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A PHYSIOLOGICAL APPROACH TO THE PROBLEM OF GENERAL ANAESTHESIA AND OF LOSS OF CONSCIOUSNESS*

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To have to prepare a lecture is a pleasant and effective way of being forced to learn about a subject. When I was approached to give this lecture, I was caught in a mood where I felt that I really ought to make an effort to find out what is known about what I would call the fundamental problem of general anaesthesia. I required this knowledge for my own experiments.

When we anaesthetize animals, human beings included, we do so in order to achieve a condition in which consciousness is lost. How is this condition brought about, and what is the physiological basis of loss of consciousness? This, in my opinion, is the fundamental problem of general anaesthesia, and this is the problem I am going to deal with.

William James (1892) said that everyone knows what consciousness is until he tries to define it. I shall not try to do so. A definition sufficient for our purpose is the one given by Stanley Cobb (1948). Consciousness is "awareness of environment and of self." If we are not fully aware either of environment or of self we have some degree of unconsciousness, and the same applies to conditions in which we are aware, not of environment, but of something different, as in dreams.

There is no need to define unconsciousness. We all know what it means. It is the experience we cannot experience, but which we all pass through, every night, when we fall asleep. It is the experience we miss when we faint or are anaesthetized.

Sleep and anaesthesia are two closely related phenomena. The main difference between the two is that we can wake up a sleeping person, or, as Purdon Martin (1949) expressed it: sleep is still a state of unconsciousness into which the messengers of consciousness can penetrate. But even this difference is not absolute and breaks down under certain conditions. Thus the central mechanisms involved in sleep and anaesthesia cannot be so different, and if we were to know what determines the difference between the waking and the sleeping state we should not be far off explaining the unconsciousness of anaesthesia.

The Cerebral Cortex and Consciousness

For a time it was supposed that consciousness was exclusively a function of the cerebral cortex. The unconsciousness which follows head injury, concussion of the brain, was attributed to diffuse cortical damage. That was the view commonly held by neurologists about 40 years ago.

Yet removal of the cerebral hemispheres does not cause loss of consciousness. Such operations were performed on various animals at the end of the last century. And if we look through the older textbooks of physiology we find more detailed accounts of the behaviour of these decorticate animals than in the modern editions. Schäfer (1900), in his textbook, gives an excellent description, including that of the famous decorticate dog of Goltz. In 1892 Goltz had succeeded in removing both cerebral hemispheres in three successive operations and in keeping the dog alive for 18 months after the final operation.

The animal was able to walk in a perfectly normal fashion; in fact, for the greater part of the day it walked restlessly up and down in its cage. But at night it would go to sleep, and it curled round in the manner normal to dogs. When awake it reacted to a loud sound or to a bright light by shaking its ears, or by shutting its eyes and turning its head away, and when its skin was pinched it snarled or barked, or turned round to bite at the hand, but in a clumsy manner. During the first few months it had to be fed by placing food at the back of its mouth; later it took food itself provided its head was placed over the dish containing the food. When meat was rendered bitter by quinine it was ejected with movements indicating dislike. There was, however, no sign of recognition of persons or other dogs, no sign of fear when threatened or of pleasure on being stroked or spoken to. The dog never wagged its tail. There was no sign of memory. For instance, when the dog was taken out of the cage, which was the normal sign for feeding, it invariably resisted, barking loudly, biting, and struggling vigorously. Thus removal of the hemispheres had produced loss of all understanding, intelligence, and memory. The condition was that of idiocy but not of unconsciousness. In fact, the dog had periods of sleep and wakefulness, of unconsciousness and consciousness, although the content of its consciousness must have been enormously different from that of a normal dog.

I also want to describe, because of the close resemblance, the behaviour of human anencephalic and hydrocephalic monsters. In these the cerebral cortex is either absent or has virtually disappeared. Some have survived for 20 years. The late Professor Cairns (1952)

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described the behaviour of what he called the human brain stem and thalamic "preparation." "It sleeps and wakes; it reacts to hunger, loud sounds, and crude visual stimuli by movements of eyes, eyelids, and facial muscles; it may see and hear; it may be able to taste and smell, to reject the unpalatable and accept such food as it likes; it can itself utter crude sounds, can cry or smile, showing displeasure when hungry and pleasure, in a babyish way, when sung to; it may be able to perform spontaneously crude movements of its limbs." Again, a condition of idiocy but not of unconsciousness. Again, periods of sleep and wakefulness; but what a restriction in the content of consciousness whilst awake. Babies pass through a somewhat similar state.

I want to use a metaphor. A room may contain a chair and a table but nothing else, or it may contain rare pieces of furniture, carpets, and pictures, and the rest of the walls may be covered with books. But at night, when it is dark, this difference is not apparent; it becomes so only when we switch on the light. The contents of the two rooms are as different as the contents of consciousness in the decorticate and the normal dog, in the anencephalic and the normal human being. The contents of consciousness—so far as the higher psychical functions are concerned—are cortical functions, but whether the room is in darkness or in bright light, whether we are conscious or not, that is not a function of the cerebral hemispheres.

Neurological Cases with Manifestations of Loss of Consciousness

And yet as recently as 1950 Jefferson and Johnson could point out that many neurologists still believed that the loss of consciousness from cerebral haemorrhage was caused by general cortical anaemia. Jefferson and Johnson describe a typical case of bleeding from a ruptured middle meningeal artery with the classical sequence of stupor—recovery—stupor. A boy of 14 fell, striking the back of his head on the floor, and, after vomiting, fell asleep, and an hour later did not reply on stimulation; then 15 minutes later he woke up, walked about, and wanted to be left alone, but then he again went to sleep. Within the next hour his condition became worse; he was brought into the operating theatre, and as soon as attempts were made to shave his head he again woke up and spoke resentfully. At operation a large liquid extradural clot was evacuated from the temporal fossa and the spurting middle meningeal artery was coagulated. After the operation, as his bandage was fixed, the boy sat up on the operating table and asked what had happened.

