often restores consciousness ⁽¹⁹⁾.

Of the numerous biochemical abnormalities consequent upon failure of hepatic function, the accumulation of ammonia is currently believed to represent the major etiologic factor in the cerebral depression which so often complicates this disorder ^(20, 21). This opinion is derived from observation of increased arterial ammonia levels and the comatogenic effects of ingestion of large amounts of protein ⁽²²⁾, gastrointestinal bleeding ^(23, 24), and administration of ammonium salts ^(25, 26), carbonic anhydrase inhibitors ^(27, 28), or thiazide diuretics ⁽²⁹⁾. The thesis also gains support from the demonstration that clinical improvement may sometimes accompany reduction of blood ammonia by such modalities as antibiotic sterilization of the gastrointestinal tract ^(30, 31), administrations of ammonia-binding agents (glutamate and L-arginine) ^(32, 33), hemodialysis ^(34, 35), and low protein diet ^(36, 37).

The presumptive mechanism by which ammonia is thought to interfere with cerebral oxidative metabolism is that of amination of alpha-ketoglutarate to form glutamate which is then further aminated to form glutamine ⁽³⁸⁾. This reaction, although satisfactorily binding some of the increased blood ammonia, depletes the Krebs cycle of alpha-ketoglutarate, thereby

removing an essential intermediate. There are, however, several discrepancies not satisfactorily explained by the ammonia hypothesis. First, there is often a poor correlation between the arterial ammonia level and the neurological status of the patient, recovery from coma frequently occurring when the arterial ammonia level is even higher than at the inception of coma ^(39, 40). Furthermore, significant reduction of arterial ammonia levels by infusion of such ammonia-binding substances as glutamate or arginine, singly or in combination, may be without clinical effect and influences neither abnormal cerebral electrical activity nor the reduced cerebral oxygen consumption ⁽⁴¹⁾.

In spite of major shortcomings of the ammonia theory, there can be little doubt that this nitrogenous substance may, nevertheless, be a significant factor in the etiology of many cases of hepatic coma. It is equally evident that other factors, i.e., hypocapnia, pH changes, and the presence of indoles or mercaptans, may play at least a contributory role ⁽²⁰⁾.

Another form of endogenous depression which may, although rarely, progress to coma is that encountered in disorders of respiratory function characterized by retention of CO₂ in high concentrations. Carbon dioxide retention may be due to alveolar hypoventilation (as in the Pickwickian syndrome) ⁽⁴²⁾, primary medullary depression ⁽⁴³⁾, alveolar-capillary block, and, possibly, hypothyroidism ⁽⁴⁴⁾. In these syndromes, hypoxemia is commonly associated with hypercapnia, and undoubtedly both contribute to the cerebral dysfunction ^(45, 46). Even in iatrogenic hypercapneic coma, precipitated by the injudicious therapeutic use of oxygen in certain cases of severe respiratory disease, arterial oxygen levels are seldom found to have been raised to normal.

Specific enzyme inhibitors of exogenous origin will also impair cerebral energy production or utilization. Some of the heavy metals are believed to exert their toxic effects upon the central nervous system by combining with the thiol groups of cerebral enzymes and co-enzymes ⁽⁴⁷⁾. Lipoic acid, a constituent of pyruvic oxidase

TABLE 7

Co-Factor Deficiency States

<i>Vitamin</i>	<i>Biological Function</i>	<i>Deficiency Effects (Neurological)</i>
B ₁ thiamin	Coccarboxylase (decarboxylation of alphaketo-acids)	Wernicke's encephalopathy; polyneuritis
B ₂ riboflavin	FAD and flavin mononucleotide (oxidation-reduction)	Not known
Pantothenic a.	CO-A (condensing and synthetic reactions)	Not known
Niacin	DPN, TPN (oxidation-reduction)	Pellagra (dementia)
B ₆ pyridoxine	Pyridoxal phosphate (transamination, deamination)	Seizures (infants)
B ₁₂ cyanocobalamine	?	Cerebral lesions (dementia); posterolateral cord degeneration

which catalyzes the oxidation of pyruvic and alpha-ketoglutaric acids, contains 2 sulfhydryl radicals which, when combined with heavy metals such as arsenic, form a stable ring compound in which the reactivity of the sulfhydryl group is lost. The importance of sulfhydryl compounds in intermediate carbohydrate oxidation renders the brain particularly vulnerable to heavy metal poisoning.

A wide variety of chemically dissimilar substances has been found to be of therapeutic value by virtue of ability to reduce perception of internal and external stimuli or to obtund the emotional reaction to such stimuli. These drugs include general anesthetics, hypnotics and sedatives, narcotic analgesics, and ataractics. All have the capacity to induce the comatose state when administered in sufficient quantities. These agents, because of their dissimilar molecular spatial configuration and the heterogeneity of cerebral enzyme distribution, probably preferentially exert their more pronounced action upon different cerebral structures or specific receptor sites⁽⁴⁸⁾.

With respect to the effects of sedatives on oxidative phosphorylation, Quastel and

co-workers⁽⁴⁹⁾ first demonstrated that barbiturates, chloral hydrate, chloretone, urethane, and avertin reversibly inhibit the in vitro oxidation of glucose, lactate, and pyruvate (but not succinate). Confirmatory in vivo studies have demonstrated that large doses of barbiturates and certain anesthetics reduce overall cerebral oxygen consumption⁽⁵⁰⁾. However, small amounts of these drugs sufficient to produce only sedation induce no measurable alteration of in vivo cerebral oxygen consumption, and it has been concluded that the clinical effect of subanesthetic quantities of barbiturates may be derived from action upon systems other than those directly involved in oxidative metabolism, or from interference with energy-utilizing processes⁽⁵¹⁾. The observation of Bain⁽⁵²⁾ that certain barbiturates interfere more with ATP formation than with oxygen consumption was the basis for the uncoupling hypothesis, according to which cerebral oxidative energy is not quantitatively transferred to ATP. This theory has been employed to explain the mechanism of action of ataractics since these drugs, even in large doses, do not inhibit oxidative metabolism. It

has been suggested, however, that instead of inducing uncoupling, they may inhibit utilization of ATP, principally in subcortical structures, by inhibition of ATP-ase. It has also been postulated that tranquilizers may infiltrate into certain specific cell membranes, effecting major changes by their physical presence and thereby altering transport processes across these membranes⁽⁵³⁾.

On examination of the various theories concerning the possible mechanism of action of depressant drugs (including even some inert gases⁽⁵⁴⁾) upon the central nervous system, it is apparent that virtually every known aspect of neurochemistry has been explored without, as yet, unequivocal support for any of these hypotheses.

The comatogenic effects of hypo— and hyperthermia have long been recognized, but there still remains a paucity of information concerning the precise mechanisms involved in the production of coma, as well as their temperature limits. In clinical experience, reversible coma of purely hypothermic etiology is rarely encountered. In most accidental cases, there has been prior central nervous system depression, as by alcohol, sedatives, trauma, etc., and the central nervous system effect of all induced hypothermia is augmented by various pharmacological agents. Cerebral metabolic studies indicate that in human hypothermic coma, cerebral oxygen consumption and blood flow are markedly reduced, the latter because of an independent cerebral vasoconstriction as well as decrease in cardiac output⁽⁵⁵⁾.

Hyperthermic coma is invariably accidental and results from failure of physiologic heat dissipation mechanisms, or from environmental changes rendering these mechanisms ineffectual. Depending on the severity and duration of the elevated body temperature, permanent brain damage, doubtless due to irreversible denaturation of protein, is not uncommon and may be anticipated if temperatures in the range of 41 degrees C. or higher persist for appreciable periods. To our knowledge, observation of cerebral metabolic changes during hyperthermic coma in man are lacking. Heyman and Patterson⁽⁵⁶⁾ demonstrated

that temperature elevations to approximately 39 to 39.5 degrees C. were associated with an increase in cerebral oxygen consumption in patients with general paresis (although normal cerebral oxygen consumption in these patients was not attained) but no change in those subjects with asymptomatic neurosyphilis (having normal rates for cerebral metabolism).

Disturbances of consciousness following administration of enzyme-inhibiting agents or severe temperature change may be relatively sudden, while that resulting from lack of essential co-factors or vitamins is usually insidious in its development, coma occurring only in advanced deficiency states, in such instances often being a manifestation of peripheral circulatory failure. Table 7 presents the recognized metabolic actions of the various B-vitamins and indicates the neurological disturbances associated with their deficiencies.

IV. Coma of Multiple Etiologies

There are numerous commonly-encountered clinical disorders in which there is undoubtedly more than one type of energy interference operating simultaneously, and their effects may be additive. Among such disorders may be included postictal coma, cerebral trauma, infection, Valsalva syncope, and intracranial space-occupying lesions. For example, in coma due to expanding lesions of the central nervous system (i.e., tumors, hemorrhage, abscess), the delivery of essential substrates to the brain may be impaired by direct or indirect compression of vascular channels, including their occlusion by herniation against the tentorium or foramen magnum, thrombosis of veins, reactive spasm of arteries, and reduction of caliber of smaller vessels, or by increased intracranial pressure. Diffusion of essential substrates may also be impaired because of altered tensions in intra— and extracellular spaces, and their utilization may not be possible because of distortion and even destruction of cellular surfaces. Not only will the above processes interfere with substrate delivery and utilization, but they will necessarily influence

enzymatic activity, with resultant generalized or local disturbances in oxidative metabolism, alterations in membrane permeability, diminished formation or utilization of neurohumors, and consequent disturbances in neuronal transmission.

Finally, it should be mentioned that

severe cerebral depression, particularly if widespread throughout the brain, may perpetuate itself indirectly by causing dysfunction of specific brain centers for regulation of such vital functions as temperature homeostasis, respiration, and blood pressure.

S U M M A R Y

In the final analysis, coma of whatever etiology is due to a disturbance in cerebral energetics in those brain areas upon which wakefulness depends. Coma may be due to interference with oxidative phosphorylation or to impaired ATP utilization so that energy required for neurobiosynthetic

reactions (i.e., maintenance of membrane permeability, synthesis of organic compounds, and transmission of neuronal impulses) is curtailed. The metabolic origins of the more commonly encountered forms of coma, according to this concept, are reviewed and illustrative data presented.

R E S U M E N

En última instancia, cualquiera que sea la etiología, el coma es determinado por una perturbación en la energética cerebral en las áreas del cerebro de las cuales depende la vigilia. El coma puede ser debido a interferencia en la fosforilación oxidativa o a la utilización defectuosa de ATP, de tal modo que hay una restricción en la energía requerida para las reacciones

neurobiosintéticas (mantenimiento de la permeabilidad de membrana, síntesis de los compuestos orgánicos, y transmisión de los impulsos neuronales). Fueron considerados los orígenes metabólicos de las formas de coma encontradas más frecuentemente, de acuerdo a este concepto, y se presentaron datos ilustrativos.

R É S U M É

En dernière analyse, le coma d'une origine quelconque s'explique par un dérangement de l'énergétique cérébrale de ces territoires cérébraux desquels l'état de veille dépend. Le coma peut s'expliquer par une interférence dans la phosphorylation oxydative, ou par l'utilisation altérée de ATP (le triphosphate d'adénosine) de façon que l'énergie requise pour les réac-

tions neurobiosynthétiques (c'est à dire la conservation de la perméabilité des membranes, la synthèse des composés organiques, et la transmission d'impulsions neuronales) est diminuée. Les origines métaboliques des formes ordinairement rencontrées du coma, selon ce concept sont revues et illustrées par les études et données présentées.

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

Letzten Endes ist Koma, unabhängig von seiner Ursache, zurückzuführen auf eine Störung der Gehirnergetik, und zwar in jenen Gehirnbezirken, von denen das Wachsein abhängt. Koma kann herrühren von einer Störung der oxydativen Phosphorylbildung oder von einer verminderten Ausnutzung des ATP (Adenosin-tri-Phosphat), sodass die Energiezufuhr gekürzt

wird, die für neurobiosynthetische Reaktionen (Erhaltung der Membranpermeabilität, Synthese organischer Verbindungen, and die Aussendung von Neuronenimpulsen) nötig ist. Mit Hilfe dieser Betrachtungen werden die im Stoffwechsel begründeten Ursachen der gängigsten Arten des Koma besprochen und mit Daten erläutert.

REFERENCES

- (1) *Lindsley, D. B.*: Psychological Phenomena and the Electroencephalogram, *Electroencephalography and Clinical Neurophysiology* 4:443, 1952.
- (2) *Mangold, R., Sokoloff, L., Conner, E., Kleinerman, J., Thurman, P. O., and Kety, S. S.*: The Effect of Sleep and Lack of Sleep on the Cerebral Circulation and Metabolism of Normal Young Men, *J. Clin. Invest.* 34: 1092, 1955.
- (3) *Lehninger, A. L.*: Oxidative Phosphorylation, *Harvey Lect.* (1953-54) 49:176, 1955.
- (4) *Rossen, R., Kabat, H., and Anderson, J. P.*: Acute Arrest of Cerebral Circulation in Man, *Arch. Neurol. & Psychiat.* 50:510, 1943.
- (5) *Kety, S. S., and Schmidt, C. F.*: The Effects of Altered Arterial Tensions of Carbon Dioxide and Oxygen on Cerebral Blood Flow and Cerebral Oxygen Consumption of Normal Young Men, *J. Clin. Invest.* 27:484, 1948.
- (6) *Meyer, J. S., and Waltz, A. G.*: In: *Anoxia and the Electroencephalogram*. J. S. Meyer and H. Gastaut, editors. Springfield, Ill. 1961, Charles C. Thomas, Publisher, p. 329.
- (7) *Finnerty, F. A., Jr. Witkin, L., and Fazekas, J. F.*: Cerebral Hemodynamics during Ischemia Induced by Acute Hypotension, *J. Clin. Invest.* 33:1227, 1954.
- (8) *Fisher, C. M.*: Clinical Syndromes in Cerebral Arterial Occlusion. In: *Pathogenesis and Treatment of Cerebrovascular Disease*, W. S. Fields, editor. Springfield, Ill. 1961, Charles C. Thomas, Publisher, chap. VII.
- (9) *Ashby, W.*: A Parallelism between the Quantitative Incidence of Carbonic Anhydrase and Functional Levels of the Central Nervous System, *J. Biol. Chem.* 152:235, 1944.
- (10) *Kerr, S. E., and Ghantus, M.*: The Carbohydrate Metabolism of Brain. II. The Effect of Varying the Carbohydrate and Insulin Supply on the Glycogen, Free Sugar, and Lactic Acid in Mammalian Brain, *J. Biol. Chem.* 116:9, 1936.
- (11) *Himwich, H. E., Bowman, K. M., Wortis, J., and Fazekas, J. F.*: Biochemical Changes Occurring in the Cerebral Blood during the Insulin Treatment of Schizophrenia, *J. Nerv. and Ment. Dis.* 89:273, 1939.
- (12) *Kety, S. S., Woodford, R. B., Harmel, M. H., Freyhan, F. A., Appel, K. E., and Schmidt, C. F.*: Cerebral Blood Flow and Metabolism in Schizophrenia: The Effects of Barbiturate Semi-narcosis, Insulin Coma and Electroshock, *Am. J. Psychiat.* 104:765, 1948.
- (13) *Fazekas, J. F., Alman, R. W., and Parrish, A. E.*: Irreversible Post-Hypoglycemic Coma, *Am. J. Med. Sci.* 222:640, 1951.
- (14) *Horecker, B. L., and Hiatt, H. H.*: Pathways of Carbohydrate Metabolism in Normal and Neoplastic Cells, *New England J. Med.* 258:177 and 225, 1958.
- (15) *Baker, Z., Fazekas, J. F., and Himwich, H. E.*: Carbohydrate Oxidation in Normal and Diabetic Cerebral Tissue, *J. Biol. Chem.* 125:545, 1936.
- (16) *Himwich, H. E., and Nahum, L. H.*: The respiratory Quotient of Brain, *Am. J. Physiol.* 101:446, 1932.
- (17) *Fazekas, J. F.*: The Management of Patients with Diabetes Mellitus, *Seminars* 12:2, 1950.
- (18) *Heyman, A., Patterson, J. L., Jr., and Jones, R. W., Jr.*: Cerebral Circulation and Metabolism in Uremia, *Circulation* 3:558, 1951.
- (19) *Schreiner, G. E.*: In: *Consciousness and the Chemical Environment of the Brain*. Columbus, Ohio. 1958, Ross Laboratories, pp. 62-65.
- (20) *Walshe, J. M.*: Biochemical Studies in Hepatic Coma, *Lectures on the Scientific Basis of Medicine* 8:407, 1958-59.
- (21) *Summerskill, W. H. H., Wolfe, S. J., and Davidson, C. S.*: The Metabolism of Ammonia and Alpha-keto Acids in Liver Disease and Hepatic Coma, *J. Clin. Invest.* 36:361, 1957.
- (22) *Hahn, M., Massen, O., Nenchi, M., and Pavlov, J.*: Die Eck'sche Fistel zwischen der unteren Hohlvene und der Pfortader und ihre Folgen für den Organismus, *Arch. f. exper. Path. u. Pharmacol.* 32:161, 1893.
- (23) *McDermott, W. V., Wareham, J., and Riddell, A. G.*: Bleeding Esophageal Varices; A Study of the Associated Hepatic Coma, *Ann. of Surg.* 144:318, 1956.
- (24) *Halstead, J. A., and Fainer, D. C.*: Clinical Aspects of Cirrhosis: Observations on Hemorrhage and Hepatic Coma, *Am. J. Gastroenterology* 21:18, 1954.
- (25) *Phillips, G. B., Schwartz, R., Gabuzda, G. J., Jr., and Davidson, C. S.*: The Syndrome of Impending Hepatic Coma in Patients with Cirrhosis of the Liver Given Certain Nitrogenous Substances, *New England J. Med.* 247:239, 1952.
- (26) *Van Caulaert, C., and Deviller, C.*: Ammonémie expérimentale après ingestion de chlorure d'ammonium chez l'homme à l'état normale et pathologique, *Compt. rend. Soc. de biol.* 111:50, 1932.
- (27) *Posner, J. B., and Plum, F.*: The Toxic Effects of Carbon Dioxide and Acetazolamide in Hepatic Encephalopathy, *J. Clin. Invest.* 39:1246, 1960.
- (28) *Dawson, A. M., DeGroote, J., Rosenthal, W. A., and Sherlock, S.*: The Effects of Diamox on Ammonia Metabolism in Liver Disease, *Clin. Sci.* 16:413, 1957.

- (29) *Sherlock, S., Read, A. E., Laidlaw, J., and Haslam, R.*: Chlorothiazide in Hepatic Cirrhosis, *Ann. New York Acad. Sci.* 71: 430, 1958.
- (30) *Faloon, W. W., and Fisher, C. J.*: Clinical Experience with Use of Neomycin in Hepatic Coma, *Arch. Int. Med.* 103:43, 1959.
- (31) *Chalmers, T. C., Sebestyen, K., and Timberlake, W. H.*: Effect of Kanamycin on Mental and Electroencephalographic Abnormalities and Tremor in Cirrhosis and Pulmonary Emphysema, *Ann. New York Acad. Sci.* 76:188, 1958.
- (32) *Walshe, J. M.*: The Effect of Glutamic Acid on the Coma of Hepatic Failure, *Lancet* 1:1075, 1953.
- (33) *Reynolds, T. B., Redeker, A. G., and Davis, P.*: Controlled Study of Effects of L-arginine on Hepatic Encephalopathy, *Am. J. Med.* 25:359, 1958.
- (34) *Kühn, H. A.*: Hepatic Coma, *Deutsche Med. Wchnschr.* 85:393, 1960.
- (35) *Kiley, J. E., Welch, H. F., Pender, J. C., and Welch, C. S.*: Removal of Blood Ammonia by Hemodialysis, *Proc. Soc. Exper. Biol. Med.* 91:489, 1956.
- (36) *Sherlock, S., Summerskill, W. H. J., and Dawson, A. M.*: The Treatment and Prognosis of Hepatic Coma, *Lancet* 2:689, 1956.
- (37) *Gabuzda, G. J., Jr., and Davidson, C. S.*: Protein Metabolism in Patients with Cirrhosis of the Liver, *Ann. New York Acad. Sci.* 57:776, 1956.
- (38) *Bessman, S. P., and Bessman, A. N.*: The Cerebral and Peripheral Uptake of Ammonia in Liver Disease with a Hypothesis for the Mechanism of Hepatic Coma, *J. Clin. Invest.* 34:622, 1955.
- (39) *Fazekas, J. F., Ticktin, H. E., Ehrmantraut, W. R., and Alman, R. W.*: Cerebral Metabolism in Hepatic Insufficiency, *Am. J. Med.* 21:843, 1956.
- (40) *Phear, E. A., Sherlock, S., and Summerskill, W. H. J.*: Blood Ammonium Levels in Liver Disease and 'Hepatic Coma,' *Lancet* 1:836, 1955.
- (41) *Young, W. K., Jr., Johnson, J. V. V., Ticktin, H. E., and Fazekas, J. F.*: Effect of Combined Administration of Ammonia-Binding Substances in Hepatic Encephalopathy, *Am. J. Med. Sci.* 238:60, 1959.
- (42) *Burwell, C. S., Robin, E. D., Whaley, R. D., and Bickelmann, A. G.*: Extreme Obesity Associated with Alveolar Hypoventilation—A Pickwickian Syndrome, *Am. J. Med.* 21:811, 1956.
- (43) *Richter, T., West, J. R., and Fishman, A. P.*: The Syndrome of Alveolar Hypoventilation and Diminished Sensitivity of the Respiratory Center, *New England J. Med.* 256:1065, 1957.
- (44) *Nordqvist, P., Dhunér, K. G., Stenberg, K., and Orndahl, G.*: Myxoedema Coma and CO₂-Retention, *Acta. med. Scand.* 166: 189, 1960.
- (45) *Austen, F. K., Carmichael, M. W., and Adams, R. D.*: Neurologic Manifestations of Chronic Pulmonary Insufficiency, *New England J. Med.* 257:579, 1957.
- (46) *Sieker, H. O., and Hickam, J. B.*: Carbon Dioxide Intoxication: The Clinical Syndrome, Its Etiology and Management with Particular Reference to the Use of Mechanical Respirators, *Medicine* 35:389, 1956.
- (47) *Peters, R. A., Stocken, L. A., and Thompson, R. H. S.*: British Anti-Lewisite (BAL), *Nature* 156:616, 1945.
- (48) *Elkes, J.*: Drug Effects in Relation to Receptor Specificity within the Brain: Some Evidence and Provisional Formulation, *Ciba Foundation Symposium on Neurological Basis of Behavior* 1958, pp. 303-332.
- (49) *Quastel, J. H.*: Effects of Drugs on Metabolism and Physiologic Activity of Brain. In: *The Biology of Mental Health and Disease*. New York 1952, Paul B. Hoeber, Inc., pp. 360-376.
- (50) *Wechsler, R. L., Dripps, R. D., and Kety, S. S.*: Blood Flow and Oxygen Consumption of the Human Brain during Anesthesia Produced by Thiopental, *Anesthesiology* 12:308, 1951.
- (51) *Larrabee, M. G.*: Effects of Anesthetics on Oxygen Consumption and Synaptic Transmission in Sympathetic Ganglia. In: *The Biology of Mental Health and Disease*. New York 1952, Paul B. Hoeber, Inc., pp. 384-388.
- (52) *Brody, T. M., and Bain, J. A.*: Effect of Barbiturates on Oxidative Phosphorylation, *Proc. Soc. Exper. Biol., New York*, 77:50, 1951.
- (53) *Grenell, R. G., May, L., McElroy, W. D., Mendelson, J.*: Some Structural and Molecular Facets of Cerebral Responses to Drugs. In: *The Effect of Pharmacologic Agents on the Nervous System*, Baltimore, Maryland, 1959, Williams and Wilkins Co., pp. 417-439.
- (54) *Pauling, L.*: A Molecular Theory of General Anesthesia, *Science* 134:15, 1961.
- (55) *Rosomoff, H. L.*: Hypothermia and the Central Nervous System. In: *The Physiology of Induced Hypothermia*, Publication 451. Washington, D. C., 1956, National Academy of Sciences, National Research Council, p. 255.
- (56) *Heyman, A., Patterson, J. L., and Nichols, F. T.*: The Effects of Induced Fever on Cerebral Functions in Neurosyphilis, *J. Clin. Invest.* 29: 1335, 1950.

Electroencephalographic Findings During Coma

CARLO LOEB

Clinica delle Malattie Nervose e Mentali —
Laboratorio di EEG - Università di Genova, Italia.
(Direttore: Prof. Cornelio Fazio).

The problem of the relationships between psychical phenomena, behaviour and cerebral electrical activity, which already Hans Berger (1932) had been confronted with, was thereafter taken into account in many pioneer EEG studies. Subsequently, after a pause in such trend of research, the classical paper by Moruzzi and Magoun "Brain stem reticular formation and activation of the EEG" called renewed attention to this fascinating problem. An explanation was given for the mechanisms underlying sleep and wakefulness in terms of subcortical regulating structures, and a theory was put forward which seemed to account satisfactorily for the patterns usually met with in clinical EEG.

Nevertheless, in the light of the subsequent experience, such a generalization proved faulty indeed. In fact, the problem of the relationships between state of consciousness and cerebral electrical activity in the man does not lend itself to any general statement, too many aspects of it, both clinical and neurophysiological, still lacking sufficient knowledge.

Among the various aspects of the problem of EEG in troubles of consciousness, one can certainly put in the foreground the question of electrographic findings in states of coma. In this regard, as Fischgold

(1957) has pointed out, the data accumulated so far turn out to be surprisingly few, if one considers the clinical impact of the topic or the huge amount of studies dedicated to other aspects of the relationship between EEG and psychical phenomena.

The present article does not claim to be an exhaustive survey of the topic. It simply represents a brief summary of some of the data of the literature and our own published and unpublished contributions. It will be centered around two main points:

I: Electroencephalographic activity during coma due to different kinds of diseases.

II: Problems in the interpretation of the EEG activity during coma.

I: EEG activity in states of coma due to different diseases

For descriptive purpose we distinguish:

- A) coma due to endogenous and exogenous toxic and miscellaneous disorders.
- B) coma due to neurological disorders.

A) Coma due to endogenous and exogenous toxic and miscellaneous disorders.

1) It is well known that an adequate sugar intake is required to meet the

metabolic needs of the nervous tissue. The degree of fall in blood sugar level corresponding to the appearance of EEG slow abnormalities and troubles of consciousness is variable (Hill, Sargant; Heppenstall, 1944; Hill, 1950). Moreover it seems well established that the critical level in essential hypoglycemia can vary from time to time even in the same individual (Ross and Loeser, 1951) and can lower even considerably without appreciable modifications of the state of consciousness (Ziegler and Presthus, 1957⁽¹⁾).

The spells of loss of consciousness brought about by blood sugar lowering can either be very brief (syncopal attacks) or last even considerably, according to the mechanisms which underlie such phenomena. I shall consider here only the prolonged loss of consciousness produced by administration of high dosages of insulin. Several authors have dealt with this topic. In a first group of studies (Hoagland et al., 1937; Himwich et al., 1939; Davis, 1943) stress was placed upon the fact that the more the blood sugar level is lowered the more slow EEG activity increases, and that the alpha rhythm suddenly ceases as soon as deep coma ensues (Himwich et al., 1939; Gibbs, Williams and Gibbs, 1940). On the other hand, a number of studies have shown that EEG abnormalities can be recorded as early as one hour before the onset of coma (Hoagland et al., 1937) and can last even after the recovery (Jeager et al., 1953), and that slow waves can be recorded without any relevant change in the state of consciousness, or a state of coma can be accompanied by a slightly abnormal EEG (Kalinowsky and Hoch, 1946). Deep coma, according to Bonnet and Malpertuy (1954), is associated with low voltage fast electric activity.

Regan et al. (1957) have shown that the EEG activity recorded during insulinic coma is not specific of such a condition,

and can appear 120 minutes before the onset of coma. Moreover, frequency analysis has shown that during this coma 44 % of alpha rhythm is still present⁽²⁾.

In cases of hypoglycemic coma due to adenoma of the insulae of Langherans, the cerebral electrical activity slows down to 6 or 2 cps, according to the depth of the coma (Hoefer et al. 1946, Howard et al. 1950, Wyke 1952, Norgaard (1958).

Few are the data of the literature concerning the relationship between EEG and state of consciousness in diabetic comas. A brief note can be found in the papers of Bickford and Butt (1935) and Romano and Engel (1944), which seem to emphasize the occurrence in such a condition of a widespread EEG slowing. An experimentally induced increase in blood sugar level to values of 300 to 400 mgs per cent brings about a slight increase in frequency of the cortical rhythms (Gibbs, Williams, Gibbs 1940, Engel, Romano, Ferris, Weeb, Stevens 1944).

2) In states of hepatic praecoma and coma, the EEG shows bilateral waves of 1 to 3 cps, with further slowing with increasing depth of coma (Cloche, 1957; Abbott, 1958).

Such activity does not exhibit any particular feature, except for its paroxysmic and bisynchronous appearance (Foley, Watson, Adams 1950, Adams and Foley 1953). Sometimes, however, slow triphasic waves, with a great positive phase, can be recorded (Bickford and Butt, 1935, Abbott 1958, Cloche 1957). Even if most often the correspondence between EEG abnormalities and state of consciousness is satisfactory, sometimes this may not be the case (Sherlock 1957, Parsons Smith et al. 1957).

In fact, there may occur severe neuropsychiatric disturbances associated with slight EEG abnormalities, or mild degrees of clinical involvement with severe EEG alterations. The triphasic waves, on the other

(1) Blood sugar level correlates with various factors, mainly age and hyperventilation (Ross and Loeser 1951, Blinn and Noel, 1949, Lloyd Smith 1950, Holmberg 1953, Morrice 1956, Vinales et al. 1956).

(2) In insulinic hypoglycemic coma as well there is the possibility of a dissociation between electric cerebral activity and degree of hypoglycemia (Weniland and Weiland 1949).

hand, are not specific of hepatic coma, since they can be found even in other conditions, but never in comas due to other causes (Bickford and Butt 1935).

3) Few data are available concerning uremic coma. According to some Authors, a diffuse aspecific slow activity can be found (Romano, Engel 1944, Sherlock 1957, Klinger 1954, Bickford and Butt 1935).

4) In other types of coma, as in coma due to malnutrition, malaria, Addison's dis-

poisoning (Berger 1937, Davis and Davis 1936, Strauss et al. 1912, Ajuriaguerra and Fischgold 1941, Massmann 1955), alcoholic poisoning (Gibbs, Gibbs and Lennox 1937, Davis et al., 1941, Greenblatt et al. 1944, Davis, Gibbs, Davis, Yetter, Trowbridge 1941), botulism (Krump 1953), thallium poisoning, analgesic mixtures, EG05 etc. (Massmann, 1955).

In comas due to barbiturate poisoning, according to some authors the EEG shows

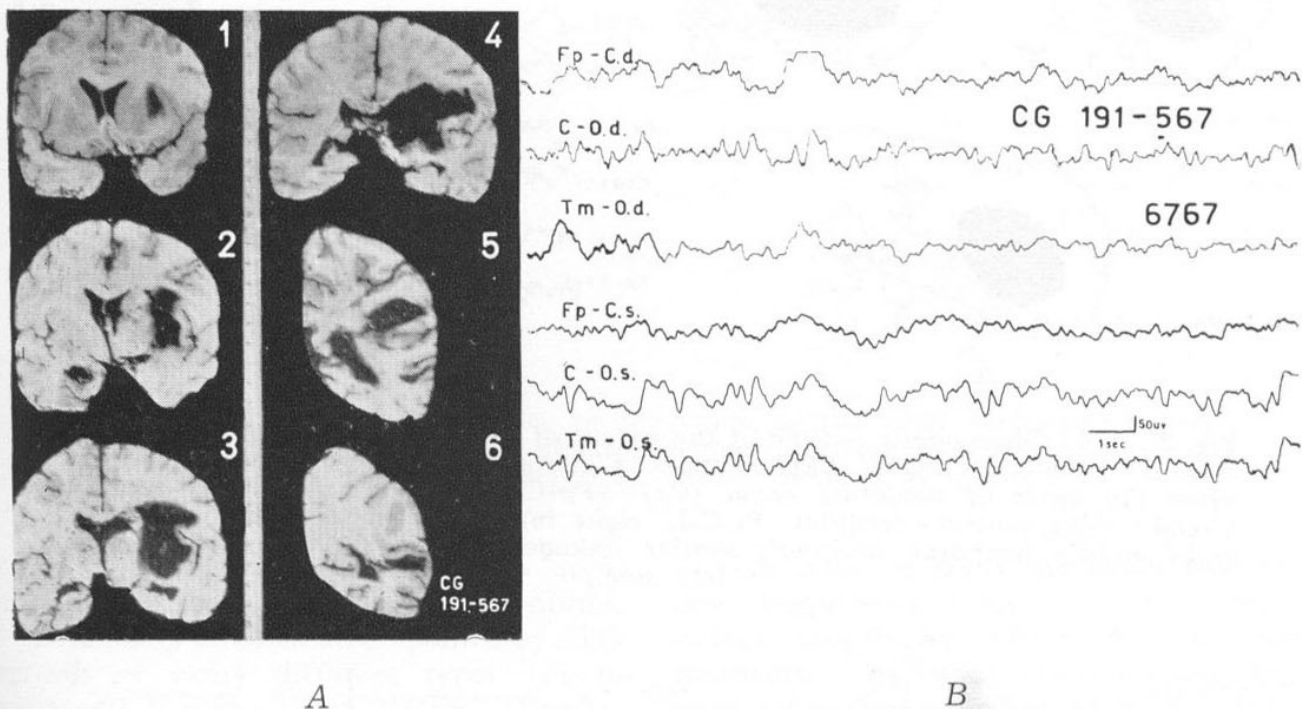


Fig. 1. — A) Massive hemispheric hemorrhage. The macroscopic section shows the extent of the paracentric left hemorrhage. B) Diffuse EEG changes. Electroencephalogram taken few hours after the onset of moderate coma (C2). (Fp-C.d.: right fronto polar-central; C-O.d.: right central-occipital; Tm-O.d.: right middle temporal occipital; similar linkages in the last three pens on the left side.)

ease, pernicious anemia, neoplastic cachexy, etc., which I do not label separately as "endocrinous comas", "anoxic comas" etc., mainly because of the paucity of the cases described in the literature, usually a slow delta activity can be encountered (Romano, Engel 1944, Hill 1950, Samson et al. 1952).

5) In various states of coma due to exogenous toxic causes, the EEG shows, diffuse aspecific slowing. To this account, one may mention the coma due to CO

a fast high voltage activity at 14-16 cps with random slow waves. The voltage progressively decreases with increasing depth of coma (Cohn et al. 1950, Talbot 1952, Samson et al. 1952). However, even if no details are given as to the state of consciousness (Schwab 1951), there seem to be "severe intoxications" accompanied by slow waves (Massmann 1955).

B) Coma due to intracranial neurological diseases.

EEG studies on this subject, carried out by Fischgold and Bounes (1946), Jasper and Buren (1953) and subsequently by Gastaut (1954), Jung (1954), Fischgold (1957), Fischgold and Mathis (1958) concern mainly cases of neoplastic, inflammatory and traumatic lesions.

The pioneer researches on the relationship between coma and electrocortical activity in humans (Davis and Davis 1939; Gibbs and Gibbs, 1941 and 1950, Hill, 1950; Schwab 1951; Strauss et al. 1952) brought to the assumption that slow organized delta activity always accompanies loss of consciousness.

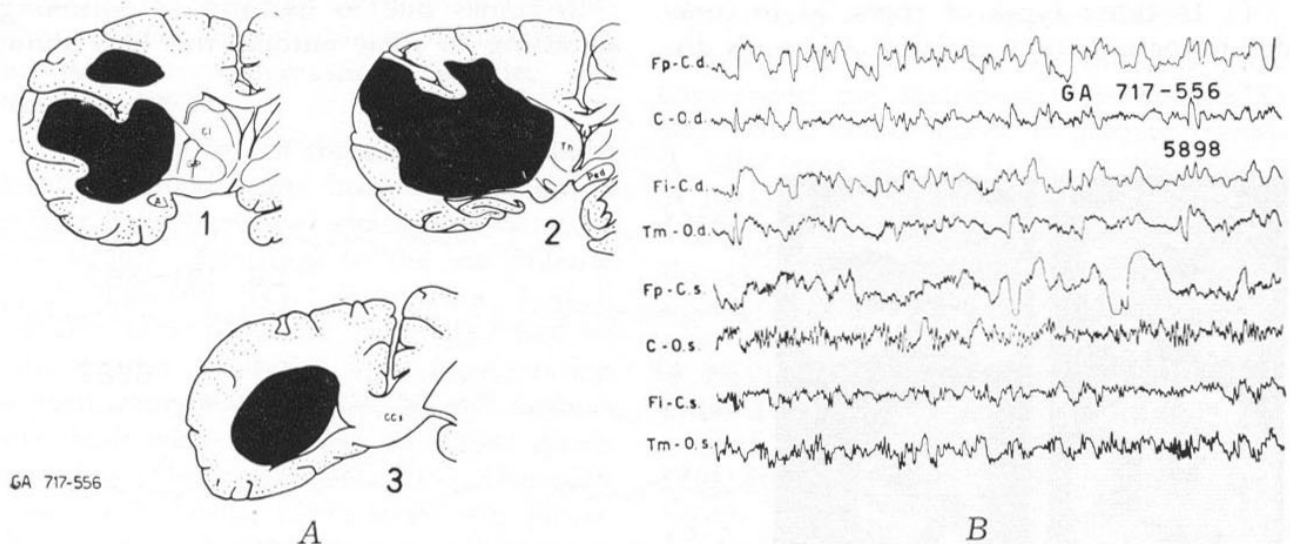


Fig. 2. — A) Diagrammatic outline of the extent of the right glioblastoma multiformis. B) Unilateral (right) EEG changes. Electroencephalogram taken few hours after the onset of moderate coma (C2). (Fp-C.d.: right fronto polar - central; C-O.d.: right central - occipital; Fi-C.d.: right inferior frontal - central; Tm-O.d.: right middle temporal - occipital; similar linkages in the last four pens on the left side.)

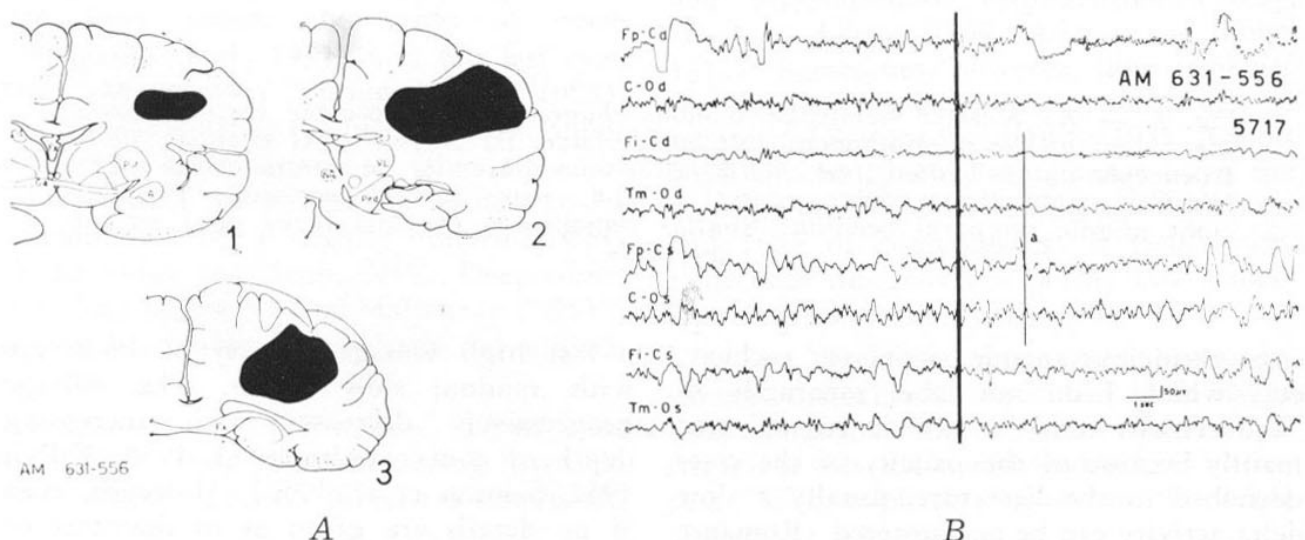


Fig. 3. — A) Diagrammatic outline of the extent of left glioblastoma multiformis. B) Unilateral (left) EEG changes. Electroencephalogram taken few hours after the onset of moderate coma (C2). Slight reactivity immediately after the opening of the eyes (a) made manually by holding the patient's eyelids). Some sporadic slow waves are recorded also in the right frontal region. (Same linkages as in fig. 4.)

