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Editorial

En la patología cerebral de todas las edades y en circunstancias etiológicas muy variadas, la anoxia constituye un factor de gran importancia en la génesis de los síntomas o de las lesiones.

Si es de grado ligero y escasa duración, los trastornos pueden ser transitorios y de relativa significación; pero si por el contrario es profunda y prolongada las alteraciones son definitivas, graves y a veces mortales.

Los factores causales de anoxia pueden actuar sobre todo el cerebro, como es el caso de la falta de una proporción adecuada de oxígeno en el aire que se respira, el paro cardiorrespiratorio, la compresión de los vasos del cuello, la presencia de un tóxico que interfiere en la utilización de oxígeno por las células, etc. Pero la anoxia también está presente en lesiones cerebrales localizadas tal como ocurre en las enfermedades vasculares isquémicas focales, en las hemorragias cerebrales limitadas, en los tumores, etc. En todos estos casos hay un defecto en el aporte sanguíneo con la consiguiente anoxia en un sector más o menos definido del cerebro.

En los casos en que la anoxia es generalizada, las diferentes partes del encéfalo no evidencian modificaciones anatomo patológicas y eléctricas de idéntica magnitud.

Señalamos(1) *que para cada sector del encéfalo existe un paralelismo en el grado de alteración anatómica demostrada por el examen histológico y el de las modificaciones en los ritmos eléctricos, siendo mayores los cambios lesionales en las estructuras que muestran primero las modificaciones electrográficas.*

En la corteza durante la anoxia el registro eléctrico pasa por una serie de estados hasta alcanzar el silencio eléctrico, en el cual desaparecen todos los ritmos y la gráfica se transforma en una línea.

Hemos estudiado experimentalmente en animales, este fenómeno del silencio eléctrico cerebral en variadas condiciones. Primero en la embolia gaseosa venosa y la anoxia cerebral por compresión de los vasos del cuello.

La embolia gaseosa venosa actúa mediante la obstrucción de la circulación pulmonar por el aire inyectado, con lo cual hay un verdadero paro circulatorio que puede ser transitorio si la burbuja gaseosa se disuelve en la sangre en tiempo, o definitivo y mortal.

En los experimentos registramos simultáneamente el electroencefalograma y el electrocardiograma y comprobamos que antes de que se modifique el primero, el segundo exhibe signos de sufrimiento con depresión del segmento ST, el cual se va acentuando a medida que el electroencefalograma se enlentece y va al silencio eléctrico. Cuando el animal se recobra, mejoran ambos registros.

Observamos también el fenómeno del silencio eléctrico cerebral en la hibernación en ratas y conejos. En todos los experimentos pudimos apreciar que aparecía en forma progresiva y que cuando se mejoraban las condiciones del animal también paulatinamente iban apareciendo los ritmos.

En la anoxia, el cerebro puede estar en silencio eléctrico y el E.E.G. volver a normalizarse, después de un período de tiempo mucho mayor que el que soportan el estado de anoxia las neuronas sin ser destruidas.

Pensamos que el silencio eléctrico, cuando es reversible, es la traducción de un mecanismo defensivo por el cual el metabolismo del cerebro se reduce a un mínimo y permite a las neuronas resistir un tiempo mayor, lo que les da más probabilidades de reaccionar una vez que las condiciones se hacen favorables(2).

En nuestras investigaciones decidimos verificar qué influencia tiene la Formación Reticular tanto en la anoxia como en la hibernación sobre la aparición y desaparición del silencio eléctrico. Para ello realizamos las experiencias en la preparación "cerveau isolé" y comprobamos claramente que el fenómeno en ambas situaciones cambia en su manera de presentarse.

Observamos que a menudo el silencio eléctrico tarda más en aparecer y que cuando en los casos de anoxia se normaliza el aporte de oxígeno o en la hibernación se recalienta al animal, la recuperación electroencefalográfica es muy lenta y dificultosa o deja totalmente de producirse.

Indudablemente la Formación Reticular es necesaria en la regulación del silencio eléctrico, fenómeno que interpretamos, cuando es reversible, como la expresión eléctrica de un mecanismo defensivo de adaptación. En otras palabras la Formación Reticular además de estar involucrada en ciertos aspectos de las actividades neuropsíquicas, tendría, si nuestro modo de ver es correcto, importancia en las funciones de defensa del cerebro frente a los factores de agresión. Este concepto aporta un factor nuevo acerca de las relaciones entre la actividad eléctrica cortical y reticular durante la anoxia. Hasta ahora se ha sostenido de que cuando la corteza está en silencio eléctrico, la formación reticular queda liberada de su control y aumenta su actividad. Nosotros creemos que debe pensarse en un mecanismo inverso, es decir que la última influye en el desarrollo del fenómeno depresivo cortical.

El tema de la anoxia cerebral se ha puesto de actualidad por las necesidades creadas por la medicina de aviación, la cirugía cardiotorácica y las enfermedades cerebrales y cardiopulmonares.

La clínica se ha beneficiado con los aportes de la electroencefalografía, por la cual no sólo se observan directamente los cambios producidos, sino que por medio de la compresión de los vasos del cuello, se introducen condiciones de anoxia unilaterales que permiten hacer una exploración funcional de la circulación cefálica. Esto significa una importante contribución en el estudio moderno de los cuadros isquémicos cerebrales.

Las investigaciones en este campo se han favorecido con la posibilidad de explorar en la intimidad de la neurona aislada; con la neuroquímica penetrando en los principios básicos del metabolismo celular; por los estudios del gasto circulatorio cerebral llevado a cabo con las técnicas modernas y por los aportes de la arteriografía aplicada al examen de los pacientes con transtornos vasculares cerebrales.

Agracemos profundamente a los destacados hombres de ciencia que han contribuido con sus trabajos a dar brillo a este número dedicado a la anoxia cerebral.

VICTOR SORIANO.

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(1) SORIANO, V. Les effets de l'embolie gazeuse sur le cerveau du chien et du lapin. Dans Actualités Neurophysiologiques — Troisième Série. A. M. Monnier, Ed. p. 83. — Masson et Cie. Paris, 1961.

(2) SORIANO, V. La Formación Reticular: Anatomía, Fisiología, Aspectos Neuropsiquiátricos. Segundo Congreso Latinoamericano de Neurología. Santiago de Chile. Noviembre 27 - Diciembre 2, p. 559, 1960.

Editorial

Anoxia is considered as a most important factor in the origin of symptoms or lesions in cerebral pathology at all ages and in different etiological circumstances.

If it is of low intensity and of short duration, the disturbances may be temporary and of little significance; but, however, if it is profound and prolonged the alterations are serious, irreversible and often fatal.

The factor causing anoxia may act on the whole brain, as in the case of unsufficient oxygen in the breathing air, cardiorespiratory arrest, compression of the blood vessels of the neck, the presence of a toxic substance interfering with the utilization of oxygen by the cells, etc.

But anoxia is also determined by more or less localized brain damage, as in the case of local ischemic vascular lesions, limited cerebral haemorrhages, tumors, etc. In all these cases there is a defective blood flow, its consequence being anoxia in more or less limited regions and areas.

Whenever anoxia is generalized the different encephalic regions do not show electrical and anatomopathological changes of the same magnitude. We have pointed out(1) *that for each encephalic section there is an analogy in the degree of anatomic alteration as shown by the histological examination and the variation of electrical rhythms, the lesional changes being larger in those structures that in the first place evidence electrographic alterations.*

During anoxia the electrical cortical rhythms pass through a series of different phases until reaching electrical silence, in which all rhythms disappear and the pattern becomes a straight line.

We studied experimentally in animals this phenomenon of cerebral electrical silence in various conditions: firstly in venous air embolism and cerebral anoxia due to compression of the blood vessels of the neck.

The venous air embolism acts through the obstruction of pulmonary circulation by the injected air; this brings about a real circulatory arrest which may be either temporary if the air bubble dissolves in the blood in time, or definitive and fatal.

In those experiments on air embolism we recorded simultaneously the electroencephalogram and the electrocardiogram, and observed that before the former undergoes any alteration, the latter exhibits signs of damage with depression of the ST segment, which deepens as the electroencephalogram slows down and approaches electrical silence. When the animal recovers, both recordings improve.

We also observed the phenomenon of cerebral electrical silence in the hibernation of rats and rabbits. In all the experiments it appeared progressively and when the conditions of the animal were improved the rhythms also began to appear.

In anoxia the brain may be in electrical silence and go back to normality after a longer period than the one the neurons are able to endure when they are damaged.

We believe that electrical silence, when reversible, evidences the existence of a defensive mechanism by means of which cerebral metabolism is reduced to a minimum allowing the neurons' larger endurance capacity, which makes them more apt to react, once the conditions have become favorable[2].

In these investigations we decided to prove what kind of influence the Reticular Formation has both in anoxia and in hibernation on the appearance and disappearance of electrical silence. For this purpose we made experiments on the "cerveau isolé" preparation and it was clearly evident that in both situations the phenomenon shows itself in quite different way.

In the "cerveau isolé" preparation, the electrical silence often delays its appearance, and when oxygen affluence is normalized in experiments of anoxia, or when in hibernation the animal is warmed up, electroencephalographic recovery is very difficult and slow or does not show at all.

The Reticular Formation is undoubtedly necessary in the regulation of the phenomenon of electrical silence, interpreted by us, when reversible, as the electrical expression of a defensive adaptation system. In other words, the Reticular Formation might have, besides its involution in certain aspects of neuropsychic activities, great importance, if we are right, in the defense of the brain from injuring factors[2]. *This concept adds a new factor with regard to the relations between both cortical and reticular electrical activity during anoxia. Up to now it was asserted that when the cortex is in electrical silence the reticular formation is released from its control and increases its activity. We believe that an inverse mechanisms is concerned, i. e., that the latter actuates on the development of the depressive cortical phenomenon.*

The subject of cerebral anoxia has been actualized due to the problems that have arisen by aviation medicine, cardiotoraxic surgery, and cardiopulmonar and cerebral diseases.

Clinical work has profited with the contribution of electroencephalography which permits not only direct observation of the changes which are produced. but also through the compression of the blood vessels of the neck, unilateral anoxic conditions are introduced that allow a functional exploration of the cephalic circulation. This is an important contribution to the modern study of cerebral ischemic diseases.

Investigations in this field have been benefited by the possibility of studying within isolated neurons; with neurochemistry which penetrates into the basic principles of cellular metabolism; by the studies of cerebral flow carried out through modern techniques and by the contributions of arteriography applied to the examination of patients with brain vascular diseases.

We are deeply indebted to the outstanding scientists who contributed with their work to enhance this issue devoted to Cerebral Anoxia.

VICTOR SORIANO.

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(1) SORIANO, V. Les effets de l'embolie gazeuse sur le cerveau du chien et du lapin. Dans Actualités Neurophysiologiques — Troisième Série. A. M. Monnier, Ed. p. 83. — Masson et Cie. Paris, 1961.

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Anoxia and Cerebral Metabolism

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INTRODUCTION

Victor Soriano has asked us to write a review on the metabolism of the brain during anoxia. We are glad to do so for all the members of our group are interested in one or another aspect of cerebral function. Moreover, a great volume of previous work has led to the conclusion that the brain is the limiting factor in tolerance to anoxia as it is the first organ to cease functioning in the absence of oxygen. The susceptibility of the brain to anoxia is greater than that of other organs because of its relatively higher oxygen intake, and its limited ability to supply adequate energy anaerobically. Yet were it not for the anaerobic processes possessed by that organ our position in regard to anoxia would be even more precarious for with them the brain can endure, for example, the fall of blood pressure and associated oxygen lack occurring with fainting. This distinction between the brain and other organs is emphasized by a comparison with voluntary muscle whose continued function in anaerobiosis is well established. The heart is able to withstand anoxia though less successfully than voluntary muscle. Nevertheless, the vulnerable position of the brain in comparison to that of the heart may be seen by the fact that in asphixial death the heart may continue beating long after failure of the respiratory centers in the brain (1, 2, 3, 4).

Two essential requirements for the sustenance of the brain are the glucose and oxygen obtained from the blood irrigating that organ. It is well known that blood sugar may be maintained at levels adequate to support the brain despite long periods of fasting as the glycogen stores of the body are utilized and protein is converted to carbohydrate. On the other hand, impairment of the oxygen supply to the brain may be caused by a failure of any link in a long chain of events beginning with the inspiration of air and ending with the final utilization of oxygen by the tissues. Anoxia may occur because of insufficient oxygen in the respired gases, as in high altitudes, or because of obstruction of the respiratory passages, either the larger ones or the bronchioles, as well as by a block at the alveolar membranes of the lung. Oxygen lack may also be caused by failure of the respiratory centers. The carriage of oxygen from the outside air to the tissues can be impaired by myocardial insufficiency, reduction of oxygen carrying power of the blood, decrease of blood pressure as in shock, relative cerebral ischemia or enzymatic inactivation at the cellular level. Even if oxygen is available the requirement may be relatively excessive as for example during convulsive seizures when oxygen want will also occur.

The relative importance of the maintenance of blood sugar and the oxygen supply may be compared during hypoglycemia and anoxia. It is well known that the brain may be able to survive intense hypoglycemia for periods up to five hours (5). In contrast anoxia may be endured success-

fully only for approximately the same number of minutes. But all the anoxic conditions mentioned above have in common with insulin hypoglycemia the impairment of the energy supply to the brain and in this regard hypoglycemia and anoxia evoke similar cerebral effects but on a different time scale. These conditions have in common metabolic changes calling upon the anaerobic resources of the brain to prolong its survival, both functional and structural. Cerebral ischemia on the other hand partakes of the stringent conditions inflicted by both anoxia and hypoglycemia. This review will be concerned with the metabolic process in the obligatory utilization of anaerobic energy resources at a time when the aerobic ones are not sufficient to maintain the body in general and the brain in particular.

Symptomatology of Acute Anoxia in Adult Human Beings

A description of the symptoms of acute anoxia affords an insight into the mechanism of action of oxygen want in the brain. Such an opportunity was provided by the inhalation of nitrogen gas originally suggested as possible remedy for schizophrenia. In this technic the nitrogen (6) is adminitered in much the same way as any gaseous or volatile narcotic, that is, by the closed system method in which a mask is fitted tightly to the face of the patient. After the oxygen supply is shut off, undiluted nitrogen is released into the mask. When the anoxia is sufficiently profound, usually by the fourth minute, the nitrogen control valve is closed and oxygen is readmitted.

During the anaerobic periods a series of 5 constellations of behavioral changes are exhibited in the subject. Among the first symptoms of anoxia is motor excitement when the patient moves his hands, legs and head voluntarily (Table I). Second after the patient has lost contact with the environment, fine myoclonic movements begin, as twitchings appear about the face, usually in the corners of the mouth. These are followed quickly by clonic contractions of all four extremities for a period of 20 - 30 seconds, while the pupils dilate and a gradually increasing tachycardia becomes evident. These movements give way in the third phase to tonic spasms and sometimes to torsion spasms. When the latter occur, they are usually preceded by conjugate deviation of the eyes. In the fourth stage spasms develop, either emprosthotonic or opisthotonic in type and the postural reflexes of Magnus and DeKleijn (7) can be elicited. Oxygen is withheld until this time. If the patient passes on to depression of the medullary centers in the fifth phase automatic respiration may temporarily cease, but it is easily restored by the physician conducting the treatment and no fatalities have been reported. When oxygen is again inspired, the patient recapitulates the same series of symptoms in an amazingly rapid succession, but not too fast to see that they

TABLE I

Symptoms of Acute Anoxia

First phase
- Salivation
- Motor Excitement
- Clouded Consciousness
- Slight Cyanosis

Second phase
- Loss of consciousness
- Myoclonic twitchings
- Clonic spasms
- Motor restlessness
- Dilated pupils
- Tachycardia

Third phase
- Tachycardia
- Tonic spasms
- Torsion spasms

Fourth phase
- Extensor spasms
- Dilated pupils
- Tachycardia

Fifth phase
- Bradycardia
- Respiratory depression
- Marked cyanosis

are directly reversed. Extensor spasms are replaced by tonic and torsion spasms and these are followed first by clonic and then by myoclonic twitchings just before contact with the environment is regained (6). It is interesting to note that a similar progression of signs are seen during the insulin hypoglycemia treatment of schizophrenia as in the anoxia induced with nitrogen inhalation.

There is evidence to show that acute anoxia results in a progressive depression beginning with the cerebral cortex and proceeding down the neuraxis to the medulla. In accordance with one viewpoint the brain represents the results of a phyletic process with succeeding accretions of new parts, each one placed immediately in front of pre-existing structures as the vertebrate phylum is ascended. On this neurophyletic basis the brain may be divided into five layers, each succeeding layer in cephalad direction being of younger phyletic age. The accompanying diagram presents this conception in a schematic manner (Figure 1).

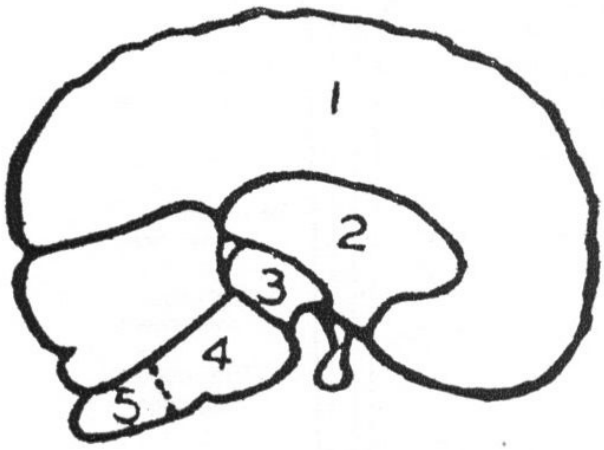

Fig. 1. — *Transverse section of brain revealing the five layers to which the symptoms of hypoglycemia have been allocated. 1) cerebral cortex, the depression of which brings on the cortical phase in hypoglycemia; 2) the subcortico-diencephalon, responsible for the symptoms of release in the second phase; 3) the mesencephalon involving the symptoms of the third phase; 4) the pons and the rostral portion of the medulla (upper) and 5) the caudad portion of the medulla (lower), releasing the premyencephalic and myencephalic symptoms respectively (5).*

When nitrogen gas is inhaled the person traverses rapidly through the first or cortical phase and loses contact with the environment, as a result of suppression of the cortical components of various cerebral functions. The second stage is characterized by release of subcortical diencephalic structures and by the appearance of myoclonic twitchings as well as a brief period of contractions of all four extremities. The individual passes on directly to the release of the tonic and torsion spasms of the third mesencephalic phase and then to the extensor spasms of the fourth premyencephalic phase and sometimes remains briefly in the myencephalic stage.

If one regards the above description as depending upon a horizontal functional organization of the brain a newer one arising from the work of Moruzzi and Magoun (8), as well as of Jasper (9) and of Bremer (10) may be characterized as vertical. As emphasized by Livingston, Haugen and Brookhart (11), the central nervous system may be regarded as divided into three vertical columns extending throughout the entire length of the central nervous system: the first includes ascending spinal pathways carrying sensory impulses that are relayed by the thalamus to specific sensory areas of the cortex. The second column consists of the descending motor pathways of the corticospinal tracts. Between these two is a third composed of indirect connections: association areas of the cerebral cortex, the reticular formation of the brainstem and the extrapyramidal motor tracts descending to the anterior horn cells of the spinal cord. The third column also possesses ascending functions in the two parts of the activities of the reticular formation (12, 13) which are continued by the diffusely projecting thalamocortical unspecific projections.

Viewing the same phenomena from the vertical conception we see that in the first phase of acute anoxia pyramidal and extrapyramidal cortical functions are first depressed and then eliminated; thus all the ensuing motor phenomena emanate from the subcortico-diencephalon. These subcortical areas gain expression in the reticulo-

spinal, the vestibulo-spinal and other extrapyramidal pathways. The tonic and torsion spasms of the third phase appear at the time of the release of the mesencephalic reticular formation. In the fourth phase the suppression of the midbrain reticular formation removes constraints both facilitatory and inhibitory usually exerted upon bulbar areas.

The events of acute anoxia brought about by the inhalation of nitrogen gas can be explained equally well by each of these two conceptions because they are different aspects of the same phenomenon and, in reality, possess in common a central core insofar as they both entail interferences with feedback mechanisms. It is this interference which is responsible for Hughlings Jackson's conception of release phenomena when he proposed that a lesion in the brain makes itself manifest by two categories of behavioral alterations, the first being the expression of the loss of the activities of the injured areas, and the second representing the result of the release of functions of other parts of the brain (14). The symptomatology of acute anoxia reveals a progressive depression of the brain to anoxia traveling from the cephalad to a caudad direction down the neuroaxis and chiefly so because oxygen consumption is highest in the cerebral hemispheres and gradually decreases until it is lowest in the medulla oblongata. It is this relatively low metabolism in the medullary region that permits respiratory activity to continue even when cortical cerebral functions are suppressed.

Symptomatology of Chronic Anoxia in Human Adult

Though the behavioral changes of acute oxygen want are definite and well known, such a clear definition does not apply to the clinical syndromes characterizing hypoxia whether due to subacute or chronic want. Usually hypoxia occurs in the course of some disease and its significance may be therefore masked or confused by the symptomatology of the underlying pathological processes. It has been established, however, that certain signs and symptoms are frequently associated with subacute oxygen want and when they occur in any combination during sickness, hypoxia should be suspected, particularly if there is known a breakdown of normal cardiovascular reactions or an impairment in the transport system of the physiological gases. Some signs of chronic hypoxia emanate from the brain and include muscular twitchings, restlessness, irritability, apprehension, apathy and delirium. But other signs are of composite origin indicating involvement of additional organs: for example, respiratory

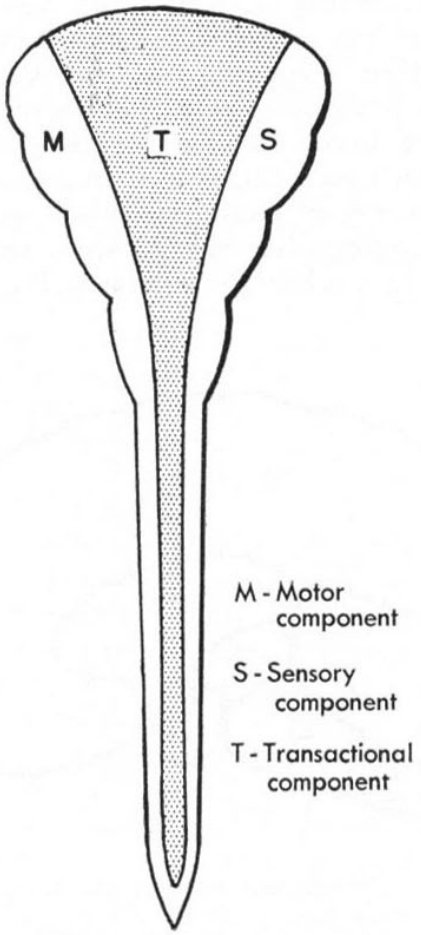

Fig. 2. — *The activities of the structures forming the transactional component (T) of the central nervous system find their expression via final common projections in the caudal reticular formation. Such activities may be initiated by the sensory input (S) and attain motor expression (M) but have an identity of their own which is greater than the sum of the two component parts (11).*

changes which include labored respiration, whether dyspnea or orthopnea or periodic breathing, or circulatory alterations such as tachycardia, arrhythmia, blood pressure changes and precordial pain. Gastrointestinal symptoms may be nausea and vomiting. It is worthwhile noting that cyanosis occurs in only a minority of the patients afflicted with hypoxia. In chronic hypoxia the balance between the aerobic versus the anaerobic processes is shifted towards the latter type though less so than in acute anoxia as some oxidations are continued.

Anoxia in the Human Neonate

The period of complete anoxia which can be endured by the adult human with complete recovery is brief; for example, the longest duration of submergence under water compatible with revival is 7-8 minutes (15). In contrast the human neonate has been reported to be able withstand acute anoxia of as long as 14 minutes with no apparent damage (16) in one case and 25 minutes in another (17). On the other hand chronic anoxia often beginning in *vitro* may lead to various neurological disorders and to death (18, 19). It is difficult, however, to distinguish between the effects of anoxia *per se* and concomitant pathological processes of different origin in the fetus. Animal studies have cast some light on this problem but as will be discussed below it is difficult to equate the physiologic age and development of the human neonate with the young of experimental animals. This problem however, continues to excite the interest of obstetricians and others concerned with the physical condition of the newborn.

Anoxia in Animals

The ability of the adult animal of all species to withstand oxygen lack is uniformly low. However, wide variations appear in the havoc wrecked by anoxia in the newborn (19a) (Fig. 3). The classic examples are the rat who is behaviorly unaffected (5) and the guinea pig who suffers extensive damage (20). The monkey who might be expected to be similar in his response to the human neonate also appears not to display much permanent damage judging by behavioral or electroencephalographic development (21, 22, 23).

Hicks (24) has recently shown that on a histological basis some retardation of dendritic development can be demonstrated in rats exposed to nitrogen for 30 minutes.

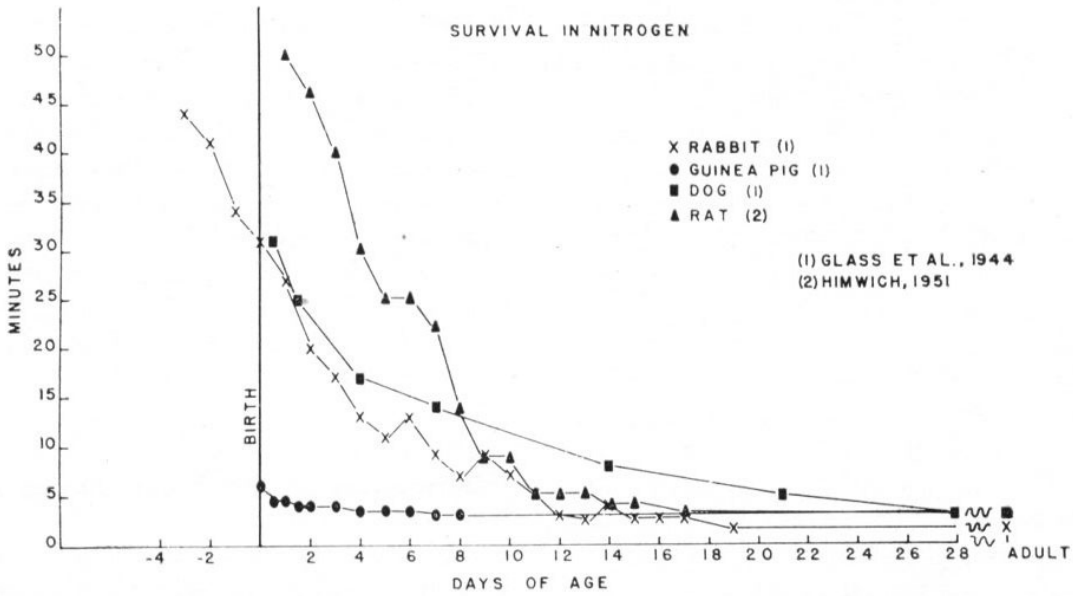

Fig. 3. — *Survival in nitrogen of animals of various ages. Adapted from (5) and (19 a).*

These changes, however, can be seen only upon careful scrutiny of matched sections. In any event they appear to have little effect on the total development of the animal.

The Czechoslovakian workers, Jílek, Mourek and their colleagues (25-29) have studied the effects of subjecting young rats to hypoxia, to starvation, and to cerebral ischemia. All these processes appear to retard cerebral development and prolong the period in which the animal is relatively resistant to anoxia.

The ability of the brain of the young animal to withstand anoxia has been related to the absence of the adult complement of enzymes necessary for oxidations. In the guinea pig the brain is already capable of conducting oxidations at the mature level as evidenced by the level of succinic dehydrogenase activity (30); in the rabbit and the rat the achievement of this level coincides with the loss of resistance to anoxia (Fig. 3). Other enzyme levels; atorase, cytochrome oxidase, and carbonic anhydrase show a similar relationship (31, 31a, 31b) (Fig. 4, 5).

In the adult animal under conditions of anoxia physical and electrical as well as biochemical changes occur in the cortex. Van Harreveld (32-34) has investigated the shifts in cortical impedance, neuronal volume and chloride placement in asphyxia-

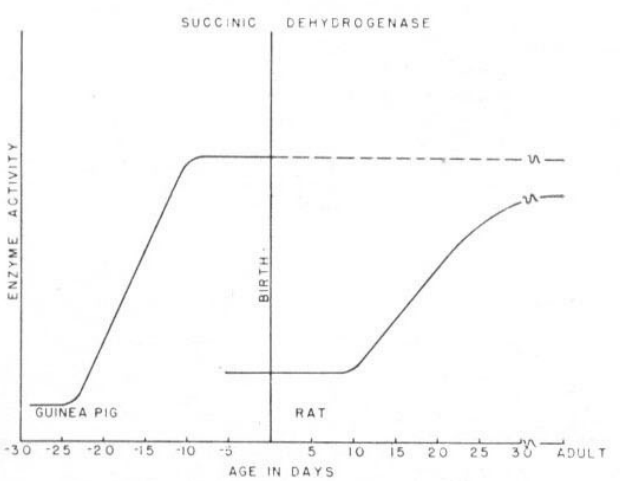

Fig. 4. — *Succinic dehydrogenase activity in brain of rats and guinea pigs of various ages. Adapted from (31) and (31 b).*

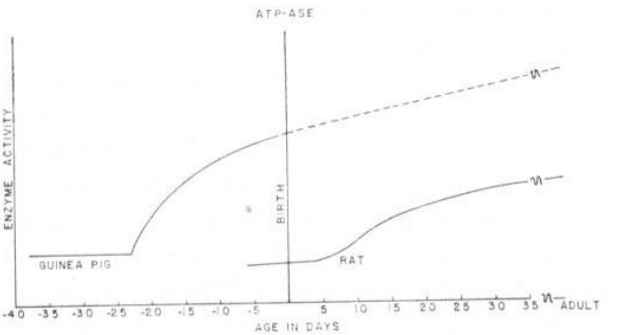

Fig. 5. — *ATP-ase activity in the brains of rats and guinea pigs at various ages. Adapted from (31) and (31 a).*

tion resulting from cerebral ischemia following arrest of the circulation. In this condition cortical impedance rises rapidly, probably due to a movement of sodium and chloride ions from "extracellular" to intracellular locations. Histochemically it can be shown that chloride accumulates in apical dendrites. The shifts of chloride taken in conjunction with the changes in water under the same experimental conditions are sufficient in Van Harreveld's opinion to explain the rise in cortical impedance occurring during asphyxiation. Mourek (35) has followed cerebral impedance during hypoxia in rats from three days of age to adulthood. Normally cerebral impedance reaches a maximum at 4 weeks of age. The effects of hypoxia on cerebral impedance are least in the young animals with correspondingly greater resistance to anoxia.

The development of resistance to altitude anoxia has been of great interest to the Iron Curtain scientists who have studied this type of anoxia in several species of animals including birds (36) and rats (28). In adult dogs, if cortical oxygen tension falls to 1/2 the normal value and subcortical values to 1/3, signs of anoxia develop (37).

Metabolism of the Brain During Anoxia

The brief period of survival in the adult is made possible chiefly by the release of energy from anaerobic processes. Among the anaerobic resources a relatively small

yield of energy is made available as substances containing unsaturated hydrogen bonds accept hydrogen atoms from compounds which are thus oxidized to yield energy. These include such unsaturated fatty acids as linoleic acid and sulfhydryl containing compounds. Glycolysis, the anaerobic breakdown of carbohydrate and especially of glucose is the most important source of anaerobic energy. In accordance with the Embden-Meyerhof scheme glucose is broken down to form pyruvic acid and finally lactic acid. In this regard it may be well to call attention to the fact that glycolysis is a wasteful process in comparison with oxidation. In glycolysis twelve molecules of carbohydrate supply approximately the same amount of energy as the oxidation of one molecule of that substance. It should also be mentioned that the glycolytic breakdown of glucose is considered to be phyletically older than oxidation, a process which has probably developed secondarily to glycolysis, the latter representing a more primitive effort of nature to afford the energy necessary for life. If this viewpoint is correct then the earlier glycolytic Embden-Meyerhof scheme may be regarded as being complemented by the later developed oxidative Krebs cycle (5).

Another important anaerobic source of energy comes from the breakdown of energy-rich phosphate bonds such as contained in phosphocreatine and adenosine triphosphate. These and similar energy-rich compounds are built up by the energy derived

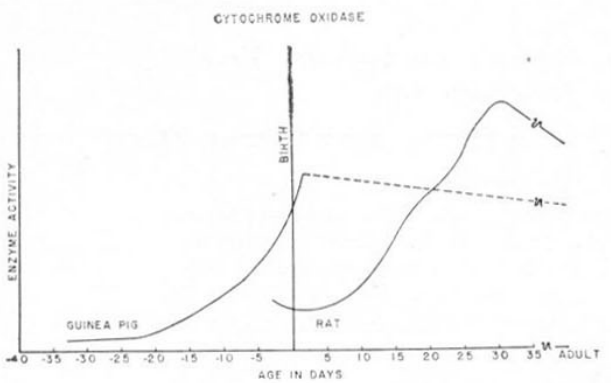

Fig. 6. — *Cytochrome oxidase activity in the brains of rats and guinea pigs of various ages. Adapted from (31) and (5).*

from glycolysis and the latter process is reversed as most of the lactic acid formed anaerobically is reconverted to carbohydrate by the energy released in oxidations. Thus there is an intimate relationship between these two chief sources of anaerobic energy; the process of glycolysis and the breakdown of energy-rich phosphate bonds. If glycolysis is stopped for any reason energy-rich phosphate bonds are depleted as a secondary result, and finally phosphocreatine and adenosine triphosphate are no longer reconstituted. Krécek and Stepánek quoted by Mourek (28) found that hypoxia had little effect on high energy phosphate compounds in the newborn, although in the adult they were rapidly depleted.

An excellent way to study anaerobic processes is afforded by experimentation with neonates, chiefly because of the strikingly slower time scale than in the adult animal. The greater ability of the newborn to withstand anoxia is conditioned not only by lower enzyme activity but also by the higher energy demands of the adult brain. It is true that with growth the capacity of the brain to obtain energy anaerobically increases, but the increase in oxidations far out-distances that of the anaerobic processes. Thus with the greater demand of energy of the adult brain, anaerobic metabolism is relegated to a secondary position in quantitative importance and without the aerobic energy support the brain and indeed life itself could not be maintained. The mature animal is therefore more vulnerable than the fetus and the neonate of most species. One way to test the hypothesis that the energy from the anaerobic source sustains the brain during anaerobiosis is to interfere with glycolysis at one point or another and determine whether there is a corresponding decrease in the duration of the anaerobic period which can be sustained. Two compounds known to depress glycolysis are iodoacetate and sodium fluoride, both of which have been employed in one or another of the following experiments: Members of a litter of rats injected with iodoacetate succumbed three minutes after being placed in nitrogen gas, whereas another untreated litter survived 50 minutes in ni-

TABLE II

Iodoacetate and Anoxia in Newborn Rats

Conditions	*Average Survival Time* minutes	*Average Lactic Acid* mg. %
Iodoacetate in air	50	41
Iodoacetate in nitrogen	3	38
Nitrogen only	50	145*

* Determined after 40 minutes of nitrogen.

trogen (Table 2). The criterion for survival used in these experiments was the maintenance of respiratory movements. That it was the lack of energy obtained from anaerobic processes that reduced the survival periods is shown by the fact that those of the control litter that were sacrificed at 40 minutes in order to determine the lactic acid content of the brain revealed an average of 145 mg % in contrast with 38 mg % for lactic acid in those who were injected with iodoacetate (38).

In the above experiments iodoacetate affected not only the brain but all the organs of the body employing the Embden-Meyerhof process for the realization of enegy. For example, following the administration of either iodoacetate or fluoride and exposure to nitrogen, the heart no longer beats after respiration has ceased, but stops practically simultaneously with respiration. In such an instance the heart rather than the brain might be the first organ to succumb to anoxia and hence the animal might die while the brain was still capable of maintaining itself if it had an adequate blood supply.

In order to dissociate the effects on brain from those on other organs, newborn rats were decapitated after having received injections of iodoacetate or of fluoride (38). As in the experiments with the intact animal, the persistance of respiratory movements was taken as the criterion of survival except that now only the severed head and not the entire body was observed. In a word, the duration of the gasping reflex of the isolated head was determined (38). In the week-old animal the isolated anemic head may gasp for many minutes. Table III shows that the average gasping time of the isolated head of one-day old rats was 20 minutes and that the injection of sodium fluoride shortened the period to seven minutes, whereas iodoacetate reduced gasping time to 2 1/2 minutes. These experiments on the duration of the gasping reflex of infant rats suggest that both iodoacetate and fluoride hinder the anaerobic processes in the respiratory centers, processes which produce the energy necessary for the nervous integration of gasping. Since these reagents act to stop glycolysis, these observations bring added support for the conclusion that the breakdown of carbohidrate according to the Embden-Meyerhof scheme is an important anaerobic source for cerebral energy.

TABLE III

Effect of Iodoacetate and Sodium Fluoride on Survival Time and Gasping Reflex of Newborn Rats

	MG. Per Gm.	Average Survival Time of Intact Animal In Air	Average Survival Time of Intact Animal In Nitrogen	Average Gasping Time of Isolated Head
		minutes	minutes	minutes
Iodoacetate	0.18	50	3	2 ½
Sodium fluoride	0.5	50	16	7
Uninjected control ..		Continues to live	50	20

In the adult too we can show that the inhibition of the anaerobic release of energy diminishes the anoxic survival period. In view of the fact that the mature animal of any species lives for such a brief time in undiluted nitrogen it is difficult to separate the individual components of the anaerobic survival for their study. For this reason, the adult animals were exposed to a mixture of nitrogen containing some oxygen. In preliminary experiments it was found that 8 % oxygen in nitrogen and 32 mg/kilo of iodoacetate gave a satisfactory period. These concentrations were therefore used on three groups of dogs anesthetized with pentobarbital to control muscular activity (Table IV). The persistence of their respiratory movements was again taken as a criterion of their survival. The first group respired 8 % oxygen, the second breathed air, but received an injection of iodoacetate, and the third was subjected to 8 % oxygen after injection with iodoacetate. In contrast to the first group of animals who lived from 1 - 4 hours and the second which averaged 127 minutes, the survival period of the third group was reduced to 4.3 minutes. Since iodoacetate interfered with glycolysis, it may be concluded that the survival period of the third group of animals in partial anoxia was cut short when the anaerobic release of energy by the Embden-Meyerhof path was stopped (39).

Stone, Marshall and Nims (40) have studied not only the processes of acute anoxia but also those of the restoration following the respiration of air. They found that when anesthetized adult cats inhale undiluted nitrogen for a brief period, lactic acid accumulates in the cerebral cortex but promptly returns towards its normal level during recovery from the anoxia (Table V). These authors not only observed an increase in lactic acid during anoxia, but also

TABLE IV

Survival Time of Adult Dogs* with 8 % Oxygen, Iodoacetate and Both

Condition	*N° of Dogs*	*Average Survival Time*
		minutes
8 % oxygen in nitrogen	5	60-240
Iodoacetate (25-49 mg./kg.)	17	127
8 % oxygen + iodoacetate (25-49 mg./kg.)	10	4.3

* Pentobarbital anesthesia was employed for these adult dogs.

TABLE V

Chemical Pattern of Cerebral Cortex Before, During and After a Short Period of Breathing Nitrogen

Breathing Nitrogen	*N° of Exper.*	*(Average) Lactic Acid Mg./100 Gm.*	*Mg. P/100 Gm. (Average) Inorganic phosphate*	*Phospho-creatin*
Before	8	17	11	13
During	6	55	14	8
After	5	25	7	14

found that inorganic phosphate likewise accumulated. One source of this inorganic phosphate must have been phosphocreatine because that substance decreased in concentration during the anoxic period. Just as the excess lactic acid disappears when oxygen is again respired, so phosphocreatine is resynthesized upon introduction of oxygen (40).

During convulsions the brain also reverts to an anaerobic metabolism despite an increased cerebral blood flow to aid aerobic processes (41, 42). Thus the brain exceeds its oxygen supply, and then like muscle, the process of glycolysis and the breakdown of phosphocreatine are anaerobic sources of energy to help sustain the hyperactivity. Lactic acid, inorganic phosphates and other metabolites accumulate in this way so that after the fit is over, energy must be made available to reestablish the pre-convulsive biochemical pattern. During this time the cerebral circulation is still maintained at a greater rate than before the convulsion in response to the vasodilator action of these metabolites. A dramatic instance is reported by Penfield (43) who observed the exposed brain of a patient in the aftermath of an epileptic seizure. The venous blood returning from the portion of the brain which had been active in the epileptic convulsion was of a distinctly more arterialized hue than the blood from the relatively quiescent cerebral tissue. In this way the brain adjusts itself to activity by a blood flow which is not entirely capable of supporting the excessive function while it is taking place, but which remains disproportionately large after the hyperactivity subsides. This excessive blood supply is used in part for the repayment of an oxygen debt acquired during convulsions.

In addition to the study of changes in carbohydrate and phosphate metabolism during anoxia many other parameters have been examined and one of these includes alterations in the amino acids of the brain. We shall present chiefly the results obtained in Dr. W. E. Stone's laboratory because they are characteristic and those of other contributors are too numerous for all of them to be included in this review.

Tews, Carter, Roa and Stone (44) studied the effect of anoxia induced by the administration of 4.5 % oxygen in nitrogen for 12 - 13 minutes to adult dogs. They observed significant increases in alanine, gamma-aminobutyric acid (GABA) glutamic acid, leucine and tyrosine. On the other hand there were decreases in aspartic acid and in a fraction consisting of methionine and cystathionine while the ammonia level was not significantly increased. Remaining unchanged, however, were most of the amino acids and related compounds: acetylaspartic acid, arginine, citric acid, glutamine, glutathione, glycerophosphoethanolamine, glycine, histidine, lysine, phenylalanine, phosphoethanolamine, serine, taurine, threonine, urea, and valine.

These workers noted the comparable effects of anoxia on lactic acid and alanine and suggested that alanine is formed from pyruvic acid by the addition of ammonia from other amino acids, and that this reaction is an alternate anaerobic pathway for pyruvic acid. Ruscák (45) explains his similar data by the transamination of pyruvic specifically by glutamic acid. Similarly, the increase of GABA may be due to the actions of the enzyme glutamic acid decarboxylase which can anaerobically catalyze the formation of GABA from glutamate (46, 47). There is so much glutamate present in the brain at this time that the smalll amount which disappears in the form of GABA is relatively insignificant. Tews *et al* (44) also noted that as in anoxia the levels of most amino acids were unchanged during convulsions produced either by picrotoxin or by pentylenetetrazol. With the former, however, a slight decrease in aspartic acid occurred while with the latter there were rises in alanine and ammonia as well as a slight fall in glutamic acid. Again, as in anoxia unassociated with convulsions, alanine increased and for the same reason, namely the transformation of the accumulated lactic and pyruvic acids to alanine. Similar to the decrease of aspartic acid during anoxia there was a slight decrease of aspartic acid with convulsions. In contrast to anoxia, however, glutamic acid did not rise, in fact, there was a small fall. The

levels of glutamic acid, however, may be regarded as a resultant of the anoxic rise and the necessity of satisfying increased energy requirements of the brain. It would seem that the tremendous utilization of energy associated with seizures came partly from the metabolism of glutamic acid. Additional evidence is available for this conclusion from studies of the fall in glutamic acid in insulin hypoglycemia. The Russian workers (48, 49) believe that the administration of glutamic acid during hypoxia stimulates certain enzyme systems and hastens the metabolism of the Krebs cycle intermediates. Kushko *et al* (50) report a decreased incorporation of S^{35} methionine into brain in both adult and young cats during anoxia. This depression was greatest in white matter and spinal cord.

SUMMARY

The well known resistance to anoxia of the newborns of many species is associated with a lower cerebral metabolic rate of the neonate as well as a higher oxygen requirement of the adult. The relatively low cerebral metabolic rate can be explained as the result of the low activities of the oxidative enzyme systems including among others those of cytochrome oxidase and succinic dehydrogenase which, however, gradually increase as part of the maturation process. Other chemical constituents in brain are beginning to show adult patterns at the time that the animals become increasingly susceptible to oxygen lack. Blocking of the anaerobic processes produces in the newborn a susceptibility to anaerobiosis similar to that seen in the adult with depression of oxidations. It seems therefore that chemical immaturity of the brain resulting necessarily in the use of anaerobic sources of energy accounts for the ability of the immature animal to survive for relatively long periods without oxygen. Specifically during anoxia the brain must rely on anaerobic sources of energy to maintain first, function and finally structure. The breakdown of glucose to pyruvic and lactic acids, the cleavage of energy-rich phosphate bonds are two important processes to yield energy at this time. The chief difference between the adult and the neonate lies in the far greater reliance on oxidations by the adult in comparison with the newborn. As a result, the newborn, can survive anaerobiosis more successfully.

In the human being too, the same principles apply; we do not know to what degree but more so than in the guinea pig and less than in the rat. These facts would tend to reduce the importance of the effects of anoxia in the human fetus and turn our thoughts to additional causes for neurological changes of the brain in the prenatal period.

RESUMEN

La bien conocida resistencia a la anoxia del recién nacido en varias especies, está asociada a su metabolismo más bajo, así como también a una mayor demanda de oxígeno en el adulto. Este metabolismo relativamente bajo del cerebro puede explicarse por la reducida actividad de algunos sistemas de enzimas oxidativas entre los que encontramos los de la oxidasa citocrómica y la dehidrogenasa succínica. Su actividad sin embargo aumenta gradualmente como parte del proceso de maduración.