This classical picture of acute compression has become so familiar that, as Jefferson and Johnson say, "surgeons and neurologists have not very often paused to inquire how the loss of consciousness comes about. It seemed to be sufficient to say that the brain was compressed and presumably anaemic."

However, this classical picture of middle meningeal haemorrhage is also produced when the extradural bleeding and compression by the clot occurs in a situation where effects on the cerebral hemispheres can be excluded; it is when the clot is below the tentorium, in the posterior fossa. Jefferson and Johnson describe such a case.

A student stepping off a moving bus, fell backwards, striking the back of his head on the ground. He became unconscious, recovered, but then again went into coma and was deeply unconscious at the time he reached the operating-table. Several burr-holes were made in the skull in search of the clot. His condition became critical, respiration stopped, and artificial ventilation had to be given. On tapping the lateral ventricle the cerebrospinal fluid was found to be under high pressure. Lowering the pressure by aspiration of C.S.F. resulted in a return of respiration but not of consciousness. But when at last, after the bone had been nibbled down towards the foramen magnum, a large clot was removed deep down in the fossa, the patient awoke and became so lively that nitrous oxide had to be given to keep him quiet while closing the wound.

This case strikingly illustrates that consciousness did not return when the general pressure on the brain was lowered, but that it did return as soon as the pressure exerted by the clot on the brain stem was removed.

For many years Jefferson (1938, 1944) had pointed out that the neurologists were wrong in assuming that the cerebral cortex was the seat of consciousness. On the contrary, he said, there is abundant evidence, if observers were only prepared to look for it, that the seat of the disturbance is the brain stem and hypothalamus. Let us look at some of this evidence, starting from the spinal cord and working upwards, making use of the familiar diagram of the brain (Fig. 1).

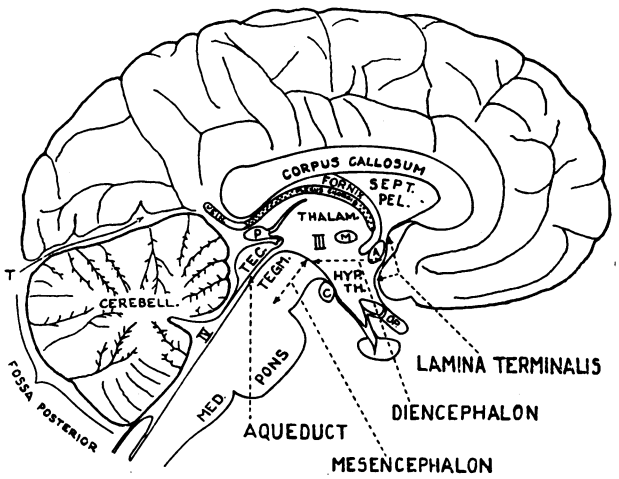


FIG. 1.—Diagram of a mid-sagittal section of the human brain to illustrate some of the terms used. A=anterior commissure; C=corpora mammillaria; Hyp. Th.=hypothalamus; M=massa intermedia; Med.=medulla oblongata; OP=optic nerve; P=pineal body; Sept. Pel.=septum pellucidum; T=tentorium; Tec.=tectum; Tegm.=tegmentum; Thalam.=thalamus; III and IV=third and fourth ventricles. The dotted area below the corpus callosum and fornix is the choroid plexus.

Spinal Cord, Medulla Oblongata, and Pons

Cairns (1952), in his review from which I have heavily drawn, pointed out that tumours of the cervical cord as high up as C 1 do not cause disturbances of consciousness so long as they do not invade the medulla oblongata; if they do, attacks of loss of consciousness may occur. Haemorrhages around the pons and medulla oblongata (Cairns, 1952), or into the substance of the pons (Jefferson, 1944), or into the fourth ventricle (Rosenfeld, 1924) produce deep coma and unconsciousness. And although tumours of the pons are rarely associated with unconsciousness the condition is easily precipitated when the surgeon interferes with the pons in operations for removal of pontile tumours. Well known also is the following accident described by Reichardt (1928).

During puncture of the cisterna a woman lost consciousness because the needle had entered the medulla oblongata. After the needle had been inserted the woman

made a sudden backward movement with her head which drove the needle 2 to 3 cm. deep into the medulla. The needle was immediately withdrawn. At the same moment the woman cried out; then she became motionless, with open staring eyes, and did not respond to loud calls. She remained so for 10 to 15 seconds and then passed through a stage resembling that after an epileptic attack before regaining full consciousness. Afterwards she said that the needle had already been in and was not painful when she suddenly felt a shock run through the right side of her body. Everything went black before her eyes and she saw her whole life rush past her like lightning. Then she lost consciousness; later she heard her name being called from a long way off.

Mesencephalon

I have not been able to find in the clinical literature any reference to lesions confined to the mesencephalon, particularly around the aqueduct, but there is one clinical affection in which the disturbance of consciousness has been associated with the aqueductal grey matter: the sleep-like condition, the somnolence or hypersomnia, of encephalitis lethargica. Economo (1931), who studied this disease during the 1916–17 epidemic, attributed the prolonged sleep to the inflammatory processes in the grey matter surrounding the upper part of the aqueduct, in the zone of transition between mesencephalon and diencephalon.