Since a common mechanism was considered to underlie coma and sleep, coma was supposed to be, from the EEG stand point equivalent to a deep sleep (Davis and Davis, 1939; Gibbs and Gibbs, 1941, and 1950; Hill, 1950; Schwab, 1951; Strauss et al. 1952).

and anatomical point of view (Loeb 1957; Loeb, 1958; Loeb, Rosadini and Poggio, 1959; Loeb, Garelo and Mastropaolo, 1960) the following main points can be stressed:

1) No particular electrographic pattern whatsoever can be considered as necessarily associated with the state of coma:

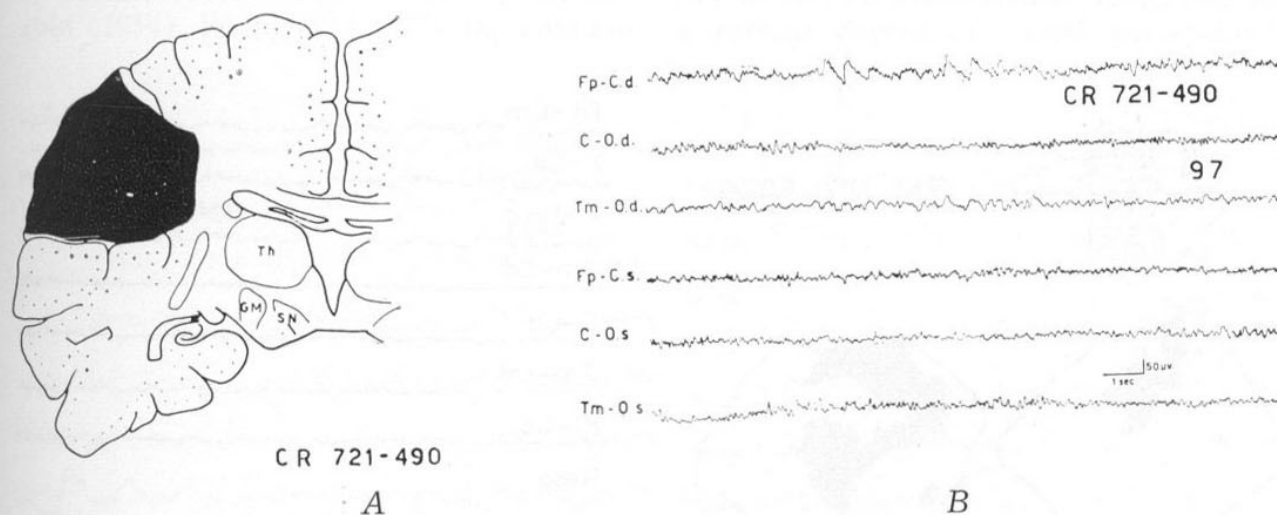


Fig. 4. — A) Diagrammatic outline of the extent of the right hemispheric tumour. B) Focal (right) EEG changes. Electroencephalogram taken few hours after the onset of moderate coma (C2). (Same linkages as in fig. 2.)

More recently evidence has been accumulated that there may be several exceptions.

Thus states of coma accompanied by EEG records of many different types (Fischgold and Bounes, 1946; Mathis, Torrubia and Fischgold, 1957) including apparently normal electrocortical activity have been reported (Loeb and Poggio, 1953; Lundervold et al., 1956).

From the study of our comatose patients⁽¹⁾ carefully carried out from the clinical, EEG

(1) The intensity of the coma observed in patients varies in a continuous spectrum from the very deepest, in which death approaches, to the very lightest, in which the patient is semiconscious. For convenience, comatose patients may be divided into 3 groups: light coma (C1), moderate coma (C2), and deep coma (C3). The parameters used for such a classification are the concurrent signs and symptoms commonly found in comatose patients. (Loeb, 1958).

Our cases consist mainly of patients suffering from cerebrovascular diseases.

i) In states of coma the entire band of slow frequencies (from 0.5 to 7 cpr), various amplitudes (from few to 300 microvolts), manifold electrographic features (slow waves, spikes, slow spike and wave activity) can be encountered.

Generalized (fig. 1), unilateral (fig. 2-3), focal (fig. 4) changes can be recorded.

Unilateral or even focal electroencephalographic changes may be observed in cases of brain stem haemorrhage associated with supratentorial lesions (haemorrhage, tumor, abscess, etc.).

Furthermore, deep coma may indeed be accompanied by electrographic activity which has a normal or borderline appearance (fig. 5).

2) There is no definite relationship between degree of coma and type or amount of concomitant electroencephalographic changes.

Patients with moderate or deep comas may exhibit either focally, unilaterally, and diffusely altered, or normal and borderline

records, whereas diffuse electroencephalographic abnormalities, sometimes fairly severe, may be seen in patients in light coma (fig. 6).

3) Electroencephalographic reactivity seems to correlate with the type of the EEG tracing, whether it be normal or slightly altered, but it is independent of the intensity of the coma.

EEG impairment, the great majority of our cases showed electrographic abnormalities similar to those recorded in patients with corresponding anatomic lesions but without modification of the state of consciousness.

ii) As to the problem of normal or borderline EEG in states of coma, from our data and that of the literature it seems possible to distinguish two groups of coma-

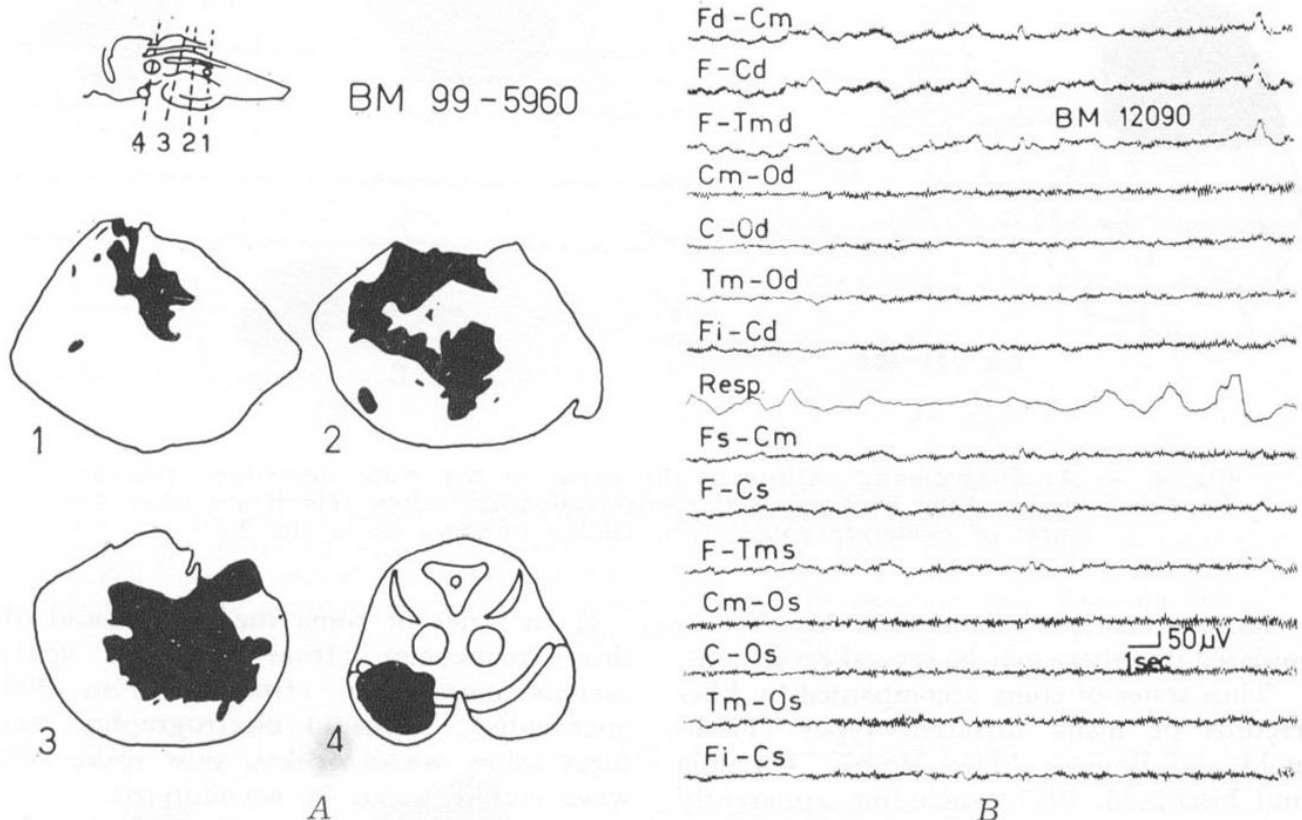


Fig. 5. — A) Diagrammatic outline of the extent of the pontomesencephalic hemorrhage. B) Normal electroencephalogram. Record taken six hours after the onset of moderate coma (C2). (Fd-Cm: right fronto polar - middle central; F-Cd: right fronto polar - central; F-Tmd: right fronto polar - middle temporal; Cm-Od: middle central - right occipital; C-Od: right central - occipital; Tm-Od: right middle temporal - occipital; Fi-Cd: right inferior frontal - central; Resp.: respiration - Similar linkages in the last seven pens on the left side.)

I would like to emphasize the apparently paradoxical fact that a normal or borderline EEG with a good reactivity can be recorded in a deeply comatose patient a short time before death.

4) Finally two more points should be stressed:

i) except some cases in which the deepening of coma was paralleled by an

tose patients who showed normal or borderline records.

In the first group belong some cases with lesions located in the posterior fossa, mostly consisting of pontine or pontomesencephalic primary haemorrhages.

The second group includes cases in which electroencephalographic records had been made a few hours before death. In these

records a reversion of an abnormal pattern to a strictly normal one, or to a pattern closely resembling the normal—even if sometimes reactivity was absent—was noticed.

5) The considerations made above hold true even with regard to EEG findings in patients exhibiting a state of "akinetic mutism". Our cases add to those described by French (1952), Cairns (1952), Lunder-vold (1954), Fischgold (1957) and confirm

of the syndrome turn out to be rather puzzling. In fact, while some signs seem to point to a marked impairment of consciousness—severe sphincter disturbances, corneal hyporeflexia, diminution of the pharyngeal reflex—the persistence of ocular movements seems to suggest that consciousness is not completely lost. Such apparently goal-directed ocular movements can in fact be considered as indicating that a certain degree of visual perception is

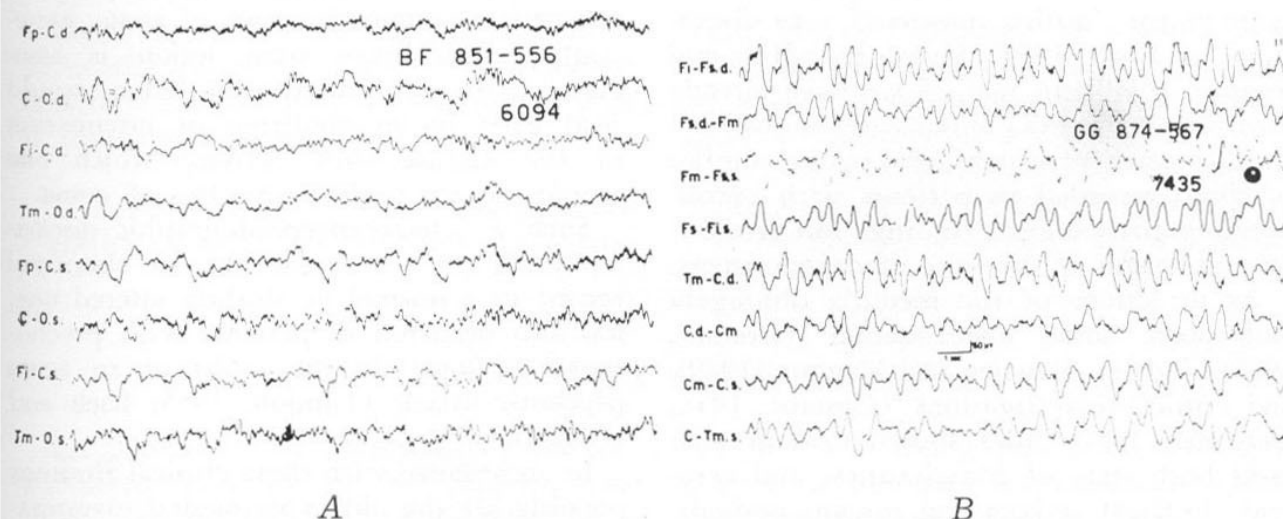


Fig. 6. — A) Slight diffuse EEG changes during deep coma (C3). (Same linkages as in fig. 6). B) Diffuse severe EEG changes during slight coma (C1). (Fi-Fs. d.: right inferior frontal - superior frontal; Fs. d.-Fm.: right superior frontal - middle frontal; Fs.-Fi.s.: left superior frontal - inferior frontal; Tm-C.d.: right middle temporal - central; C.d.-Cm.: right central - middle central; Cm-C.s.: middle central - left central; C-Tm.s.: middle central - left middle temporal.)

the fact that akinetic mutism can be accompanied by various types of EEG records, most frequently by tracings with slow activity and absence of reactivity.

The existence of a condition of "akinetic mutism" as postulated by some Authors (Cairns, 1952) was strongly questioned. Nevertheless, if we want only to refer with such designation to states of loss of consciousness with preservation of a certain amount of directed ocular motility, it can be said that this syndrome occurs more frequently than it was previously thought. The state of akinetic mutism can be preceded or followed by a coma or by a normal level of consciousness, and can last from a few hours to some months. Some aspects

preserved. On the basis of some considerations however, (Loeb, Garelo and Mastropalo, 1960) such movements are to be considered as reflex involuntary reactions, independent from visual perception. The condition of akinetic mutism can therefore be defined as a state of moderate coma, with total loss of consciousness and preservation of some reflex activities, e.g. reflex ocular movements. Actually, in the clinical practice the state of akinetic mutism can be observed only when coma intervenes gradually or its impairment and regression run a slow course without any severe general and neurological involvement masking the clinical picture. From the pathological standpoint it does not seem possible

(Loeb et al., 1960) to relate the syndrome to the involvement of any particular region of the brain.

II: Problems in the interpretation of the EEG activity in states of coma

The correspondence between electroencephalographic and pathological data was satisfactory in most of our cases. Namely, the EEG correlated well with the site of the anatomical lesions or the general variations of the "milieu interieur" (see discussion in Loeb 1958, Loeb, Rosadini and Poggio, 1959). In fact, as we have already mentioned, the EEG abnormalities observed in our cases of coma were quite similar to those recorded in patients with corresponding pathological findings but without any alteration of the state of consciousness.

As to lesions of the medulla oblongata and pons, some experimental (Bremer, 1935; Lindsley, Bowden and Magoun, 1949) and clinical investigations (Gastaut, 1954; Oerthner, 1957) have shown that in such cases both state of consciousness and cerebral electrical activity can remain unmodified.

On the contrary no data are available to explain on the basis of the present knowledge how a deep state of coma can be associated with an electroencephalographic record containing no organized delta activity.

We may reach the same conclusion, which we already made (Loeb, Rosadini and Poggio, 1959), that the nervous structures regulating the electric cortical activity differ from those regulating the state of consciousness or that these structures have different functional activities, so that the state of consciousness can be involved while the EEG can or can not be modified.

I have to stress that the current assumption that the alert condition corresponds to low amplitude fast frequency electric cortical activity, and deep sleep (and extensively, loss of consciousness) to slow organized electrocortical activity, was also disproved by some recent clinical and experimental investigations (Dement, 1958; Jouvet et al., 1959; Hara et al., 1960) which

brought to the conclusion that low voltage and fast activity can be associated with deep sleep.

In this connection, new data are offered to the present discussion.

In fact, if one considers the experimental data reported above, it is no more surprising to find a normal or borderline record associated with deep coma, since a condition of loss of consciousness as deep sleep is, has similar "normal" tracings.

Moreover, one might suppose tentatively that the peculiar functional activity of the subcortical systems in cases of coma, especially when brain stem lesion is associated with a supratentorial lesion, would lead even to an abolition or attenuation of the diffuse slow activity which one would expect to find in cases of coma.

Such a "electroencephalographic normalization", or a reversion of an abnormal record to a normal or slightly altered one, has also occurred in patients with psychomotor epilepsy in the midst of an acute psychotic attack (Landolt, 1955; Loeb and Gilberti, 1956).

In accordance with these clinical findings possibly are the old experimental investigations of Arduini and Lairy Bounes, 1952; Lairy Bounes, Parma, Zanchetti, 1952) and particularly the disappearance of the synchronizing responses during deep sleep (Rossi et al., 1961).

I fully realize the danger of transferring to the human coma the data provided by experimental investigations. Nonetheless, I think it worthwhile to stress the analogy between these findings and our own cases.

The interpretation of the mechanisms underlying deep sleep with low amplitude fast electric cortical activity is still rather controversial; an active inhibition of the subcortical synchronizing systems was supposed to take place (Rossi et al., 1961).

The analogy is probably brought too far and caution is particularly needed.

Anyway, whatever the physiological process involved may be, we have to stress that at the present time some experimental electrographic models are available to compare, almost tentatively, to all the EEG patterns occurring during states of loss of consciousness in man.

SUMMARY

The data of literature and personal contributions concerning the EEG during coma are summarized as follows:

I. The electroencephalographic activity in coma due both (a) to toxic and miscellaneous general diseases and (b) to neuro-

logical intracranial processes, is described and some electro-clinical considerations are put forward.

II. Some tentative explanations of the electrographic findings in the light of some new experimental approaches are discussed.

RESUMEN

Datos de la literatura y contribuciones personales en relación con la electroencefalografía durante el coma son referidos de la siguiente manera:

1. Se describe la actividad electroencefalográfica en el coma debido a (a) enferme-

dades tóxicas y generales de distinto orden y (b) procesos neurológicos intracraneos. Se adelantan al respecto algunas consideraciones electroclínicas.

2. Son discutidos algunos intentos de explicación de los hallazgos electrográficos a la luz de nuevos estudios experimentales.

RÉSUMÉ

Les données de la littérature et des contributions personnelles en rapport avec l'EEG pendant le coma, se résument de la manière suivante:

1. L'activité électroencéphalographique dans le coma due (a) aux maladies toxiques et variées maladies générales, et (b) à

des procès neurologiques intracrâniens, est décrite, et quelques considérations electro-cliniques sont présentées.

2. Quelques explications provisoires concernant les découvertes electrographiques, qui découlent de quelques nouveaux approchements expérimentaux, sont discutés.

ZUSAMMENFASSUNG

Die Daten aus der Literatur und die persönlichen Beiträge bezüglich des EEG im Koma können folgendermassen zusammengefasst werden:

1. Es wird die elektroencephalographische Aktivität im Koma, verursacht (a) durch toxische oder verschiedene allgemeine

Erkrankungen und (b) durch endokranielle neurologische Prozesse, beschrieben und einige elektro-klinische Betrachtungen angestellt.

2. Es werden mögliche Erklärungen der elektrographischen Befunde im Lichte einiger neuer experimenteller Erkenntnisse besprochen.

REFERENCES

Abbott, J. A.: Blood ammonia levels EEG's, and states of consciousness in patients with liver diseases. EEG Clin. Neurophysiol.: 1956, 8, 525.

Adams, R. D.; Foley, J. M.: The neurological disorder associated with liver disease. Ass. Res. Nerv. Ment. Dis.: 1953, 32, 198-237. Williams and Wilkins Co., Baltimore.

- Ajuriaguerra, J.; Fischgold, H.: L'EEG dans l'intoxication oxycarbonée. *Sem. des Hop.*: 1946, 22, 1242-1245.
- Arduini, A.; Lairy-Bouines, G. C.: Action de la stimulation électrique de la formation réticulaire et des stimulations sensorielles sur les ondes strychniques corticales chez le chat "encéphale isolé". *EEG. Clin. Neurophysiol.*: 1952, 4, 503-512.
- Berger, H.: Ueber das Elektrenkephalogram des Menschen 5. Mitteilung. *Arch. f. Psych.*: 1932, 98, 231-254.
- Bickford, R. G.; Butt, H. R.: Hepatic coma: the electroencephalographic pattern. *J. Clin. Invest.*: 1935, 340, 790-799.
- Blinn, K. A.; Noell W. K.: Continuous measurement of alveolar CO₂ tension during the hyperventilation test in routine electroencephalography. *EEG Clin. Neurophysiol.*: 1949, 1, 333-342.
- Bonnet, H.; Malpertuy, G.: Corrélations électrobiocliniques au cours des "comas" insuliniques chez 18 malades mentaux. *Rev. Neurol.*: 1954, 91, 455-456.
- Bremer, F.: Cerveau isolé et physiologie du sommeil. *C. R. Soc. Biol.*: 1935, 118, 1235-1236.
- Cairns, H.: Disturbances of consciousness with lesions of the brain stem and diencephalon. *Brain*: 1952, 75, 109-146.
- Cloche, R.: Etude électroencephalographique de quelques cas de coma hépatique. *Presse Med.*: 1957, 65, 135-138.
- Davis, P. A.: 1943, cit. da Hill.
- Davis, P. A.; Davis H.: Electrical activity of the brain. Its relation to physiological states and to states of impaired consciousness. *Ass. Res. Nerv. Ment. Dis.*: 1936, 19, 50-62. Williams and Wilkins Co., Baltimore.
- Davis, P. A.; Gibbs, F. A.; Davis, H.; Jetter, W. W.; Trowbridge, E. H.: The effects of alcohol upon the electroencephalogram. *Quart. J. Studies on Alcohol*: 1941, 1, 626-637.
- Davis, P. A. et al.: 1941, cit. da Hill.
- Engel, G. L.; Romano, J.; Ferris, E. B.; Webb, J. P.; Stevens, G. D.: A simple method of determining frequency spectrums in the EEG. *Arch. Neurol. Psych.*: 1944, 51, 134-146.
- Fischgold, H.: La conscience et ses modifications. Systèmes de référence en EEG clinique. I^o Congrès Int. des Sciences Neurol. Réunions plénières. Rapport et discussion II. pp. 181-213. Acta Medica Belgica, Bruxelles, 1957.
- Fischgold, H.; Bouines, G.: Explorations électroencephalographiques des états comateux. *Sem. des Hop.*: 1946, 22, 1245-1247.
- Fischgold, H.; Mathis, P.: Obnubilations, comas et stupeurs. Masson, Paris, 1958.
- Fischgold, H.; Torrubia, H.; Mathis, P.; Arfel, G.: Réaction électroencéphalographique d'éveil dans le coma. *Presse Méd.*: 1955, 63, 1231-1233.
- Foley, J. M.; Watson, C. W.; Adams, R. D.: Significance of the electroencephalographic changes in hepatic coma. *Trans. Amer. Neurol. Ass.*: 1950, 76, 161-165.
- French, J. D.: Brain lesions associated with prolonged unconsciousness. *Arch. Neurol. Psych.*: 1952, 68, 727-740.
- Gastaut, H.: The brain stem and cerebral electrogenesis in relation to consciousness. In "Brain mechanism and consciousness" pp. 249-279, C. Thomas, Springfield, Ill. 1954.
- Gibbs, F. A.; Williams, D.; Gibbs, E. L.: Modification of the cortical frequency spectrum by changes in CO₂, blood sugar, and O₂. *J. Neurophysiol.*: 1940, 3, 49-58.
- Gibbs, F. A.; Gibbs, E. L.: Atlas of EEG. Addison Wesley Press, Massachusetts, 1941, vol. 1.
- Gibbs, F. A.; Gibbs, E. L.: Atlas of EEG. Addison Wesley Press, Massachusetts, 1950, vol. 1.
- Greenblatt, M.; Levin, S.; Cori, F.: The EEG associated with chronic alcoholism, alcoholic psychosis and alcoholic convulsion. *Arch. Neurol. Psych.*: 1944, 52, 290-295.
- Heppenstall, M. E.: The relation between the effects of the blood sugar levels and hyperventilation on the EEG. *J. Neurol. Neurosurg. Psych.*: 1944, 7, 112-118.
- Hill, D.; Sargant, W.; Heppenstall, M. E.: Cit. da Hill.
- Hill, D.: Psychiatry: in "Electroencephalography" Ed. Hill. a. Parr; Mc Donald, London, 1950.
- Himwich, H. E.; Hadidian, Z.; Fazekas, J. F.; Hoagland, H.: Cerebral metabolism and electrical activity during insulin hypoglycemia in man. *Am. J. Physiol.*: 1939, 125, 578-585.
- Hoagland, H.; Cameron, D. E.; Rubin, M. A.: Electroencephalogram of Schizophrenies during insulin treatments. *Am. J. Psych.*: 1937, 94, 183-208.
- Hoagland, H.; Rubin, M. A.; Cameron, D. E.: The EEG of Schizophrenies during insulin hypoglycemia and recovery. *Am. J. Physiol.*: 1937, 120, 559-570.
- Hoefer, P.; Suttman, S.; Sando, I.: Convulsive states and coma in cases of islet cell adenoma of the pancreas. *Am. J. Psych.*: 1946, 102, 486-495.
- Holmberg, G.: The electroencephalogram during hypoxia and hyperventilation. *EEG. Clin. Neurophysiol.*: 1953, 5, 371-376.

- Howard, J.; Moss, H.; Rhoads, J.: Hyperinsulinism and islet cell tumors of the pancreas. *Surg. Gynec. Obstetrics*: 1950, 90, 417-455.
- Jung, R.: Correlation of bioelectrical and autonomic phenomena with alterations of consciousness and arousal in man: in "Brain mechanism and consciousness" pp. 310-339, C. Thomas, Springfield, 111, 1954.
- Jasper, H.; Van Buren, J.: Interrelationship between cortex and subcortical structures: clinical electroencephalographic studies. *EEG Clin. Neurophysiol.*: 1953, Suppl. 4, 168-188.
- Jeager, C. L.; Simon, A.; Margolis, L. H.; Burch, N. R.: Electroencephalographic studies in posthypoglycemic coma. *J. Nerv. Ment. Dis.*: 1953, 118, 435-441.
- Kalinowsky, L. B.; Hoch, P. H.: Stock treatment. New York, Grune a. Stratton, 1946, pp. 79-81.
- Klinger, M.: EEG observations in uremia. *EEG Clin. Neurophysiol.*: 1954, 6, 519.
- Krump, J. E.: Electroencephalographical observations during a botulisme endemia. *EEG Clin. Neurophysiol.*: 1953, 5, 122.
- Lairy, G. C.: Organisation de l'electroencephalogramme normal et pathologique. Aspect clinique. *Rev. Neurol.*: 1956, 94, 749-801.
- Lairy-Bouines, G. C.; Parma, M.; Zanchetti, A.: Modifications pendant la réaction d'arrêt de Berger de l'activité convulsive produite par l'application locale de strychnine sur le cortex cérébral du lapin. *EEG Clin. Neurophysiol.*: 1952, 4, 495-502.
- Landolt, H.: Ueber Verstimmungen, Dämmerzustände und schizophrene Zustandsbilder bei Epilepsie. *Schw. Arch. f. Neurol. Psych.*: 76, 313-321, 1955.
- Lindsley, D. E.; Bowden, J.; Magoun, H. W.: Effect upon EEG of acute injury to the brain stem activating system. *EEG Clin. Neurophysiol.*: 1949, 1, 475-486.
- Lloyd-Smith, D. L.: The EEG during hyperventilation followed by apnoea. *EEG Clin. Neurophysiol.*: 1950, 2, 289-296.
- Loeb, C.: Electroencephalographic changes during the state of coma. *EEG Clin. Neurophysiol.*: 1948, 10, 589-606.
- Loeb, C.; Garello, L.; Mastropaolo, C.: Aspetti clinici di alcuni particolari stati di perdita di coscienza. A proposito del cosiddetto "mutismo acinetico". *Arch. Psicol. Neurol. Psych.*: 1960, 21, 3-16.
- Loeb, C.; Giberti, F.: Considerazioni cliniche ed elettroencefalografiche a proposito di sindromi psicotiche in soggetti epilettici. *Sistema Nervoso*: 1957, 9, 219-229.
- Loeb, C.; Poggio, G. F.: Electroencephalograms in a case with pontomesencephalic haemorrhage. *EEG Clin. Neurophysiol.*: 1953, 5, 295-296.
- Loeb, C.; Rosadini, G.: Correlazioni anatomico-elettiche nella perdita di coscienza. *Neurone*: 1957, 5.
- Loeb, C.; Rosadini, G.; Poggio, G. F.: Electroencephalograms during coma. Normal and borderline records in 5 patients. *Neurology*: 1959, 9, 610-618.
- Lundervold, A.: Electroencephalographic changes in a case of acute cerebral anoxia unconscious for about three years. *EEG Clin. Neurophysiol.*: 1954, 6, 311-315.
- Lundervold, A.; Hange, T.; Löken, A. C.: Unusual EEG in unconscious patient with brain stem atrophy. *EEG Clin. Neurophysiol.*: 1956, 8, 665-670.
- Massman, H.: EEG findings in exogenous intoxications. *EEG Clin. Neurophysiol.*: 1955, 7, 661.
- Mathis, P.; Torubia, H.; Fischgold, H.: Réactivité, périodicité et corrélation corticocardiorespiratoire dans le coma: in "Conditionnement et réactivité in EEG". *EEG Clin. Neurophysiol.*; Suppl. N. 6, 453-462. Ed. Masson, Paris, 1957.
- Morrice, J. K. W.: Slow wave production in the EEG with reference to hyperpnoea, carbon dioxide and autonomic balance. *EEG Clin. Neurophysiol.*: 1956, 8, 49-72.
- Moruzzi, G.; Magoun, H. W.: Brain stem reticular formation and activation of the EEG. *EEG Clin. Neurophysiol.*: 1949, 1, 455-473.
- Norgaard, K.: Electroencephalography in two cases of insuloma. *Ugeskrift for Laeger*, 1950, 112, 258-261, da *Excerpta Med.*: Neurol. and Psych. 1950, sect. VIII; 3, 834, nr. 3203.
- Orthner, H.: Pathologische Anatomie der von hypothalamus ausgelösten Bewusstseinsstörungen. I^o Congres Int. des Science Neurol. Réunions plénières. Rapports et discussion, II, pp. 77-96. Acta Medica Belgica, Bruxelles, 1957.
- Parsons Smith, G.; Summerskill, W. H. J.; Dawson, A. M.; Sherlock, S.: Cit. da Sherlock S.
- Regan, P.F.; Broune: Electroencephalography frequency analysis and consciousness. *J. Nerv. Ment. Dis.*: 1957, 124, 142-147.
- Romano, J.; Engel, G. L.: Délirium I. EEG Date. *Arch. Neurol. Psych.*: 1944, 51, 356-364.
- Ross, I. S.; Loeser, L. H.: Electroencephalographic findings in essential hypoglycemia. *EEG Clin. Neurophysiol.*: 1951, 3, 141-148.

- Rossi, G. F.; Favale, E.; Hara, T.; Giussani, A.; Sacco, G.: Researches on the nervous mechanisms underlying deep sleep in the cat. *Arch. Ital. Biol.*: 99, 270-292, 1961.
- Samson, D. C.; Swisher, S. M.; Christian, R. M.; Engel, G. L.: Cerebral metabolic disturbance and delirium in pernicious anemia. *Arch. Int. Med.*: 1952, 90, 4-14.
- Schwab, R.: EEG in clinical practice: W. B. Saunders Co. Philadelphia - London 1951.
- Sherlock, S.: Altered consciousness in liver failure (hepatic precoma and coma) I^o *Congres Int. des Sciences Neurol. Réunions plénières: Rapport et discussion II*, pp. 115-133. *Acta Medica Belgica*, Bruxelles, 1957.
- Strauss, H.; Ostow, M.; Greenstein, L.: Diagnostic electroencephalography. Grune a. Stratton, New York, 1952.
- Talbot, D. R.: Electroencephalographic evidence of barbiturate poisoning damage to the central nervous system. *EEG. Clin. Neurophysiol.*: 1952, 4, 112.
- Vinoles, J. J.; Rabelo, C.; Fuster, B.; Bogacz, J.: EEG. changes during hyperpnoea. *EEG Clin. Neurophysiol.*: 1956, 8, 152.
- Weniland, W. L.; Weiland, G.: Über elektroencephalographische Beobachtungen beim Insulin Shock. *Arch. f. Psych. und Nervenkr.* 1949, 83, 34-44.
- Wyke, B. D.: Brain function and blood sugar: observations based on a case of islet cell adenoma of the pancreas. *EEG Clin. Neurophysiol.*: 1952, 4, 339-350.
- Ziegler, D. K.; Presthus, J.: Normal electroencephalogram at deep levels of hypoglycemia. *EEG Clin. Neurophysiol.*: 1957, 9, 523-526.

Réactivité du Tracé E.E.G. dans le Coma

par Dr. FISCHGOLD

Hopital de la Pitié - Paris.

INTRODUCTION

De 1946 à 1959 l'auteur de ces lignes s'est intéressé aux comas, en tant que clinicien et électro-encéphalographiste(5, 6, 7, 10); des difficultés d'ordre médico-légal, ne lui ont permis qu'exceptionnellement les contrôles anatomiques requis.

D'une première période (Hôpital Ste Anne, 1945-1951), en collaboration avec Madame Lairy, s'est dégagée la notion de *primauté de la réactivité* dans la séméiologie E.E.G. des comas; il s'agissait uniquement de comas aigus post-traumatiques(5).

Au cours d'une seconde période (Hôpital de La Pitié, 1952-1959) avec la collaboration de P. Mathis et Madame G. Arfel, le tracé E.E.G. a été complété par la polygraphie cardio-respiratoire, toujours sur des traumatisés de la tête.

Mais après 1950, les progrès de la réanimation et de l'assistance neuro-respiratoire, ont permis l'étude de nouveaux types de malades: *comas de plus en plus prolongés*, se transformant en états vigiles purement végétatifs, maintenus en vie pendant des mois et des années; *régressions psychomotrices*(7) post-comateuses avec retour du cycle veille-sommeil (Docteurs Gerbeaux et Vermeil); enfin *comas dépassés* (P. Mollaret et M. Goulon(16)).

Depuis 1959, avec le départ de notre collaborateur et ami P. Mathis, nos recherches ont dévié sur le sommeil de nuit, avec la collaboration de B. A. Schwartz et G. Guilbaud.

Entre temps, les recherches cliniques et électrographiques dans les altérations neurologiques de la conscience n'ont fait que

se développer; en plus à partir de 1950, nous sentons tous une vigoureuse impulsion neuro-physiologique de la part de F. Bremer, G. Moruzzi et H. Magoun, P. Dell et Coll., G. Moruzzi et Coll., et celle plus récente de M. Jouvet.

Une journée entière a été consacrée aux *"Etats de conscience en Neurologie"*, sous la Direction de Sir Goeffrey Jefferson, à l'occasion du Premier Congrès International des Sciences Neurologiques(11).

Les contributions de Sabina Strich, Sheila Sherlock, R. Orthner ont apporté une notion neuro-pathologique importante, celle de la *dégénérescence de la substance blanche*, dans les *prolongements des comas traumatiques*.

A Rome, au VII^e Congrès International de Neurologie(1), sous l'optique nouvelle de la *Neuro-Chimie*, neuf rapports (S. Okinaka, Nayrac, Bickford, Rohmer et Kurtz, Waelsh et Coll., Geiger, Dastur, Posner, Bogacz) reprisent l'Encéphalopathie Hépatique, tandis que 12 rapports(1) (Bodechtel, Steegmann, Schneider, Quastel, Ketty, Bernsmeier, Fazio, Gastaut, Krump, Loeb et Coll., Goulon, Christophe et Coll., Krump, Meyer et Coll.) traitèrent l'Encéphalopathie Anoxique aiguë ou chronique, d'origine cardiaque, respiratoire ou cérébrovasculaire.

En France, simultanément aux recherches de l'Hôpital Ste Anne et de l'Hôpital de La Pitié, plusieurs Centres Neurologiques-Neuro-Chirurgicaux ou de Réanimation se sont orientés vers l'étude et le traitement des Comas; au Centre de Réanimation Neuro-Respiratoire de l'Hôpital Claude-Bernard, P. Mollaret, M. Goulon et Madame

P. Christophe ont dégagé et approfondi le syndrome de "coma dépassé", ainsi que les conséquences de l'anoxie d'origine cardio-respiratoire sur l'encéphale(16, 1).

A Lyon, sous la direction de MM. Wertheimer, Dechaume et Juvet*, l'encéphalopathie post-traumatique a été repensée sous le double angle anatomo-pathologique et neuro-physiologique(4, 8, 18, 19, 20).

Enfin, nous avons suivi de près les travaux dirigés par Madame G. Arfel, MM. Brion et Vourc'h dans le Service de Réanimation du C.M.C. Foch sur les comas anoxiques(15).

Cette énumération très incomplète montre l'intérêt suscité au cours des 10 dernières années par les états comateux et l'optique dans laquelle nous allons reconsidérer nos propos antérieurs.

LE TRACE DE COMA

Dans l'ouvrage publié en 1959 avec Mathis(7), nous faisons état de 155 malades, dont 67 d'étiologie traumatique; la séméiologie électro-encéphalographique des états d'obnubilation, de coma et de stupeur nous paraissait alors relativement indépendante de l'étiologie (l'intoxication barbiturique mise à part).

Mais, à la lumière de recherches pratiquées dans d'autres laboratoires, sur des malades d'étiologie non traumatique, des pathogénies multiples nous ont paru impliquer des mécanismes physiologiques distincts et des lésions anatomiques différentes.

La fig. 1 montre un échantillonnage de 70 tracés E.E.G., qui va du tracé "nul" du coma dépassé, au tracé ample, lent, monotone et polymorphe du coma carus; du tracé composé de figures épileptiques, aux rythmes monomorphes et aux activités alpha (8-12 c/s) ou rapides (14-20 c/s) d'allure presque normale; la relation entre le tracé et l'état de conscience, étroite dans certains cas, se relâche dans d'autres.

C'est ainsi que Röhmer et Kurtz, ont montré dans leur rapport de Rome(1) que

l'hyperamoniémie artérielle et veineuse constitue un chaînon important dans l'éclosion du coma hépatique; hyperamoniémie en relation étroite avec les modifications électro-encéphalographiques; mais l'hyperamoniémie aussi bien que les anomalies du tracé E.E.G. *précèdent et peuvent suivre* les troubles neuro-psychiques. L'E.E.G., dans ce cas, n'est qu'à titre transitoire, en liaison avec l'état de conscience. Dans les comas hépatiques, le facteur endogène, autotoxique, agit sur l'encéphale, même en dehors de toute modification de la conscience; et d'après Bogacz et Coll.(3), 88 sur 121 malades atteints d'insuffisance hépatique, montraient des tracés altérés, avec une conscience apparemment non altérée.

D'autre part le mécanisme toxique rend probable une imprégnation identique des 2 hémisphères et des structures modulatrices tandis que le choc traumatique réalise des points d'impact étendus, asymétriques, variables et inégaux, selon les circonstances physiques de l'accident et l'état cérébral du sujet.