Otras sustancias que entran en la constitución del cerebro comienzan a evidenciar características típicamente adultas en el momento en que los animales se vuelven progresivamente susceptibles a la falta de oxígeno. El bloqueo de los procesos anaeróbicos provoca en el recién nacido una susceptibilidad a la anaerobiosis similar a la que

presenta el adulto con depresión de las oxidaciones. Por lo tanto la inmadurez química del cerebro que resulta necesariamente del uso de fuentes de energía anaerobias, justificaría la capacidad del animal aún no maduro a sobrevivir sin oxígeno durante períodos bastante largos. En especial mientras dura la anoxia, el cerebro debe depender de fuentes de energía para mantener en primer lugar su función y además su estructura. La transformación de la glucosa en ácido pirúvico y láctico y la destrucción de las uniones de fosfatos ricas en energía, constituyen dos importantes procesos para generar energía en estas circunstancias. La principal diferencia entre el adulto y el recién nacido reside en una mayor dependencia en las oxidaciones en el adulto en comparación al recién nacido, de lo que resulta que este último es más apto a sobrevivir la anaerobiosis.

También son válidos los mismos principios en el ser humano, y aunque no sabemos en qué medida, podemos afirmar que es en mayor grado que en el cobayo y en menor que en la rata. Esta realidad tendería a disminuir la importancia de la anoxia en el feto humano y nos inclinaría a pensar en causas adicionales para explicar las modificaciones neurológicas del cerebro en el período prenatal.

RÉSUMÉ

La résistance bien connue des nouveau-nés dans certaines espèces à l'anoxie est associée à un rythme métabolique bas qui les caractérise comme aussi à la plus grande exigeance d'oxygène chez l'adulte. Ce rythme métabolique cérébral relativement bas peut être expliqué comme le résultat des activités réduites de certains systèmes d'enzymes oxidatives comme ceux de cytochrome oxidase et succinic dehydrogenase, qui graduellement augmente comme partie du procès de maturation. D'autres substances constitutives du cerveau commencent à montrer des caractéristiques adultes au moment où les animaux deviennent de plus en plus susceptibles au manque d'oxygène. Le blocage des procès anaérobies produit dans le nouveau-né una susceptibilité à l'anaérobiose pareille à celle présentée par l'adulte avec dépression d'oxidations. Il paraît par conséquent, que l'immaturité chimique du cerveau qui résulte nécessairement de l'usage de sources d'énergie anaérobies justifierait la capacité de l'animal inmature à survivre pendant des périodes assez longues sans oxygène. Particulièrement autant qui dure l'anoxie le cerveau doit dépendre de sources d'énergie pour maintenir en premier lieu sa fonction et puis sa structure. La transformation du glucose en acide pyruvique et lactique, et la destruction des unions riches en énergie des phosphates constituent deux procès importants pour procurer de l'énergie en ces moments. La principale différence entre l'adulte et le nouveau-né réside dans une plus grande dépendance aux oxidations dans l'adulte, en comparaison avec le nouveau-né. Comme résultat, le nouveau-né est plus apte à survivre à l' anaérobiose.

Les mêmes principes se font valoir pour l'homme, et même si nous ne savons pas dans quelle mesure, nous pouvons affirmer que c'est à un plus haut degré que dans le cobaye et plus bas que dans le rat. Ces faits nous inclineraient à réduire l'importance des effets de l'anoxie sur le phoetus humain, et nous pousseraient à penser aux causes aditionnelles des modifications neurologiques du cerveau dans le période prénatale.

ZUSAMMENFASSUNG

Die bekannte Widerstandskraft der Neugeborenen vieler Arten gegen die Anoxie haengt mit dem geringeren cerebralen Grundstoffwechsel und mit dem hoeheren Sauerstoffkonsum beim Erwachsenen zusammen. Der relativ niedrige cerebrale

Grundstoffwechsel kann als das Ergebnis geringerer Aktivitaet der oxidativen Enzymsysteme, unter anderem auch der Citochromo-oxidase und der Succinyl-Dehydrogenase angesehen werden. Die Aktivitaet dieser Enzymsysteme verehrt sich allmaehlich als Teil des Reifungsprozesses.

Andere chemische Bestandteile im Gehirn beginnen wie beim Erwachsenen zu dem Zeitpunkt zu bestehen, in dem die Tiere beginnen gegenueber dem Sauerstoffmangel empfindlich zu sein. Die Blockierung der anaerobischen Prozesse ruft beim Neugeborenen eine Empfindlichkeit gegenueber der Anaerobiosis hervor, die aehnlich wie beim Erwachsenen bei der Minderung der Oxidationen ist.

Deshalb scheint es, dass die chemische Unreife des Gehirns, die notwendigerweise zur Benutzung der anaeroben Energiequellen fuehrt, ein Zeugnis der Faehigkeit des unreifen Tieres ist, ohne Sauerstoff waehrend einer ziemlich langen Zeit ueberleben zu koennen. Besonders das Gehirn muss waehrend der Anoxie von anaeroben Energiequellen abhaengen, um Funktion und Struktur zu erhalten.

Der Abbau der Glukose zu Brenztrauben- und Milchsaeure und die Spaltung der energiereichen Phosphat Bindungen sind zwei wichtige Prozesse, um in dieser Periode Energie zu spenden. Der Hauptunterschied zwischen Erwachsenen und Neugeborenen besteht in der viel groesseren Abhaengigkeit von den Oxidationen beim Erwachsenen als beim Neugeborenen, deshalb kann das neugeborene Wesen die Anaerobiosis viel erfolgreicher ueberstehen.

Auch beim Menschen spielen dieselben Prinzipien eine Rolle, obwohl wir nicht wissen bis zu welchem Grade, auf jeden Fall mehr als beim Meerschweinchen und weniger als bei der Ratte. Durch diese Tatsachen wuerde die Bedeutung der Wirkung der Anoxie beim menschlichen Foetus geringer sein, und wir muessten unsere Aufmerksamkeit weiteren Ursachen der neurologischen Veraenderungen im Gehirn waehrend der praenatalen Periode zuwenden.

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Deficiencias Neurológicas en Monos Recién Nacidos Sometidos a Asfixia Neonatal[1]

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Se piensa que numerosos trastornos neurológicos que se manifiestan en el niño son causados por condiciones desfavorables que actúan durante la vida prenatal, natal y la postnatal inmediata. Cuanto mayor atención se presta a las relaciones materno-fetales, tanto mejor se aprecia la deficiencia actualmente existente en los conocimientos relativos a estos períodos de la vida. La ignorancia con respecto a la fisiología del feto y a la fisiología materna durante la gestación, son causas de accidentes que pueden producir retardo mental en los descendientes y también desórdenes del sistema neuromotor, tales como el grupo de afecciones involucradas con el término "parálisis cerebral" (conocida en inglés como "cerebral palsy").

El papel que desempeña la asfixia perinatal en la etiología de los defectos neurológicos y psicológicos en el vástago ha sido debatido durante un siglo y la literatura sobre la materia tiene profusión de artículos, informes y testimonios que reflejan opiniones a favor y en contra. Aunque confinemos nuestra atención a los pocos escritos serios, hallaremos un cuadro confuso en cuanto a la terminología y también la falta de una comprensión cabal de lo que acontece antes y durante el parto. Es esta una materia en la que las investigaciones clínicas han sido singularmente ineficaces. A pesar de ello, los experimentos con animales han sido pocos y muy espaciados. Algunos estiman que las condiciones prenatales y del parto en el ser humano son tan distintas de aquellas que existen en los animales, que resulta inútil todo intento de realizar estudios en el laboratorio. Considero que, debido a la naturaleza de los problemas, no es posible resolverlos exclusivamente mediante estudios humanos y que la información urgentemente requerida podrá obtenerse únicamente si se realizan experimentos con animales de laboratorio. No hay duda de que los experimentos con animales han de guiar al investigador clínico hacia la solución de numerosos problemas en esta materia, tal

[1] Conferencia pronunciada por invitación en el IX° Congreso de Obstetricia y Ginecología, Viña del Mar, Chile, en noviembre de 1961. Las investigaciones que forman la base de esta presentación fueron realizadas por miembros del personal del Laboratorio de Fisiología Perinatal y de la Escuela de Medicina, Universidad de Puerto Rico.

como ya ha sido el caso en otras. Llevados a cabo en forma correcta, tales experimentos pueden corregir flagrantes errores conceptuales que aún impiden un enfoque apropiado del problema.

Lejos de mí el sostener que los experimentos con animales han de sustituir enteramente las investigaciones clínicas con seres humanos. Pero estas últimas, para que sean válidas, requieren controles muchas veces difíciles de realizar; los estudios con seres humanos requieren muchos años de esfuerzos coordinados antes de poder ser evaluados, y además resultan sumamente onerosos. La experiencia ha demostrado que son muchos los conocimientos básicos, aplicables a la especie humana, que pueden adquirirse rápidamente en experimentos con animales, a un costo que es tan sólo una fracción de las erogaciones que demandan las investigaciones clínicas.

He de limitar mi presentación al papel que desempeña la asfixia perinatal en la etiología de los defectos neurológicos. Debemos preguntarnos hasta qué punto son comparables las condiciones en animales con aquellas en el ser humano. Existen marcadas diferencias de especie en la placentación y en la madurez del individuo en el instante de su nacimiento, no obstante lo cual numerosos parámetros fisiológicos básicos son similares. Por ejemplo, el mecanismo de la iniciación de la respiración es fundamentalmente el mismo en el feto humano que en el de otros animales.

El mono rhesus, *Macaca mulatta,* se presta en forma ideal para la experimentación debido a su similitud fisiológica con el hombre. Gran parte de lo que he de expresar en esta conferencia se basa en experimentos llevados a cabo con monos rhesus en el Laboratorio de Fisiología Perinatal, en San Juan, Puerto Rico.

Historia Natural de la Asfixia en el Nacimiento

Antes de proceder a la descripción de algunos de nuestros experimentos, y antes de indicar la forma en que se han producido experimentalmente desórdenes neurológicos, tal como la parálisis cerebral y también antes de demostrar la neuropatología resultante de la asfixia, he de tratar de rectificar ciertos conceptos erróneos que prevalecen con respecto a la fisiología del feto en los mamíferos.

Un concepto erróneo, actualmente muy difundido, es que en condiciones normales, el feto humano se desarrolla en un medio de baja tensión de oxígeno. Tal opinión se deriva principalmente de medidas en la saturación de oxígeno hechas en la sangre del cordón umbilical, obtenida durante el parto, (por lo general mediante operación cesárea) oportunidad en que la saturación de la sangre con oxígeno es muy baja, generalmente inferior al cuarenta por ciento. La frase "el Monte Everest del útero" refleja este punto de vista. Por el contrario, la sangre que circula de la placenta hacia el feto tiene una elevada saturación de oxígeno. Aún después de haberse mezclado con sangre venosa en el corazón fetal, la sangre extraída de la arteria carótida del feto del mono tiene una saturación de oxígeno del setenta y nueve por ciento. La sangre que retorna del feto a la placenta, para ser reoxigenada, aún sigue saturada en un cincuenta y ocho por ciento. La diferencia media de saturación de oxígeno entre la sangre de la carótida y de la femoral, es aproximadamente de nueve por ciento. Estos valores fueron obtenidos en nuestros laboratorios por Dawes y sus colegas, con muestras de sangre extraídas por medio de cateterización de los vasos del feto intrauterinamente. El corazón fetal latía a una frecuencia normal. Parecería ser que, bajo las condiciones de los experimentos citados, el feto no está sufriendo de escasez de oxígeno, y que probablemente no tiene necesidad de recurrir a la glicolisis aneróbica. Para que la glucosa y el lactato de la sangre se alteren significativamente, es necesario que se produzca un estado de hipoxia marcado, con descenso de la saturación de oxígeno bajo el cuarenta por ciento.

Existe cierta confusión con respecto al término "apnea del recién nacido". Algunos consideran que la apnea después del nacimiento indica que el recién nacido está hipóxico o asfixiado. Ello no es necesaria-

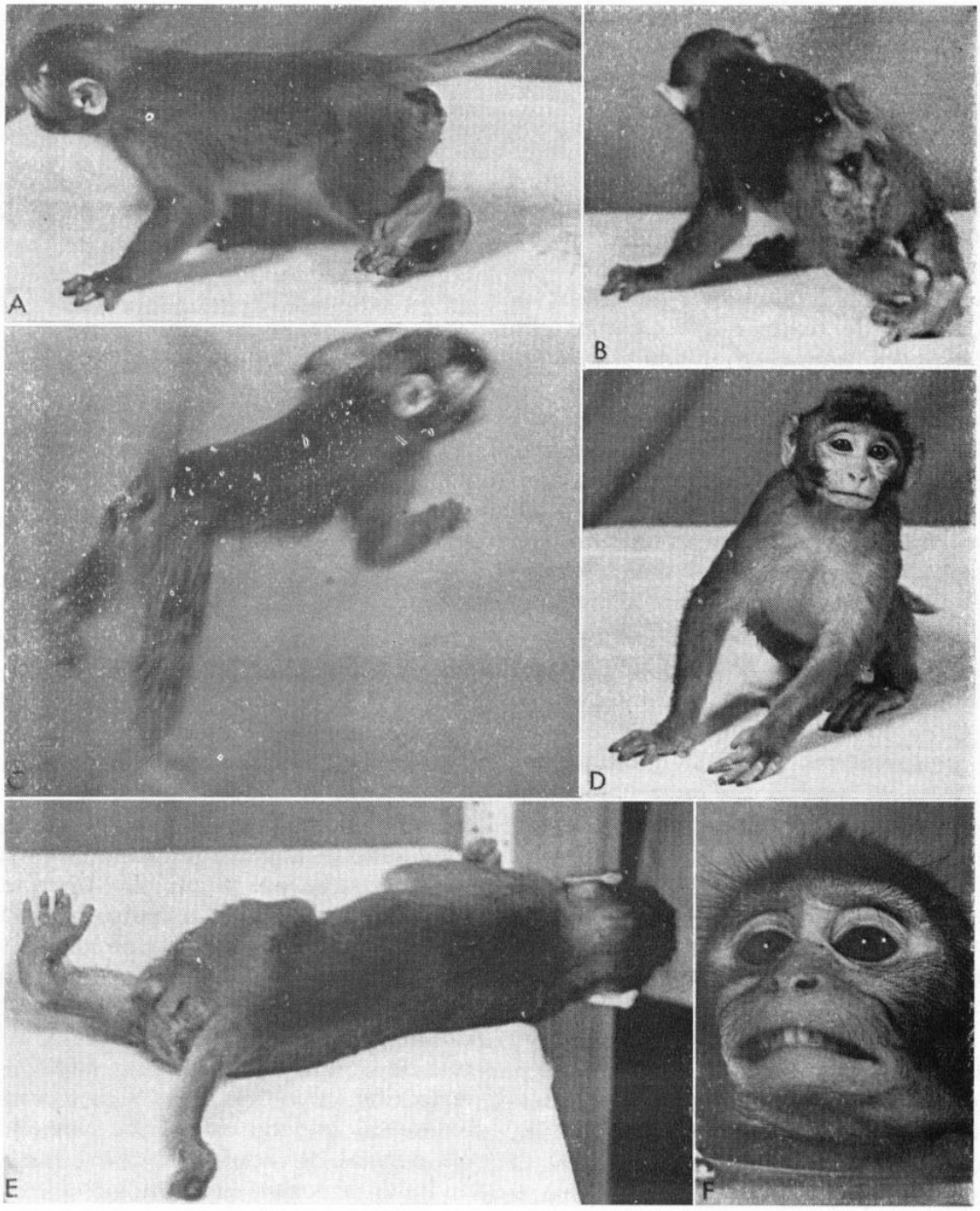

Fig. 1. — *Defectos neurológicos y de comportamiento de un mono a los 389 días de edad asfixiado y resucitado al nacer. Locomoción (A y B) es lenta, inestable, y demuestra cruzamiento de las patas traseras (marcha en forma de tijeras). En C se observa una brusca descarga motora masiva, incapacidad para enderezarse, en E. D y F muestran postura y expresión facial anormal. Reproducido con permiso de Academic Press, Inc., New York (Exptl. Neurol. 1:130-154, 1959).*

mente así. En algunos casos el recién nacido está simplemente narcotizado. En el útero, en condiciones normales, el feto no narcotizado está inactivo y apneico. Al final de la gestación, el feto puede ser activado pasajeramente mediante diversas clases de estímulos. El mecanismo de activación puede ser inhibido por medio de anestésicos su-

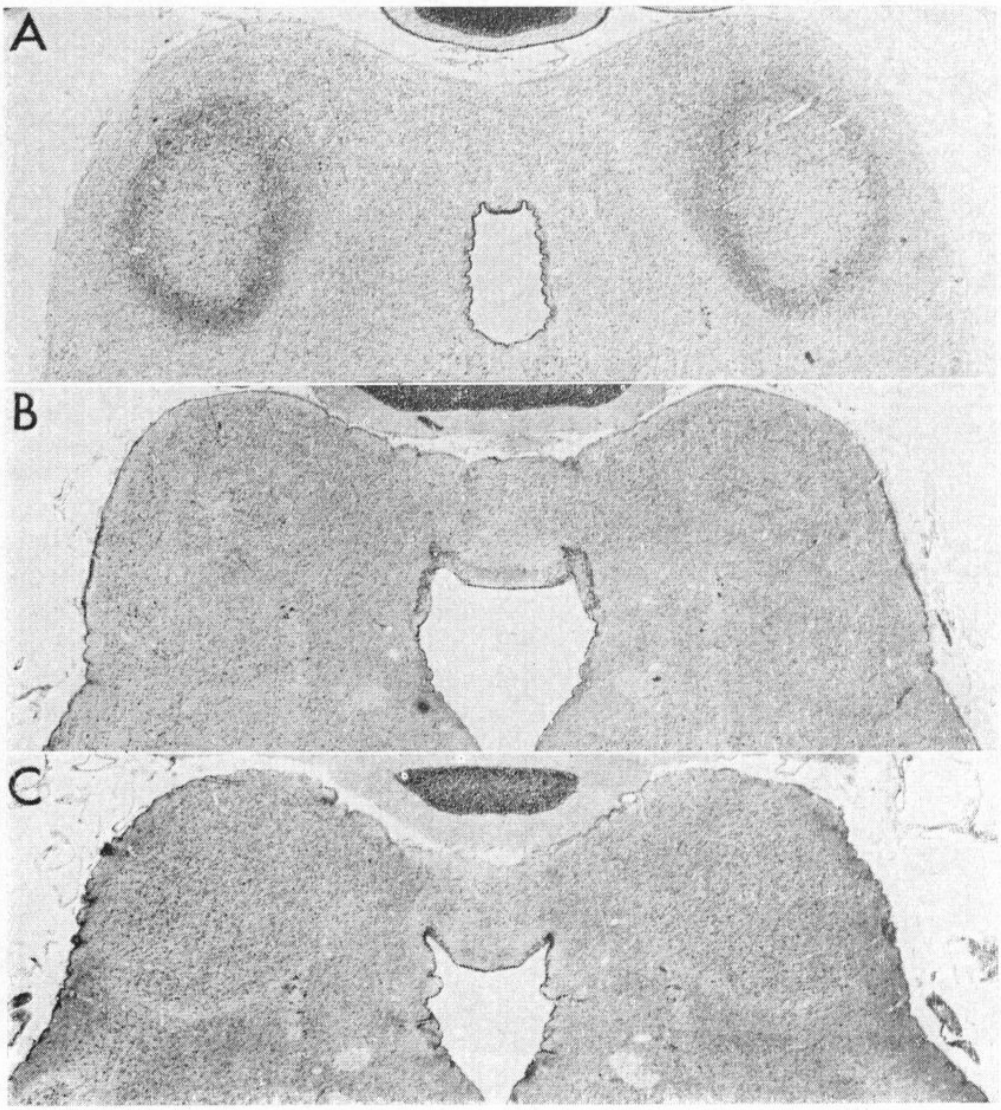

Fig. 2. — *Secciones a través de los tubérculos cuadrigéminos posteriores de tres monos: (A) 9 días después de la asfixia; (B) 290 días después de la asfixia; y (C) control no-asfixiado. En A, las lesiones muestran necrosis del núcleo de cada lado, rodeado por anillos de macrófagos. En B, las lesiones han sido substituídas por cicatrices gliales. En C, se observa la apariencia normal de los núcleos. Cortes de 10-μ en tinción de Tionina. Reproducido con permiso de Academic Press, Inc., New York (Exptl. Neurol. 1:130-154, 1959).*

ministrados a la madre. En los experimentos con animales no es necesario administrar drogas a la madre, y por lo tanto es posible observar el comportamiento fisiológico normal del feto en el útero durante el nacimiento. El nacimiento es seguido de una inmediata disminución en la saturación de oxígeno de la sangre que va al recién nacido desde la placenta. Esta hipoxia, potencializada por impulsos nerviosos aferentes causados por el cambio de medio a medida que el feto emerge, produce una activación del recién nacido. En ausencia de narcosis, el recién nacido se activa, se inician los movimientos respiratorios rítmicos, se establece la función pulmonar, aumenta el contenido de oxígeno en la sangre y se evita la asfixia. Sin embargo, si se impide la entrada de aire a los pulmones hasta que la saturación en la sangre caiga bajo vein-

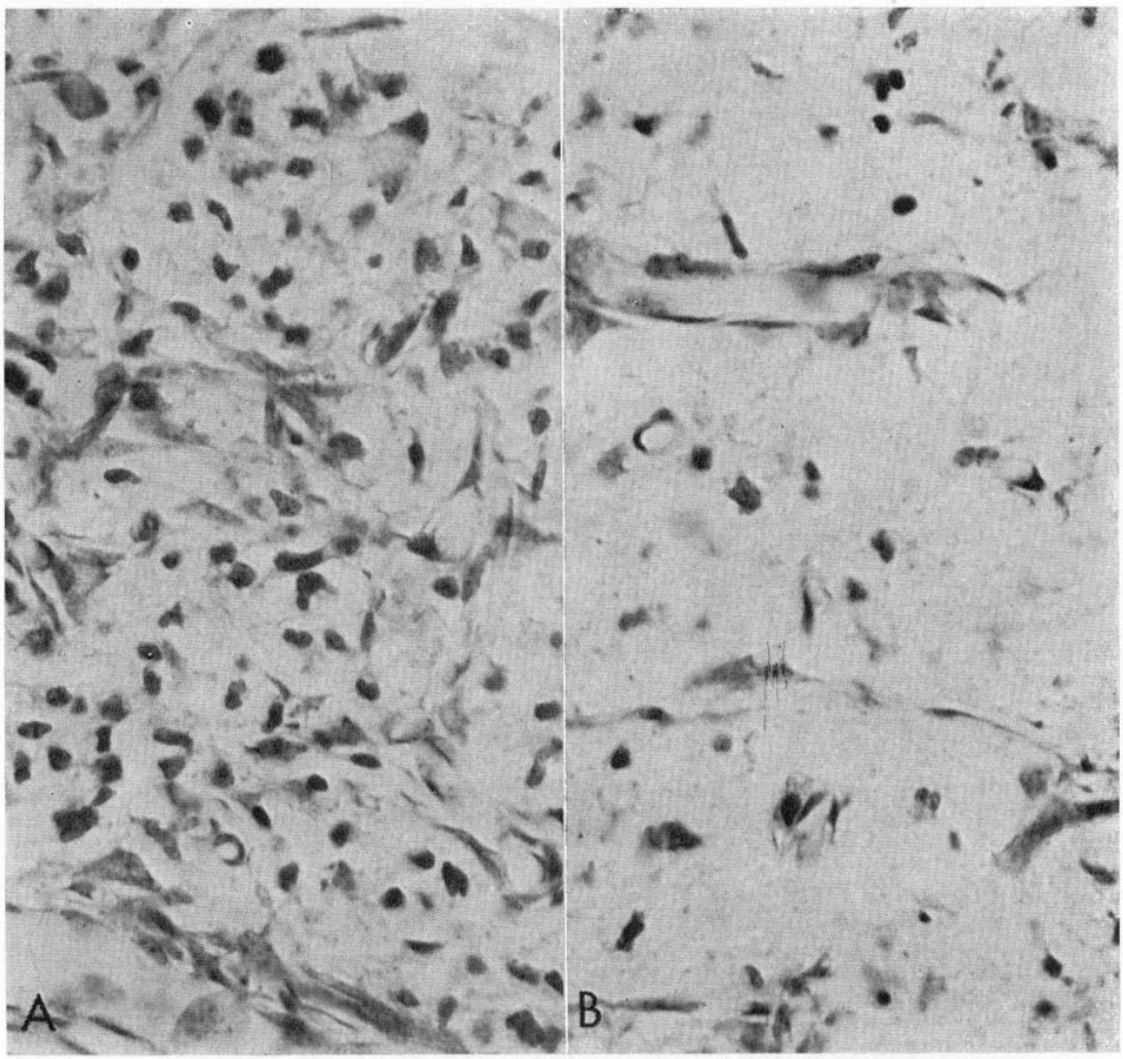

Fig. 3. — *Microfotografía del corte en la Fig. 2A aumentado para ilustrar el anillo obscuro exterior (A) y el centro de la lesión (B). Reproducido con permiso de la "Association for Research in Nervous and Mental Disease" (Research Publ. A.R.N.M.D.* 39:*169-182, 1962).*

ticinco por ciento de oxígeno en la sangre que va al cerebro, estos movimientos respiratorios fisiológicos cesan y a continuación el recién nacido comienza a demostrar falta de oxígeno. Comienzan las boqueadas lentas y rítmicas, que eventualmente cesan y el recién nacido se torna nuevamente apneico. Esta es la apnea asfíctica y el recién nacido que la experimenta no comenzará a respirar en forma espontánea. Debe ser resucitado sin demora y aunque parezca normal, es probable que haya sufrido lesiones en el cerebro.

Permítasenos recapitular las fases que se producen en el momento del nacimiento cuando se asfixia un feto no narcotizado: a) El feto está fisiológicamente apneico mientras recibe de la placenta un suministro normal de oxígeno. b) Con la disminución de la saturación de oxígeno el recién nacido comienza a ejecutar movimientos respiratorios rítmicos que normalmente establecen la respiración pulmonar. c) Si se impide la entrada de aire a los pulmones estos movimientos respiratorios cesan y se produce un segundo período breve de apnea. d) Después de varios minutos de apnea, la violenta descarga motora resulta en grandes movimientos respiratorios y comienzan entonces las boqueadas asfícticas; en esta etapa la sangre fetal prácticamente carece de oxígeno. e) En el mono las boqueadas cesan más

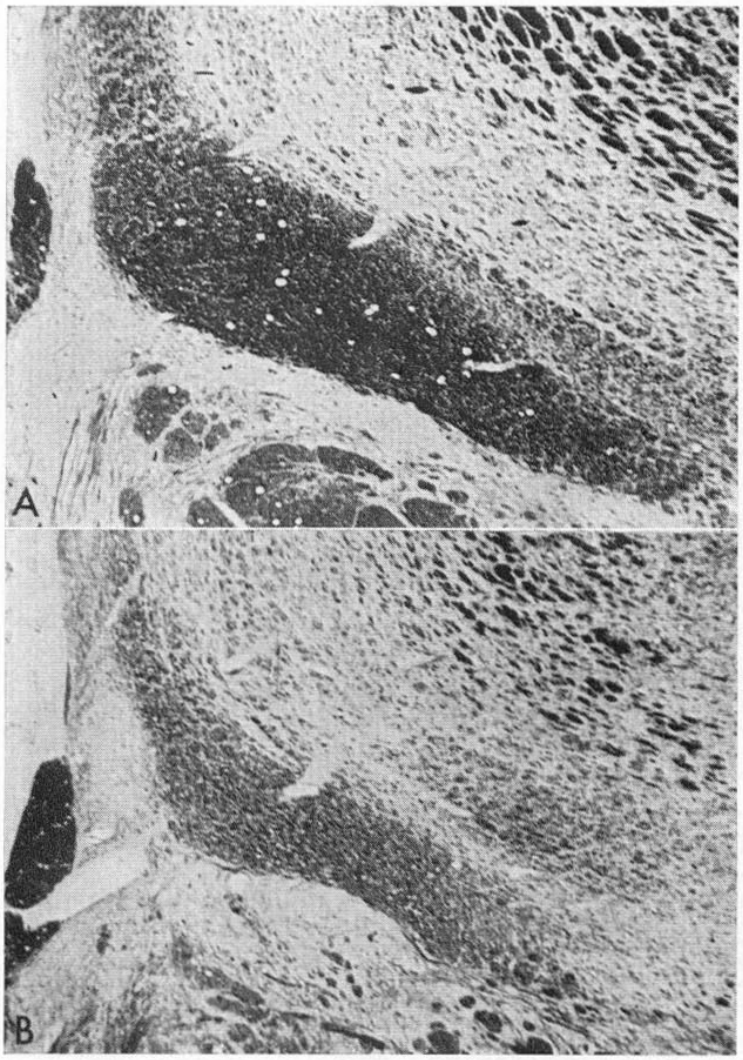

Fig. 4. — *Atrofia y pérdida de mielina (B) en las vías sensoriales después de lesiones asfícticas en el pedúnculo cerebral, comparado con control (A). Tinción mielina.*

o menos diez minutos después de iniciada la asfixia y el recién nacido se torna nuevamente apneico; esta apnea es causada por la asfixia y parece indicar el comienzo de cambios de carácter irreversible en el sistema nervioso del feto.

La asfixia produce también cambios bioquímicos y circulatorios: se acumula ácido láctico y el pH de la sangre desciende; la presión arterial cae; la frecuencia de los latidos del corazón fetal, que normalmente se acerca a doscientos latidos por minuto, puede descender a treinta o menos latidos por minuto. Cuando se han producido estos cambios, para que el recién nacido sobreviva es necesario realizar la resucitación.

Desconocemos cuánto tiempo pueden persistir estas condiciones adversas después de la resucitación del mono recién nacido; tampoco conocemos el papel que desempeña cada uno de estos factores en la producción de las lesiones neurológicas. El mono recién nacido puede recuperarse de una asfixia de aproximadamente diez minutos de duración, sin presentar indicios clínicos aparentes y persistentes de lesiones cerebrales. Tal animal puede no requerir resucitación, ya que diez minutos de asfixia no siempre son suficientes para causar apnea asfíctica. Pero si la asfixia dura más de diez minutos, en todos los casos ha sido posible demostrar la presencia de efectos neurológicos.

Los Animales de Laboratorio

Antes de presentar nuestros experimentos sobre asfixia neonatal en el mono y los

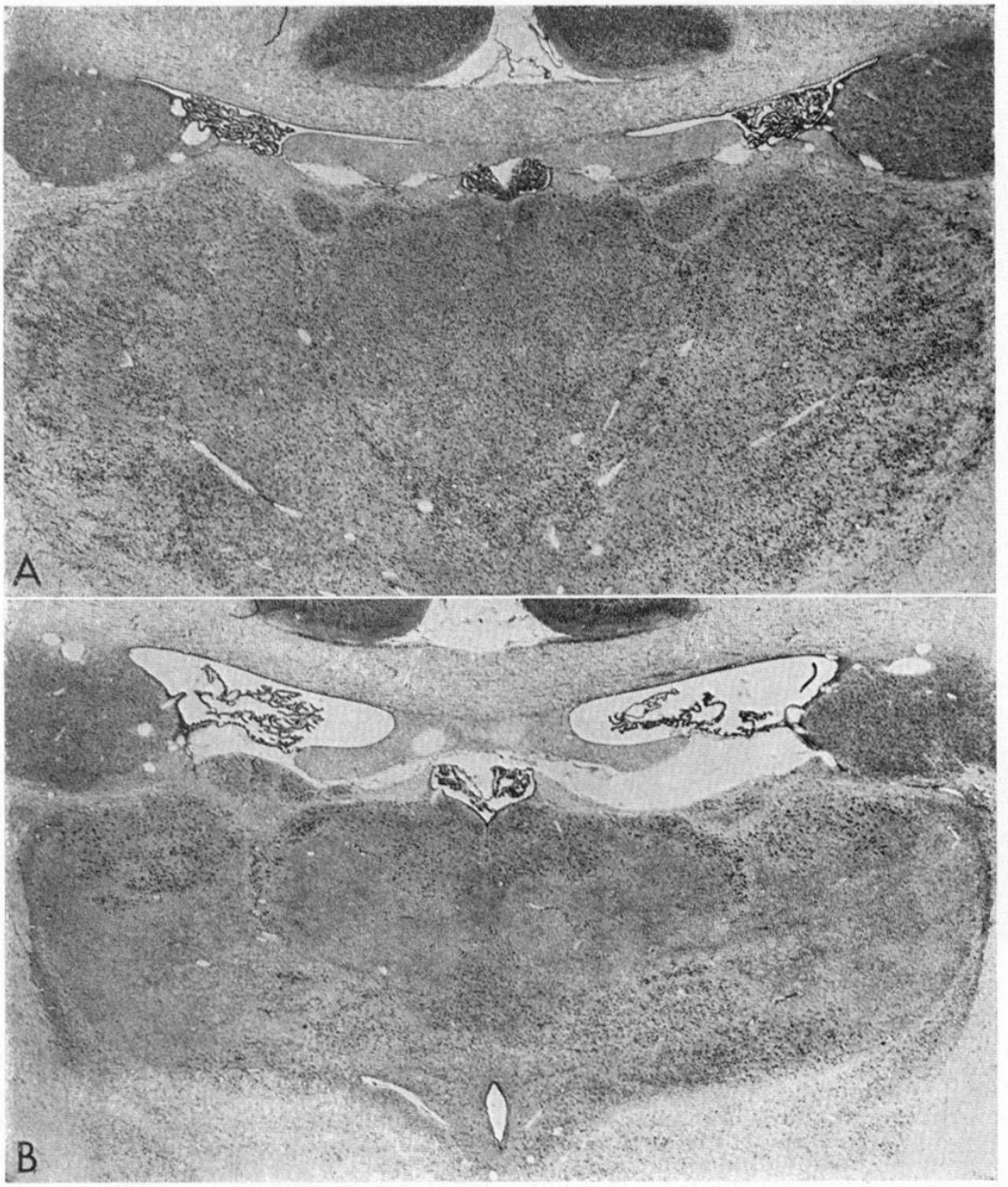

Fig. 5. — *El diencéfalo del control no-asfixiado (A) comparado con la misma región (B) en un mono nacido espontáneamente en presentación de pie. Retención de la cabeza que condujo a la asfixia requiriendo resucitación. Obsérvese la atrofia bilateral de los tálamos en B. Tinción Tionina.*

defectos neuropatológicos resultantes, he de hacer referencia a la fuente de nuestro suministro de animales.

Tenemos una colonia enjaulada de cría de más de doscientas monas adultas y sanas. Los ciclos menstruales se verifican por medio de inspecciones diarias, a la misma hora todos los días, a los efectos de establecer las características individuales de cada mona. En el momento oportuno, del noveno al décimosegundo día del ciclo, la hembra es juntada con un macho compatible por un período de veinticuatro horas, para efecto de lograr un apareamiento regulado. Los ciclos menstruales de las monas son casi idénticos a los ciclos de las mujeres. La du-

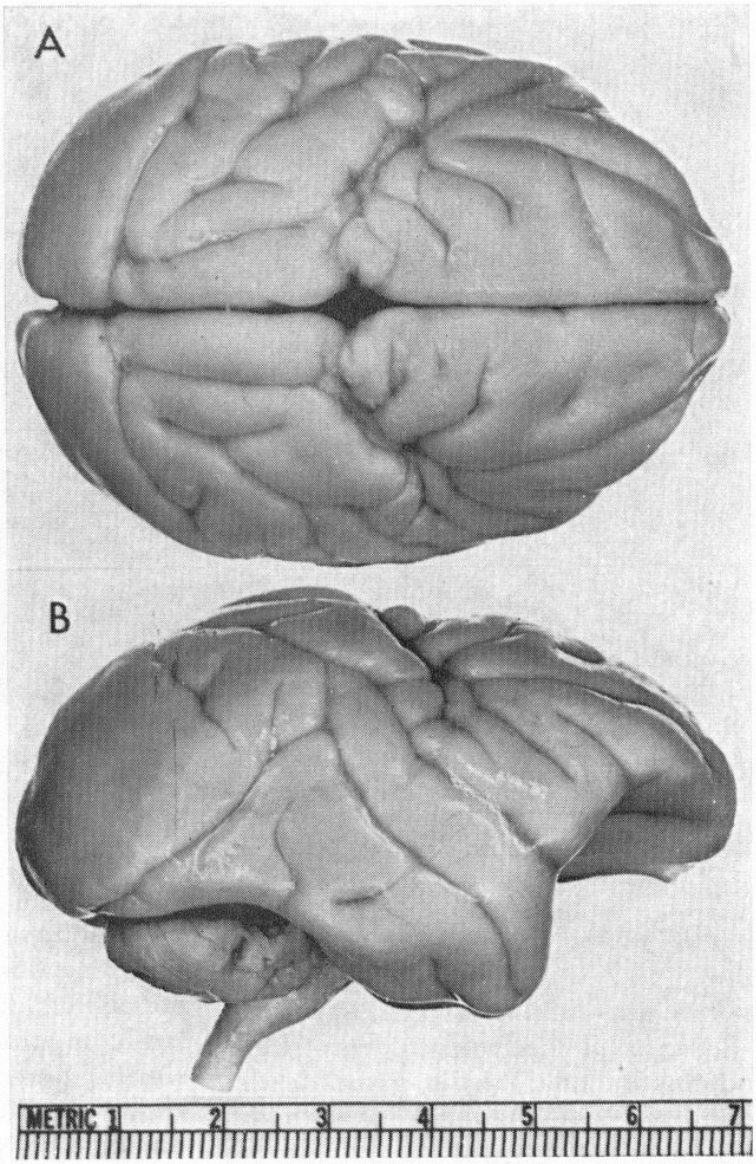

Fig. 6. — *El cerebro del mono mostrado en la Fig. 1. Atrofia en las regiones de la cisura central notándose en ambos lados. Reproducido con permiso de Academic Press, Inc., New York (Exptl. Neurol. 1:130-154, 1959)*

ración del período de gestación presenta variaciones individuales, teniendo un valor promedio aproximado de ciento sesenta y ocho días. En nuestra colonia se han producido nacimientos espontáneos de vástagos vivos, totalmente desarrollados, entre los ciento cincuenta y cuatro días y los ciento setenta y siete días de gestación.

Producción de la Asfixia Perinatal Experimental

Se realiza la operación cesárea bajo anestesia local entre los ciento cincuenta y seis y ciento sesenta y ocho días de gestación. Se extrae el saco amniótico íntegro con el feto en su interior y se le deja así por algunos minutos. Por este procedimiento, hemos asfixiado sesenta y nueve monos recién nacidos. En la mayoría de ellos la asfixia se prolongó hasta alcanzar la etapa de apnea asfíctica. Se abrió luego el saco amniótico extrayendo el monito, y se procedió a efectuar la resucitación, a veces sin éxito. En la película cinematográfica que exhibiremos se ilustra la técnica correspondiente. [2]

[2] Copias de esta película narrada en español e inglés están archivadas en el Laboratorio de Fisiología Perinatal, Institutos Nacionales de Salud, Bethesda 14, Maryland.

Fig. 7. — *Lesión cerebelosa en el mono mostrado en la Fig. 1. Reproducido con permiso de Academic Press, Inc., New York (Exptl. Neurol. 1:130-154, 1959).*

Defectos Neurológicos

Los monos que fueron asfixiados y resucitados durante el nacimiento, mostraron luego indicios de una amplia gama de defectos que reflejaban lesiones ocasionadas al sistema nervioso central. Entre los defectos más comunes se halla el estado de coma persistente, estado epiléptico, anormalidades en la locomoción, el enderezamiento y la marcha, trastornos del equilibrio e impedimentos en las funciones sensoriales, incluyendo sordera, así como la imposibilidad de chupar o tragar. Los defectos neurológicos persistieron solamente por pocos días en algunos animales que parecían poder compensar lesiones menores, en forma tal que más tarde parecieran normales. Los defectos más pronunciados persistieron a lo largo de toda la vida del animal (Fig. 1). La alimentación constituyó uno de los problemas principales. Fue necesario suministrar cuidados y atención durante las veinticuatro horas del día. Uno de los monos, que fue sacrificado a los diez y ocho meses de vida, requirió que se le alimentara a mano durante la totalidad de su vida. Los animales asfixiados y resucitados, nacidos por operación cesárea, fueron comparados con otros nacidos en forma similar pero no asfixiados. Fueron comparados también con monos nacidos espontáneamente y alejados de la madre, y con monos criados por la madre en un medio ambiente natural en una pequeña isla en la que se aloja una colonia en libertad..

Según se ilustra en la película, los experimentos con monos rhesus demuestran claramente que la asfixia, con los cambios bioquímicos asociados, es capaz de producir defectos neurológicos similares a la afección que en el ser humano se designa comúnmente con el nombre de "enfermedad de Little", o también "parálisis cerebral".

Histopatología de la Asfixia en el Parto

En diversas oportunidades, después de la resucitación, los animales asfixiados y varios animales de control fueron sacrificados y sometidos a estudios histológicos. Los mo-

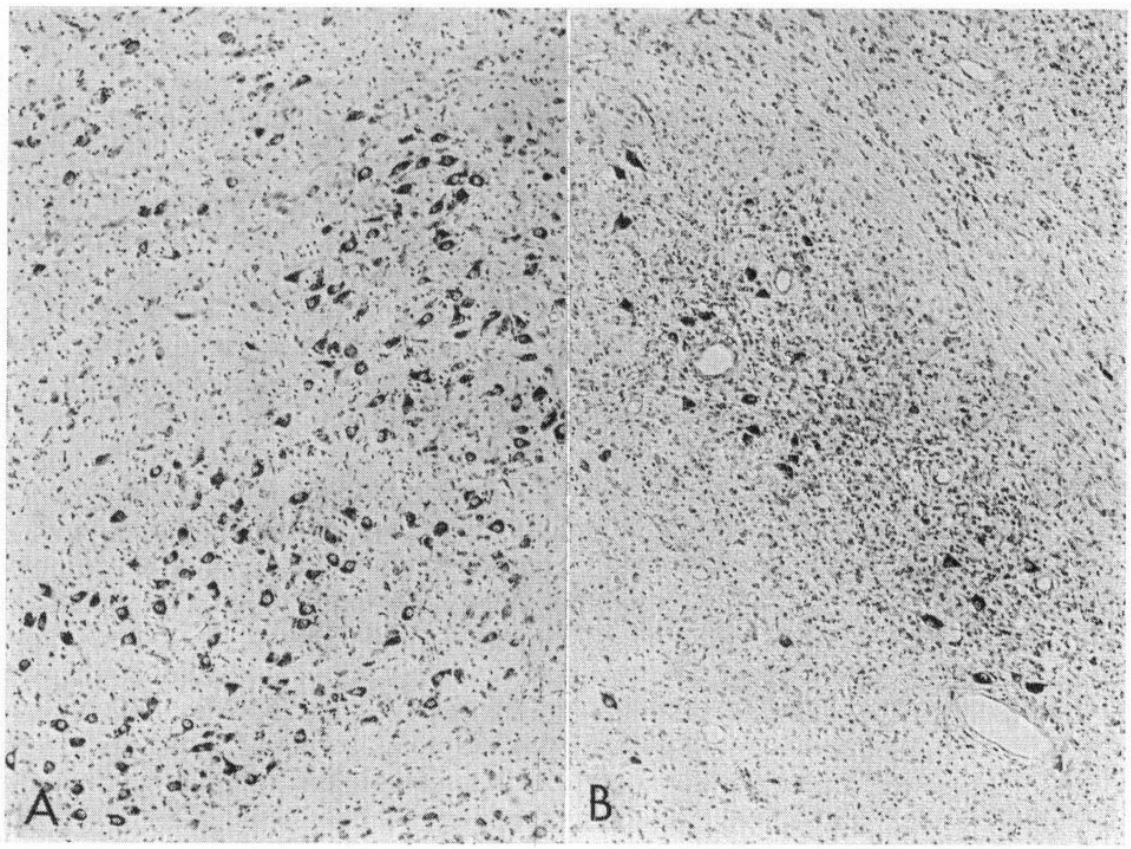

Fig. 8. — *Núcleo motor del nervio trigémino de un control no asfixiado (A) y uno asfixiado durante el nacimiento mostrando destrucción parcial de las neuronas, y reacción glial. Cortes con tinción Tionina. Reproducido con permiso de la "Association for Research in Nervous and Mental Disease" (Research Publ. A.R.N.M.D. 39:169-182, 1962).*

nos fueron ligeramente anestesiados con Nembutal y se realizó una perfusión de fijación con formalina, técnica ésta que permite la muerte casi instantánea y la preservación de los elementos nerviosos *in situ*. Por medio de este método hemos podido obtener material más adecuado para estudios citológicos de los que pueden hacerse con seres humanos.

La asfixia y sus consecuencias concomitantes bioquímicas y hemodinámicas parecen tener efectos inmediatos y directos sobre las neuronas y las células de la neuroglia del sistema nervioso central del mono, dando por resultado una extensiva citólisis primaria. Este efecto no se relaciona directamente con la distribución vascular. Solamente se encontró sangre extravasada en los tejidos cerebrales de dos animales; uno de ellos en estado epiléptico y el otro después de parto traumático. No pudimos confirmar la tesis de que la asfixia durante el parto es una causa primaria de hemorragias cerebrales.

La citólisis primaria por lo general se produjo en forma bilateralmente simétrica y su extensión depende de la severidad de la asfixia (Fig. 2). La fase inicial de la citólisis se observó dentro de los dos a cuatro días después de la asfixia y en el décimo día estaba marcada por una reacción microglial. Las células nerviosas grandes del tipo motor fueron menos afectadas que las pequeñas interneuronas. En algunos núcleos, todas las células de la neuroglia fueron destruídas (Fig. 3); en otros, se produjo la hipertrofia y la hiperplasia de los astrocitos. Los vasos sanguíneos permanecieron intactos y a los diez días después de la asfixia, pudo observarse la proliferación de

fibroblastos desde la adventicia vascular en los centros más severamente afectados por el proceso inicial.

En los haces de fibras mielínicas del sistema nervioso central se encontró una degeneración secundaria pero estas lesiones se relacionaban más bien con la pérdida de células nerviosas que con la destrucción primaria de mielina (Fig. 4).