Diencephalon

Unconsciousness in one form or the other, intermittent or continuous, with or without fits, is characteristic of lesions in the upper brain stem and thalamus—that is, in the diencephalon. The symptoms vary according to the location of the lesion. Unconsciousness associated with a rise in body temperature, hyperthermia, is a sign of acute injury of the hypothalamus. Attacks of unconsciousness resembling *petit mal*, or minor epilepsy followed by major fits, occur with lesions located in the anterior part of the third ventricle and involving the anterior medial parts of the thalamus. Then there is the well-known condition of long-lasting continuous unconsciousness, for weeks or months, where the condition resembles more natural sleep, but where the patient cannot be roused to full wakefulness for any length of time. This condition is characteristic of some tumours in the third ventricle, arising from below the floor of the ventricle. Also in this category belong the sudden attacks of unconsciousness encountered during brain operations under local analgesia during manipulation of the lamina terminalis, the anterior wall of the third ventricle. Cairns describes the case of a child who quite suddenly ceased to respond for a minute when he operated on the lamina terminalis in order to get into the third ventricle; and after the lamina terminalis was opened the child had several short-lasting fits with loss of consciousness. The reverse happens when a tumour in the third ventricle is a cyst and is aspirated under local analgesia through a frontal burr-hole. The stuporous patient is promptly aroused as soon as the cyst is emptied.

Jefferson and Johnson (1950) published a map (reproduced in the upper part of Fig. 2) which gives the area, damage of which leads to depression of consciousness, to hypersomnia, or to coma. The area covers most of the lesions discussed except those in the medulla oblongata and lower part of the pons. The lower map is a more recent one by Jefferson (1958); the area extends more anteriorly to the septum pellucidum and hypocampus. The evidence for this extension rests on cases of unconsciousness from bleeding aneurysms of the anterior cerebral and the anterior communicating arteries.

Epilepsy

There is one clinical manifestation of unconsciousness which has nothing to do with sleep—the unconsciousness of the epileptic fit: the sudden attack of unconsciousness with generalized convulsions, the *grand mal*; or the brief interruption in the stream of consciousness, with or without arrest of bodily movement, the *petit mal*. What brings about the unconsciousness? Records taken from the cerebral cortex during these conditions show what is called "seizure discharges." This abnormal discharge does not originate in the cortex, it only spreads to the cortex, and the spread is from below, from subcortical

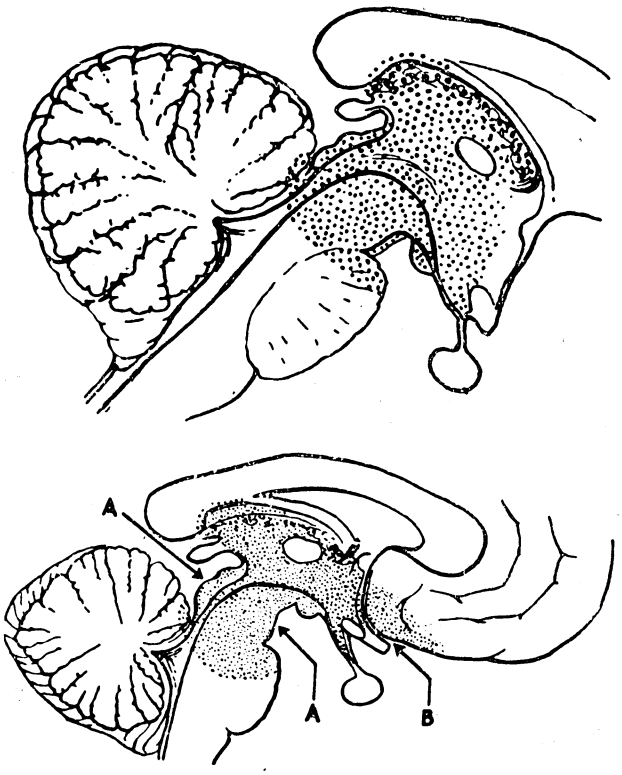


FIG. 2.—Area of brain associated with consciousness. Upper diagram from Jefferson and Johnson, 1950; lower diagram from Jefferson, 1958. Below: Diagram of posterior (A) and anterior (B) critical points in relation to consciousness. Stippling represents area most related to preservation of conscious states.

regions, from what Penfield and Jasper (1954) termed the "centrencephalic system." The unconsciousness results, they say, from an abnormal discharge in the centrencephalic system.

By definition, the centrencephalic system refers to neurone systems which connect both hemispheres and which are located in the central core of the upper brain stem from the thalamus down to the medulla oblongata. We may ask, has a system of such a wide distribution really a meaning from the anatomical or physiological point of view? Whatever the answer—and the centrencephalic system has certainly met with strong criticism on this account—this concept of Penfield and Jasper has given us a new understanding of the mechanism by which unconsciousness is brought about during the epileptic seizure. I particularly want to stress

that unconsciousness is again attributed to the mesencephalon and diencephalon, and, as we shall see, this is also very much the conclusion arrived at by the physiologist.

Approach of the Physiologist to the Problem of Consciousness

Let us start with the E.E.G. By leading off with electrodes either placed on the skull or inserted through a little burr hole made in the bone and resting on the dura, we can record the electrical activity of the cerebral cortex. The record, the so-called E.E.G., differs during wakefulness and sleep. During wakefulness or alertness we record low-voltage fast activity; during sleep, high-voltage slow-wave activity and spindle bursts. This is illustrated in Fig. 3. It is the E.E.G. of a cat. Four cortical records are taken from the anterior and posterior regions of the left and right hemispheres. At the beginning of the record the cat is asleep, and we record high-voltage slow-wave activity and spindle bursts typical for sleep. At the arrow the cat is awakened by a hand-clap, and the arousal causes desynchronization of the high-voltage slow-wave pattern.