Dans les observations de Loeb(12, 13) l'étiologie vasculaire des comas favorise des lésions plus localisées, avec anomalies électro-encéphalographiques unilatérales (7 cas sur 25) ou focales (3 cas sur 25). Or, c'est justement Loeb qui a relevé dans ses observations de comas, nombre de tracés normaux ou à la limite de la normale.

Et ce n'est pas par pur hasard que nous nous trouvons en accord étroit avec le groupe de Lyon et les constatations de M. Trillet(19), sur des observations d'encéphalopathies post-traumatiques déterminées et traitées dans des conditions identiques aux nôtres.

La confrontation des tracés de comateux d'étiologie différente, l'examen anatomique des pièces, le bilan neurochimique et endocrinien, donnent aux différentes catégories de comateux un cachet particulier.

Enfin, du point de vue E.E.G., il y a lieu d'avoir présentes à l'esprit les conditions physiques de l'enregistrement: les électrodes appliquées sur le scalp enregistrent surtout les "*activités de la convexité des hémisphères*"; les faces internes et inférieures, avec les circonvolutions si importantes de

* Un neuro-chirurgien, un neurologue et un neurophysiologiste.

l'hippocampe et du système limbique, ont peu de chance de se faire entendre au niveau du scalp; l'activité du tronc cérébral et de ses noyaux échappe totalement. Seul, M. Jouvét a utilisé des électrodes profondes dans les comas dépassés, pour vérifier la mort du tissu nerveux ou enregistrer des activités non perçues sur le scalp(19).

COMA et SOMMEIL

Avant de discuter la réactivité du tracé E.E.G., nous allons revenir sur les relations du sommeil et du coma.

Certains neurophysiologistes ont identifié les perturbations déterminées sur l'animal par section, ablation ou destruction dans l'encéphale, aux comas pathologiques ou au sommeil physiologique; des cliniciens ont en retour considéré les comas comme des hyper- ou para-somnies.

Nous pensons qu'une analyse plus aiguë, incite plutôt à démembrer le groupement des hypersomnies qu'à réunir des conditions expérimentales, physiologiques, pharmacologiques et pathologiques si diverses.

Les troubles du comportement, déterminés sur l'animal au laboratoire sont multiples, selon que l'acte expérimental réalise des lésions hautes ou basses étendues ou localisées; également suivant que des lésions plus ou moins extensives sont réalisées, d'emblée ou par interventions successives.

Du cortex au bulbe, avec une prédilection pour le di- et le mésencéphale, la veille et le sommeil se trouvent modulés, déclenchés ou favorisés par la manipulation de nombreuses formations: certains aires corticales, noyaux thalamiques ou di-encéphaliques, formation réticulée, tectum mésencéphalique, noyaux réticulaires de la protubérance, corps mamilaires, faisceau solitaire du bulbe; s'y ajoutent des formations extracérébrales, comme les IX et Xe paires, le sinus carotidien les analyseurs sensoriels (Ie, IIe et Ve).

D'où l'impression que la suppression brusque de certaines afférences ou convergences, implique des modifications du comportement vigile, en relation avec l'étendue

des lésions pathologiques ou expérimentales plus qu'avec la formation limitée intéressée.

En plus, qu'il s'agisse du cycle veille-sommeil, de fonctions motrices, alimentaires ou autres, si l'animal reste en vie, après la mutilation expérimentale, le déficit fonctionnel tend à s'effacer au fur et à mesure qu'on s'éloigne du moment de la destruction aiguë.

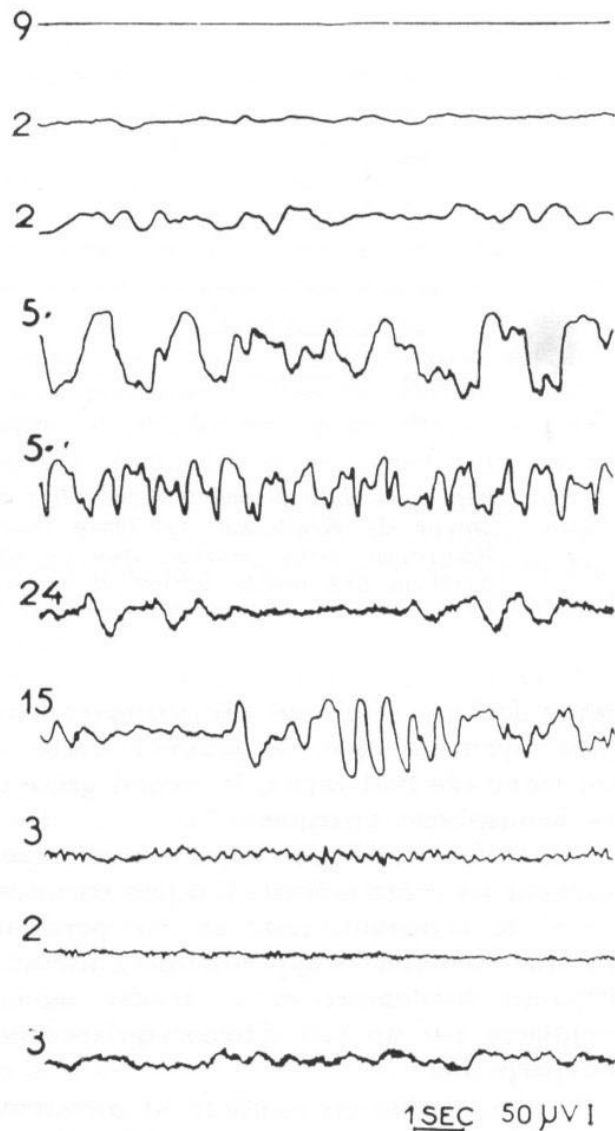


Fig. 1. — Toutes les figures électriques sont visibles dans le coma; sur 70 tracés (dérivations fronto-rolandiques, à l'exception de l'avant-dernier). Sur 70 tracés, il y en a 5 qui comme morphologie, rappellent le stade de sommeil des mouvements oculaires ou sommeil "rapide" de Jouvét.

Pour le cycle veille-sommeil, les systèmes qui interviennent dans sa régulation paraissent particulièrement étendus et résistants à l'agression; de sorte que dans ce domaine, la durée de survie paraît particulièrement importante pour distinguer l'effet aigu du choc expérimental du déficit résiduel.

Et, il suffit de maintenir en vie, l'animal un temps assez long pour que l'hypermnie s'atténue ou disparaisse: le chien sans hémisphères de Goltz ou le chien avec d'énormes destructions di- et mésencépha-

L'hypermnie comportementale avec les yeux fermés n'est que le symptôme transitoire d'un syndrome comateux qui perturbe la vie végétative et anéantit la vie mentale du sujet.

Du point de vue biologique, l'hypermnie du comateux se distingue du sommeil, *parce qu'elle se continue jour et nuit*; le sommeil physiologique satisfait un besoin de repos pendant la nuit et cesse de lui-même une fois ce besoin satisfait; l'hypermnie du coma aigu reste sans relation étroite avec le jour et la nuit, et comme

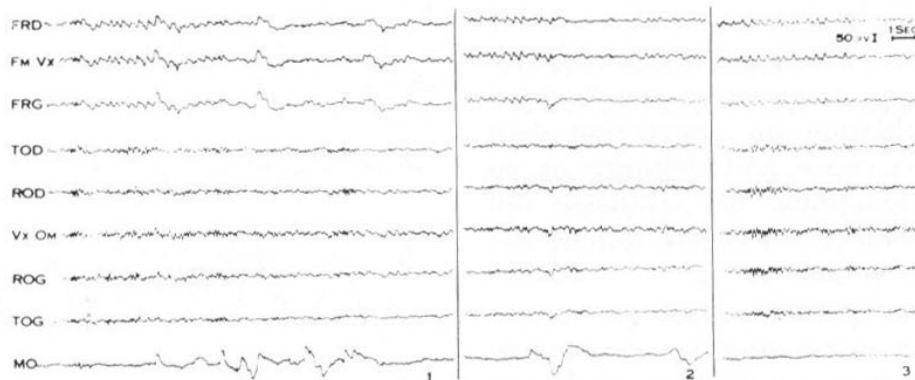


Fig. 2. — Les 8 tracés supérieurs montrent le stade des mouvements oculaires de Kleitman; le 9ème inscrit les mouvements oculaires. Comme Kleitman, nous pensons que ce stade est caractérisé surtout par la disparition des ondes lentes et sa situation intermédiaire entre les cycles; les mouvements oculaires peuvent manquer.

liques de Sager, finissent par retrouver leur cycle hychémérique, le premier grâce à son tronc cérébral intact, le second grâce à ses hémisphères épargnées(7).

Ainsi les recherches expérimentales rejoignent les constatations cliniques récentes, car si le comateux reste en vie pendant quelques semaines l'hypermnie s'atténue, disparaît totalement et se trouve même remplacée par un état d'hypervigilance ou d'hyperpathie.

La réanimation en assurant au comateux une respiration, une tension artérielle et certains métabolismes essentiels, prolonge sa vie et permet d'arriver à un stade où l'hypermnie se dissipe et la vie végétative se regularise; pourtant le cerveau a considérablement souffert et les retours à la normale après ces prolongements du coma restent exceptionnels.

on peut le voir dans les obnubilations prolongées sans effet réparateur sur l'organisme.

Du point de vue électrique, les différences l'emportent sur les ressemblances et le tracé du coma ne se recoupe que dans certaines conditions, avec celui du sommeil.

Au stade I du coma ou de l'obnubilation, le tracé n'est ni celui du stade A ni celui du stade B de sommeil; les bouffées monomorphes frontales, rappellent plutôt le sommeil de l'enfant que celui de l'adulte.

Au stade III du coma, le tracé est lent comme dans le sommeil profond D et E; mais il est monotone pendant des heures; tandis que dans le sommeil physiologique, les figures très lentes sont soumises à des modifications continues, qui apparaissent et disparaissent selon les fluctuations de la profondeur.

Enfin, il est peu probable qu'on trouve dans le coma aigu, quelle que soit sa profondeur, ce stade particulier de sommeil, caractérisé par une activité E.E.G. de l'ordre du rythme alpha, peu ample, accompagnée de mouvements oculaires; à moins, comme nous allons le préciser plus loin, qu'on fasse les vérifications exigées par Juvet, qui le premier s'attaque à cet aspect du coma.

Or, c'est ce stade de sommeil (période des rêves de Kleitman; sommeil rhombencéphalique rapide de Juvet), qui imprime au sommeil de nuit son découpage en cycles si particulier à l'homme (fig. 2).

L'enregistrement prolongé de nuit dans des salles d'hôpital silencieuses, des comas aigus, vaut la peine d'être fait, malgré des difficultés signalées avec raison par Pellin(18).

Pellin(18) a d'ailleurs publié une observation d'enregistrement prolongé de nuit dans le coma:

—Un garçon de 14 ans, fait une chute de bicyclette avec traumatisme crânien et perte de connaissance immédiate; il est enregistré le 26^e jour, pendant toute la nuit. Sur ce premier tracé, pratiqué à l'état de coma aigu, on enregistre un rythme de base de 3-4 c/s avec quelques ondes de 1-4 c/s en avant; le tracé reste identique pendant six heures; l'activité électro-myographique du biceps est toujours présente; *les cycles du sommeil de nuit ont donc disparu.*

Après ce premier enregistrement, on évacue un hématome sousdural et (60 jours après) on pratique un nouvel enregistrement de nuit; d'emblée on constate "la disparition de la monotonie du tracé de nuit"; même le rythme de veille anormal de 5 c/s sur la région postérieure du crâne, subit la modulation des cycles de Kleitman; cinq fois, entre 19 heures et 3 heures du matin, le rythme de base ample et lent du sommeil s'aplatit, avec fuseaux de 12-13 c/s en avant et une activité de 5 c/s régulière en arrière; en ces moments s'inscrivent, en plus des mouvements rapides des globes oculaires, une respiration accélérée, un rythme cardiaque ralenti, surtout *l'activité électromyographique cesse.*

Cette phase appelée par Juvet "rhombencéphalique" des mouvements oculaires

qui sépare les cycles, occupe 25 % de la durée de la nuit de sommeil; c'est la présence intermittente de cette phase qui permet dans le cas de Pellin, d'affirmer que l'hypersomnie du traumatisé, se rapproche du sommeil physiologique.

Enfin, dans un tout dernier travail; Juvet apporte une contribution décisive à la dissociation des comas et du sommeil: selon ses recherches, le syndrome de décortication (triple flexion des membres supérieurs, hyperextension des membres inférieurs) dû aux lésions de la substance blanche hémisphérique s'accompagne de périodes de sommeil à ondes "rapides" rhombencéphaliques; ces périodes occupent 20 à 25 % du cycle nyctéméral et se caractérisent par des mouvements oculaires rapides, une disparition du tonus musculaire des biceps et des variations cardio-respiratoires. Par contre dans le syndrome de *décérébration* (avec membres supérieurs et inférieurs en hyperextension) et yeux ouverts, avec lésion de la formation réticulaire pontique, et mésencéphalique postérieure au niveau du noyau rouge, la contracture du biceps ne se relâche que pendant 2 % de la durée des enregistrements.

Sur le malade décérébré le sommeil comportemental et la période des mouvements oculaires rapides ont donc pratiquement disparu.

S'il y a plusieurs types et degrés de comas, nous connaissons au moins deux mécanismes inhibiteurs du système d'éveil responsables de deux types de sommeil:

—le sommeil connu depuis les premières recherches de Loomis et Davis, appelé par M. Juvet(8) le sommeil "lent"; il nécessite la présence du cortex hémisphérique.

—les périodes décrites par Kleitman comme celles des "rêves et des mouvements oculaires", par Juvet comme "phase rhomboïde" ou sommeil "rapide"; ce type de tracé caractérisé chez l'homme par des fréquences alpha ou thêta aplaties, voisin du tracé de veille, est accompagné de mouvements oculaires et de la suspension de toute activité musculaire; il nécessite selon Juvet l'intégrité de la région mésencéphalique et de la protubérance, car il disparaît si le noyau réticulaire pontique postérieur est détruit. Cette phase rhombencéphalique

nécessite pour se manifester un système différent de la F.R.A.A. et du cortex convexe des hémisphères; il s'agit du "Limbic Mid Brain Circuit" de Brodal et Kaada qui relie la protubérance à l'hippocampe (fig. 3).

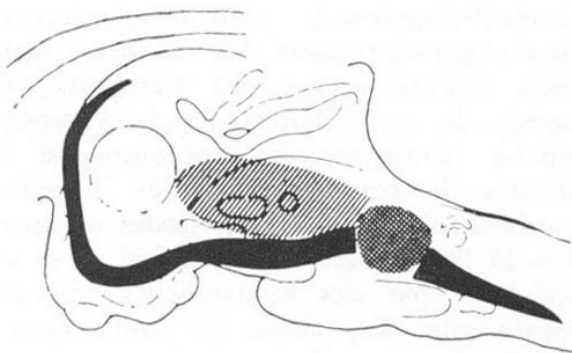


Fig. 3. — Schéma de M. Jouvét; en pointillé noyau RPC (réticulo-ponto-caudal), centre déclenchant de la phase de sommeil rapide (fig. 2); en hachure partie rostrale de la FRAA; en noir: en avant voies ponto-lymbiques, en arrière FR inhibitrice bulbaire.

Carlo Loeb(13), déjà cité, a pu localiser des lésions vasculaires dans le tronc cérébral des comateux, tout en reconnaissant qu'il serait "trop beau" de trouver dans le tronc cérébral de l'homme des lésions comparables à celles produites au laboratoire.

Ce fut peut-être le cas de Kaada et Cool. (9) qui trouvent dans un coma par lésion vasculaire, un tracé rapide de bas voltage, sans ondes lentes authentiques et *aréactif*; l'examen anatomique leur a montré les lésions les plus sévères dans la protubérance, tandis que la jonction ponto-mésencéphalique paraissait épargnée.

Kaada identifie pour son malade le tracé "plat et rapide" à celui recueilli par Battini et Coll.(2) sur la préparation "médiopontine prétrigéminal" et rapporte l'absence des ondes lentes à la destruction des structures synchronisantes qui, selon les mêmes auteurs, siègent dans l'extrémité caudale du tronc.

Une telle assimilation ne va pas sans inconvénients; car les chats médiopontins prétrigéminaux sont plus éveillés que les

autres; c'est pas le cas du comateux de Kaada, qui en plus, ne réagit pas aux stimuli...

Pellin a fait état dans sa thèse de 6 malades examinés au cours d'états prolongés post-comateux (26 jours, 3 ans, 7 mois, plus d'un an, 2 mois 1/2, durée non indiquée).

Grâce à l'enregistrement électromyographique, introduit par Jouvét dans l'exploration du sommeil et du coma Pellin constate que ces malades décortiqués ou décérébrés, avec lésions du néo-cortex, de la substance blanche ou du tronc cérébral, peuvent montrer un état effectif "d'hypervigilance" comme nous l'avons indiqué nous-mêmes(7).

Sur de tels malades, les cycles ou la périodicité du sommeil se laisse reconnaître par électromyographie, grâce au silence électrique des muscles de la nuque ou du bras; le sommeil rhombencéphalique ou rapide dure plus ou moins longtemps, selon que les systèmes qui le commandent ont récupéré ou non leurs possibilités fonctionnelles.

De telles observations prouvent également qu'au cours de la période prolongée post-comateuse, le sommeil revient, mais avec une répartition temporelle encore différente de celle du nyctémère normal.

Les rapports du coma et du sommeil apparaissent donc très différents, selon qu'on examine le malade à l'état aigu ou chronique; l'existence d'un sommeil rapide ou "rhombencéphalique" est en train de modifier nos techniques d'étude du coma et nos interprétations du tracé:

—l'électromyographie préconisée par Jouvét, devrait s'incorporer dans l'étude polygraphique des états comateux ou des prolongements chroniques du coma;

—les tracés rapides dans les comas aigus, méritent d'être reconsidérés à leur tour; correspondent-ils au ménagement lésionnel du pôle antérieur du mésencéphale (préparation médiopontine prétrigéminal) ou à un système réticulo-protubérantiell-lymbique épargné par la lésion?

Si on juge certains tracés rapides publiés par Loeb, *avec réaction d'arrêt*, une lésion médio-pontine prétrigéminalisée devient possible; si par contre le tracé rapide ne

montre pas de réactivité, il y aurait lieu de l'identifier au sommeil rapide rhombencéphalique-limbique de Jouvét, avec son élévation considérable du seuil.

—Enfin, posons une dernière question: existe-t-il des rêves dans les états comateux? Si les mouvements rapides oculaires étaient obligatoirement la traduction d'un état onirique visuel, la réponse serait aisée; mais il est infiniment plus facile "d'interroger" un dormeur qu'un obnubilé; et s'il n'y a pas de rêves, encore existe-t-il dans les comas légers des états hallucinatoires, des illusions ou d'autres troubles du jugement qui rendent la réponse difficile; peut-être pas impossible.

REACTIVITE dans les ETATS COMATEUX AIGUS et POST-COMATEUX CHRONIQUES

En admettant la classification schématique des comas aigus en Stade I (obnubilation), stade II (coma proprement dit) et Stade III (coma carus) le tableau suivant (7), montre que *la réactivité s'efface à mesure que la conscience vigile s'atténue ou disparaît.*

On peut voir que les différents modes de réactivité, disparaissent dans un ordre assez constant:

—quand le coma s'approfondit, le blocage des figures delta monomorphes fron-

tales par stimulation s'atténue, tandis que l'évocation des mêmes figures survoltées sur tracé plat reste encore possible;

—l'éveil des figures delta sur tracé plat, constitue la dernière forme de réactivité, avant que la continuité et la monotonie du coma carus s'installe;

—ces figures delta monomorphes peuvent prendre une allure périodique spontanée, en relation pourtant avec la périodicité respiratoire, dans le coma de profondeur moyenne;

—tant que le coma ne dépasse pas le stade de la simple obnubilation, la réactivité reste présente, à condition de trouver le stimulus approprié, auditif ou de préférence nociceptif;

—la réactivité constitue, plus que la morphologie des ondes, leur amplitude ou leur fréquence, un indice de la profondeur du coma. (Fig. 4, 5, 6, 7 et 8).

Ces conclusions(7) de 1959 restent valables, à condition de leur accorder le sens de probabilité statistique et non de "lois".

Loeb(11, 12) fait quelques réserves à leur sujet, mais il nous semble qu'il leur a accordé une signification plus rigide que nous.

Voyons d'abord le matériel de Loeb; sur 25 comateux, 15 montrent des anomalies E.E.G. diffuses, plus ou moins comparables aux tracés post-traumatiques; les autres 10, accusent des anomalies unilatérales ou en

TABLEAU I

MODALITES DES REACTIONS D'EVEIL dans les COMAS

Stade	Nombre de cas	EVEILS delta monom front.	SUR TRACES thêta alpha + bêta	PLATS + alpha par. occ.	Blocage ou Réaction d'arrêt sur		Corrélations cortico-respiratoires
					delta monomorphe	alpha	
I. Obnubilation	19	13	8	17	11	15	7
II. (Coma)	26	22	13	16	3	5	19
III. (Coma carus)	16	4	1	3	0	0	2

foyer. Or, sur 15 comateux "diffus", un seul avait une réactivité considérée par Loeb comme "minime"; c'était un comateux léger C1 dans la classification de Loeb identique à la nôtre C1, C2, C3); les autres 14 appartenant aux comas plus profonds (C2 et C3) n'avaient pas de réactivité. Sur les 7 cas avec anomalies unilatérales, 5 étaient des comas C2 et sur ces 5, dans 2 cas, la réactivité était minime, dans 3 abolie; enfin le seul coma C3 unilatéral avait également la réactivité abolie.

Mais, du moment qu'il y a contradiction même apparente, c'est qu'on emploie les mêmes termes avec des sens différents, ou que la technique n'est pas la même...

L'atténuation ou la disparition de la réactivité, se retrouvent avec une bonne probabilité dans les comas profonds; mais cette *concordance électro-clinique* ne fournit pas d'éléments pronostiques, si elle n'est

relevée qu'au cours d'un seul enregistrement; la réactivité E.E.G. n'informe que sur l'état fonctionnel du cortex de la convexité et indirectement sur l'efficacité des structures souscorticales de modulation; le cortex de la convexité n'est pas tout l'encéphale et encore moins tout l'organisme.

Et, le pronostic vital est surtout fonction de l'état circulatoire et respiratoire des variations métaboliques ou thermiques.

Enfin, disparition ou retour de la réactivité acquièrent une signification très différente dans un coma aigu ou dans ses prolongements chroniques.

Pour les *comas aigus*, l'étiologie, l'étendue et la réversibilité des lésions dominent le pronostic.

Ainsi sur notre matériel(7), nous avons compté 10 comas aigus avec décérébration; 9 sont décédés, un seul a guéri; mais il s'agissait pour ce dernier d'une intoxication

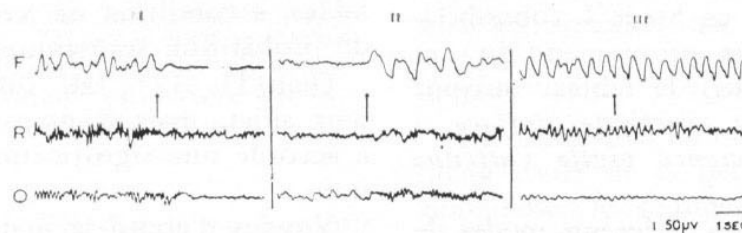


Fig. 4. — Types de réactivité dans le coma aigu: Stade I, aplatissement des figures survoltées antérieures et du rythme alpha; Stade II, apparition d'une figure survoltée en avant et d'un rythme alpha en arrière; Stade III, pas de réactivité.



Fig. 5. — C., 13 ans, coma I après artériographie carotidienne gauche. A. Une heure après: coma léger; bouffées monomorphes apparues après un coup de sifflet; cette réactivité n'existe pas à gauche (côté artériographié); B. 4ème jour; les figures monomorphes deviennent symétriques. C, D et E conscience normale, 8 jours, 2 semaines, 4 mois après; on voit que les figures monomorphes existent même sans trouble de la conscience, mais s'accroissent avant de disparaître. N. Les figures électriques anormales ne sont donc pas liées au coma mais à une lésion en régression; la conscience perturbée constitue la conséquence psychologique de la lésion hémisphérique gauche.

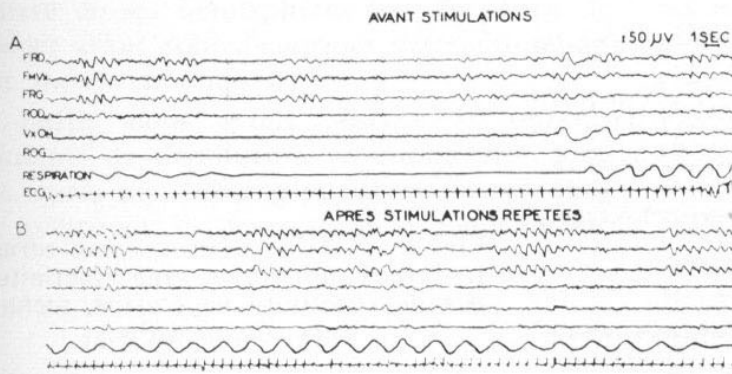


Fig. 6. — D., 69 ans, coma I: hypertension; hémiplegie gauche. A. Respiration périodique, ralentissement du coeur; pendant l'apnée atténuation des figures monomorphes; B. Après stimulations répétées, accélération cardio-respiratoire, activation des bouffées monomorphes.

au gardénal. Malgré l'absence de toute réactivité électrique *au moment de l'enregistrement*, le malade a guéri sans séquelles parce que la substance toxique a pu être éliminée, avant que des perturbations végétatives irréversibles s'installent.

Par contre, parmi les malades décédés, deux avaient conservé une certaine réactivité; les stimuli faisaient apparaître des ondes delta monomorphes et accéléraient la respiration.

Il s'agissait chez le premier d'un anévrisme intra-crânien, chez le second d'une encéphalite, affections qui se sont terminées par mort, du fait des lésions qu'elles ont entraînées.

Parmi les 10 comas aigus par encéphalopathie anoxique de Mirallié(15), nous retenons trois, pour discussion:

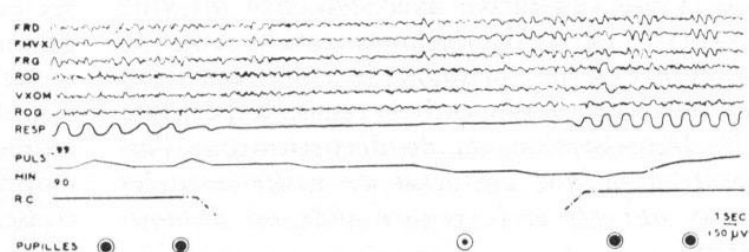
—pour le premier, il s'agit d'un arrêt cardiaque brutal au cours d'une pneumectomie; les battements cardiaques reprennent après massage du coeur et le malade entre dans un coma de stade III avec polypnée marquée et hypertonie de décortication. Les 2 premiers jours, le tracé ne montre aucune réactivité; le 3e jour, la réactivité commence à revenir, mais le 7e jour, le malade meurt brusquement. A l'autopsie on trouve une énorme thrombose de l'artère pulmo-

naire; le retour de la réactivité témoignait d'une amélioration fonctionnelle au niveau du Système Nerveux Central, tandis que l'embolus pulmonaire évoluait pour son propre compte, avec ses graves conséquences.

—La seconde observation concerne un coma anoxique après obstruction bronchique, due à l'inhalation de matières vomies durant la nuit; le coma III initial, est suivi d'une inconscience prolongée avec décès au 47e. jour; la réactivité réapparaît au 14e. jour et reste présente jusqu'à la fin; mais le pronostic vital se préparait au niveau des poumons;

—plus significative est la troisième observation publiée et par nous(7), et par Mirallié. Il s'agit d'un arrêt cardiaque d'environ 5 minutes au cours d'une intervention sur la moelle cervico-dorsale. La malade montre un tracé nul, 15 minutes après la syncope et se trouve en inconscience complète avec aréflexie et paroxysmes de contracture. A partir du 4e jour, les réflexes reviennent, la malade ouvre les yeux, comprend et exécute les ordres, mais ne sait plus parler; l'activité delta et thêta revient à son tour, et la réaction d'arrêt s'ébauche. Les jours suivants, l'état neurologique continue à s'améliorer et la malade écrit lisi-

Fig. 7. — L. R., 62 ans, coma II, corrélations entre l'activité monomorphe, l'apnée, la bradycardie et la pupille; la réduction de l'activité monomorphe s'accompagne d'apnée, bradycardie, myosis et disparition du réflexe cornéen.



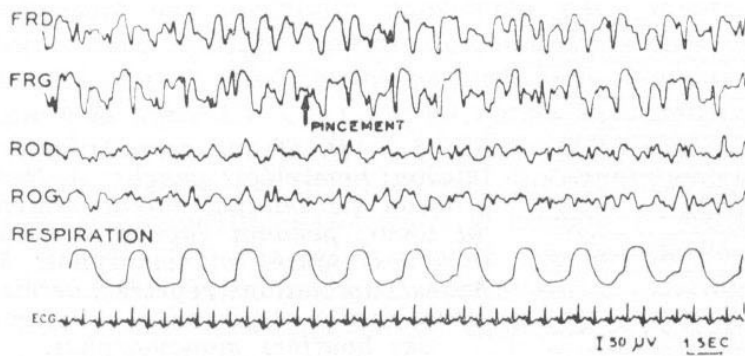


Fig. 8. — Z. W., 42 ans, coma carus III; tracé monotone, sans réactivité; pas de réactivité végétative; tachypnée, tachycardie.

blement sur une ardoise; son tracé devient presque normal avec une bonne réaction d'arrêt. (Fig. 9).

Mais pendant que les suites de l'accident anoxique s'effacent et qu'elle récupère un E.E.G. normal, la malade fait une localisation pulmonaire fébrile et meurt brusquement le 12e. jour.

A l'autopsie on constate des lésions pulmonaires congestives et une compression médullaire brutale au niveau de C7-D1.

Dans ces cas de comas aigus allant jusqu'à l'aréflexie totale, l'absence de réactivité du tracé est quasi constante au stade initial.

Si le malade reste en vie pendant quelque temps, on peut assister à l'allègement du coma, à la réapparition des réflexes céphaliques, au retour d'un tracé normal et de la réactivité E.E.G.

La normalisation du tracé et la réapparition de la réactivité électrique, constituent dans l'immédiat un bon signe de récupération cérébrale.

Néanmoins, le pronostic vital de ces malades dépend également de leur état cardiopulmonaire.

Dans les *prolongements chroniques des comas*, connus sous les noms d'inconscience prolongée, syndrome apalique, complexe anoétique, stupeur hypertonique, il s'agit presque toujours d'une encéphalopathie post-traumatique ou anoxique(19); ces états se caractérisent par la régularisation de la vie végétative avec démence ou "vide mental" perte de communication avec le monde externe, manque de compréhension et d'exécution des ordres reçus, hypertonie de décérébration ou de décortication; *l'aspect somatique est celui de veille avec les yeux ouverts et le regard vide ou douloureux.*

Chez ces malades, l'hypersomnie du coma a totalement disparu pour faire place quelquefois à une hypervigilance; il faut guetter des heures pour surprendre une courte période de chute des paupières — facilement obtenue par une injection de nembutal.

Du point de vue histologique, ces malades montrent presque régulièrement une dégénérescence diffuse de la substance blanche sous-corticale avec respect relatif du cortex; décrite par Mme S. Strich(11) et confirmée par M. Trillet(19), cette lésion explique mieux qu'une atteinte de la FRAA, rarement constatée et le "vide mental" de ces malades et leur décortication.

Par ailleurs, certains de ces malades (2 sur 9 dans notre série) montrent après allègement de l'hypersomnie, une réaction d'arrêt qui manquait au moment du coma(7).

Lundervolt(1) dans une observation bien connue, avait signalé le retour de la réaction d'arrêt 15 mois après l'accident anoxique suivi de coma initial.

De même, sur 5 cas d'encéphalopathie anoxique, Trillet(19) vit réapparaître la réactivité 3 fois, il s'agissait d'une réactivité faible ou recueillie sur des électrodes profondes.

Dans ces observations, la réactivité revient tard, à une période où l'hypersomnie et les troubles végétatifs se sont dissipés; certains secteurs du système modulateur de la vigilance, ayant échappé à la destruction aiguë récupèrent leurs fonctions ou se font remplacer par des éléments épargnés au moment du coma initial; ainsi arrive à se maintenir cette *conscience fruste* (crude consciousness de Cairns), qui rappelle la période de récupération du chien de Goltz

privé de ses hémisphères, ou du chien de Sager ayant subi d'énormes destructions di- et mésencéphaliques.

Enfin, nous avons observé 10 enfants atteints de dissolution psychomotrice totale, après une méningite tuberculeuse; deux à quatre ans et demi après le coma initial,

ces enfants stupides et calmes, sans aucune possibilité de contact parlé, compréhension visuelle ou auditive, ont récupéré un rythme nyctéméral normal. Réveillés le matin, ils ouvrent les yeux; ils dorment la nuit avec les yeux fermés.

Quelques-uns de ces malades présentent une réactivité électrique incontestable (fig. 10); cette réactivité ne s'accompagne d'aucune récupération psychomotrice, mais le retour du nyctémère et des fonctions viscérales, leur permet de survivre, à condition qu'ils soient alimentés à la sonde, qu'on leur évite les escarres par un nettoyage et un entretien continu de la peau.

Dans ces cas, le retour de la réactivité s'insère dans un *bon pronostic vital* et dans un *misérable pronostic fonctionnel*.

La réactivité aux stimuli externes et ses diverses modalités ne reste donc pas identique le long des semaines ou des mois; son absence ou sa présence, à l'occasion d'un seul enregistrement, constituent un indice de profondeur du coma pour le moment de l'enregistrement; mais pas pour toute la durée du coma.

A ces considérations d'ordre temporaire et évolutif, nous devons ajouter un dernier aspect: la réactivité peut s'exercer sur un territoire et être abolie sur un autre, au cours du même examen.

Tel fut le cas chez certains malades de Loeb, à lésions vasculaires hémisphériques unilatérales.

La réactivité du tracé E.E.G. constitue donc un indice, soumis à de nombreuses variantes quantitatives ou qualitatives, temporelles ou topographiques; ce n'est pas une réponse globale de l'organisme; car pendant que le cerveau récupère, des accidents cardio-pulmonaires peuvent contre-carrer et réduire à néant la récupération du cerveau.

Enfin, la *réactivité du tracé E.E.G. ne constitue qu'un des facteurs de la réactivité générale*. Dechaume et Juvet (20), distinguent dans les troubles prolongés de la conscience: une perception de degrés différents (P); une réactivité (R) aspécifique (réflexe d'orientation et réaction d'éveil); une réactivité mimique à la douleur (D);

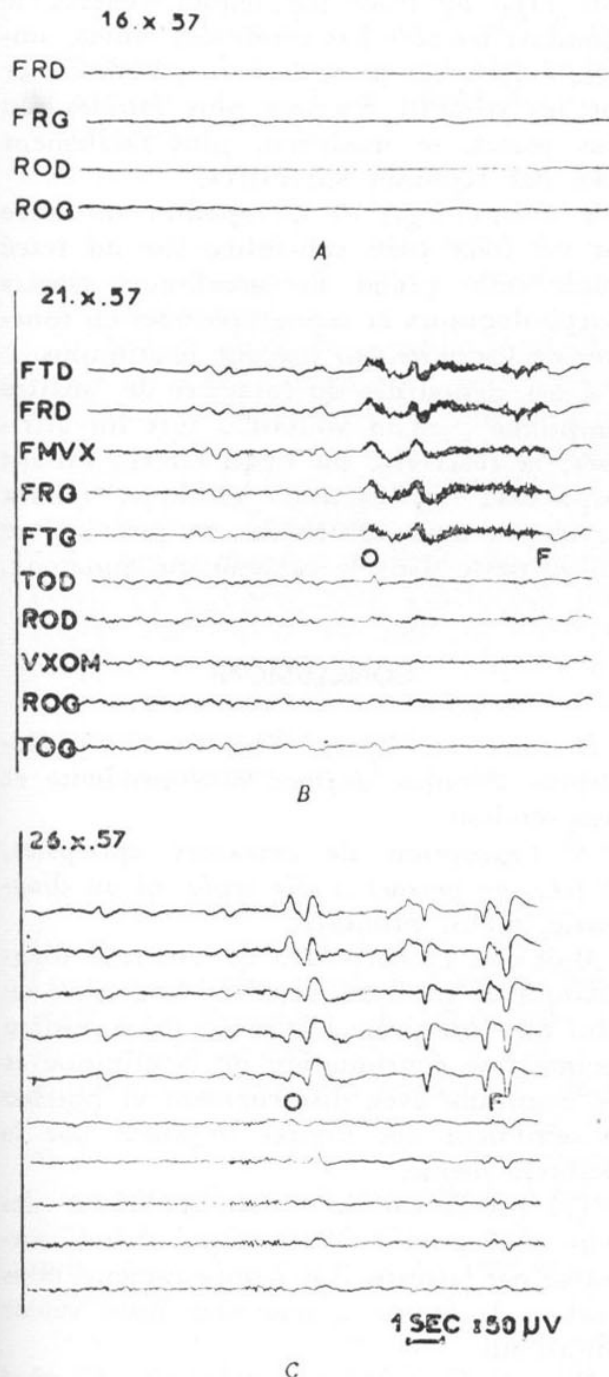


Fig. 9. — H., 57 ans, Syncope péroopératoire. A. Un quart d'heure après, tracé nul. B. 10 jour après, retour d'un EEG normal, avec réaction d'arrêt.

une réactivité végétative (V), dans laquelle le stimulus noci-ceptif entraîne des modifications du rythme cardiaque ou respiratoire.

Les auteurs lyonnais, notent leurs malades avec des lettres et des numéros croissants (P 1, P 2, P 3, P 4, P 5; R 1, R 2, R 3; D 1, D 3, D 4; V 1 et V 2) selon que la perception ou les différentes réactivités se dégradent.

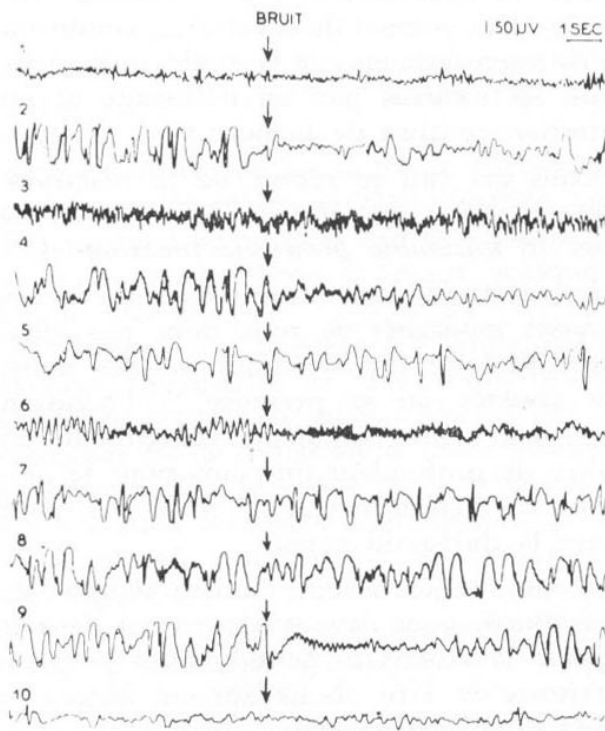


Fig. 10. — Tracés de 10 enfants atteints de dissolution psycho-motrice après comas dus à une méningite bacillaire; deux à quatre ans après le coma aigu, tous dorment la nuit et se réveillent le matin. En 2, 4 et 6, la réactivité est revenue, malgré le déficit neurologique et psychique total.