Numerosas partes del sistema nervioso central acusaron cambios estructurales en uno u otro de los ejemplares. No obstante, en muy pocas ocasiones se había afectado la neocorteza cerebral y fueron pocos los casos que acusaron lesiones en la corteza del cerebelo. El tálamo y el pedúnculo cerebral fueron las partes más afectadas en forma regular. En todos los animales asfixiados y resucitados que se han estudiado histológicamente se ha encontrado que las lesiones se disponían en forma simétrica bilateral. Los núcleos más comúnmente dañados fueron los del tubérculo cuadrigémino posterior, gracilis, medial cuneato, vestibulares, los núcleos cerebelosos dentados, los núcleos talámicos ventrales y laterales y porciones del globus pallidus y del putamen. La destrucción por lo general se confinó exactamente a los límites de un núcleo ya que los tejidos neurales de la vecindad inmediata al núcleo no acusaban lesiones.

Un animal asfixiado solamente durante ocho y medio minutos y liberado antes de que cesaran las boqueadas asfícticas, no requirió resucitación y fue sacrificado durante el décimo día de vida, después de acusar solamente deficiencias neurológicas pasajeras. Los cambios histológicos en el cerebro fueron mínimos. La cromatólisis se presentó en células de núcleos tales como el tubérculo cuadrigémino posterior y se estimó que se había producido un ligero aumento en el número de microglia (Fig. 2).

En los cerebros de animales que sufrieron asfixia perinatal y que fueron sacrificados a los diez o más meses de edad, los lugares de lesiones primarias con frecuencia estaban marcados por gliosis, habiendo desaparecido la reacción microcítica. Se hallaron cambios atróficos en los núcleos del tálamo (Fig. 5) y del pedúnculo cerebral.

Los animales en estado epiléptico o aquellos que experimentaron de vez en cuando ataques de tal naturaleza, fueron los únicos que indicaron daños de la neocorteza causados por la asfixia (Fig. 6). Los animales que eran atáxicos y que tenían dificultades para enderezarse acusaban lesiones en los núcleos vestibulares y en los del cerebelo (Fig. 7). Las únicas lesiones de la línea media fueron halladas en el vermis del cerebelo de dos animales. En otras partes las lesiones causadas por asfixia fueron bilateralmente simétricas. No nos fue posible medir hasta qué punto se afectó la función del oído. Sin embargo, un animal parecía haber quedado totalmente sordo y su cerebro tenía severas lesiones bilaterales del tubérculo cuadrigémino posterior y en prácticamente todos los demás núcleos del sistema auditivo central. La hiporreacción de los animales frente al manoseo y a los estímulos sensoriales, puede ser relacionada con la presencia de lesiones en los núcleos de los funículos dorsales y en otros núcleos aferentes somáticos, tales como los nervios trigeminales. Dos monos bebés que vivieron durante varios días en un estado de coma exhibieron extensas lesiones confluentes a través de la formación reticular en ambos lados del cerebro medio. Si bien las neuronas motoras primarias se mostraron más resistentes a los efectos de la asfixia que otros elementos nerviosos más pequeños, aquellas del núcleo oculomotor y del núcleo del trigémino (Fig. 8) en ambos lados han sido afectadas en algunos animales.

Las lesiones encefálicas observadas histológicamente en monos asfixiados y resucitados durante su nacimiento pueden relacionarse en alguna forma con una mayor necesidad de oxígeno por parte de ciertos grupos de núcleos. Aún no estamos en condiciones de interpretar cabalmente las observaciones. Es evidente que estamos frente a un proceso destructivo que es común a todos los monos asfixiados. Las diferencias se presentan, principalmente, tan sólo en cuanto a la extensión de la destrucción causada. Igual cuadro ofrece el material humano si se concentra la atención en los centros del diencéfalo y del pedúnculo cerebral.

Estos experimentos con asfixia perinatal en el mono, han colocado claramente en primer plano un horizonte que previamente apenas había sido observado a través de un velo de especulación. Los defectos neurológicos e histológicos que resultan de la asfixia durante el nacimiento han sido suficientemente demostrados como para permitir un enfoque inteligente de las medidas de prevención y terapéuticas. En la actualidad, en el laboratorio, dedicamos nuestra atención a tales medidas.

RESUMEN

Este artículo hace un resumen de algunas observaciones sobre monos rhesus de edad gestacional conocida, los cuales fueron asfixiados y resucitados durante el nacimiento por cesárea bajo anestesia local. Las secuelas neurológicas y neuropatológicas son descritas e ilustradas. Todos estos monos asfixiados al nacer durante diez o más minutos demostraron anormalidades funcionales. Ninguno de los controles nacidos por procedimientos similares, pero sin asfixia, tuvo defectos. Una gran variedad de signos deficitarios fue desplegada y algunos animales quedaron severa y permanentemente incapacitados, semejando niños con parálisis cerebral.

Los cerebros de animales sacrificados entre las edades de 2 días a 2 años fueron estudiados para observar cambios histológicos, siendo comparados con los cerebros de controles no asfixiados. Se encontró un patrón consistente de lesión neural no hemorrágica en todos los monos en experimentación. Los núcleos del pedúnculo cerebral fueron simétricamente afectados.

Los más comúnmente dañados fueron los núcleos de los tubérculos cuadrigéminos posteriores, los de Goll y los de Burdach, los núcleos del cerebelo, el grupo posterior ventral de los núcleos talámicos, los globus pallidus, los putamen y vestibulares. Las lesiones se iniciaron con lisis y desaparición de células nerviosas y de algunas neuroglias. Hubo pérdida secundaria de las vainas de mielina. Se observó reacción de astrocitos, células endoteliales, células vasculares adventicias y fagocitos en todos los monos durante la etapa aguda. En cerebros de los que sobrevivieron algunos meses o más, la reacción fagocítica había declinado y las lesiones circunscritas se caracterizaron por gliosis. Se observó lesión central del vermis del cerebelo en algunos animales severamente lesionados. Se encontraron lesiones corticales atróficas bilaterales en varios animales que habían experimentado períodos de sufrimiento después de nacer. La patología predominante en todos los animales asfixiados fue la del tálamo y la del pedúnculo cerebral. Los núcleos de los sistemas auditivo central, vestibular, y somático fueron grandemente lesionados; correlacionado con lo anterior se observó deterioro de la facultad auditiva y de la función vestibular así como hiporreactividad a la reacción de manoseo.

SUMMARY

This article summarizes some observations on rhesus monkeys of known gestational age that were asphyxiated and resuscitated during birth at cesarean section under local anesthesia. The neurological and neuropathological sequelae are described and illustrated. All infant monkeys asphyxiated for 10 minutes or more exhibited functional abnormalities. None of the controls delivered by similar procedures but without asphyxiation had defects. A wide range of defective behavior was displayed and some animals were severely and permanently crippled, resembling human infants with cerebral palsy.

The brains of animals killed between 2 days and 2 years of age were studied for histological changes, being compared with

the brains of nonasphyxiated controls. A consistent pattern of nonhemorrhagic neural damage was encountered in all the experimental monkeys. Nuclei of the brain stem were symmetrically affected. Those most commonly damaged were the nuclei of the inferior colliculi, gracile and cuneate nuclei, nuclei of the cerebellum, ventral posterior group of thalamic nuclei, globus pallidus, putamen and vestibular nuclei. Lesions began with lysis and disappearance of nerve cells and some neuroglia cells.

Secondary loss of myelin sheaths occurred. Reaction of astrocytes, endothelial cells, vascular adventitial cells, and phagocytes was observed in all the monkeys during the acute stage. In brains of those living several months or more, the phagocytic reaction had subsided and the circumscribed lesions were marked by gliosis. A central lesion of the vermis of the cerebellum was found in a few severely damaged animals. Bilateral atrophic lesions of the cerebral cortex were encountered in several animals which had experienced periods of postnatal distress. The predominant pathology in all asphyxiated animals was that of the thalamus and brain stem. Nuclei of the central auditory, vestibular, and somatic systems were heavily damaged; correlated with this were impairment of hearing, vestibular function and hyporeactivity to handling.

RÉSUMÉ

Cet article résume quelques observations sur les singes Rhesus d'âge connu de la gestation, lesquels étaient asphyxiés et ressuscités pendant la naissance à l'opération césarienne sous l'anesthésie locale. Les séquelles névrologiques et névropathiques sont décrites et illustrées. Tous les singes infantiles, asphyxiés pour dix minutes ou plus, exhibèrent des anomalies fonctionnelles. Aucun d'entre les témoins délivrés par procédés semblables, mais sans asphyxie, eut des défauts. Un champ étendu de comportement anormal était montré, et quelques animaux étaient mutilés avec sévérité et d'une façon permanente, ressemblant des enfants humains avec paralysie cérébrale.

Les cerveaux d'animaux tués entre l'âge de deux jours et deux ans étaient étudiés pour les altérations histologiques, étant comparés avec les cerveaux des témoins non-asphyxiés. Un modèle constant de lésion neurale non-hémorragique était trouvé dans tous les singes expérimentaux. Les noyaux du tronc cérébral étaient affectés symétriquement. Les noyaux affectés le plus ordinairement étaient les noyaux de la paire postérieure des tubercules quadrijumeaux (de la moelle allongée) le noyau de Goll et le noyau de Burdach, les noyaux du cervelet, le groupe ventral postérieur des noyaux de la couche optique, le globus pallidus, le putamen, et les noyaux vestibulaires. Les lésions commençaient avec la lyse et la disparition des cellules nerveuses et de quelques cellules névrogliques. La perte secondaire des gaines de myéline se présenta. Une réaction des cellules araignées, des cellules endothéliaux, des cellules vasculaires adventitielles, et des phagocytes était notée dans tous les singes pendant la phase aigüe. Dans les cerveaux de ceux qui survecurent pendant quelques mois ou plus la réaction phagocytaire avait diminué, et les lésions circonscrites étaient indiquées par la gliose. Une lésion centrale du vermis cérébelleux était trouvée dans des rares animaux endommagés sévèrement. Quelques lésions atrophiques bilatérales de l'écorce cérébrale étaient rencontrées dans plusieurs animaux qui avaient éprouvé des périodes d'affliction par les suites de naissance. La pathologie prédominante dans tous les animaux asphyxiés était celle du thalamus et du tronc cérébral. Les noyaux du système auditif central, du système vestibulaire, et du système somatique étaient endommagés lourdement. Mis en corrélation avec ceci, etaient le trouble auditif, la fonction vestibulaire, et la hyporéactivité au traitement.

ZUSAMMENFASSUNG

Dieser Artikel fasst einige Beobachtungen über Rhesus-Affen vom bekannten Graviditätsalter zusammen, die während der Geburt bei Anwendung des Kaiserschnittes mit Lokalanästhesie asphyxiert und wiederbelebt wurden. Die neurologischen und neuropathologischen Folgeerscheinungen sind beschrieben und illustriert. Alle die 10 oder mehr Minuten asphyxierten infantilen Affen haben funktionelle Abweichungen gezeigt. Keine der Kontrollen, die durch ein entsprechendes Verfahren doch ohne Asphyxierung entbunden wurden, erwiesen Defekte. Man hat einen weiten Bereich des mangelhaften Verhaltens beobachtet und einige Tiere wurden stark und dauernd verkrüppelt, vergleichend mit den menschlichen Säuglingen mit Gehirnlähmung.

Die Gehirne von Tieren, die sich im Alter von 2 Tagen bis 2 Jahren befanden, wurden für histologische Veränderungen gegenüber den Gehirnen von nicht-asphyxierten Kontrollen untersucht. Bei allen experimentellen Affen wurde ein übereinstimmendes Bild der nicht-blutigen Neuralschädigung gefunden. Die Kerne des Hirnstammes wurden symmetrisch betroffen. Meistens wurden die Kerne der inferioren Colliculi, die Gollschen und Burdachschen Kerne, die ventrale Hintergruppe der Thalamuskerne, die Palaestriata, das Putamen und die Vestibulariskerne betroffen. Die Läsionen traten mit einer Gewebsauflösung und Verschwinden von Nervenzellen und einigen Neurogliazellen auf. Es entstand ein sekundärer Verlust von Markscheiden. Bei allen Affen hat man während des akuten Stadiums die Reaktion der Astrocyten, Epitheloidzellen, Gefässadventitiazellen und Phagocyten beobachtet. In den Gehirnen von denen, die mehrere Monate und länger gelebt hatten, hat die Phagocytenreaktion nachgelassen und die begrenzten Läsionen wurden durch Gliose gekennzeichnet. Bei einigen stark beschädigten Tieren hat man eine zentrale Verletzung des Kleinhirnwurmes festgestellt. Doppelseitige atrophische Verletzungen der Hirnrinde wurden bei mehreren Tieren gefunden, die die Perioden der postnatalen Störung durchgemacht hatten. Bei allen asphyxierten Tieren hat man als den vorwiegenden pathologischen Befund den des Thalamus und des Hirnstammes festgestellt. Die Kerne der zentralen Gehörs, Vestibularis und Somatosystemen wurden stark verletzt; dementsprechend wurden eine Abschwächung des Hörvermögens, der Vestibularisfunktion und eine Unteraktivitaet gegen Behandlung beobachtet.

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Antenatal and Paranatal Anoxia

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The first significant historical concept regarding the possibility of paranatal asphyxia as a cause of physical crippling and cerebral palsy seems to be buried in the medical literature of the 18th century. It seems evident, nevertheless, that some ideas linking dystocia with physical impairment were current in foregoing centuries. For example, we read in the New Testament that when Peter and John went to worship in the temple in Jerusalem in the first half century of the Christian era, they were asked for alms by a man who was crippled in his lower extremities "from his mother's womb" (Acts 3:2). This simple statement suggests that it was common knowledge that some individuals were indeed crippled from the time of birth. However, since the writer of the book of Acts was Luke the physician, it is quite possible that medical men of this period may have held this concept as common knowledge. The relation of this crippled state to respiratory or cardiac difficulties incident to dystocia was probably not understood. Luke's description of the crippled individual strongly suggests that the beggar was afflicted with spastic diplegia, a condition which Little (1853) described only a scant century ago when he suggested its origin in anoxia at the time of birth.

While there must have been some recognition of the various results of dystocia in the intervening centuries, there is no clear pronouncement until the time of Little that respiratory difficulties at the time of birth were responsible for the physical state now generally known as cerebral palsy. From this time, a full century has passed and with it many attempts to evaluate the etiological factors in children afflicted with paralysis, epilepsy, and idiocy. Natal anoxia was only one of half a dozen or more possibilities which were mentioned by the various writers on the subject of abnormal lesions in the brain found in these three clinical syndromes. As a rule, the possibility of anoxia was mentioned only to be ruled out as exemplified in the learned discussions of Osler (1889) and Freud (1897).

Paranatal anoxia was really not seriously considered as a cause of these difficulties until many years later. This was due to the lack of knowledge of the effects of anoxia. A recognition of what paranatal anoxia might do has been made well within the past few decades when an understanding was reached as to the effects of cerebral anoxia in later life. Continuing from this time it has been possible to elaborate on the potencies regarding paranatal and even antenatal anoxia as the cause of serious damage to the brain. It has also been possible to point to it as a cause of cerebral palsy, mental defficiency, and various types of convulsive disorders.

Etiology of Antenatal Ischemia-anoxia and Paranatal Anoxia. — There are many causes of circulatory damage to the fetal brain as it is here considered. *Predisposing factors,* such as prematurity, primacy of

birth, the male sex, births of older mothers, and possibly births in certain countries and under special circumstances, play a variable role in this regard.

Precipitating factors of maternal origin are a marked decrease in blood pressure, anemia, failing heart, exanguination, maternal asphyxia, shock, toxemias of pregnancy, bleeding from abruptio placentae and placenta praevia, and excessive sedation or anesthesia. Fetal factors are compression or kinking of the umbilical cord, increased intracranial pressure incident to dystocia and inhalation of anmiotic fluid or vaginal mucous. In many instances, there is a combination of factors, maternal and fetal, or intrauterine, para- and even postnatal, working together to produce their noxious effect.

Relation of Ischemia to Anoxia in fetal life

The occurrence of certain types of brain lesions, already well advanced at the time of birth, has made us aware that certain pathogenic processes are at work during fetal life. A study of the more severe of these lesions has suggested the similarity of some of them to occlusive vascular lesions of the postnatal period. This is marked not only by the distribution of the defects in the brain within the well-known areas of arterial distribution of the cerebral hemispheres, but also by the nature of the lesions themselves. On the other hand, the less severe changes, usually involving the cortex in one instance, or the cortex and subcortical white matter in the other, bear the hall-marks of an anoxic state. Thus it appears that this spectrum of lesions may be divided into two subgroups: (1) those involving the carotid circulation bilaterally and (2) those involving one or more of the individual cerebral arteries.

Bilateral Occlusion of the Carotid System. In this somewhat complex group of relatively rare cases, the impairment of the arterial circulation is widespread and bilateral suggesting that the carotid system of vessels has been preponderantly affected. If the facts were known, it is very likely that a wide spectrum of lesions with almost every variation between the very mild to the most severe could be found. However, most of the cases fall into four groups. While most of these lesions are roughly symmetrical, some of them show a greater extent of damage in one hemisphere than in the other.

The first group of cases showing minor damage of the cortex, or cortex and subcortex shows varying degrees of microscopic changes in the form of laminar necrosis so characteristic of anoxic change. This pathologic picture has come to be known as Alpers' disease, or *chronic progressive degeneration of the cerebral gray matter* (Fig. 1, A). A recent survey of this problem reviews six reported examples of this state, to which the present writer has been able to add five more coming under his observation (Courville, 1960). In some examples, the entire brain shows the effect of an impoverished circulation indicative of a total ischemia. A study of the clinical histories, often inadequate, at times suggests an ante- or paranatal circulatory disorder.

The second group of cases shows *parietal softening of the cerebral centrum* as well as the cortex. The basal ganglia, being composed of gray matter, may also be involved as shown in the accompanying figure (Fig. 1, B). The deep portions of the cerebral white matter are usually morphologically intact although undergoing a degree of gliosis. A number of the cases in this group also show a greater extent of damage in one hemisphere than in the other as the illustrations of Schwartz (1961) clearly show.

The third group of cases with *subtotal softening of the forebrain* is characterized by a profound change in the brain structure, showing this organ to be reduced to a "bag of mush" (Fig. 1, C). The total decorticate rigidity, convulsions, and amentia occurring in early infancy have led the earlier German contributors to designate this clinical state as "infant without brain". In his recent review of the literature; the present writer reviewed reports of a dozen or more cases, to which four personnally studied cases were added (Cour-

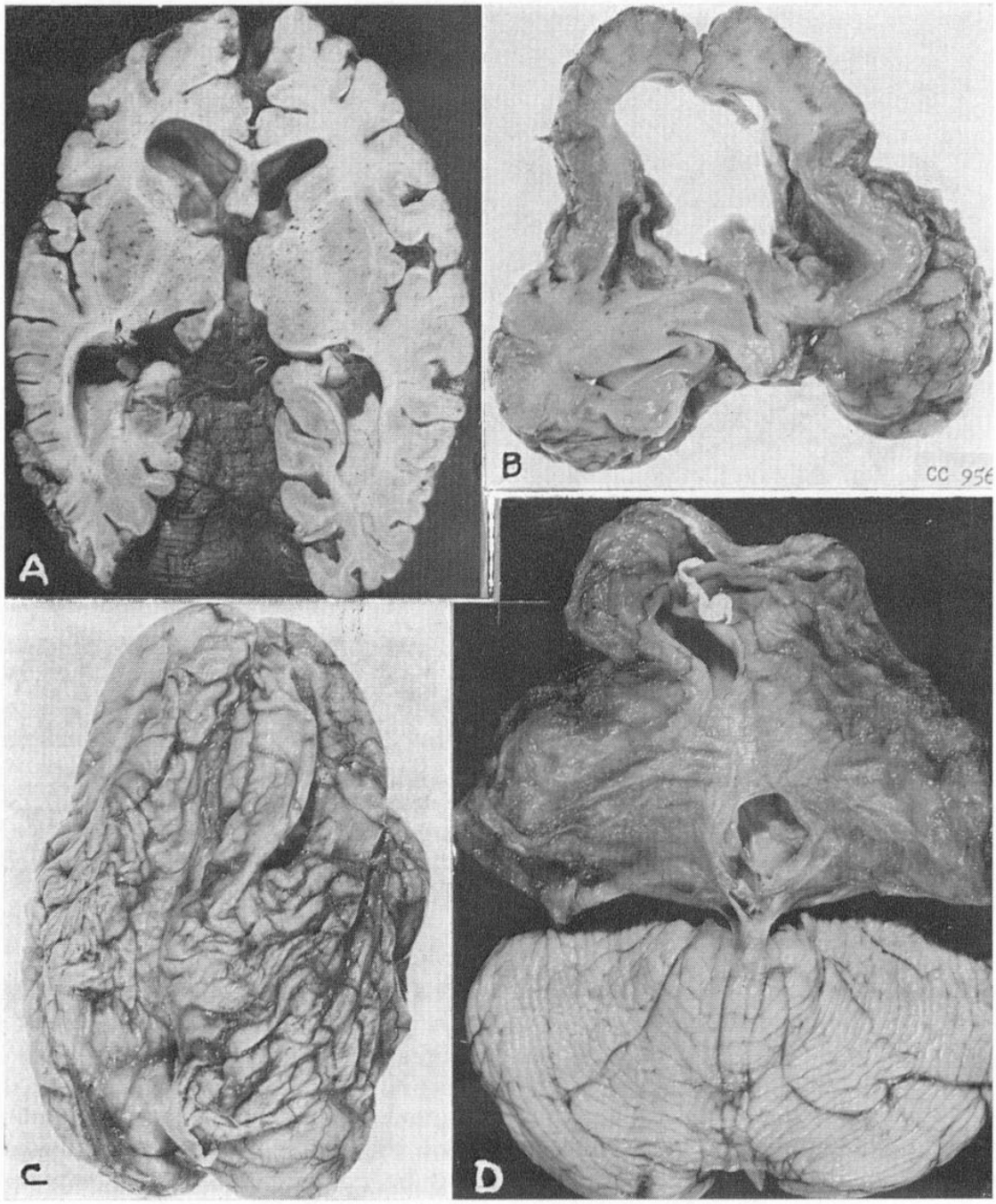

Fig. 1. — *Antenatal Ischemia-Anoxia Affecting Chiefly the Carotid System. A) Progressive degeneration of the cerebral gray matter (Alpers' disease). B) Progressive softening of the cortex, subcortex and basal ganglia. Note advanced degree of softening of the corpus striatum. C) Subtotal softening of the telencephalon ("Infant without brain"). D) Hydrenencephaly.*

ville, 1960). It seems obvious that these lesions were but an advanced degree of softening when compared to the second group.

The fourth group with *total softening of the forebrain* must have had an early interference with the carotid circulation, for there is little more than a few remnants, at best, of gliotic brain tissue between the leptomeninges and ependyma. While in most cases the basal portion of the temporal lobe, the brain stem and cerebellum are fairly well preserved, in some instances the entire brain has suffered to some degree

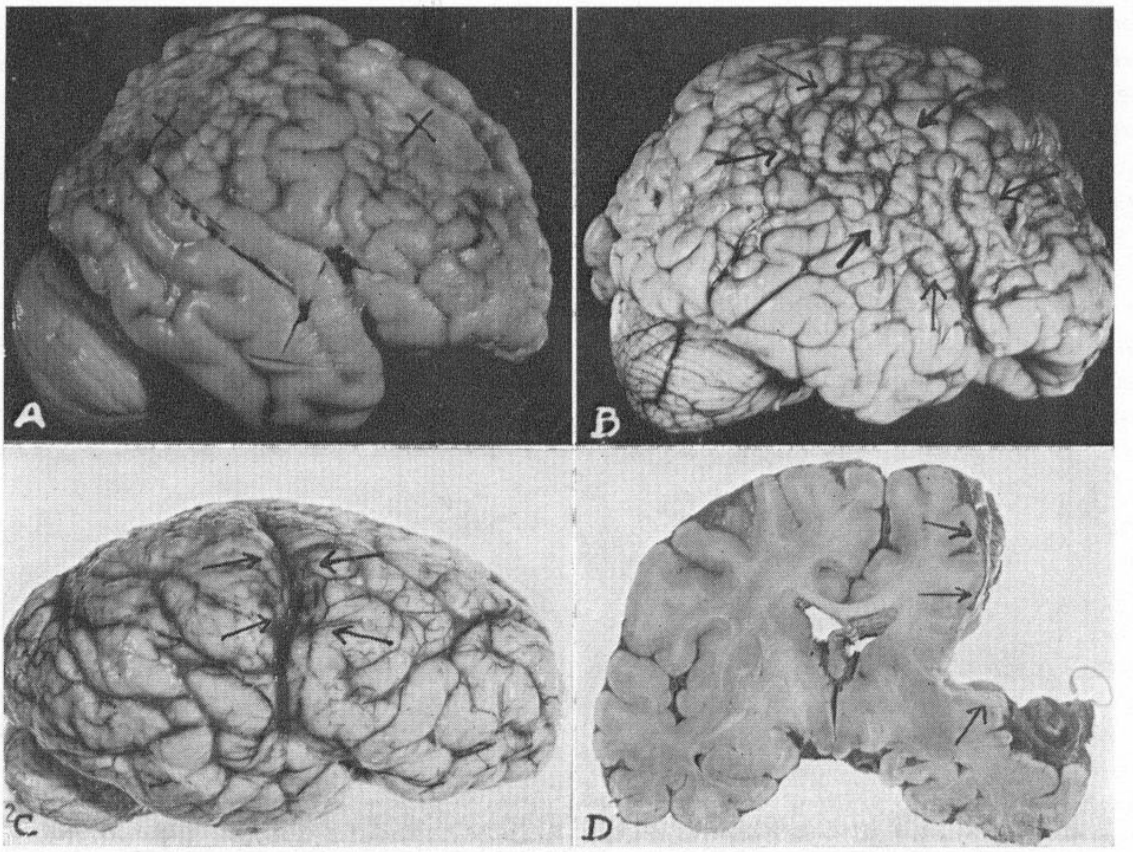

Fig. 2. — *Antenatal Ischemia-Anoxia Affecting One or More Single Arterial System. A) Double areas of softening of right frontal and parietal lobes. B) Area of microgyria (nodular sclerosis) of right central area (arrows). C) Slit-like defect in pallium (incomplete porencephaly) (arrows). D) Complete left cerebral porencephaly (arrows).*

from ischemia. The fluid-filled sac has been designated as a *hydrenencephaly* (Fig. 1, D).

Such gross lesions can mean only that some sort of interference with the arterial circulation in the brain must occur during intrauterine life. The cause and nature of such occlusions are largely unknown. Some of them must be due to congenital deviations in vascular formation or in the tissues or structures through which these vessels pass. For example, the disclosure at autopsy of a recently born child with bilaterally compressed carotid arteries by excessive growth of the sphenoid bone, was the obvious cause of an advanced degree of hydrencephaly. There must be other causes of interference with cerebral circulation including congenitally small vessels or those affected by intrauterine disease, but of these we know very little.

The cortical changes of more localized character are obviously the result of various degrees of occlusion of one or more isolated cerebral arteries. In this group there is another group of lesions dependent also upon the degree of arterial occlusion. There may be an *area of softening* corresponding to the distribution of the artery in question. If the artery is totally occluded, an incomplete or complete gross defect (*porencephaly*) results. When the circulation is only partially interfered with but is of long standing, dating from early pregnancy, an area of *nodular cortical atrophy* will result (See Fig. 2).

The chief problem in this more circumscribed group of lesions is that of its etiology. Judging from their counterparts in adult life, one would conclude that a local arterial obstruction such as embolism or thrombosis would be its cause. But in

fetal life, whether early or late, what condition or disease can cause such a local obstruction? Could it be due to some transitory functional state whose cause is no longer evident when the lesion is exposed at autopsy?

In the writer's earlier study on the problem of nodular atrophy or sclerosis (Courville, 1957), the observation that was made showed a number of these lesions which were multiple and symmetrically located in the two cerebral hemispheres. This observation would suggest that the branches supplying these foci might imply a simultaneous stimulation of the carotid arteries, perhaps at the time of birth by the fingers of the accoucheur about the neck of the infant during delivery. It is also possible that loops of the umbilical cord about the infant's neck might serve a similar function.

In addition to this group of definite ischemic lesions, one is obliged to consider also the less well defined cases in which a combination of ischemia-anoxia apparently plays the essential role in their production. Such lesions present gross changes suggestive of ischemic and microscopic alterations (laminar loss of nerve cells, laminar necrosis or scar formation.) It is likely to result from any interference of the circulation through the connecting link from the intrauterine placenta to the body of the fetus, the umbilical cord.

It is well known, of course, that gross lesions of the placenta, such as severe infarctions, may produce anoxic lesions of the fetal brain. Likewise, mechanical obstructions of the umbilical cord such as twists, knots, and congenitally short cords may be the cause of such a situation. But it should be remembered also that any qualitative defects in the maternal circulation would likewise produce similar effects on the fetal brain, a fact which is often overlooked. Bleeding during the first trimester of pregnancy, profound anemias either due to loss of blood or diseases of the blood itself, and impairment of the maternal circulation due to cardiac failure are all possibilities that are sometimes unrecognized. Then, of course, actual combination lesions of anoxia and ischemia would also contribute to the complexity of the lesion. And in such cases, the changes in the brain may bear the telltale signs of both ischemia and anoxia. However, now that we have come to understand the essential effects of anoxia, it is not so difficult to distinguish ischemic from purely anoxial lesions.

When an autopsy which discloses a cerebral lesion of long standing is done in early postnatal life, or even in early infancy, complex and extensive changes may show some of these mixed lesions in a child who was normally born. Particularly in premature infants, the delivery may well have been entirely normal occurring without any difficulty in the birth process.

Dystocia: Birth Injury versus Paranatal Anoxia

In many instances involving studies of birth histories of those individuals who present some of the characteristic syndromes of cerebral palsy, convulsive disorders, or complex forms of mental defficiency, it is often extremely difficult to evaluate the record even when the hospital chart is available for survey. Incredible as it may seem, the record is often blank as far as adequate information is concerned. Sometimes this is due to carelessness on the part of the medical attendants but at other times there is a question whether evidence is deliberately omitted or so obscured as to mislead any reviewer from determining the facts. Even in cases where a degree of dystocia has been present, one finds a rather confused picture of prematurity, respiratory or circulatory difficulties during the infant's short life, or incomplete descriptions of any neurological manifestations which may have occurred.

In true dystocia with prolonged labor incident to obvious mechanical difficulties, problems resolve themselves into either (1) failure of the kinetic forces or (2) physical obstructions of the birth canal. In a case of a failure of mechanical forces the problem is not so difficult, for it is betrayed by the fact that labor does not proceed as it should. However, in a case of possible

physical and internal obstructions, the problem is more difficult, for these may be hidden within the birth canal or remain undiscovered for want of adequate examination. In these cases, physical trauma, anoxia, or some other pathological states (erythroblastosis, toxemia, dehydration, inflammation, or sepsis) often demand consideration.

Whether *prematurity* is a factor or not can usually be determined from the record of pregnancy and from evaluation of the fetus itself. In such cases, at autopsy one finds a variety of intracranial hemorrhages, from minor to severe, and from minimal subarachnoid effusions to major intracerebral or intraventricular extravasations. Nevertheless it is often extremely difficult to be sure what part prematurity plays in causing the death of the infant.

It is somewhat simpler to evaluate *physical trauma.* In such cases one finds hematomas of the scalp in the form of caput succedaneum, evidences of overriding of the cranial bones, occasionally actual fractures of the skull, but more characteristically a laceration of the dural reduplications with gross subdural hemorrhage. All these lesions strongly suggesting a deformation of the skull during its passage through the birth canal are sufficient to produce a fatal issue. Very rarely laceration of the brain occurs as a result of depressed fracture of the skull.

On the other hand, evidences of an anoxic state are not always very clear cut. If this factor is significant there will be definite and unmistakable evidences of respiratory and/or circulatory difficulty. One cannot always tell off hand whether this respiratory difficulty arises from an excessive intracranial pressure on the respiratory center, or actual involvement of the lungs in the form of congestion, actual pneumonia, hyaline membrane disease, inhalation of mucous, etc. Such intrinsic or extrinsic factors as anesthesia, recent exposure to asphyxiating gasses on the part of the mother, excessive sedation of the mother, prolonged use of drugs, or the intercurrence of virus disorders may also play their part. On the other hand a clear history of manifest paranatal anoxia such as an unusually slow or rapid fetal heart *in utero,* meconium in the amniotic fluid, cyanosis versus palor of the newborn infant, the continued respiratory irregularities, early muscular twitchings, actual convulsive disorders, or the presence of flaccid or spastic paralysis are all quite suggestive. (These manifest items when preceded by vaginal bleeding incident to placenta praevia or premature separation of the placenta or the findings of multiple loops of the cord about the neck cannot be dismissed lightly). The subsequent development of a baby who cries more or less persistently without cause ("cry baby") or of an infant which appears to be a feeding problem also suggests some difficulty. It is then only after months or even a year has passed, that one comes face to face with the conclusion that the child has suffered from birth damage, although the birth record failed to state just what the trouble might have been.

The presence of *other factors* mentioned above, i. e. erythroblastosis, maternal toxemia, obvious infectious condition, dehydration, or sepsis are usually sufficient to account *per se,* for fetal death, and physical trauma or anoxia can be excluded.

Residuals of Paranatal Anoxia

How then is one to know what the nature of the deforming lesion really is?

At times one has no other choice than to await the gradual unfolding of the clinical picture before it is possible to know what the residuals and the proper mechanism really are, insofar as possible anoxia is concerned. However, during life it is sometimes warranted to do electroencephalograms or rarely angiograms to assist in making this decision.

Almost every pathologist recognizes that in this group he has to deal with brain lesions which have few counterparts in routine autopsies. He has learned, however, to compare anoxic deaths in later life, which exhibit severe congestion, spotty subarachnoid hemorrhages, and petechiae or even focal subcortical hemorrhages in the brain, with deaths in newborn children

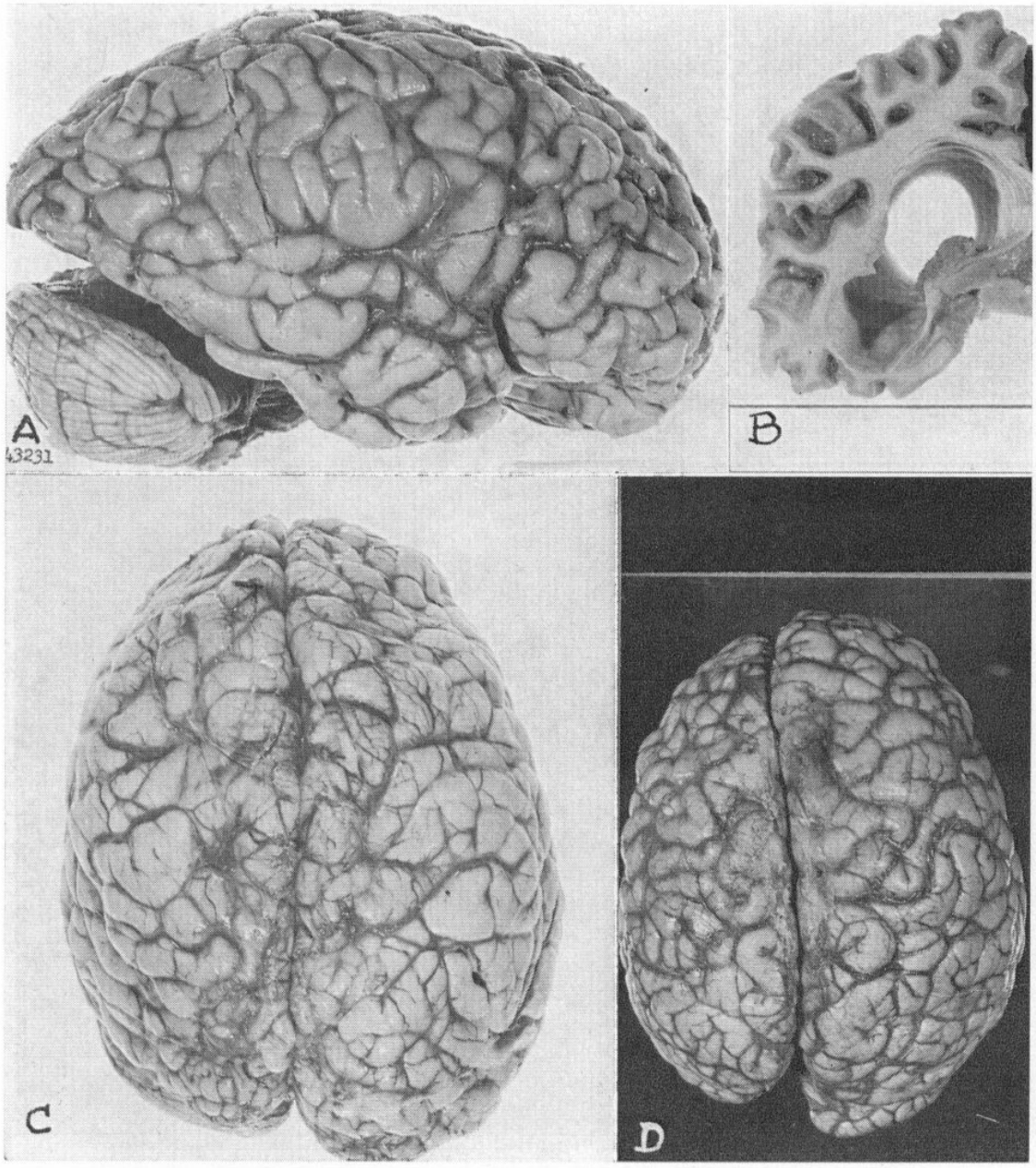

Fig. 3. — *Diffuse Cortical Atrophy Incident to a Mild Ischemic-Anoxia State. A) Mild atrophy of entire cerebrum (note size of cerebellum for comparison). B) Severe uniform degeneration with secondary gliosis of cerebral cortex. C) Left hemispheral atrophy in one-year-old infant. D) Similar change in a thirty-year-old male, hemiparetic since birth.*

which present similar lesions. He would therefore agree that such manifest items might have a similar significance in case of paranatal anoxia. But it is the later residuals which have developed only after a number of years that present real problems in evaluation.

The essential difference in the cerebral lesions of early life, as contrasted with similar adult ones, is largely due to the softer texture of the fetal and postnatal brain. Because the interstitial structure is immature, any interference with the cerebral circulation will result in a rapid breakdown of the affected tissue. Hence these lesions incident to antenatal ischemia and paranatal anoxia often present gross morphological alterations.

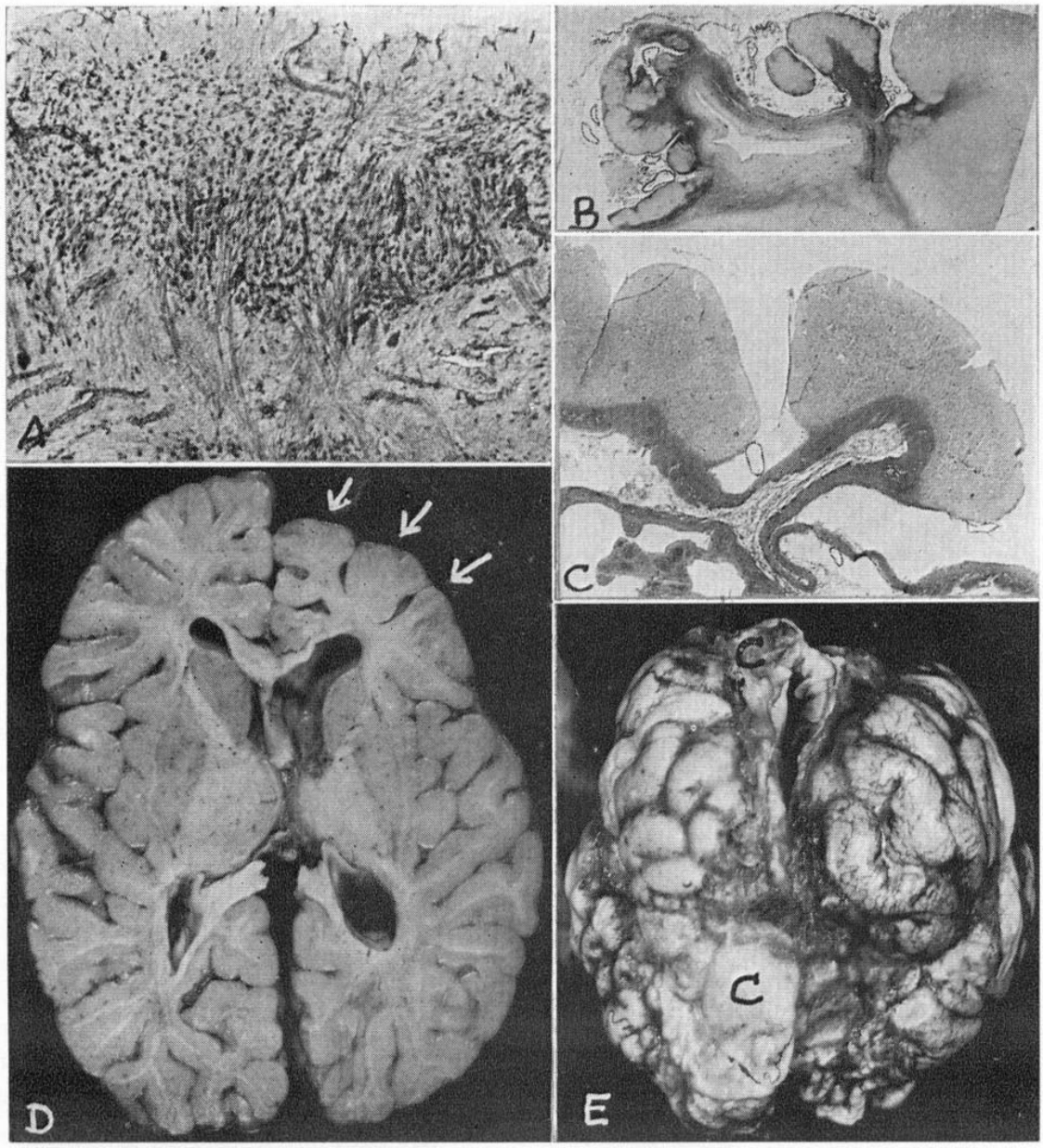

Fig. 4. — *Characteristic Cortical-Subcortical Changes Incident to Paranatal Anoxia. A) Focal cortical scar with typical "bundles of grain" glial fibers. B) Characteristic changes in nodular cortical atrophy incident to combined ischemic-anoxic state. The "mushroom" gyri, subcortical demyelination, gliosis and cyst formation are typical of these lesions which are often epileptogenic. C) Typical nodular cortex and subcortical degenerative changes associated with chronic infantile cystic degeneration (See figure 5). D) Lobar atrophy with gliosis of underlying white matter. E) Extremely atrophic and deformed brain showing cortical-subcortical cyst formation (C) associated with nodular cortical sclerosis. Unaltered convolutions show compensatory hypertrophy.*

It is well, therefore, to briefly review what changes are produced in the brain by anoxia in adult life and compare them with similar lesions in children with gross deformities of the brain following some sort of episode at birth.

Uniform Cerebral Atrophies. — One group of lesions dating back to birth are the uniform cerebral atrophies which may be either bilateral and universal or unilateral. How can one account for an atrophy of *one* cerebral hemisphere on the basis of

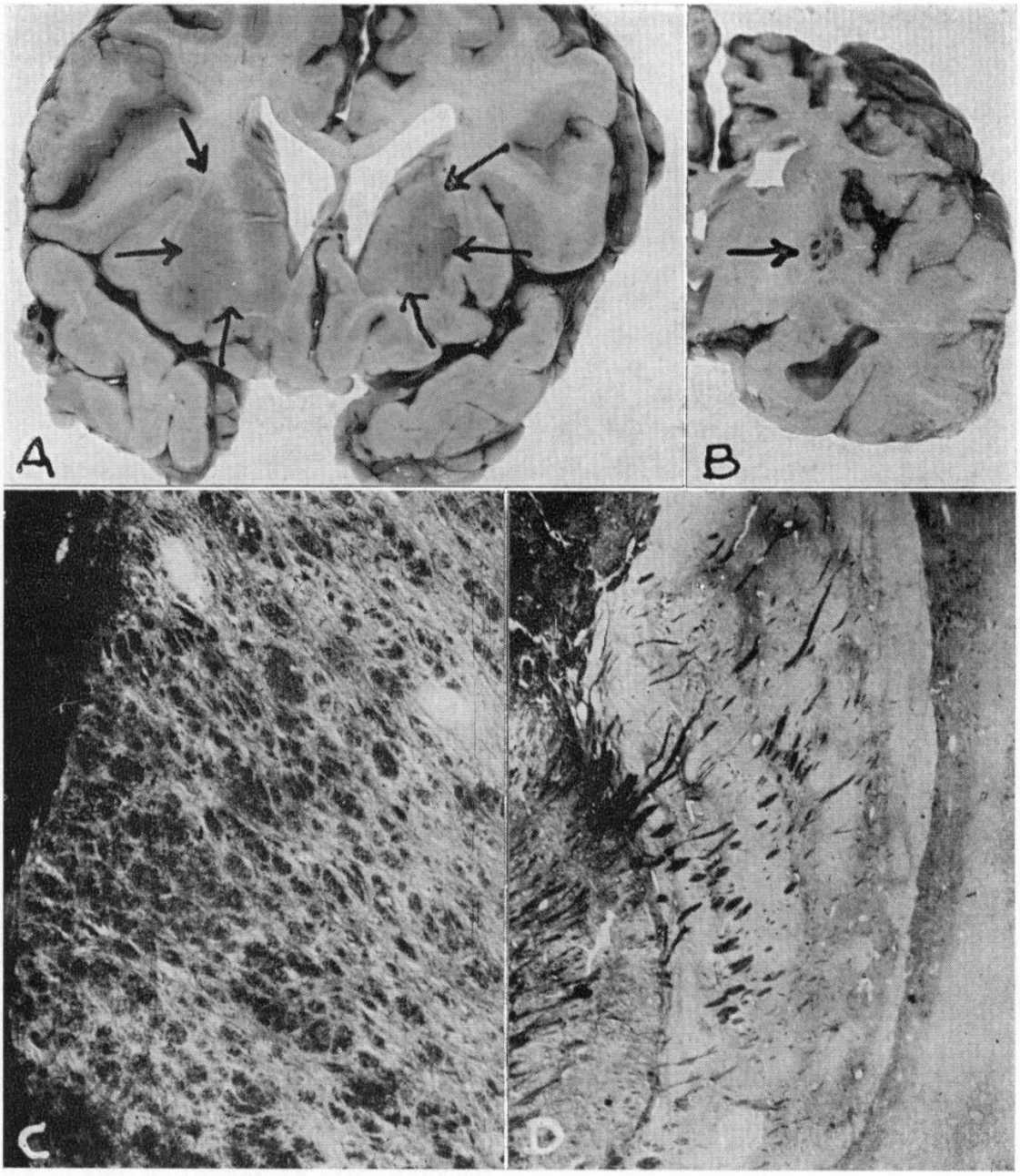

Fig. 5. — *Residual Changes in Basal Ganglia Following Paranatal Anoxia A) Atrophy of one or both corpora striata may be responsible for hemichorea or choreoathetosis. In this case atrophy of the left sided structure has taken place. B) Cystic degeneration of corpus striatum. This may occur as single in multiple cystic cavities. C) While the pathogenesis of status marmoratus is not yet known, its common association with dystocia is recognized. D) The changes in the lenticular and associated nuclear masses as found in status dysmyelinisatus can often be found in individuals who have survived, at least temporarily, a severe degree of cerebral anoxia.*

anoxia at birth which is presumably a *generalized* effect? This would be difficult to explain were it not for the experimental studies of Windle and his associates (1950). In the production of fetal anoxia in guinea pigs, these investigators noted the uniform

atrophy of a hemisphere or even of a single lobe. The mechanism is obscure but the possibilities seem clearly demonstrated.