High-voltage slow-wave activity is also recorded in many forms of anaesthesia, but there are other effects, varying according to the kind of anaesthesia. They illustrate that many anaesthetics, apart from producing sleep and loss of consciousness, have additional central actions, which can affect the E.E.G. but need not have anything to do with the essential problem of anaesthesia —loss of consciousness.

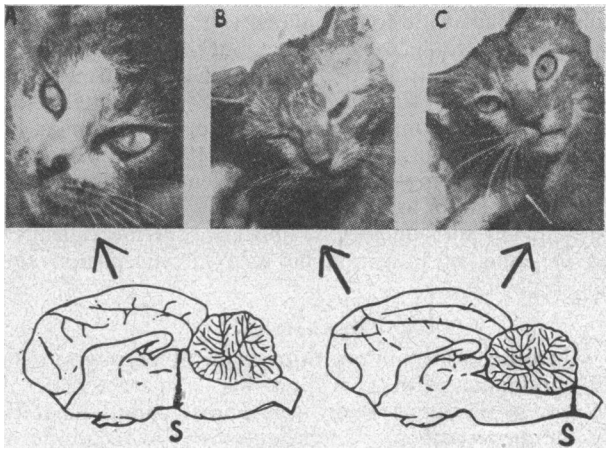
There is the other question: Is this pattern of cortical activity always associated with loss of consciousness, or can it also occur during wakefulness? It can. Small doses of atropine, hyoscyamine, as well as morphine bring about the typical sleep pattern without producing sleep or signs of impaired consciousness (Andrews, 1941; Cahen and Wikler, 1944; Funderburk and Case, 1951; Wikler, 1952; Bradley and Elkes, 1953, 1957; Bradley and Hance, 1957). However, such dissociation between behaviour and E.E.G. is a rare exception, and it need not prevent us, so long as we keep it in mind, from using the high-voltage slow-wave pattern as a sign signalling loss of consciousness.

Cerveau and Encéphale Isolé

The next step in the analysis of this high-voltage slow-wave sleep pattern we owe to the Belgian physiologist Bremer (1935, 1936), who introduced the so-called "cerveau isolé" and the "encéphale isolé" preparation. These preparations are illustrated in Fig. 4, which is from one of his early papers.

Bremer started from the hypothesis that sleep is the result of suppression of the impulses which usually reach the cortex, or, as he expressed it, results from more-or-less complete deafferentation of the telencephalon—that is, the cortex, the rhinencephalon, and the corpora striata—and that the high-voltage slow-wave activity pattern is the rhythm of the cortex when no longer bombarded by these impulses.

To test this hypothesis he made a transverse section under ether anaesthesia through the brain of a cat at a level between the superior and inferior colliculi but preserving the blood supply to the cortex. The left side of Fig. 4 shows the plane of transection. After the ether has blown off, the head of such a cerveau isolé behaves as if it were asleep. The pupils are slit-like; the eyeballs have swayed downwards, the nictitating membrane, that is, the third lid, is relaxed and usually covers the eye. There is no awakening reaction to smell or light,



CERVEAU ISOLÉ. ENCÉPHALE ISOLÉ.

FIG. 4.—Cerveau isolé and encéphale isolé preparation of the cat. (From Bremer, 1935.)

although both the olfactory and the optic nerve have remained connected with the upper part of the brain. And if leads are taken off from the cortex the record shows the typical high-voltage slow-wave sleep-pattern. Some preparations were kept alive for days, and the cat's head was asleep all the time.

In the encéphale isolé the section is made below the medulla oblongata, as illustrated on the right side of Fig. 4; all cranial nerves remain connected with the upper portion of the brain. The encéphale isolé preparation exhibits mainly periods of wakefulness which alternate with periods of sleep. The eyes are wide open, the nictitating membrane is withdrawn, the pupils are dilated, and their diameter changes from moment to moment. The eyes show small exploratory movements, and will follow an object, but if the object is quickly brought close to the eye the lids close. Sounds, particularly voices, produce ear movements, such as orientation of the ears towards the sound. But the cat exhibits no emotional reaction either of fear or of anger; it seems to be emotionally undisturbed. As Bremer expressed it, "l'animal donne l'impression de regarder paisiblement ce qui l'entoure." When the preparation is asleep the E.E.G. pattern of the encéphale isolé is that characteristic for sleep, but when it is woken up—for instance, by a noise—the slow high-voltage waves are at once broken up, desynchronized, and replaced by low-voltage fast activity.

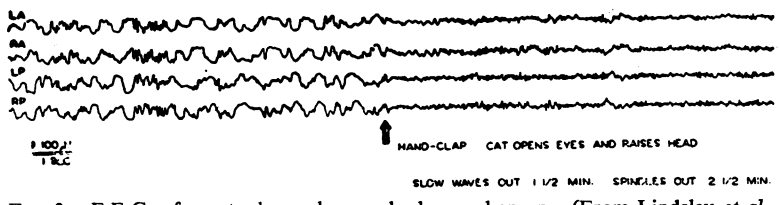


FIG. 3.—E.E.G. of a cat when asleep and when woken up. (From Lindsley *et al.*, 1950.)

These beautiful observations seemed to bear out the idea of Bremer that sleep is the result of deafferentation of the cortex, and yet, in anaesthesia, impulses from the periphery reach the cortex. When, in an anaesthetized cat or in a sleeping encéphale isolé, we stimulate an afferent nerve, a strong evoked response is produced in the sensory area of the cortex. In fact, the response is greater than that elicited during the waking state, as illustrated in Fig. 5 on a preparation in which the transection of the brain stem was made at a level between that of the cerveau and the encéphale isolé, in front of the medulla. Such a prebulbar preparation behaves like an encéphale isolé, but has the advantage of exhibiting a more stable sleep, from which it can be awakened. Fig. 5 shows records from the acoustic cortical area. D gives the size of the pupils which indicates whether the cat's head is asleep or awake.