Cette notation facilite une séméiologie précise, une comparaison des examens d'un jour à l'autre et la constitution de courbes évolutives.

En cherchant la réactivité électrique de la convexité hémisphérique, telle qu'elle se laisse enregistrer sur le cuir chevelu, nous employons les mêmes stimuli que les cliniciens; la réponse, par contre, est particulière, car elle provient directement de la convexité des hémisphères, sans l'intermédiaire d'un effecteur périphérique.

En suivant l'école lyonnaise, nous devrions à notre tour, mieux définir les stimuli employés; pour toute réactivité, il y aura lieu de noter:

—la *nature du stimulus* sensoriel ou noci-ceptif; *son intensité*; *sa répétition*; *son contenu significatif*; il ne suffit pas de constater que le tracé du comateux est réactif, encore faut-il savoir à *quoi il réagit*;

—le *type de tracé* sur lequel s'exerce le stimulus; les activités cérébrales lentes, amples, monotones ne se laissent pas modifier par les stimuli; d'autres plus rapides, ou plus plates, se modifient plus facilement avec des réponses survoltées;

—la *morphologie de la réponse*: survoltée sur un tracé plat, sub-voltée sur un tracé ample, elle prend de nombreux aspects morphologiques et topographiques en fonction de l'activité qui précède le stimulus.

Ainsi, dépouillée du caractère de "maître symptôme", qu'on voulait à tort lui attribuer, la réactivité du tracé E.E.G., faisant corps avec la réactivité clinique, rendra service en nous informant un peu, sur ce qui se passe dans le cerveau du comateux.

CONCLUSION

D'année en année, l'Electro-Encéphalographie clinique devient plus prudente et plus modeste.

A l'exception de certaines épilepsies, l'E.E.G. ne permet à *elle seule*, ni un diagnostic, ni un pronostic.

Mais elle s'incorpore à la démarche diagnostique et pronostique, dans la mesure où celui qui interprète les tracés, les considère comme une continuation de la clinique et les manipule avec discernement et possède le sentiment des limites imposées par la méthode même.

Tel fut le cas de l'examen E.E.G. des états comateux: sous-estimé au début, sur-évalué par la suite, il se trouve ramené, nous voulons le croire, à une plus juste valeur aujourd'hui.

En ce qui concerne la réactivité du tracé E.E.G., sans faire de sa présence un signe de bon pronostic vital, nous pensons qu'il vaut mieux pour un comateux de réagir aux stimuli, que de ne pas réagir...

R É S U M É

1. L'auteur a exposé ses constatations sur les comas en 1957 au Congrès International des Sciences Neurologiques de Bruxelles et deux ans plus tard dans "Obnubilations, comas et stupeurs" publié en collaboration avec P. Mathis.

Deux notions se sont dégagées de ces travaux poursuivis depuis 1945:

—la réactivité d'un tracé E.E.G. de coma a plus de valeur que le type des rythmes, la morphologie et la fréquence des figures électriques;

—le coma ne se réduit pas à une hypersomnie; c'est une perturbation grave de la vie du cerveau et de l'organisme accompagnée à l'état aigu de signes comportementaux de sommeil.

2. Malgré quelques objections, la réapparition de la réactivité E.E.G. reste un indice favorable de récupération cérébrale à condition qu'il n'y ait pas des complications cardio-pulmonaires ou d'autres viscères qui assombrissent l'évolution.

3. Les recherches récentes de l'école de Lyon, développées sous l'influence de P. Jouvét confirment en tout la distinction proposée entre le sommeil physiologique et les différents états comateux ou leurs prolongements chroniques.

Les cliniciens de Lyon ont constaté

comme nous que l'hypersomnie —symptôme passager du coma aigu— peut se transformer dans un état particulier d'hypervieille si le malade est maintenu en vie.

4. En enregistrant l'électromyogramme des muscles fléchisseurs et en considérant le tonus musculaire en relation avec le tracé E.E.G. l'école de Lyon a démontré que l'atténuation de la conscience et l'hypersomnie du coma aigu réfléchissent une perturbation dans la F.R.A.A.; par contre le sommeil physiologique avec sa périodicité et sa période rhombencéphalique des mouvements oculaires, nécessite un "Limbic Mid-Brain Circuit" indemne.

5. Grâce aux développements des études anatomopathologiques et neurophysiologiques des dernières années, les comas de décortication et de décérébration commencent à être différenciés à la lumière de deux systèmes distincts: cortex de la convexité — F.R.A.A. (F. Brenner, H. Magoun, G. Moruzzi et coll.); "Limb-Mid Brain Circuit" de Brodal et Nanta, mis en valeur par M. Jouvét.

La réactivité dans les lésions intéressant des structures si distinctes, devra être à son tour reconsidérée sous cette nouvelle optique.

R E S U M E N

1. El autor ha expuesto sus comprobaciones en cuanto al coma en 1957 en el Congreso Internacional de Ciencias Neurológicas de Bruselas y dos años más tarde en "Obnubilaciones, comas y estupores", publicado en colaboración con P. Mathis.

De estos trabajos, llevados a cabo desde el año 1945, se desprenden dos nociones:

—la reactividad de un trazado E.E.G. de coma tiene más valor que el tipo de ritmos, la morfología y la frecuencia de las ondas eléctricas;

—el coma no se reduce a un hipersomnio; es una perturbación grave de la vida del cerebro y del organismo, acompañada en su estado agudo de ciertos signos del sueño.

2. A pesar de algunas objeciones, la reaparición de la reactividad E.E.G. sigue sien-

do un índice favorable de recuperación del cerebro, siempre y cuando no haya complicaciones cardiopulmonares o de otras vísceras que agraven la evolución.

3. Las recientes investigaciones de la escuela de Lyon, desarrolladas a instancias de P. Jouvét, confirman totalmente la distinción propuesta entre el sueño fisiológico y los diferentes estados comatosos agudos o sus prolongamientos crónicos.

Los clínicos de Lyon han comprobado al igual que nosotros que el hipersomnio —síntoma pasajero de coma agudo— puede transformarse en un estado especial de hipervigilia si el enfermo permanece con vida.

4. Registrando el electromiograma de los músculos flexores y considerando el

tono muscular en relación con el trazado E.E.G. la escuela de Lyon demostró que la atenuación de la conciencia y el hypersomnio del coma agudo reflejan una perturbación en la F.R.A.A.; contrariamente a esto el sueño fisiológico con su periodicidad y su período romboencefálico de los movimientos oculares, implica necesariamente un "Limbic Mid-Brain Circuit" indemne.

5. Gracias al desarrollo de los estudios anatómopatológicos y neurofisiológicos de los últimos años, los comas de decorti-

cación y de decerebración comienzan a ser diferenciados a la luz de dos sistemas distintos; corteza de la convexidad — F.R.A.A. (F. Brenner, H. Magoun, G. Moruzzi y colaboradores); "Limb Mid-Brain Circuit" de Brodal y Nanta, subrayado por Jouvét.

La reactividad en las lesiones que afectan estructuras tan distintas, deberá ser a su vez reconsiderada bajo este nuevo enfoque.

SUMMARY

1. The author exposed his assertions on comas in 1957 at the International Congress on Neurological Science in Brussels and also two years later in "Obnubilations, comas and stupors" published in collaboration with P. Mathis.

Two notions result from this work carried on since 1945:

—the reactivity of E.E.G. pattern in coma is more important than the kind of rhythm, or the morphology and frequency of electrical waves;

—coma does not mean only hypersomnia; it is a serious disturbance in brain and body's life associated in its acute state to some of the aspects of sleep.

2. In spite of some objections, the appearance of E.E.G. reactivity remains a favorable index of cerebral recovery as long as there are no cardiopulmonar or other complications to darken the evolution.

3. The recent research carried on by the school of Lyon under P. Jouvét's influence totally confirms the proposed distinction between physiological sleep and the different states of coma and their chronic prolongations.

The clinicians of Lyon have proved as well as we did, that hypersomnia —transitory symptom of acute coma— may become a particular state of hyper-wakefulness if the patient is kept alive.

4. By recording the electromyogram of the flexing muscles and by considering muscular tonus related to E.E.G. pattern, the school of Lyon has shown that conscience attenuation and hypersomnia of acute coma reflex a perturbation on the R.F.A.A.; on the other hand physiological sleep with its periodicity and its rombocephalic period of the eye movements needs an undamaged Limbic Mid-Brain Circuit.

5. Thanks to the latest developments in anatomopathological and neurophysiological studies, decortication and decerebration comas are being distinguished under the light of two different systems: convexity cortex — R.F.A.A. (F. Brenner, H. Magoun, G. Moruzzi and coll.); Limb Mid-Brain Circuit by Brodal and Nanta, corroborated by M. Jouvét.

Reactivity of the lesions affecting such different structures shall have to be reconsidered according to this new view.

ZUSAMMENFASSUNG

1. Der Verfasser hat seine Feststellungen ueber Koma 1957 auf dem Internationalen Kongress fuer Neurologische Wissenschaften in Bruessel, und zwei Jahre spaeter in der zusammen mit P. Mathis veroeffentlich-

ten Monographie "Obnubilationen, Komas und Stupor" auseinandergesetzt.

In diesen Arbeiten, die seit 1945 durchgefuehrt worden sind, heben sich zwei Dinge hervor:

—Die Reaktivitaet eines EEG im Koma hat groesseren Wert als der Rhythmustyp, die Morphologie und Frequenz der elektrischen Figuren.

—Das Koma ist nicht nur ein "Ueberschlaf"; es ist eine ernste Lebensstoerung des Gehirns und des Organismus begleitet von einem akuten Zustand von Symptomen die dem Schlaf eigen sind.

2. Trotz einiger Objektionen bleibt dies Wiedererscheinen der EEG-Reaktivitaet ein guenstiges Zeichen der Erholung des Gehirns unter der Bedingung, dass keine kardiopulmonaeren Komplikationen oder die anderer Organe die Evolution verschlimmern.

3. Die neueren Forschungen der lyoner Schule unter dem Einfluss von P. Jouvét bestaetigen vollkommen die vorgeschlagene Unterscheidung zwischen physiologischen Schlaf und den verschiedenen akuten komatoesen Zustaenden, die sich in einen besonderen Zustand des Ueberwachseins umwandeln koennen, wenn der Kranke am Leben erhalten wird.

4. Indem die lyoner Schule ein Elektromyogramm der Flexoren gemacht und den Muskeltonus in Bezug auf das EEG betrachtet hat, bewies sie, dass die Minderung des Bewusstseins und der "Ueberschlaf" des akuten Komats eine Stoerung im FRAA widerspiegeln; dagegen benoetigt der physiologische Schlaf mit seiner Periodizitaet und seiner rhombencephalischen Periode der Augenbewegungen einen intakten "Limbischen Mittelhirnkreislauf".

5. Dank der Entwicklung der pathologisch —anatomischen und neurophysiologischen Studien der letzten Jahre, beginnt das Entrindungs— und Enthirnungs— Koma im Licht zweier verschiedener Systeme zu differenzieren; Konvexitätsrinde —F.R. A.A. (F. Brenner, H. Magoun, G. Moruzzi und Mitarb.) "Limbus-Mittelhirnkreislauf" von Brodal und Nanta, die durch M. Jouvét in ihrer Bedeutung hervorgehoben worden sind.

Die Reaktivitaet bei Laesionen von so verschiedenen Strukturen muss ihrerseits unter diesem neuen Gesichtspunkt wiederstudiert werden.

BIBLIOGRAPHIE SOMMAIRE

Les titres notés avec un + contiennent une bibliographie très complète; on y trouvera les publications citées dans le texte, absentes dans cette bibliographie sommaire.

(1) + Atti del VII Congresso Internazionale di Neurologia. Un vol. 626 pages, 1961, Edizione per il Congresso.

(2) Batini C., Moruzzi G., Palestini M., Rossi G. F. and Zanchetti A.: Plusieurs mémoires consacrés à la préparation médio-pontine prétrigeminale — Arch. Ital. de Biologie 1959-97.

(3) Bocacz J., Arcos-Pérez M. et García-Aust E.: Pathophysiological Significance of the Electroencephalographic Abnormalities of Hepatic Coma. Acta Neurol. Latino-amer. 1960, 6, 232-242.

(4) Dechaume J. et Jouvét M.: Etude sémiologique des troubles prolongés de la conscience. Ses bases physiologiques. Lyon Médical, 1960, 21, 1401-1420.

(5) Fischgold H. et Bounes G. C.: Explorations électro-encéphalographiques des états comateux. Sem. Hôp. Paris, 1946, 22, pp. 1245-1246.

(6) + Fischgold H.: La conscience et ses modifications. Systèmes de référence en E.E.G. clinique. Premier Congrès International Sc. Neurologiques. Bruxelles. 1957, Seconde journée commune, pp. 181-208.

(7) + Fischgold H. et Mathis P.: Obnubilations, comas et stupeurs. Suppl. N° 11 E.E.G. Clin. Neurophysiol. 1959, Masson et Cie, Paris.

(8) Fischgold H.: Discussion 234-236 in *The nature of Sleep*, 1961, J. et A. Churchill.

(9) + Jouvét M.: Recherches sur les structures nerveuses et les mécanismes responsables des différentes phases du sommeil physiologique. Arch. Ital. de Biol. 1962, C. 2, 125-206.

(10) Jouvét M.: Sur l'existence d'un système hypnique ponto-limbique. Ses rapports avec l'activité onirique. In *Physiologie de l'Hippocampe* 1962, Ed. C.N.R.S. Paris.

(11) Kaada B. R., Harmark W. et Stokke O.: Deep coma associated with desynchronization in E.E.G. E.E.G. Clin. Neurophysiol. 1961, 13: 785-789.

- (12) *Lairy-Bounes G. C. et Fischgold H.*: Réactions E.E.G. diffuses aux stimulations sensorielles. E.E.G. Neurophysiol. 1953, 5, pp. 343-362.
- (13) + Les Etats de conscience en neurologie. Deuxième Journée commune du Premier Congrès International des Sciences Neurologiques. Un vol. 233 p., 1957, Acta Medica Belgica.
- (14) *Loeb C., Rosadini G. et Poggio G. F.*: Electroencephalograms during coma. Neurology 1959, 9, 610-618.
- (15) *Loeb C.*: Electroencephalographic changes during the state of coma. E.E.G. Clin. Neurophysiol. 1958, 10: 579-606.
- (16) *Lundervolt A.*: Electroencephalic changes in a case of acute anoxia unconscious for about three years. E.E.G. Clin Neurophysiol. 1954, 6, 311-315.
- (17) *Miraillie P.*: A propos de quelques cas de comas anoxiques: Etude clinique électroencéphalographique et anatomopathologique. Thèse Nantes 1961-62.
- (18) *Mollaret P. et Goulon M.*: Le Coma dépassé (Mémoire préliminaire). Rev. Neurol. 1959, 101, 3-15.
- (19) *Mollaret P. et Bertrand I. et Mme Mollaret H.*: Coma dépassé et névroses nerveuses centrales massives. Rev. Neurol. 1959, 101, 1, 116-139.
- (20) *Pellin P.*: Sommeils et "Comas". Thèse Lyon, 1960, Impr. R. Gauthier.
- (21) *Schwartz B. A.*: E.E.G. et mouvements oculaires dans le sommeil de nuit. Electroench. clin. Neurophysiol. 1962, 14: 126-128.
- (22) + *Trillet M. M.*: L'encéphalopathie post-traumatique: Comas prolongés et "morts du cerveau". Journal de Médecine de Lyon, 1961, n° 987, 988 et 992 tiré à part de 169 pages.
- (23) *Wertheimer P. et Descottes J.*: Traumatologie crânienne. 1961 - Masson et Cie.

Insulin Coma

VICTOR SORIANO, OVIDIO H. CERVIÑO and HECTOR PUPPO

John F. Fulton's Laboratory of Experimental Neurology and
the Psychiatric Clinic - Montevideo.

As a consequence of high doses of insulin given to psychiatric patients submitted to insulinic shock treatment, very low rates of glycemia are obtained in them, which leads to deep changes in the nervous function.

The respiratory quotient of the brain is equal to unity —Himwich and Nahoum⁽¹⁰⁾; Himwich⁽¹¹⁾— which means that glucose is its main substrate in the origin of its energy. This is very important in explaining the preceding paragraph.

When glycemia rates decrease to about 20 to 30 mgrs. per cent or less, stupor and a state of coma may appear; if this state becomes accentuated (glycemia usually is between 10 mgrs. and 0 %) great biochemical and electrophysiological disturbances accompany the clinical picture.

Blood normally provides the central nervous system with a much higher quantity of glucose than the brain needs —Fazekas⁽⁶⁾— the proportion between what is available and what is strictly necessary is 10 to 1. It is therefore surprising to find a coma state when glycemia is about 30 mgrs. per cent, and when there still is excessive glucose to satisfy the neurons' needs. It is certainly very difficult for it to pass from the blood into the nervous elements, which means that it has a low permeability quotient.

In the hypoglycemia state the brain's oxygen consumption is diminished. The cerebral blood flow remains without change.

Sometimes insulinic coma is irreversible; prolonged hypoglycemia brings about a deficiency in cerebral energy, leading to definitive neuronal disturbances. This se-

rious situation is caused by the prolongation and depth of coma. In this case cerebral blood flow decreases progressively; this does not occur in current cases of insulinic coma; a gradual increase in the vascular resistance of the brain is observed, and there is a very low oxygen consumption, which has to be attributed to disturbances in enzymatic activity.

The amount of insulin needed to provoke the low rates of hypoglycemia noted above, differs from one patient to another. There is no strict parallel between glycemia figures and conscience state. In addition to the individual differences there are psychical ambiental factors that may favour or impede the appearance of coma. It is difficult to bring an apprehensive, watchful, skeptical patient to coma. If there are various sensitive stimuli around, such as light, noises, moving persons, application of instruments, punctions, etc., these are factors which make it more difficult for the patient to lose consciousness.

The insulinic shock presents, besides insulin excess, hypoglycemia, metabolic changes in fat and proteins, accompanied by some other changes, some of them very significant and closely connected with the increase of glucose metabolism. Potassium diminishes, and also inorganic phosphates — Harris and col.⁽⁹⁾, Thorley and Kay⁽¹⁶⁾, Kay and Thorley⁽¹²⁾ — going with the glucose of extracellular fluid to the cell, and aminoacids and acetylcholine.

The hemoconcentration resulting from abundant sweating provokes an increase of proteins and sodium and a decrease of

chlorides. Serotonine increases. There are hormonal changes, some of them being of little significance as the ones related to sexual hormones, thyroid, glucagon and prolactin; others are very important such as the effect on the ACTH and the hormone of growth and the lowering of their levels. The influence on the metabolism of adrenaline and the 11-17 oxicorticosteroids are to be considered also.

up at intervals until they are completely detached from the environment.

They enter a phase of akinetic mutism during which they remain with their eyes open; when the observer threatens the patient with his hand a positive blinking response is obtained.

There is no possibility of obtaining an answer to any kind of request. Later on, coma increasing in depth may set in. Du-

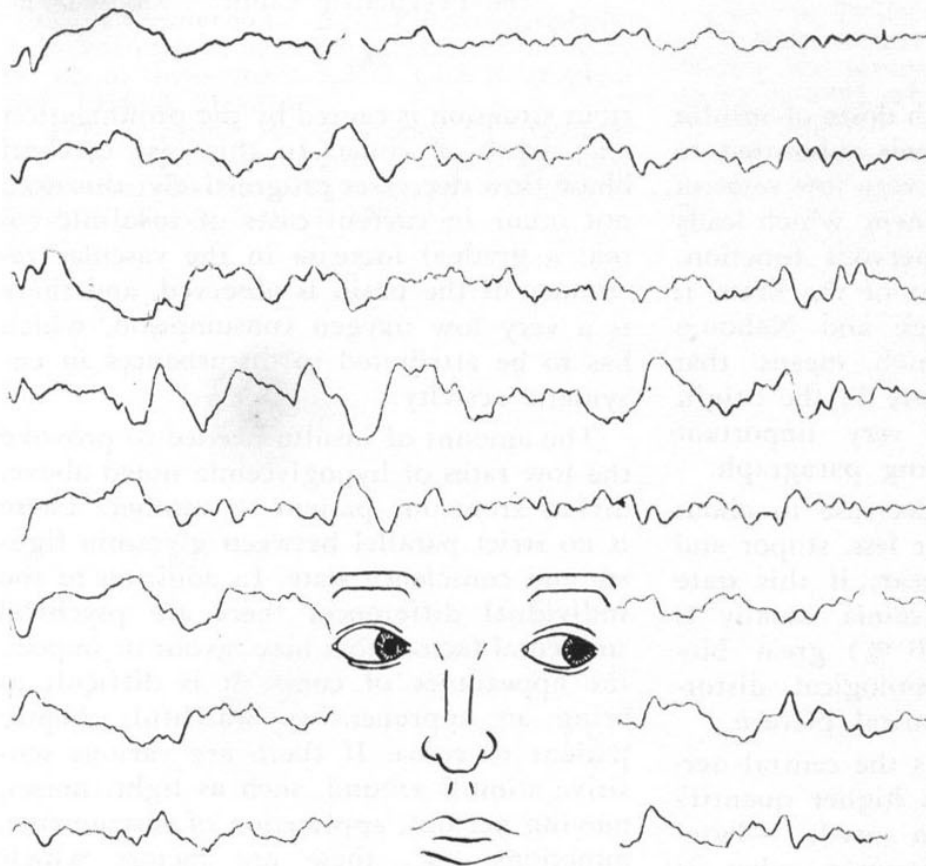


Fig. 1. — When EEG slows down there is deviation. Rapid response of nystagmus diminishes or disappears.

CLINICAL MANIFESTATIONS

Patients fall progressively into coma; they become apathetic, their answers are slow and it is observed that first of all they become unable to solve easy calculations. When hypoglycemia is more advanced they stop answering, they stare with an apparent effort to understand a question; some patients, moments after the question has been changed, answer the previous one, others repeat always the same answer. They seem to fall asleep; at the beginning they may sometimes wake

ring the patient's evolution to coma a period of psychomotor excitement may occur; during this period, if he has not been given a sedative, the patient shakes, turns about in his bed while he pronounces expressions going from lamentations to insults; if he is not held tightly he falls from his bed, hurting himself against the floor. Myoclonus of different parts of the body, head, eyelids, lips, chin and extremities may be observed; at the beginning they are localized, later on they spread and generalize synchronically and a real convulsion with post convulsive coma may occur. Sometimes

the patient recovers partially from his unconsciousness to follow the evolution towards insulinic coma.

Important neurological changes are observed in somatic and autonomic functions during the evolution of hypoglycemia.

At the beginning muscular tonus may diminish and hyperpasivity and hyperextensibility in the extremities are observed; before falling into coma during a previous period of akinetic mutism, temporary states of hypertonus in flexion or extension may appear in some cases.

Besides, other neurologic manifestations may be observed; it is common to detect asymmetries, as if the modifications of the nervous tissue which accompany the metabolic perturbation were not exactly the same on both sides. In more advanced periods tonic manifestations are originated with flexion in the upper extremities and extension in the lower ones.

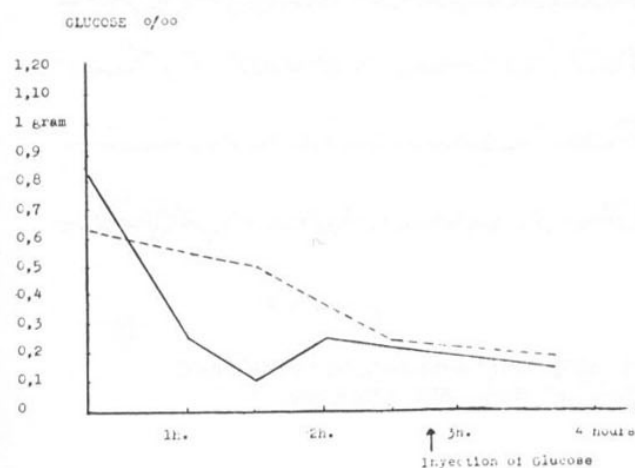


Fig. 2. — Curve of glucose in blood (continuous line) and in CSF.

Some patients evidence torsion spasms during this period. Later on, the flexed extremities become extended and then all four extremities remain extended. Everything occurs as if the descending reticular function would maintain its action on the muscular tonus, free from inhibiting influences of other nervous structures having been perturbed earlier by hypoglycemia, (Himwich's mesencephalic and premiencephalic periods). When coma becomes more

profound (myelencephalic period) a universal depression of the nervous function is produced accompanied by hypotonus, generalized areflexy, very often then with concomitant loss of the cornean reflex. Before arriving at these last phases which are very dangerous for the life of the patients, we have sometimes seen that reflectivity is much diminished or abolished.

During hypoglycemia profound reflectivity experiments interesting modifications: reflexes often become hiperactive, sometimes polycynetic and occasionally are accompanied by clonus. There are patients in which increased responses are diffuse; in others they occur in some of the reflexes; asymmetry in the responses is frequently observed. During the evolution of hypoglycemia the same reflex changes the way of presenting itself, it increases and declines.

The plantar cutaneous reflex usually changes its response; it is done in extension (sign of Babinski). This phenomenon is related to the changes previously mentioned affecting the pyramidal system. Some patients show the Babinski's sign simultaneously in both extremities, others begin with a unilateral Babinski and the other cutaneous plantar indifferent, and afterwards both cutaneous plantar become in extension.

During hypoglycemia some abnormal reflexes may appear, for instance the reflex of Toulouse Vulpas (percussion on the lips' orbicular, its abnormal answer consists in its contraction, sometimes the formation of a snout); its existence means diffuse suffering of the brain or lesions on both hemispheres; in some patients it becomes positive in early periods of hypoglycemia and increases as time goes by and decreases afterwards. For an example we mention the evolution of this reflex in one of our cases: "three hours after the injection of 160 insulin units; the patients showed a state of akinetic mutism accompanied by a weak Toulouse Vulpas, 20 minutes later the reflex increased; the patient remained in the same state until 3 hours 40' after the injection; 4 hours later the reflex became weaker and 10 minutes later it was not obtained any more". The appearance of this pathologic reflex is not a constant fact.

A true suction reflex may appear, as if the releases produced by the process made the functional expression of the nervous system go back to more primitive ontogenical periods.

LABERINTHINE STIMULATION

This kind of observation has given us interesting results. We have produced these stimulations introducing cold water into the

pid response diminished and afterward disappeared, leaving the eyes with a clear deviation toward the irrigated side.

We have obtained deviation without quick response in a case with a very slow electroencephalogram, without the patient being unconscious, and being hardly asleep; but it was possible to communicate with her and she answered simple questions. When there is unconsciousness, the same phenomenon is observed with conjugated deviation of the head and of the eyes; on

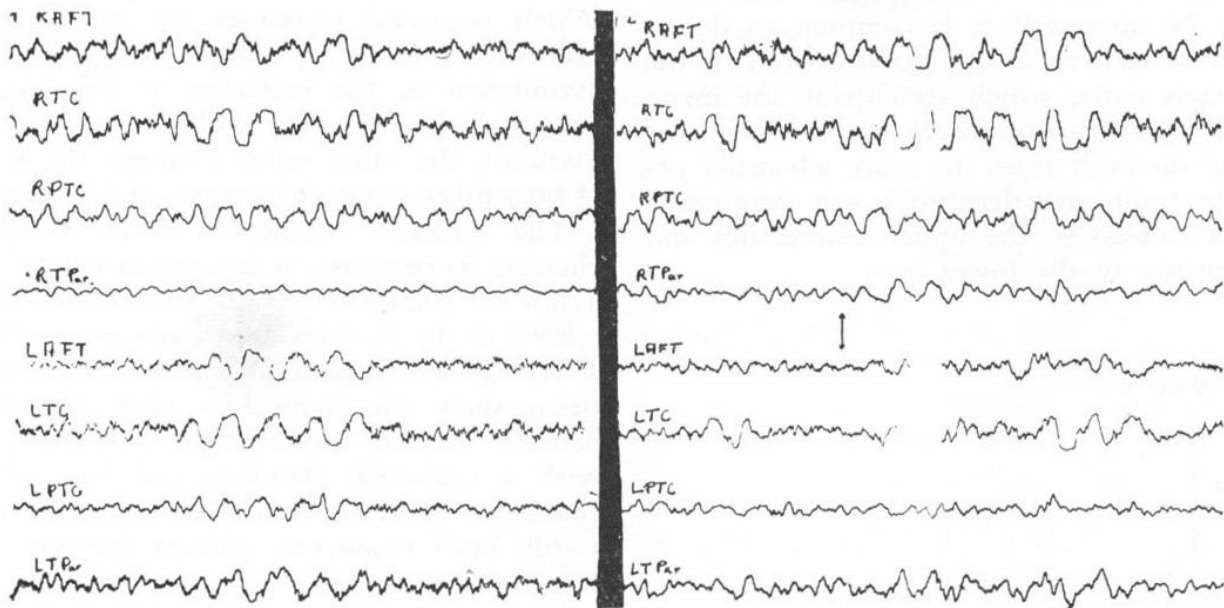


Figure 3

Figure 4

Fig. 3. — Asymmetry between right and left temporoparietal leads.

Fig. 4. — Painful stimulation on face. No changes.

external auditory canal. The volume of water used was of 60 to 100 c.c. Usually the patients were also under electroencephalographic control. The results obtained were varied.

We observed the following: that in conscious patients and with minor electroencephalographic alterations, the labyrinthine reaction was not largely beyond the normal, nystagmus appeared towards the opposite side of the irrigated ear and a sensation of vertigo while nystagmus lasted. But when the electroencephalogram showed a pronounced slowness and above all when there was obnubilation of consciousness, the ra-

pid response diminished and afterward disappeared, leaving the eyes with a clear deviation toward the irrigated side.

We will mention the following case: a patient had had an injection of 200 u. of insulin. 4 hours thereafter we found just traces of glycemia.

She was torpid but not unconscious, the record became slower with an abundance of delta and theta rhythms; the prick on the face shows lack of reactivity in the electroencephalographic record. At this point the spray of cold water, instead of

causing nystagmus as on previous occasions, showed a clear deviation. At 4 hours and 13 minutes, we noticed that upon stimulating the right ear, the eyes, before deviating to the right, wandered as if there existed and internuclear paralysis, the left eye rolled to the centre and upwards, the right rolled slowly on a horizontal level; later both eyes were fixed on the extreme lateral right for two minutes.

One of our patients was very agitated before being in state of akinetic mutism

A review of studies involving the autonomic system as reflected in the Mecholyt or Funkestein Test have been made by Bennett⁽²⁾. Intense dehydration is a very important syndrome of early appearance during the insulinic shock.

Patients evidence abundant and characteristic sweating. Other symptoms help to dehydration: an increase of the gastric secretion has been proved (this is easy to appreciate with the same tube through which the patient receives the syrup that

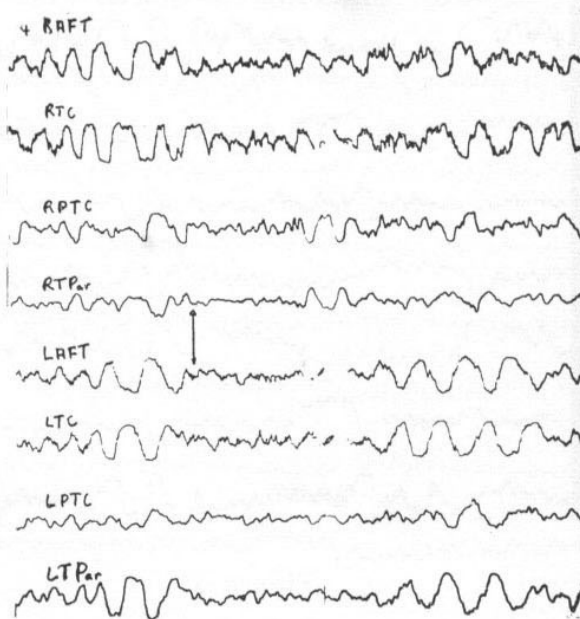


Figure 5

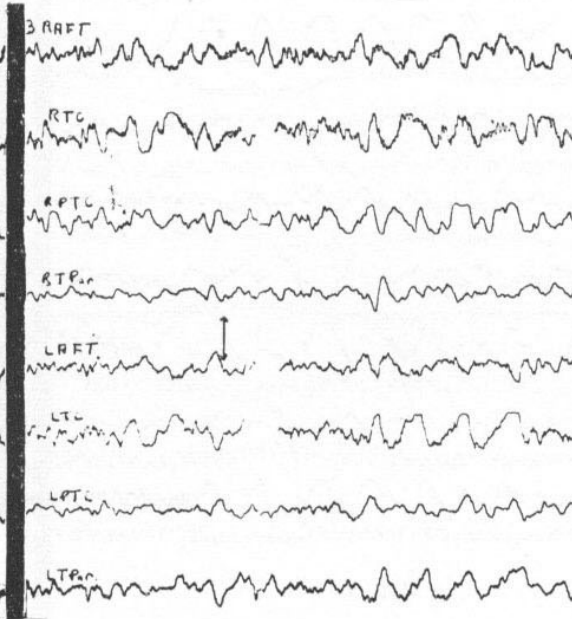


Figure 6

Fig. 5. — Stimulation lasts 12 seconds. Very short response.
Fig. 6. — At the end of 12 seconds stimulation. No changes.

and later in coma. Contrary to what usually was seen the electroencephalogram was hardly slow during unconsciousness. However labyrinthic stimulation always produced a clear ocular deviation. When coma was deeper, cold water originated no response. In this case ocular deviation was not related to a slow electroencephalogram; but it was to a decrease of consciousness.

AUTONOMIC MANIFESTATIONS

In the autonomic manifestations modifications take place which have deserved several studies.

takes him out of coma) which reaches 800 c.c. in some cases; abundant salivation; tears are frequent; urine emission is increased and in certain comas pulmonary hyperventilation appears.

The elimination of fluids provokes an augmentation of osmotic concentration in the interstice, which leads to the cell's loss of water as a compensation; this means cellular dehydration. The patients complain of strong thirst and lose weight, Billet and Cols.⁽³⁾.

Arterial pressure falls slightly at the beginning, but later shows a tendency to increase sometimes to high degrees. Cuta-

neous capillaries evidence a certain degree of hypotony in their walls; after rubbing the skin of the abdominal wall, a frank and persistent reddening band is originated like the meningeal line of Trousseau, described as sign of meningeal syndrome; which as it is known, may be found in other clinical pictures.

(in prolonged comas the injection of potassium chloride may be of benefit); there is an increase of adrenalin (one reason for arterial pressure to elevate), and serotonin diminishing of aminoacid and of acetylcholine; there is a modification in ACTH and in 11-17 oxicorticosteroids. Bennett ⁽²⁾ reviews studies with the glucose and Insulin

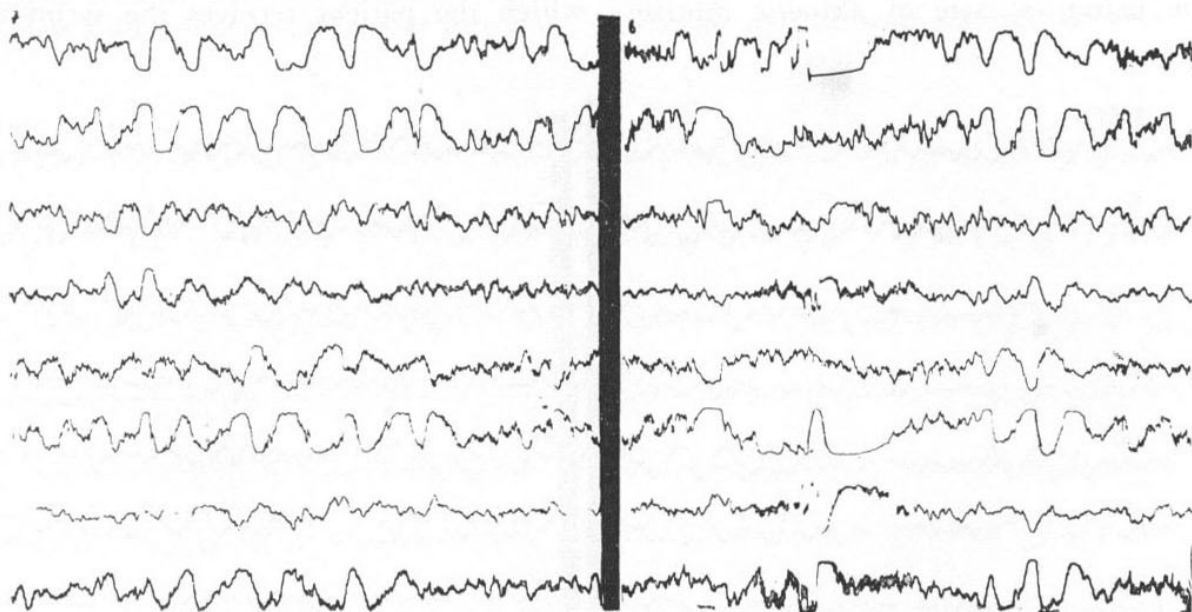


Figure 7

Figure 8

Fig. 7. — Patient is drinking sirup.

Fig. 8. — Patient taking sirup by tablespoon.

Pulse accelerates and pupils dilate and in advanced hypoglycemia lose their light reactions.

HUMORAL PICTURE

As we have explained above hypoglycemia is neither in close parallelism with the injected insulin nor with the clinical findings. During the insulinic shock a tendency to increase, or at least to retain, the sodium ion is observed; a diminishing of potassium, which follows that of glucose, and the PO_4 ion, and produces electrocardiographic alterations, hypotonus, diaphragmatic paralysis, lethargy, loss of weight;

Tolerance Tests; and on the contrainsulin hormones.

Correlation between the glucose of blood and the cerebrospinal fluid during hypoglycemic shock

We have studied the correlation between the decrease of glucose in blood and the cerebrospinal fluid. For this purpose we made blood and cerebrospinal fluid extractions before and after the insulin injection, and after the glucose injection or the ingestion of syrup. Every half an hour or hour samples were taken.

We observed some facts worth mention-

ing: a) The decrease of glucose in the blood is much quicker than in the cerebrospinal fluid. More than 2 hours may pass before a significant change is observed in the values of glucose in CSF, and the fall of glucose follows a curved line with much less slope than in the blood. b) During our observations, which took periods of 4 to 5 hours after the insulin injection, glycemia reached a lower value than the glucose in

fluid is not a mere osmotic phenomenon; there is a real cellular activity (perhaps there is utilization of glucose in the nervous and glial tissue adjacent to the cerebrospinal fluid, Darson⁽⁵⁾) which is surely enormously disturbed during the insulinic shock.