Two types of these general atrophies of the brain are to be distinguished. Those resulting from a mild anoxemia followed only by a selective loss of nerve cells, are characterized by a reduction in the size of the brain as a whole with preservation of its external markings and its internal architecture. The second group which result from a more severe degree of anoxia with damage to the interstitial as well as the parenchymatous elements, are characterized by a gliosis as well as a more profound degree of the cortex with ultimate replacement of the nerve cell population. Because of the extreme degree of uniform cortical atrophy, these specimens are sometimes described as a "walnut kernel brain" (See Fig. 3).

Progressive Deterioration of the Cerebral Cortex. — Many children with deforming lesions of the brain as are being considered here, present some degree of deterioration with histologic changes in the cortical gray matter. These changes may be divided into two groups: those in which spotty or laminar cell loss occurs, and those which show a laminar necrosis and/or scarring often leading to nodular sclerosis (Courville, 1960, 1961). To those who have had experience with the progressive changes of anoxia in adult life, it is not difficult to recognize a similar pathogenesis of similar lesions childhood. It has been known that those who survive for a relatively short time or who have experienced a less severe degree of cerebral anoxia will present this peculiar pattern of spoty or laminar cell loss (Courville, 1938). A more profound lesion is characterized by the presence of focal necrosis, laminar necrosis, and the formation of laminar scars. Similar changes in the deformed brains of children can mean only that there has been some profound circulatory disturbance present in which ischemia and/or cerebral anoxia have played a similar role. These points have been pointed out in previous studies by the writer (Courville, 1959).

Cortical-subcortical Necrosis with Cyst and Scar Formations. — These lesions, common in the brains of cerebral palsied children, are not too common in cerebral anoxia of adult life. This is probably because they are present only in certain types of anoxia. However, the writer has pointed out several examples of cerebral damage due to carbon monoxide asphyxia in which these cortical scars or cortical-subcortical cysts are not unexpected findings (Courville, 1955). Therefore one should not be surprised that these same lesions —sometimes small, sometimes fairly large— are found in epileptic children operated upon by Penfield and his associates (1942). They should now be recognized as residuals of the paranatal cerebral anoxias (Fig. 4).

Changes in the Basal Ganglia. — Alterations in the corpus striatum, particularly the globus pallidus, and at times in the thalamus as well, point out the vulnerability of this part of the brain to cerebral anoxic states. This is seen in the red softenings, the necrotic areas, and the ultimate cyst-like defects and scars found in patients who have experienced moderately severe anoxic episodes. Why then should one be surprised at the various ganglionic lesions or clinical states with involvement of the extrapyramidal system in cerebral palsied individuals? Viewing the catalogue of these changes one finds a diffuse cell loss, gliosis, atrophy, or actual structural damage to these regions in individuals who have had some sort of difficulty at birth (Fig. 5). The structural alterations in status dysmyelinisatus have a close similarity in subacute anoxic episodes in later life (Courville, 1961). Although status marmoratus seems to be commonly found in children who have a history of "birth injury" (Malamud, 1950), no satisfactory mechanism of production on an anoxic basis has been forthcoming. This problem, too, has been reviewed by the author in related studies (Courville, 1961).

Central Cyst Formation. — Perhaps no other lesion has been so involved in controversy as to its etiology, as has the relatively rare chronic cystic degeneration of the cerebral white matter in infancy (Fig. 6, A). Fortunately these lesions are rare, perhaps because they involve ultimately a mentally defective quadriplegic in-

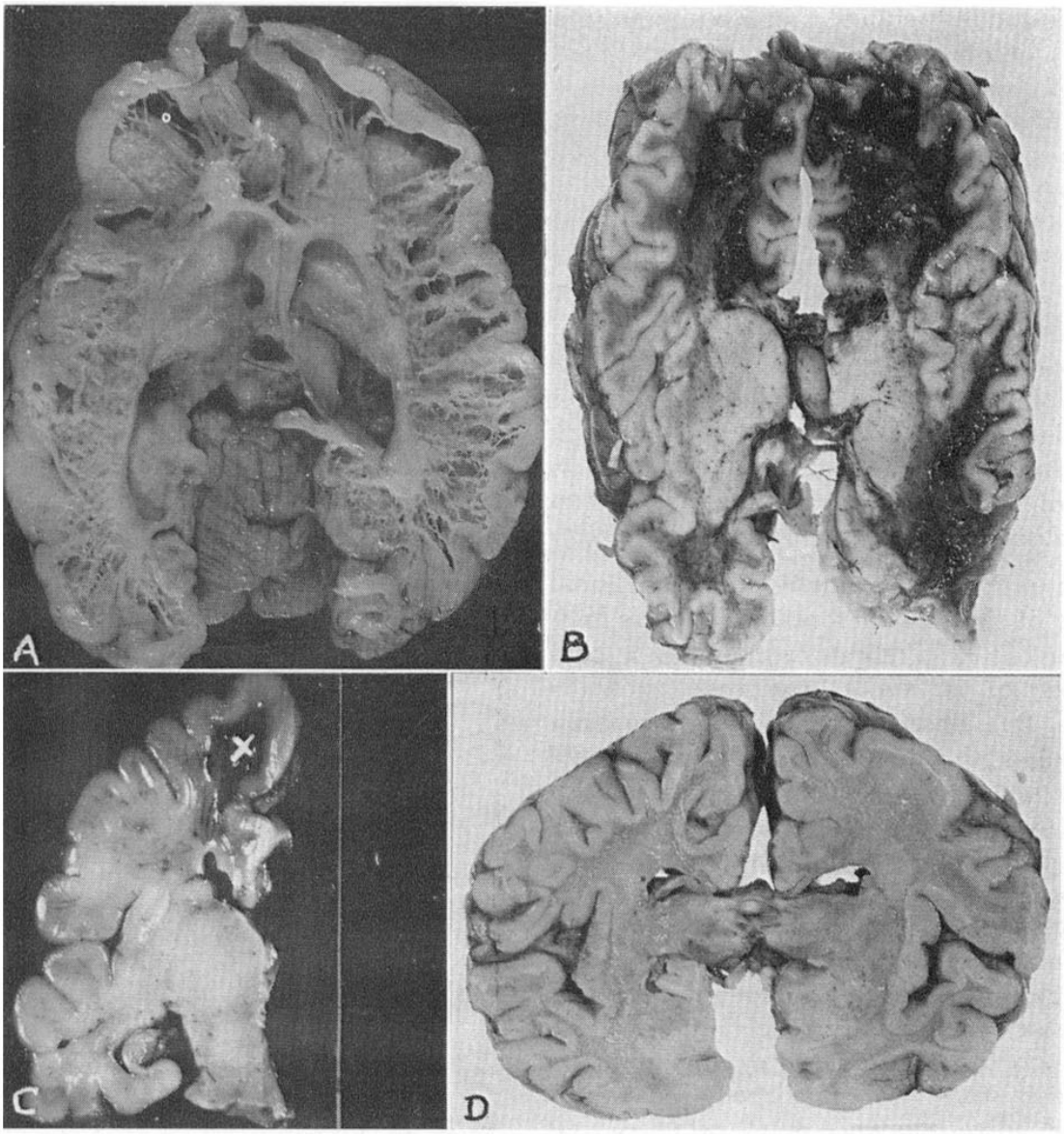

Fig. 6. — *Presumed Postanoxic Central Lesions of Infancy and Childhood. A) Chronic infantile cystic degeneration leading to death within a few months to years. B) The cause of this condition has been debatable, but the author believes it to be the result of a widespread hemorrhagic softening following severe paranatal anoxia as shown here. C) Focal softening leading to cyst formation as shown at X probably has a similar genesis. D) Diffuse sclerosis. If widespread demyelination occurs at all after paranatal anoxia as occasionally follows anoxias of adult life, a lesion resembling diffuse sclerosis must result. Many reporters of this disease have observed a close resemblance between diffuse sclerosis and central demyelination following carbon monoxide asphyxia.*

fant. Schwartz (1924) has pointed out that in his experience these lesions are the result of occlusion of veins of Galen with consequent multiple hemorrhagic foci in the cerebral white matter of young children. In attempting to refute this conclusion, the present writer has pointed out that in known cases of thrombosis or occlusion of the veins of Galen which have been so often alleged to be causative of these lesions, survival for any length of time is not possible (Courville, 1959). On the other hand, such lesions occurring in childhood lead to a progressive downhill course with death usually within a year. Moreover the ultimate residual lesions are such as to pretty

well preclude venous thrombosis as the cause. The writer has shown that focal central cyst formation is a residual of chronic effects of cerebral anoxia (Courville, 1959). This has been found particularly in cases of long-standing residuals which are often associated with changes in the cerebral cortex (Courville, 1953 and 1955). In such lesions the cysts are rather isolated although they may be multiple, occurring in different portions of the cerebral centrum. It may well be that some of the individual cysts that have been described have been the result of anoxia although, of course, they are perhaps more likely to be due to thrombosis or embolism of other etiology.

Even more important is the occasional finding of multiple hemorrhagic foci which fill the entire cerebral centrum as a consequence of anoxia at the time of birth (Fig. 6, B). Three of these cases have been described with their comparison to multiple cyst formation in infancy or early childhood (Courville, 1960). Under the circumstances it seems quite likely that with these multiple lesions there is a breakdown in the white matter, leaving these cysts as a consequence of this process and precipitating a slowly progressive deteriorative disease which results ultimately in multiple cyst formation in the central white matter. Since this study was published, the writer has had correspondence with other individuals who have had similar cases. More recently Lu et al. (1962) found a borderline case which seemed to be a modified form of the same situation. While in his case, the history of paranatal anoxia was anything but adequate, the possibility of anoxic etiology was still suggested by the nature of the lesion, posing as a hypothesis the possibility that something happened *in utero* rather than at the time of birth.

Regional or Generalized Demyelination. As a result of focal changes in the cortex because of a profound loss of parenchymatous elements, one occasionally finds in the subcortical area, either patches of demyelination, gliosis, or sometimes of actual cyst formation. These lesions are localized and have relatively little resemblance to any pathologic cerebral lesions other than perhaps focal cortical atrophy due to embolism, or occasionally due to focal changes from localized trauma.

However, the type of demyelination which is of interest in the present study, is that of widespread areas in which the white matter undergoes more or less complete and uniform loss of myelin sheaths. This type of change has been found after temporary complete arrest of the circulation (Grant, Weinberger and Gibbon, 1939) or, for reasons that are not clear, in individuals who have experienced a severe episode of cerebral anoxia under general anesthesia (O'Brien and Steegman, 1938). In a number of these cases in which the patient has survived for many months, even a year or more, there was found at autopsy a widespread loss of myelin which simulated the picture seen in incomplete cases of diffuse sclerosis. The resemblance was limited to the gross findings. It was also noticed that the type of demyelination which occurs and the mechanism involved, namely through a reduction in size of the arterioles penetrating from the cortex or basal ganglia, showed similar patterns. As our original premise indicated, we are also able to find counterparts in children, of these post-anoxic lesions in the adult brain. Certain states of change comparable to these anoxias of adult life are also distinguishable.

Therefore the question may be raised: if this is true as far as widespread demyelination in adult life is concerned, what lesion in early life are we to interpret as being actually postanoxial?

The only one that we are acquainted with is that which has been perhaps somewhat loosely incorporated under the term of diffuse sclerosis (Fig. 6, D). It is true, of course, that according to classifications of histologists and neuropathologists in general, several different groupings have been mentioned. (Infantile, childhood, adolescent, and adult forms have been described). The writer has been studying this problem of similarities between these postanoxic states and diffuse sclerosis. A

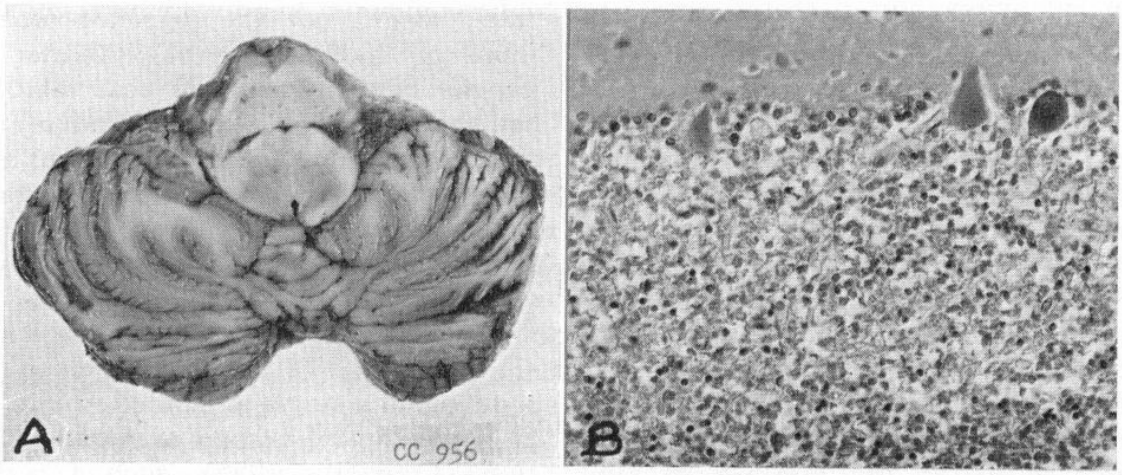

Fig. 7. — *Cerebellar Changes Incident to Paranatal Anoxia. While the cerebellum is by no means as susceptable to damage by oxygen want, changes do occur in the form of gross cerebellar atrophy (A) from progressive loss of the Purkinje cells and cells of the granular layer (B) as shown in this figure.*

similarity which, by the way, has been noted by observers other than myself (Grinker, 1927; Meyer, 1928).

It is recognized that there are some genuine shortcomings in such a conclusion. First of all it is recognized that, chemically speaking, the by-products of the deterioration of myelin in these various cases differ from one group to another. However, in a personal query to one of the authorities on neurochemistry (Dr. Cumings) the problem of the real significance of chemical variations was brought up. Dr. Cumings was unable to give any recognized explanation for this situation and did not know whether the speed with which demyelination occurred had any bearing on the chemical character of the by-products.

Another serious question is that of the familial incidence of some of these cases. It is important to point out that this incidence is *familial* and not hereditary. In other words, as far as is known by the writer, there is no hereditary tendency to this degeneration. To be paired off against this familial tendency is the familial tendency for cerebral palsy to occur in more than one sibling. In some cases it involves siblings who present at autopsy, similar lesions; in other cases the difference may be actually structural in character. The influences controlling this familial incidence are not particularly remarkable. While these problems, chemical behavior of by products of myelin degeneration and familial incidence, cannot be completely answered at this time, neither can they be utilized as arguments against the possibility that in some way either anoxia, or ischemia and anoxia in combination may be responsible for these conditions. The writer proposes to hold to this thesis until there is irrefutable evidence to the contrary.

Cerebellar Degeneration. — It is well known, certainly, from the evidence found in anoxias of later life, that the structures in the posterior fossa, namely the cerebellum and brain stem, are not particularly susceptible to these effects. Whether this is due to the fact that these structures have a different blood supply, one perhaps not so ammenable to the influences of the carotid sinus, or whether due to some unexplainable mystery of the organization of the animal economy is uncertain. The fact remains that the vital centers found in the medulla as well as the various structures and tissues of the cerebellum, are not so likely to be affected structurally by the

anoxic process. This is particularly true of the brain stem. The cerebellum, on the other hand, may show changes usually in the cellular layers of the cortex and in certain focalized areas (in which focal ischemia must play an important part as it does in the cerebral cortex). We have, for instance, the Purkinje cell layer whose individual elements are particularly sensitive to the anoxic state. The same thing is true of the granule cell layer, in which we find residuals of these paranatal anoxias as zones in which the resident cells are seriously interfered with. At any rate we do find in cerebral palsied children, in which the cerebellum is examined more or less routinely, cell changes —sometimes quite limited in extent, sometimes a little more widespread— which are, almost certainly, tokens of an anoxic state (Fig. 7). This problem has been made the subject of a special examination, the details of which can be consulted if further information is desired (Courville, 1959).

Combined Lesions. — If there is one characteristic above another of these presumed postnatal anoxic states, it is that rarely do we find one in which a single lesion accounts for the deformation of the brain. In most cases, two, three, or even more individual lesions result from different pathogenic processes. The writer therefore wishes to pose the following question. If these individual lesions are best accounted for as being the residuals of a postanoxic state, would not the presence of two or more of these lesions of a similar pathogenesis be further proof that all of them had their origin in a state of anoxia presumably before or during the birth process? The writer believes that such is actually the case, and the multiplicity of these lesions serves as specific support for this conclusion.

This very multiplicity also must have its significance. We know that even in the residuals of a single anoxic etiological factor as is the case of carbon monoxide intoxication (Courville, 1955), such a variety of patterns of pathology occur. Therefore it seems logical to believe that when dealing with as complex a process as anoxia, involving so many basic etiological factors as are at work in cases of paranatal anoxia, such multiplicity of lesions and such variations in the end picture must certainly be significant. It is recognized that the complete pathological picture depends upon the intensity of the process, the length of time during which it is at work, the fluctuations which may well occur during the process, and the intercurrence of ischemic alterations such as result from more or less persistent vasomotor changes. It is only when we take into consideration all of the factors involved in paranatal anoxia, that we are in a position to appreciate the complex and varied pathological picture that is to be found in these cases.

SUMMARY

It has taken almost two thousand years of the Christian era to trace the total history of paranatal cerebral anoxia in general, to say nothing of that preceding or following the birth process. Crippling of children from the mother's womb, as was so well expressed by St. Luke, the physician-apostle, certainly speaks to this end. One realizes that it has been only in the last 150 years that the total pathology of this condition has been even considered, and only in the last 25 years been given serious consideration as to its true etiology.

As has been already stated, because of the extreme complexity and bewildering variety of lesions found in these children whose clinical manifestations date back to birth, the confusion first as to the etiology and then of the pathogenesis of these lesions from anoxia or anoxia and ischemia is not surprising.

Our knowledge of the effects of ischemia, anoxia, and changes particularly of the cerebral cortex, indicates that more than one process may be at work in a given case. We find evidences of arterial occlusion, of

metabolic intoxication, of anemia, and of other circulatory disturbances, that demand critical evaluation in interpreting the complex patterns presented.

The problem of dystocia is one of great importance. The question arises: does dystocia produce only true traumatic damage in the form of tentorial tears with subdural hemorrhage, or is it also responsible at times for producing anoxia secondary to the development of increased intracranial pressure? It is recognized that hemorrhage may be a result of either trauma or anoxia. However, it is also recognized that subdural hemorrhage, especially when associated with molding of the fetal head, tentorial tears, and external lesions (i. e. caput succedaneum), may be considered truly traumatic. On the other hand it is also realized that a high percentage of children who are stillborn, who die within the first few days after birth, or who are born prematurely, may present a variety of etiological factors which must be considered.

We have to deal with the total picture of anoxia during intrauterine life and the birth process, as *cryptic* (that due to some intrauterine cause) versus *manifest* (that due to the birth process itself). When such a lesion is already far advanced at the time of birth, there can be little doubt that the lesion is of intrauterine etiology. Many of these lesions have, in the past, been confused with true congenital lesions. However, a careful analysis of the problem can usually determine whether it is one or the other.

A study of the residual lesions following cerebral anoxias of later life has given us a series of patterns for comparison with these lesions of early life which are responsible for cerebral palsy, complex convulsive states, and profound mental defects. Generalized atrophy, diffuse or nodular atrophies of the cerebral cortex marked by focal or laminar necrosis and acellularity of the components of the corpus striatum either with or without gliosis, or the presence of such unusual states as status dysmyelinisatus or status marmoratus characterize a total lesion which brings about characteristic pyramidal changes in the postnatal life. And then we have focal or diffuse demyelinisation as well as central lesions such as gliosis and cyst formation. Focal degenerations of the cerebellum are also to be considered in this group. The multiplicity of lesions certainly suggests a complex process which can act in more than one way to produce its baleful effects. All these moreover, speak for a paranatal anoxia. Nevertheless one might wish to exclude such gross lesions as hydrencephaly, porencephaly, diffuse cortical softening and similar obvious circulatory difficulties which are presumably due to intrauterine ischemia.

The only sure way to check critically the factors involved in the production of these lesions, the only way in which one can prove the truth or falsity of the presumption of lesions here described, is to give diligent attention to all possible sources of information. It is not alone the history of pregnancy itself, whether of accidents in the first or third trimester. It is not alone a question of the health of the mother and any untoward event which may have occurred during these fateful months. But it is the attention given to the various clinical manifestations during the period of labor and the birth process which is important. The clinical study of possible neurological symptoms occurring not only immediately following birth, respiratory irregularities, and cyanosis which are evidences of cerebral cortical irritation, but also during the first 6 months of life in the form of emotional irritability ("cry baby") and feeding problems. It is no longer necessary to wait until unequivocal signs of motor paralysis, convulsive disorders, or delayed physical and mental development make their appearance. When significant clinical manifestations have developed in a patient whose brain presents gross malforming lesions, it seems only fair to recognize the possibility that anoxia, either due to ischemia in intrauterine life or true anoxia during the birth process, may play an important role in this picture.

RESUMEN

Alrededor de dos mil años de la Era Cristiana han sido necesarios para trazar la historia completa de la anoxia cerebral paranatal en sus generalidades, sin mencionar los casos en que se presenta previa o posteriormente al nacimiento. La invalidez del niño provocada dentro del vientre materno, como lo expresara sabiamente San Lucas, el médico-apóstol, se refiere a ésta. Si nos detenemos a analizar, vemos que recién en los últimos 150 años se ha comenzado a considerar la patología total de este estado y que recién en los últimos 25 años se le ha dedicado seria atención a su verdadera etiología.

La confusión en cuanto a la etiología y también a la patogénesis de estas lesiones de anoxia o bien de anoxia e isquemia no debe sorprendernos, ya que se ha comprobado que estas lesiones, cuyas manifestaciones clínicas datan del nacimiento, son muy variadas y complejas en extremo.

Nuestro conocimiento de los efectos de la isquemia, la anoxia y otras modificaciones, particularmente de la corteza cerebral, indica que más de un proceso puede estar en juego en determinados casos. Se encuentran evidencias de oclusión arterial, de intoxicación metabólica, de anemia o de otras alteraciones circulatorias que exigen una valorización crítica tendiente a determinar la importancia de los complejos datos que se presentan.

El problema de la distocia es de capital importancia, y plantea el siguiente interrogante: ¿Es responsable la distocia solamente de las lesiones traumáticas manifestadas en la forma de desgarramientos tentoriales con hemorragia subdural, o produce también en algunas ocasiones la anoxia secundaria a la aparición de la hipertensión intracraneana? Se admite que una hemorragia puede resultar tanto de un traumatismo como de la anoxia.

Sin embargo también se admite que las hemorragias subdurales pueden ser consideradas como traumáticas, especialmente cuando aparecen asociadas a la deformación de la cabeza del feto, desgarramientos tentoriales y lesiones externas. Por otro lado se ha visto que un alto porcentaje de recién nacidos muertos, prematuros o fallecidos en los primeros días que suceden al nacimiento, pueden presentar una serie de factores etiológicos, que deben ser tenidos en cuenta.

Tenemos que manejarnos con el cuadro total de la anoxia, durante el período de vida intrauterina y a lo largo del proceso del nacimiento.

Cuando la lesión se presenta en un estado avanzado en el momento de nacer el niño, casi no queda duda en cuanto a su etiología intrauterina. Tanto es así, que antiguamente eran confundidas con verdaderas lesiones congénitas. Sólo un cuidadoso análisis del problema permite determinar si corresponde a un grupo o al otro.

Un estudio de las lesiones residuales que resultan de anoxias cerebrales a una edad avanzada, nos ha proporcionado una serie de datos para comparar con lesiones producidas a edad temprana, responsables de parálisis cerebral, complejos estados convulsivos y graves defectos mentales. Las lesiones que traen aparejados cambios piramidales característicos en la vida post-natal son: Atrofia generalizada, atrofias difusas o nodulares de la corteza cerebral con necrosis difusa o nodular y acelularidad con o sin gliosis de los componentes del cuerpo estriado, o bien por la presencia de estados tan inusuales como el "status dysmyelinisatus" o el "status marmoratus". Entonces tenemos desmielinización focal o difusa así como también lesiones centrales tales como gliosis y la formación de quiste. Las degeneraciones focales del cerebelo deben incluirse en este grupo. La multiplicidad de las lesiones da la pauta de la complejidad del proceso que actuando de una u otra forma produce efectos funestos. Todos ellos son válidos en lo que se refiere a la anoxia paranatal. Sin embargo se da en excluir las lesiones voluminosas tales como la hidroencefalia, la porencefalia, el reblandecimiento difuso de la corteza cerebral y otras alteraciones circulatorias evidentes, presumiblemente debidas a una isquemia intrauterina.

La única manera de probar la verdad o

falsedad de la presunción en cuanto a las lesiones aquí descritas, y de comprobar con espíritu crítico cuales son los factores involucrados en la provocación de las mismas, es prestándole especial atención a todas las posibles fuentes de información.

Además de considerar el período del embarazo o los accidentes ocurridos a la madre durante el primer o tercer trimestre, debe atenderse por ser importantes a las diversas manifestaciones clínicas apreciables durante el período de trabajo y el proceso del nacimiento del niño. Debe hacerse un estudio clínico, no sólo de los síntomas neurológicos que aparecen inmediatamente después del nacimiento, irregularidades respiratorias y cianosis, que evidencian una irritación de la corteza cerebral, sino también la irritabilidad emocional (niño llorón) y los problemas relacionados con la nutrición durante los primeros 6 meses de vida del niño. Ya no es necesario esperar la aparición de signos inequívocos de parálisis motora, alteraciones convulsivas o de retardo físico y mental. En el momento en que determinadas manifestaciones clínicas significativas se han desarrollado y evolucionan en un paciente cuyo cerebro presenta grandes lesiones, se justifica el hecho de atribuir importancia en el cuadro mórbido a una posible anoxia, ya sea debida a una isquemia durante la vida intrauterina, o que se trate de una anoxia verdadera producida durante el proceso del nacimiento.

RÉSUMÉ

A peu près vingt siècles de l'Ere Chrétienne ont été nécéssaires pour tracer l'histoire totale de l'anoxie cérébrale paranatale dans ses généralités, sans parler des cas où elle se présente avant ou après la naissance.

L'invalidité de l'enfant provoquée dans le ventre de la mère, d'après l'expression de Saint-Luc, le médecin-apôtre, se rapporte à cet état. En analisant un peu, nous voyons que c'est seulement dans les derniers 150 ans qu'on a commencé à considérer la pathologie totale de cet état et que c'est dans les derniers 25 ans qu'on a donné de l'importance à sa vraie étiologie.

La confusion qui régnait en ce qui concernait l'étiologie ainsi que la pathogénèse de ces lésions d'anoxie ou d'anoxie et ischémie ne doit pas nous surprendre puisqu'on a constaté que ces lésions, dont les manifestations cliniques datent du moment de la naissance son très variées et extrèmement complexes.

Notre connaissance des effets produits par l'ischémie, l'anoxie et d'autres modifications, celles de l'écorce cérébrale en particulier, indique que dans certains cas plus d'un procès peut être en jeu. On trouve des évidences d'occlusion artérielle, d'intoxication métabolique, d'anémie ou d'autres altérations circulatoires, qui exigent une évaluation critique visant une détermination de l'importance des complexes données qui se présentent.

Le problème de la dystocie a une importance capitale et pose la question suivante: Est-ce que la dystocie provoque seulement les lésions traumatiques telles que les déchirures tentorielles accompagnées d'hémorrhagie subdurale, ou bien est-elle responsable aussi de l'anoxie secondaire à l'apparition de l'hypertension intracranienne? On admet qu'une hémorrhagie peut aussi bien résulter d'un traumatisme que de l'anoxie. Cependant on admet aussi que les hémorrhagies subdurales peuvent être considerées comme traumatiques, particulièrement quand elles apparaissent associées a la déformation de la tête du foetus, à des déchirures tentorielles et a des lésions externes. Mais on a vu par contre, qu'un haut pourcentage d'enfants nés morts, prématurément ou décédés dans les premiers jours qui succèdent à la naissance, peuvent présenter une série de facteurs étiologiques desquels on doit tenir compte.

Nous devons travailler avec le cadre total de l'anoxie, pendant la période de vie intrautérine et tout le long du procès de la naissance. Quand la lésion est dans un état avancé au moment de la naissance de l'en-

fant, il n'y a presque pas de doute quant à son etiologie intrautérine, ce qui explique que les lésions de ce genre fussent confondues autrefois avec les vraies lésions congénitales. C'est seulement après une soigneuse analyse du problème qu'ont peut determiner auquel des deux groupes appartient la lésion.

Une étude des lésions résiduelles qui résultent des anoxies cérébrales chez des personnes agées nous a fourni un nombre de données à comparer avec les lésions responsables de paralysie cérébrale, d'états convulsifs très complexes et de graves défauts mentaux produites dans des enfants. Les lésions qui produisent des changements pyramidaux caractéristiques dans la vie postnatale sont: l'atrophie généralisée, les atrophies diffuses ou nodulaires de l'écorce cérébrale accompagnées de nécrose diffuse ou nodulaire et acellularité avec ou sans glyose des composants du corps strié, ou la présence de certains états aussi inusuels que le "status dysmyelinisatus" ou le "status marmoratus". Nous avons alors une démyelinisation phocale ou diffuse et aussi des lésions centrales telles que la gliose et la formation de kystes. Les dégénérations phocales du cervelet doivent être inclues dans ce même groupe. La diversité des lésions donne une idée de la compléxité du procés qui agissant d'une façon ou de l'autre provoque des effets funestes. Eux tous sont valables en ce qui concerne l'anoxie paranatale. Cependant on a l'habitude d'exclure les lésions volumineuses telles que l'hydroencéphalie, la porencéphalie, le ramollissement diffus de l'écorce cérébrale et d'autres altérations circulatoires évidentes, qu'on présume dues à une ischémie intrautérine.

La seule façon de constater si la présomption quant aux lesions ici décrites est fausse ou vraie, et de prouver d'un esprit critique quels sont les facteurs qui contribuent à provoquer ces lesions, est de prêter une attention très speciale à toutes les sources d'information possibles. Au lieu de considérer seulement la période de la grossesse ou les accidents de la mère ayant eu lieu pendant le premier ou le troisième trimestre, il faut tenir compte aussi des manifestations cliniques qui apparaissent dans la période du travail et pendant le procès de la naissance de l'enfant, puisqu'elles résultent très importantes. Il faut faire une étude clinique, non seulement des symptomes neurologiques qui apparaissent immédiatement après la naissance, des irritabilités respiratoires et cyanoses, qui accusent une irritation de l'écorce cérébrale, mais aussi des problèmes en relation avec la nutrition pendant les premiers six mois de vie de l'enfant. Il n'est plus nécéssaire d'attendre l'apparition de signes indubitables de paralysie motrice, d'altérations convulsives ou de retardement physique ou mental. Quand certaines manifestations cliniques significatives se sont developpées chez un patient dont le cerveau présente de grandes malformations, il est juste d'attribuer quelque importance dans le cadre morbide, à une anoxie possible, qu'elle soit due à une ischémie produite pendant la période de vie intrautérine ou qu'il s'agisse d'une anoxie vraie produite pendant le procès de la naissance.

ZUSAMMENFASSUNG

Man kann ungefaehr 2.000 Jahre der christlichen Aera die totale Geschichte der paranatalen cerebralen Anoxie im Allgemeinen verfolgen, ganz zu schweigen ueber die Anoxie vor oder nach der Geburt. Die Verkrueppelung des Kindes vom Muterleib her wie es so gut bei St. Lukas, dem Arzt-Apostel, ausgedrueckt ist, spricht sicherlich in diesem Sinne. Es ist aber festzustellen, dass erst in den letzten 150 Jahren die gesamte Pathologie dieser Krankheit auch nur in Betracht gezogen und erst in den letzten 25 Jahren ihre wirkliche Aetiologie gruendlich studiert worden ist.

Es ist schon festgestellt worden, dass wegen der ausserordentlichen Kompliziert heit und der erstaunlich vielen Spielarten von Laesionen bei diesen Kindern, dessen klinische Erscheinungen seit der Geburt bestehen, die Verwirrung ueber die Aetio-

logie und dann ueber die Pathogenie dieser durch Anoxie oder Anoxie und Ischemie bedingten Laesionen nicht ueberrascht.

Unsere Kenntnisse ueber die Wirkungen von Ischemie und Anoxie und die Veraenderungen besonders der Hirnrinde zeigen an, dass mehr als ein Prozess in einem gegebenen Fall im Spiele ist. Wir finden Anzeichen von arteriellem Verschluss, von Stoffwechselintoxikation von Anemie und anderen Kreislaufstoerungen, die ein kritisches Abwaegen bei der Ausdeutung dieser komplizierten Bilder erfordern.

Das Problem der Dystozie ist von grosser Bedeutung. Es erhebt sich die Frage: produziert die Dystozie nur eine traumatische Laesion im Sinne von tentoriellen Einrissen mit subduralen Blutungen oder ist sie zuweilen auch verantwortlich fuer die Anoxie infolge der Entwicklung einer Vermehrung des intrakraniellen Druckes. Man weiss, dass die Blutung sowohl durch Trauma als auch durch Anoxie bedingt sein kann. Man weiss jedoch auch, dass die subdurale Blutung als wirklich traumatisch angesehen werden kann, besonders wenn sie mit der Umformung des foetalen Kopfes, mit tentoriellen Einrissen und aeusseren Verletzungen (z. B. caput succedaneum) einhergeht. Andererseits hat man auch festgestellt, dass ein hoher Prozentsatz von totgeborenen Kindern, oder Kindern die innerhalb der ersten Tage nach der Geburt sterben oder die zu frueh geboren sind, eine Vielheit aetiologischer Faktoren presentieren, die in Betracht gezogen werden muessen. Wir haben es mit dem Gesamtbild der Anoxie waehrend des intrauterinen Lebens oder waehrend des Geburtsaktes zu tun, im Sinne von "cryptischen" (d. H. durch irgend eine intrauterine Ursache) Faktoren gegenueber von "manifesten" Faktoren (d. h. durch den Geburtsakt selbst). Wenn solch eine Laesion im Moment der Geburt weit vorgeschritten ist, so kann kein Zweifel bestehen, dass es sich um eine Laesion intrauterinen Ursprunges handelt. Viele dieser Laesionen sind frueher mit den wirklichen kongenitalen Laesionen verwechselt worden. Immerhin eine sorgfaeltige Analyse des Problems macht es gewoehnlich moeglich, in dem einen oder anderen Sinne die Bestimmung zuzutreffen.

Das Studium der Restlaesionen nach Faellen von zerebraler Anoxie im spaeteren Leben hat uns eine Reihe von Bildern in die Hand gegeben zum Vergleich mit diesen Laesionen der ersten Lebenstage, die fuer die zerebrale Paralyse, den komplizierten Krampfzustaenden und die schweren Geistesdefekte verantwortlich sind. Die generalisierte Atrophie, diffuse oder nodulaere Atrophie der Hirnrinde mit fokaler oder Schichtnekrose und Azellularitaet der Bestandteile des Corpus striatum mit oder ohne Gliose, oder das Vorhandensein so ungewoehnlicher Zustaende wie der status dysmyelinisatus oder status marmoratus charakterisieren eine totale Laesion, die charakteristische pyramidale Veraenderungen im postnatalen Leben mit sich bringen.

Dann haben wir die fokale oder diffuse demyelinisierung als auch zentrale Laesionen, wie z. B. die Gliosis und die Zystenbildung. Zu dieser Gruppe gehoeren auch die fokalen Degenerationen des Kleinhirns. Die Vielheit der Laesionen lassen gewiss an einen komplizierten Prozess denken, der in mehr als einer Weise wirken kann, um seine verkrueppelnden Effekte hervorzubringen.

All diese sprechen ausserdem im Sinne einer paranatalen Anoxie. Man moechte immerhin ausschliessen die schweren Veraenderungen wie z.B. die Hydrozephalie, die Porencephalie, die diffuse Rindenerweichung und aehnliche offensichtliche Kreislaufstoerungen, d i e wahrscheinlich durch intrauterine Ischemie verursacht sind.

Der einzige sichere Weg die diese Laesionen betreffenden Faktoren zu pruefen und die einzige Art die Richtigkeit oder Unrichtigkeit der Annahme von den hier beschriebenen Laesionen nachzuweisen besteht darin, allen moeglichen Informationsquellen gebuehrende Aufmerksamkeit zu schenken. Es handelt sich nicht nur um die Gesundheit der Mutter und um irgend eienen ungluecklichen Zwischenfall, der sich waehrend dieser schicksalsvollen Monate ereignet haben kann, sondern es handelt sich hauptsaechlich um die Aufmerksamkeit die man den verschiedenen klinischen Erscheinungen waehrend der Ge-

burtswehen und waehrend des Geburtsaktes schenken muss. Das klinische Studium eventueller neurologischer Symptome nicht nur unmittelbar nach der Geburt, Unregelmaessigkeiten der Atemfunktion und Zyanose, die Zeichen von Hirnrindenreizung sind, sondern auch waehrend der ersten sechs Lebensmonate im Sinne der emotionellen Irritabilitaet ("schreiende Kinder") und der Probleme der Nahrungsaufnahme. Es ist nicht mehr laenger notwendig zu warten bis absolut sichere Zeichen von motorischer Paralyse, Kraempfen oder verzoegerter koerperlicher und geistiger Entwicklung in Erscheinung treten. Wenn sich bedeutsame klinische Erscheinungen in einem Patienten entwickelt haben, dessen Gehirn grobe Bildungsstoerungen aufweisst, ist es nur logisch die Moeglichkeit anzuerkennen, dass die Anoxie entweder durch Ischemie waehrend des intrauterinen Lebens oder wirkliche Anoxie waehrend des Geburtsaktes eine wichtige Rolle in diesem klinischen Bilde spielen.

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The Pathogenesis of Disturbances of Cerebral Blood Flow*

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It is impossible to treat a disease rationally while its pathogenesis is obscure. One can only work on an empirical basis of "trial and error". The success of the modern treatment of disturbances of cerebral blood flow is based on knowledge of the pathophysiology and pathogenesis of these disorders part of which stems from the basal sciences:

1) *Normal cerebral blood flow:* I would here particularly mention Heymans, Opitz and Schneider as well as Schneider and his co-workers. I would also mention, 2) *The nitrous oxide method of Kety and Schmidt,* which permits measurement in human subjects with normal or pathological blood flow even though this only gives a global figure and 3) *The team of Denny-Brown and John Meyer* who have completed the studies of local investigation of the cerebral blood flow in monkeys. Finally I would mention, 4) *Serial angiography* amongst others Tönnis and Schiefer, who were able to demonstrate stenosis or closure of cerebral arteries and local changes in the circulation within the brain.

I believe, however, that these results would not have alone sufficed to improve our knowledge of cerebral blood flow disturbances so extensively if they had not been used to analyse both the *pathological* and the *morphological* changes in the cerebral blood flow. It is possible in this way firstly to analyse the pathogenesis of infarcts after death and by complete comparison with the clinical data let the films so to speak run backwards so that the individual factors responsible for the production of such disturbances of blood flow can be recognised. These results have in the last few years been widely published and I hesitate to write about them yet once more. I will, however, attempt to give a survey on the present state of our knowledge indicating the remaining problems.

The Vascular Tree and the Problems of Arteriosclerosis

If we are going to analyse the haemodynamic mechanism of disturbances of blood flow we must concern ourselves with the vascular tree. This may in young persons show extensive variations in lumen. We know however, that these changes are less related to *nervous* reflex mechanisms than to the local effect of metabolites. We are familiar for example with *dilatation* by lactic acid and the carbon dioxide content of the blood. In older persons however, such changes appear to be restricted because the vessel wall can become extensively sclerotic even if the changes are no more than a "physiosclerosis", i.e. the normal increase in collagenous connective tissue which is to be expected with increasing age. The therapeutic results which can be achieved with

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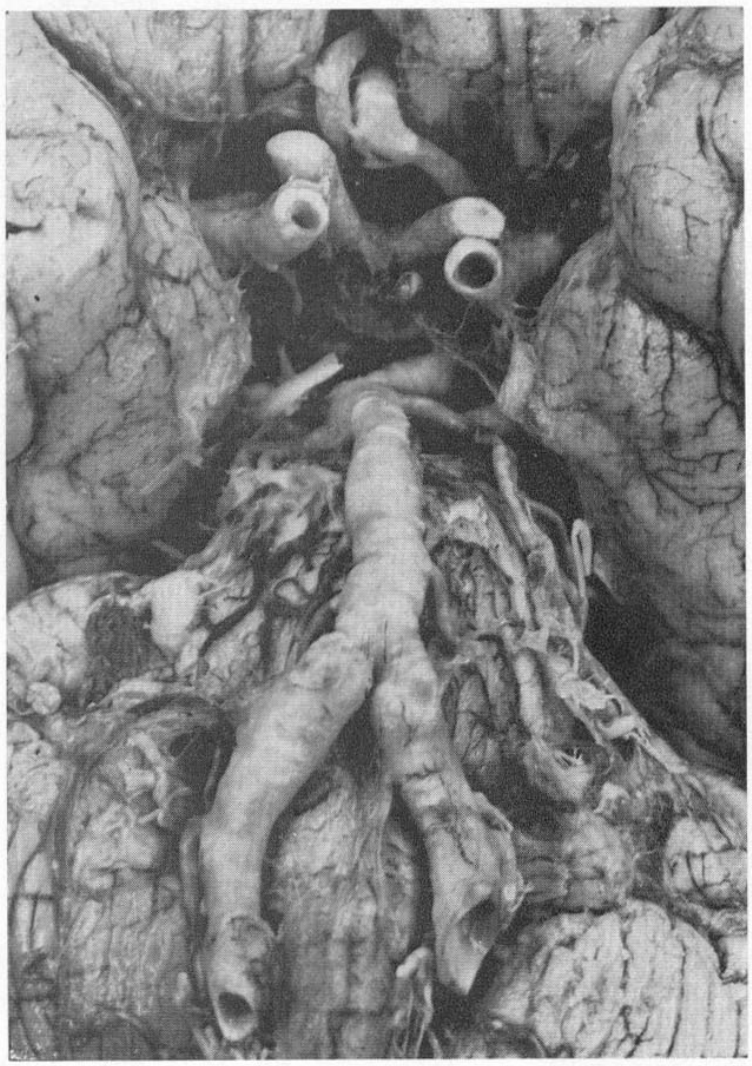


Fig. 1. — *Severe arteriosclerosis of all basal vessels with stenosis of the lumen (so-called pipe-stem arteries). This is frequently encountered in severe diabetic mellitus. On the left vertebral artery one can recognize at the point of penetration through the dura of aneurysmal sacculation.*

administration of oxygen —5 % carbon dioxide— show that even in older persons it is possible for such physiological regulation to increase blood flow. Because carbon dioxide probably acts through a widening of the vessels we must ask ourselves whether *vasoconstriction* or even *spasm* may not occur (Zülch 1959). That local vascular spasm in the brain can occur is certain. We see such —large— vessels in spasm in angiography in the neighbourhood of ruptured sacular aneurysms. We know also of local spasm of small vessels on the surface of the brain from experimental observations with irritation of the intima, for example in the powdered glass emboli of Villaret and Cachera.

Clinical observations show us that in about 5 % of cases haemorrhagic infarcts occur at the height of an attack of increased blood pressure. We, therefore, today postulate that under the effect of mounting high blood pressure a spastic narrowing of arteries can occur —in physiology known as the Bayliss effect— and thereby lead to a haemorrhagic infarct. We have published a series of completely investigated cases of this type. We have even completely investigated one of these cases anatomically and in it were only able to demonstrate a quite minimal stenosing arteriosclerosis and no local cause for deficient blood flow.

Such spastic narrowing of arterioles under the influence of a wave of high pressure has been demonstrated in experiments on white rats which suggest (Byrom) that this is the mechanism of the brain changes in eclampsia.