The tracings 1 and 3 were taken while the preparation was asleep. We see, under A, the typical high-voltage slow-wave activity with a spindle burst at the end. At B a strong auditory-evoked response was elicited by an electric shock applied to the auditory pathway in the medial geniculate nucleus. C is the same as B, but taken on a slower time-base to show the after-discharge. There are always eight superimposed evoked responses. When the preparation has been aroused at 2 by blowing air into the nostrils, and when the record is activated and desynchronized—when the pupils are dilated and the eyes move about—the evoked response is much smaller.

Similar results are obtained in anaesthetized cats. The cortex thus receives the signals in anaesthesia as they travel up the ascending pathways. Bremer's results and his concept of deafferentation of the cortex thus requires some additional interpretation. This has been provided by Moruzzi and Magoun (1949) in their classical paper on "The brain stem reticular formation and activation of the E.E.G."

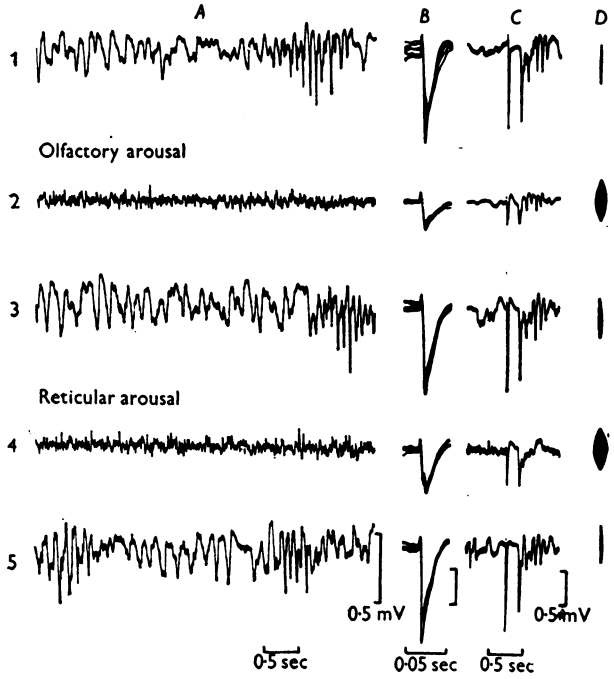


FIG. 5.—Records from the acoustic cortical area of a prebulbar preparation of the cat. B and C, superimposed impulses. D, size of pupil. At 1, 3, and 5, preparation "asleep"; at 2, aroused by blowing air into the nostrils, and at 4 by electrical stimulation of the reticular formation. (From Desmedt and La Grutta, 1957.)

The Reticular Activating System

In the central core of the brain stem from the medulla through the tegmentum of the mesencephalon to the diencephalon, to the epithalamus, subthalamus, and thalamus, we find diffuse aggregations of cells of different types and sizes, separated by a wealth of fibres travelling in all directions; the reticular formation. This diffuse system in the middle of the brain stem exerts an activating influence on the cortex, and it receives sensory signals from collaterals of all kinds of ascending fibres,

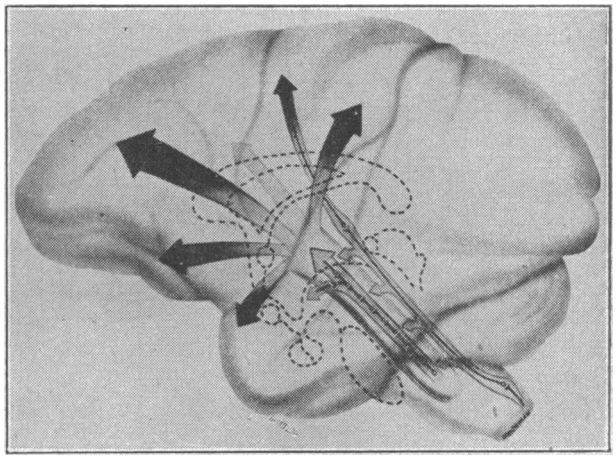


FIG. 6.—Lateral view of monkey's brain within which is projected the classical somatic afferent pathway to the sensory cortex and the ascending reticular system in the central brain stem, receiving afferent collaterals and projecting diffusely to the cortex. (From Magoun, 1954.)

from the somato-sensory fibres in the medial lemnisci, from the auditory fibres in the lateral lemnisci, from the other cranial nerves, and from visceral afferent fibres. An ascending fibre which passes along the classical pathway direct to a specific area in the cortex via its relay nuclei, gives off collaterals to the reticular formation, which then in turn sends impulses to practically the whole cortex, desynchronizing its high-voltage slow-wave activity and activating or alerting the cortex. This arrangement is illustrated in Figs. 6 and 7.

Fig. 6 is a lateral view of the monkey's brain within which is projected the classical somatic afferent path to the sensory cortex and the ascending reticular system, receiving afferent collaterals and projecting diffusely to the cortex. In Fig. 7 the classical

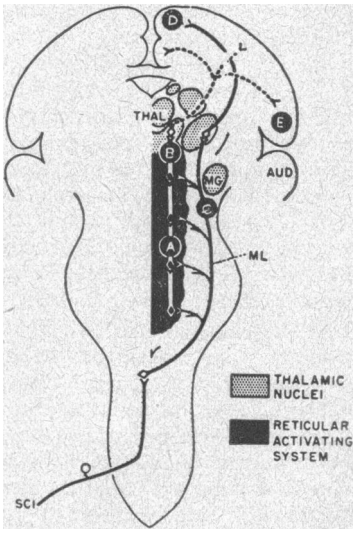


FIG. 7.—Diagram of brain showing classical somatic afferent pathway to sensory cortex (solid line) and ascending reticular system (black) with its diffuse cortical projections. (From French, Verzeano, and Magoun, 1953.)

somatic afferent pathway is represented by the solid line. It starts from the sciatic nerve, passes the nucleus gracilis, then via the medial lemniscus and the thalamic relay nucleus to the sensory cortex. The dotted lines represent the ascending reticular system with its diffuse cortical projection.