In some patients we made correlative studies of potassium, sodium, calcium and magnesium in different moments of hy-

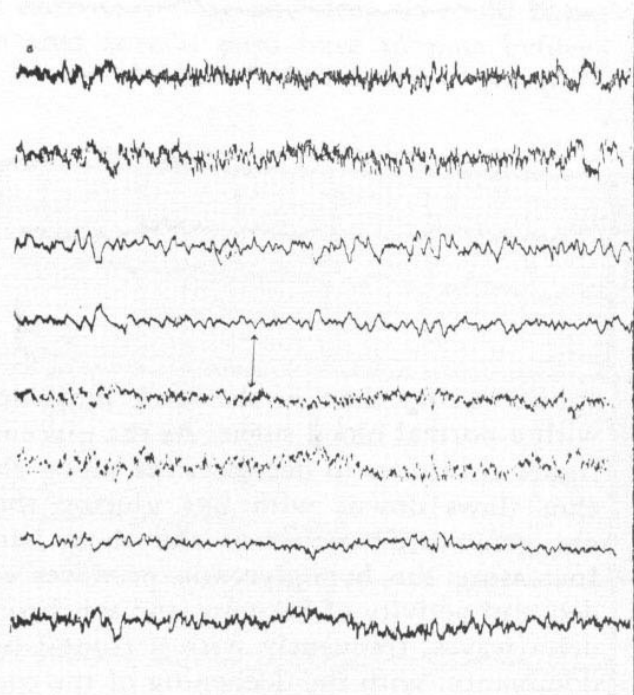


Figure 9

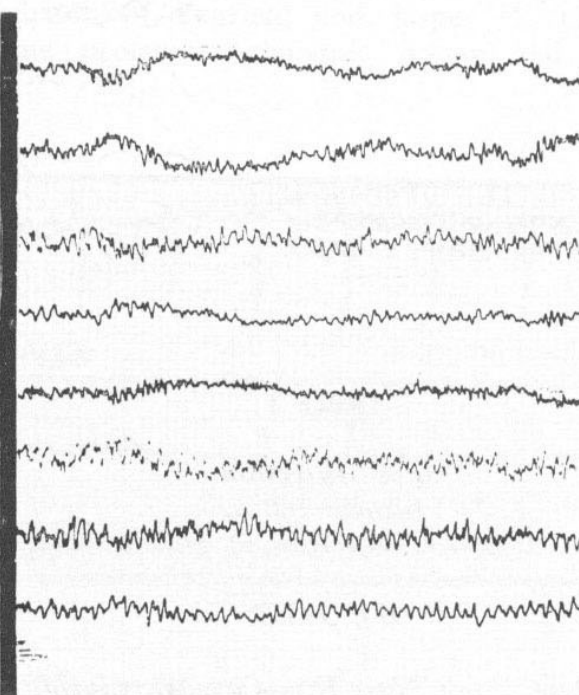


Figure 10

Fig. 9. — Glycemia still high, 109 mgrs. per cent. Painful stimulation.

Fig. 10. — Relationship between glucose and EEG. Glycemia very low, 19 mgrs. per cent. No major changes in EEG.

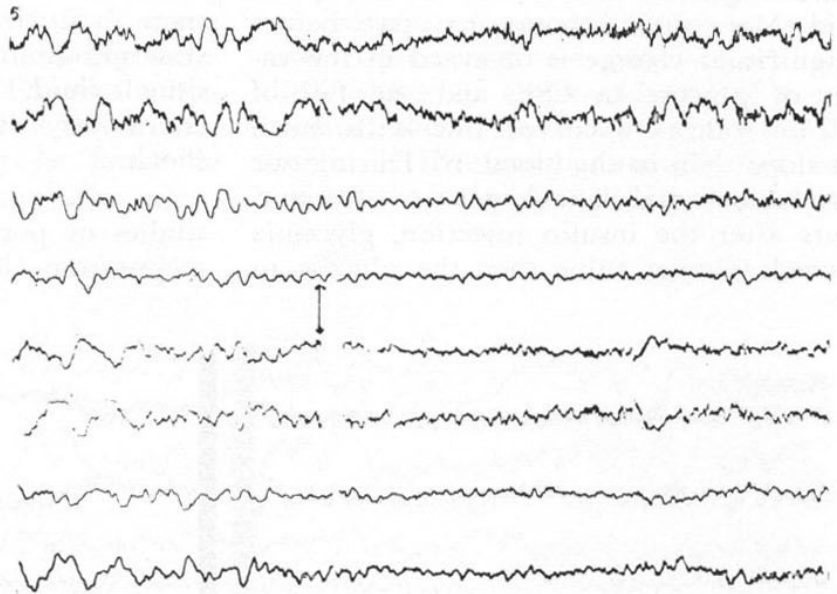
CSF: that is to say an inversion between the figures of both glucoses took place. c) In those patients where a strong descent of the glucose in CSF occurred, the figures reached approached those of glycemia, as if there existed an equilibrium in low values.

These observations demonstrate that the variation of glycemia and glucose in an intercellular fluid such as the cerebrospinal fluid did not occur concomitantly during the insulinic shock. In normal conditions there is a bigger quantity of glucose in blood than in the cerebrospinal fluid; this means that the passage of glucose to the

poglycemia. The following results have been obtained in one of the studied patients: (Table 1).

EEG

The electroencephalogram during hypoglycemia shows modifications which become more pronounced as the figures of glycemia descend. The first changes observed in some persons, are an increasing sensitivity to hyperventilation, the discharge of slow bilateral and slow synchronic waves of a frequency of 3 per second, tend to



Fif. 11. — Patient is being interrogated — some little changes.

TABLE I

6:30' Injection

Insulin 160 u.

9:40' i.v. injection of glucose

BLOOD

Time	Na	K	Ca	Mg	Cloride
8:45' a.m.	141	2,5	3,1	1,0	5,40
9:35' "	140	2,4	2,6	1,0	5,40
10 "	144	2,4	2,1	1,0	5,40
10:30' "	148	2,9	2,2	0,8	5,40
11 "	142	3,6	2,8	0,8	5,40
	meq/l			g NaCl/l	

CEREBRO-SPINAL FLUID

Time	Na	K	Ca	Mg	Cloride
8:45' a.m.	136	3,0	1,8	0,8	7,21
9:30' "	139	2,7	1,6	0,8	7,60
10 "	142	2,2	1,5	0,8	7,69
10:30, "	142	2,5	1,4	0,8	7,47
11 "	138	3,2	1,7	0,8	7,38
	meq/l			g NaCl/l	

Comparative changes of some electrolytes in blood and CSF.

appear earlier than in the same individual with a normal blood sugar. As the glycemia figure continues to decrease, the alpha rhythm slows down; with less glucose there are generalized waves of the theta band. Increasing the hypoglycemia produces evidence of activity of bilateral and synchronic delta waves, frequently with a frontal predominance; with the deepening of the coma this increases and slows down even more.

Everything indicates a defective production of cerebral energy.

Asymmetries can be observed, in the same way as in a clinical examination, also in the electroencephalogram; in some cases reaching the point of constituting an abnormal focal activity. If no neurological lesion exists, these facts can be related to vascular modifications and edema. Discharges of spikes or of slow spikes and waves, can rarely be found in an electroencephalographic examination. In the origin of all these electroencephalographic abnormalities it may be possible that, besides the hypoglycemia associated with a decrease of the consumption of oxygen, edema of the brain, and changes in the electrolytes, principally of the potassium, may exist.

When, by furnishing sugar, the glycemia is brought to the normal level, in the large

majority of these cases, the electroencephalogram normalizes together with the glycemia. If this is repaired slowly (absorption of sugar by the gastric wall) the record modifies also in a gradual way. If on the contrary, the patient recovers from his coma by a quick intravenous injection of hypertonic glucose solution the record will show dramatically in a few moments the disappearance of these abnormalities.

Occasionally in cases in which the coma has been very long and deep, it could happen that several days have to pass before

by the subcorticiodiencephalon, mesencephalon, rostral medulla and caudal medulla.

Advances in neurophysiology in the last years have given support to the concept developed by Livingston and cols. of vertical stratification of the central nervous system which contains: a) a sensitive afferent column, b) a motor efferent column, and c) a central column integrated by: 1) association regions and interneuronal systems of the cerebral cortex, 2) the centrencephalon of Penfield and Jasper⁽¹⁴⁾ (Diffuse projection thalamic system and the

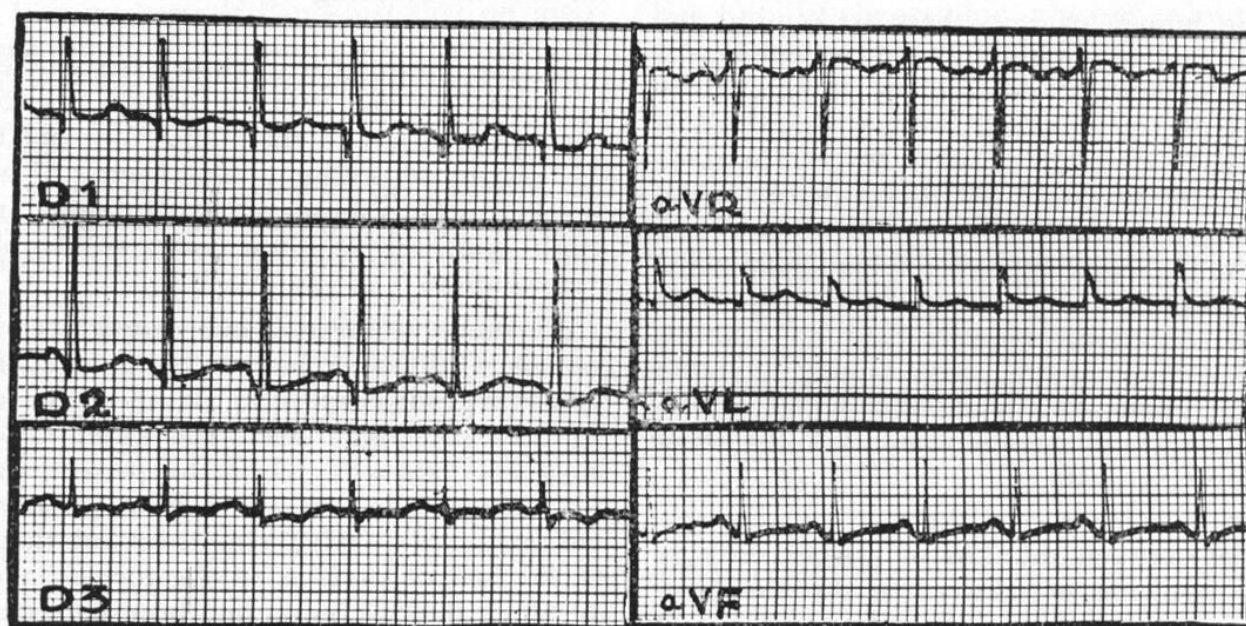


Fig. 12. — EKG — Modification in the repolarization of moderate degree.

the abnormalities are totally corrected. On rare occasions focal electroencephalographic disturbances persist, as does also the low cerebral consumption of oxygen, even after the glucose has raised in the blood to its normal level. After so called irreversible coma there is a desorganization of the alpha rhythm, dominated by irregular delta activity of low voltage, Cadilhac and cols.⁽⁴⁾.

Himwich following the doctrine of Hughlings Jackson of the central nervous system organization in phyletic layers admitted that in insulin shock cerebral cortex is depressed first and depression continues successively

reticular formation of the brain stem) and 3) the interneuronal gray matter of the spinal cord. The central column (c) would be first affected in insulin shock.

We shall now mention certain experimental studies related to hypoglycemia, which support this concept and will permit us to interpret some of our electroencephalographic observations.

Arduini and Arduini⁽¹⁾ expressed that in hypoglycemia, in anoxia and in anesthesia, if there is acoustic stimulation, the potentials evoked in the reticular formation, are blocked.

Van Meter, Owens and Himwich⁽¹⁸⁾

have reported that the cortical and subcortical alerting response to painful stimuli disappears in the hypoglycemic rabbit. We think that our observations in human beings agree with these experimental results.

The rhinencephalon is closely related to the reticular activating system.

In animal experimentation Tokizane and Swayer⁽¹⁷⁾ demonstrated, that in deep insulin hypoglycemia, frequently appears EEG seizure activity usually originated in subcortical centers of the rhinencephalon.

Besides, in prolonged insulin hypoglycemia, damage has been found in rhinencephalic areas.

In human patients there are clinical and electroencephalographic pictures during the insulin shock that can be attributed to changes in rhinencephalon: Psychomotor excitation; epileptic seizures and in some cases the temporal projection of the initial changes in the EEG.

At present we are studying electroencephalographic manifestations of patients with hypoglycemia provoked by insulinic shock. Some of them have been observed in coma, others slightly obnubilated and finally others whose consciousness did not show important changes.

It is evident that there is no close parallel between the dose of injected insulin, the resulting hypoglycemia, the electroencephalographic changes and the degree of alteration in consciousness. A 20 mgrs. per cent glycemia may appear in a conscious patient as well as in one being in coma. Profoundly increasing slowness of rhythm can be registered in slightly obnubilated patients, who understand and answer our questions and make easy calculations correctly.

Reactivity

While we make these observations and during the encephalographic recording we submit the patients to different kinds of stimuli in order to document the electroencephalographic reactions.

Fischgold and Mathis⁽⁷⁾ searched for electroencephalogram's reactivity on stimuli in

obnubilated, stupored and comatose patients with organic encephalic lesions, chiefly traumatism, hematomas and tumours.

They encountered in the obnubilated state, an electroencephalographic arousal with appearance on the basic rhythm, of delta, theta or alpha rhythms, and the present delta rhythms are blocked up.

If the coma state is not profound, emerging delta, theta or alpha rhythms may be seen; there will hardly be a blocking up of delta or alpha rhythms.

Delta, theta or alpha rhythms hardly ever appear in an arousal in coma carus and there is no blocking up of the pre-existent rhythm.

All this means that in those cases studied by Fischgold and Mathis the electroencephalogram reacts to the stimuli applied to the patient according to the degree of alteration of consciousness and that there are frank reactions in those cases of simple obnubilation.

We have submitted our hypoglycemic patients to different kinds of stimuli: a) in all cases pricks, especially on the face, sometimes prolonged ones, and other times short and frequent. b) if the patient was not unconscious, we asked him questions and made him solve simple calculations. c) in cases of patients in the former state in whom hypoglycemia had been corrected slowly by means of the administration of some spoonfuls of sirup (one patient drank it from a jug she herself held), the electroencephalogram was continued to observe the effect these manoeuvres would have on it. d) voluntary eye closing and opening when this was possible.

Reactivity has also been explored after having injected hypertonic glucose solutions and coma suppressed with a practically normal electroencephalogram. Responses were somewhat different in each patient, and it was very frequently observed that the electroencephalogram's reactivity was scarce or did not appear at all most of the time, in insulinic shock hypoglycemia. We observed that:

A) When the patient is unconscious, even if the coma is not profound (opened

eyes, palpebral reaction to threatening persisting and corneal reflex alive) there is no change in the electroencephalogram with prolonged or short and frequent pricking.

B) If the patient is not unconscious but great changes exist in the electroencephalogram, such as an abundance of theta and delta rhythms, pain provoking stimuli may not cause any change in the pattern; and if any, it is of short duration (acceleration and decrease of voltage), 3 to 4 seconds, with immediate return to the previous slowness. When the stimulus stops, the pattern remains unchanged.

In some cases it happened that on interrogating and on asking some elementary calculations, the electroencephalogram evidenced insignificant changes or no changes at all.

In one of the patients the pattern was not even modified when she was drinking sirup from a glass that she herself was holding.

C) When the record of a patient in situation (b) shows some reactivity during the exploration, some minutes afterwards

the same may disappear even with no changes in consciousness, when a new painful stimulus is applied.

D) Some patients, not being unconscious and presenting an electroencephalogram without great changes (no more than some brief discharges of theta rhythms) also show little or no reaction.

E) Eye opening and closing hardly ever originates the changes observed in normal persons; sometimes there are no modifications at all and if any, they are brief and slight.

F) Patients in coma are returned to consciousness by means of an intravenous injection of hypertonic glucose solution. The electroencephalogram changes fundamentally, and becomes almost normal. We have tried painful stimuli on the face of the patient some minutes after the injection and we have found hyporeactivity most of the time.

Summing up we can say that in insulin shock the electroencephalogram shows little or no reactivity, either for arousal or arrest reactions. This happens before, during and after unconsciousness.

SUMMARY

Psychiatric patients submitted to insulinic shock treatment were examined from the somatic viewpoint.

We describe the observations of patients' clinical evolution until coma.

Among the explorations undertaken, the laberinthic stimulation with cold water has been pointed out. In this stimulation it was stated that the quick response of the nystagmus disappears when the hypoglycemia is accompanied by obnubilation of consciousness, stupor or coma, or if consciousness is only slightly affected, when the electroencephalographic rhythms visibly slacken.

Comparative studies were carried through of glucose, electrolytes in the blood and C.S.F. The blood glucose diminishes quic-

ker than the C.S.F. glucose, and may reach even lower figures than in the latter one. When the decrease is abrupt in both fluids, the figures are practically identical.

Electroencephalographic, electrocardiographic and electromyographic observations were effected.

We investigated the reactivity towards several stimuli in the electroencephalogram—nociceptive, proprioceptive, sensitive, psychic—and it was found that during the insulinic shock, before loss of consciousness, later on in stupor or coma and after elimination of the hypoglycemia, the electroencephalographic pattern shows very few or no reactivity. This apparently shows that in human beings, as well as in animals used in experimentation, the reticular formation is affected in an early stage.

RESUMEN

Pacientes psiquiátricos sometidos al tratamiento con el shock insulínico fueron estudiados del punto de vista somático.

Describimos las observaciones de la evolución clínica de los pacientes hasta llegar al coma.

Entre las exploraciones practicadas se destacó la estimulación laberíntica con agua fría. En ella se señala la desaparición de la respuesta rápida del nistagmus cuando la hipoglucemia se acompaña de obnubilación de la conciencia, estupor o coma, o si la conciencia está poco afectada, cuando los ritmos electroencefalográficos se enlentecen en forma manifiesta.

Se hicieron estudios comparativos de la glucosa y electrolitos en la sangre y líquido cefalorraquídeo. La glucosa en la sangre desciende en forma mucho más rápida que en el líquido cefalorraquídeo y puede al-

canzar cifras más bajas que en éste. Cuando el descenso es pronunciado en los dos fluidos, las cifras tienen valores prácticamente iguales.

Se realizaron observaciones electroencefalográficas, electrocardiográficas y electromiográficas.

En el electroencefalograma se buscó la reactividad a diferentes clases de estímulos, nociceptivos, propioceptivos, sensoriales, psíquicos y se comprobó que durante el shock insulínico, antes de la pérdida de la conciencia, más tarde en el estupor o el coma y después de corregida la hipoglucemia, el trazado electroencefalográfico acusa muy escasa o ninguna reactividad, lo que puede evidenciar de que en el hombre, lo mismo que en los animales de experimentación, la Formación Reticular se afecta precozmente.

RÉSUMÉ

Des patients psychiatriques soumis au traitement du shock insulinique ont été étudiés du point de vue somatique.

Nous décrivons les observations de l'évolution clinique des patients jusqu'au coma.

Parmi les explorations pratiquées la stimulation labyrinthique avec de l'eau froide s'est distinguée. On signale la disparition de la réponse rapide du nistagmus quand l'hypoglycémie est accompagnée d'obnubilation de la conscience, de stupeur ou de coma, ou bien si la conscience est légèrement affectée, quand les rythmes deviennent décidément plus lents.

On a fait des études comparatives du glucose et des électrolytes dans le sang et dans le liquide céphalo-rachidien. Le glucose diminue beaucoup plus rapidement dans le sang que dans le liquide céphalo-rachidien et peut atteindre des chiffres plus

basses que dans celui-ci. Quand la chute est prononcée dans les deux fluides, les chiffres ont des valeurs pratiquement identiques.

Des observations électroencéphalographiques, électrocardiographiques et électromyographiques ont été faites.

Dans l'électroencéphalogramme on a cherché différentes espèces de stimuli; nociceptifs, propioceptifs, sensoriels, psychiques; et on a prouvé que pendant le shock insulinique, avant la perte de conscience, plus tard dans la stupeur ou le coma et après l'élimination de l'hypoglycémie, le tracé électroencéphalographique accuse une réactivité très faible ou nulle. Ceci peut montrer que, aussi bien chez l'homme que chez les animaux d'expérimentation, la formation réticulaire est précocement affectée.

ZUSAMMENFASSUNG

Psychiatrische Patienten, die mit Insulin-shock behandelt wurden, werden vom somatischen Gesichtspunkt aus untersucht.

Es wird die klinische Entwicklung der Patienten beschrieben, bis sie zum Koma kommen.

Unter den beschriebenen Untersuchungsmethoden wird besonders hervorgehoben die Stimulierung des Labyrinths durch kaltes Wasser. Bei dieser beobachtet man das Verschwinden des raschen Ansprechens des Nystagmus, wenn die Hypoglykaemie begleitet ist von Bewusstseinsabnahme, von Stupor oder Koma, oder wenn das Bewusstsein wenig leidet, wenn die elektroenzephalischen Rhythmen in klarer Weise verlangsamt sind.

Es wurden vergleichende Studien gemacht betreffs des Blutzuckers und der Elektrolyten im Blut und im Liquor. Der Zucker nimmt im Blut viel rascher ab als im Liquor und kann kleinere Ziffern erreichen

in Letzterem. Wenn die Abnahme sehr stark ist in beiden Flüssigkeiten, dann sind die Ziffern praktisch gleich.

Es wurden elektroenzephalographische und elektromyographische Untersuchungen und ausserdem ein EKG gemacht.

In EEG suchte man die Reaktion auf verschiedene Arten von Reizen, nociceptive, proprioceptive, sensorielle und psychische und man fand, dass waehrend des Insulin-shocks, vor dem Bewusstseinsverlust, spaeter beim Stupor oder beim Koma und nachdem die Hypoglykaemie korrigiert ist, das EEG wenig oder keine Reaktion ausweist, was darauf hinweist, dass beim Menschen wie beim Tier die "Formation Reticular" fruehzeitig angegriffen ist.

BIBLIOGRAPHY

- (1) *Ardnini, A. and Ardnini, M. G.*: Effect of drugs and metabolic alterations on brain stem arousal mechanisms. *J. Pharmacol. & Exper. Therap.* 110: 76 (1954).
- (2) *Bennett, I. F.*: Hormonal and other blood changes occurring during insulin hypoglycemia treatment. In *Insulin Treatment in Psychiatry*. Max Rinkel and Harold E. Himwich editors. New York Philosophical Library, 1959, p. 45.
- (3) *Billet, J., Lafon, R. and Billet, B.*: Modifications biologiques apportées par une injection de haute dose d'insuline chez des sujets non diabétiques. Hypothèse sur la pathogénie du coma insulinaire. *Ann. méd. psychol.*, 1: 175, 1953.
- (4) *Cadilhac, J., Ribstein, M. and Jean, R.*: EEG et troubles métaboliques. *Rev. Neurol.* 100: 270, 1959.
- (5) *Darson, H.*: Handbook of Physiology. Neurophysiology, John Field, H. W. Magoun, Victor E. Hall. Volume III, p. 1779, 1960. American Physiological Society. Washington Physiological Society. Washington D. C.
- (6) *Fazekas, J. F. and Alman, R. W.*: Coma. Springfield, Illinois, Charles C. Thomas, 1962 p. 30.
- (7) *Fischgold, H. and Mathis, P.*: Obnubilations comas et stupeurs. Paris, Masson et Cie.: 1959, p. 16.
- (8) *Geilhorn, E.*: Physiological Foundations of Neurology and Psychiatry. The University of Minnesota Press, Minneapolis, 1953.
- (9) *Harris, M. M., Blalock, J. R. and Horwitz, W. A.*: Metabolic studies during insulin hypoglycemia therapy of the psychoses. *A. M. A. Arch. Neurol. & Psychiat.* 40: 116, 1938.
- (10) *Himwich, H. E.*: Brain Metabolism and Cerebral Disorders. Baltimore, Williams and Wilkins Co., 1951 pp. 23-25.
- (11) *Himwich, H. E. and Nahum, L. H.*: The respiratory quotient of the brain. *Amer. J. Physiol.* 90: 389, 1929. *Ibid.* 101: 446, 1932.
- (12) *Kay, W. W. and Thorley, A. S.*: Some biochemical aspects of hypoglycemia coma. *Proc. Roy. Soc. Med.* 44: 973, 1951.
- (13) *Livingston, W. K., Hangen, F. P. and Brookhart, J. M.*: Functional organization of the central nervous system. *Neurology*, 4: 485, 1954.
- (14) *Penfield, W. and Jasper, H.*: Epilepsy and the Functional Anatomy of the Human Brain - Boston - Little, Brown and Co., 1954.
- (15) *Rinkel, M. and Himwich, H. E.*: Insulin Treatment in Psychiatry. New York, Philosophical Library, 1959.
- (16) *Thorley, A. S. and Kay, W. W.*: Some biochemical aspects of hypoglycaemic coma. *Proc. Roy. Soc. Med.* 44: 969, 1951.
- (17) *Tokizane, T. and Sawyer, C. H.*: Sites of origin of hypoglycemic seizures in the rabbit. *A. M. A. Arch. Neurol. & Psychiat.*, 77: 259, 1957.
- (18) *Van Meter, W. G., Owens, H. F., and Himwich, H. E.*: Cortical and rhinencephalic electrical potentials during hypoglycemia. *A. M. A. Arch. Neurol. & Psychiat.*, 80: 314, 1958.

Coma due to Cerebral Trauma

W. RITCHIE RUSSELL

Director, Department of Neurology,
United Oxford Hospitals, England.

This short article is chiefly concerned with the coma caused by head injury and not with the complications of other injuries such as fat embolisms which may lead to coma.

There are several problems of terminology when speaking of head trauma for these injuries may damage the scalp, the skull, the special sense organs, the meninges, the blood vessels (leading to haemorrhage from the scalp, nose, ear, or within the skull) and most important of all, the brain. Further the site of brain damage will vary with the type of injury. A generalised commotion will usually occur as the chief result, but in addition there may be local areas of bruising and laceration on the surface of the cerebral hemispheres.

Our main concern here is with head injuries which are associated with a severe degree of *Comotio Cerebri*.

Most of the head injuries that occur in civilian practice are caused by a sudden change of velocity imparted to the head. This change of velocity is most commonly in a negative direction as when the head strikes a hard surface in falling or when the head, while travelling in a road vehicle, is involved in a collision. The acceleration forces involved may be very high (minus 300-400 G) and these cause destructive distortions and other forces within the brain substance. These were studied by Holbourn

in 1943 and demonstrated with the assistance of high speed cinematography by Pudenz and Sheldon (1946).

Such injuries may be immediately fatal but it is of special interest to study the brains of those who were nearly killed but whose lives were saved for a time by special surgical techniques, and in whom after a very severe injury there was dementia, unconsciousness and paralysis for the rest of life. As Strich has reported (1956) some of these cases show gross destruction of nerve fibre tracts throughout the brain, changes of a type which are to be expected if the distortions and shearing stresses known to occur are very severe. In such cases the delay of weeks or months between injury and death allows time for cellular changes to occur which can be demonstrated by the pathologist to an extent that is impossible in the immediately fatal cases. However there have been several studies of the changes that appear in the nerve cells, myelin sheaths, severed axons and neuroglia soon after cerebral trauma (Courville 1960, Strich 1961), and these confirm that widespread neuronal tearing occurs in severe closed head injury.

These severe injuries are associated with deep coma and the precise mechanism of such profound loss of consciousness is a matter of interest. The well established effect of brain stem mechanisms on consciousness has led some to the view that

traumatic coma is caused by brain stem lesions. All parts of the brain stem must certainly be subjected to distorting forces in head injury but the bulky hemispheres are the most vulnerable and there is no need to look beyond the gross distortions of the hemispheres to explain the chief features of traumatic coma. The hemispheres are most affected by such distortions owing to their size and shape, and are physiologically just as likely to inactivate brain stem mechanisms as the other way round. The part played by the direct injury to the brain stem in the ordinary case of cerebral commotion is therefore largely a matter of conjecture.

In the study of traumatic coma the most important clinical feature is often concerned with its duration. It is of course well known that the delayed appearance of coma after partial or full recovery of consciousness is an important indication that cerebral compression may be developing and may require urgent surgical relief. In the absence of any such emergency the duration of coma assumes great importance for in studying *commotio cerebri* we meet the remarkable characteristic of nervous system injury which is that the severity of the injury is reflected in *the duration* of disturbed function. This is well seen also in cases of spinal concussion or in direct trauma to a peripheral nerve, where it may often be observed that the severity of the injury is related directly to the duration of disability.

The *duration* of coma after head injury is therefore an important guide to severity. The term coma is however used in many ways, and some restrict it to the most profound state of unconsciousness in which no bodily or reflex responses can be obtained. Whatever interpretation may be given to the term coma, there can now be no doubt that the best guide to the severity of an uncomplicated closed head injury is the duration of loss of full consciousness (Russell, 1959), and the duration of deep coma is equally significant. This is a most important fact for it indicates that the descriptions of head injury in terms of *concussion*, *contusion* or

laceration of the brain are no longer acceptable as being a sound basis for the classification of severity. The absence or presence of such visible lesions in the brain at post-mortem or at operation give no satisfactory picture of the severity of the general cerebral commotion, the main consequences of which are invisible. Similarly the presence or absence of skull fracture may be unimportant in relation to severity though of course complications such as dural haemorrhage or meningitis are vital from the point of view of treatment.

The basic disorder therefore in traumatic coma is often not amenable to treatment and the surgeon should attempt to separate in his mind the general effect of the cerebral commotion from the careful observations which will enable him to recognize treatable complications or epiphenomena which require surgical intervention.

In this connection repeated observations on the degree of unconsciousness are of the greatest importance for uncomplicated traumatic coma should be most profound immediately after the injury and should lighten steadily at a rate which is related to the severity of the injury. Any change in consciousness which is at variance with the improvement to be expected must therefore cause anxiety regarding the possible development of some complication requiring active intervention. In this connection it must of course be realized that a restless and even violent patient is *more* conscious than one who is inactive and unresponsive.

A special difficulty arises when the patient who has been deeply unconscious from the moment of injury, fails to improve, or whose condition worsens perhaps with some inhalation pneumonia. Here there is no lucid interval to help in diagnosing the development of cerebral compression by haemorrhage, and for this reason many surgeons prefer in such cases to make several burr holes in the skull so as to ensure that there are no massive collections of dural haemorrhage which might be endangering recovery. In such severe cases dural haemorrhage and cortical damage will often be seen at operation

and the precise contribution to the clinical picture of these visible findings is often difficult to assess.

The special hazards of traumatic coma are similar to those of deep anaesthesia when there is no expert at hand to care for the patient. The swallowing reflexes may be absent and the airway may be obstructed owing to the effects of a fractured jaw. Blood or vomit if inhaled at this stage is perhaps the most important cause of death, and survival may depend on correct first-aid treatment. In this connection ambulance workers should learn to transport unconscious patients in the semi-prone posture so that secretions in the mouth and throat will drain away and thus the danger of vomiting will be lessened.

In all patients with traumatic coma due to head injury it is important to remember that other injuries are common and are in such circumstances difficult to recognize. Of special importance is the recognition of injury to the cervical spine and any difficulty experienced in being able to stimulate movement of the legs during clinical examination should be observed with caution. The spontaneous breathing of a patient with injury to the spinal cord in the neck is highly characteristic if the spinal cord has been injured for there is no movement of the intercostal muscles in breathing and the upper limbs tend to adopt an attitude of abduction at the shoulder, flexion at the elbow and supination at the wrist.

In the worst cases of traumatic coma there is a tendency for decerebrate rigidity to develop and to persist in the cases that are never going to recover consciousness. Decerebrate postures will of course be obscured if the upper spinal cord is also injured.

The stages of recovery from traumatic coma may progress to a return of consciousness in a few minutes, a few hours, or days, or weeks, or never at all. These stages are rather similar in all degrees of commotion although the speed with which they appear varies from minutes to weeks according to the severity of brain damage.

During the stages of recovery the patient is unable to memorize anything and therefore after recovery has amnesia for all the period of disturbed consciousness. It is for this reason that the duration of amnesia in relation to a head injury —the post-traumatic amnesia (P.T.A.)— has such an important and lasting influence on the subsequent assessment of severity (Russell, 1932, 1959).

Retrograde Amnesia (R. A.)

The problem of retrograde amnesia is not only of academic importance, for its occurrence is invariable after traumatic concussive coma of even short duration. It is of course of great interest in relation to the study of brain mechanisms, that coma caused by concussion blocks the memory of events which just preceded the head injury. Existing evidence indicates that there must be some succeeding moments of normal brain activity for new events to be stored, and that R.A. depends on this period of normal activity being cut short by the paralysing effect of concussion. A similar phenomenon occurs in relation to electric convulsion therapy. This is such a constant effect of traumatic coma that it comes to play an important part in the retrospective assessment of head injury cases. There is a tendency for the duration of R.A. to be related to the duration of P.T.A. (Russell and Nathan, 1946), and in addition there is a remarkable tendency for information acquired shortly before the injury to be more vulnerable and therefore forgotten, whereas the older memories are usually well preserved.

Terminology

The differing ways in which the term coma is used has already been referred to and it has been pointed out that most authorities use it to describe a very profound degree of loss of consciousness. As a diagnostic category however it has little meaning in itself for the critical factor in

assessment does not depend on the occurrence of coma but on the duration of coma. Similarly there has been some confusion regarding the term concussion for some have used the term to indicate a grade of injury regarding which there is only a very short period of traumatic coma, in which there is no visible pathological change (should the brain be available for study), and from which complete recovery occurs. With this definition therefore the occurrence of a post-concussional syndrome becomes a contradiction.

In fact of course there is no possible means of distinguishing harmless "concussions" from other degrees of cerebral commotion, for as Jefferson (1942) pointed out we are always dealing with the invisible effects on the cerebral neurones, of contusion or distortion. Brock (1960) advises that this quandary be resolved by using the terms *transient* concussion, *prolonged* concussion or *fatal* concussion. However as the term concussion suggests a momentary phenomenon the use of *prolonged* concussion is not very satisfactory. The writer prefers the term traumatic cerebral commotion with the clear inference that grades of severity are principally related to the duration of disturbed consciousness or to the duration of deep coma. The occurrence of complications may of course dominate the clinical picture but the effects of these are more clearly assessed when the severity of the primary

cerebral commotion can be indicated by the duration of immediate post-traumatic coma. The *duration* of disordered brain function must therefore be brought into all attempts to grade severity of closed head injury. It is for this reason that the duration of traumatic coma, the duration of traumatic confusion (evidenced by the duration of post-traumatic amnesia) are of such very great importance in classification.

All such rules however have exceptions in clinical practice. In a few instances unconsciousness is prolonged for several weeks and yet a good clinical recovery occurs. In such cases the possibility of a localized upper brain stem lesion has to be considered. In a survey conducted by the Society of British Neurological Surgeons, there was evidence that children could survive in coma for as long as 12 weeks and ultimately make a useful functional recovery. In adults, on the other hand, the evidence was that it was extremely rare for a patient who had been comatose for longer than 4 weeks to make any kind of useful recovery (Pennybacker, 1962).

Finally it should be emphasized that our knowledge of the physical basis of consciousness of memorizing and of storing memories etc. is so very limited that it is still impossible to assess with accuracy either the immediate or remote effects of head injury on the more subtle aspects of human intellect.

S U M M A R Y

Most head injuries that occur in civilian practice involve a sudden change of velocity to the head (300-400 G). This sets up shearing stresses which interrupt or destroy nerve fibres, especially within the cerebral hemispheres, and these gross hemisphere lesions are likely to lead to coma without the brain stem being necessarily involved. The changes of cerebral commotion are difficult to see with the microscope and indeed have been called "invisible". The severity of brain damage may often be related most accurately to the *duration* of disordered function, so that

any classification of head injury used must include the duration of coma or the duration of traumatic amnesia. The previously used grades of injury such as concussion, contusion or laceration are no longer acceptable. First aid treatment of traumatic coma involves careful posturing to avoid inhalation of vomit. Associated injuries to the spinal cord must not be overlooked. Coma which lasts for more than twelve weeks in the child or more than four weeks in the adult is very unlikely to be followed by a useful degree of recovery.

RESUMEN

La mayor parte de los traumatismos cefálicos que se presentan en la práctica civil llevan implicados un cambio en la velocidad de la cabeza (300-400 G.). Esto determina sacudidas violentas, las cuales interrumpen o destruyen fibras nerviosas, especialmente dentro de los hemisferios cerebrales y estas grandes lesiones hemisféricas probablemente conducen al coma, sin que el tronco cerebral esté necesariamente afectado. Los cambios que ocurren con la conmoción cerebral son difíciles de apreciar con el microscopio, en realidad han sido llamados "invisibles". La severidad del daño cerebral a menudo está en relación directa con la *duración* de la perturbación funcional, de tal modo que cualquier cla-

sificación que se haga del trauma cefálico, debe tener en cuenta la duración del coma o la duración de la amnesia traumática. No pueden seguir aceptándose las gradaciones en la intensidad de la alteración cerebral tales como la conmoción, contusión o laceración. Desde los primeros momentos del tratamiento del coma traumático, debe considerarse una posición adecuada para evitar la inhalación del vómito. Especial cuidado debe ponerse para evitar desconocer lesiones medulares asociadas. Cuando el coma dura más de doce semanas en el niño o más de 4 semanas en el adulto es muy poco probable que pueda ser seguido por un grado de recuperación aceptable.

R É S U M É

La plupart des lésions cérébrales qui se présentent pendant la pratique civile impliquent un brusque changement de vitesse dans le tête (300 - 400 G.). Ceci détermine de violentes secousses qui interrompent ou détruisent les fibres nerveuses, surtout celles des hémisphères cérébraux, et ces grandes lésions hémisphériques ont la possibilité de conduire au coma sans que le tronc cérébral soit nécessairement affecté. Les changements de la commotion cérébrale sont difficiles à voir avec le microscope et ont été appelés en réalité "invisibles". La sévérité de la lésion cérébrale peut assez souvent être en relation directe avec la durée de la fonction déré-

glée, de façon que chaque classification de lésion cérébrale quelle qu'elle soit, doit inclure la durée du coma ou bien la durée de l'amnésie traumatique. Les degrés préalablement considérés comme la concussion, la contusion ou la laceration ne sont plus acceptables. Le traitement de premier secours du coma traumatique implique une posture soignée pour éviter l'inhalation du vomissement. Les lésions associées à la moelle spinale ne doivent pas être négligées. Le coma durant plus de douze semaines chez l'enfant ou plus de quatre semaines chez l'adulte a peu de probabilités d'être suivi d'un degré utile de récupération.

ZUSAMMENFASSUNG

Die meisten Kopftraumen, die sich in der zivilen Praxis ereignen, sind durch eine plötzliche Geschwindigkeitsänderung des Kopfes hervorgerufen (300 a 400 G.). Dadurch werden scherende Kräfte hervorgerufen, die Nervenfasern, besonders in den Hirnhemisphaeren unterbrechen oder zerstören. Diese groben Verletzungen in den Hemisphaeren können zum Koma führen, ohne dass notwendigerweise der Hirnstamm betroffen ist. Die

Veraenderungen bei der Hirnerschuetterung sind schwerlich mit dem Mikroskop zu sehen und deshalb "unsichtbar" genannt worden. Die Schwere der Hirnlaesion kann oft sehr exakt mit der *Dauer* der gestoerten Funktion in Beziehung gebracht werden, sodass jedwede anzuwendende Klassifizierung der Kopfverletzungen die Dauer des Komats oder die Dauer der traumatischen Amnesie mit in Betracht ziehen muss.

Die fruher ueblichen Grade der Laesion wie Gehirnerschuetterung, Kontusion oder Laceration sind nicht mehr annehmbar. Die Behandlung bei der Ersten Hilfe im Falle eines traumatischen Komas betrifft die sorgfaeltige Lagerung, um das Inhalieren des Erbrochenen zu vermeiden. Kompl-

zierende Verletzungen des Rueckenmarks duerfen nicht uebersehen werden. Es ist sehr unwahrscheinlich, dass ein Koma von mehr als 12 Wochen beim Kinde und mehr als 4 Wochen beim Erwachsenen zu einem irgendwie nuetzlichen Grade der Genesung fuehren kann.

REFERENCES

- Brock, S.: 'Injuries of the Brain and Spinal Cord'. Fourth edition. London: Cassell. (1960).
 Courville, C. B.: In 'Injuries of the Brain and Spinal Cord' Edited by Brock. Fourth edition. London: Cassell. (1960).
 Holbourn, A. H. S.: Lancet, 2, 438. (1943).
 Jefferson, G.: Glasg. Med. J., 20, 77. (1942).
 Pennybacker, J.: Personal communication. (1962).
 Pudenz, R. H. and Sheldon, C. W.: J. Neurosurg 3, 487. (1946).
 Russell, W. R.: Brain, 55, 549. (1932).
 Russell, W. R.: 'Brain: Memory: Learning' Oxford: Clarendon Press. (1959).
 Russell, W. R. and Nathan, P.: Brain, 64, 197. (1946).
 Strich, S. J.: J. Neurol. Neurosurg. Psychiat., 19, 163. (1956).
 Strich, S. J.: Lancet, 2, 443. (1961).