In summary: we therefore believe that the physiological mechanisms for regulating the

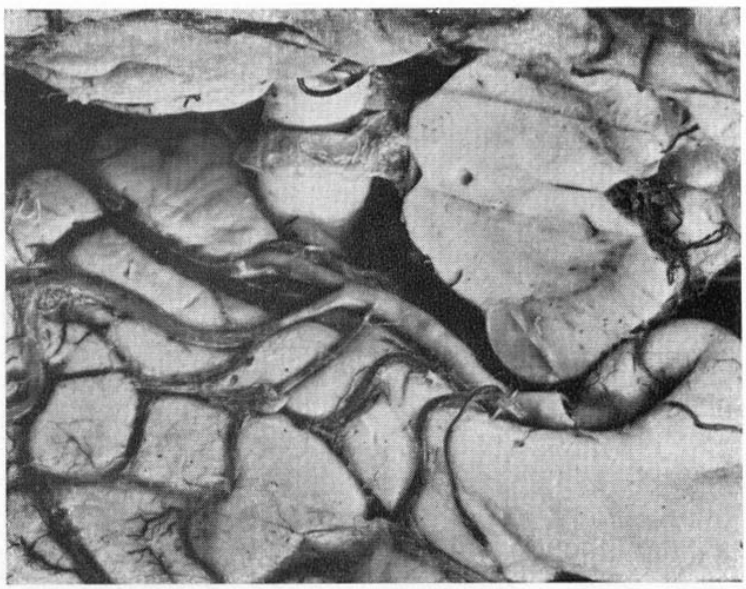


Fig. 2. — *Proximal type of arteriosclerosis; here the changes cease on leaving the cisterns; the posterior cerebral artery can be seen running in the cisterna ambiens. Its branches only show arteriosclerotic plaques for quite a short distance.*

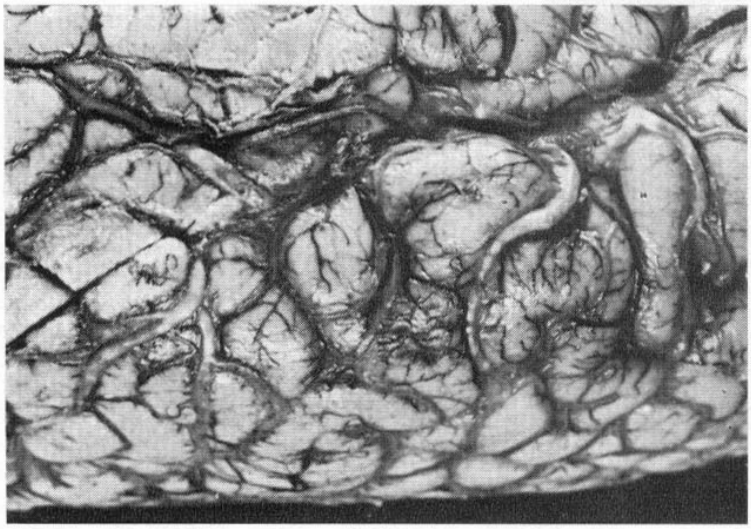


Fig. 3. — *Distal type of arteriosclerosis: one recognize the arteries of the first distribution extending out of the Sylvian fissure onto the convexity. They are generally very severely degenerated by stenosing arteriosclerosis.*

calibre of vessels in older persons are markedly restricted because of physiosclerosis or arteriosclerosis of the vessels. They are, however, still present (particularly under the effect of carbon dioxide breathing). In rare cases spastic narrowing of arteries or arterioles is encountered. So much for the disorders of regulation of the vascular tree.

We can test the actual regulatory efficiency of the cerebral vessels at any time by simple tests: where definite foci of E.E.G. abnormality are present one can find out whether they disappear with administration of oxygen and carbon dioxide etc.

The second point is the change of the *vessel wall* by disease i.e. through arteriosclerosis. Certainly all sclerotic change in the vessel wall from the physiological point of view operates as a stenosis for the systolic pulse wave because of the loss of elasticity. In this connection there are two possibilities. There may either be an ectasia (dilatation) or stenosis (fig. 7) of the arteries through atheroma and cellular proliferation of the intima.

We are seeking at the moment in our institute to define and classify arteriosclerosis of the brain as precisely as possible. It is very difficult to form general conclusions; in our experience there is scarcely any definite correlation between arteriosclerosis of the extracranial viscera, for example the coronary arteries or the aorta or the peripheral arteries, and arterioscle-

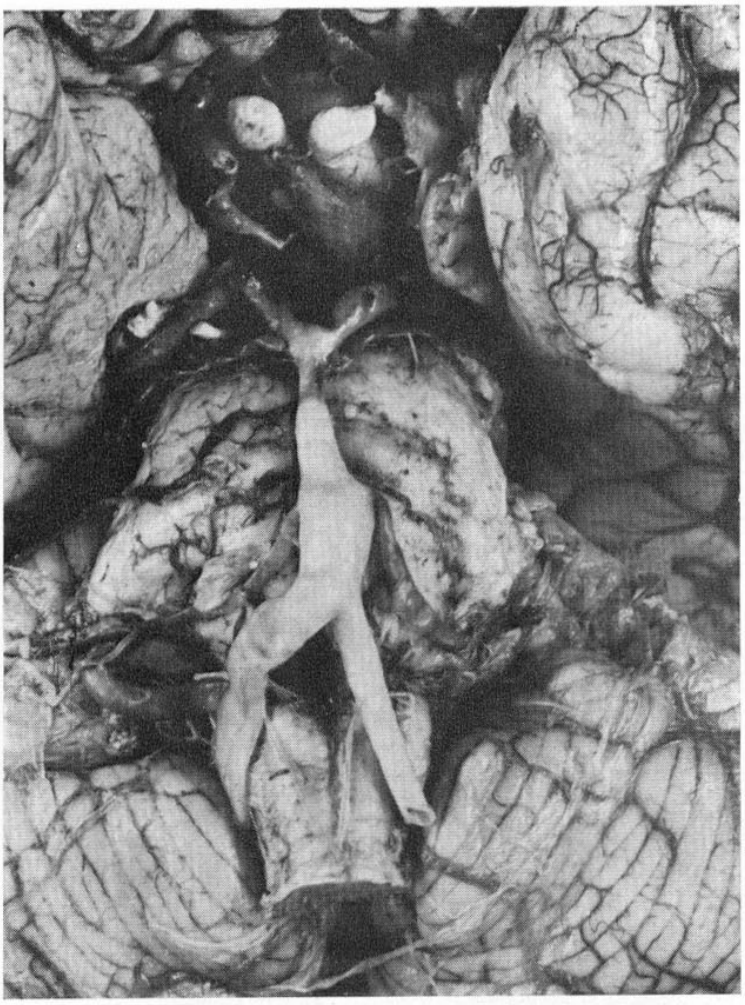


Fig. 4. — *Arteriosclerosis predominantly confined to the basilar artery of both vertebral arteries. It is predominantly of the sclerosing ectasic type but also shows the deposition of atheroma. The two carotids and the remaining arteries of the Circle of Willis are, apart from the point of bifurcation of the basilar artery (which again is severely affected) relatively free from arteriosclerosis.*

rosis of the brain. Only in the most severe, for example *diabetic,* arteriopathies of the body does one find a severe generalised arteriosclerosis of the brain (fig. 1). On the contrary we find all possible discrepancies; severe brain arteriosclerosis without arteriosclerosis of the extracranial viscera and coronary arteries and the reverse. And the findings are not at all uniform. We find in the brain for example, gross stenosing arteriosclerosis of the proximal type when the arteries at the base of the brain are affected (fig. 2) but those on the convexity are only a little affected. We may find on the other hand a ubiquitous distribution of arteriosclerosis up to the small meningeal arteries (fig. 3). We may find a predominant involvement of the basilar artery with sparing of the carotids and vice-versa, i. e. arteriosclerosis of the carotids without much involvement of the basilar. We have particular sites of predilection for arteriosclerosis in the brain as in the rest of the body. Here haemodynamic effects play a role, particularly *turbulance* i. e. changes in the uniform direction of the blood stream.

Arteriosclerosis is particularly found where the arteries are fixed, for example where they penetrate the dura, or at the junction or bifurcation points of large arteries, particularly in the so-called distal carina (Ove Hassler), this is, for example, particularly marked at the bifurcation of the basilar artery (fig. 6). It also has a special predilection for the bowing of arteries, for example in the middle cerebral artery 1 cm. behind the origin from the carotid artery or the curving of the anterior cerebral artery around the corpus callosum.

As varieties one can mention generalised (fig. 17) and patchy (figs. 5 and 8) types. For example we find isolated and extrem-

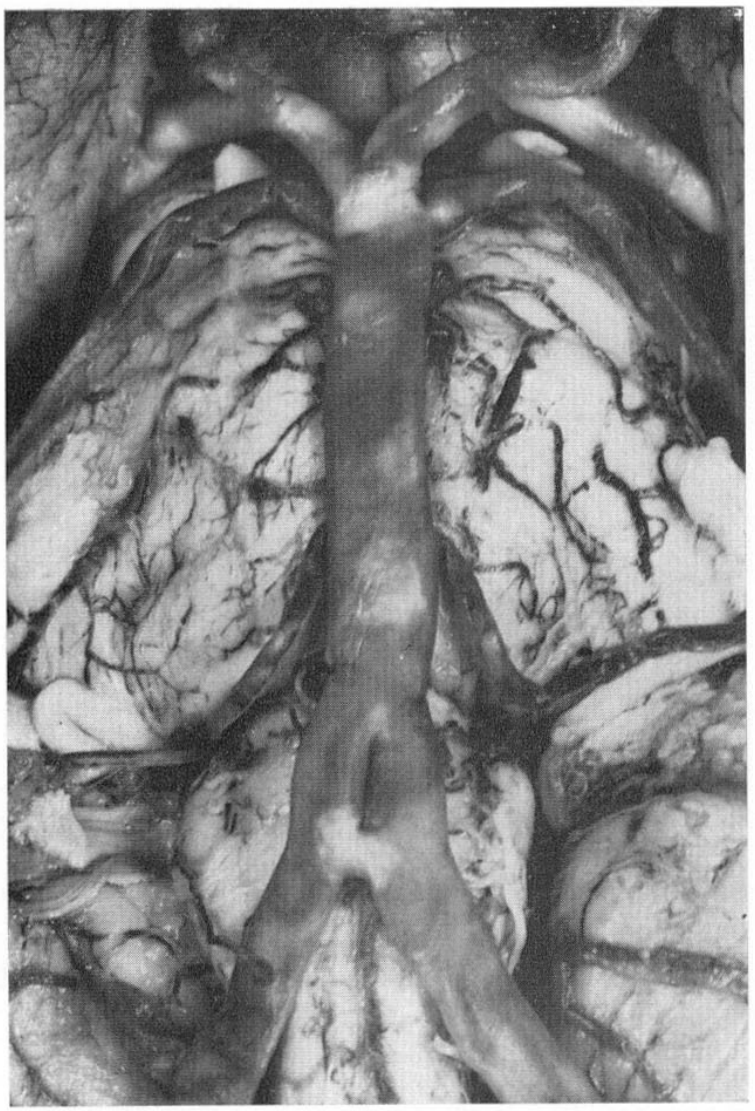


Fig. 5. — *Marked patchy arteriosclerosis, which is seeded particularly strongly at the bifurcation point of the basilar. At the point of union of the vertebral arteries there is an arteria communicans with button-hole formation. The distally lying arteria communicans shows severe arteriosclerosis changes.*

ely severely stenosing plaques on certain arteries (fig. 8) without the other arteries being significantly affected.

An important question here requires to be answered; we have not been able to establish a definite relationship of grades of arteriosclerosis in the brain arteries to blood pressure. We encounter cases with high blood pressure over many years without any arteriosclerosis of the brain arteries and alternatively the most severe arteriosclerosis in the brains of patients who have even had a fall in blood pressure. On the other hand again one frequently encounters cerebral arteriosclerosis in hypertensive patients who have died early with renal hypertension (see also Liebegott).

Primary Cerebral Vascular Thrombosis (Fig. 11).

Important and far from clear at present is the frequency with which primary cerebral arterial thrombosis is the origin of an infarct. Formally this was quite naturally put forward as the most frequent origin, so that one in clinical jargon used the terms "infarct" or "softening" and "cerebral thrombosis" as interchangeable. In the meantime angiographic investigations have shown that at least 80 % of infarcts occur in the presence of *patent* arteries (Tatelman) and of the remaining thromboses many appeared to be secondary that is to say they occur after the onset of the infarct.

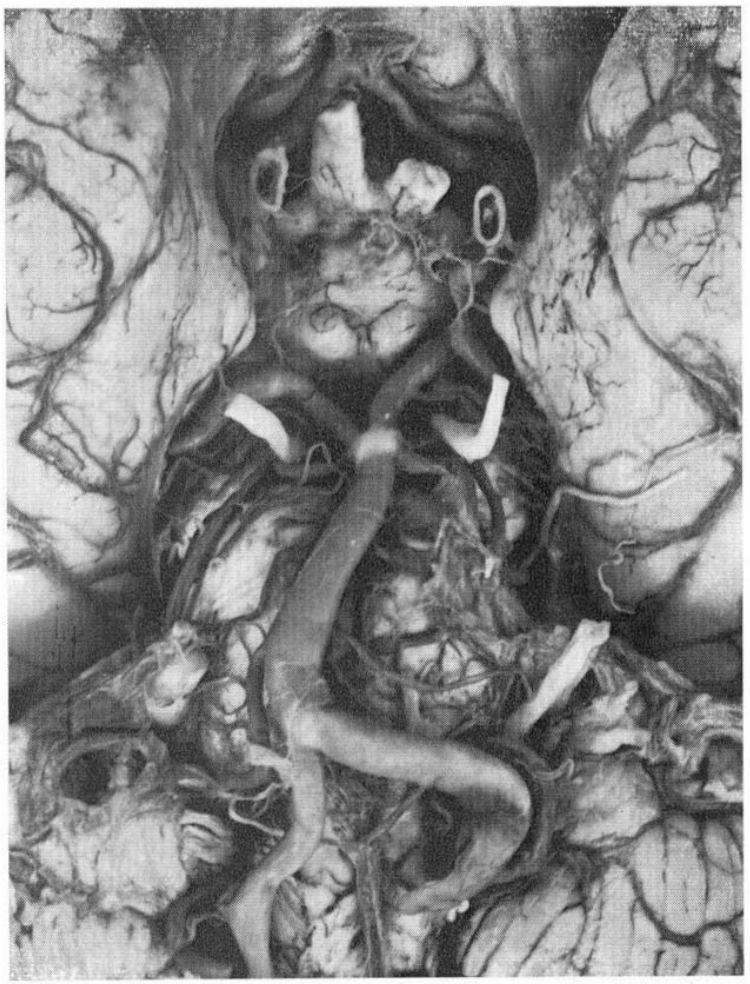


Fig. 6. — *Early stage of arteriosclerosis: this is patchily distributed at the bifurcation point of the basilar into the two posterior cerebral arteries.*

Certainly this question also demands more complete morphological and statistical investigation. The majority of all infarcts certainly occur with "patent" but stenosed arteries.

Consideration of the significance of such stenosis for the blood flow recalls the following concepts from physiological teaching which state quite clearly that where blood flow is defective it can only be overcome if the pressure is raised proximal to the stenosis that is to say in the general circulation. If this is done the distally lying region may well be adequately nourished by collateral anastomoses.

Now we come to the subject of *anastomoses* and *collateral* nutrition of the brain. We have in the meanwhile learnt (and *re*-learnt, because this well substantiated thesis originates from the time of Heubner i. e. from the year 1872) that we can demonstrate the cerebral vascular system on the surface of the brain as a network (fig. 9), in which the three main vascular systems of the anterior, posterior and middle cerebral arteries as well as the cerebellar arteries are connected by *meningeal* anastomoses. These have been particularly carefully demonstrated in morphological investigations undertaken in collaboration by Van der Eecken and Raymond Adams who further discussed the functional significance of the arrangements. However the main system of anastomoses is that of the *Circle of Willis* which joins all the cerebral arteries in a basal ring system, but is only complete in about a quarter of the cases. In a further quarter of the cases there are great deviations, while in the remaining 50 % variations occur in which a particular constellation of vascular occlusions can play a decisive and disadvantageous role. Unfortunately one can only detect these variations of the circle of Willis in individual cases as

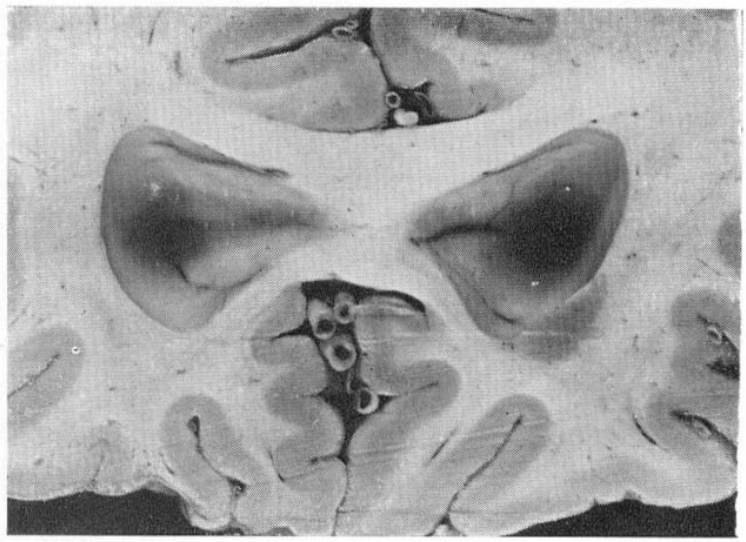


Fig. 7. — *Stenosing type of arteriosclerosis on the dividing branches of the anterior cerebral artery. An epicallosal artery shows an old thrombosis in process of organisation.*

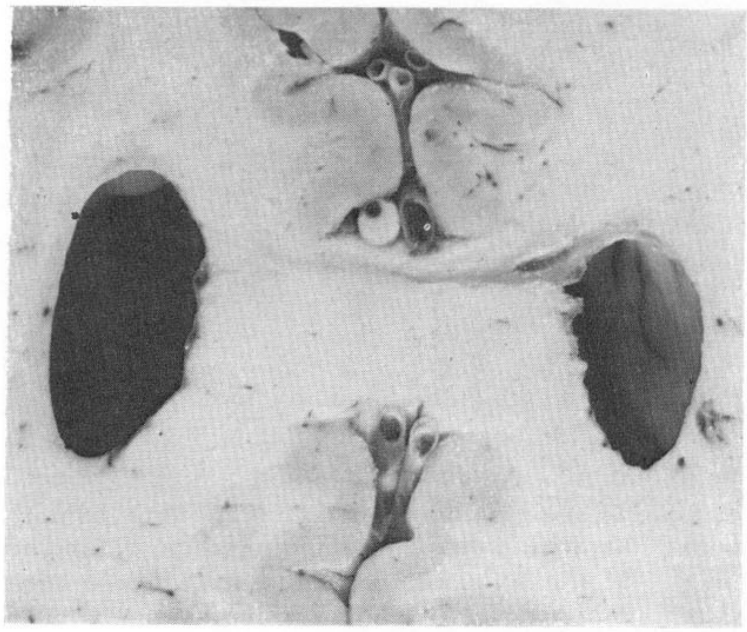


Fig. 8. — *Eccentric arteriosclerosis with high grade narrowing of the lumen of the left pericallosal artery just behind the point of division. View from in front of a slice of brain.*

a result of secondary phenomena. One method for testing is for example compression of the carotid artery under E.E.G. control. This and other tests, for example, serial angiography with compression of the carotid on the other side, have been repeatedly discussed by Gastaut and his school. The significance of the meningeal anastomoses (fig. 9) mentioned above in relation to the closure of a vessel cannot be too strongly stressed. However, we still do not have any extensive information —and herein lies the difficulty— on 1) physiological variation of the arrangement, 2) the possibility of a *widening* of the lumen of the meningeal anastomoses through "work hyperthophy" and 3) the danger of *stenosis* through distal arteriosclerosis. In young subjects one may anticipate a regular enlargement of these meningeal anastomoses under conditions of increased blood flow. Such vascular dilatations are well known, for example, after closure of the middle cerebral artery through embolism. We know on the other hand, that the blood vessels supplying an angioma are often dilated to many times their normal calibre and can retract to normal following its removal. There are therefore normally extraordinary variations in calibre of collaterals in the brain. However, the dilatation often comes far too late to remedy the impoverished situation brought

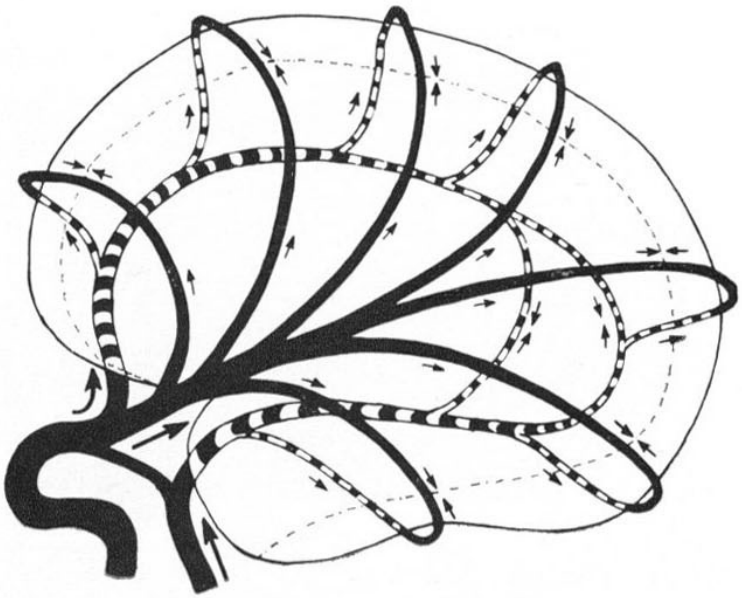


Fig. 9. — *Rough schematic demonstration of the vascular net on the outer surface of the brain.*

about by the ischaemia. We have never observed formation of *new, large, previously non-existant* collaterals.

The situation in the brain is therefore fundamentally different from that of the heart; while in the heart in three to four weeks new anastomoses and collaterals can form and to a large extent satisfy the infarcted, only partly destroyed, region, so that a work hyperthophy of the muscle can to a large extent restore the infarcted area to a functional state, this is impossible in the brain. In regard to the collateral supply of the brain the decisive factors are the anastomoses available at the moment of interrumption of the blood supply and the haemodynamic situation. Actually the filling of the occluded vascular territory by retrograde flow through the anastomoses —which have a relatively small calibre of 1/2 to 1 mm.— is impeded because these anastomoses form a functional stenosis for the cerebral vascular tree. Behind it the retrograde filled arterial system widens still further.

That a training of these anastomoses is possible has been shown by Gurdjian and others who in patients with carotid occlusion instituted a "collateral vessel training" by compressing the contra-lateral carotid until symptoms occur. It was then possible to prolong through this practice the tolerable period of occlusion. Apart from this important, *extracerebral* but *intracranially* situated vascular net of the brain we must concern ourselves with the extracranial connections of the large cerebral vessels. The rich *anastomosing network* of the external with the internal carotid arteries via the *ophthalmic artery* has been known since a long time and was described recently by Dilenge and Fischgold. The following picture shows the three anastomoses between the external carotid artery (fig. 10) and the ophthalmic artery retrograde to the carotid. They pass 1) via the ethmoidal artery 2) the dorsal basal artery and 3) the frontal artery. The last can be seen extending from the superficial temporal artery to the frontal artery outside the skull (fig. 11). Apart from these, extracranial branches from the external carotid artery anastomose with the vertebral artery and fill the latter through its muscular branches. (Such anastomoses can develop in the most impressive manner, for example via the anterior spinal artery into the vertebral artery!). How can one test these anastomosing networks? A good clinical history, and serial angiography with provoking — and test techniques under EEG control can possibly demonstrate the efficiency of the collaterals.

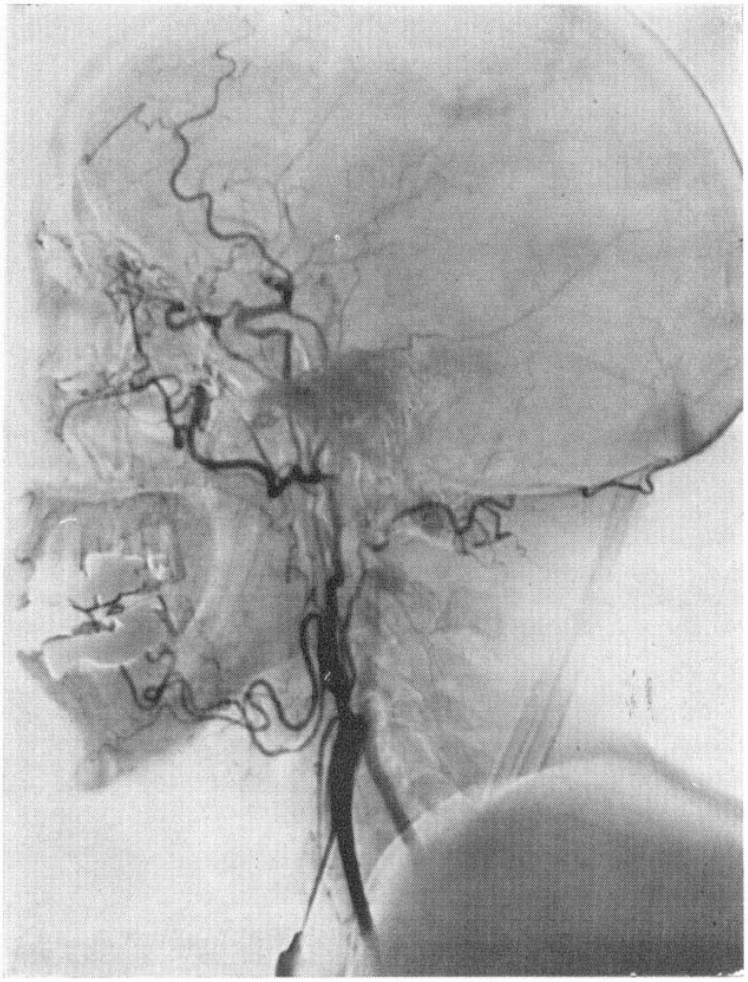


Fig. 10. — *Angiogram of a right sided carotid occlusion with anastomoses with the ophthalmic artery. One sees the principal anastomoses from the external carotid via the ethmoid artery running to the ophthalmic artery and apart from this also the two additional anastomoses between the dorsal nasal and frontal arteries. One sees at the point of the needle the interruption of the internal carotid artery, the three anastomoses already mentioned, the retrograde filling of the ophthalmic artery as well as the contrast medium in the anterior cerebral and middle cerebral artery (and the over-lying external vessels). The internal carotid artery is filled in a retrograde manner up to the base of the skull.*

The third problem I have already shortly mentioned as an illustration of the haemodynamic significance of a stenosis of the vascular tree for the blood flow; it concerns the significance of *blood* pressure for the maintainance of the blood circulation; the findings of the physiologists show for young subjects a linear relationship between blood pressure and blood flow but only in certain regions. Much closer is their relationship in the sclerosed and eventually stenosed, badly regulated vascular system of the *aged*.

Those practising clinical medicine have known of these relationships for a long time. The German physician Traube in 1854 pointed out quite unequivocally the significance of blood pressure for the development of collaterals at the moment of disturbance of the blood flow and the French clinicians at the beginning of this century had already come to similar conclusions.

However, Denny-Brown was the first, in 1951, to demonstrate the significance of falls of blood pressure for the production of intermittent disturbances of blood flow disturbances in an indubitable and almost experimental manner. He started with the concept originating from German clinical practice (Friedrich Kaufmann), that small intermittent disturbances could be brought about by *angiospasm*. He was able to show still better by complete measurements of blood pressure that always at the moment of a fall of blood pressure below a particular value a disturbance of the blood flow of the brain occurred with particular symptoms which disappeared after elevation of the blood pressure. Each patient appeared to have "his own critical blood pressure", which in many patients was hypotensive, in others normotensive but in many others could have hypertensive values. In disturbances of blood flow at the moment of the disturbance it is therefore important to

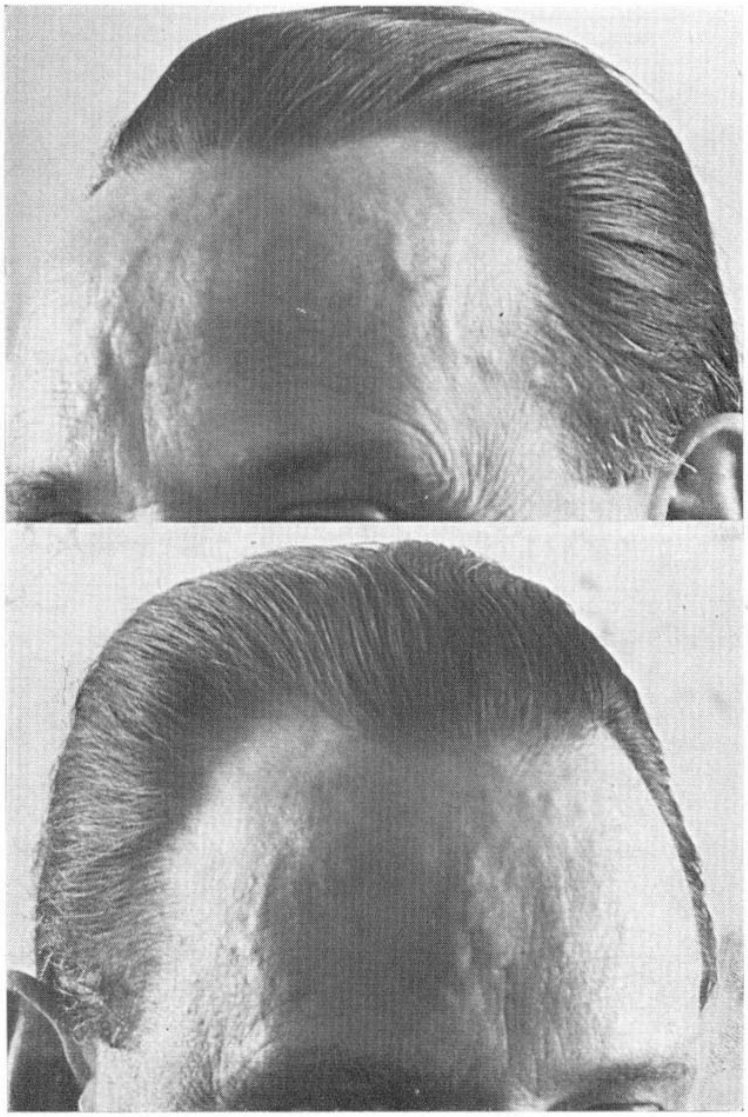
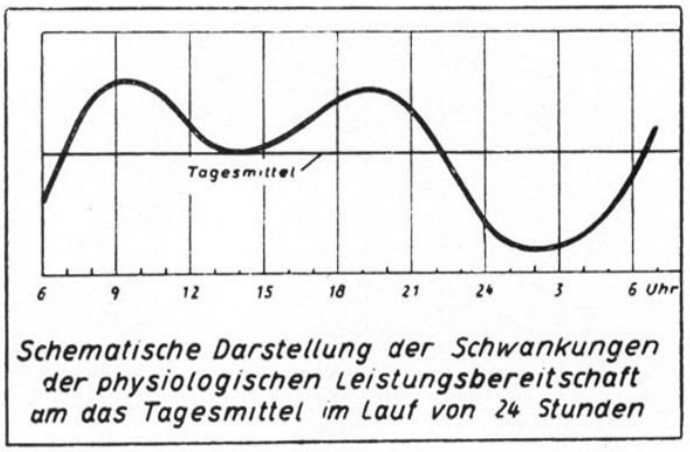
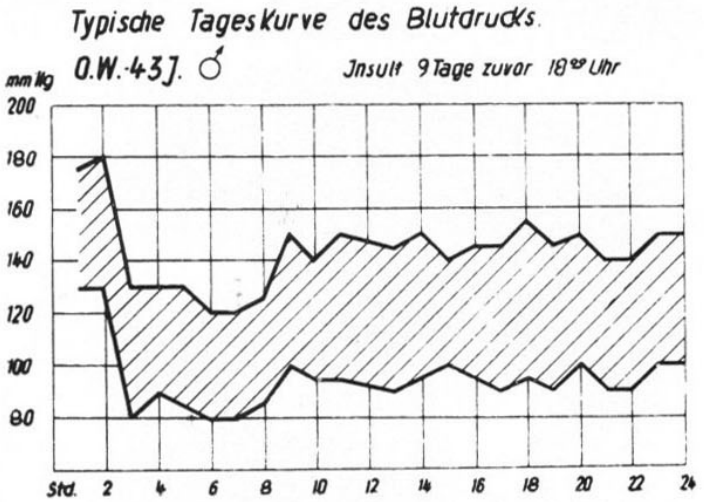


Fig. 11. — *In a 49 year old patient with left sided carotid occlusion (and quite slight reversible right hemisyndrome without aphasia) one sees the external collateral circulation via the superficial temporal arteries to the right and left frontal arteries particularly clearly. From there both ophthalmic arteries fill in a retrograde manner (with development of collateral circulation "pulsation under the hat").*

know what level of blood pressure is necessary for that particular patient under normal conditions to overcome the stenosis of his vascular tree. In this connection I must stress how little value is an estimation made on one occasion only. Even physiologically the blood pressure reading in human beings varies markedly and the following curve shows you for example the great differences in pressure at different times of the day in healthy persons (fig. 12). There is a decline shortly after midnight, the time at which many heart and brain infarcts occur. In such cases the patient wakes up with a hemiplegia. It is however, necessary to recognize the difference from the coronary circulation. Here anoxia of the heart muscle causes the well-known pain of angina pectoris or the breathlessness of cardiac asthma i. e. symptoms which wake the patient up. In the brain paraesthesias certainly occur but do not usually lead to the awakening of the patient. Only occasional patients observe this at midnight. The patient wakes up in the morning with the catastrophe already developed so that many hours must have elapsed after the beginning of the circulatory disturbance before treatment can be commenced.

This nocturnal fall in blood pressure is quite clearly demonstrated in many patients after the attack and is definitely the principal factor in causing this "lesion at rest". It appears that there is a definite type of patient with a tendency to a "vegetative ataxia" in the regulation of blood pressure.





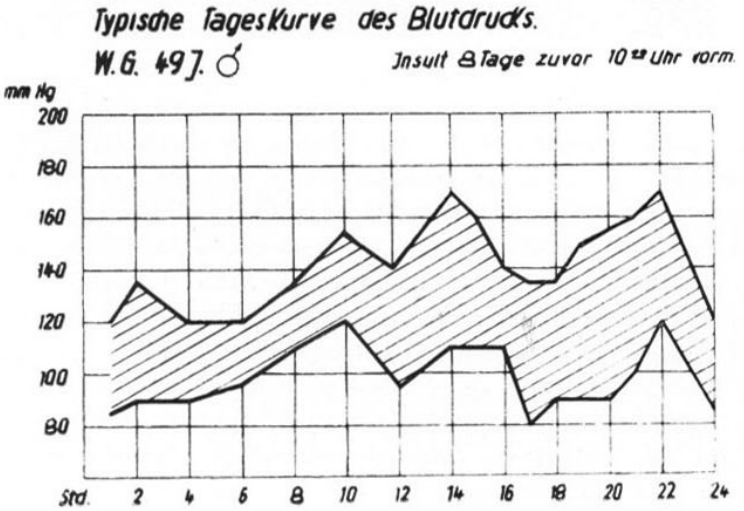


Fig. 12. — *Rythmical variation in blood pressure at different times of the day. Above: Curve of normal vegetative regulation and physiological efficiency (after Graf). Middle and below: typical daily curve from patient over one week after an apoplectic lesion with cerebral blood flow disturbance. In both patients the drop in blood pressure in the hours of early morning on many days after the lesion was particularly characteristic.*

In these patients a particularly marked swing can lead to an infarct, particularly if other infarctogenic factors are present. Such tendencies will have particularly marked and deleterious effects in patients with stenosing localized plaques on the cerebral arteries. Under these circumstances a fall in blood pressure can lead to an infarct if the

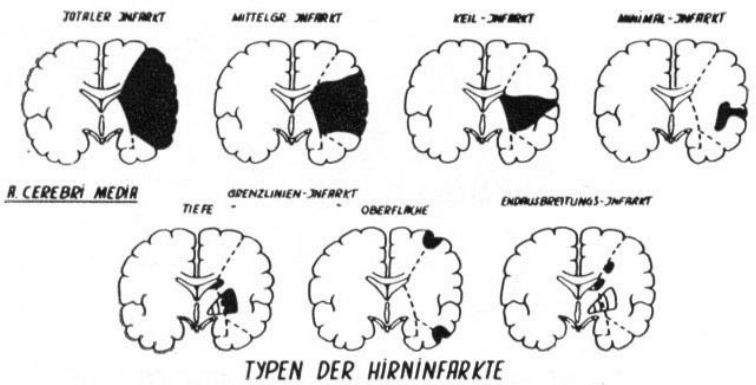


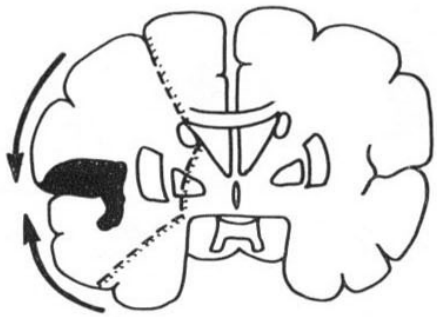
Fig. 13. — *The above series shows the different sizes of infarcts which follow a total occlusion of the middle cerebral artery. On the right the "minimal infarct", in which the greater part of the irrigation territory is covered by meningeal anastomoses from neighbouring vessels. The lower series shows on the left a border line infarct between the basal ganglia vessels and the middle cerebral artery. In the middle; border line infarct between the middle cerebral artery on the one side and anterior and posterior cerebral arteries on the other. Right: Terminal territory infarct with formation of a cyst in the centrum semiovale and in the head of the caudate nucleus.*

collateral circulation does not open up sufficiently. We feel that we are right to think nowadays that such a transient and defective blood flow may be the origin of "syncopal attacks" as Behrend and Gastaut have shown. This appears to be associated with a local disturbance of blood flow in the brain stem.

The fourth problem concerns the *distribution* of infarcts. Our ideas on infarcts in the irigation territory of individual cerebral vessels are based on the splendid observations of Foix whose premature death is much to be regretted, and we have also learnt to distinguish the syndromes corresponding to the affected territories. However, we are today able to interprete a greater number of the infarcts which in former days were designated as "atypical" by the rational use of the rules mentioned above. We know therefore the typical distribution of infarcts of the individual large arteries (fig. 13).

The *extent* of infarcts varies greatly because of the variable participation by the *collaterals.* I would like to illustrate this by reference to the middle cerebral artery infarcts of the brain. One finds in this connection, total but also partial infarcts of varying size. There are wedge-shaped or minimal infarcts depending on how much of the territory of the middle cerebral artery in its obstructed state is taken over by the posterior or anterior cerebral artery. The same applies to infarcts of the posterior and anterior arteries. An unfortunate combination of circumstances results in the minimal infarct in the middle or posterior cerebral artery territories affecting particularly *important* centres, namely the Broca's speech centre and insula in the one case and the calcarine cortex in the other (fig. 14). This explains the clinically often observed defect of expressive aphasia or an isolated homonymous hemienopia without any other symptoms.

The varying size of the infarcts is easily explained in terms of the collateral supply through anastomoses, but I would however, bring to your notice a new haemodynamic principle viz. the *endangering* of the *extreme periphery* of a vascular territory at the moment of *defective blood flow.* Max Schneider, the Cologne physiologist, has shown that in an irrigation system the last field shows a particular tendency to dry up from lack of water (fig. 15). This applies also to the border zone between two systems. If one applies the principle of the "last field" to the different territories of the brain circulation, so one is in position to interpret further types of infarcts which have previously defied explanation. Thus there is an endangered zone lying on the *surface* of the brain. It lies on the border line between the three large main arteries, between the anterior and posterior on the one hand and the middle cerebral artery on the other. This ring zone is for example, degenerated in granular atrophy. Within its borders we can also see fresh haemorrhagic infarcts.



Besondere Gefährdung von Sprachzentrum und Calcarina durch Lage der Mitte der Versorgungsgebiete.

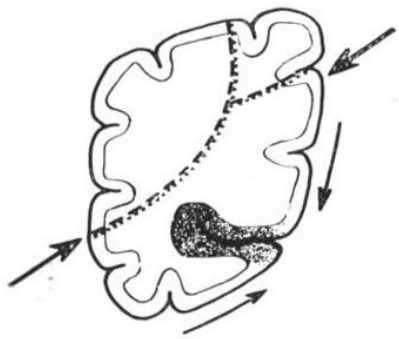


Fig. 14. — *Small infarcts in the middle and posterior cerebral artery territories which correspond to the important speech centre of the frontal operculum and insula as well as the primary visual centre of the calcarine region.*

A similar border zone is found in the *depths* of the brain between the deep basal ganglia system nourished by Heubner's artery and the *lenticulo-striate* artery on the one hand and the superficial cortical irrigation by the middle cerebral artery on the other. The corresponding haemorrhagic infarcts mostly pass through the head of the caudate nucleus and the putamen. These infarcts are particularly important and interesting because they probably escape electro-encephalographic analysis in spite of the global neurological hemisyndrome.

On this principle we can analyse yet other types of infarcts in relation to the border line zones and the jargon expression "last field" is today in use in the vocabulary of all nations. At this stage you will perhaps ask whether this interesting and academic knowledge and discussion have any real significance for treatment. I would point out straight away, that *stenosis* of an artery can cause a peripheral fall in blood pressure which can only be overcome by increasing the pressure proximal to the obstruction. The elevation of blood pressure through drugs is today no longer a problem. But you will quite rightly protest that the disturbances of the blood flow which occur with ischaemia, for example complete arrest of the cerebral blood flow, can lead to a degeneration of the tissue so rapidly, actually in 3-5 minutes, that any medical treatment can only come too late.

Now one can first point out that complete arrest of blood flow, for example through embolism or general cardiac arrest, is a *rare* occurence. In cardiac arrest — Adams-Stokes seizures, overdose of narcosis etc. — it is in fact a question of the *duration* of ischaemia which determines whether the brain will be able to recover. In embolism the result is dependant on the immediate coming into play of the collaterals as I mentioned earlier. Here therefore the *morphological arrangement* of the anastomoses and the *blood pressure* are vital. Far more frequent than arrest is defective blood flow — *cerebrovascular* insufficiency as it is known in the Anglo-Saxon literature where one speaks of the syndrome of vertebro-basilar and carotid insufficiency

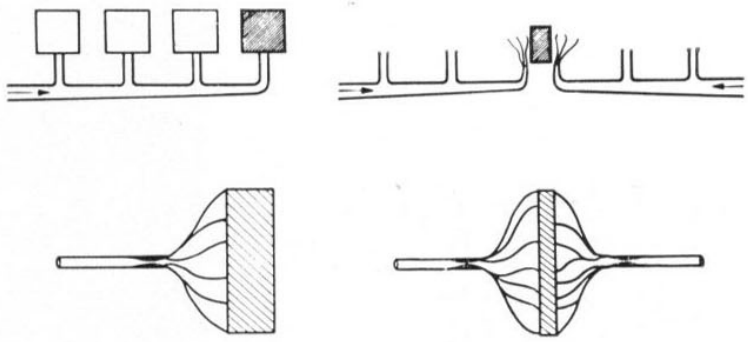


Fig. 15. — *Schematic demonstration of the principle of threatened vitality of the terminal region of an irrigation system or border zone between two irrigation systems.*

(Millikan et al.) and of the combined insufficiency in the vascular territories of both (according to site and grade of stenosis. Yates and Hutchinson). What is the significance of such a deficient blood flow for the function of the cerebral tissue? Here we come to a fifth important point, namely the reserves of the cerebral blood flow and the *different* levels for a *functional* and a morphological disturbance of blood flow.

In contrast to the heart, the brain has a blood flow reserve of 100 % i. e. symptoms (gross electrophysiological disturbances and neurological paralysis either of the extremities or of speech) only appear when the blood flow falls below 50 % of the normal. But this level of blood flow (under 50 %) causes no damage to the tissue. This only occurs with a fall below 15 % of normal blood flow i. e. —20 % of the normal supply of oxygen— a different figure because in the arterio-venous difference there normally remains unused oxygen in the venous blood, which however is used under conditions of deficiency. Therefore it is only when there is a fall below 1/5 of the normal that *necrosis occurs.* The blood flow in the reversible syndromes of cerebral vascular insufficiency lies in this "safety zone" of 1/3 of the total blood flow — between the two levels. How do we know whether a paralysis is still reversible? Unfortunately up to now *neither clinical* nor *biological* means permit one to determine whether a neurological syndrome has been caused by an *irreversible infarct* or by a reversible deficiency of blood flow. One must in *each case* for a certain time *presume* the *possibility* of a *reversible blood flow disturbance* i. e. that the blood flow lies between the levels of the safety zone and continues to be maintained there —even if a total closure of a vessel is shown— because an extensive collateral blood flow can come to exist through anastomoses.

We must therefore treat with the greatest energy, and the further course will show us whether an irreversible infarct has already developed or whether we are dealing only with a reversible disturbance of blood flow. At present there is no clinical procedure that gives us the answer immediately. A certain —negative— diagnostic *evidence* is often provided of course by the *temporal* relationship between the occurence of the disturbance, that is to say the first symptoms and the beginning of effective treatment. We know that the longer a collapse with fall of blood pressure has been present the worse will be the prognosis even with careful and resourceful treatment.

I would like here to refer to a case which I have recently published in which the patient already four years previously had a lesion of the right side of the brain but had completely recovered. He was a hypertensive patient and he came again to our clinic one hour after a left sided cerebral lesion with partial aphasia and paralysis of the corner of the mouth. We treated him energetically and already in the first days there was a continuous slight improvement. Then on the 7th. day there was a sudden change and with increasing breathlessness of the patient there developed a state of confusion. It appeared that the patient had developed a cardiac infarct at a moment when he was

Fig. 16 a. — *12 cms. long thrombus, about 4 days old, lying proximal to the point of division of the carotid artery.*
Fig. 16 b. — *Enlargement of the upper part of 16 a. One clearly recognises the stenosing arteriosclerosis at the beginning of the internal carotid artery (right) while the external carotid (left) remains relatively free. The thrombus extends into the interna in the form of a small nodule.*

Fig. 16 a Fig. 16 b

not observed. There developed a fall in the blood pressure which had been previously raised, a severe tachycardia in spite of all treatment. Only with difficulty could the blood pressure in the succeeding days be maintained with arterenol at a systolic value of 130/150. In spite of this the condition of the patient deteriorated, he developed a flaccid hemiplegia, loss of consciousness and died.