The conduction time of an impulse travelling via the classical ascending pathway reached the cortex at D in 11 msec., but, travelling to E via the reticular formation with its numerous synaptic relays, it took 54 msec., from the sciatic to A, 13 m.sec., and from A to B, 41 m.sec.

When we arouse, alert, or awaken a "sleeping" cortex by an afferent stimulus, say, by stimulation of the sciatic nerve or, as in the experiments of Desmedt and La Grutta (1957), by stimulation of the olfactory nerve —air was blown into the nostrils—the arousal, the desynchronization, is mediated not via the classical direct ascending pathways but via these collaterals to the reticular formation. We can arouse a "sleeping" cortex also by direct stimulation of the reticular formation through electrodes inserted into this system. In fact, it was Moruzzi and Magoun (1949) who first clearly demonstrated that the E.E.G. in a lightly anaesthetized animal can be desynchronized by stimulation of the reticular formation in the brain stem. This effect is shown in the prebulbar preparation used by Desmedt and La Grutta in Fig. 5, line 4 of which shows the arousal of the cat's head by direct stimulation of the reticular formation.

This kind of technique is now widely used. Bradley and Key (1958) used it to find out if a drug which prevents arousal does so by acting on these collaterals or on the reticular formation itself. If the drug acts on the collaterals it will prevent arousal from afferent stimulation, but without affecting the classical ascending pathways, and without preventing the arousal on direct stimulation of the reticular formation. If it acts on the system itself, direct stimulation of the system will also be ineffective.

The present concept of the reticular formation regards this structure as a unit which is activated as a whole. This concept has been extremely fruitful, and has greatly advanced our knowledge of the physiological function of the structures located in the central core of the brain stem. However, it is necessary to point out that the reticular formation consists of numerous anatomically discrete nuclei, as shown by Olszewski (1954), by Olszewski and Baxter (1954), and by Brodal (1957). Each of these nuclei may subserve distinct functions, and their final elucidation may entail changes in our present concept of the reticular formation—as happened with the views originally held on the function of the hypothalamus.

At present, however, we are justified in stating that arousal, wakefulness, or the conscious state can be expressed in physiological terms as a function of the ascending reticular formation in alerting the cortex. In the primitive simile I used at the beginning of the lecture, the switching on of the light to illuminate the room would correspond to the alerting function of the ascending reticular system. Bremer's concept that sleep is a functional deafferentation of the cerebrum is essentially true, though not in the sense originally envisaged. At that time only the classical ascending paths to the cortex were known. It is not interruption of these pathways, but functional deafferentation from the medial portion of the brain stem, or elimination of the waking influence of the ascending reticular activating system, which explains his results. This has been confirmed by placing lesions within the area of the ascending reticular formation.

Lesions in the Reticular Activating System

When Lindsley, Bowden, and Magoun (1949) performed their first experiments of this kind, they in a way changed the behaviour of a waking encéphale isolé of the cat into that of the permanently sleeping cerveau isolé by discrete lesions placed within the area of the ascending reticular formation. Lesions outside this area did not produce this behavioural change.

Later, Lindsley *et al.* (1950) obtained similar results in chronic experiments. Fig. 8 is taken from their paper. At A is shown a cat which is awake and standing, and the E.E.G. gives the characteristic awake pattern. This

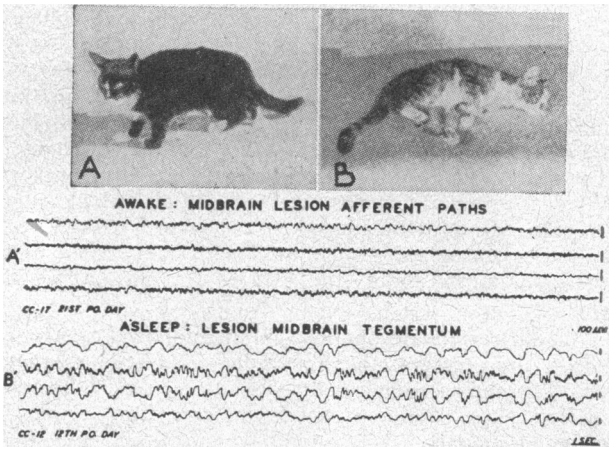


Fig. 8.—Effect on behaviour and E.E.G. of a chronic lesion in the lateral parts of the mid-brain interrupting the ascending sensory pathways (A and A') and of a chronic lesion in the central part of the tegmentum (B and B'). (From Lindsley *et al.*, 1950.)

cat has a chronic lesion in the lateral parts of the mid-brain interrupting the sensory paths but sparing the central core. B shows a cat lying asleep and giving the characteristic sleeping E.E.G. This cat has a chronic lesion in the central part of the tegmentum, sparing the sensory pathways.

Similar chronic somnolence with electroencephalographic synchrony was obtained with diencephalic lesions bordering the third ventricle. In Fig. 9, from the same paper, paramedian lesions which produced such somnolence are projected into the mid-sagittal-plane of the brain stem. A is a tegmental, B a subthalamic, and C a subthalamic-thalamic lesion. These cats, when undisturbed, lay motionless on their sides, somnolent or asleep. At the beginning they could not be aroused, but after days or weeks, according to the site of the lesion, an afferent stimulus—for instance, a buzzer—would arouse them for a moment, as shown by desynchronization of the E.E.G. This activation differed from normal arousal in that it terminated almost immediately upon the cessation of the arousing stimulus.