Coma Produced by Expansive Intracranial Processes

EDWIN BOLDREY, M. D.

From the Division of Neurological Surgery, University of California School of Medicine, San Francisco 22, California.

In this present day of widespread interest in and alertness on the part of the medical profession to the possible presence of an expanding intracranial lesion, the presence of coma as a sign or symptom of such a lesion has become gratifyingly less and less. Under some conditions, though, rarely however, it is inescapable for it may be an early sign of such disease. It will always continue to some extent as a late sign, too, for the level of medical discipline in the profession can never surpass the intelligent complement of the population which it serves. There will always be patients who fail to present themselves until the late stages of the disease process, and usually then expecting a miracle.

For the purpose of the following discussion, coma will be interpreted to mean a state of absolute unconsciousness, as judged by the absence of any psychologically understandable response (including, for example, change of expression) to external stimuli or inner need⁽¹⁾. In the same context, expansive intracranial process will be assumed to mean a focalized lesion of varying size which, by some aspect of its nature, can be expected to enlarge in its dimensions. We are to discuss, therefore, the production of a pathophysiologic entity—absence of consciousness (coma)—by one of a group of specific pathologic processes

whose common property is the occupation of increasing amounts of space within the confines of the cranial cavity. To do this, some further delineation would seem to be in order. The first relates to the organic basis of coma.

From the anatomic-physiologic standpoint, consciousness and its counterpart, coma, are becoming considered more and more as being associated with that central portion of the brain known as the reticular formation. Any disease process therefore, which results in loss of consciousness, or coma, must be considered to be located anatomic-ally in or directly adjacent to this region or to be affecting it functionally through its more intimate connections. To interfere with consciousness it would seem that the reticular formation, then, must be rendered temporarily or permanently inactive. Our discussion, therefore, will center around methods whereby the expanding lesions within the brain accomplish this end.

The second factor requiring some identifying delineation is related to the scope of the term "expansive intracranial processes". In addition to the intracranial neoplasms, it would seem appropriate to include the abscesses and the hematomas as such, disregarding in each instance, etiology. The latter two categories unquestionably fall within the limits of our discussion.

Expansive intracranial processes may produce coma by a number of ways. These include: location, character of the lesion, reaction of surrounding tissues, speed or rate of development of disrupting effect, and by indirection through the generalized disturbance of such as that of nutrition and electrolytes.

The association of coma with neoplasm and, less frequently, with abscesses and hematoma occupying the region of the thalamus bilaterally and, to some extent, involving the upper brain stem has been known to neurologists for many years indeed. The connection was certainly recognized by the physiologist, Sherrington⁽²⁾, and in the opinion of some, the appreciation of the relationship of this area with consciousness was recognized by Sir Charles Bell⁽³⁾ some 65 years earlier. Sir Geoffrey Jefferson^(4, 5) re-emphasized the importance of the region and more recently mentioned it in his chapter which appeared in the volume "Reticular Formation of the Brain"⁽⁶⁾. Contributions by a number of other investigators (French⁽⁷⁾, Magoun⁽⁸⁾, Penfield^(9, 10), Scoville⁽¹¹⁾, and Walker⁽¹²⁾) have served to substantiate the localization of at least the major representation of what is known as consciousness or, in its absence, coma.

The gliomas are the most common neoplasms directly involving the thalamus and the upper brain stem. Intrinsically located, the most recurrent of these are the astrocytomas, though ependymomas, glioblastoma multiforme, oligodendroglioma, and polar spongioblastoma may invade the area, but less frequently. Hematomas in this region may be within the ventricle involving the nervous tissue secondarily. Small hematomas are recognized as agonal findings under a variety of circumstances usually associated with generalized increase of intracranial pressure. Abscesses are not common in this area, being located more frequently in the periphery. Occasionally they will occur, though, as will the granulomas, and when properly situated will be associated with impairment or absence of consciousness. Tuberculomas are not rare here. The seriousness of such developments however must be eminently apparent. In the production of coma it is important to bear in

mind that the lesion must be bilateral to have its effect and, if bilateral and producing coma, the lesion must be regarded as inexorably irreversible. It is doubtful that when such a tumor location has been proved satisfactorily any present therapeutic effort — surgical, radiologic, or chemical is warranted.

Pressure from without onto the thalamus and upper brain stem can influence this reticular formation, producing disruption of consciousness. The pressure of the colloid cyst of the third ventricle, or the intraventricular masses similarly located, is usually augmented by the increase of intracranial pressure jamming the cyst against the ventricular wall and the adjacent foraminae. Cysts about the sella turcica, usually regarded as arising from cell remnants of the stomadeal anlage of the anterior pituitary, may reach the size where direct pressure upon the inferior part of the midbrain or on the diencephalon may be of such degree as to impair consciousness. The same may apply to the larger chromophobe adenomas which have burst through the diaphragm of the sella to pour over the dorsum sellae into the posterior fossa⁽¹³⁾. Meningiomas, perineurial fibroblastomas of the 3th nerve, and polar spongioblastomas arising from the optic pathways and chiasm may similarly have an effect by direct compression on this sensitive region.

The tumors arising from the pineal posteriorly likewise can reach sufficient size to impair function by transmitted compression.

Large masses, neoplastic, infectious, or hemorrhagic which are at a greater distance may also have an effect. Growths in the midline as in parasagittal region may cause an actual displacement of the brain stem with "buckling"^(14, 15). The degree of this buckling may embarrass the function of the affected region and interfere with consciousness. Among the more common of the tumors having this effect would be the parasagittal meningiomas, particularly those arising in the parietal or paracentral region.

Lateral displacement of the brain stem by lesions in the middle fossa or anterior displacement by expansile masses in the oc-

capital area may also compress the stem in such a manner as to interfere with blood supply at the capillary level or in the larger branches, even occasionally in the main arterial or venous components, particularly the basilar artery or the great cerebral vein of Galen and its tributary galenic system. Space-occupying lesions in the posterior fossa by their very size likewise displace the stem laterally, posteriorly, or forward. The effect of lesions in this region is usually considerably augmented by the increase of intracranial pressure and downward migration of the more mobile cerebellum with its direct oppressive effect on nervous tissue in the brain stem as well as by interference with blood supply.

It has been considered by some that the presence of a bilateral frontal neoplasm may produce coma. It is our feeling, that while consciousness and responsiveness may be seriously obtunded by bilateral frontal lesions, consciousness as such, is not a function *per se* of these structures. It is doubtful that even interruption of the cortical connections with the brain stem and thalamus can be of sufficient extent and magnitude to produce true coma. Large masses in the frontal region, however, are likely to result in actual displacement of the central centers with embarrassed function.

The character of the disturbing lesion will also have some relationship to the production of coma. In the earlier paragraphs we have mentioned the invasive tumors which primarily implicate the region of the reticular formation. The polar spongioblastoma may insinuate itself in almost a symbiotic relationship to the normal cells and may reach excessive size before the function of these cells will have been stifled. The metastatic growth or the glioblastoma multiforme developing in more vigorous fashion and with more ruthless effect will be less tolerant of normal tissue and will impair consciousness with greater rapidity and certainty. The infectious processes and the hemorrhagic processes are even more rapid in development as a rule and engender more tissue response in the surrounding areas, interfering with nutrition and disrupting function, therefore, even more acutely. The character of the lesion at a distance is less

directly related to the effect on consciousness, except as it develops its effective role by point of time and by effect upon the surrounding tissues even at a distance.

This leads us then to some remaining factors of greatest consequence, in particular the reaction of the surrounding tissue and the speed or rate of development of the disrupting effect.

Of the neoplasms, the metastatic growths and the glioblastoma multiforme produce the most violent reaction on the part of the surrounding tissue. Hemispherical or at times generalized cerebral edema is a major factor in the development of symptomatology in both of these lesions and may develop with impressive rapidity. Tiny metastases in appropriate situations in the brain stem can produce interference with consciousness, greatly exceeding that anticipated from the mere size of the offending mass itself. To a less degree, the same can be said of glioblastoma multiforme, though its proclivity in migration along fiber pathways makes this trend less apparent in the study of the final pathologic process.

Abscess and granuloma are essentially in the same category as the metastatic growths, though their effect upon tissue reaction at a distance may be less. The catastrophic effect of hematoma also invokes the second factor—speed or rate of development as well as that of local tissue reaction.

The role of the rate of progress of a disrupting lesion on the central nervous system has become increasingly recognized in recent years. In the case of those lesions affecting the reticular formation, this is indeed well demonstrated. The sudden development of a space-occupying lesion such as hematoma within or directly adjacent to this region will produce abrupt loss of consciousness. Direct, sudden pressure on the area may not be the sole etiologic factor associated, vasoconstriction (vasospasm) which often results and which reduces the blood supply to this area may also be significant. The slower development of effect of abscesses and granulomas alluded to above will impair consciousness more gradually but still, because of rapid swelling of the surrounding tissue and the morbidity of the cells in nearby regions, will conspire to fa-

cilitate the impairment of consciousness in the early stages of disease. Slowly developing masses, such as the indolent gliomas, meningiomas, or cysts may result in considerable distortion or displacement of the brain stem and thalamus before consciousness is interfered with.

Under the latter circumstances, some extraneous force may enter the picture to produce loss of consciousness by the introduction of a third element. The sudden addition to the volume of space-occupying lesions by such an occurrence as a hemorrhage within it will have an obvious effect. A sudden strain, as at stool, by increasing the intracranial contents through venous obstruction may likewise affect the marginally functioning central mechanism adversely. Increased intracranial pressure per se must reach tremendous levels before consciousness will be interfered with, though it has been demonstrated by many methods, including angiography, that greatly increased pressure may indeed slow down the rate of blood flow through vascular channels. The slowly developing pressure within the cranium may be accommodated for by the vascular system if time for adjustment is provided. The sudden increase of pressure, however, precludes tissue adaptation and may cause loss of consciousness through actual interference with adequate arterial supply. Similarly, massive venous obstruction at points of transfer from the brain to the dural sinuses, as well as direct sudden compression of the centers themselves may likewise represent cause for disruption of function. The ambulatory patient with brain tumor who is found unconscious at the toilet, having strained at stool, is still not a rarity in the wards of the general hospital. Sudden shifts of poorly anchored masses or of mobile intrinsic tissue such as the cerebellar tonsils or the hippocampus may interrupt a marginally functioning midbrain and, for example, may be the result of lumbar puncture for any purpose. The consequence may be catastrophic. This factor has become a particularly disturbing one in recent years due to the questionable teaching by some that manipulative gas/fluid exchange can be safely carried out in the face of recognized intracranial hypertension. The insult is too

often further augmented by the "routine" addition of the jugular compression (Queckenstedt) test.

Convulsive seizures are common in patients with intracranial masses and may play a part in production of coma in these conditions. The factors of sudden violent strain, and of venous engorgement, are the offending additions to the situation which is already marginal.

Many intracranial lesions have been regarded as having a potential association with electrolyte imbalance. There can be little question as to the valid implication of those about the hypophysis and hypothalamus, as well as those in the lower medulla and fourth ventricle. Sodium levels seem to be particularly susceptible with fluids directly or indirectly related. While relatively low serum sodium may be well tolerated by the normal and even desirable in certain conditions such as cardiovascular decompensation, the alteration in blood brain barrier associated with many intracranial neoplasms and the crowding of the contents of the cavity inherent with all sizable growths makes this systemic disturbance in a patient with brain tumor one of potential major import. The wet brain, often thus complementing the disturbed organ, may tip the balance adversely and may provide the final element ending in disaster. If recognized though, the reversal of the electrolyte imbalance may be dramatically rewarding, deep coma often becoming dispelled in but a few hours.

The adverse effects of over-hydration, of respiratory depression, and of alkalosis are similarly based; correction of the deficit when recognized is similarly rewarding for the moment. It is apparent, of course, that the revival is limited to the effect of correction of the added factor, though, and the basic neoplasm must still be removed.

After incomplete removal of many intracranial tumors, ionizing radiation has been employed often to supplement the surgery and, at times, it has even been used as the major therapeutic device. During the second month post-radiation, it is commonplace to see exacerbation of symptoms even to the point of coma. This is regarded as

a delayed effect of radiation with tissue swelling, rapid in development, as the major pathologic basis. Again, the addition of fluid to tissues already anatomically and

physiologically impaired affects the central mechanism of consciousness, interfering with conscious activity. Large doses of steroids are usually of benefit.

S U M M A R Y

Coma associated with expansive intracranial processes is the result of involvement, directly or indirectly, of the reticular formation — that functional complex regarded as being represented in the central core of the brain from the region of the thalamus, caudad into the medulla. The processes under review affect this area directly due

to location in it of the mass or indirectly through displacement and compression, interference with blood supply or by stifling of function by edema. Indirect involvement may be reversed if the problem is treated early; direct involvement carries a grave prognosis.

R E S U M E N

El coma que está asociado a una lesión intracraneana expansiva, es consecuencia de la perturbación directa o indirecta de la formación reticular — ese complejo neuronal que está presente en la parte central del tronco cerebral desde la región del tálamo hasta el bulbo raquídeo. Los procesos que estudiamos afectan esta región sea directamente por la localización de la lesión en

ella o indirectamente desplazándola y comprimiéndola, interfiriendo en el aflujo de sangre, o sofocándola funcionalmente por edema. El compromiso indirecto del tronco cerebral puede ser reversible si el tratamiento se hace temprano; en cambio el compromiso directo lleva en sí un pronóstico grave.

R É S U M É

Le coma associé avec une lésion intracranienne expansive est le résultat direct ou indirect d'une perturbation de la formation réticulaire — ce complexe fonctionnel qu'on croit représenté dans la partie centrale du tronc cérébral dès la région thalamique jusqu'au bulbe rachidien. Les lésions ci — discutées affectent cette région directement

à cause de l'emplacement de la masse, ou indirectement par déplacement et compression, par l'interférence dans l'apport sanguin, ou en étouffant la fonction par un oedème. Un embarras indirect peut-être réversible si la condition est traitée de bon temps; un embarras direct indique un pronostique grave.

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

Ein Koma das mit einem expansivem intrakraniellen Prozess verbunden ist, ist das Resultat einer direkten oder indirekten Mitbeteiligung der retikulären Formation — diesem funktionellen Komplex von dem man annimmt, dass er im Zentralkern des Gehirnes, caudal von der thalamischen Gegend nach der Medulla Prolongata zu seinen Sitz hat. Die hieroben besprochenen Prozesse haben eine direkte Wirkung auf diese Ge-

gend hervorgerufen durch die sich da befindende Masse, oder sie haben eine indirekte Wirkung durch Verschiebung und Kompression, mit Störungen in der Blutzufuhr, oder durch ein Oedem das die Funktion erstickt. Indirekte Mitbeteiligung kann korrigiert werden, wenn der Zustand gleich unter Behandlung kommt; direkte Mitbeteiligung führt eine ernste Prognose mit sich.

REFERENCES

- (1) M. R. C.: War Memorandum N° 4. Brain Injuries Committee. A Glossary of Psychological Terms Commonly Used in Cases of Head Injury.
- (2) Sherrington, Sir Charles S.: Reticular Formation in: Reticular Formation of the Brain, Henry Ford Hospital International Symposium. Little, Brown and Company, Boston, 1958, pp. 730-731.
- (3) Bell, Sir Charles: Cortex in: Reticular Formation of the Brain, Henry Ford Hospital International Symposium. Little, Brown and Company, Boston, 1958, p. 730.
- (4) Jefferson, Sir Geoffrey: The Tentorial Pressure Cone. A.M.A. Arch. Neurol. & Psychiat. 40:857, 1938.
- (5) Jefferson, Sir Geoffrey: The Nature of Concussion. Brit. Med. J. 1:1-5, 1944.
- (6) Jefferson, Sir Geoffrey: The Reticular Formation and Clinical Neurology, in: Reticular Formation of the Brain. Henry Ford Hospital International Symposium. Little, Brown and Company. Boston, 1958, pp. 729-738.
- (7) French, John D.: Corticofugal Connections with the Reticular Formation, in: Reticular Formation of the Brain. Henry Ford Hospital International Symposium. Little, Brown and Company. Boston, 1958, pp. 491-505.
- (8) Magoun, Horace W.: Cortex, Brain Stem in: Reticular Formation of the Brain. Henry Ford Hospital International Symposium. Little, Brown and Company. Boston, 1958, p. 730.
- (9) Penfield, Wilder: Cortex in: Reticular Formation of the Brain. Henry Ford Hospital International Symposium. Little, Brown and Company. Boston, 1958, p. 730.
- (10) Penfield, Wilder: Cerebral Cortex and Consciousness. The Harvey Lectures (1936-37). 32:35-69. 1937.
- (11) Scoville, W.: Observations of Consciousness and Seizure Formation Following Stimulation of Septal and Uncal Areas in Man. Proc. First Internat. Cong. Neurol. Sci., Brussels, 1957.
- (12) Walker, A. Earl: Discussion in: Reticular Formation of the Brain. Henry Ford Hospital International Symposium. Little, Brown and Company. Boston, 1958, pp. 741-743.
- (13) Decourt, Jacques.; David; Marcel; Michard, J. P. and West, Bernard: Coma hypopituitaire au cours d'un adénome hypophysaire. Etude physiopathologique et thérapeutique. Soc. Med. des Hopit. de Paris. 1954, pp. 110-134.
- (14) Howell, D. A.: Upper brain stem compression and foraminal impaction with intracranial space-occupying lesions and brain swelling. Brain. 82:525-550. 1959.
- (15) Howell, D. A.: Longitudinal brain stem compression with buckling. Arch. Neurol. 4:572-579. 1961.

Coma Hépatique des Cirrheses

G. BOUDIN et R. LABET

(Paris).

Les encéphalopathies des cirrheses, selon l'expression de Fauvert, ont fait l'objet de nombreux travaux récents dont le but est le démembrement du coma hépatique, amorcé par les anciens auteurs. Ces travaux sont appuyés sur le concept de l'hyperammoniémie, lequel ne saurait prétendre tout expliquer.

HISTORIQUE

L'étude des relations foie-système nerveux commence en 1861 avec la parution du traité pratique des maladies du foie de Frerichs: celui-ci signale l'existence de deux phases évolutives de l'ictère grave, l'une d'excitation, l'autre de coma.

En 1887, Hahn et Pávlov décrivent le syndrome d'intoxication à la viande chez le chien porteur d'une fistule d'Eck et rendent l'ammoniaque responsable de l'évolution comateuse.

Lancereaux, en 1899, a le mérite de la première tentative de démembrement du coma hépatique en décrivant des accidents neuropsychiques transitoires au cours de cirrheses apparemment bien compensées.

Vers 1929-1933, Van Caulaert et Deviller précisent le rôle nocif de l'ammoniaque sur l'état de conscience des cirrhotiques ayant ingéré du chlorure d'ammonium.

Les travaux modernes ont confirmé le polymorphisme de telles encéphalopathies. L'étude d'ensemble d'Adams et Foley (1949) revêt un intérêt capital en isolant le syndrome porto-cave. Citons également

les travaux en France de Fauvert, Cachin, Stahl et Rohmer, en Grande-Bretagne de Sherlock et Summerskill.

De tous ces travaux, il ressort schématiquement deux aspects physiopathologiques majeurs:

—les cirrheses avec insuffisance hépatique grave irréversible;

—les cirrheses bien compensées où domine l'hypertension portale. Il va sans dire que tous les intermédiaires entre ces positions extrêmes peuvent être observés.

ETIOLOGIE

—*La fréquence* des encéphalopathies des cirrheses (E. C.) est élevée si on les recherche systématiquement. Ainsi Fauvert les trouve dans près d'un quart des cas d'une série de 252 cirrheses.

—*Le type de la cirrhose*: la cirrhose éthylique constitue la cause majeure du fait de sa fréquence absolue et de l'importance habituelle des anastomoses porto-caves. Le degré de l'insuffisance hépatique est fort variable, illustrant l'intervention de mécanismes physio-pathologiques non univoques. Les cirrheses d'autres natures exposent aux mêmes accidents neuro-psychiatriques dont le dénominateur commun est soit la grande insuffisance hépatique soit les dérivations porto-caves. Il en va de même dans l'encéphalopathie de Gayet-Wernicke où le dénominateur commun est le facteur carenciel qu'il soit éthylique ou non.

Les facteurs déclenchants

L'E.C. peut survenir spontanément, constituant l'aboutissant irrémédiable de la déchéance cellulaire hépatique.

Mais les facteurs déclenchants sont fréquents (50 % des 73 cas de Fauvert), ils sont d'ordre clinique, médicamenteux et chirurgical.

a) Facteurs cliniques:

—Diététique: régime hyperprotidique abusif.

—Hémorragies digestives, facteur le plus fréquent dans la série de Fauvert (14/37), elles mettent en valeur le rôle du court circuit porto-cave et répondent typiquement au coma post-hémorragique différé de Cahera.

—Causes infectieuses: si toutes les infections générales intercurrentes peuvent déclencher une poussée d'insuffisance hépatique, il faut surtout insister sur les infections intestinales avec diarrhée qui augmentent considérablement la teneur en produits ammoniacaux du tronc porte (diarrhée comatigène de Caroli).

b) Facteurs médicamenteux: on a incriminé:

—la méthionine, le plasma, les hydrolysats de protéine.

—les résines échangeuses d'ions ammonium.

—les sédatifs (barbituriques et dérivés opiacés).

—les diurétiques non mercuriels (chlorure d'ammonium, acétazolamide, chlorthiazide).

—les dérivés du cortisol.

Le mécanisme d'action est variable, parfois méconnu (apport excessif d'ammoniac, non-utilisation par les tissus périphériques, rôle associé de l'hypokaliémie, etc...).

c) Facteurs chirurgicaux.

—Les anastomoses porto-caves se compliquent d'encéphalopathie dans 10 à 30 % des cas, l'accident pouvant être immédiat ou tardif (de l'ordre de quelques mois). Ce sont surtout les dérivations totales qui exposent à de tels accidents, démontrant le rôle contingent de l'atteinte hépatique dans la variété porto-cave. Cette notion apparaîtrait nettement dans l'observation de Mac

Dermott (1945) où une dérivation lors de l'exérèse d'un cancer pancréatique provoqua plusieurs comas transitoires à l'occasion d'apport protidique excessif, le foie étant indemne.

—les paracentèses abondantes peuvent avoir des conséquences mortelles. Leur mécanisme est assez particulier, mettant en jeu des désordres électrolytiques.

ETUDE CLINIQUE

Nous envisagerons la symptomatologie commune aux E.C., puis les modalités cliniques.

Le début est habituellement annoncé par le flapping-tremor (60 % pour Fauvert), suivi de troubles de l'humeur et du comportement. Mais parfois les troubles psychiques sont inauguraux; dans quelques cas, le coma peut apparaître d'emblée.

Période d'état

Nous devons insister sur l'extrême variabilité d'un jour à l'autre, voire d'une heure à l'autre, des manifestations neuro-psychiques.

1) Les troubles psychiques

Ils attirent, en règle, l'attention, sans être, pour autant, constants (90 % selon Fauvert).

Ce sont — des troubles de la conscience

— des troubles du comportement

— l'altération des fonctions intellectuelles.

a) Les troubles de la conscience.

Leur variabilité est remarquable, allant de:

—simples troubles du sommeil telles l'inversion du rythme nyctéméral, l'hyper-somnie diurne, irrésistible, de type léthargique;

—à l'obnubilation légère avec bradypsychie aprosexie, bradykinésie;

—à la confusion mentale avec désorientation temporo-spatiale, palilalie, répétition d'un geste (le malade refait plusieurs fois son lit), fréquence d'épisodes oniriques ou crépusculaires avec délire hallucinatoire surtout visuel et généralement calme.

—au maximum, coma (60 % selon Fauvert), calme sans stertor, avec attitude en flexion des membres inférieurs, disparition du flapping-tremor et abolition des réflexes ostéo-tendineux. Quelques mouvements involontaires peuvent être notés. Même profond, ce coma peut régresser complètement.

b) Les troubles du comportement.

Ils sont notés surtout dans les formes chroniques:

—Parfois un acte absurde inaugure la maladie. On dit qu'un malade d'Hippocrate aboyait brusquement; un malade de Lancereaux déposait des ordures dans la salle ou contre les meubles; il est souvent rapporté que le malade urine et défèque dans la salle (Sherlock, Cachin...).

—Ailleurs, l'attention est attirée par un changement d'humeur chez un cirrhotique: calme et docile, il devient irritable, coléreux, agité (Klippel parlait de "folie hépatique").

—Le plus souvent, le cirrhotique devient apathique, se désintéresse de son état et de l'entourage. La perte de l'autocritique et la jovialité éventuelle peuvent en imposer pour un syndrome frontal. Rappelons que plusieurs malades de Summerskill ont été recrutés dans un hôpital psychiatrique.

—Enfin un syndrome dépressif a été observé.

D'une manière générale, on retiendra que tout trouble du comportement, même discret, chez un cirrhotique doit faire redouter l'installation rapide d'un coma hépatique.

c) L'altération des fonctions intellectuelles,

consiste, en l'absence de confusion importante, en un syndrome aphaso-apraxo-agnosique, apraxie constructive, agnosie de l'espace gauche (Summerskill).

II) Les troubles neurologiques

Leur expression est diffuse, sans signe de localisation.

a) *Le flapping-tremor* (Adams et Foley).

—Un des signes cardinaux du syndrome, il est le signe le plus fréquent (77 % pour Fauvert, voire 89 % des cas si l'on exclut les comas profonds).

—Signe habituellement le plus précoce, sa valeur diagnostique est considérable: chez un cirrhotique, il fait craindre l'imminence du coma. Mais il n'est pas pathognomonique, témoignant d'un désordre métabolique qui peut être également urémique, hypokaliémique ou anoxique. Cette restriction n'a pas une grande portée pratique car le contexte clinique est fort différent.

—Il ne s'agit pas d'un tremblement mais d'une dystonie d'attitude que l'on doit rapprocher des autres manifestations extrapyramidales. Il comporte des secousses brusques, assez amples (quelques cms), survenant en salves irrégulières assez lentes (0,5 - 2/sec). Son siège d'élection est la main, on le recherche le bras tendu, la main en pronation, doigts écartés: nul au repos complet, il apparaît après une phase de latence qui peut atteindre une minute: doigts et paume sont animés de mouvements de flexion-extension avec déviation latérale des doigts évoquant un battement d'aile.

—Son extension peut intéresser tout le membre supérieur (pose des mains sur la tête), plus rarement le membre inférieur et la face. Au maximum, tout le corps est animé de secousses quand le sujet est assis au bord de son lit.

—Il s'accroît sous l'effet des émotions, de la fatigue, pour disparaître, au contraire, lors d'un coma profond. Si l'évolution est favorable, sa disparition s'observe après celles des troubles de conscience.

b) *Les troubles du tonus.*

Fort variables et d'une grande fréquence (3/4 cas), ils consistent en:

—hypertonie extra-pyramidale avec rigidité plastique, roue dentée modérée. L'association au flapping-tremor constitue une forte présomption d'E.C.

—rarement, contracture de type méningé ou tétanique avec trismus.

—au stade de coma léger, possibilité de persévération des attitudes passives, de phénomènes de préhension et succion, de mouvements involontaires de la face. Ces anomalies, en cas de coma profond font place à une grande hypotonie.

c) *Les convulsions.*

Leur fréquence est diversement appréciée: rares pour Sherlock et Fauvert, elles s'observent dans 1/3 cas d'Adams et Foley. Leur survenue semble dépendre surtout de la grande insuffisance hépatique. Boudin et Coll en ont observé six cas lors de la décompensation grave de cirrhose. Ce sont des crises généralisées ou focalisées sans substratum anatomique décelable.

d) *Les réflexes ostéo-tendineux* peuvent être exagérés et associés à un signe de Babinski transitoire. Les anomalies ont pu en imposer pour une lésion cérébrale en foyer, en cas d'unilatéralité; ici, encore, l'examen anatomique s'est avéré normal.

III) Les signes d'accompagnement

Le foetor hépaticus est le plus important: connu de longue date dans l'ictère grave terminal, il est signalé dans l'encéphalopathie porto-cave et même dans des affections non hépatiques, tel le cancer gastrique.

Assez fréquent (30 à 45 % cas), il consiste en une odeur fécale et sucrée comparée à celle d'un fruit pourri; il serait dû à l'élimination pulmonaire de méthyl-mercaptop, dérivé de la méthionine.

—l'ascite, les oedèmes, l'ictère, les hémorragies diffuses témoignent d'une insuffisance hépatique évolutive.

LES ANOMALIES ELECTRIQUES

Mises en valeur par Foley, Watson et Adams (1949), elles contribuent à isoler ce syndrome:

—ce sont des bouffées d'ondes lentes (1-2 c/sec) et surtout des éléments triphasiques. Des anomalies de type épileptique

(pointe, pointe-onde dégradée) peuvent être notées (Boudin).

—la topographie se caractérise par l'apparition frontale des ondes qui se généralisent d'avant en arrière de façon bilatérale, symétrique et synchrone.

—elles précèdent souvent les premiers troubles de conscience; leur grande labilité interdit de formuler un pronostic fâcheux sur l'examen d'un seul tracé.

—sans être spécifiques, elles ont une grande valeur d'orientation. Leurs corrélations avec les signes cliniques sont dans l'ensemble satisfaisantes; celles avec l'ammoniémie sont également correctes dans le cadre restreint de l'encéphalopathie porto-cave.

BILAN BIOLOGIQUE

Certaines anomalies biologiques ont un intérêt pratique limité:

—les électrolyses sanguines et l'équilibre acido-basique ne sont en cause que dans des circonstances particulières sur lesquelles nous reviendrons.

—la glycémie reste dans des limites normales; son abaissement s'observe dans le coma terminal sans paraître, pour autant, déterminant à lui seul.

—les perturbations du métabolisme azoté sont variables. L'hyperazotémie est plus fréquente que l'hypoazotémie. Signalons ici l'hyperpolypeptidémie et l'hyperpolypeptidorachie (à noter que le L.C.R. est en règle normal).

—*Les tests hépatiques fonctionnels* sont variables, fonction de l'intervention prépondérante ou non du mécanisme hépatique.

—*Les perturbations du métabolisme intermédiaire* (acide pyruvique, lactique et α cétaglutarique) sont intéressantes par les perspectives qu'elles ouvrent.

—*Mais la grande anomalie biologique est l'hyperammoniémie:*

—son association aux anomalies cliniques et électriques autorise à porter le diagnostic d'E.C.

—elle peut atteindre 5 fois son chiffre normal en cas d'hémorragie digestive.

Mais sa technique est délicate, exige un dosage immédiat par un biologiste

entraîné. (Le taux peut être multiplié par 4 si le dosage est effectué une heure après le prélèvement). Le taux normal est inférieur à 50 microgrammes pour 100 cc. de plasma, selon la méthode de Conway.

—sa valeur est contestée, car elle est absente dans 10 % des cas de comas (Sherlock) ou peut être isolée sans traduction clinique.

—nous reviendrons sur ces critiques, mais signalons dès maintenant que son interprétation est surtout valable dans la variété porto-cave.

EVOLUTION

Le caractère non univoque des E.C. se retrouve dans l'évolution.

—la mort peut apparaître rapidement inévitable; elle survient en 5 à 10 jours dans la moitié des cas.

—ailleurs, la régression spontanée ou hâtée par le traitement s'observe en moins d'une semaine, voire en 48 heures. Cette discordance évolutive ne peut dépendre, dans ses grandes lignes, que de mécanismes différents. Dans cette éventualité, le coma post-hémorragique différé (48 heures après une hémorragie digestive abondante) s'individualise par sa brutalité d'installation, son mécanisme physiopathologique apparemment simple et sa gravité immédiate atténuée.

—de toute façon, l'équilibre du malade demeure précaire et est exposé à de nouveaux comas transitoires ou définitifs. (Coma hépatique à rechutes).

—lorsque ces accidents se multiplient, ils peuvent réaliser l'encéphalopathie porto-cave chronique (Sherlock) qui est rare (5 % cas) et est caractérisée par la richesse des troubles psychiques la rareté du coma, qui expliquent que la majorité de ces cas ait été recueillie en milieu psychiatrique: démence organique (Delay, Summerskill), dépression chronique, délire paranoïde (Delay).

Ces formes chroniques ont, pour la plupart, des épreuves hépatiques fonctionnelles peu troublées.

A cet endroit, se pose le problème ce que certains ont appelé du mauvais terme

de maladie de Wilson sporadique: il a été décrit des observations ayant une similitude clinique (neurologique et hépatique), et anatomique (glie hépatique) avec la maladie de Wilson héréditaire, à cette différence majeure près, qu'il n'existait pas les perturbations métaboliques cuivriques ni l'anneau vert cornéen qui leur est lié (Nayrac). Il s'agirait pour Baltzan de formes chroniques d'encéphalopathie porto-cave.

LE PRONOSTIC des E.C. est grave:

Dans l'immédiat, on peut retenir comme facteurs relativement favorables:

—l'existence de facteurs déclenchants nets (hémorragie digestive, chlorthiazide).

—l'absence d'insuffisance hépatique grave (syndrome hémorragique diffus, ictère, etc....).

—l'absence de coma profond, d'hyperazotémie avec oligurie.

—la longueur d'évolution.

—plus tard, le risque de récurrences est élevé: pour Fauvert, 80 % des malades meurent dans l'année.

FORMES CLINIQUES

Schématiquement, on oppose l'encéphalopathie terminale à l'encéphalopathie portocave.

A — L'encéphalopathie cirrhotique terminale.

(ou coma hépatique terminal) se caractérise par:

—l'existence d'une cirrhose toujours évidente avec des signes nets d'insuffisance hépatique grave.

—l'absence ou la discrétion de facteurs déclenchants, la déchéance cellulaire étant suffisante à déclencher le coma.

—une évolution stéréotypée et toujours inexorable.

—l'absence de corrélation étroite avec l'ammoniémie.

On conçoit aisément que cette variété mette en jeu des perturbations métaboliques complexes dont l'hyperammoniémie par faillite de l'uréogénèse hépatique est un élément accessoire. C'est en quelque sorte une E.C. avec hyperammoniémie facultative.

B — *L'encéphalopathie porto-cave.*

L'hyperammoniémie joue ici un rôle déterminant.

—Cliniquement, la cirrhose est en règle hypertrophique, anascitique avec souvent, mais non toujours, une splénomégalie. L'hypertension portale est indispensable mais ses stigmates ne sont pas toujours évidents (la circulation collatérale abdominale peut être absente). C'est souligner l'intérêt des radiographies de l'oesophage à la recherche de varices, de la splénoportographie, malheureusement, elles ne sont pas toujours concluantes. Exceptionnellement, on découvre une anastomose congénitale.

Autre fait important, l'atteinte cellulaire hépatique est modérée avec un taux de prothrombine en règle supérieur à 50 %; cette notion conditionne l'évolution favorable.

Ainsi, les troubles neuro-psychiques peuvent ne pas attirer l'attention sur la cirrhose responsable qui reste volontiers latente; il s'ensuit que le mode de recrutement de ces deux catégories de malades est schématiquement différent.

—les facteurs déclenchants sont pratiquement constants et justifient la dénomination anglo-saxonne parfois donnée d'encéphalopathie "exogène".

—l'hyperammoniémie semble ne devoir jamais être en défaut si l'on prend soin d'effectuer des dosages précoces et successifs.

—l'évolution est habituellement réversible, éventuellement chronique.

Le concept de l'encéphalopathie par hyperammoniémie répond à une réalité mais celle-ci a des limites restreintes et il n'est pas dans l'intention de ses défenseurs d'englober tous les comas hépatiques sous ce vocable. Dans une pathologie aussi complexe que la pathologie hépatique, on ne peut être surpris d'observer de nombreux cas ne répondant pas rigoureusement à ce concept, tous les intermédiaires étant possibles avec la forme précédente.

Physiopathologie de l'encéphalopathie porto-cave.

C'est une encéphalopathie par hyperammoniémie, favorisée par des court-circuits porto cave.

I — la réalité des court-circuits porto-caves n'est plus à démontrer au cours des

cirrhoses (expériences sur chien porteur de fistule d'Eck, anastomoses chirurgicales, observation radio-clinique).

L'importance du court-circuit sanguin est évidente, les dérivations porto-caves termino-latérales étant les plus redoutables. De plus, l'épreuve de surcharge ammoniacale a été proposée comme test de la valeur fonctionnelle de la circulation portale.

II — la réalité de l'hyperammoniémie et de son rôle toxique.

a) le métabolisme de l'ammoniaque mérite un bref rappel:

—l'ammoniaque circulant provient de deux sources:

—l'une exogène, digestive, la plus importante, liée à la dégradation intestinale des protides, surtout grâce aux bactéries locales. Ceci rend compte de la haute teneur du tronc porte en ammoniaque.

—l'autre, endogène, due à la désamination endogène des acides aminés dans les tissus (surtout muscles et cerveau).

—l'ammoniémie circule à un taux faible.

—son devenir est multiple.

—une fraction est éliminée par les reins.

—une autre se lie aux acides aminés pour former notamment la glutamine.

—la majeure partie intervient dans l'uréogénèse hépatique par la cycle de Krebs.

Ainsi, l'intestin joue un rôle important dans l'ammoniogénèse. Le foie constitue un puissant barrage à la circulation de l'ammoniaque portale.

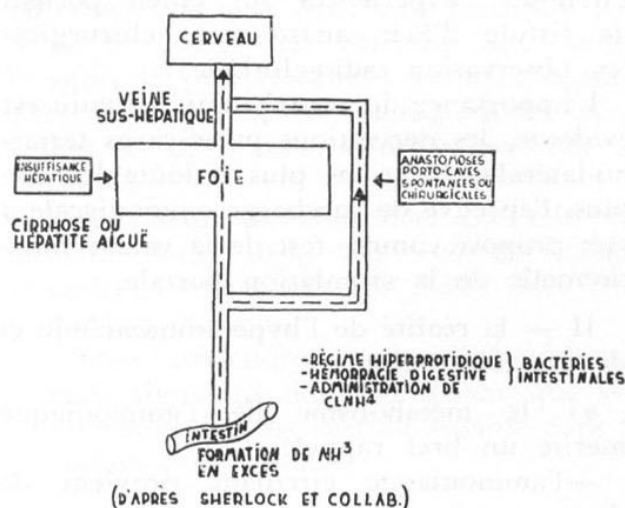
b) dans l'encéphalopathie porto-cave: (voir Schéma N° 1).

—l'hyperammoniémie est pratiquement constante, les études dynamiques l'ont démontré.

—cette hyperammoniémie dépend:

—d'un excès d'apport déjà signalé.

—de la disparition du barrage hépatique qui relève de deux facteurs: l'absence d'uréogénèse par faillite hépatique, qui n'intervient pas ici théoriquement et surtout l'existence des court-circuits porto-caves.



Schema 1

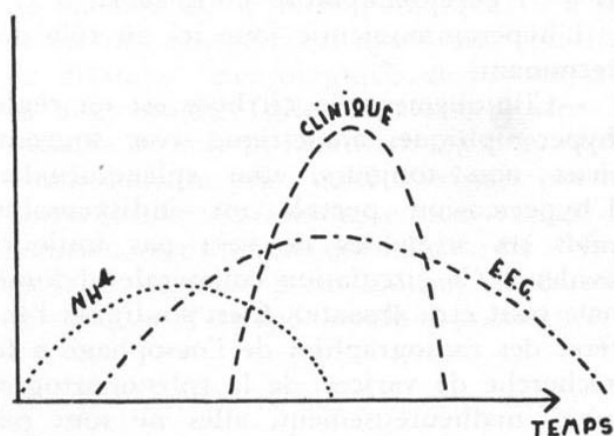
—Cette hyperammoniémie est responsable des faits cliniques: c'est là le point le plus débattu. Les conclusions de Rohmer au Congrès de Rome, sur les corrélations cliniques et électriques méritent d'être rapportées:

—la surcharge ammoniacale expérimentale peut donner des anomalies électriques et cliniques en tout point comparables à celles observées spontanément,

—ces corrélations sont valables s'il existe à la fois une hyperammoniémie artérielle et veineuse, surtout si l'un des facteurs suivants est retrouvé: anémie, hypokaliémie, alcalose respiratoire, encéphalopathie éthylique chronique.