At autopsy the left carotid artery just above the bifurcation showed a stenosing old arteriosclerotic calcified plaque. Proximal to this lay a 12 cm. long fresh thrombus (fig. 16 a and b) i. e. it *was obviously more recent than 11 days.* The cerebral findings were particularly interesting; there was a delicate basal arterial system, an old broken right sided cerebral infarct in the lower parietal region and a *fresh* vascular injection in Broca's area and the left insular cortex. This corresponded histologically to a lesion four days old, (fig. 17).

I would like then to stress that the first lesion of 11 days before death had not come to a histological infarct although clinically a syndrome of aphasia, corner of the mouth paralysis and transient arm paralysis had occurred. It was only the second lesion at 7 days associated with or following thrombosis of the carotid that had led to *irreversible* tissue disturbance in this region.

Here then neither the syndrome nor the time elapsing between the lesion and beginning of treatment were able to provide information concerning the reversibility of the disturbance of blood flow. You see how right it is to insist on an energetic treatment prolonged over a long period in order to permit the restoration of cerebral blood flow *in every patient with a cerebral lesion* as a result of circulatory disturbance. As this case shows a rich collateral circulation is obviously required over a long period in order to prevent the development of such an irreversible infarct.

My *survey* over the various pathophysiological viewpoints in the development of cerebral blood flow disturbance and infarcts is now actually at an *end.* But I would like in conclusion to attempt to show the connection with clinical concepts of today somewhat more closely by demonstrating once more how the data provided can clearly be put to use in clinical work and lead the way to a *clinical classification* of the type of lesion which in my view has considerable *therapeutic* value.

I believe one can recognise four main types of lesion; 1) the *lesion at rest,* which is present in the morning on waking but probably has already developed after the critical fall of blood pressure shortly after

Fig. 17 a. — *Relatively normal cerebral cortex in paraffin embedding (see case of fig. 16 a and text). The investigated block lies somewhat outside the point where macroscopically vascular injection could be seen.*

Fig. 17 b. — *From the region with macroscopically visible vascular injection. There is clear ischaemic cell damage visible in the nerve cells with commencing proliferation of the capillary endothelium. Compound granular corpuscles are beginning to form but still do not lie free in the tissues.*

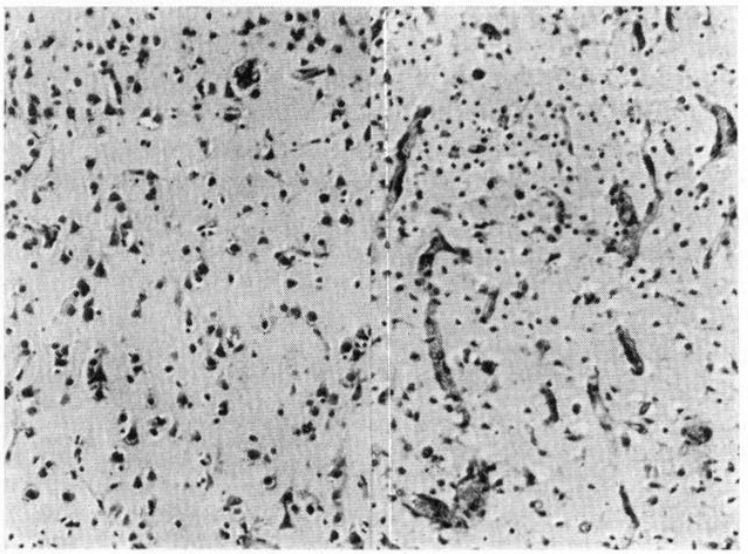


Fig. 17 a Fig. 17 b

midnight. I showed you the corresponding blood pressure curve.

We also have 2) the *stress lesion* in which physical exertion together with an acute decompensation of the heart with lowered blood pressure can lead to an insufficiency of cerebral blood flow and thereby to the lesion. We have 3) the converse, namely the *relaxation lesion,* which can occur as a result of an acute collapse or hours of more gradual general relaxation; here there is an acute or sub-acute fall in blood pressure which is particularly effective if it coincides with a physiological fall in the daily rythm. I have here described for example, the case of the head of a great insurance company who after long years of struggle in his desire to solve a personal problem succeeded in doing so and in joy over this —I would say in happy relief— which it is recognised can lead to a fall in blood pressure — and after a heavy lunch suffered a sub-acute lesion with aphasia and hemianopia which was however reversible during the following weeks. This patient whose blood pressure is shown here had marked afternoon falls in blood pressure. So there were three factors operative; afternoon drops in pressure, mealtime drops and "relaxation". Such attacks of relaxation with tendency to collapse are found particularly in a certain type of person whom I would like to designate as the "vegetative ataxic" type of moderate hypertensive who not infrequently experience attacks called by the Americans "intermittent insufficiency". Finally there is yet a fourth *main type of lesion* the primary *cardiogenic type;* here it is primary acute insufficiency of the heart itself, mostly as a result of a coronary infarct, which brings about the cerebral lesion.

One of the classical examples in history is that of the American President Eisenhower, who suffered a transient aphasic syndrome at the time of his second coronary infarct. This was described in the American newspapers of his time in correct medical detail although the dubious interpretation at that time was that of cerebral embolism. Not related to these four types of attacks of drop in blood pressure is probably the lesion associated with an *episode of raised blood pressure.* Its pathogenesis certainly demands a more complete clarification and verification. Reference to the Bayliss effect of physiology which leads to spasm of the arterioles must at the moment suffice as explanation together with the fact that morphologically the lesions consist mostly of an incomplete haemorrhagic infarct.

Now I am really at the end. I believe that out of these pathophysiological con-

cepts the right line for treatment is indicated. One can today outline it in the form of items of a programme. For the present discussion I consider it particularly valuable that for the first time a uniform picture of the pathogenesis of lesions is possible and that this can be based equally on the morphological end results of tissue necrosis, on the clinical data of normal and disturbed blood flow, on the very complete physiological and pathophysiological experimental measurements on the normal and disturbed circulation of the brains in animals and finally on angiographic findings in patients.

Of course this is still a global outlining of a picture whose individual features we must still work upon more completely but these concepts can perhaps lead us to study further experiences in detail and integrate them into the collective picture. Perhaps it will then also be possible to treat the cerebral lesion with better results than has previously been possible. I believe that the *morphological* examination of the brains of patients who have died after a brain lesion and the complete analysis of the clinical evolution can give us the one definite basis for such studies.

SUMMARY

Several concepts are presented concerning the pathogenesis of cerebral blood flow disturbances which are based on an integration of the morphological picture of the infarct, the clinical data and new findings in physiology and pathophysiology of cerebral blood flow.

Changes from stenosing arteriosclerosis, the collateral daily variations and episodic drops in blood pressure as well as other factors are active in producing the defective blood flow. The rules governing the threat to the vitality of the periphery of an irrigation territory —particularly the border zones of two vascular territories— are of great importance. All these view points must be considered in modern treatment.

RESUMEN

Los diversos conceptos presentados en este trabajo, relacionados con la patogénesis de las alteraciones en la corriente sanguínea del cerebro están basadas en la integración del cuadro morfológico del infarto, en los datos clínicos y en los nuevos descubrimientos hechos en la fisiología y la patofisiología de la corriente sanguínea del cerebro. Tanto los cambios de la arterioesclerosis estenosante, de las diarias variaciones colaterales y los descensos episódicos de la presión arterial, así como también otros factores participan en la producción de deficiencia en la corriente sanguínea. Las reglas que rigen la amenaza de la vitalidad en la periferia de un territorio de irrigación, especialmente en la zona limítrofe de dos terrenos vasculares, tienen gran importancia. Todos estos puntos de vista deben ser considerados en un tratamiento moderno.

RÉSUMÉ

Cet article présente plusieurs idées concernant la pathogénèse des altérations du courant sanguin du cerveau, basées sur l'integration du cadre morphologique de l'infarctus, sur les données cliniques et sur les nouvelles découvertes dans les domaines de la physiologie et la pathophysiologie du courant sanguin du cerveau. Les changements de l'artériosclerose stenosante, les fréquentes variations collatérales et les chutes épisodiques de la pression arterielle, ainsi que d'autres facteurs, contribuent

activement à rendre le courant sanguin défectuex. Les règles qui gouvernent la menace à la vitalité dans la périphérie d'un térritoire d'irrigation —particulièrement les zones limitrophes entre deux territoires vasculaires— ont une grande importance. Tous ces points de vue doivent être considerés dans un traitement moderne.

ZUSAMMENFASSUNG

Es werden einige Vorstellungen über die Pathogenese der Hirndurchblutungsstörungen entwickelt, die auf einer Integration des morphologischen Bildes der Infarkte, der klinischen Daten und neuerer Ergebnisse der Physiologie und Pathophysiologie der Hirndurchblutung basieren. Veränderungen durch stenosierende Arteriosklerose, die kollateralen Tagesschwankungen und Abfallkrisen des Blutdrucks sowie andere Faktoren sind wirksam, um die Mangeldurchblutung zu provozieren. Dazu spielen eine wesentliche Rolle die Regeln über die Gefährdung der Peripherie eines Versorgungsgebietes bzw. der Grenzflächen zweier Gefässterritorien. Alle diese Gesichtspunkte müssen bei einer modernen Therapie berücksichtigt werden.

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L'Encéphalopathie Anoxique dans les Maladies Respiratoires et Circulatoires

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La prévention des lésions cérébrales anoxiques est le souci majeur de la réanimation dans les affections respiratoires et circulatoires. L'encéphalopathie anoxique a fait l'objet de nombreuses études récentes portant sur l'anatomie pathologique, la physiopathologie, la symptomatologie clinique et électrique, au XIVe. Congrès des Pédiatres de Langue Française, au Colloque de Marseille de 1959, et surtout au Congrès International des Sciences Neurologiques de Rome (1961). Au centre de Réanimation Neuro-Respiratoire de l'hôpital Claude Bernard à Paris, nous avons observé et traité de nombreaux malades en détresse respiratoire et circulatoire; les constatations que nous avons faites ont été développées dans plusieurs rapports et articles; ce sont les plus intéressantes d'entre elles que nous reprendrons dans ce travail.

Bases physiopathologiques de l'encéphalopathie anoxique

L'anoxie se définit au niveau cellulaire par le défaut d'apport ou d'utilisation de l'oxygène, défaut total ou partiel, brusque ou progressif; les conséquences peuvent donc être très différentes, selon les cas, sur le métabolisme cérébral. Dans les maladies respiratoires et circulatoires, l'anoxie tissulaire est consécutive à l'anoxémie ou à l'hypoxémie hypoxiques et de type stagnant, ces deux types d'hypoxémie étant souvent intriqués. Dans la plupart des cas, l'hypoxémie n'est pas seule en jeu; il s'y associe des troubles de l'équilibre acide-base: acidose ou alcalose respiratoires, acidose fixe; l'intrication de ces facteurs, tous nocifs pour le système nerveux, rend difficile l'appréciation de leur responsabilité réciproque dans la survenue de l'encéphalopathie anoxique en pathologie.

I) Retentissement de l'hypoxémie sur le fonctionnement cérébral

Le tissu nerveux est particulièrement sensible à l'hypoxémie. En effet la consommation cérébrale d'oxygène représente 20 p. 100 de la consommation totale de l'organisme et l'activité cérébrale ne peut se pour suivre lorsqu'existe une anoxémie. Dans les conditions physiologiques normales, le cerveau tire essentiellement son énergie de processus aérobies. L'oxygène consommé sert de façon pratiquement exclusive à la transformation du glucose en CO_2 et H_2O, soit directement, soit par formation intermédiaire d'acide pyruvique. Les quantités d'oxygène qui disparaissent du sang artériel lors de la traversée cérébrale, sont celles qui correspondent à la combustion du glucose disparu (l'utilisation du glucose étant de 5 mg. pour 100 g. par minute, soit 70 mg. environ par minute pour l'ensemble du cerveau).

La consommation d'oxygène par le cerveau, calculée *in vivo* à partir de la mesure du débit sanguin cérébral et de la différence de teneur en O_2 du sang artériel et du sang veineux (de la jugulaire interne) est de 3 à 3,3 ml. pour 100 g. par minute, soit 45 à 50 ml. pour l'ensemble du cerveau. Le métabolisme cérébral n'est cependant pas uniformément réparti; il varie d'un point à l'autre de l'encéphale. De même, il n'est pas identique aux différentes périodes de la vie: ainsi chez un enfant de 5 ans, la consommation d'oxygène est de l'ordre de 5,1 ml. pour 100 g. et par minute. Le métabolisme cérébral subit également avec l'âge des modifications topographiques et devient plus important dans les formations phylogénétiquement récentes (télencéphale). *In vivo,* oxygène et glucose assurent ainsi le métabolisme cérébral; *in vitro,* Quastel, étudiant la respiration tissulaire cérébrale à partir de tranches de cerveau baignant en liquide de Ringer, a constaté que le cerveau est capable d'oxyder d'autres substances que le glucose, ainsi le fructose, le mannose, le galactose, l'acide L glutamique, les acides gras, l'acide lactique; mais ces substances susceptibles d'être utilisées par le cerveau *in vitro* ne protègent pas les fonctions cérébrales comme le glucose *in vivo,* sans doute en raison de la vitesse insuffisante de leur transfert à travers la barrière hémo-cérébrale.

En cas d'hypoxémie, un certain nombre de réactions entrent en jeu afin de préserver au mieux le métabolisme cérébral. Ce sont essentiellement: l'augmentation du débit sanguin cérébral et l'augmentation de "l'extraction" de l'oxygène par le tissu cérébral.

—L'augmentation du débit sanguin cérébral est assurée à tension artérielle constante, par une vaso-dilatation des artérioles. Le tonus des vaisseaux cérébraux obéit à une régulation autonome qui s'effectue en fonction de la pO_2, de la pCO_2 et du pH du sang et des milieux tissulaires ambiants (M. Schneider). Ainsi l'inhalation par l'homme d'oxygène à 10 p. 100 entraine une augmentation de 50 à 70 p. 100 du débit sanguin cérébral si bien qu'il n'y a pas de diminution de la consommation d'oxygène. Cependant cette réponse circulatoire cérébrale compensatrice de l'anoxémie peut être entravée par l'augmentation de la viscosité sanguine, par la polyglobulie, par l'artériosclérose.

—L'augmentation de l'extraction d'oxygène du sang est un second mécanisme compensateur qui ne peut jouer qu'à conditions que la pO_2 reste encore relativement élevée.

Quand ces réactions ne suffisent plus à compenser l'hypoxémie, le cerveau est encore capable d'utiliser une partie du glucose en anaérobiose, d'où l'augmentation rapide de la teneur du cerveau anoxique en acide lactique. En fait, les réserves glycogéniques cérébrales étant faibles (de l'ordre de 1 p. 1000 alors que celles du coeur sont plus élevées, de l'ordre de 6 p. 1000), 3 minutes d'hypoxie les épuisent complétement.

Ainsi la tolérance du cerveau à l'anoxie est-elle très limitée, le télencéphale, les noyaux gris centraux étant plus vite atteints que le tronc cérébral (à l'exception de la substance réticulée).

Il est difficile d'établir de strictes relations entre l'apparition des signes cliniques et le degré des perturbations du métabolisme cellulaire, dûes à l'anoxie; comme le souligne judicieusement M. Schneider, la défaillance de quelques cellules essentielles peut interrompre des "complexes de fonctions". Il y aurait confusion mentale pour une consommation d'oxygène par minute de 2,5 ml. pour 100 g. et coma pour une consommation de 2,3 ml.

Ce qui importe en définitive, c'est le "seuil critique", c'est à dire le moment à partir duquel se produisent des lésions irréversibles d'un nombre croissant de neurones. Ischémie et anoxémie anoxique, qui aboutissent toutes les deux à l'anoxie cellulaire, doivent être cependant distinguées l'une de l'autre, quant au pronostic, parce que dans l'anoxémie anoxique, les fonctions nutritives, et les fonctions tampons du sang sont maintenues un certain temps alors que dans l'ischémie du collapsus cardio-vasculaire et à fortiori de l'arrêt cardiaque, elles sont rapidement ou brusquement interrompues.

De ces données physiopathologiques on doit retenir en matière de thérapeutique, l'obligation:

— d'assurer un apport énergétique sous forme de glucose, toute hypoglycémie aggravant les effets de l'anoxie.

— de maintenir une tension artérielle suffisante par l'injection d'analeptiques (noradrénaline, néosynéphrine), et au besoin par le massage du coeur par voie externe ou interne afin d'assurer le débit sanguin cérébral.

— de rétablir l'oxygénation du sang artériel sans augmenter en même temps l'hypercapnie.

II) Le retentissement de l'hypercapnie et de l'hypocapnie sur le fonctionnement cérébral

L'hypercapnie peut en effet entrainer à elle seule des troubles de la conscience allant jusqu'au coma (narcose au CO_2). Elle provoque une vaso-dilatation cérébrale, le débit sanguin cérébral s'adaptant aux modifications de la $paCO_2$ sans seuil et avec une très grande sensibilité. Dans les états d'anoxie avec hypercapnie, la vaso-dilatation cérébrale est très précoce et très intense. A l'opposé, l'hypocapnie entraine une réduction du débit sanguin cérébral avec vasoconstriction d'où hypoxie ischémique (Davis et Wallace; Holmberg; Lubin et Price; Vinoles; Meyer et Gotoh); mais lorsque la chute de la pO_2 est inférieure à 20 mm. Hg. il se produit une vaso-dilatation. En plus de l'anoxie ischémique, l'hypocapnie et l'alcalose gazeuse modifient la courbe de dissociation de l'oxyhémoglobine (effet Bohr), exagérant l'hypoxie cellulaire. On comprend dans ces conditions la somme de répercussions fâcheuses sur le fonctionnement cérébral de l'association hypoxémie-hypocapnie.

On a beaucoup discuté pour savoir si, dans les états d'hypercapnie, c'était la rétention de CO_2 ou l'acidose qui entravaient le fonctionnement cérébral. Pour Goldensohn; Lubin et Price; Swanson, Stavney et Plum, l'hypercapnie agirait indépendamment du pH sanguin, soit par abaissement du pH intra-cellulaire, soit du fait d'une action spécifique du CO_2. Il est cependant très difficile de dissocier les effets respectifs de l'acidose et de la rétention de CO_2. C'est dans cette idée que nous avons étudié les effets du T.H.A.M. (tri-hydroxy-méthyl-aminométhane) au cours de l'acidose respiratoire aiguë provoquée chez le chien curarisé par la respiration par diffusion d'oxygène pur. Chez 8 chiens, après 30 minutes de respiration par diffusion, le pH a chuté au dessous de 6,95, la $paCO_2$ s'est élevée entre 107 et 345 mm. de Hg., l'HbO_2 s'est maintenue entre 94 et 97 % chez 5 chiens et s'est abaissée modérément chez les 3 autres. L'E.E.G., enregistré à partir d'électrodes enfoncées au contact de l'os, s'est modifié dans 5 cas. A la 31e. minute, on a injecté par voie veineuse una dose de T.H.A.M. comprise entre 0,25 et 0.30 g. par kg.; sous son influence, les autres conditions restant les mêmes, on a observé una baisse de la $paCO_2$, une élévation du CO_2 total plasmatique et du pH; sur les 5 tracés E.E.G. qui étaient modifiés, 3 ont repris leur type initial. Le T.H.A.M. a été essayé dans le traitement des insuffisances respiratoires aiguës avec acidose gazeuse décompensée et dans le traitement des comas barbituriques afin de favoriser l'épuration de l'acide barbiturique grâce à l'alcalose métabolique. Mais son application clinique doit être très prudente chez ces sujets ventilant spantanément car il produit une profonde hypoventilation.

III) L'étude des gaz du sang artériel, et de l'E.E.G. ne renseigne que très imparfaitement sur ce qui se passe au niveau des cellules cérébrales pendant l'anoxie. Durant ces dernières années des recherches plus approfondies ont été menées expérimentalement par Nicols chez le Rat soumis au CO_2 à 24 p. 100 et par J. S. Meyer chez le Singe grâce à la mesure polarographique de la pO_2 tissulaire au niveau du cortex.

En clinique, l'étude de l'encéphalopathie anoxique se base sur les signes cliniques, E.E.G., sur les gaz du sang artériel et sur leur évolution comparée sous l'effet du traitement. L'enregistrement de potentiels profonds recueillis par des électrodes enfoncées dans le cerveau, n'à été tenté par M. Jouvet que dans la circonstance exceptionnelle du "coma dépassé".

Etude clinique et électroencéphalographique

Nous n'envisagerons que les 2 éventualités suivantes:

—l'encéphalopathie respiratoire des bronchopneumopathies chroniques, parce qu'elle représente un problème très fréquent.

— la syncope cardiaque traitée par massage du coeur, parce qu'elle constitue l'accident anoxique majeur.

L'ENCEPHALOPATHIE RESPIRATOIRE DES BRONCHOPNEUMOPATHIES CHRONIQUES

I) Symptomatologie

Elle survient soit brusquement à l'occasion d'une poussée aiguë de décompensation respiratoire provoquée par une surinfection pulmonaire par exemple, soit progressivement au fur et à mesure de l'aggravation de la broncho-pneumopathie chronique.

1) Les signes neurologiques.

Ils ont été étudiés en particulier par Comroe (1950), Westlake (1956), Chiche (1956), Austen, Carmichael et Adams (1957), Conn (1957). La céphalée est fréquente, précédant souvent les autres signes; elle est diffuse, maxima au réveil. L'attention peut être attirée par des troubles de l'humeur, les malades sont souvent euphoriques ou irascibles, agités ou somnolents avec inversion de leur rythme nycthéméral; il n'est pas rare d'observer un état confuso-onirique. Les troubles de la conscience peuvent aller de la simple obnubilation au coma le plus profond. Celui-ci peut être déclenché par une thérapeutique inappropriée comme l'oxygénothérapie intensive ou l'administration de médications dépressives (morphine, barbituriques). Les réflexes tendineux peuvent être abolis de façon symétrique. Les mouvements anormaux sont fréquents; le "flapping tremor" ou "astérixie" est presque constant; des myoclonies sont de constatation banale; par contre les crises d'épilepsie nous ont paru rares.

2) Les signes ophtalmologiques.

Les modifications du fond d'oeil se caractérisent par la cyanose rétinienne, l'hyperhémie papillaire, la dilatation des veines qui deviennent tortueuses. L'oedème papillaire par contre est relativement rare; nous en avons relevé 37 cas dans la littérature, en plus de 4 cas personnels observés parmi 133 insuffisants respiratoires chroniques.

3) Les signes E.E.G.

L'enregistrement E.E.G. se heurte souvent à des difficultés techniques du fait de l'importance de la gêne respiratoire et de l'agitation du malade. Les tracés présentent des anomalies d'importance variable:

— dysrythmie mineure faite d'ondes théta diffuses;

— bouffées d'ondes delta monomorphes, plus ou moins rythmiques, de haut voltage, hypersynchrones, à projection symétrique fronto-temporale, survenant sur un rythme de base ralenti avec ou sans réactivité;

— désorganisation complête du tracé avec delta diffus sans réactivité.

Ces différents types peuvent s'observer successivement; il faut souligner que le degré des altérations n'est pas strictement proportionnel à l'état de la conscience et au degré des troubles de l'hématose au moment de l'enregistrement. *Nous n'avons jamais trouvé de grapho-éléments qui pourraient être considérés comme spécifiques de l'encéphalopathie respiratoire.*

4) Signes biologiques.

Au point de vue biologique, il existe constamment une anoxémie et une hypercapnie plus ou moins compensées par l'élévation des bicarbonates. Des modifications de la kaliémie, de la glycémie, une hyperammoniémie ont été signalées.

II) Diagnostic

Le diagnostic de l'encéphalopathie respiratoire est en règle facile en raison du con-

texte clinique. Mais il est des cas où l'origine respiratoire d'un coma est moins évidente quand on ignore les antécédents; la cyanose peut aussi bien s'expliquer par des troubles respiratoires secondaires à un coma répondant à une autre étiologie. On peut, surtout s'il existe un oedème papillaire, être orienté vers une affection neuro-chirurgicale (Conn). A l'opposé, une affection encéphalitique peut se compliquer de coma respiratoire qui, s'il n'est pas reconnu et traité, peut être rattaché à tort à la seule évolution de la maladie neurologique.

III) Traitement

Le traitement exige une surveillance médicale permanente par des personnels médical et infirmier qualifiés et des moyens

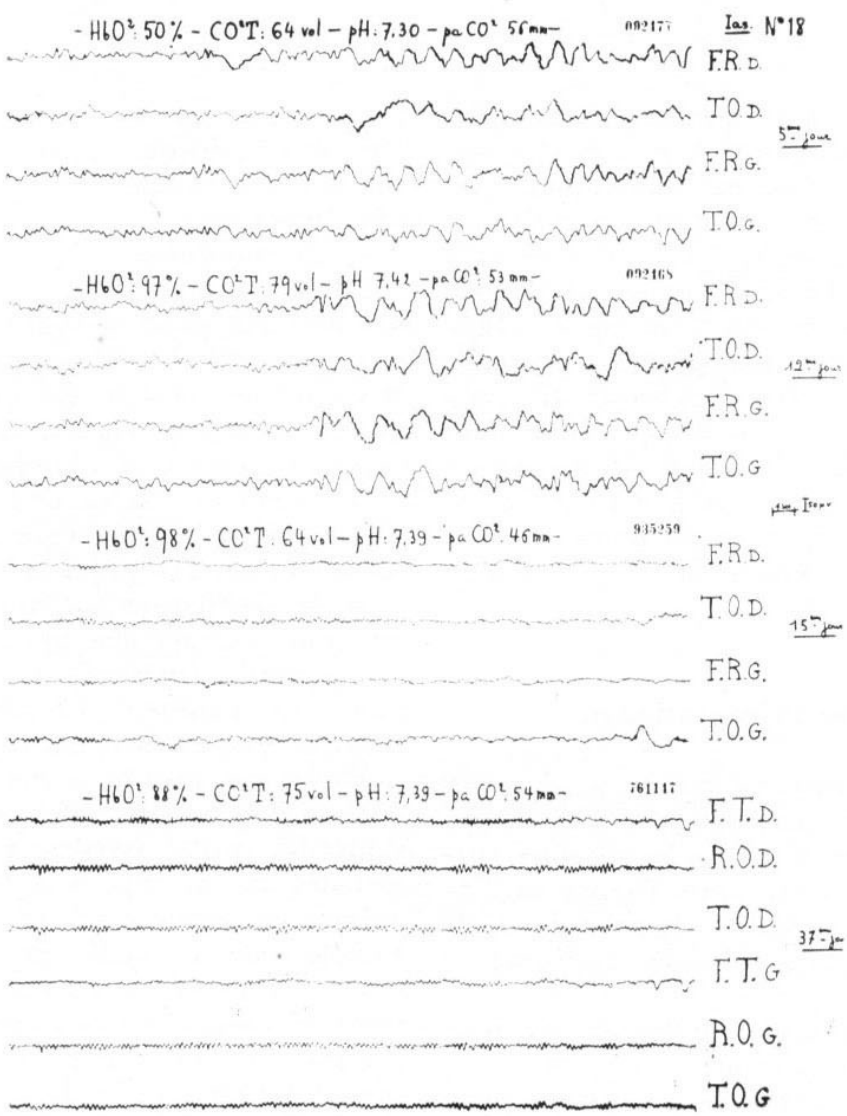

Fig. 1. — *Hospitalisé le 9-XII-57. Du II au 20-XII en poumon d'acier, reçoit 3 gr. de Diamox et 175 mgr. d'ACTH en perfusion intra-veineuse. Trachéotomie le 20-XII-57; respiration artificielle par appareil d'Engström jusqu'au 30-XII-57.*
Corrélations EEG-gaz du sang avant et après trachéotomie: le 14-XII (5ème jour) EEG type III avant trachéotomie; le 21-XII (11ème jour) EEG type III et le 24-XII (15ème jour) EEG type I, le malade respire artificiellement par appareil d'Engström. Le 15-I-58 (37ème jour) EEG type normal, respiration spontanée.

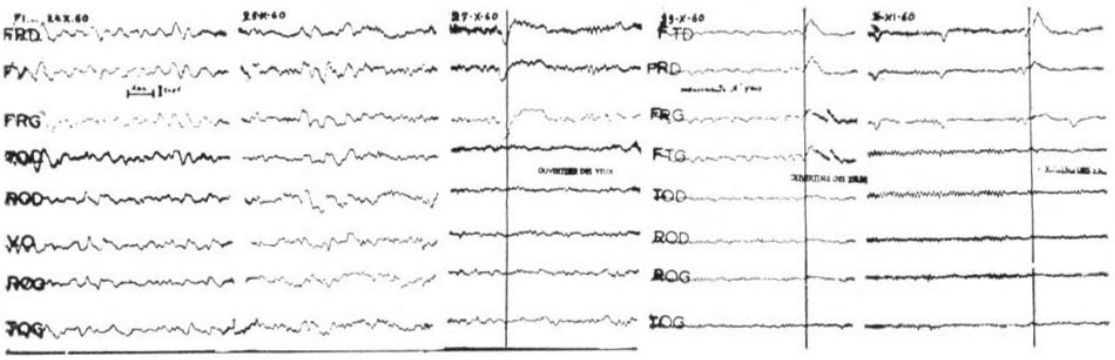

Fig. 2.

techniques importants. L'évolution doit être suivie sur la confrontation répétée des signes cliniques, E.E.G. et biologiques, car, comme nous l'avons montré en 1959 au Colloque de Marseille, les renseignements fournis par un mode d'examen isolé sont insuffisants et trompeurs, les signes cliniques, électriques et biologiques n'évoluant pas toujours de façon synchrone. Ils peuvent, sous l'effet de la thérapeutique, être aggravés ou améliorés, *indépendamment les uns des autres.* Ainsi l'oxygénothérapie intensive peut corriger en quelques minutes l'anoxémie mais risque d'entrainer une narcose au CO_2.

A) Les indications thérapeutiques.

Le but du traitement est de corriger au mieux et au plus vite l'hypoxémie et l'hypercapnie, et par là même, les troubles nerveux et circulatoires, (insuffisance cardiaque droite, polyglobulie). Il faut donc rétablir une ventilation alvéolaire efficace et pour cela:

— libérer les voies respiratoires de tout encombrement important;

— augmenter le volume d'air courant par la respiration artificielle ou par la stimulation des centres respiratoires;

— assurer une oxygénation *correcte mais qui ne soit pas suivie d'une augmentation de l'hypercapnie,* puisque l'on sait bien à l'heure actuelle qu'une oxygénothérapie excessive chez une emphysèmateux respirant spontanément, supprime l'effet stimulant de l'hypoxémie, sur les chémorécepteurs aortiques et carotidiens, accroit ainsi l'hypoventilation et provoque une hypercapnie aiguë sans hypoxémie.

1) *La respiration artificielle* (fig. 1).

Elle est indiquée chez les malades en coma profond, dont la ventilation spontanée et superficielle ne balaye que l'espace mort, et quand les résultats des examens biologiques sont très perturbés. La temporisation expose à l'apnéee et à la syncope cardiaque.

Au poumon d'acier dont l'efficacité est limitée par le blocage de la cage thoracique, habituel chez l'emphysémateux, il faut préférer la ventilation par voie endotrachéale en ayant recours aux appareils à contrôle volumétrique (appareil d'Engström, ou appareil de l'Hôpital Claude Bernard). La trachéotomie est nécessaire car l'intubation trachéale ne peut être maintenue plus de 24 heures sous peine de provoquer des lésions des cordes vocales; or chez tous les malades de ce type que nous avons été obligés de soumettre à la respiration artificielle, celle-ci a dû être maintenue, au minimum, pendant plusieurs jours. La ventilation-minute, la fréquence respiratoire, la pression de l'air inhalé, la dépression expiratoire seront réglées de telle façon que la respiration artificielle soit bien supportée du point de vue circulatoire; toute reventilation un peu trop brusque risque, en effet, d'être suivie d'une chute de la tension artérielle qu'il faudra corriger au plus vite par la perfusion d'analeptiques (noradrénaline, néosynéphrine). De même nous avons très souvent constaté une hypokalié-

F... HOMME DE 49 ANS. HOSPITALISATION LE 24 OCTOBRE 1960

Date	Traitement	Signes neurologiques	Signes Ophtalmologiques	Signes cardio-vasculaires	Hemo-gramme	HbO2	pH	CO2t	paCO2	Hema-tocrite	L.C.R.	Electroence-phalogramme
24/10/60	Diamox (6c) Oxygène Antibiot.	Obnubilation Flapping tremor Myoclonies	Oedeme papillaire + + Hyperhemie papillaire + + Dilatation veineuse + + + Hemorragies maculaires T.A.R.: 35	pouls: 120; T.A.: II/6 hepatomegalie + + R.H.J.; Harzer ECG: surcharge droite	H.: 6M3 L. 9.800 P.N.: 65 %	55°/°	7,3	78 vol	68 mm	64°/°		TYPE III
25/10/60	Diamox (6c) Oxygène Antibiot.	Conscient. Flapping tremor	Oedeme papillaire + + Hyperhemie papillaire + + Dilatation veineuse +	signes cardio-vasculaires identiques; P.V.: 16cm		79°/°	7,29	75 vol	67 mm	60°/°	P: 30 cm Al: 0,50 1 elem.	TYPE III
26/10/60	Diamox (6c) Oxygène Antibiot.	Conscient aucun signe neurologique	Oedeme papillaire ± Hyperhemie papillaire + + Dilatation veineuse ±	signes cardio-vasculaires identiques								
27/10/60	Diamox (6c) Oxygène Antibiot.	Conscient aucun signe neurologique	Hyperhemie papillaire + Dilatation veineuse ±	signes cardio-vasculaires identiques; P.V.: 10 cm		85°/°	7,27	57 vol	54 mm			TYPE II
29/10/60	Oxygène	R.A.S.	Hyperhemie papillaire + Dilatation veineuse — T.A.R.: 30	pouls: 100; T.A.: II/6 hepatomegalie +	H. 4M9 L.: 11.000 P.N.: 76 °/°	87,5°/°	7,33	71 vol	59 mm	62°/°		TYPE I
30/10/60	Diamox (3c) Oxygène	R.A.S.	Idem	Idem							P: 13 cm	
31/10/60	Diamox (4c) Oxygène	R.A.S.	Idem	Idem		91,5°/°	7,30	61 vol	54 mm	63°/°		Normal

mie succédant à l'hyperkaliémie de la période asphyxique. Quand l'adaptation du malade à l'appareil n'est pas parfaite, il sera quelquefois nécessaire d'administrer de petites doses de morphine pour déprimer les centres respiratoires. La durée de la respiration artificielle sera fonction de l'évolution des signes cliniques; elle ne sera jamais interrompue brusquement mais par palliers.

2) *Le traitement médicamenteux* (fig. 2; tableau N° 1).

Dans la grande majorité des cas, il est suffisant et comprend:

— l'oxygénation prudente par sonde nasale, de préférence au masque en général incommode, en faisant passer 2 à 3 litres par minute d'oxygène à 50 p. 100 en azote.

— des analeptiques respiratoires: caféïne, sous forme de café ou en injections; micorène en perfusion intraveineuse dilué dans du sérum glucosé isotonique.

— de l'acétazolamide *(diamox)* per os ou par injection intraveineuse; il accroit la diurèse et par conséquent soulage la circulation, fait éliminer des bicarbonates et stimule la respiration.

— des corticoïdes, sous forme de deltacortisone, et des antibiotiques, à large spectre (pénicilline, streptomycine).

— en cas d'encombrement respiratoire modéré, il sera parfois nécessaire de faire une broncho-aspiration par bronchoscopie, ce qui peut éviter une trachéotomie.

— un apport glucidique par voie veineuse sous forme de sérum glucosé, du potassium, éventuellement des analeptiques vasculaires compléteront cette thérapeutique.

B) Les résultats du traitement et l'évolution.

1) Dans certains cas traités trop tardivement, l'évolution fatale ne peut être évitée; il en a été ainsi par exemple chez une récente malade emphysémateuse qui présenta une encéphalopathie respiratoire après broncho-pneumopathie aiguë compliquée de pneumothorax; une syncope cardiaque survint quelques minutes après trachéotomie et mise en train de la respiration artificielle; un massage du coeur par voie externe pendant 35 minutes permit la reprise des mouvements cardiaques spontanés, sans qu'il se soit produit de mydriase; mais la malade comateuse devait décéder 12 heures plus tard.

2) Dans la majorité des cas, le pronostic est fonction de trois ordres de facteurs:

— la durée et l'intensité des troubles de l'hématose avant tout traitement;

— les facteurs circulatoires associés: à hypoxémies égales, l'anoxie cérébrale est d'autant plus marquée que s'y ajoute une ischémie, soit générale du fait de la chute du débit cérébral, soit locale du fait de l'artériosclérose;

— l'état antérieur du cerveau, notamment la survenue d'épisodes anoxiques cérébraux.

a) *l'évolution peut être très satisfaisante.* Chez les malades soumis à la respiration artificielle, la regression des troubles de la conscience et des signes neurologiques est plus rapide que chez les malades soumis au seul traitement médicamenteux. Les mouvements anormaux, flapping tremor en particulier, sont souvent encore constatés chez des malades redevenus conscients. La cyanose rétinienne disparait en même temps que l'hypoxémie se corrige; la dilatation des veines rétiniennes regresse à peu près parallélement à la chute de la $paCO_2$; l'oedème papillaire est plus long à s'estomper; par contre l'hyperhémie papillaire et les tortuosités des veines persistent et semblent être des signes permanents d'insuffisance respiratoire chronique évoluant depuis plusieurs annés. L'hypertension du liquide céphalo-rachidien regresse parallèlement à la correction des signes biologiques.

Quant à l'E.E.G., il nous est apparu que sa correction demande un délai de plusieurs jours, quels que soient le type de traitement et la rapidité de correction de l'hypoxémie et de l'hypercapnie. Le retour du rythme *alpha* ou sa meilleure modulation est le premier critère d'amélioration, accompagné ou suivi de l'appauvrissement du tracé en ondes delta; celles-ci redeviennent rythmiques; lorsque les ondes delta sont en voie de disparition, elles ont toujours tendance à se localiser sur les dérivations antérieures; le dernier stade pathologique consiste en une intrication en proportion variable de rythmes alpha et d'ondes théta avec ou sans

réactivité. Ces dernières modifications persistent encore chez des malades qui n'ont plus aucun signe neurologique. La réapparition d'une bonne réaction d'arrêt visuel précède la normalisation complète du tracé. Celui-ci reste normal même dans les cas où les gaz du sang artériel se perturbent à nouveau après l'arrêt du traitement: ceci est surtout net chez les malades qui ont été soumis à la respiration artificielle et ceci

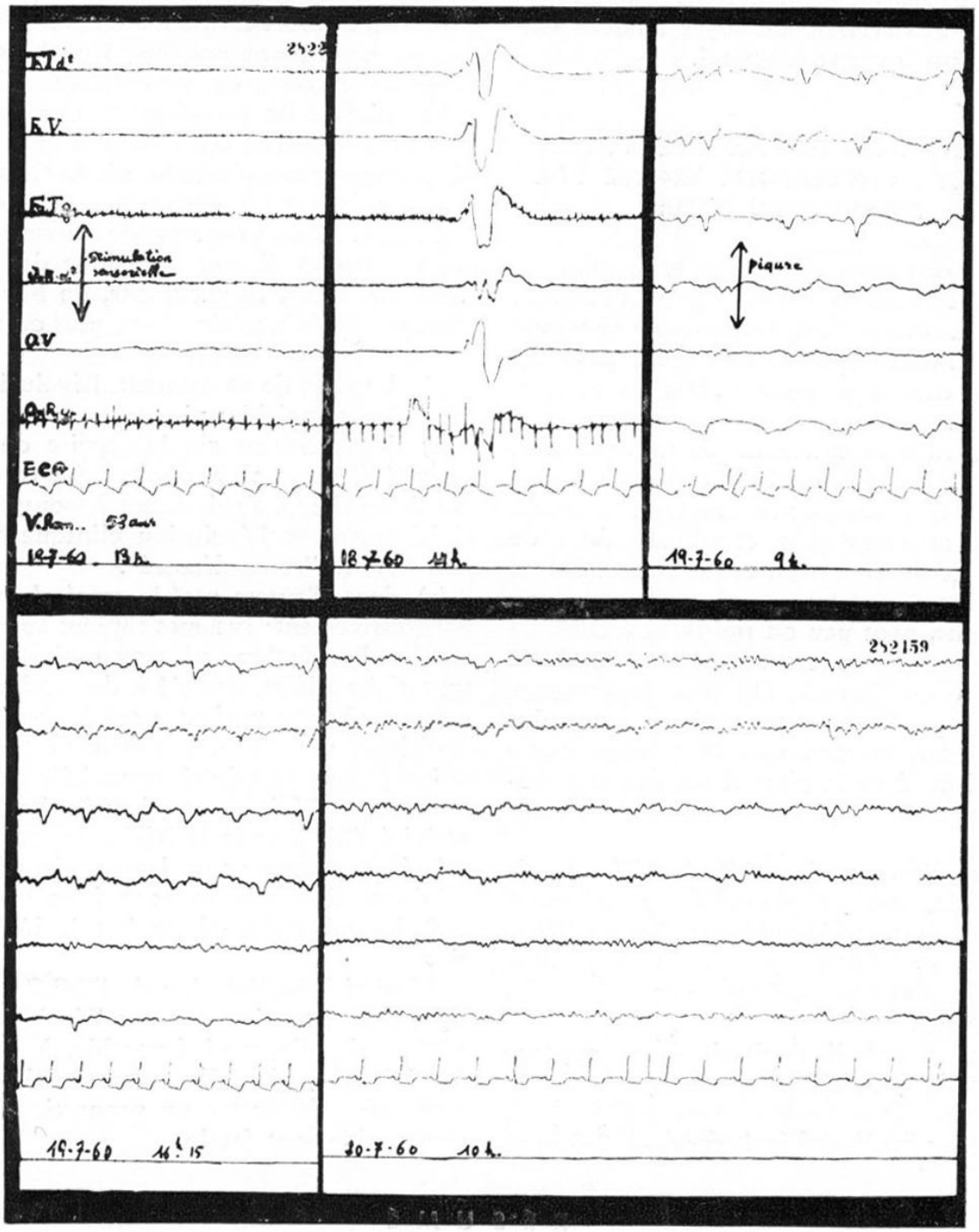

Fig. 3. — *Coma barbiturique. Syncope cardiaque le 18.7.60 vers 12 h. Massage cardiaque par voie endo-thoracique. Le premier E.E.G. a été enregistré dans l'heure qui a suivi le massage cardiaque.*

suggère une adaptation du système nerveux aux conditions biologiques crées par la maladie pulmonaire.

b) *L'évolution des signes neurologiques n'est pas toujours aussi favorable,* alors même que le traitement a entrainé une amélioration de l'hématose. Les malades restent plus ou moins obnubilés. D'autres fois, après disparition des anomalies diffuses de l'E.E.G., s'extériorise un foyer d'ondes lentes, le plus souvent temporal.

L'ENCEPHALOPATHIE ANOXIQUE APRES SYNCOPE CIRCULATOIRE TRAITEE PAR MASSAGE DU COEUR

Alors que dans les asphyxies les plus sévères le traitement, s'il est rapide et efficace, arrive à éviter très souvent la survenue d'une encéphalopathie anoxique, dans les grands désordres circulatoires et surtout après arrêt cardiaque traité par massage il n'en est malheureusement pas souvent ainsi. Quand la mort immediate a pu être évitée, on voit trop souvent se développer des tableaux neurologiques complexes faits de signes de décortication et de décérébration. Assez rares sont les cas où la récupération est bonne, avec peu ou pas de séquelles. La responsabilité de ces séquelles incombe à la durée de l'anoxie. On peut espérer que le massage du coeur par voie externe, plus rapidement exécuté que le massage endothoracique dans la plupart des cas, augmentera le pourcentage des ressuscitations réussies.

Afin d'essayer de saisir un élément de pronostic, nous avons étudié, sur des tracés enregistrés quotidiennement, les modifications de l'E.E.G. chez 8 malades qui avaient subi un massage cardiaque par voie endothoracique.

Dans 3 cas, il s'agissait d'une syncope anesthésique et le massage avait été fait sur la table d'intervention; dans les 5 autres cas l'arrêt cardiaque etait survenu, 2 fois au cours d'une poliomyélite aiguë, une fois au cours d'une myasthénie, une fois au cours d'un coma barbiturique, une fois pendant une rachianesthésie. Le temps qui s'est écoulé entre l'arrêt du coeur et le début du massage a varié de 2 à 5 minutes; la reprise des mouvements spontanés s'est effectuée de 2 à 15 minutes après le début du massage. La respiration artificielle était déjà pratiquée avant l'arrêt cardiaque ou a été établie le plus rapidement possible. L'évolution de l'E.E.G. dans ces cas a été variable: (fig. 3)

1) pendant les premières heures qui suivent le massage, le tracé est habituellement plat, sans aucune réactivité cérébrale appréciable malgré les amplifications maxima.