Lesions in the lower part of the reticular formation did not produce the sleep-like condition. The cat with the lesion D remained awake. The more rostral lesion of the peri-aqueductal grey matter (E) which invaded the caudal part of the thalamus produced somnolence and synchronization of the E.E.G. for about a week; later the cat became progressively more wakeful.

Lesions in the rostral part of the activating system of the monkeys appeared to affect the behaviour and electrocortical activity of the animal even more drastically than in cats. Fig. 10 shows midsagittal reconstructions of brain-stem lesions which rendered the monkeys totally and permanently helpless and produced synchronous E.E.G.s incapable of activation. French and Magoun (1952) describe the condition in the monkeys as one simulating coma, or at least stupor, in man. And "as in such states in man, these animals would occasionally respond briefly to intense stimuli by reflex withdrawal of extremities or by diffuse inappropriate movement, at which time the eyes would open in a superficial semblance of wakefulness; but at no time was there any suggestion that the animal was alertly responsive to the stimuli or to his surroundings."

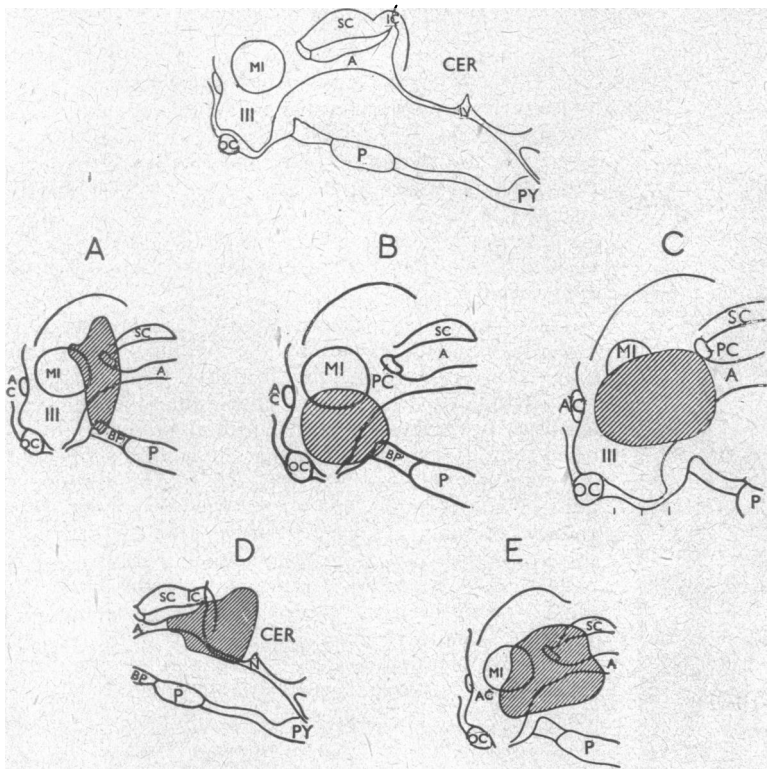


FIG. 9.—Paramedian brain-stem lesions in cats (A to E) projected into the mid-sagittal plane of the brain stem. Upper diagram: mid-sagittal plane of cat's brain for orientation. A=aqueduct; CER=cerebellum; IC and SC=inferior and superior colliculi; MI=massa intermedia; P=pons; Py=pyramidal crossing; III and IV=third and fourth ventricles. For details of the lesions and the behavioural changes they produce, see text. (From Lindsley *et al.*, 1950.)

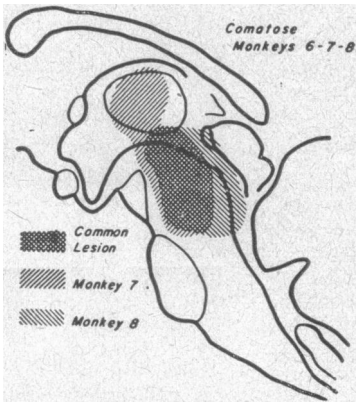


FIG. 10.—Experimental brain-stem lesions in three monkeys which produced a state simulating coma or stupor in man and a synchronous E.E.G. which could not be activated. Lesions projected into the mid-sagittal plane of the brain stem. (From French and Magoun, 1952.)

After having given in the mid-saggital plane reconstructions of the lesions which in cats and monkeys produce a state of somnolence, I want to return to Fig. 2, and, although the area given by Jefferson is a little more extensive, the similarity is striking, and I think many of the clinical cases of loss of consciousness reviewed at the beginning of the lecture can safely be expressed in physiological terms as an interference with the ascending reticular activating system.

An analysis of neurological cases involving loss of consciousness must start with a search for changes in this part of the brain stem. Take, for example, the stupor of concussion: Foltz and Schmidt (1956) compared the evoked potentials on stimulation of the sciatic nerve in the reticular formation with that in the classical sensory path of the medial lemniscus after an accelerating blow on the monkey's head. "The responses in the reticular formation were selectively, uniformly, and dramatically absent after a sufficient blow on the head," whereas the responses in the lemniscus remained unchanged. This is shown in Fig. 11.

Sleep Produced by Excitation of Certain Brain-stem Areas

There is an observation by Hess (1944, 1954) which at first sight does not seem to conform with the general picture given of the mechanisms responsible for sleep and wakefulness. Hess found that cats curled up and went to sleep in a wholly normal manner when he stimulated certain medially situated brain-stem areas in the diencephalon—the massa intermedia or the intralaminar thalamic nuclei—through implanted electrodes, but only—and this is important—when stimulation was with low frequency and low voltage. The E.E.G. showed the typical slow high-voltage wave pattern as shown by Hess, Koella, and Akert (1953).