—quant au mécanisme intime d'action, il se réduit à des hypothèses: intoxication exogène ou plutôt endogène avec blocage du cycle de Krebs à un niveau encore discuté.

A notre avis, si l'on prend soin de faire une étude dynamique, la réalité de l'encéphalopathie porto-cave paraît ne pas faire de doute. Il faut avoir à l'esprit que les perturbations biologiques, électriques et cliniques sont décalées dans le temps, que les perturbations biologiques sont obligatoires et que leur expression électrique et surtout clinique sont facultatives (voir Schéma N° 2). Enfin les études biochimiques à venir montreront si l'ammoniaque peut être seule en cause, si d'autres désordres métaboliques interviennent en association avec elle, si même elle n'est en fait



Schema 2

que le témoin d'un trouble complexe du métabolisme intermédiaire.

ANATOMIE PATHOLOGIQUE

Adams et Foley ont décrit, dans le cerveau, des altérations de la glie (hyperplasie astrocytaire, état spongieux des régions avoisinantes) prédominant dans le cortex cérébral, le thalamus, les noyaux lenticulaires et dentelés, le noyau rouge. Dans certains cas, l'hyperplasie accentuée et généralisée de la glie astrocytaire rappelle par son importance celle des dégénérescences hépato-lenticulaires.

DIAGNOSTIC DIFFERENTIEL

Il se pose schématiquement dans trois circonstances:

La cirrhose éthylique est connue:

- après avoir écarté la grande insuffisance hépatique,
- on discute, en cas d'hémorragie, a) le coma post-hémorragique immédiat, lié au collapsus, mais l'enchaînement avec le coma différé est possible et b) un accident cérébral hémorragique (surtout hématome sous dural).
- ailleurs, on discute les comas électrolytiques qui représentent un autre aspect du démembrement du coma hépatique.

On distingue: 1) le coma hyponatrémique, hypochlorémique et hyperazotémique au cours de grands syndromes ascitiques et oedémateux. Une paracentèse abondante est souvent responsable.

2) le coma hypokaliémique, hypochlorémique avec augmentation de la réserve alcaline, à la suite de vomissements ou diarrhée profuse, ou encore après emploi abusif de diurétiques. Ce coma calme, hypotonique, s'accompagne d'une augmentation de l'espace Q.T. à l'E.C.G. Le risque de collapsus cardio-vasculaire est élevé. Ces types de comas peuvent se compliquer d'E.C., montrant bien la complexité clinique de tels faits.

L'éthylisme, seul, est connu:

On discute surtout les deux autres grandes complications neuropsychiques de l'alcoolisme chronique.

—L'encéphalopathie de Gayet-Wernicke.

Les troubles du tonus et de la conscience peuvent prêter à confusion. Mais la phase prodromique est beaucoup plus longue, l'altération de l'état général souvent plus marquée en raison de la nature carencielle du syndrome, les troubles oculaires ont une grande valeur lorsqu'ils existent, l'évolution est plus longue avec possibilité de syndrome de Korsakoff.

—les délires alcooliques aigus et subaigus (delirium tremens).

Leur expression psychiatrique est riche, dominée par l'onirisme.

Les signes généraux sont particulièrement intenses dans le delirium tremens.

Le syndrome biologique différent.

L'évolution, par contre, est sensiblement superposable.

Dans ces éventualités, la possibilité d'association ou de succession doit être également prise en considération.

Il faut se rappeler, dans le doute le rôle nocif des glucides dans l'encéphalopathie de Gayet-Wernicke.

Citons enfin, dans ce groupe, l'hématome sous dural, et le coma post-épileptique chez un éthylique.

Dernière éventualité, l'éthylisme est ignoré:

Les erreurs diagnostiques sont fréquentes, mais il faut penser, devant tout accident neuro-psychique brutal, transitoire, récidivant, à l'éventualité d'affections métaboliques (encéphalopathie porto-cave, hypoglycémie, porphyrie, dyskaliémie, par exemple).

TRAITEMENT

Si l'on écarte le coma terminal, le traitement est dirigé contre trois facteurs:

Les sources d'ammoniaque.

- Régime exempt de protides, pauvre en lipides, et très riche en glucides. La reprise des protides sera prudente: en cas d'amélioration franche, 25 g. par jour pendant 8 jours, puis augmentation progressive sous contrôle E.E.G.
- lavement intestinal évacuateur, surtout en cas d'hémorragie. En cas de nécessité, la transfusion sera toujours de sang frais.
- antibiothérapie per os
auréomycine 1,5 à 3 g/24 h.
néomycine 1 à 2 g/24 h.

Contre l'hyperammoniémie.

- l'acide glutamique (Walshe): il fixe l'ammoniaque dans les tissus et permettrait la formation de glutamine, atoxique. On emploie des perfusions intra-veineuses quotidiennes de 40 g de glutamate de Calcium dans 1.000 ml. de sérum glucosé à 10 %.
- l'arginine favoriserait l'uréogénèse hépatique, exigeant donc une fonction hépatique peu troublée. Les perfusions intraveineuses sont de 10 à 25 g en 2 ou 3 fois par 24 h. Récemment on a proposé l'association avec l'acide malique (Cachin).

L'action de ces produits est controversée. A vrai dire, leur emploi paraît surtout justifié dans l'encéphalopathie porto-cave, mais leur efficacité est difficilement appréciable en raison de la tendance spontanée à la réversibilité de cette variété. Leur étude ne mérite pas moins d'être poursuivie.

Contre les conséquences cérébrales de l'hyperammoniémie, on dispose du sérum glucosé hypertonique.

En fait, le véritable traitement est préventif, permettant de réduire la fréquence

de ces accidents qui, tôt ou tard s'avèrent redoutables.

La prescription, dans les cirrhoses, verra:

- à éviter les régimes hyperprotidiques encore qu'un grand syndrome oedémateux risque de poser des problèmes difficiles à résoudre.
- à employer avec précaution les diurétiques non mercuriels sous surveillance et à éviter le chlorure d'ammonium et les résines à radical ammoniacal.
- à proscrire le sang conservé,
- enfin, à éviter les dérivés du cortisol en période évolutive (De Gennes).

SUMMARY

When trying to divide hepatic coma, the concept of hyperammonemia gives some satisfactory information for a certain number of encephalopathies of cirrhosis.

Ethylic cirrhosis are particularly liable to such accidents. Among the numerous starting factors, the digestive bleedings rank first.

The clinical description composed of neuro-psychic troubles, which are now well-known, is suggestive, as well as some electroencephalographical anomalies.

But we must distinguish:

—the terminal encephalopathy of the cirrhosis in which the hepatic cellular lesion prevails, if it is not exclusive; this is a cirrhotic encephalopathy with facultative hyperammonemia.

—The porto-cava encephalopathy in which the porto-cava shortcircuits are determining; it is an encephalopathy by hyperammonemia in which the favouring factors play an often obvious precipitating part.

The prognosis depends from the physiopathological mechanism.

RESUMEN

En el intento de estudio del coma hepático, la hiperamoniemia aporta datos satisfactorios para un determinado número de encefalopatías de la cirrosis.

Las cirrosis etílicas son las que están más expuestas a estos accidentes. Entre los numerosos factores que provocan la encefalopatía, las hemorragias digestivas ocupan un lugar fundamental.

El cuadro clínico constituido por alteraciones neuropsíquicas que actualmente son objeto de estudio, es sugestivo así como también determinadas anomalías electroencefalográficas.

Podemos distinguir:

—la encefalopatía terminal de las cirrosis, en la que la lesión hepática celular es dominante y puede llegar a ser exclusiva; es ésta una encefalopatía cirrótica con hiperamoniemia facultativa.

—la encefalopatía porto-cava, en la que los cortocircuitos son determinantes; es ésta una encefalopatía por hiperamoniemia; el rol de los factores que favorecen su precipitación es a menudo evidente.

El pronóstico está en función del mecanismo fisiopatológico.

R É S U M É

Dans l'essai de démemberement du coma hépatique, le concept de l'hyperammoniémie apporte une donnée satisfaisante pour un certain nombre d'encephalopathies des cirrheses.

Ce sont surtout les cirrheses éthyliques qui sont exposées à de tels accidents. Parmi les nombreux facteurs déclenchants, les hémorragies digestives tiennent la première place.

Le tableau clinique fait de troubles neuro-psychiques actuellement bien étudiés est évocateur, de même que certaines anomalies électroencéphalographiques.

Mais l'on doit distinguer:

— l'encéphalopathie terminale des cirrheses où l'atteinte hépatique cellulaire est dominante sinon exclusive; c'est une encéphalopathie cirrhotique avec hyperammoniémie facultative.

— L'encéphalopathie porto-cave où les courts-circuits porto-cave sont déterminants; c'est une encéphalopathie par hyperammoniémie où les facteurs favorisants jouent un rôle précipitant souvent évident.

Le pronostic est en fonction du mécanisme physio-pathologique.

ZUSAMMENFASSUNG

Im Versuch der Zerteilung des hepatischen Komas erklärt die Hyperammoniämie einige neuro-psychische Störungen der Leberzirrhosen.

Die wichtigsten Ursachen sind die alkoholische Zirrhosen. Besonders durch Magen-Darmblutung ist die Encephalopathie hervorgerufen.

Die neuro-psychischen Störungen und die Anomalien des E.E.G. sind charakteristisch genug um einen diagnostischen Wert zu besitzen.

Zu unterscheiden sind:

— Die Encephalopathie der Zirrhosen mit vorherrschender oder ausschliessender Leberinsuffizienz: in dieser Encephalopathie spielt die Hyperammoniämie eine fakultative Rolle;

— Die Encephalopathie der Zirrhosen mit portalen Anastomosen: in diesem Fall spielt die Hyperammoniämie eine grosse Rolle, und wird besonders durch begünstigende Faktoren hervorgerufen.

Die Prognose hängt von dem physiopathologischen Mechanismus ab.

BIBLIOGRAPHIE

(1) Adams, R. D. et Foley, J. M.: "The neurological disorder associated with liver disease". Res. Pub. Ass. Res. Nerv. Ment. Dis. 1953, 32 p. 198-237.

(2) Aimard M. G.: "Contribution à l'étude de l'encéphalopathie porto-cave". Journal de Médecine de Lyon N° 962-963 5 et 20 Mars 1960.

(3) Bouding, Barbizet J., Brions, Nivet M., et Masson S.: "Epilepsie subintrante et grande insuffisance hépatique. Etude clinique, électrique et anatomique de 6 cirrheses, éthyliques, ascitiques avec état de mal". B. M. Sol. Med. Hôp. Paris. — Mars 1959 75 N° 9-10-11 p. 301-313.

(4) Cachin, M.: "Encéphalopathie porto-cave". Presse Médicale 23.5.1959 N° 25 pp. 1031-1034.

(5) Cachin, M.: "Le traitement de la grande insuffisance hépatique par l'association acide malique - arginine. Presse Médicale 1er.-7-1961. — 1961 - 69 N° 32 pages 1473-75.

(6) Delay J., Lemperiere T., Widlocher, D. et Rondot P.: "Comas hépatiques transitoires chez une alcoolique chronique avec anastomose porto-cave congénitale. Evolution démentielle". Annales Médico-psychologiques. — Oct. 1958 116 N° 3 pages 505-510.

(7) Foley Jim, Watson C. W. et Adams, R. D.: "La signification des modifications électro-encéphalographiques dans le coma hépatique". Trans. Am. Neurol. Ass. 1950 75 pages 161-165.

(8) *Labet R.*: "Encéphalopathie porto-cave". Encyclopédie médico-chirurgicale Psychiatrie 37 670 E 10. — 10. 1969 (Bibliographie).

(9) *Mac Der Mott W. V. et Adams, R.*: "Episodic stupor associated with ECK fistula in the human with particular reference to the metabolism of ammonia". J. of clin. Invest. 1954. — 33 N° 1 1-9.

(10) *Nayrac, P.*: "Troubles neurologiques au cours des maladies du foie". VII congrès international de Neurologie. Rome 10-15 Sept. 1961. — pages 75-99.

(11) *Rohmer F. et Kurtz D.*: "E.E.G. et ammoniémie dans les troubles nerveux des affections hépatiques". VIIème Congrès international de Neurologie. — Rome 10-15 Sept 1961 pages 115-163.

(12) *Schepper P. (de)*: "Les acides alpha-cétoniques sanguins; étude clinique et expérimentale en cas de pathologie hépatique". Rev. franc. Et clin. et biol. Mars 1958 N° 3 pages 211-220.

(13) *Sherlock S.*: "Coma et précoma hépatique (encéphalopathie porto-cave)". Rev. Inter. Hépat. 1956 6 N° 7 887-907.

(14) *Sherlock S., Summerskill W. H. J., White L. P. et Phear E. A.*: "Encéphalopathie portale systématique. Complications neurologiques dans les maladies du foie". Lancer 4 Sept. 1954. — 267 453-457.

(15) *Summerskill W. H. J.*: "Aspects cliniques et métaboliques du coma hépatique; étude de 105 cas". Rev. Med. chir. Mal. Foie. Juin 1957 32 N° 2. — 1-12.

(16) *Walshe J. M.*: "L'acide glutamique dans le coma hépatique Lancer", 18. 6. 1955. 268 N° 68-77 1235-1239.

Vascular Coma

RAYMOND HIERONS, M.B. B.Sc. M.R.C.P.

Consultant Neurologist, The Brook Hospital,
London S.E.18. England.

In 1934 Solomon and Aring analysed the cause of a thousand cases of coma admitted to the Boston City Hospital. Alcohol was responsible for 59%; the next most common causes were trauma (13%), then cerebrovascular disease (10%). It seems probable that if present day statistics from an average general hospital were available, alcoholic cases would be fewer and coma due to trauma and cerebrovascular disease would be correspondingly greater. It is proposed in this paper, to discuss some of the problems which arise in the diagnosis of states of drowsiness, stupor or coma from common vascular processes.

In hospital practice, a difficulty which often arises in this group of cases, is an inadequate history. Frequently this cannot be avoided and immediate decisions have to be taken without accurate information about the development of coma, or of the past history. Important details of history may have to be extracted from such people as the police, or from an acquaintance who may bring the patient to hospital but fail to visit them again. A telephone call to a previous doctor or hospital may sometimes elicit important evidence.

Spontaneous Cerebral Haemorrhage and Cerebral Thrombosis

Cerebral haemorrhage is probably the commonest vascular cause of coma. Aring and Merritt's (1935) paper still deserves close study, particularly for the distinctions

they suggest in differentiating haemorrhage from thrombosis. Unconsciousness at the onset, was present in half their cases of haemorrhage compared to a third of their cases of thrombosis (it is important to emphasise that their series was derived from pathologically verified cases and therefore the thromboses were an unusually severe group and not comparable to the average case).

Coma at the time of admission to hospital, was very much more common in their cases of haemorrhage, i.e. in 68% compared to 39% of the thromboses. This showed that deterioration in the level of consciousness over several hours was frequent in haemorrhage. Aring and Merritt also emphasised that a history of sudden severe headache and vomiting is a valuable indication of haemorrhage. Disturbances of respiration, especially Cheyne-Stokes breathing also strongly suggests haemorrhage, particularly when this development occurs soon after the onset. Signs of neck stiffness, rapidly increasing paralysis and bilateral extensor plantar responses also suggest haemorrhage.

The same authors emphasised that examination of the C.S.F. although helpful was not infallible. The fluid was normal in 20% of the haemorrhage cases and on the other hand in 10% of the thromboses the fluid was slightly xanthochromic.

Thus it must be frankly admitted that the diagnosis of haemorrhage from thrombosis is occasionally impossible. This was again emphasised by Dalsgaard-Nielson

(1956) who analysed 1,000 personal cases. In spite of a particular interest in this question, the clinical diagnosis of cerebral haemorrhage was not confirmed at post-mortem in 10% of cases.

Occasionally there is improvement in the level of consciousness and in power of the paralysed limbs in cerebral haemorrhage but then after several days drowsiness and coma return.

Papilloedema is found in roughly one third of cases of cerebral haemorrhage and only rarely in thrombosis.

Angiography also may not distinguish haemorrhage from thrombosis. Even with large intracerebral haemorrhage this may occasionally be normal and sometimes with infarction there is displacement of the cerebral vessels. (Bull (1961) recently discussed the radiological aspects).

If we leave Aring and Merritt's fatal cases, it is probably true that a great many cases of cerebral thrombosis disturbances of consciousness are uncommon and when this occurs it is usually slight, rarely more than drowsiness and lasting for not more than a few hours. Even in carotid thrombosis of catastrophic onset, with extensive infarction and signs of severe hemiplegia, hemianopia and sensory impairment, impairment of consciousness is uncommon and not prolonged.

Exceptions to this generalisation occur in the presence of epilepsy and where there are multiple infarcts. Thus when a previous stroke has occurred, even followed by a good recovery, another episode particularly if it involves the other side of the brain, may sometimes lead to stupor, rarely to coma. Under such circumstances there are usually bilateral signs.

Cerebral Emboli

Barham Carter (1957) has discussed the problems involved in cerebral emboli, when coma appears to be more common (coma was present in 24 out of 108 cases — personal communication). The diagnosis is made on the very sudden development, often within seconds of hemiplegia, hemianopia or aphasia in a patient suffering from either

auricular fibrillation, a recent myocardial infarction, mitral stenosis without fibrillation or bacterial endocarditis. Usually the impairment of consciousness is not deep and is usually short lived. The C.S.F. is usually clear but may be bloodstained or xanthochromic in a small proportion.

Subarachnoid Haemorrhage from Aneurysms and Angiomas

Walton (1956) considered that loss of consciousness was the first manifestation of subarachnoid haemorrhage in 20% of cases and also in a further 5% which start with a convulsion. When bleeding occurs from aneurysms of the anterior cerebral and anterior communicating arteries, loss of consciousness is even more frequent. Coma was the first sign of bleeding in more than half the cases of anteriorly situated aneurysms described by Logue (1956). This author suggested that the initial escape of blood into the subarachnoid space narrows the arteries, particularly the perforating vessels to the hypothalamus, basal ganglia and internal capsule, and this is responsible for the loss of consciousness. This narrowing if prolonged, leads to infarction of brain. Another factor in producing coma in certain cases is bleeding into the substance of the brain.

Frequently, the duration of unconsciousness is short and on recovering usually within an hour, there is severe headache and other features of this condition. Occasionally the level of consciousness deteriorates and death may even occur, without localising signs. The pathological findings in such cases usually consist of massive rupture, into one or both frontal lobes or in the case of a posterior communicating aneurysm, into the temporal lobe or even into the cerebral peduncle.

An example of recurrent loss of consciousness which may occur with recurrent bleeding, was the following. A woman of 31 and four months pregnant, collapsed in the lavatory and was found unconscious, but began to make inaudible sounds after 20 minutes. A few hours later on admission to hospital, she was restless but able to

answer very simple questions. The left pupil was slightly larger than the right and both were inactive to light and the ocular axes were divergent. The plantar responses were both extensor although there was no difference in power of the limbs. Over some hours she improved and was then able to answer questions sensibly. It was then possible to demonstrate slight right sided weakness and there was also stiffness of the neck and a subhyaloid haemorrhage. Lumbar puncture revealed a xanthochromic fluid under a high pressure and the urine contained albumen. Arteriography revealed a small aneurysm arising from the left anterior communicating artery. Both anterior cerebral arteries were well filled by injection of the left carotid artery but filling from the right side was inadequate. During the first week she improved steadily. Then a second loss of consciousness occurred suddenly during which she was seen to clench her teeth, the head turned to the left and the arms extended. After about 10 minutes she complained of severe headache. Next day a further retinal haemorrhage was evident although there was no other change in the signs. A third attack of loss of consciousness lasting only a few minutes duration occurred a few days later, with vomiting and a severe headache upon recovering. A further lumbar puncture confirmed that another bleed had occurred. Immediately following this procedure the arms and legs were extended, she was cyanosed and lost consciousness. On recovering, within a few minutes, she said that she felt better but a short time later she began to writhe about, throwing her arms and legs around, grimacing and spitting. Observers thought she was hysterical, but an hour later she responded only feebly to painful stimuli, breathed heavily, the pupils were small and inactive and she died a few hours later.

Examination of the brain revealed a moderate subarachnoid haemorrhage with blood clot around the olfactory bulbs, surrounding the pituitary stalk, along the Sylvian fissures, filling the inter-peduncular fissure, the ventral surface of the pons, upper medulla, under surface of the cerebellum and the cisterna magna. A small

aneurysm was present on the left anterior cerebral artery just in front of the optic chiasm. This had ruptured upwards into the left anterior horn of the ventricle and both ventricular systems were filled with blood clot.

It would seem that the first bleed led to loss of consciousness, perhaps due to an intracerebral haematoma (in view of the mild right hemiparesis on recovering her senses). Three further brief episodes of loss of consciousness occurred lasting only a matter of minutes, probably associated with epilepsy. The fifth consisted of increasing coma over several hours. All five episodes of impairment of consciousness were associated with evidence of further bleeding.

Deterioration in the level of consciousness may develop gradually a few days after a subarachnoid bleed as in the next case, due to an intra cerebral haematoma.

A previously healthy woman of 26 years, suddenly remarked to her husband that she had a headache. He asked if she would like some aspirin but she refused, and she also complained of feeling dizzy. She then leaned her head against his shoulder and began to sink to the ground unconscious, the whole episode taking less than a minute. The husband noticed that her right arm and leg were stiff and sticking out. By the time she was admitted to hospital half an hour later, she was able to say a few words. Examination revealed stiffness of the neck and spastic weakness of the right side.

The level of consciousness improved during the first day and there was also some recovery in the right sided weakness. Later she became increasingly drowsy and three days after the onset she was stuporose, although if stimulated by a loud voice she was able to say that she had a headache and could obey simple commands. She was, however, disorientated in time and place and lapsed immediately into stupor when left alone. There was no evidence of dysphasia so far as one could examine her. No voluntary movement was seen in the right arm although slight movement was possible in the leg. Both plantars were extensor the right more so than the left. Some impairment to pin prick was present on the right

side up to the shoulder. Apart from stiffness of the neck there were no other signs.

The urine contained sugar and the C.S.F. was under a pressure of 290 mms, grossly bloodstained and the supernatant fluid was faintly xanthochromic.

Angiography revealed a small angiomatic malformation, high up over the convexity of the left frontal lobe, a little in front of the Rolandic fissure but in the A.P. views there was no shift.

Following this, Mr. Murray Falconer removed the angioma and also a large clot which filled the greater part of the frontal lobe which had opened into the frontal horn of the lateral ventricle. Subsequently she made a slow but steady improvement. One year later she had only slight weakness of the right leg and five years later, apart from a few epileptic attacks she reported that she was well.

An example of delayed development of coma, from an intracerebral haemorrhage, is shown by the following case and also illustrates how an intracerebral clot may for some time not cause any alteration in the level of consciousness.

A woman of 56, while scrubbing the floor at the hospital where she worked, suddenly developed a severe bifrontal headache. This increased in intensity and was associated with repeated vomiting. She was able to go home by taxi. She also had dizziness, her surroundings seemed to rotate from right to left. The following day the dizziness had gone, but headache, vomiting and general malaise persisted. She remained in bed at home for two days, but three days after the acute episode, she was able to walk a few hundred yards to see her doctor, although she still had a severe headache and felt ill. She was told to go home to bed. On the way back her legs became weak and she had to be helped into a shop to have a rest and when she got back to bed she noticed that her headache was rather more severe.

Later that day she had her first fit and had a total of 8 over the course of a few hours. On admission to hospital she was unconscious with signs of a spastic left hemiplegia. Both plantars were extensor.

The C.S.F. was heavily bloodstained under a pressure of 180 mms.

During the next few days power improved in the left side and when transferred to the Neurosurgical Unit a week after the onset she was free from headache.

On examination she was alert and sensible. The only abnormalities consisted of very slight left sided weakness, and bilateral extensor plantar responses.

She remained well and without headache. Angiography disclosed a small aneurysm on one of the marginal branches of the anterior cerebral artery at a plane about 2 cm. behind the genu of the corpus callosum. Behind this there was stretching of several other branches of the anterior cerebral artery suggesting a large clot which passed backwards to the mid vertex. In the A.P. views there was a shift of a large part of the anterior cerebral artery to the left.

In spite of the suggestion of a large intracerebral clot she was very well, not complaining of headache and with only very slight left sided weakness, although both plantar responses were extensor. One evening 10 minutes after a consultation between Surgeon and Neurologist, when the latter was advising against operation, she was suddenly found unconscious, although responding to painful stimuli, sweating and trying to open her eyelids. It is possible she might have had a fit although a nurse had been present on the other side of the screen and had heard nothing. There was some movement of the right limbs but not of the left. Following this she improved slightly but half an hour later became unresponsive, started having periodic respirations and vomiting. An immediated right frontal craniotomy was therefore carried out by Mr. Murray Falconer. A large intracerebral clot was removed from the right frontal lobe. The medial portion of the right frontal lobe had herniated under the flax to the other side. The aneurysm which originated on a small branch artery of the anterior cerebral was removed.

Six months after operation at follow up she was active and intelligent and showed

only slight weakness of the left hand and of dorsiflexion of the foot. Six years later she reported by letter that she was perfectly well.

It is important to recognise that intracerebral haemorrhage may occur and result in coma and yet bilateral angiograms show no shift or abnormality. Walsh's (1958) series showed this to be the case in 1/3 of his cases. He urged that when this condition is suspected clinically, particularly with disturbance of consciousness and one or both pupils inactive to light, biparietal burr holes should be made. Then, if a haematoma is encountered it is aspirated but if not ventriculography should be undertaken as this may then reveal a haematoma even with normal arteriograms. Walsh also described how occasionally a small angioma may produce a haematoma and angiography not reveal the vascular malformation.

Subdural haematoma may occasionally result from a subarachnoid haemorrhage and Logue (1951) estimates that this is responsible for 8% of cases. In these cases headache usually persists after the subarachnoid bleed and then over a period, occasionally as long as five weeks drowsiness or coma develop which may fluctuate and usually associated with signs of hemiparesis together with alterations in the pupils.

Posterior Fossa Aneurysms

Helen Dimsdale and Logue (1959) have recently discussed the diagnosis and surgical treatment of these cases. They emphasised that following bleeding there is frequently depression in the level of consciousness and this rapidly improves. Occasionally there are epileptic attacks. Other features consist of transient weakness of the limbs, usually of both sides together with pyramidal signs, alteration in the size of the pupils, (inequality, constriction or dilatation), sixth nerve palsy (or on both sides) and transient nystagmus. It was emphasised that bilateral vertebral arteriograms may be necessary to show the lesion and that good results can follow surgical treatment.

There is some evidence to suggest that blood in the subarachnoid space may result in confusion, drowsiness, fits and also papilloedema, sixth nerve palsies, nystagmus and bulbar signs. Henson and Croft (1956) have described such cases where the source of the bleeding originated from the spinal cord (usually angiomas) and such manifestations were prominent after the blood tracked up into the skull.

Cerebral Infarction following Subarachnoid Haemorrhage

The development of signs of hemiparesis or hemiplegia in association with subarachnoid bleeding, particularly when there is drowsiness or stupor makes one suspect an intracerebral haematoma. The condition may however, be due to infarction produced by a collection of blood kinking or stretching vessels or as some believe, by the breaking down of haemoglobin liberating a substance which produces spasm.

A consecutive series of cases of fatal bleeds from aneurysm were studied pathologically by Tomlinson (1959). He found bleeding into the brain in 53% (a third of these were massive extending into the ventricles) while in 78% there was cerebral infarction (of which half were massive).

An example of the difficulty in making this distinction also indicating the impossibility, at times of distinguishing hypertensive cerebral haemorrhage from that due to an aneurysm, is illustrated by the following:

This patient had her first pregnancy induced, in the seventh month, because of hypertension (blood pressure 210/150) and albuminuria. Over the next 5 years the hypertension persisted, although the albuminuria disappeared, the lowest B.P. was 180/105, although usually it was higher. At the age of 44, she suddenly developed, over the course of a few minutes, weakness of the right side, together with headache and vomiting. By the time her doctor was called she was dazed, confused, unable to speak and had a right hemiplegia. On admission to hospital she was drowsy, rest-

less, incontinent of urine, severely dysphasic with stiffness of the neck and profound paralysis of the right arm and leg. The B.P. was 205/105 and x-ray of the chest showed enlargement of the left ventricle and unfolding of the aorta. Examination of the C.S.F. confirmed the presence of a subarachnoid blood.

The following day she was able to swallow and less drowsy. Five weeks later when transferred to the Neurosurgical Unit she showed a moderate degree of dysphasia, inability to do simple calculation, a right homonymous hemianopia with some sparing of the upper quadrant, haemorrhage in both discs together with cotton wool patches on the right and constriction of the arteries. There was no facial weakness but signs of moderate weakness of the right side together with profound impairment of sense of position in the right arm and ankle and loss to light touch over the right arm and leg with impairment over the trunk.

The E.E.G. showed irregular slow activity throughout the anterior half of the left hemisphere. Angiography revealed an aneurysm of the terminal carotid on the left with minimal displacement of the anterior cerebral to the right suggesting the presence of an intra cerebral haematoma.

The left common carotid was tied in stages. She was thought to have a parietal intracerebral haematoma but subsequently ventriculography showed only slight dilatation of the whole of the left lateral ventricle. She slowly improved and eventually was able to do simple household tasks although was moderate hemiplegic and slightly dysphasic. This state persisted 8 years later.

Spontaneous Cerebellar Haemorrhage

In recent years there has been a renewed interest in the diagnosis and surgical treatment of this type of haemorrhage. The majority of these cases present in stupor or coma. Gowers (1893) left us an excellent description. This is what he wrote:

"Loss of consciousness is as common as in haemorrhage elsewhere, and presents

the same variations in its degree. There is often no initial paralysis; sometimes there is hemiplegia, due to pressure, and it may be on the same side as the haemorrhage, or on the opposite side, according as the pressure is exerted on the pons or on the medulla. The absence of hemiplegia is more significant than its presence. The pressure may also cause various paralyses in the parts supplied by the cranial nerves that arise from the pons and medulla. The state of the pupils varies; vision is unaffected. Vomiting is more frequent than in haemorrhage elsewhere, being met with in half the cases, and it is also more often persistent. It may occur without, as well as with, loss of consciousness. If recovery takes place, the pressure-effects, including the hemiplegia, pass away, and the only lasting symptom is cerebellar unsteadiness, which persists in some, but not in all cases. Haemorrhage into the cerebellum often bursts into the fourth ventricle, causing fatal depression of the functions of the medulla. When the middle cerebellar peduncle is the seat of the haemorrhage, the characteristic symptoms, forced lateral position of the head, difference in height of the eyes, and a tendency to lie on one side, and even to rotate, is usually distinct, even sometimes at the onset during the stage of apoplexy, and if the patient is conscious, there is usually intense vertigo."

Hypertension and atherosclerosis are responsible for the majority of cases, but occasionally, in younger patients, angioma or aneurysm occur.

Recently McKissock, Richardson and Walsh (1960) have described how the condition may develop in a gradual or episodic manner. Cerebellar signs are prominent. The C.S.F. may occasionally be normal. Drowsiness in this group may gradually develop over some days, rarely over a few weeks. The mortality in their series, surgically treated was related to the level of consciousness. They plead that in subarachnoid haemorrhage with drowsiness, when bilateral carotid angiograms are normal, early complete visualisation of the ventricular system is essential to recognise this condition.

Primary Pontine Haemorrhage

Often the first manifestation is coma. Occasionally sudden headache and vomiting may occur first but are soon followed by drowsiness. Disturbances of respiration either stertorous or Cheyne Stokes in type and pin point pupils are frequently present. In the early stages there may be signs of crossed paralysis but rapidly bilateral signs are evident. At times convulsions may occur. It may be impossible in certain cases to distinguish pontine from cerebellar haemorrhage on account of the pontine compression which may occur in certain cases of cerebellar haemorrhage.

In the great majority of cases death occurs within 12 hours although rare examples are reported with survival.

Stenosis and Occlusion of the Basilar Artery

Gowers in 1893 gave a concise description of this condition and pointed out how the hemiplegia may fluctuate — one side may become weak and then improve, then the other side may be affected and later the first side be affected again. The facial and trigeminal nerves may be affected in a variable way. Usually dysarthria and difficulty with swallowing occur. Occasionally there is defective conjugate gaze of the eyes. Disturbances of consciousness are prominent and to quote Gower's words "The patient may lie for some days in a state of incomplete coma, can be roused to open his eyes, but does not speak. Convulsions occasionally attend the onset, but are on the whole not frequent; they may be general or partial; one limb or one side of the face may escape."

More recently Kubik and Adams (1946) in an important clinical and pathological study emphasised the frequency of disturbances of the level of consciousness varying from confusion to coma. Coma was the first manifestation in every case of embolism compared to 20% of those due to thrombosis although at some time impairment of consciousness occurred in every case. Temporary

improvement of hours, days or weeks may occur although in fatal cases coma was invariably a prominent feature.

Occasionally headache may be prominent in this condition. This has been thought to be due to vascular dilatation in an attempt to establish collateral circulation.

Anoxia, Hypoxia, and Hypotension

Circulatory or respiratory arrest of more than a few minutes leads to deep coma due to widespread neuronal changes in the brain. Lesser degrees of damage may be produced by arrhythmia or severe hypotension. Cases are occasionally encountered after general surgical procedures when the patient remains unconscious after the anaesthetic. In others the damage may occur after the operation as a result of being nursed propped up in bed and in these circumstances muscle relaxant drugs may be the factor responsible. Similar cases occasionally follow operations on the heart. This latter group may eventually give us more precise knowledge as it is only under these circumstances that accurate and detailed study of the blood pressure and contraction of the heart are available throughout the operation and immediately afterwards.

Similar effects may also occur in severe myocardial infarction, dissecting aneurysm, following severe haemorrhage or the injudicious reduction in the blood pressure in patients with hypertension. Varying degrees of disturbed consciousness, sometimes to the extent of coma may be seen in any of these conditions and it is probable that severe hypotension is the cause. Narrowing or occlusion of the main vessels to the brain or of the cerebral arteries may of course be an added factor.

Neurological disturbances of which impairment of consciousness is often a feature, may also complicate long standing respiratory insufficiency. This is most commonly chronic bronchitis and emphysema associated with right heart failure. At times the respiratory and cardiac disturbances are overshadowed by drowsiness, confusion or even stupor or coma and there is often

headache, papilloedema, tremor and jerking movements of the limbs. This condition is probably largely due to a reduction in the arterial oxygen saturation combined with retention of carbon dioxide.

Acute Hypertensive Encephalopathy

In the past this term was frequently used to cover many cerebral disturbances in hypertensive patients which we would today

regard as cerebral infarctions. The experimental work of Byrom (1954) has however, demonstrated the mechanism of this condition although in clinical practice such cases are extremely rare. It occurs in a setting of severe hypertension and an additional rise in blood pressure usually preceeds the attack. Headache, followed by convulsions either focal or generalised usually occur followed by stupor or coma. Lowering of the blood pressure may be followed by rapid recovery.

SUMMARY

Vascular disease of the brain is frequently responsible for states of impaired consciousness ranging from drowsiness to coma. This paper is concerned with some of the problems which arise in the diagnosis of such cases.

Spontaneous cerebral haemorrhage is the most frequently encountered. In the majority the differentiation from cerebral infarction is relatively easy although occasionally there are considerable difficulties. The significance of headache, vomiting, rapidly increasing paralysis, bilateral extensor plantar responses, papilloedema, the composition of the C.S.F. and angiography in making this distinction are discussed.

Coma is present in about 25% of cases of cerebral emboli. The manifestations of basilar artery occlusion are described in

which disturbances of consciousness are prominent. Brief consideration is given to cerebellar haemorrhage and to spontaneous pontine haemorrhage.

Some of the problems which arise in subarachnoid haemorrhage from aneurysms and angiomas are described and particularly complications such as intracerebral haemorrhage and cerebral infarction. It is emphasised that bilateral angiography may fail to reveal a haematoma and the necessity when such a condition is suspected, with a patient in coma and with one or both pupils inactive to light, to perform biparietal burr holes and if aspiration is negative, to proceed with ventriculography.

Finally such conditions as anoxia, hypoxia, hypotension and hypertensive encephalopathy are discussed.

RESUMEN

Las enfermedades vasculares del cerebro son responsables con frecuencia de estados en los que la conciencia está afectada en grados que van de la obnubilación al coma. Este trabajo trata de algunos de los problemas que se presentan por el diagnóstico de estos cuadros clínicos.

La afección que se encuentra con más frecuencia es la hemorragia cerebral espontánea. Generalmente su diferenciación del infarto cerebral es relativamente fácil, aunque en algunas ocasiones se presentan gran-

des dificultades. Con el fin de llegar a distinguir las dos lesiones, se discute el significado de las cefalalgias, vómitos, las parálisis que avanzan rápidamente, las respuestas plantares extensoras bilaterales, el edema de papila, la composición del líquido cefalorraquídeo y la angiografía.

El coma está presente en alrededor del 25% de los casos de embolia cerebral. Se describieron las manifestaciones de la oclusión de la arteria basilar en el curso de la cual son prominentes los trastornos de la

conciencia. Se hicieron breves consideraciones relativas, a la hemorragia cerebelosa y a la hemorragia pontina espontánea.

Fueron tratados algunos de los problemas que aparecen en las hemorragias subaracnoides por aneurismas y angiomas, particularmente ciertas complicaciones tales como la hemorragia intracerebral y el infarto ce-

rebral. Se insistió en que la arteriografía bilateral puede no revelar un hematoma y que cuando éste es sospechado en un paciente en coma, con una o las dos pupilas sin reacción a la luz, se hace necesario practicar en ambas regiones parietales, agujeros de trépano y si la aspiración es negativa, realizar la ventriculografía.

R É S U M É

Une maladie vasculaire du cerveau est souvent responsable d'un état de dérangement de la conscience qui varie de la somnolence au coma. Ce travail s'occupe de quelques problèmes qui se posent au cours du procès diagnostique de cas résultants d'une pathologie vasculaire du cerveau.

La plus fréquente est une haemorrhagie cérébrale spontanée. Dans la plupart des cas la différence entre elle et un infarctus du cerveau est relativement facile — bien que de temps en temps les difficultés pour le diagnostic sont considérables. L'importance du mal de tête, des vomissements, de la paralysie qui augmente, le signe bilatéral de Babinski, l'oedème de la pupille, la composition du liquide céphalo-rachidien, angiographie, sont discutés pour faire le diagnostic différentiel.

Le coma se présente dans environ 25 % de cas d'embolie cérébrale. Les manifestations de l'occlusion de l'artérie basilaire au

cours desquelles le dérangement de la conscience est évidente, sont décrites. Une brève considération est donnée à l'haemorrhagie du cerebellum et à l'haemorrhagie spontanée du pont.

Quelques problèmes résultants d'une haemorrhagie subarachnoidale et de l'aneurisme et angioma sont décrits et en particulier les complications comme l'haemorrhagie intra-cérébrale et l'infarctus du cerveau. Il est souligné que l'angiographie bilatérale peut manquer à découvrir un haematome et dans le cas où cette condition est en doute avec le malade dans le coma, les pupilles n'agissant pas à la lumière, il faut faire une trépanation bipariétale et si l'aspiration est négative, il faut considérer une ventriculographie.

Finalement les conditions comme anoxia, hypoxie, hypotension et encéphalopathie hypertensive sont discutées.