2) puis dans une seconde phase, apparaissent sur ce silence électrique des paroxysmes pointus, bisynchrones, de haut voltage, généralisés, périodiques, plus ou moins rapprochés les uns des autres;

3) A partir de ce moment, l'évolution de l'E.E.G. est variable:

a) dans certains cas la reprise de cette activité électrique anormale a été très temporaire, l'E.E.G. s'aplatissant à nouveau définitivement et l'évolution clinique se faisant vers le "coma dépassé".

b) dans d'autres cas, le tracé s'améliore progressivement: rythmes rapides au vertex; reprise d'un rythme plus ou moins lent de type théta diffus, associé à des ondes delta polymorphes se projetant sur les territoires antérieurs et centraux, et souvent coupé de pointes, sans réactivité sensorielle pendant longtemps. Mais cette récupération d'une activité E.E.G. assez satisfaisante, qui pourrait farre augurer une bonne récupération clinique, s'est très souvent faite chez des malades qui sont restés en état de décérébration.

Ainsi si l'amélioration de l'E.E.G. ne signifie pas nécessairement que l'évolution clinique soit elle aussi favorable, à l'opposé on doit se garder, devant un tracé apparament plat, de porter un pronostic d'évolution rapidement fatale.

RÉSUMÉ

Dans ce travail les auteurs reprennent les constatations les plus intéressantes sur l'encéphalopathie anoxique, après avoir observé et traité des malades en détresse respiratoire

et circulatoire au Centre de Réanimation Neuro-Respiratoire à l'Hôpital Claude Bernard à Paris.

Dans les maladies respiratoires et circulatoires l'anoxie tissulaire est consécutive à l'anoxémie ou à l'hypoxémie hypoxiques et de type stagnant, ces deux types d'hypoxémie étant souvent intriqués. Dans la plupart des cas l'hypoxémie n'est pas seule en jeu; il s'y associe des troubles de l'équilibre acide-base: acidose ou alcalose respiratoire, acidose fixe; l'intrication de ces facteurs, tous nocifs pour le système nerveux, rend difficile l'appréciation de leur responsabilité réciproque dans la survenue de l'encéphalopathie anoxique en pathologie.

Il est difficile d'établir de strictes relations entre l'apparition des signes cliniques et le dégré des perturbations du metabolisme cellulaire du cerveau. On a prouvé que la tolérance du cerveau à l'anoxie est très limitée, le télencephale, les noyaux gris centraux étant plus vite atteints que le tronc cérébral (à l'exception de la substance réticulée); ce qui importe en définitive, c'est le "seuil critique", c'est à dire le moment à partir duquel se produisent des lésions irréversibles d'un nombre croissant de neurones.

Les auteurs envisagent les 2 eventualités suivantes:

1) L'encéphalopathie respiratoire des bronchopneumopathies chroniques, parce qu'elle représente un problème tres fréquent, et
2) La syncope cardiaque traitée par massage du coeur, parce qu'elle constitue l'accident anoxique majeur.

Dans le premier cas on analyse soigneusement les aspects les plus divers (symptomatologie, diagnostic, traitement et ses résultats) qui prouvent que même dans les asphyxies les plus sévères un traitement rapide et efficace arrive à éviter très souvent la survenue d'une encéphalopathie anoxique.

Dans les cas de grands désordres circulatoires, par contre, et surtout après arrêt cardiaque traité par massage, survient la mort immédiate ou, dans le meilleur des cas on voit se développer des tableaux neurologiques complexes de décortication et de décérébration. Assez rares sont les cas où la récupération est bonne, avec peu ou pas de séquelles.

RESUMEN

En este trabajo los autores presentan las comprobaciones más interesantes sobre la encefalopatía anóxica, después de haber observado y tratado pacientes con afecciones respiratorias y circulatorias en el Centro de Reanimación Neurorespiratoria del Hospital Claude Bernard de París.

En las afecciones respiratorias y circulatorias la anoxia de los tejidos es consecutiva a la anoxemia hipóxica, o a la hipoxemia hipóxica y de éstasis; estos dos tipos de hipoxemia a menudo se dan juntos. En la mayoría de los casos no está únicamente la hipoxemia en juego, sino que es acompañada por alteraciones del equilibrio ácido-base: acidosis o alcalosis respiratoria, acidosis fija; todos estos factores, nocivos para el sistema nervioso, actúan en forma intrincada, haciendo difícil la apreciación de su responsabilidad recíproca al sobrevenir la encefalopatía anóxica.

Es sumamente difícil establecer relaciones estrictas entre la aparición de los síntomas clínicos y el grado de las perturbaciones del metabolismo celular del cerebro. Se ha probado que la tolerancia del cerebro a la anoxia es muy limitada, y que antes que el tronco cerebral (a excepción de la sustancia reticular) los primeros atacados son el telencéfalo y los núcleos grises centrales; lo que importa en definitiva es el "umbral crítico", es decir el momento a partir del cual se producen lesiones irreversibles en un número creciente de neuronas.

Los autores consideran las siguientes eventualidades:

1) La encefalopatía respiratoria de las bronconeumopatías crónicas, ya que éstas constituyen un problema muy frecuente, y
2) el síncope cardíaco tratado con masaje del corazón, ya que constituye el accidente anóxico más grave.

En el primero de los casos son cuidadosamente analizados los aspectos más diversos (sintomatología, diagnóstico, tratamiento y resultados del mismo) y se comprueba que aún en los casos más severos de asfixia un tratamiento rápido y eficaz llega a menudo a evitar la aparición de la encefalopatía anóxica.

En los casos de desórdenes circulatorios graves, por el contrario, y en particular luego de un paro cardíaco, sobreviene la muerte o, en el mejor de los casos, se observa el desarrollo de complejos cuadros neurológicos de decortización y descerebración. Rara vez se obtiene una buena recuperación con pocos o ningún vestigio.

SUMMARY

This paper contains the most interesting statements on anoxic encephalopathy, after having observed and treated patients with respiratory and circulatory deficiencies at the Neurorespiratory Reanimation Center of the Claude Bernard Hospital in Paris.

In respiratory and circulatory diseases anoxia of the tissues comes as a sequel of hypoxic anoxemia, or otherwise is provoked by hypoxic hypoxemia or of stagnant type, both types hypoxemia often appearing intricated. Most of the times hypoxemia is accompanied by alterations of the acid-base equilibrium: respiratory acidosis or alkalosis fixed acidoxis; the intrication of these factors, all of them noxious for the nervous system, makes it difficult to establish their reciprocal responsability in the pathology of anoxic encephalopathy.

It is difficult to establish strict relations between the appearance of clinical symptoms and the degree of perturbation of the brain's cellular metabolism. It has been proved that the brain evidences little tolerance towards anoxia, and that before the brain stem (with exception of the reticular substance) the telencephalon and the central grey nuclei are first of all affected. What is most important is to determine the "critical threshold", that is to say, the moment since which irreversible lesions appear on an increasing number of neurons.

The authors consider the following possibilities:

1) Respiratory encephalopathy in chronical broncopneumopathies, these being a frequently observed problem, and
2) Heart syncope treated with massage, this being the most serious anoxic accident.

The first possibility is carefully studied in its various aspects (symptomatology, diagnosis, treatment and its results) and it is proved that even in most severe asphyxies a quick and efficient treatment may often avoid the appearance of anoxic encephalopathy.

In those cases of serious circulatory perturbations, on the contrary, and particularly after heart arrest, treated with massage, immediate death overcomes; if not, complex neurologic pictures of decortication and decerebration are observed. Hardly ever it is possible to obtain a good recovery with few or no sequels at all.

ZUSAMMENFASSUNG

In dieser Arbeit nehmen die Autoren die interessantesten Feststellungen ueber die anoxische Encephalopathie wieder auf, nachdem sie Kranke mit Atem - und Kreislaufstoerungen im Centre de Réanimation Neuro-Respiratoire des Hospitals Claude Bernard in Paris beobachtet und behandelt haben.

Bei den respiratorischen und Kreislauf erkrankungen ist die Gewebsanoxie Folge der Anoxaemie oder der hypoxischen Hypoxaemie und der Stauungshypoxaemie, wobei beide Arten der Hypoxaemie oft vermischt sind. Bei den meisten Faellen handelt es sich nicht nur um die Hypoxaemie allein; sie kommt zusammen mit Stoerungen des Saeure - Basengleichwichtes, der respiratorischen Azidosis oder Alkalosis, oder der fixierten Azidosis vor. Die Vermischung dieser Faktoren, die alle fuer das Nervensystem schaedlich sind, macht es schwer, die Verantwortung eines jeden Faktors beim Eintreten der anoxischen Encephalopathie in der Pathologie abzuschaetzen.

Est ist schwer strikte Beziehungen zwischen dem Auftreten der klinischen Zeichen und dem Grade der Stoerungen im zellulaeren Stoffwechsel des Gehirns aufzustellen. Man hat nachgewiesen, dass die Toleranz des Gehirns gegenueber der Anoxie sehr beschraenkt ist, wobei das Telencephalon und die Grauen Zentralkerne schneller betroffen werden als der Hirnstamm (mit Ausnahme der Sustantia Reticularis); was im Grunde entscheidend ist, ist die "kritische Schwelle", d.h. der Augenblick von dem an irreversible Laesionen von einer immer groesser werdenden Menge von Neuronen erzeugt werden.

Die Autoren ziehen zwei Moeglichkeiten in Betracht:

1) Die Respiratorische Encephalopathie der chronischen Bronchopneumopathien, weil sie ein sehr haeufiges Problem darstellen, und
2) den mit Herzmassage behandelten Herzstillstand, weil er einen schweren anoxischen Krankheitszustand darstellt.

Im ersten Falle wird man sorgfalltig die verschiedensten Aspekte, wie Symptome, Diagnostik, Behandlung und ihre Ergebnisse, analysieren und feststellen, dass selbst bei den schwersten Faellen von Asphyxie eine schnelle und wirkungsvolle Behandlung sehr oft das Eintreten einer anoxischen Encephalopathie vermeiden kann.

In den Faellen schwerster Kreislaufstoerungen, dagegen, vor allem beim Herzstillstand, der mit Herzmassage behandelt ist, tritt der sofortige Tod ein oder, im besten Falle, entwickeln sich komplizierte neurologische Krankheitsbilder der Entrindung und der Dezerebration. Die Faelle von guter Wiederherstellung mit kleinen oder ueberhaupt keinen Foalgeerscheinungen sind sehr selten.

Effects of Anoxia on Brain Function and Behaviour

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Of all the organs in the body none is more dependent on an adequate supply of oxygen than the brain. The fact that 12 per cent of the cardiac output goes to the cerebral circulation and 20 per cent of the basal oxygen consumption of the body is accounted for by the brain provides evidence for this. Nor can this circulation be arrested with impunity. Though isolated cases of more prolonged interruption of the cerebral circulation with recovery have been reported, cessation of blood-flow to the brain for a period of two minutes usually causes irrecoverable damage to the cerebral neurones. The need to ensure an adequate cerebral blood-flow under all circumstances is therefore abundantly clear.

There are many situations in which the oxygen supply to the brain may be imperilled, but the majority of these involve a fall in blood pressure and in blood-flow. Thus any condition which produces a reduction of cardiac output may lead to a fall in cerebral blood-flow, if the compensatory mechanisms of the circulation are inadequate. Common among these conditions is cardiac infarction. Every clinician must have encountered the case in which a cardiac infarction presented as a stroke. Some of these cases are due to emboli, but many are due to the fall in cardiac output which may accompany infarction and so leading to cerebral ischaemia. Stokes-Adams attacks are another well recognised cause of generalized cerebral ischaemia, and attacks of cardiac dysrhythmia such as paroxysmal tachycardia, and atrial fibrillation provide further examples. All these conditions are commonly encountered in clinical practice.

A fall in blood volume may also lead ultimately to a reduction of the cerebral blood-flow. Massive haemorrhage from the gastro-intestinal tract, or as a result of trauma, may produce syncope and signs of focal cerebral damage. Severe dehydration with the consequent reduction of blood-volume may produce the same effects though more slowly. Alternatively, the volume of the blood may not be reduced in absolute terms, but may be reduced relatively when generalized dilatation of arterioles or capillaries occurs. The effects on the cerebral circulation are the same.

A failure of venous return to the heart may also impair the cerebral blood-flow if the cardiac output falls sufficiently. This may occur when circulatory reflexes do not function properly. Obstruction to the pulmonary circulation has the same effect.

Even though cerebral blood-flow is maintained, cerebral anoxia may still occur if the oxygen carrying capacity of the blood is reduced. Carbon monoxide poisoning is probably the commonest example of this group. Chronic anaemia of severe degree may also be responsible for cerebral anoxia. Thus the optic atrophy, mental confusion

and dementia which may be associated with Addisonian pernicious anaemia may well be due to the anoxia rather than to any specific metabolic defect.

Oxygenation of the brain also requires that the carrying capacity of the cerebral blood vessels be adequate. Stenosis or occlusion of a main supplying vessel such as one of the carotid or vertebral arteries may cause localized ischaemia if the collateral circulation is inadequate. If more than one vessel is involved as is common (Hutchinson and Yates, 1957), the ischaemia may be more generalized. Diffuse obliterative disease of the smaller vessels has the same result. The dementia, which may be associated with cerebral arteriosclerosis, is an example of this.

Finally, cerebral anoxia may occur when the demands of the brain are increased above normal levels. This happens in infective and pyrexial illnesses, and delirium which is associated with illness of this type may be a manifestation of this.

There is therefore a variety of ways in which the oxygen supply to the brain may be impaired. These have been enumerated at some length because many of them are encountered in every day clinical practice. Not infrequently so much attention is devoted to the primary condition, that the disastrous complication of cerebral anoxia is overlooked or receives inadequate treatment. The effects of prolonged cerebral anoxia are so grave that it must always receive immediate attention whenever it develops, or is threatened. Failure to do this may result in the primary cause being successfully dealt with, but the patient left in a state of permanent dementia or even as a chronic decorticate or decerebrate preparation.

The pathological changes associated with cerebral anoxia are, as might be expected, diffuse, being found in the cerebral cortex, Ammon's horn, cerebellar cortex, globus pallidus and corpus strictum (Meyer 1956). Certain structures are, however, more vulnerable than others, the Purkinje cells of the cerebellum, the globus pallidus and the myelin sheaths being among these. Whether this increased vulnerability depends upon the specific needs of these nervous structures or upon anatomical determinants of their blood-supply is uncertain. In the case of the Purkinje cells it would seem likely, because of their diffuse distribution throughout the cerebellum, to be the former. In the case of the globus pallidus, on the other hand, it would seem likely to be the latter. However, it is well recognized that the globus pallidus is specially liable to damage by carbon monoxide poisoning (Denny-Brown 1960) hence biochemical factors may also be at work here.

There is one factor that is of great importance in the genesis of the lesions of cerebral anoxia and that is the development of cerebral oedema. The chain of events seems to be that initial hypoxia causes toxic damage to the walls of the capillaries. Protein escapes through the damaged walls drawing fluid after it. This accumulation of fluid in the extra-cellular space has a two-fold effect. It acts as a physical barrier to the diffusion of oxygen, thereby aggravating the anoxia; it also causes pressure on veins and arteries so further impeding the blood supply. A vicious spiral is thereby started. This situation is not peculiar to cerebral anoxia, but is also seen in closed head injuries. Though the oedema is diffuse it may be responsible for lesions in specific sites (Lindenberg 1955). Thus arteries or veins which lie against the sharp edges of the dural folds such as the falx or tentorium, may be more readily compressed when there is a generalised rise of intracranial pressure. The lesions in Ammon's horn are almost certainly due to herniation of the temporal lobe through the tentorial opening. From the clinical point of view the important thing is that the cerebral oedema can be relieved.

The clinical picture produced by cerebral anoxia varies greatly according to the cause of the anoxia and the circumstances in which it develops. Catastrophic events such as a massive gastro-intestinal bleeding may obscure the picture. The patient loses consciousness, as might be expected, and it is only when he fails to recover consciousness after blood volume and pressure have been restored that the possibility of cerebral

damage is appreciated. Alternatively, the patient may recover consciousness fairly quickly, but behave in an abnormal fashion. His memory for events leading up to his sudden illness may be impaired or lost, or there may be more profound memory loss covering events of most of the patient's life. Vision may be impaired with a hemianopia or scotomata or there may be complete blindness. This may not be appreciated at first as the patient may not make any spontaneous complaint about it; it is only when his unusual behaviour leads to further investigation that the fact of his loss of vision is established. Similarly, careful neurological examination often reveals evidence of extensive cerebral damage.

It is, however, more helpful to recognize threatened cerebral anoxia than to become aware of it after it has occurred. Of first importance is the need to be aware of the circumstances which may give rise to it. Thus in any condition in which a fall of blood-pressure or blood volume is likely to occur, or respiratory function becomes impaired, the physician must be on the alert for signs of cerebral anoxia.

One of the first signs of cerebral anoxia is anxiety and restlessness. The patient becomes querulous and seeks constant attention and reassurance. He finds it difficult to sleep and if he gets off to sleep frequently wakens in an anxious frame of mind. Headache, blurred vision and disturbed behaviour may also occur, and sweating may be a permanent feature. It is important that the significance of these signs be appreciated. If it is thought that the patient is merely neurotic and he is given a sedative to calm him, the anoxia may be aggravated and his condition worsened. It is oxygen he needs, not sedatives.

The earliest signs of cerebral anoxia may be observed experimentally when the blood pressure is deliberately lowered by the use of hypotensive drugs while the patient is lying on a tilting table. The first sign is usually a slight deepening of respiration. The patient's concentration becomes impaired; he yawns, seems sleepy and cannot recite a phrase he has been taught, or the days of the week, with the same alacrity he could a moment or two earlier. His reaction time becomes prolonged, and if the cerebral blood pressure is not restored by lowering the head the patient develops syncope. Neurological examination at the pre-syncopal stage may reveal Babinski's plantar responses.

The more chronic picture of mild cerebral anoxia is seen in patients with severe anaemia or chronic respiratory insufficiency, though in the latter instance the picture may be complicated by retention of carbon dioxide. The patient is chronically fatigued. He finds concentration difficult and work involving higher cerebral functions is less well performed than formerly. He becomes irritable and judgement is frequently impaired. Everything is an effort, and so the patient loses initiative and shows increasing reluctance to undertake any task.

The clinical syndromes associated with the cerebral damage which may follow anoxia have been described by several authors including Allison (1956), Richardson, Chambers and Heywood (1959) and Bedford (1955, 1956, 1957). The last author has given detailed accounts of the conditions encountered. He was mainly concerned with the effects of cerebral anoxia in old people, but the same effects may be seen in young persons also. The difference between the young and the old is only that of the ease with which overt evidence of damage is produced. Bedford groups the clinical pictures into two, those which are apparently fully reversible and those which are permanent. Among the former he lists confusional states, especially at night or following the administration of drugs, sleep disturbances, periodic breathing, "organic neurasthenia" and transient focal signs. Among the more permanent syndromes are again "organic neurasthenia", dementia of varying degrees, and focal cerebral damage.

The dementia may be of all degrees of severity. It may be so mild as to pass unnoticed except by those who knew the patient intimately prior to the anoxic incident. Sometimes even close associates may notice nothing, but the patient himself is

aware that his memory is not so good as formerly, that he finds it harder to concentrate or that he cannot grasp the point of a problem with the same ease he did before. The dementia may also be more profound up to the stage at which the patient is completely helpless, and may be truly said to be decorticate.

Among the types of focal cerebral damage that are encountered are epilepsy, hemiplegia and impairment of vision, this last being usually of cortical type and easily labelled as hysterical by the inexperienced. Signs of damage to the basal ganglia may occur as, for example, in the Parkinsonian picture which frequently follows carbon monoxide poisoning. Athetosis may also supervene. Signs of damage to the parietal lobe may be found with spatial disorientation, agnosia and apraxia.

Prognosis after an anoxic event is difficult. The most important guide is the duration of the loss of consciousness. Coma of more than 24 hours duration usually leads to death, or if the patient survives, he is likely to achieve only a vegetative existence (Allison 1956). Deficits of neurological function due to focal cerebral damage do not, on the whole, recover so well as do the diffuse disorders of cerebral function (Richardson et al. 1959), though this difference may be to some extent spurious due to the fact that diffuse deficits are less obvious than focal disturbances unless specific formal testing is done.

The most important thing in the treatment of cerebral anoxia is to prevent it. This may seem a truism, yet it is surprising how prevalent are threats to the oxygenation of the brain. It is also chastening to realize how many of these threats are iatrogenic in origin. The hazards of anaesthesia especially dental gas administered in the upright posture, have been well studied by Bourne (1957). The striking feature of his study was the frequency of evidence of cerebral anoxia after dental gas anaesthesia, and of failure to realize the significance of the symptoms. He recounts one instance in which recovery of consciousness was delayed, yet the patient was hauled into a taxi and sent home in a confused condition.

The administration of sedatives and respiratory depressants to the elderly, or to patients whose cerebral oxygenation is already threatened by some pre-existing condition, is another potent cause of cerebral anoxia, and the incautions use of hypotensive drugs must also be added to the list. Nursing a patient in the sitting position, irrespective of the state of the cerebral circulation, is a further example. Failure to anticipate respiratory insufficiency in those conditions, such as poliomyelitis, polyneuritis, myasthenia gravis, poisoning and head-injury in which it is likely to occur may also permit an unnecessary period of cerebral anoxia. All these hazards could be avoided by greater awareness of the possibility of cerebral anoxia and the seriousness of its consequences.

When cerebral anoxia does occur the remedy must be directed to its cause. As a fall in cerebral blood-flow is a common factor to many causes, lowering the patient's head will immediately bring some relief and will provide the necessary time to institute more complex measures such as the administration of pressor agents or the restoration of blood-volume. The administration of oxygen can be of value, but the automatic institution of oxygen therapy is often accompanied by a failure to appreciate and remedy the primary reason for the cerebral anoxia. Moreover, it is of no use to give oxygen, unless it will reach the brain. Measures must be taken to ensure that there is a good airway, and if spontaneous respiration has ceased, or is inadequate, artificial respiration must be given. If the oxygen which crosses the alveolar membrane is to reach the brain cerebral blood pressure and flow must also be adequate, hence, as already mentioned, the patient's head must, if necessary, be lowered.

The second line of treatment is directed to the alleviation of cerebral oedema should that develop. This is especially likely to be the cause of deterioration after an initial period of improvement. Blurring of the optic discs and a high pressure in the cerebrospinal fluid are confirmatory signs. Many authors have stressed the value of

dehydration therapy (Sadove, Wyant and Gittelson 1956, Argent and Cope 1956, Cope 1960). The use of intravenous urea in sucrose, which has largely replaced the older methods of intravenous sucrose or glucose or enemata of magnesium sulphate, is of great efficacy in these circumstances.

Cerebral anoxia is by no means a rarity, especially in old people. It occurs as a complication of many illnesses, and also unfortunately of many therapeutic procedures. Its presence is often overlooked until serious and irrevocable damage has been done. It behoves every physician to avoid causing cerebral anoxia, to be alert to its development as a complication of other illness and to be quick to remedy it when it does occur.

SUMMARY

The brain is extremely dependent on an adequate oxygen supply utilizing no less than 20 per cent of the basic oxygen consumption of the body. Any situation which leads to a fall in blood pressure, blood-flow, blood volume, ventilation, the oxygen carrying capacity of the blood, or to narrowing of the cerebral blood vessels may lead to cerebral anoxia. In clinical terms this means that cardiac infarction or arrythmia, massive haemorrhage, dehydration, poisoning especially by CO_2, anaemia and cerebral arteriosclerosis may give rise to cerebral anoxia. It is important to remember that a threatened anoxia may become a reality as a result of the administration of an anaesthetic or a sedative especially to the elderly.

The earliest signs of anoxia are anxiety, restlessness, insomnia, headache and disturbed behaviour. As these symptoms may be readily labelled as neurotic, it is important that the physician bear in mind the possibility of cerebral anoxia as their cause. Following severe acute anoxia the patient is often unconscious for a time. He may recover consciousness and then show signs of cerebral damage such as confusion, dementia, visual field defects, hemiplegia and Babinski responses. Later he may develop epilepsy or Parkinsonism, and in some cases a relapse into further coma occurs. These delayed signs may well be due to the development of cerebral oedema which is a frequent and serious complication of anoxia.

The first point in therapy is to try and anticipate and prevent the development of anoxia in those situations in which it is liable to occur. Especially, care should be taken not to precipitate anoxia by the unwise use of sedatives, or anaesthesia, or by allowing dehydration or blood loss to progress to a serious degree. The need to administer oxygen is obvious, but the need to ensure it reaches the brain is less obvious. This means maintaining a good air-way, giving artificial respiration when necessary and keeping up the blood pressure. Lowering the head is a simple and easy way to improve cerebral blood flow. Cerebral oedema can be combatted by the intravenous administration of urea in sucrose.

RESUMEN

El cerebro depende en alto grado de un adecuado suministro de oxígeno, utilizando no menos que el 20% del oxígeno consumido por el cuerpo humano. Cualquier circunstancia que conduzca a un descenso en la presión arterial, en el flujo sanguíneo, en el volumen de la sangre, en la ventilación, en la capacidad de transportar oxígeno de la sangre o al estrechamiento de los vasos sanguíneos del cerebro puede acarrear la anoxia cerebral. En términos clínicos esto significa que tanto el infarto cardíaco, o una arritmia, como una hemorragia masiva, la deshidratación, el envenenamiento espe-

cialmente por CO_2, la anemia o la arterioesclerosis cerebral pueden provocar la anoxia cerebral. Es importante recordar que un estado potencial de anoxia puede llegar a transformarse en anoxia real como resultado de la administración de anestésicos o sedantes, principalmente en personas de edad.

Los primeros síntomas de la anoxia son: ansiedad, desasosiego, insomnio, dolores de cabeza y un comportamiento alterado. Dado que estos síntomas pueden sugerir en un primer momento el rótulo de neurosis, es importante que el médico tenga en cuenta la posibilidad de la anoxia cerebral como causa de los mismos. Luego de una anoxia aguda el paciente permanece a menudo inconsciente por un tiempo. Puede recobrar el conocimiento y presentar síntomas de lesión cerebral tales como confusión, demencia, deficiencias en el campo visual, hemiplejia y signo de Babinski. Más tarde puede desarrollar epilepsia o parkinsonismo, y en algunos casos retornar al estado de coma. Estos signos demorados pueden deberse al desarrollo de un edema cerebral, que constituye una complicación seria y frecuente de la anoxia.

Lo más importante en la terapia es tratar, anticipar y evitar el desarrollo de la anoxia en aquellas circunstancias que la pueden provocar. Debe evitarse muy especialmente precipitar la anoxia por medio del uso imprudente de sedantes o anestesia, o permitiendo que la deshidratación o la pérdida de sangre llegue a un grado que revista seriedad. Es obvia la necesidad de administrar oxígeno, aunque es menos obvia la seguridad de que el oxígeno llegue al cerebro. Esto implica mantener libre la vía respiratoria, suministrando respiración artificial si fuera necesario y manteniendo alta la presión arterial. Inclinar la cabeza del paciente hacia abajo es un método sencillo de mejorar el flujo sanguíneo. El edema cerebral puede ser combatido por medio de la administración intravenosa de urea en sucrosa.

RÉSUMÉ

Le cerveau dépend particulièrement d'une bonne ressource d'oxygène, car il utilise pas moins de 20 pour cent de la consommation basique d'oxygène du corps. Toute situation menant à une chute dans la pression arterielle, le flux sanguin, le volume sanguin, la ventilation ou dans la capacité de transporter de l'oxygène du sang, ou entrainant l'étrecissement des vaisseaux sanguins, peut provoquer une anoxie cérébrale. En termes cliniques ceci signifie que l'infarctus ou l'arrythmie cardiaque, l'hémorrhagie massive, la déhydratation, l'empoisonnement particulièrement par CO_2, l'anémie et l'artériosclérose cérébrale peuvent faire surgir l'anoxie cérébrale. Il est très important à signaler qu'une menace d'anoxie peut devenir une réalité comme résultat de l'administration d'une anesthésie ou d'un sédatif, chez les personnes âgées en particulier.

Les premiers signes d'anoxie sont anxiété, agitation, insomnie, mal de tête et comportement irregulier. Etant donné que ces symptômes peuvent faire penser à une nevrose, il est important pour le medecin de considérer l'anoxie comme leur cause probable. Après une anoxie grave et dangereuse le patient reste souvent inconscient un certain temps. Il peut se faire qu'il recupère ses sens et qu'il présente des signes de dommage cérébral tels que la confusion, la folie, des irregularités au champs visuel, l'hémiplégie et des signes de Babinski. Plus tard le malade peut developper de l'épilepsie ou du Parkinsonism, et quelquefois il survient une rechute au coma. Ces signes retardés peuvent très bien se devoir au developpement d'un oedème cérébral, qui constitue une complication fréquente et grave du coma.

Le plus important dans la thérapeutique est d'essayer d'anticiper et d'éviter le développement de l'anoxie dans ces situations où il existe la probabilité qu'elle survienne. Surtout il faut faire attention de ne pas précipiter l'anoxie que ce soit par l'usage imprudent de sédatifs ou d'anesthésies ou

bien en permettant la déhydratation ou la perte de sang à un degré tres poussé. Bien que le besoin d'administrer de l'oxygène soit clair, il n'est pas si sûr que celui-ci atteigne le cerveau. Ceci peut être obtenu en maintenant une bonne voie d'aérage, par moyen de la respiration artificielle s'il est nécessaire et en maintenant la pression artérielle haute. Baisser la tête du patient est une méthode simple et facile pour améliorer le courant sanguin du cerveau. L'oedème cerebral peut être combattu par moyen de l'administration intraveineuse d'urée en sucrose.

ZUSAMMENFASSUNG

Das Gehirn ist ausserordentlich von einer guten Sauerstoffversorgung abhaengig, und verbraucht nicht weniger als 20 % des Sauerstoffgrundverbrauches des Organismus. Jeder Zustand der zu einer Minderung des Blutdrucks, des Blutzuflusses, des Blutvolumens, der Ventilierung, der Sauerstoffoerderungsfaehigkeit des Blutes oder die Verengerung der Gehirngefaesse kann zur zerebralen Anoxie fuehren. Im klinischen Sinne bedeutet dies, dass ein Herzinfarkt oder eine Arrhytmie, eine massive Haemorrhagie, die Deshydratierung, eine Vergiftung, vor allem mit CO_2, die Anaemie und die zerebrale Arteriosklerose zu einer zerebralen Anoxie fuehren koennen. Es ist wichtig zu wissen, dass eine drohende Anoxie Realitaet werden kann infolge der Verabreichung eines Anaesthetikums oder eines Sedativums, besonders bei aelteren Leuten.

Die ersten Zeichen der Anoxie sind Angst, Ruhelosigkeit, Schlaflosigkeit und Stoerungen im Benehmen. Da diese Symptome leicht als neurotisch angesehen werden koennen, ist es wichtig, dass der Arzt die Moeglichkeit einer zerebralen Anoxie als ihre Ursache im Sinne behaelt. Infolge einer schweren akuten Anoxie ist der Patient oft eine zeitlang bewusstlos. Er kann das Bewusstsein wieder gewinnen und dann Zeichen einer zerebralen Laesion wie Verwirrung, Demenz, Defekte im Gesichtsfeld, Hemiplegie und Babinski aufweisen. Spaeter mag sich eine Epilepsie oder ein Parkinsonismus entwickeln, und in einigen Faellen wiederholt sich das Koma. Diese spaeten Zeichen koennen auch durch ein Hirnoedem, welches eine haeufige und ernste Komplikation der Anoxie ist, bedingt sein.

Zunaechst muss man bei der Behandlung versuchen, zuvorzukommen und zu verhindern, dass eine Anoxie in den krankhaften Zustaenden, in denen sie vorzukommen pflegt, sich entwickelt. Besonders soll man sich hueten, eine Anoxie durch den unvorsichtigen Gebrauch von Sedativa und Aneasthetica, oder indem man Dehidrierung und Blutverlusst zu einen schweren Grade entwickeln laesst herauf zu beschwoeren. Die notwendigkeit der Verabreichung von Sauerstoff ist klar, aber die Notwendigkeit, dass er auch sicher das Gehirn erreicht ist weniger klar. Das bedeutet, die Lutwege freizuhalten, indem man zur kuenstlichen Atmung schreitet, wenn es notwendig ist und auch den Blutdruck auf einem adequaten Niveau zu halten. Das Niederhalten des Kopfes ist eine einfache und leichte Art, den Blutkreislauf im Gehirn zu bessern. Das Hirnoedem kann durch die endovenoese Injektion von Harnstoff in Sucrose bekaempft werden.

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Electroencephalography in Cerebral Anoxia

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Since cerebral anoxia, affects primarily the cortex of the brain, one would expect to find accompanying changes in the electroencephalogram. In the early stage, cerebral anoxia would affect the physiological reactions of the cortex directly incident to circulatory fluctuations. Later the dysrhythmia results from actual pathological changes. Because the electroencephalogram records the electrical activity of the cerebral cortex, this modality gives rather specific information as to whether the changes be physiological or pathological, borderline or profound.

In the early or physiological stage, a generalized disturbance (due to angiospasms) produces a physiological block of the brain cells. This stage, however, is often reversible, leading to clinical improvement of the patient's state. This improvement is predictable by the early occurrence of reversible changes in the electroencephalogram. In the pathological state, the EEG changes are more profound and are not completely reversible. If the pathological state persists more than a week, there is danger that the abnormal EEG changes may be more or less permanent and consistent with the more or less persistent psychiatric and neurological findings.

This subject will be presented in seven sections: 1) cerebral anoxia as exemplified by the effects of carbon monoxide, 2) general characteristics of brain waves in cerebral anoxia, 3) EEG changes from carbon dioxide, 4) acute cerebral hypoxia, 5) EEG changes in clinical cerebral anoxia, 6) the EEG as an indication for the use of procaine therapy in asphyxia, and 7) cerebral anoxia after cardiac standstill.

Cerebral Anoxia as Exemplified by the Effects of Carbon Monoxide

Cerebral anoxia due to carbon monoxide appears to be the cause of accidental deaths more often than any other form of anoxia other than that associated with birth. This observation is based in part upon study of a series of cases in the Los Angeles County Hospital. In this locality, this type of cerebral anoxia is usually due to fumes from unventilated gas heaters in closed rooms, especially during the cold weather. Natural gas is ordinarily used. It does not contain carbon monoxide *per se* and can cause death by asphyxiation only when at least 60 percent of the air in the room is replaced by the gas. By contrast, concentrations of more than 0.06 percent of carbon monoxide are detrimental, and a concentration of 0.02 percent is rapidly fatal. Since at least 15 percent oxygen is necessary to support combustion of gas and as low as 8 percent oxygen in the respired air is sufficient to maintain life, depletion of oxygen in room air is not of paramount importance in fatal asphyxiation when the heater continues burning, although it can be a contributing factor.

Carbon monoxide has no specific toxic action aside from its affinity for hemoglobin, which is 200 to 400 times stronger than oxygen. In the early stages, symptoms of acute or chronic poisoning are not very specific. Headache, dullness, fatigue, nausea, abdominal cramps, and even vomiting and diarrhea do not, in themselves, rouse suspicion of poisoning by carbon monoxide. In acute poisoning, an extraordinary muscle weakness immediately precedes coma. At this critical stage sudden realization of the danger comes too late, for the victim finds it impossible to open a door or raise a window. He may manage to get out of bed, only to collapse on the floor.

As in asphyxia of other causes, there are three results from exposure: 1) death, 2) full recovery, and 3) partial recovery with residual ill effects. However, with the rescue of victims from a near-fatality, survival with more or less serious residual effects is not only possible but increasingly common.

In the crisis of survival, the state of the circulatory condition is the critical factor. As in cardiac resuscitation, support of respiration is the only possible approach under ordinary conditions with the chances of survival further increased by the administration of pure oxygen.

The critical level of carbon monoxide intoxication is about fifty percent of saturation. A level above seventy-five percent is immediately fatal. A correct correlation between clinical effects and laboratory determinations can be made only when one remembers that carbon monoxide is rapidly eliminated from the blood of survivors, about half of it being eliminated in the first hour. All traces may be gone in as short a time as four hours from the time of rescue.

The survivors of a serious exposure to carbon monoxide show various residual effects. Pneumonitis, disorders of the heart, gangrene of the extremities, and pressure sores are reported. Here we are concerned with the residuals in the nervous system. Courville summarizes the pathologic findings in the central nervous system (depending on age of lesions) as follows: hyperemia of the brain, hemorrhages of various sizes in the globus pallidus or the subcortical white matter, gross softening of the globus pallidus incident to acute necrosis, calcium-iron deposits in the small blood vessels, cyst formation, and vascular scars. The clinical syndromes in survivors include protracted coma, psychosis, parkinsonism, polyneuritis, blindness, and asthenic states. Painful spasms of skeletal muscles are especially characteristic during the early phase of recovery.

General Characteristics of Brain Waves in Cerebral Anoxia

The brain wave characteristics in cerebral anoxia are dependent upon the metabolic and pathological changes of the brain cells. The metabolic changes of the brain cells are not easily defined because the *normal brain wave* itself is constantly shifting from one phase to another. The wave form also varies from one region of the brain to another in normal states. The brain wave itself is the result of the synchronized actions of cortical nerve cells. This synchronization is maximal in relaxation and sleep during which time the amplitude is high. On the other hand during alertness and mental activity, the brain cells are active only in a random fashion as they perform their special functions. The synchronization decreases and the electroencephalogram becomes relatively low in amplitude or relatively flat.

The most characteristic rhythm of the brain during relaxation with the eyes closed is the *alpha rhythm* (Fig. 1, alpha rhythm and Fig. 2 B) whose frequency is from 8 to 12 cycles per second in adults. This activity is usually maximal in the posterior half of the head. As a rule the alpha rhythm is symmetrical in frequency and amplitude in the right and left hemispheres. However, this alpha rhythm is not always stable especially from birth to twenty years of age. The alpha rhythm is constantly undergoing maturation changes in frequency, stability and amplitude. Recognition of this unstable period of maturity of the brain activity is absolutely necessary for the interpretation

of the EEG. Instability is present not only in children at all times, but also in about twenty percent of the normal adult population as residuals of maturity (immature brain rhythms in adult).

Alpha rhythm activity is suppressed or inhibited when the eyes are open. In the anterior half of the head the waves occur in a faster rhythm (from 13 to 30 cycles per second) which is called beta activity and has no diagnostic importance. The normality of brain function is demonstrated, therefore, by beta activity recorded in the anterior half of the brain and by the characteristic alpha activity recorded in the posterior half of the brain. This is usually uniform in both hemispheres. Thus, the important early sign of cerebral dysfunction is the recording of the asymmetries or changes in the rhythm on one side of the head. An acute destructive lesion in one hemisphere can cause partial or complete suppression of the normal alpha rhythm on the side of the lesion.

Abnormal brain waves are classified according to the wave forms and their distribution over the brain areas (i. e. frontal, parietal, occipital or temporal). The abnormal waves are dependent on the following factors: 1) frequency, 2) voltage, 3) wave forms, and 4) the modification of the wave forms to alerting mental activity, eye opening, hyperventilation, sleep, medication or sensory stimulation. The abnormal waves can occur in one lobe, in the right and left lobes, in one entire hemisphere, or in both hemispheres. Thus, the abnormal waves can be recorded as focal (frontal, temporal etc.); bilateral (bifrontal, bitemporal, etc.); right or left hemisphere, or generalized when recorded from all regions of the brain.

In cerebral anoxia, we are usually concerned with abnormal wave forms, especially delta activity which is recorded from all regions of the cortex (scalp). These *delta waves* (Fig. 1, synchronized delta rhythm; decayed delta; Fig. 2 A; Fig. 3 A and 3 B; and Fig. 4 A) are complex, irregular, slow and varying from one half to three cycles per second. The true pathological delta waves are not altered by metabolic changes, level of consciousness, sensory stimulation, opening and closing the eyes, hyperventilation, sleep and external stimuli. A true delta activity can be produced by a brain tumor, vascular lesion, an infection, and above all, cerebral anoxia.

In contrast to the delta waves, there is another wave form which is called a *theta rhythm,* having a frequency of from 4 to 7 cycles per second (Fig. 1, high voltage alpha-theta rhythm). In comparison to the delta, the theta waves are unstable and intermittent, and can be influenced by metabolic changes and external stimuli. These include the constitutional epileptic discharges which are called the paroxysmal cerebral dysrhythmias, and result from petit mal, grand mal and psychomotor seizures. Being highly organized, these dysrhythmias command specific pathways for their regulation. This is the reverse of the delta waves, which are the manifestations of nonirritable sick brain cells.

EEG Changes from Carbon Dioxide

Characteristic changes are induced by the inhalation of carbon dioxide. It is well known that the accumulation of carbon dioxide produces altered consciousness during which time there is a definite slowing of the brain waves. These waves are very sensitive to changes in the amount of carbon dioxide in the blood, as recalled by Brazier (1943). She concluded that a decrease in the carbon dioxide tension of arterial blood, as a result of hyperventilation, produces high-voltage slow waves. Dr. Brazier believes that the slowing of the brain function is the result of a decrease on carbon dioxide in the blood, and is not due to anoxia secondary to vasoconstriction. She also noted that an increase in the carbon dioxide tension of arterial blood increased the average frequency of brain potentials, and that inhalation of a mixture of 10 percent carbon dioxide in oxygen decreased the voltage of the slow waves produced by hyperventilation and petit mal.

On the other hand, Holmberg (1953) reported that hyperventilation with oxygen produced less slowing in brain waves than

was produced by hyperventilation when the air was maintained with 20 percent concentration of oxygen. He further pointed out that the waves produced by hyperventilation were suppressed when the patient inhaled small quantities of amyl nitrate which brings about a state of vasodilation.

The effect on the electroencephalogram of inadequate cerebral oxygenation, is well known. Hymans *et al* (1937) found that cerebral circulatory arrest in animals, for more than five minutes, suppressed the vital centers of the brain which are necessary for survival. Lennox *et al* (1938) recorded the electroencephalogram of patients who were suffering from syncope or other orthostatic hypotension. They noted that when consciousness was suddenly lost, high-voltage, slow waves appeared after six to eight seconds of circulatory arrest. Shortly thereafter, the slow activity became progressively slower and lost amplitude until the record was completely flattened. The EEG pattern gradually returned to normal after an adequate cerebral blood flow was restored. Iwama (1950) also observed that the electroencephalogram of patients after a marked lack of oxygen, showed small fast activity within sixty seconds, and that this fast activity was replaced by slow large waves in from two to three minutes. Recovery was in reverse order but a completely normal pattern was not restored for a considerable time.

To sum up, the electroencephalogram is a sensitive indicator of the presence of cerebral anoxia. This state will result first in an increase in frequency and amplitude of the waves which are then replaced by pronounced high voltage slow waves, and finally a decrease in frequency ultimately resulting in a complete flat tracing. When cerebral anoxia is only temporary (hypoxia), that is producing only a physiological block such as in anesthesia, the event of the electric activity is in reverse, from flat to delta, to theta, and gradually, to alpha activity. However, when cerebral anoxia produces partial damage tho the neuron, the reverse event is incomplete, usually remaining in the delta phase.

Acute Cerebral Hypoxia

The electroencephalographic changes are the same in animals and in man during hypoxia and anoxia. This aspect of cerebral anoxia and the electroencephalogram was presented in greater detail at the Marseille Colliquim (Gaustat and Meyer, 1961).

In both animals and man, the EEG shows simple slowing appearing in the bifrontal

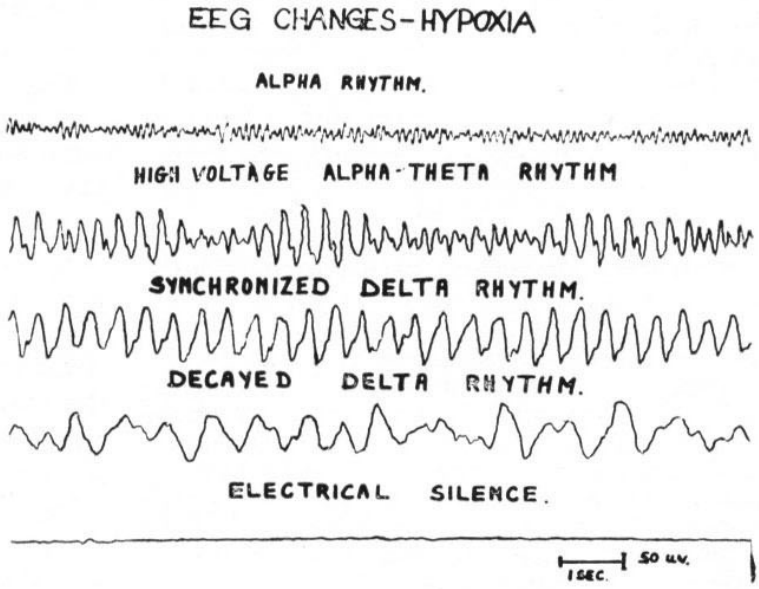

Fig. 1. — *EEG of a 39-year-old male showing characteristic changes of cerebral hypoxia produced by a mixture of gases low in oxygen (general anesthesia for abdominal surgery).*

area, followed by delta waves and then electrical silence. This sequence is reversed from electrical silence to delta waves to simple slowing and finally the restoration of normal alpha rhythm. This occurs whether due to hypoxia from inhalation of nitrogen or a mixture of gases having a low oxygen content, ischemic hypoxia secondary to cardio-inhibitory vasodepressor reflexes, or comprenssion of the carotid artery of the neck or the aorta and superior vena cava during thoracic surgery.

All the above conditions produce similar electroencephalographic changes in which the patient before anesthesia, shows alpha rhythm while after anesthesia becomes increased in amplitude to high alpha-theta rhythm (Fig. 1). At this stage, there is gradual progressive slowing of the rhythm in which synchronous delta rhythm appears (Fig. 1). The entire delta rhythm decays as the hypoxia continues. Irregular, slow delta activity finally disappears and electrical silence (Fig. 1) is recorded. As soon as hypoxia is terminated by discontinuing the mixture of gases, and inhalation of oxygen reestablishes normal circulation, the recovery of the cerebral rhythm takes place by going from electrical silence to decayed delta rhythm, to synchronous delta rhythm, to high alpha-theta rhythm and finally to normal rhythm.

The most characteristic feature therefore of the electroencephalogram in hypoxia is the to and fro fluctuation of the brain activity from alpha to theta, to delta, to electrical silence and back again to full recovery.