ZUSAMMENFASSUNG

Zirkulationskrankheiten des Gehirns sind öfters verantwortlich für Bewusstseinstörungen die von Schläffigkeit bis Coma erstrecken.

Diese Arbeit behandelt gewisse Diagnosenprobleme die sich als Resultat ähnlicher Zirkulationspathologie ergeben.

Hauptsächlich treten spontane Gehirnblutungen ein. Meistens sind diese leicht von Gehirnfarkten zu unterscheiden, aber manchmal erweisen sich grosse Schwierigkeiten. Die Bedeutung von Kopfschmerzen, Erbrechen, schnell fortschreitenden Lähmung bilaterale Babinski-Erscheinung, Pupillenschwellungen, Analyse der Lumbar-

flüssigkeit und Angiographie für die Begründung der Diagnose werden bezweifelt.

Coma erscheint in 25% der Fälle von Gehirnebolie. Die Erscheinungen bei Arteria Basilaris Okklusion in denen Bewusstseinstörungen erscheinen, werden untersucht. Kleingeirnblutungen und spontane Blutungen des Pons werden kurz beschrieben.

Gewisse Probleme der Subarachnoidblutungen durch Aneurismus und Angioma werden beschrieben — ebenso Komplikationen wie Gehirnblutungen und Infarctus Cerebri.

Es wird hervorgehoben dass doppelseitige Angiographie ein Haematoma übersehen kann, und in einem solchen Fall wenn die Existenz eines Haematomas in Verdacht ist — also wenn der Patient komatos ist, eine oder beide Pupillen auf Licht nicht reagieren — dann müssen biparietale Trep-

hinlöcher unternommen werden, und wenn keine Gehirnblutung gefunden wird, muss Ventriculographie unternommen werden.

Zum Schluss werden Zustände wie Anoxie, Hypoxie, niedriger Blutdruck und hypertensive Enkephalopathie behandelt.

REFERENCES

- Aring, C. D. & Merritt, H. H.: Arch. Int. Med. 56, 435-456, 1935.
- Bull, J. W. D.: Use and Limitations of angiography in the diagnosis of vascular lesions of the brain. Neurology, 11, 80-85, 1961.
- Byron, F. B.: The Pathogenesis of Hypertensive Encephalopathy and its Relation to the Malignant Phase of Hypertension. Lancet 2, 201-211, 1954.
- Carter, A. B.: The Immediate treatment of Cerebral Embolism. Quart J. Med. 26, 335-348, 1957.
- Carter, A. B.: Personal Communication 1962.
- Dimsdale, H. and Logue, V.: Ruptured Posterior Fossa Aneurysms and their Surgical Treatment. J. Neurol. Neurosurg. and Psychiatry. 22, 202-217, 1959.
- Gowers, W. R.: A Manual of Diseases of the Nervous System (second edition) Vol. 2 pages 402 and 438, 1893, London.
- Henson, R. A. and Croft, P. B.: Spontaneous Spinal Subarachnoid Haemorrhage. Quart. J. Med. 25, 53-66, 1956.
- Logue, V.: In Modern Trends in Neurology. Edited by A. Fielding. Page 381, 1951, London.
- Logue, V.: Surgery in Spontaneous Subarachnoid Haemorrhage, Operative Treatment of Aneurysms on the Anterior Cerebral and Anterior Communicating Artery. Brit. Med. J. 1, 473-479, 1956.
- Kubik, C. S. and Adams, R. D.: Occlusion of the Basilar Artery — A Clinical and Pathological Study. Brain. 69, 73-121, 1946.
- McKissock, W., Richardson, A. and Walsh, L.: Spontaneous Cerebellar Haemorrhage. A study of 34 Consecutive Cases. Brain. 83, 1-9, 1960.
- Dalsgaard - Nielson, T.: Some Clinical Experience in the Treatment of Cerebral Apoplexy. (1000 cases). Acta. psychiat. scand. suppl. 108, 101-119, 1956.
- Solomon, P. and Aring, C. D.: The Causes of Coma in Patients entering a General Hospital. Amer. J. of Med. Sc. 188, 805-811, 1934.
- Tomlinson, B. E.: A study of Brain Changes in Ruptured Intracranial Aneurysms. Journ. Clin. Path. 12, 391-399, 1959.
- Walsh, L. S.: Intracranial Haemorrhage. Diagnosis and Treatment. Proceedings. Roy. Soc. Med. London. 51, 217-219, 1958.
- Walton, J. N.: Subarachnoid Haemorrhage. Edinburgh and London, 1956.

Treatment of Prolonged Coma

P. C. GAUTIER-SMITH, M. D.

Physician, National Hospital for Nervous Diseases,
Queen Square, London.

Effective treatment of prolonged coma has become of the greatest importance in recent years. With more efficient means available for keeping comatose patients alive for a long time, has come the realisation that complete recovery may sometimes follow extended periods of unconsciousness. Thus, patients with head injuries and encephalitis may be left with little if any functional deficit, even if they have been in coma for many days.

The word coma implies a complete loss of consciousness. In the context of treatment, however, this definition is far too narrow. Of even greater importance both numerically and in terms of prognosis, are those patients who, while retaining awareness of their surroundings, are so completely paralysed that they are incapable of doing anything for themselves. The principles underlying the treatment of these two groups are identical. Acute infective polyneuritis, poliomyelitis and myasthenia gravis all may give rise to states of profound weakness, from which complete or partial recovery may be expected, even after many weeks. In addition to that brought about by disease processes, paralysis is sometimes induced artificially. The treatment of severe tetanus has been revolutionised by this method. Complete relaxation produced by curare may need to be prolonged for up to three weeks.

PRINCIPLES OF TREATMENT

The treatment of any form of coma or paralysis should of course be directed primarily at the cause. In many conditions and in particular those cited above, no effective means are available. Treatment, therefore, has essentially to be symptomatic, while the mechanisms that govern consciousness and voluntary movement are enabled to recover.

A. Management of respiration.

Respiratory failure is the greatest danger to the comatose patient and the most common cause of death. Even if the respiratory muscles are working satisfactorily, obstruction of the air passages can easily occur. The tongue may fall back and secretions may pool in the pharynx. Correct positioning is all important in the prevention of these complications. The patient should be nursed in the semi-prone or prone position, never in the supine and the foot of the bed should be raised about 18 inches. If the pharyngeal structures are flaccid, an airway should be inserted.

Aspiration from mouth and pharynx.

Despite these measures, aspiration with an electric sucker may be required to remove secretions. A fairly stiff catheter is best

employed. Suction should be carried out under direct vision to avoid traumatising the mucous membranes. Occasionally, bronchoscopy is needed if vomit or secretions have been aspirated into the trachea and bronchi.

Tracheotomy.

Correct positioning and suction may be ineffective in clearing the pharynx. In this situation tracheotomy should be carried out. The procedure should not be delayed too long. Waiting until the patient is cyanosed or until partial respiratory obstruction has occurred, greatly adds to the hazards of the operation. Under these circumstances it may have to be performed by an inexperienced person and in addition, anoxic patients are a poor anaesthetic risk. Planned tracheotomy by a skilled surgeon is a safe procedure.

Flanged rubber tracheotomy tubes are best used. The flange prevents the tube from slipping into one or other of the main bronchi, a serious hazard when other types are used. An inflatable latex cuff around the tube prevents secretions or stomach contents from entering the lungs. In theory, the cuffs should be let down periodically to prevent pressure necrosis of the trachea. In practice, provided that they are not over inflated, the risk of this complication is negligible.

Once the tracheotomy is established, physiotherapy to the chest and suction with a catheter should be carried out regularly. Careful positioning also helps to drain secretions. Careful and continuous observation is necessary to ensure that the bronchi do not become obstructed.

Defective movement of one side of the chest, a rise in pulse and blood pressure and cyanosis are all signs that indicate the possibility of a blocked bronchus. If percussion and suction do not clear it, bronchoscopy may be necessary.

Secretions often become sticky and tenacious if the inspired air is too dry. To combat this, an artificial humidifier should be used. Air, which passes over water in a thermostatically controlled bath (Marshall and Spalding, 1953), is a satisfactory

arrangement. The temperature of the air delivered to the patient should be kept at 37°C (99.5°F).

Assisted respiration.

Despite a satisfactory airway, the patient may either be so deeply comatose or so severely paralysed, that spontaneous respirations are inadequate to maintain life. Under these circumstances, some form of assisted respiration will be required.

The first type of artificial respirator to be used was the cabinet. This consists of an airtight tank, which encloses the patient completely, apart from his head and neck. Air, provided by electrically driven bellows, is alternately extracted from and blown into the tank. Removal of the air produces a negative pressure inside the cabinet and expansion of the chest occurs, air being drawn into the lungs. Conversely, when air is blown into the cabinet a positive pressure is induced, which compresses the chest and produces expiration.

There are a number of serious disadvantages to this apparatus. The strong negative phase sucks pharyngeal secretions into the lungs and even if this is prevented by tracheotomy and adaptation of the neck fitting, access to the patient for nursing care, physiotherapy and diagnostic procedures is still difficult. The machines are also bulky and expensive.

Management of assisted breathing has been greatly simplified by the introduction of intermittent positive pressure respiration. As long ago as 1811, Sir Benjamin Brodie kept a she-ass, which had been completely paralysed with curare, alive for several hours by repiring it with a pair of fireside bellows inserted into the trachea. The animal subsequently made a complete recovery. This principle was forgotten until its reintroduction by Lassen (1953) during the severe epidemic of poliomyelitis in Denmark in 1952. The method is very simple. Air is blown into the lungs by way of an endotracheal tube and expiration occurs as the result of the elastic recoil of the chest. Initially, manually operated bellows were used but soon electrically driven machines were devised and now there are many types

available. Air is delivered through a humidifier, which is connected to the tracheotomy, with an intervening valve and suction connection. This apparatus is cheaper, easier to use and safer than the cabinet. Access to the patient is unobstructed and all nursing and therapeutic procedures are simplified.

The decision regarding the necessity for tracheotomy and assisted respiration must be a clinical one. Once instituted, artificial ventilation is controlled by observations of pulse and blood pressure and by estimation of the $p\text{CO}_2$. The rebreathing technique (Campbell and Howell, 1960) is a simple and reliable method. The minute volume is set at a level which can be calculated from a nomogram (Radford, 1955). Alterations of the stroke volume are usually made when necessary, rather than changing the rate.

Routine suction and physiotherapy must of course be carried out in the same way that has already been described in the section on tracheotomy. Scrupulous care must be taken to avoid infection. The use of prophylactic antibiotics is probably best avoided, their employment being confined to the treatment of established infections.

When the patient begins to recover, the machine should be disconnected for gradually increasing periods of time. The next step is to release the cuff of the tracheotomy tube and to cork it. The tube should be left in situ until the patient can cough and clear secretions satisfactorily.

B. Care of the skin.

Constant vigilance and attention to detail are essential in the prevention of decubitus ulcers. Prophylaxis is all important. The established ulcer is difficult to treat and may even threaten life. Loss of vasomotor control and sensory disturbance are important predisposing factors but the skin breaks down as the result of pressure and friction. The earliest sign is reddening of the skin, indicating transient disturbance of the circulation. This is followed by evidence of superficial skin damage as shown by reddening of the skin, not disappearing

with relief of pressure, blister formation and loss of superficial epithelium. Finally, necrosis of the underlying tissue occurs and osteomyelitis and septicaemia may supervene. The sites most likely to feel the effects of pressure are the bony areas most poorly protected by underlying soft tissue. The heels, femoral trochanters and sacrum are the most commonly affected but any bony point is greatly at risk.

Almost all decubitus ulcers are preventable. Prolonged pressure on any one point must be avoided and so the patient should be turned at least every two hours. Turning must be carried out quite relentlessly even though, in such diseases as acute infective polyneuritis, it may be unpleasant for the patient. A wide variety of positions can be utilised including the prone.

Avoidance of friction to the skin is equally important. There should be no knots, buttons or buckles on the patient's clothing and the sheets should be kept free of crumbs and creases. Bedclothes must be kept dry and scrupulously clean. The patient must be turned with great care, being lifted rather than rolled to avoid friction burns. The skin should be washed regularly all over with soap and water, prolonged gentle massage being used.

Pressure sores can develop very rapidly and patients may well have established ulcers when first admitted to hospital. In these cases, there must be no pressure on the sore at all. The sacrum and the trochanters are the commonest sites and the prone position is most valuable. Necrotic portions of the ulcers should be excised and dressings carried out using a no touch technique. Initially, the wound should be packed with gauze soaked in a mild antiseptic, such as *ensol* but once granulation starts, there should be as little dressing as possible. Protein loss, which may amount to as much as 50 grams in 24 hours (Harper 1945), must be replaced and anaemia corrected by the administration of iron or if necessary by blood transfusion.

C. Feeding.

Prolonged coma gives rise to conditions which favour the production of water and

electrolyte disturbances. Not only is ingestion impossible but the normal losses through the skin and respiration may be greatly increased. Liquids and food may be provided either intravenously or by gastric tube. Some authors, for example Le Beau et al (1958), favour the former method on the grounds that with gastric intubation there is a great danger of aspiration of food into the lungs. They point out that this danger does not exist when a tracheotomy has been performed. Most other workers, while being aware of this hazard, have found that nasogastric feeding is more satisfactory for the long term, even if a tracheotomy has not been done. This method can be used indefinitely with good results except when there is a paralytic ileus. Intravenous therapy, even if a polythene catheter is threaded into a main vein, can only be kept up for a limited period, owing to the dangers of thrombosis, infection and overloading the circulation. It is nevertheless very valuable in the rapid correction of electrolyte imbalance.

Plastic gastric tubes are the most satisfactory. They are less irritant than rubber and being firmer, are easier to introduce. Great care must be taken to ensure that the tube has not entered the trachea. Higgins et al (1954) have described a regime for long term nasogastric feedings. For the first 12 hours, they recommend that no liquids are given. Fluid feeding is then begun gradually with 60 mls (2 ounces) of water or of diluted milk given every 1 or 2 hours for the first 4 to 8 hours. The stomach is aspirated before each feed. A milk-glucose and water regime is then commenced. 1800 mls (3 pints) of milk with 300 grams of glucose, diluted with 600 to 800 mls (1 to 3 pints) of water, are given in the 24 hours in divided feeds every 2 hours. This mixture provides 2,250 calories, 50 grams of protein, 300 grams of glucose and 0.85 grams of sodium. After 24 to 48 hours, unless hyperchloraemia has resulted, 600 mls (1 pint) of Ringer-Fischer solution is substituted for 600 mls of water. This brings up the 24 hour sodium intake to 2.0 grams. Daily electrolyte estimations should be made at this stage.

After 4 or 5 days a higher protein intake can be given. A satisfactory mixture is 225 grams carbohydrate, 100 grams of protein and a 100 grams of fat, giving, 2,200 calories. The whole is diluted with from 2,400 to 3,600 mls (4 to 6 pints) of water, including 600 mls (1 pint) of Ringer-Fischer solution. Adequate amounts of vitamins and iron are added. Finally, if electrolyte balance is still satisfactory, 2,700 calories with 250 grams of carbohydrate, 130 grms of protein and 130 grams of fat can be given indefinitely.

Barron and Fallis (1953) believe that no commercially prepared formula can replace natural food. They used a blender or liquifying machine and reported their experience of the tube feeding of 200 patients. 1300 calories could be included in 1000 mls of fluid. The diet was well tolerated.

If the regime outlined above is instituted from the beginning, satisfactory control of electrolytes is usually achieved. A careful watch must be kept and any disturbance must receive appropriate treatment. Complications are rare. Diarrhea is a fairly constant but minor side effect but usually requires no specific treatment.

D. Care of the bladder.

The unconscious or totally paralysed patient will develop either incontinence or retention of urine. In the former, urine should be collected in a urinal whenever possible. In the case of female patients, disposable pads can be used but these are unsatisfactory and catheterisation and tidal drainage is preferable. Whenever incontinence occurs, care must be taken to ensure that the condition is not retention with overflow.

When retention is present, intermittent catheterisation every 6 hours should be carried out for the first 3 days. If an indwelling catheter is inserted at the beginning, there is danger of mucosal ulceration. Catheterisation should be performed with the use of a no touch technique. If coma or paralysis lasts for longer than 3 days, tidal drainage should be instituted. A Foley catheter with a 5 ml

bulb is inserted into the bladder and is attached to the apparatus, originally introduced by Munro (1943), which acts as a siphon. The frequency of action is determined by the rate of filling, which can easily be controlled. The catheter should be changed every day at first and later on every third or fourth, the urethra being irrigated with flavazole to prevent encrustation. The whole apparatus should be taken down and resterilised weekly. If the urine is alkaline, an acetic acid, boric acid solution can be used and if acid, normal saline, containing silver nitrate and potassium permanganate. With strict attention to detail, this method can be used with success almost indefinitely.

Suprapubic cystotomy has been advocated by some but, as Guttman (1946) has pointed out, infection is not necessarily prevented by this method. Recovery of normal bladder function is also more difficult to establish.

E. Care of the bowels.

Management of the bowels is not so difficult a problem as that of the bladder. If there is constipation, regular olive oil enemas should be given every second or third day. Occasionally, manual removal may be necessary.

Diarrhoea, the result of a largely liquid diet, is not uncommon. It often requires no treatment but if severe, will respond to chalk and opium mixtures.

F. Care of the eyes.

In cases of prolonged coma, the eyes tend to fall open and corneal drying, ulceration and perforation may occur. The use of pads is to be avoided. The eyes may be open under them and the danger of corneal abrasion is very great. The lids may be closed by attaching tape from the upper lid to the cheek. Alternatively, a modified tarsorrhaphy can be carried out. 1/2% methyl cellulose or mineral oil drops should be instilled regularly throughout the 24 hours. The cornea should be stained twice weekly to detect ulceration. Antibiotics can be applied should the need arise.

G. Cure of the mouth.

In unconscious patients the mouth falls open and the buccal mucous membranes dry out. These conditions favour the development of parotitis and so the mouth should be swabbed out every 2 hours with a weak solution of glycerin and thymol. The presence of an airway predisposes to ulceration and regular inspection of the mouth should therefore be carried out.

H. Prevention of contractures and atrophy.

Passive movement of all joints should be carried out at least once or better twice a day. Particular care should be taken to prevent foot drop. Pressure on the lateral popliteal nerve at the neck of the fibula must be avoided and the feet should not be allowed to take up a position of excessive plantar flexion.

I. Temperature regulation.

Temperature control is often deranged in coma states, a rise being much more common than a fall. The cause, such as a chest or urinary infection, should of course be treated whenever possible. Frequently, however, there is a disturbance of the regulation mechanisms with the brain stem and treatment must be symptomatic. Hypothermia is hardly ever a cause for anxiety and temperatures as low as 33.9°C (93°F) require no therapy. Hyperthermia is much more dangerous. A rise of rectal temperature of over 39.2°C (102.5°F) requires treatment. The patient should be nursed unclothed and the room temperature reduced to 15.5°C (60°F). Electric fanning, sponging with tepid water, covering with a damp sheet and ice packs may be required. Colonic irrigations with cold tap water can also be used. Drugs such as aspirin and chlorpromazine are rarely necessary and should be avoided.

J. Control of blood pressure.

Disturbances of blood pressure are frequently encountered. Regular observations should be made. Both high and low read-

ings are frequently associated with poorly controlled respiration, which is the first thing to consider.

In the presence of a diminution in peripheral vascular tone, vasopressor agents may be necessary. The most effective is 1-nor-epinephrine, given intravenously, 4 mls in 1000 mls of 5% glucose. This drug

carries with it the danger of thrombophlebitis and necrosis of subcutaneous tissues, if it leaks outside the vein. Neosynephrine, 5-10 mgm in 500 mls of 5% glucose, is safer. Intramuscular vasopressor drugs are disappointing.

Hypotensive agents may be needed to control a persistent rise in blood pressure.

DISCUSSION

It can be seen that the long term treatment of the deeply unconscious or profoundly paralysed patient requires good team work and organisation. Medical, nursing and therapeutic care must be of the highest order. Patients needing assisted respiration are probably best treated in special units. It is only in this way that sufficient experience can be gained in the details of

management and it is on this experience that success depends. The comatose patient requires constant observation and should not be left unattended throughout the 24 hours. It is very difficult to fulfil all the requirements in a general ward, without disrupting the routine and disturbing the other patients.

SUMMARY

The principles of treatment of cases of prolonged coma and of long standing and severe paralysis are the same. The latter group is of great importance as in many cases the chances of complete recovery are good. While treatment must be directed at the cause whenever possible, in most cases symptomatic measures are the only ones available.

The detailed management of the patient is described in separate sections. The following points are stressed:—

1) An adequate airway is essential. Tracheotomy may be required. Intermittent positive pressure is the safest and most effective means of applying assisted respiration.

2) Decubitus ulcers should be prevented by constant turning and scrupulous cleanliness. Methods of treating the established case are outlined.

3) Nutrition is best maintained by nasogastric feeding, which can be continued indefinitely. Intravenous fluids may occasionally be required. A feeding regime is described.

4) Intermittent catheterisation followed by tidal drainage is necessary when retention of urine occurs. Regular enemas prevent severe constipation.

5) Partial tarsorrhaphy prevents corneal abrasions and ulcers.

6) Joints should be kept mobile. Correct positioning prevents foot drop and pressure palsies.

7) Control of temperature can be achieved by simple measures. Hyperthermia is more important than hypothermia. Drugs are not indicated.

8) Blood pressure should be kept within the physiological range of the particular patient. Hypotensive drugs and vasopressor agents may be needed.

Treatment of the deeply unconscious or severely paralysed patient requires constant attention to detail and the highest standard of medical, nursing and therapeutic care. The use of special units for this purpose is advocated.

RESUMEN

Son idénticos los principios que rigen el tratamiento de los casos de coma prolongado y de las parálisis severas y de larga duración. Es muy importante la correcta atención de los enfermos de este último grupo puesto que en numerosas ocasiones existen buenas probabilidades de una recuperación completa. Siempre que sea posible debe realizarse el tratamiento etiológico aunque en la práctica en la mayor parte de los casos sólo puede hacerse terapéutica sintomática.

Los cuidados fueron descritos con detalle en distintos capítulos y se insistió en los siguientes puntos:

1) Es esencial un adecuado pasaje de aire. Puede ser necesaria la traqueotomía. El medio más efectivo y seguro de realizar la respiración asistida, consiste en la presión positiva intermitente.

2) Las úlceras de decúbito deben evitarse realizando constantes cambios de posición y con una escrupulosa higiene. Fueron expuestos los métodos para tratar la lesión constituida.

3) El mejor modo de mantener la nutrición es por medio de la sonda nasogástrica, el cual puede ser continuado indefi-

nidamente. En algunas ocasiones deben inyectarse fluidos intravenosos. Fue descrito un régimen alimenticio adecuado.

4) Si hay retención de orina es necesario el cateterismo intermitente seguido por avenamiento en marea ("tidal drainage"). Enemas regulares evitan el estreñimiento severo.

5) La tarsorrafia parcial previene las exco-riaciones y úlceras de la córnea.

6) Deben movilizarse las articulaciones. Las posiciones correctas impiden la caída del pie y las parálisis por presión.

7) El control de la temperatura puede ser alcanzado por medidas simples. La hipotermia es más importante que la hipotermia. No es necesario indicar drogas.

8) Debe tratarse de que la presión sanguínea sea mantenida dentro de los límites fisiológicos del paciente. Pueden hacerse necesarias las drogas hipotensoras y agentes vasopresores. El tratamiento del enfermo profundamente inconciente o severamente paralizado requiere atención constante y minuciosa y el nivel más alto de cuidados médicos y de enfermería. Se aboga por la creación de centros especiales.

R É S U M É

Les principes de traitement des cas de coma prolongés et de longue durée ainsi que ceux de paralysies sévères sont les mêmes. Ce dernier groupe est d'une importance capitale car dans beaucoup de cas les chances de rétablissement (guérison) complet sont bonnes. Tandis que le traitement étiologique est de rigueur tant que cela est possible, dans la plupart des cas il ne peut être que symptomatique. Les soins détaillés sont décrits en divers chapitres.

Les points suivants sont relevés.

1) Un passage d'air adéquat est essentiel. Trachéotomie est parfois indiquée. Le moyen le plus efficace et le plus sûr pour appliquer la respiration assistée est la pression positive intermittente.

2) Les escarres de décubitus sont à prévenir par des changements de position

constants et par une hygiène scrupuleuse. Les méthodes de traitement pour les cas en question sont exposées.

3) Le meilleur moyen d'assurer la nutrition est par tube naso-gastrique, qui peut être continué indéfiniment. Parfois des liquides intraveineux doivent être administrés. Un régime d'alimentation est décrit.

4) La catheterisation intermittente suivie par "tidal drainage" est nécessaire en cas de rétention d'urine. Des enemas réguliers empêchent la constipation sévère.

5) Une tarsorrhaphie partielle prévient les exco-riations et les ulcères de la cornée.

6) Les articulations doivent être maintenues mobiles. Une posture correct évite la chute du pied et les paralysies par pression.

7) Le contrôle de la température peut être achevé par de simples mesures. L'hyperthermie est plus importante que l'hypothermie. Des médicaments ne sont pas indiqués.

8) La tension artérielle doit être tenue dans des limites physiologiques du malade en question. Des médicaments hypotensifs

et vasopresseurs peuvent s'avérer nécessaires.

Le traitement d'un malade en coma profond et avec des paralysies sévères nécessite une attention constante aux détails et le standard de soins médicaux, infirmiers et thérapeutiques le plus élevé. Des centres spéciaux, à cet effet sont recommandés.

ZUSAMMENFASSUNG

Die Grundsätze der Behandlung von Fällen eines verlängerten und lang anhaltenden Komas, sowohl als schlimme Paralyse sind die gleichen. Diese letztere Gruppe ist von grösster Wichtigkeit, da in vielen Fällen die Möglichkeit einer vollkommenen Genesung besteht. Während die Behandlung vorzüglicher Weise kausal orientiert sein soll stehen in den meisten Fällen nur symptomatische Massnahmen zur Verfügung.

Die einzelnen Punkte der Krankenbehandlung werden in verschiedenen Abschnitten beschrieben. Zu hervorheben sind:

1) Ein ausreichender Luftweg (Atemweg) ist notwendig. Eine Tracheotomie ist manchmal erfordert. Die sicherste und wirksamste Methode van Hilfsatmung ist die intermittierende positive Pression.

2) Druckgeschwüre sind zu vermeiden durch beständiges Drehen und skrupulöse Sauberkeit. Die Methoden der Einzelbehandlung werden unterstrichen.

3) Die Ernährung wird am besten erhalten durch naso-gastrische Fütterung die ununterbrochen fortgesetzt werden kann.

Intravenöse Flüssigkeit ist gelegentlich erfordert. Eine spezielle Ernährungsmethode ist beschrieben.

4) Wiederholte Sondierungen gefolgt von "tidal drainage" ist nötig bei Harnretention. Regelmässige Klistiers verhindern schwere Konstipation.

5) Partielle Tarsorrhaphie verhindert Ulcus und Abrasio cornea.

6) Die Gelenke müssen in Bewegung gehalten werden. Eine korrekte Liegestellung bekämpft Fussfall und Druckparalyse.

7) Eine Temperaturkontrolle ist einfach auszuführen. Hyperthermie ist wichtiger als Hypothermie. Medikamente sind nicht nötig.

8) Blutdruck muss in den physiologischen Grenzen des Kranken gehalten werden. Hypotensive Drogen und Vasopressoren können von Nutzen sein.

Die Behandlung eines tiefen bewusstlosen und paralyseierten Patienten verlangt eine beständige auf Einzelheiten gerichtete Aufmerksamkeit, und die beste ärztliche und therapeutische Pflege. Eine spezialisierte Einheit ist für diesen Zweck zu empfehlen.

BIBLIOGRAPHY

- Barron, J.; Fallis, L. S.: Tube feeding with liquefied whole food. *Surg. Forum* 4, 519, 1953.
 Campbell, E. J. M.; Howell, J. B. L.: Simple rapid methods of stimulating arterial and mixed venous p CO₂. *Brit. med. J.* 1, 458, 1960.
 Guttmann, L.: Rehabilitation after injuries to the spinal cord and cauda equina. *Brit. J. phys. Med.* IX, 162, 1946.
 Harper, H. A.: War wounds of spinal cord: nutritional aspects of care of paralysed patient. *J. Amer. med. Ass.* 129, 160, 1945.
 Hoggins, G.; Lewin, W.; O'Brien, J. R. P.; Taylor, W. H.: Metabolic disorders in head injury. *Lancet* i, 61, 1954.
 Lassen, H. C. A.: A preliminary report on

- the 1952 epidemic of poliomyelitis in Copenhagen with special reference to the treatment of acute respiratory insufficiency. *Lancet* i, 37, 1953.
 Le Beau, J.; Funck-Bretano, J. L.; Castaigne: Le traitement des comas prolongés. *Presse med.* 66, 829, 1958.
 Marshall, J.; Spalding, J. M. K.: Humidification in positive pressure respiration for bulbospinal paralysis. *Lancet* ii, 1022, 1953.
 Munro, D.: Tidal drainage and cystometry in treatment of sepsis associated with spinal cord injuries; study of 165 cases. *New Engl. J. Med.* 229, 6, 1943.
 Radford, E. P.: Ventilation standards for use in artificial respiration. *J. appl. Physiol.* 7, 451, 1955.

Personality

DEREK ERNEST DENNY-BROWN, O.B.E., M. D.
(N.Z.) D. Phil. (Oxford) LL.D (hon. Wayne),
Dr. hon. causa (Brasil), F.A.C.P.
James Jackson Putnam, Professor of Neurology,
Harvard University, Director Neurological Unit,
Boston City Hospital.

Dr. Denny-Brown has influenced contemporary clinical neurology as much as any other living scientist. He is a man of many parts and none of them are dull. He was born June 1, 1901 in Christchurch, New Zealand of parents of English and Scots descent and is a naturalized citizen of the United States. In 1924 he graduated in medicine from Otago University in New Zealand with a special interest in neuroanatomy and neuromuscular



physiology. He spent three years from 1925-1928 with Sir Charles Sherrington as a Beit Memorial Fellow at Oxford University. Here he became a world-famous neurophysiologist, collaborating with Sir Charles Sherrington, Liddell, Cooper and Sir John Eccles on studies of stimulation of the cerebral cortex, neuromuscular reflex activity of the spinal cord, postural reflexes and the histology of stripped muscle.

After absorbing the teachings of the most distinguished neurophysiologist in the world at Sherrington's most productive period, Denny-Brown then became a house-officer at the National Hos-

pital for Nervous Diseases, Queen Square, London where decades of greatness under Gowers, Hughlings-Jackson and Sir Victor Horsley had resulted in one of the finest centers for neurological instruction of

all time. Here, Denny gained much inspiration from the teachings of Kinnier Wilson (who fostered his interest in Wilson's Disease, involuntary movements and apraxia) Sir Charles Symonds (from whom he gained much of his clinical knowledge); and Sir Francis Walshe (from whom he gained critical application of neurophysiology in the clinical setting). Among the other distinguished teachers were Godwin Greenfield (whence his formidable knowledge of nerve, muscle and neuropathology); Sir Henry Head and Sir Gordon Holmes. The latter two immortal neurologists undoubtedly influenced his thinking in problems of cortical and motor function. In 1931 he became Registrar at Guy's Hospital, in 1935 he was appointed as Neurologist to St. Bartholomew's Hospital in London, and in 1936 he was appointed Assistant Physician to the National Hospital, Queen Square.

These were fruitful years, and despite the need to support himself and his growing family by private practice, he carried out clinical and basic research at his own expense. This accounted for his amazing resourcefulness and ability to construct his own crude but working apparatus out of any materials readily at hand. He worked with Graeme Robertson (the famous Australian neurologist and pioneer of pneumography) who was a fellow house-officer, on the physiology of micturition, which still stands as a classic monograph. An interesting sidelight is that some of the studies were performed by the two investigators using each other as subjects, which Denny once maintained was the most uncomfortable and tedious investigation in which he had participated. The work on the pathology of sciatica, the bladder in transverse lesions of the spinal cord and clinical observations on localized epileptic seizures were also made with his old friend, Graeme Robertson. His studies encompassed the physiology of shivering and defecation and clinical studies of intracranial tumor (with Sir Hugh Cairns).

In 1936 he was Goulstonian lecturer of the Royal College of Physicians and in the same year accepted a Rockefeller Traveling Fellowship to Yale University which was to influence both his life and neurology in the United States. During this fellowship he worked with John Fulton and learned experimental brain surgery in animals, using Harvey Cushing's techniques and increased his knowledge of electrophysiological techniques. During his year in the United States he was also shrewdly appraised by the American academicians, and in 1939, he was appointed Professor of Neurology at Harvard University. He contracted severe infectious hepatitis in New Haven but continued to work, and as a result, had some residual liver damage. Since that time he seldom drank more than one cocktail! While he was working at Yale he shared the laboratory facilities with A. Earl Walker and learned a great deal from him concerning the maintenance and handling of a monkey colony. He once told me that Dr. Walker had such a way with monkeys that he was occasionally seen walking through the halls of the medical school with three monkeys suspended from his arms.

In 1938, as a result of his pioneer work with J. B. Pennybacker (Oxford) on electromyography, Denny-Brown was the first to accurately define fibrillation and fasciculation in voluntary muscle. His appointment at Harvard was delayed by the outbreak of World War II in which he served with distinction as a medical officer. War did not interrupt his investigation, however, and in 1940 he published his classic monograph on experimental cerebral concussion with Dr. Ritchie Russell (an old bicycle wheel was used as the fulcrum for the concussion apparatus). In 1941, he published his first study on myotonia (with S. Nevin, who himself earned world-wide recognition as an authority on myopathies) and a clinical paper on delayed collapse after head injury, with Dennis Williams.

In 1941 he assumed his appointment at Harvard and shared his knowledge of head injury with that of Kurt Goldstein, writing the foreword to the latter's book on after effects of brain injuries in war.

In 1943 he wrote his excellent description of paralysis agitans in Cecil's Textbook of Medicine, and studied various injuries of peripheral nerve (with C. Brenner). Meanwhile, he was reorganizing the Neurological Unit at the Boston City Hospital where at that time his associates included Houston Merritt, Fred and Erna Gibbs, William Lennox and Raymond Adams. All these associates were eventually to assume positions of great responsibility in academic neurology throughout the United States.

His distinguished papers continued to flow after his appointment to Harvard, and up to the present time, number approximately 150. In 1944 he published with Houston Merritt, Arnold Friedman and Charles Brenner on post-traumatic headache. His writings include his monumental monograph in the Oxford System of Medicine entitled, "Diseases of the Basal Ganglia and Subthalamic Nuclei", another on regeneration of nerve and his classic monograph on neurological conditions resulting from prolonged and severe dietary restriction. This interesting paper resulted from his year of absence from Harvard (1945-1946), serving as a brigadier in the British Army as consulting neurologist to the Indian theatre, where he reviewed the case records of prisoners of war.

In 1948 he published an important contribution entitled, "Primary sensory neuropathy with muscular changes associated with carcinoma" which was the first of a number of degenerative neurological conditions later described by others in association with carcinoma. His contact with the excellent internists at Harvard has always been considered by Denny to be a profitable one for neurology and his paper with William Castle, Maxwell Finland and Lionel Berk on the effectiveness of vitamin B₁₂ in combined system disease is proof of it.

In 1948 he began his brilliant association with Lahut Uzman that unfortunately was terminated by Uzman's death (age 39) shortly after his appointment to the chair of pediatric neurology at Harvard. Their first paper on amino-aciduria in Wilson's disease was the result of work done while Uzman was an intern at the Boston City Hospital. At the

same time he published with Henrik Seyffarth on the grasp reflex, which was the first of a brilliant series of applications of Sherringtonian physiology to clinical neurology. It is the writer's opinion that this is Denny-Brown's unique gift to clinical neurology, for there followed a whole series of similar papers classifying neurological signs and symptoms in physiological terms. These include the motor function of the agrular frontal cortex (with E. H. Botterell) and the nature of spasticity (with T. E. Twitchel and Saenz-Arroyo). Disintegration of motor function resulting from cerebral lesions and the other series of papers on the parietal, temporal and occipital lobes and the basal ganglia here summarized in his Croonian lectures (1960) and the Sherrington Memorial Lectures (1962).

Denny-Brown's books include, "Reflex Activity of the Spinal Cord" with Creed, Eccles, Liddell and Sherrington, "Selected Writings of Sir Charles Sherrington", "Handbook of Neurological Examination and Case Recording", "Diseases of Muscle" (with Raymond Adams and C. Pierson) and "The Basal Ganglia and Their Relation to Disorders of Movement".

These are some of his achievements, but what of the man? He is tall (6 feet), trim, and with his greying moustache has a military bearing. A shy man, he has the English manner of speech and diffidence. He has mannerisms, some of which he inherited from his earlier teachers. He fingers the lapels of his white hospital coat on rounds and I have been told Sir Charles Symonds and Kinnier Wilson did this. When impatient, he rubs his right hand (this is because he suffers from causalgia which followed a traumatic amputation of the third digit (annulus). This troubles him a great deal for though it does not spoil his technical skill as an experimental surgeon, it makes for some difficulties; furthermore, his right hand is sensitive and a firm handshake causes him pain. Like many able men he is subject to migraine and the only time I have seen him excuse himself from an experiment was due to a severe migraine attack.

He works steadily and long hours with an industry and single-mindedness that leaves men half his age exhausted. He has a charming family of four boys and his attractive wife, Sylvia, entertains warmly in the English manner. His oldest son, Bruce, is completing his last year in medicine at McGill University.

For relaxation he likes to spend his time at his summer home in Maine where he sails and enjoys the outdoor life. I have never seen him happier than when he was driving a jeep and clearing logs from his estate.

As a teacher, we found him never dull, always stimulating and critical. If he was wrong about a case, he was brilliantly so, and there was much to be learned from what he said. He was so demanding of high standards for himself and his department that at times he appeared egocentric and was difficult to live with. After such moments he was capable of great personal charm. The most delightful aspects of his per-

sonality were seen during collaboration in the laboratory, at lunch, over coffee at 11:00 A. M. and 4:00 P. M. (every day), and when he was the informal clinical "attending physician" to a small group of residents for two months of each year.

His "grand rounds" as I recall them were brilliant but less relaxed, and would sometimes last from morning to early afternoon with resulting discomfort to all from fatigue and hunger.

His numerous capabilities were astounding. The first polygraphic recordings of cerebral blood flow and metabolism that I made with him and Harry Fang included a discarded cooky tin, cardboard boxes, and sawn woodwork, refurbished galvanometers and pieces of a broken hand-mirror from my wife's purse. The gear box for the kymographic camera was so stiff only Denny could move it, and it was only after three years of constant use that I happened to discover the oil-box had never been filled since the apparatus was purchased (for studies on concussion) some years before. As far as I know the oil was never added. The amazing thing was that everything worked that he put together (and he enjoyed doing this as part of the challenge of research). I learned neurology, neurophysiology, neuropathology, neuroanatomy, neuro-ophthalmology, electrophysiology, carpentry, sheet metal work, apparatus design, electronics, writing, lettering, photography and the excitement of investigation for its own sake all from Denny. He is an excellent artist and many of the illustrations for his books and papers were drawn by his own hand.

A naturalized American, he brought the finest of English neurology to the United States and has trained over 300 men, many of whom are now professors of academic neurology. The citation that accompanied the honorary degree of Doctor of Laws awarded by Wayne State University states the case for Denny-Brown. It reads, "An inspiring and effective director of research projects, he has trained many of the world's leading scientists in modern neurological techniques; by his penetrating insights and brilliant deductions, he has broadened the concepts and pioneered in exploring new techniques in neurological research. This work has laid the foundation for an advancement of knowledge rarely matched in the career of any scientist in modern medicine".

JOHN STIRLING MEYER, M. D.,
Professor and Chairman,
Department of Neurology,
Wayne State University,
College of Medicine,
Detroit, Michigan.