EEG Changes in Clinical Cerebral Anoxia*

Experience has shown that there is a fairly consistent correlation between the clinical manifestations and the electroencephalographic findings in cerebral anoxia. The consistency in this pattern is to be noted whether the patient has made a rapid recovery, a moderately slow recovery, or no recovery at all.

In those patients who have experienced only a transitory hypoxia, the electroencephalogram showed normal activity. There was neither slowing nor fast activity recorded. These findings were consistent with the clinical picture when the patient showed no physical changes either mental or neurological. Usually such individuals suffered only temporarily from a clouded consciousness. Beyond this, the three most outstanding patterns are: 1) reversible, 2) nonreversible, and 3) fatal.

Reversible Phase: In those instances when unconsciousness persisted 3 or 4 hours, definite changes in the electrical activity of the brain was recorded. These reversible cases generally first showed an immediate fluctuating delta activity which persisted for a day or so. The delta was then replaced by fluctuating theta waves for a day or two and finally, normal nonfluctuating alpha rhythm replaced completely both delta and theta activity. Thus, in these cases the electrical activity of the brain was completely reversible to normal (usually within a week) denoting that the brain cells had undergone only an impairment of physiological function. In these patients, unconsciousness and reversible positive neurological signs are typical as demonstrated by the following case.

Case 1. A 31 year old male had been in a room with a lighted gas heater for about 18 hours, when he was found unconscious. On admission to the hospital, the right upper and right lower extremities were slightly spastic, while the left lower extremity was somewhat flaccid. All the deep reflexes were markedly hyperactive, the temperature and pulse were slightly elevated, the cranial nerves were intact, and possitive Babinski and Chaddock signs were present bilaterally. Soon after admission an EEG (Fig. 2 A) revealed generalized, somewhat synchronous delta activity. On the second day the patient began to regain conscious-

* The current use of the terms *hypoxia* and *anoxia* seems to follow the suggestions of Wiggers (1941). *Hypoxia* is used to characterize symptoms of oxygen want from which the patient fully recovers. On the other hand, anoxia is reserved for situations in which individuals have experienced severe degrees of oxygen want resulting in signs of permanent damage to the brain with or without fatal issue.

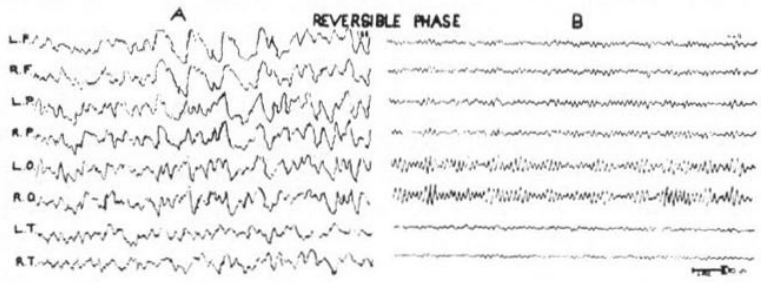

Fig. 2. (Case 1). — *Showing the reversible phase of carbon monoxide asphyxia.*

ness and the EEG showed theta and alpha activity. By the third day he was completely oriented, all the neurological signs had disappeared, and the third brain wave (Fig. 2 B) was normal.

Comment. — During the first 24 hours of hospitalization the patient received only oxygen inhalation. This case demonstrates the value of the electroencephalogram as a prognostic sign, for the second EEG showed improvement which predicted clinical recovery, and was substantiated by the normal EEG on the third day.

Nonreversible Phase: In cases severely affected from the beginning, only slow delta activity is evident. Within a few days some theta and even slight alpha activity tends to return. In most instances, however the EEG record consists of slow, irreversible wave paterns. This is the typical EEG pattern under these circumstances where there has been more or less permanent brain damage. When this activity persists after a week, in a severe anoxia episode with carbon monoxide, the abnormal EEG findings have been found to be consistent with permanent nonreversible clinical and neurological abnormalities. In this group are those who have had long exposure to carbon monoxide resulting in definite brain damage, as demonstrated by the following case.

Case 2. A 46 year old woman attempted suicide by breathing carbon monoxide gas from the exhaust of her automobile in a closed garage. The exact length of exposure was unknown. When found the patient was cyanotic and with shallow breathing. On admission to the hospital the pupils were dilated, there was somewhat generalized spasticity, and the patient was very confused. Babinski and Chaddock signs were positive. The EEG on admission, showed generalized, decayed, and slow delta activity (Fig. 3 A). On the second day, the patient's neurological signs became more pronounced and the spasticity was somewhat increased in all four extremities. On the fifth day the EEG showed no improvement but continued to show delta activity. By the third week the EEG (Fig. 3 B) still showed no improvement and all the EEG showed fluctuation from high to low voltage delta waves.

Comment. — This patient demonstrated a stationary case — survival but without recovery showing all the signs of severe brain damage.

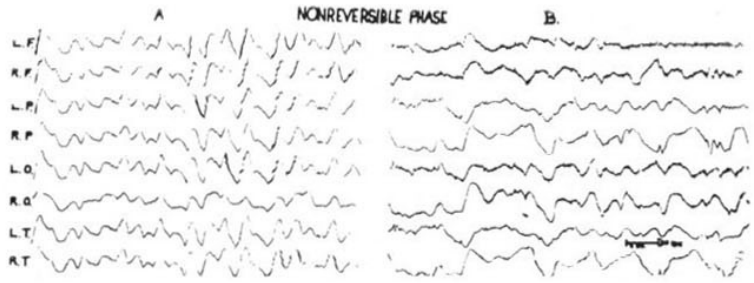

Fig. 3. (Case 2). — *Showing EEG changes of cerebral anoxia in non-reversible phase.*

Fatal Phase: In fatal cases, the EEG revealed very slow delta activity from the beginning which persisted with a gradual reduction in voltage until the tracing became flat before the patient expired. These patients from the stage of admission onward showed no signs of recovery but remained in a profound state of unconsciousness until expiration. As is stated above, accidental death is more commonly due to carbon monoxide than to any other form of extraneous asphyxiation. The following case is an example of the fatal phase.

Case 3. A 53 year old woman who had been contemplating suicide was found in her garage with a rubber hose connecting the exhaust of her car to her mouth. She was rushed to the hospital. On admission, she was profoundly unconscious and extremely cyanotic. The brain wave showed extreme slow decayed delta activity with voltage fluctuation (Fig. 4 A, electrical silence). The patient was placed in a respirator and received supportive treatment. The next day she showed no signs of improvement. The pulse became very weak and the respiration shallow, with generalized circulatory deficiency. The brain wave recorded about two hours before the patient expired, showed no specific activity (Fig. 4 B, electrical silence). The fluctuation disappeared and electrical silence persisted.

Comment. — In this case the EEG showed only the image of the severe effect of carbon monoxide poisoning on the brain.

The EEG as an Indication for the use of Procaine Therapy in Asphyxia

The use of intravenous procaine hydrochloride in the treatment of asphyxia due to carbon monoxide was reported by Olsen, Ray, Marinacci and Amyes (1949) and by Marinacci (1949).

The brain wave, as a specific indicator of the function of the cerebral cortex, can be used as a guide to establish the degree of severity of cerebral anoxia, especially in cases of acute asphyxia. The EEG can be used not only as a guide in treatment by intravenous procaine therapy but also as a means of prognostic evaluation of the degree of brain damage. For instance, patients suffering from acute asphyxia can be divided into three specific categories. Among these three classifications appear those cases which have been exposed to asphyxia, and are in a state of unconsciousness with or without neurological manifestations. In the first group, the brain wave is relatively normal and shows a predominance of alpha waves (Fig. 1, alpha rhythm). Thus the presence of alpha activity denotes excellent prognosis. This normal activity indicates that the brain has received little or no damage and the patient usually recovers in a few hours. No specific treatment is required in these cases and intravenous procaine therapy is not indicated.

In the second group of cases, there is a state of unconsciousness and the brain shows slow, moderate waves (Fig. 1, high voltage alpha and theta rhythm). These findings indicate that only the brain function is slightly impaired and no specific therapy is required as the patients usually recover within 24 hours. The presence of alpha-theta voltage activity denotes a favorable prognosis. However, the patient should be observed and the brain wave repeated until alpha rhythm is fully restored.

The third group of cases also presents a state of unconsciousness. Here the brain

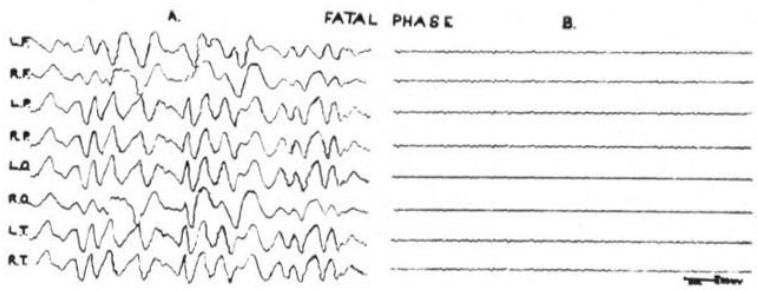

Fig. 4. (Case 3). — *Showing EEG changes of a fatal case of cerebral anoxia.*

Case 4. A 27 year old man had been in a room with a lighted gas heater for as long as 36 hours when found. His skin was pallid and respirations shallow.

On admission, he was semi-stuporous. The right extremities were slightly spastic. The deep reflexes were generally hyperactive with bilateral Babinski signs. About an hour after admission a left hemiparesis was noted. The carboxyhemoglobin saturation was 10 percent.

The evening of admission he was given 0.5 Gm. of procaine hydrochloride intravennously (0.1 percent solution in physiologic saline). On the second day an injection was started at 7:15 p.m. and continued slowly. At 9:00 p.m. he felt well except for pain in his extremities on movement. At 9:25 p.m. he was definitely more responsive and asked for a drink of water. Shortly thereafter he began to comprehend better and answered more readily. He moved about more. The neurological signs improved.

On the third day he sat up in bed by himself and moved all extremities well. On the fourth day he was ambulatory. After two more days the only residual finding was slight weakness of the left foot.

The carbon dioxide combining power of the blood on admission was 40 vol. per cent. The non-protein nitrogen was 60 mg. per 100 cc. The blood Wassermann reaction was negative.

The electroencephalographic findings are shown in the accompanying figure (Fig. 5). A series of three electroencephalograms were taken from Oct. 28 to Nov. 3, 1948. The pre-procaine therapy electroencephalogram showed continous fluctuating high voltage (100 to 300 microvolts) delta activity from all leads. The electroencephalogram the following day (post-procaine therapy) showed improvement. The electroencephalogram of four days later showed normal alpha activity.

Comment: In this case the treatment was limited to oxygen inhalation, intravenous physiologic saline solution procaine hydrochloride.

Cerebral Anoxia After Cardiac Standstill

It is not uncommon for the clinician to be confronted with patients who have experienced short periods of cardiac standstill resulting from various causes. With the majority of these patients, such episodes are so short that the pulse, respiration, and state of consciousness are fully restored within a matter of seconds. The clinician therefore presumes full recovery after restoration of normal blood pressure, pulse and respiration. He has reason to expect an ultimate return of mental alertness without residual paralysis. However, isolated cases have been observed to present subsequent signs of cerebral anoxia even hours after such episodes. It appears that in such a situation the cardiac rhythm and peripheral circulation have been restored completely, while the vasomotor centers appear to have become unstable. This instability eventually produces a delayed vasoconstriction of the cerebral arteries with subsequent ischemic episodes.

The clinician should be on guard for such lapses after apparent immediate recovery from acute episodes of cerebral anoxia. On occasion it has been shown that patients can have a lucid interval following a cardiac standstill, as demonstrated by the following case.

Case 5. A 45 year old female suffered a short cardiac arrest during a simple reduction of dislocation of the right shoulder under sodium pentothal. Within two minutes the patient's blood pressure, heartbeat, and state of consciousness all returned to normal, and the patient was sent home with no apparent ill effects. Twenty-eight hours later however, she became confused, followed by unconsciousness. Becoming rigid, she was rushed by ambulance to the hospital with characteristic clinical signs of cerebral anoxia. On admission, the electroencephalogram showed generalized delta activity with pulsating fluctuation from delta to electrical silence.

Comment: While not common, this mechanism of recurrent symptoms seems to be due to fluctuations of vasomotor activity producing delayed ischemic effects on the

cerebral cortex. This fluctuation of vasomotor activity parallels the pulsating fluctuation of the brain wave. This pulsating fluctuation of the vasomotor centers appears to be an attempt to restore an adequate cortical circulation.

As a rule, therefore, an electroencephalogram should be taken on any patient who has had an acute episode of cerebral anoxia, especially those consequent to cardiac arrest. The patient should be observed util the cerebral activity returns to normal and remains normal for at least 3 to 4 days. In short, the brain wave should be used as a specific indicator of a disordered brain function regardless of the apparent clinical manifestations. One must be continually on guard for the apparently lucid intervals but with fluctuating dysrhythmia which probably indicates an associated vasomotor instability.

In contrast to the brain wave in cerebral hypoxia, where the activity fluctuates to and fro from alpha to electrical silence (Fig. 1) in nonreversible cerebral anoxia, the fluctuation is within a more narrow range, i. e. from synchronous delta, to decayed delta, to electrical silence and with residual dysrhythmia.

SUMMARY

Cerebral anoxia affects primarily the cortex of the brain. One should therefore expect to find accompanying changes in the brain wave pattern.

Incident to circulatory fluctuations in the early stage of ceerbral hypoxia, such changes are the result of abnormal physiological reactions of the cortex. In later stages, abnormal brain waves probably result from actual pathological changes in the cortex. Since the EEG records the electrical activity of the cerebral cortex, this modality gives nearly specific information as to whether the changes are physiological or pathological, or either borderline or profound in nature.

Carbon monoxide is one of the most common causes of cerebral anoxia. The effects of asphyxia due to carbon dioxide tends to produce changes in the brain waves which are usually benign in nature. In acute cerebral hypoxia, a mixture of gases low in oxygen content produce the most characteristic fluctuating changes in the brain wave. These changes can be followed sequentially from normal wave activity to slight slowing to extreme slowing of wave activity and finally to electrical silence. The process is often readily reversed by allowing the inhalation of oxygen. The clinical application of the EEG in acute cerebral anoxia is an indispensible tool in assessing the prognosis or degree of brain damage in acute cerebral anoxia of any type. The treatment of cerebral anoxia by procaine hydrochloride has been found to be of benefit by restoring the normal vasomotor balance of the cerebral arteries and arterioles.

Therefore the brain wave is a specific indicator of the cortical state after acute anoxia. Hence serial electroencephalograms can be used, not only as diagnostic tools, but also as a factor in prognosis and indicator for the use of procaine therapy. Finally the clinician should be on guard for the misleading lucid intervals after cerebral anoxia. At least, the patient should not be considered as fully recovered from acute cerebral anoxia until the patterns of the brain waves show no fluctuation and have returned to normal.

RESUMEN

La anoxia cerebral afecta primariamente la corteza cerebral; por lo tanto debe esperarse que el trazado electroencefalográfico acuse modificaciones.

Esas modificaciones, resultan de las reacciones fisiológicas anormales de la corteza, consecuencia de las fluctuaciones circulatorias durante la primera etapa de hipoxia

cerebral. En las etapas posteriores, las ondas cerebrales anormales son secundarias probablemente a verdaderas alteraciones patológicas corticales.

Al registrar la actividad eléctrica de la corteza cerebral, el EEG prooprciona información específica, permitiendo determinar si los cambios son fisiológicos o patológicos y si son leves o profundos.

El monóxido de carbono es uno de los causantes más comunes de la anoxia cerebral. Los efectos de la asfixia provocada por dióxido de carbono tienden a producir en el EEG modificaciones generalmente de naturaleza benigna. En los casos de hipoxia cerebral aguda, los cambios fluctuantes más característicos son producidos por una mezcla de gases que contiene poco oxígeno. Estas modificaciones pueden ser seguidas progresivamente desde el período de actividad normal, después el enlentecimiento ligero, el enlentecimiento extremo hasta finalmente el silencio eléctrico. A menudo se logra hacer reversible este período con gran rapidez al permitir la inhalación de oxígeno. La aplicación clínica del EEG en los casos de anoxia cerebral aguda resulta indispensable para hacer el diagnóstico o para determinar el grado de la lesión cerebral en cualquier tipo de anoxia cerebral aguda. Se ha comprobado que es beneficioso el empleo del clorhidrato de procaína en el tratamiento de la anoxia cerebral ya que restituye a las arterias y arteriolas su balance vasomotor normal.

Por lo tanto el electroencefalograma constituye un indicador específico del estado de la corteza posterior a la anoxia aguda, y es por esto que los electroencefalogramas seriados pueden ser usados no sólo como instrumentos para el diagnóstico, sino también como factor en el pronóstico y como indicador para el uso de una terapia basada en la procaína. Finalmente el clínico no debe dejarse confundir por los intervalos lúcidos que aparecen a continuación de la anoxia cerebral. Por lo menos no se debe considerar al paciente como totalmente repuesto de una anoxia cerebral aguda hasta que el ritmo electroencefalográfico haya dejado de evidenciar fluctuaciones y vuelto a la normalidad.

RÉSUMÉ

L'anoxie cérébrale affecte primairement l'écorce cérébrale et par conséquent on doit supposer que le schéma electroencéphalographique accusera des modifications.

Ces modifications, qui résultent des réactions physiologiques anormales de l'écorce, influent dans la provocation de fluctuations circulatoires pendant la première étape de l'hypoxie cérébrale. Dans les étapes postérieures, l'irrégularité des ondes electroencéphalographiques résulte probablement des modifications pathologiques réelles de l'écorce. En régistrant l'activité électrique de l'écorce cérébrale, l'EEG fournit une information spécifique, qui permet de déterminer si les changements sont physiologiques ou pathologiques et s'ils sont de nature légère ou profonde.

Le monoxide de carbone est une des causes les plus communes d'anoxie cérébrale. Les effets de l'asphyxie provoquée par le dioxide de carbone ont une tendance à produire des modifications généralement bénignes dans les ondes. Dans les cas d'hypoxie cérébrale aiguë, les fluctuations les plus caractéristiques son produites par un mélange de gaz divers contenant peu d'oxygène. Ces modifications peuvent être suivies à travers toutes les étapes dès la période d'activité normale jusqu'au silence electrique. On parvient parfois à obtenir la reversion de ce procès en permettant l'inhalation d'oxygène. L'aplication clinique de l'EEG dans les cas d'anoxie est indispensable pour faire le diagnostique ou pour déterminer le degré de la lésion dans n'importe quelle espèce d'anoxie. On a prouvé que l'emploi du clorhydrate de procaïne est bénéficieux dans le traitement de l'anoxie cérébrale puisqu'il restitue le bilan vasomoteur normal aux artères et artérioles.

Par conséquent l'onde electroencéphalographique constitue un indicateur spécifique de l'état de l'écorce après l'anoxie ai-

guë. Ceci fait que les électroencéphalogrammes en série puissent être employés non seulement comme instruments pour le diagnostique, mais aussi comme facteur dans la prognose et comme indicateur pour l'emploi d'une thérapie basée dans la procaïne. Finalement, le clinicien doit être en garde contre les déroutants intervalles de lucidité qui suivent l'anoxie cérébrale. Au moins, le patient ne doit pas être considéré comme totalement guéri d'une anoxie cérébrale aiguë jusqu'à ce que les ondes electroencéphalographiques deviennent normales, ne montrant plus de fluctuations.

ZUSAMMENFASSUNG

Die cerebrale Anoxie schaedigt in erster Linie die Hirnrinde. Deshalb sollte man entsprechende Veraenderungen der EEG finden. Bei Kreislauf veraenderungen in den ersten Phasen cerebraler Hypoxie sind solche Veraenderungen das Ergebnis anormaler physiologischer Reaktionen der Rinde. Spaeter sind die anormalen Hirnwellen wahrscheinlich das Ergebnis von schon pathologischen Veraenderungen der Rinde. Da das EEG die elektrische. Aktivitaet der Hirnrinde aufzeichnet, geben diese Veraenderungen eine fast spezifische Information, ob die Veraenderungen physiologisch oder pathologisch, ob es Grenzfaelle oder sehr starke Veraenderungen, sind.

Das Kohlenmonoxyd ist eine der gewoehnlichsten Ursachen cerebraler Anoxie. Die Effekte der Asphyxie durch CO_2 produzieren Veraenderungen im EEG, die gewoehnlich gutartiger Natur sind. Bei der akuten cerebralen Hypoxie produziert eine Mischung von Gasen mit geringem Sauerstoffgehalt hoechst charakteristische fluktierende Veraenderungen im EEG. Die Veraenderungen koennen Schritt fuer Schritt verfolgt werden, von der normalen Aktivitaet bis zur leichten und dan aeussersten Verlangsamung der Zacken und schliesslich des elektrischen Schweigens. Der Prozess wird oft durch die Inhalierung von Sauerstoff leicht aufgehalten. Die klinische Anwendung des EEG bei der akuten cerebralen Anoxie jeglicher Art ist unentbehrlich, um ein Urteil ueber die Prognose oder den Grad cerebraler Laesion haben zu koennen. Die Behandlung der cerebralen Anoxie mit Procain-chlorhydrat hat sich als wohltaetig erwiesen, indem das normale vasomotorische Gleichgewicht der cerebralen Arterien und Arteriolen wieder hergestellt wird.

Deshalb sind die Hirnableitungen spezifische Anzeiger des Zustandes der Hirnrinde nach einer akuten Anoxie. Daher koennen die EEG in Serie nicht nur als diagnostisches Hilfsmittel, sondern auch als Faktor bei Prognose und Indikator fuer die Therapie mit Novocain benutzt werden. Schliesslich sollte der Kliniker auf der Hut vor den irrefuehrenden lichten Intervallen nach cerebraler Anoxie sein. Zumindestens sollte der Patient nicht als vollstaendig von der akuten cerebralen Anoxie wiederhergestellt angesehen werden bevor die Zacken der Hirnalbleitungen keine Fluktuierungen mehr aufweisen und die Normalitaet wiederhergestellt ist.

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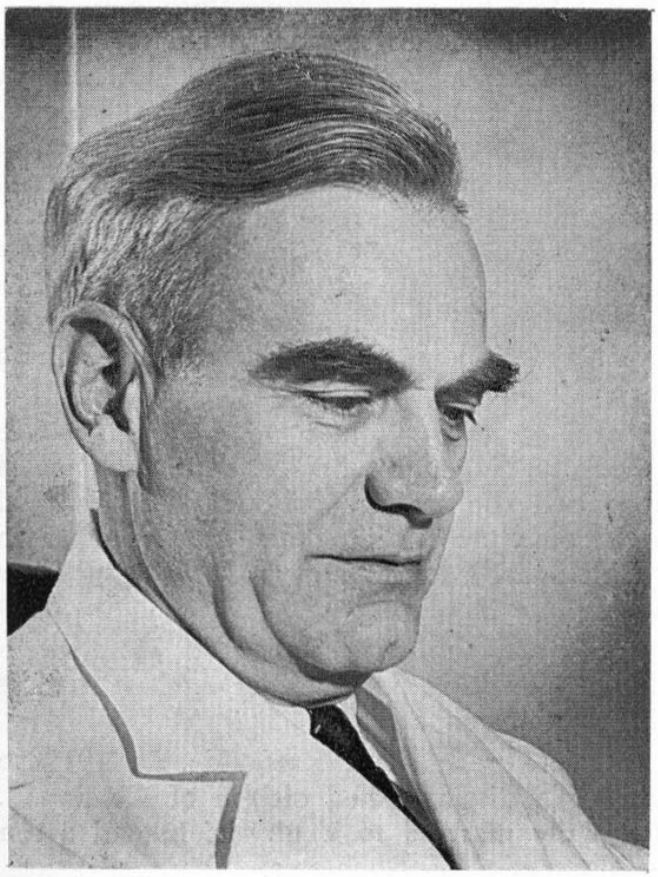
Personality

Dr. CHARLES D. ARING

Dr. Charles D. Aring was born on the family farm in Dent, Ohio, on June 21, 1904, the only surviving child of parents then in their forty-third year, both of whom he had lost before his sixth birthday. His father, whom he never saw, was of German and Flemish descent (Aring, Willkie); his mother, English and French (Dair, Perrine). An attack of poliomyelitis in infancy is likely to have been important in Dr. Aring's intellectual development. He learned to read around the age of 3 or 4, and became an avid reader during formative years.



Reared in an orphanage for nine years with some one hundred children, he made the choice to transfer to the adjacent Cincinnati General Hospital at the age of 15, when it became required of him to take on his own support. His first employment was as an office boy. Simultaneously he attended night high school. School at night after a day's work, while one's peers were at play, was an arduous means of passing by the ambush of the young days. He recalls this period as the most difficult of his formative years. But busyness took precedence over adolescence. Dr. Aring learned what there was to learn about the workings of a large hospital during the decade he served in various at the Cincinnati General Hospital.

Dr. Arthur C. Bachmeyer, then Superintendent of the Cincinnati General Hospital and Dean of the University of Cincinnati College of Medicine, considered him destined for a career in medical administration. Medical college was readily

available and with Dean Bachmeyer as his mentor, the goal seemed eminently achievable. Having learned the functioning of the hospital by service in its administrative posts, there was little reason to halt the quest.

Dr. Aring attended the University of Cincinnati and later its College of Medicine, graduating in 1929 with the degrees of B. S. and M. D. During academic years he was in charge of the information office of the Cincinnati General Hospital during evenings; and simultaneously was assistant manager, then manager of the Medical College Bookstore during medical school. The latter post acquainted him thoroughly with the making and marketing of medical books, a step toward his developing familiarity with things literate.

Despite the fact that he had been on his own since he was 15 years of age, his only living relative being a maiden aunt, he was one of those rare students who at graduation are better off financially than at the time they entered medical school. The financial crisis that shattered the post-war economy went unnoticed by him. Engrossed in his medical career and administrative commitments, he was completely unaware of this catastrophe. Backed by Dean Bachmeyer, Dr. Aring completed a rotating intership at the Cincinnati General Hospital. Then he was appointed Chief Receiving Physician in the busy Admitting Ward of the hospital. This post demanded eight hours daily of him. It seemed certain that this would lead to a career in administrative medicine.

Fifty-six hours a week was a slight task, his having become accustomed to twice that. So he cast for something to do in his spare time. He had spent two fascinating months on the neuropsychiatric wards during his rotating internship, when sixty beds were completely his and another intern colleague's charge, there being no residency program in neurology or psychiatry at that time. Some dramatic moments were experienced by the two of them when the epidemic of Jamaica Ginger Palsy broke out and the service was swamped with some 300 extra admissions. This completely disrupted what had been a harmoniously functioning, well-organized albeit amateurish service. Patients with this then unknown disease, overflowed onto the Contagious Wards of the hospital. For a few weeks they were carefully isolated since it was not known whether or not the ailment was an infectious one. Dr. Aring recorded the study of this "new disease" in a thesis submitted for membership in the American Neurological Association (The systemic nervous affinity of triorthocresyl phosphate poisoning [Jamaica Ginger Palsy] Brain 65:47, 1942.)

Administrative ability gathered over so many years came to his aid when the time arrived to decide on a specialty. With a knowledge of the law of supply and demand, Dr. Aring appraised the scarcity of talent in the field then in Cincinnati, and decided to become the first resident ever to train in Neuropsychiatry (1930-31) at the Cincinnati General Hospital. He thus filled the free hours when not administering the Receiving Ward.

Dr. Aring derived much insight and pleasure in both posts. A close supervision of interns led him to the delights of intimate teaching, a duty that he was to perform with brilliance throughout his career.

This heavy schedule did not interfere with the distaff side. In 1931 he married Mary Shroder, the daughter of a distinguished citizen of Cincinnati. They have two children, a daughter now married to a physician, and a son currently a medical student at the University of Rochester.

THREE YEARS IN BOSTON

To be a first-rate psychiatrist in the early 1930's, it was well to become grounded in neurology. Following the advice of an intern at the Cincinnati

General Hospital who was from Harvard, Dr. Aring applied for neurological training to Dr. James Ayer at the Massachusetts General Hospital. His application was passed along to Dr. Stanley Cobb at the Boston City Hospital, since the former had filled his residency program for 1932. In the interim before beginning training in neurology, Dr. Aring devoted six months as a ward physician at the Longview State Hospital in Cincinnati.

Three years in a famed neurological center, not only turned him away from administration but enhanced the idea of becoming a neurologist. In retrospect, Dr. Aring believes that his decision was the result of the inspiring influence of the neurological talent then gathered at the Boston City Hospital, under the direction of Drs. Stanley Cobb and Abraham Myerson. What a concentration of neurological talent under one roof! Besides Cobb and Myerson, there were Jacob Finesinger, Henry S. Forbes, Frank Fremont-Smith, Erna and Frederic Gibbs, William Lennox, Maxwell MacDonald, H. Houston Merritt, Donald Munro, Merrill Moore, Tracy Putnam, and Paul Yakovlev, among others, to say nothing of a remarkable house staff. Six months of the three years of the Boston sojourn were spent in pediatric neurology at the Children's Hospital with Dr. Bronson Crothers.

During these formative years, Dr. Aring contributed a share to the maintenance of medical knowledge. He instructed in the courses in Neuroanatomy and Neuropathology at the Harvard Medical School. He worked at elucidating the intricate problem of the relationship between muscular atrophy and dystrophy with Stanley Cobb, and on coma with Philip Solomon, and on cerebrovascular disease with H. Houston Merritt.

The art of teaching was imparted to him under the direction of a most gifted practitioner thereof, Dr. Stanley Cobb. Dr. Aring states that Cobb was one of the greatest, if not the greatest, of the exponents of the teaching art that he found anywhere. With his proverbial modesty, Dr. Aring adds, "If one could not develop clinical skill under the aegis of a staff such as then at the Neurological Unit, to say nothing of the intimate supervision of a superb house staff, one had to be resistant indeed." He recalls with considerable delight the physicians with whom he shared this world. Among his instructors was Houston Merritt, whose superb diagnostic skill was being tested continually by all of the house staff. The many research endeavors in progress then included those directed by Cobb on the cerebral circulation, and studies on cerebrospinal fluid by Merritt and Fremont-Smith. Lennox's devotion to and knowledge of people with epilepsy was a continuing stimulus. The charm of the French school with its accent on the virtues of exposition was represented by Yakovlev, a pupil of Babinski; who, besides focusing attention on this important aspect of medical education, was studying all kinds of degenerative neurological diseases. The Gibbses were beginning the work that helped to lay the cornerstone of electroencephalography in America. Abraham Myerson's common sense in neurology and psychiatry was an outstanding contribution to the Boston City Hospital neurological scene, reinforced by his medico-legal astuteness. Tracy Putnam's uniquely original ideas into many facets of neurological science, and the enlightening studies of Donald Munro and Timothy Leary that were unveiling the mystery of subdural and extradural accumulations of blood were of utmost importance to him during this training.

Not without regret Dr. Aring departed this fascinating environment. Not far from Boston, the neurophysiological laboratory in New Haven directed by John F. Fulton was attracting neurologists, neurophysiologists, neurosurgeons and psychiatrists interested in a basic knowledge of the nervous system.

Dr. Aring was awarded a Sterling Fellowship at the Yale University School of Medicine to work with Dr. Fulton (1934-1935). As he said, he was "introduced to the marvelous Fultonian world, an offshoot of the Sherringtonian, but expanded to include besides neurophysiology; primatology, chemistry, endocrinology, psychology, and bibliography." This was a fine environment for a perceptive and inquisitive intellect. Fulton characteristically surrounded himself with interesting people, and attracted visitors of great moment to New Haven. While engaged in research at Yale, Dr. Aring delivered lectures in neurophysiology, and was a moderator for one of the student groups in physiology.

Some ten years after Dr. Aring left Fulton's laboratory, I was at Yale trying to familiarize myself with the work of those who preceded me. I read the records of the investigations of Aring and Fulton concerning cerebral-cerebellar relationships, and on shivering as it related to brain lesions in primates. I was struck by the importance of their studies on cerebellar tremor in the monkey, and later the influence this has had on the surgical approaches to the correction of abnormal movements.

A literary interest encouraged while Dr. Aring had access to the fine neurological library of Stanley Cobb was expanded by Fulton's tremendous holdings in all fields related to medicine, especially those concerned with history and science. John Fulton exerted a powerful influence on all who came within the range of his sparkling personality. In his paper, "The Future of Neurology", Dr. Aring recalls John Fulton as a teacher: "During John Fulton's professorship in physiology, he was a fine practitioner of Trotter's serene sanity which is the scientific mind, since he gave to every fresh idea its one intense moment of cool but imaginative attention before venturing to mark it for rejection or suspense. He was ever aware that youth must be encouraged to think for himself and that one of the functions of the good teacher is that of treading gently, though not flabbily, when dealing with developing minds. Teacher, investigator, and handler of ideas, all of these were the concern of John Fulton the physiologist. In these several roles he has had as much to do with present day neurology as any modern physiologist, and it is a good wager that via his pupils he will have much to do with the neurology of the future. And his encouragement of patterns of collaboration among highly specialized disciplines and people, is apt to be the method of the future from which neurological revelations will be derived."

EUROPEAN TRAVEL

Dr. Aring spent the next year at the National Hospital in London, on a Rockefeller Fellowship. Most of this time was devoted to a clinical clerkship with Dr. Gordon Holmes, and in the neuropathological laboratory of Dr. J. Godwin Greenfield. During this year he devoted one-half day weekly to the second-hand book shops, collecting a basic library in neurology and psychiatry. He achieved the near impossible of adding a valued volume, the Works of Sylvius, to John Fulton's vast collection. This book, uncovered one afternoon at the famed London bookshop, Foyles, was a small recompense for the value received at Yale. It is worthy of record that the cost was but a few shillings, some measure of the feasibility of gathering together a library in the mid-thirties.

Now Dr. Aring had the time and the inclination to become enamored of the classics of literature and of poetry, and of music. The impulse for this seemed to appear out of nowhere, since there had been no exposure to any of it in

his formative years. He had read avidly, but, as he says, it was mostly trash. He now looks upon the childhood reading of anything as a useful preliminary. He had found the sketchy literature courses in high school and college enjoyable, but these had been swamped by the science requirements in a pre-medical curriculum. It can be said that his liberal education had its foundation during his postgraduate training, when he met up with exemplars of the classical tradition.

To deepen his knowledge of histology, he repaired to Madrid where, with Hortega, he devoted several months acquiring the art of the silver staining techniques. Thence he moved on to Breslau, and to clinical and pathological studies with Otfried Foerster and Oskar Gagel.

In this manner the former office boy of the Cincinnati General Hospital became a man, equipped with the skills of neurology, neurophysiology, neurohistology, and neuropathology, besides the other riches that life poured into his experiences. Dr. Aring then returned to the faculty of his Alma Mater.

NEUROLOGICAL CAREER IN CINCINNATI

Gone were the lonely uncertainties of childhood. The "nose to the grindstone" posture had afforded the best of training. He had been immensely favored by falling under the influence of some of the world's leading medical teachers. He had no all-encompassing relatives, so devastating to the youngster without funds, and he had been left free to choose a career. Now he was ready to bring to medical teaching the full experience of an unusual though deprived childhood, of a career in administration, and of the best of neurological training to say nothing of a burgeoning love of the arts.

What impression did Dr. Aring create on his return to Cincinnati? Dr. William B. Bean, the Editor in Chief of the Archives of Internal Medicine, tells of it: "My first recollections of Charles Aring date back to 1937 when I had just come to Cincinnati as a senior resident of medicine. My first service was neurology. I was immediately struck by the personality of the neurologist in charge, Dr. Charles Aring, who had theoretical as well as practical skill and know-how. Limping ever so slightly from an ancient poliomyelitis, he was full of an astonishing lore about medical history both local and general. Then and now, one of his strongest characteristics was wide reading and a fascination with books. To him more responsive pupils he introduced Wilfred Trotter, Sir Francis Walshe, Albert J. Nock, Daniel Drake and many other distinguished thinkers and writers. He has an inquiring and perceptive mind. One of the most striking traits of Dr. Aring's personality is his concern with medical education at its highest level."

In the opening lines of the Convocation address in 1947, Dr. Aring said: "For the faculty I welcome you warmly and sincerely with the thought foremost that soon you will be our colleagues. With that advantage offered you by youth, some of you must become our betters. In this spirit, I trust we will do what we may to make the year a realistically enlightening and maturing one."

Few teachers come better equipped than Dr. Aring to help the student mature as a professional man. He continued: "You may hardly do an effective and happy medical practice if you remain afraid to brush aside those innuendos of the immature, those persons who will not outgrow childish notions, one of the more absurd of them being that an acquaintance with culture is correlated with effeminacy." He quoted Mark Twain: "If your doctor knows only medicine, you may be sure he does not know even medicine."

One of Dr. Aring's contributions to contemporary medicine is the emphasis he always gives language as a tool of science. Beautiful thought ought not be clothed in poor idiomatic expression, and this was clearly expressed before the Convocation audience. "Though I would not choose for you among knowledge, I would like to make a practical recommendation, to urge you not to relinquish the study and more important the continued testing of your ability to use your own language. The physician has been at a disadvantage lately by his limited ability to express himself which is about proportional to the length of time he has spent in medicine. I cannot begin to describe the grief that such a deficit engenders."

"An appreciation of the value of language leads to the acknowledgment of three rules for good expression. The first and possibly the most important is to have a point; the second is to make it out, and the third is that it should be made out in eighteen-carat, impeccable, idiomatic English."

What worthwhile advice to the burgeoning student mind! Universities are not for the purpose of the delivering of experts in different branches of knowledge, but for the development of truly cultured men. As Alfred North Whitehead said, "The fate of intellectual civilization of the world today is to no inconsiderable extent in the keeping of our universities." Science ought not to be dehumanized, and nothing is more human than language. I cannot resist quoting a remark in this sense made by Dr. Aring in this memorable address: "The way of using language as an instrument distresses many scientists, for their aim is to pin a word down to a specific meaning, and they would be completely happy if they could eschew words altogether and use symbols as the chemist and physicist do. I need hardly tell you that this is not a course that may be followed by those whose commodity is people."

There is something Oslerian about the way Dr. Aring goes about the building of student personality. Only those who feel deeply the responsability for the future professional person ought to be in teaching posts. How many young minds are stultified in the orbit of unskilled teachers? It is comforting to watch Dr. Aring moulding the student with wise advice: "The guidance that I know about in the development of the habits of thinking is to read the best that has been thought and said in the world. The effect of keeping good company in literature or in life is dynamogenous, elevating, bracing; keeping indifferent company is enervating, retarding. You may not be aware how few of you will have the fortitude to follow this reasonably straightforward and valuable recommendation. Universal literacy has, in its ruthless manner very nearly obliterated the best that has been thought and said, as our increasingly blunted senses are bombarded by stuff geared to a lowest common denominator."

There are some gifted personalities whose habits and attitudes are a living example of the best. Dr. Aring belongs to this kind, always striving to improve himself and his surroundings, trying to assist others not to be fooled by mere appearances. Through his teaching and his writings Dr. Aring displays the real and lasting values. He puts the weight of his experience into defending the sick against the incompetent. Working in tandem with the sufferer is a main concern of the prospective doctor, according to him. He has little use for the authoritarian physician.

Dr. Aring elicits the best in others, because he gives the best of himself and recognizes such qualities in others. The following is somewhat illustrative. In 1949 Dr. Aring was a member of a team teaching psychosomatic medicine to Army medical officers at the Letterman General Hospital in San Francisco. "During that two weeks' stint," says Dr. Mack Lipkin, another team member, "he showed himself a brilliant teacher, informed, dedicated, sensitive, lucid, and a warm compassionate clinician. I recall one incident during luncheon one

day with several young officer physicians; one of them commented on Charles's lecture that morning: "After he had been talking for a few minutes, I noticed he rarely looked at the class, but stared out the window at the sky. By the end of the lecture I thought it appropriate that he should look toward Heaven, because I have never heard a more inspired lecture."

Says Lipkin, "Aring has been regarded by his colleagues as an outstanding teacher truly devoted to his professional calling, and in the opinion of some of them, the best model of the profession for the medical student. Inspiring and devoted to the perfection of every aspect of the medical curriculum, Dr. Aring has imparted a beneficial influence in those universities that have been lucky enough to have him on their staffs."

Dr. Aring is directly responsible for the creation of two chairs of Neurology in medical schools in the United States. When in 1947 Dr. Aring left the University of California, after two years as Professor of Neurology, he had won the respect of the students as well as the faculty. It is reported that the student body signed a petition in an attempt to persuade Dr. Aring to remain with them, instead of removing to Cincinnati.

In an epoch when words and political maneuvering serve to mask intention —ends seemingly justifying means— it is a pleasure to write about a self-made man whose scientific growth parallels the development of a well-balanced, mature attitude toward life. "Know thyself", said the Delphic Oracle; Dr. Aring has tried to know himself, by one means and another, among them the chastening experience of a personal psychoanalysis. The latter was achieved under the aegis of a Rockefeller Foundation grant.

Knowing himself and others has rendered a well-controlled personality with a pervasive influence on everyone in touch with him whether in person or by the written word. We can gather through his papers and through the word of his many friends Dr. Aring's care about improving human relations, not only professor and student, and doctor and patient, but among all those who in one way or another deal with people. As he remarks, we must do our best to root out what Shakespeare termed, "the insolence of office."

It is not surprising to find him appraised by Dr. Denis Williams of the National Hospital, London, as "more than anyone else responsible for the re-emergence of American medical neurology as a major force in American medical life. In a Socratic way he has known himself, and he has known that his contribution has been to modify from the security of his own deep knowledge the whole trend of thinking in American Neurology today." Someone of his friends has said that he is known by his broad reading which has led to an extraordinarily well-balanced, but searching intellect which reveals the scholar but never the pedant. His membership on the Editorial Board of eight medical publications during his professional career is an index of his concern with the literature.

Dr. William Bean says of him: "In conversation he is quizzical, presents a demeanor of one whom it would be difficult to surprise, almost impossible to upset. He is not taken in by appearance but seeks out immediately cardinal points. He has the capacity for intense concentration whether it be in reading or in conversation or in dealing with patients. One gets the impression in talking with him that his attention is undivided and fused on the person in his presence. He is courteous, with the distinguished air of a scholar and gentleman. As a correspondent, he has been a great stimulus, suggesting books to read, presenting novel ideas, sending papers for comments or criticism and he has the ability to transfer himself to the written page of a letter so that one can enjoy friendship with him at a distance when it is not possible to

see him. He has an air of gentleness, of quiet calm reflecting composure and a well-balanced character, a skeptical view of life; and the world has not led him to sourness but rather to a gentle tolerance of the innumerable foibles of his fellow man."

Dr. Aring is regarded as a loyal and devoted friend, profoundly courteous, considerate, glad to be helpful, but never intrusive. His sense of humor has been described as charming, never malicious and never witty at the expense of others. Though probably aware of the short-comings of others, he seems to prefer to ignore these and to focus on what is fine about people. It is said that he is far more interested in what is good in another's presentation than what is wrong with it.

There is no better description of a true and good friend, and happily this attitude is not restricted to a few. Dr. Aring extends himself to students, patients, and even those who come in contact with him for the first time; nobody opens a letter from him nor has a conversation with him that does not render a warm, pleasant impression. This is far more uncommon than we realize. I am reminded of the advice of Epictetus: "Why do you exhort me to be like others? I would not be like the purple if I were like linen thread."

Dr. Aring is a member of the Literary Club of Cincinnati; he loves the best in music. When visiting New York with one of his friends, he asked by way of entertainment to be introduced to the teachers of English and Philosophy at Columbia; to visit the best of the less well-known art museums; occasionally he has wanted an evening with Mozart, or at the theater where he prefers comedy to tragedy. According to him, there is too much of the latter in every day experience. He is liberal in his political views, and his ideals are not entangled by any kind of prejudice concerning race, creed, or color. He has the courageous steel of those who are ready to fight for the principles of justice and human decency which stand first in his opinion. No wonder Lincoln is among his heroes; as someone has pointed out, Dr. Aring is Lincolnesque.

Dr. Aring's writings are profound and constructive. Besides works in neurology and psychiatry, they include essays in medical education, and the relationship of the classical and scientific approaches, as they may be combined in human understanding. I append the final sentences of a lovely paper published in the American Scholar under the title, "The Case Becomes Less Strange", concerning the creation and the plot of *The Strange Case of Dr. Jekyll and Mr. Hyde.* I consider that they clearly point up a rule for resolving conflicting life forces residing at different levels within the self. "So the resolution of the Jekyll-Hyde dilemma is not repression or suicide or death, which in any of their derivations is a quick way out, but rather the cultivation and harvest of the strengths and constructions —the by-products, if you will— of the partial evil. Here is the work to separate men from boys; faint hearts need not apply. These are among the modern uses of psychiatry. That psychiatry is not a panacea, the jackals who howl after it will remind us. If my thesis is correct, jackals too have their uses. So do faint hearts, but not in the work of pioneering. Perhaps theirs is the chore to keep each of us properly humble."

This ample view of man and life has made of Dr. Aring, as Dr. Milton Rosenbaum says, "one of the great medical clinicians of his time in that he is more than just a skilled diagnostician. He is capable of establishing the kind of one-to-one relationship with the patient that will last as long as the patient needs him. The help that Dr. Aring can give a patient is directed to the patient-human being with all that this implies rather than to a neurological subject. In other words, there are many outstanding neurologists to whom I

would refer a patient for a diagnostic evaluation, but in my opinion there are only a few and Dr. Aring is one of them, to whom I would refer a neurological patient for diagnosis as well as treatment."

SUMMING UP

Many yesterdays are the summing up of life. I remember a delightful short story which began with an innocent question asked by a child of her father: "Daddy, where did yesterday go?" If we could but answer, we ought to say that yesterday is in every, today, ripening experience; yesterdays are what we want to be, the shape of our mind, the quality of our reactions, the direction of our life. The office boy of yesteryear has metamorphosed into today's Professor of Neurology; a philosopher neurologist with an amused twinkle in the eyes beneath the bushy eyebrows. Yesterday and today have met in him, as inevitably it must in each of us!

VICTOR SORIANO.