To understand this observation we must go back to an old observation by Dempsey and Morrison (1942), usually called the "recruiting response of the diffuse thalamo-cortical system"; and to explain it I shall make use of a diagram (Fig. 12) from Bradley (1958). It shows the general arrangement of the diffuse thalamic projection system and the reticular activating system. Dempsey and Morison stimulated, in cats under

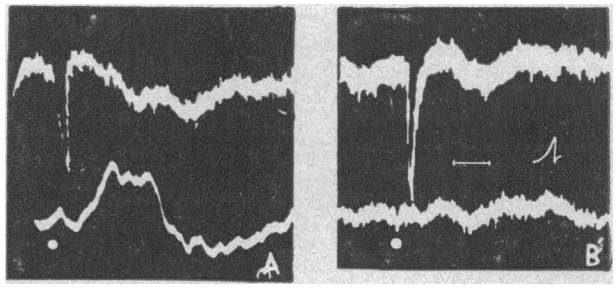


FIG. 11.—Oscilloscope record of concomitant evoked potentials in brain-stem reticular formation (lower trace) and medial lemniscus (upper trace). At A, control without concussion; at B, after acceleration concussion produced by a blow against the monkey's head. (From Foltz and Schmidt, 1956.)

pentobarbitone sodium ("nembutal") anaesthesia, these medially situated thalamic nuclei, which are not the relay stations for the specific projection system to localized areas of the cortex—these, as shown in Fig. 12, are the lateral nuclei. The medial nuclei project diffusely to the cortex, like the reticular activating system; they are, in fact, sometimes included in this system. When Dempsey and Morison stimulated this region, but only with low frequencies, 8-12/sec., they

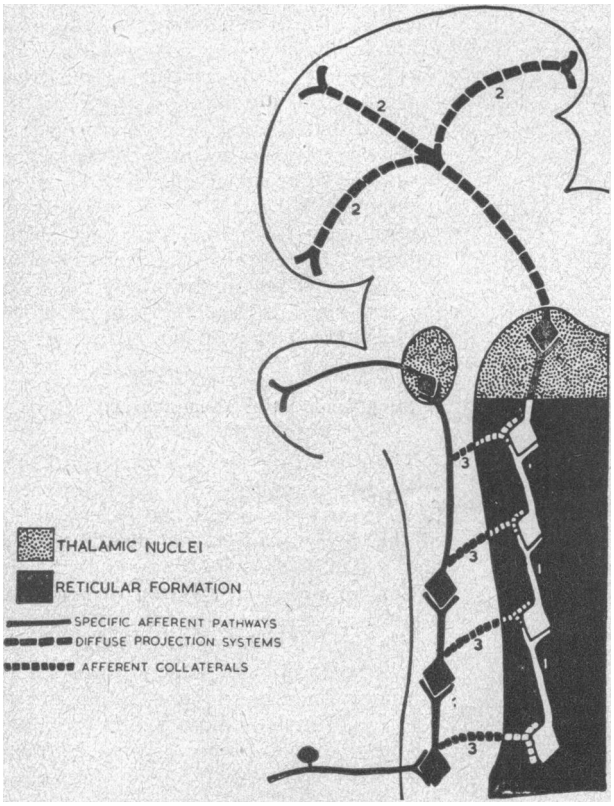


FIG. 12.—Diagrammatic representation of the reticular formation and the diffuse thalamic projection system. (From Bradley, 1958.)

recorded from the whole cortex high-voltage slow waves, one for each shock. At the beginning of stimulation these waves increased in amplitude; they recruited to a maximum: therefore the term "recruiting response." According to Dempsey and Morison, the recruiting response is identical with the spontaneous bursts of high-voltage 8-10/sec. activity which are so characteristic of deep pentobarbitone sodium anaesthesia.

It is interesting that we can drive the cortex in this rhythm on stimulation from the medial thalamic nuclei provided we use weak current and a rate of stimulation close to that of the normal slow rhythm of the sleeping brain.

Hess probably stimulated this diffuse thalamic projection system, producing something akin to the recruiting response. Hess also used a stimulation rate of 8/sec.

Hess's sleeping cats were easily aroused, for instance, by the smell of meat, and this is in accord with the finding by Moruzzi and Magoun that in the encéphale isolé the recruiting response is abolished by sensory stimulation, such as loud whistling, blowing on the head or eyes, or rubbing the nose, or by direct stimulation of the bulbar reticular formation.

Thus stimulation in this region, with low voltage and low frequencies, resulted in the recruiting response of Dempsey and Morison and led to sleep in the experiments of Hess. And stimulation of the reticular activating system, directly or indirectly through collaterals from the ascending paths, abolished the recruiting response and led to arousal.

Reticular Formation and Anaesthesia

There is now this question: Is the unconsciousness of anaesthesia the result of reversible reduction of activity in this region? Have anaesthetics, even if they act diffusely upon the brain, a predilection for the reticular activating system; and does block of the ascending conduction in this medially situated system of the brain stem provide a neural basis for the anaesthetic state?

These questions have been asked by French, Verzeano, and Magoun (1953), and by the Arduinis (1954), and have been answered in the affirmative. These authors have convincingly shown that anaesthetics block impulses propagated over the medial pathways of the brain stem to the cortex, but that the laterally conducted impulses remain unimpaired and reach the cortex. Fig. 13 shows in a monkey evoked responses to an auditory stimulus recorded from the reticular formation and from the lateral direct ascending pathway to the cortex—that is, from the lateral lemniscus. The evoked response in the reticular formation is abolished after one minute of ether anaesthesia; the response in the lateral lemniscus remains unimpaired even after eight minutes of ether anaesthesia.

The susceptibility of the brain-stem reticular formation to anaesthetics is not surprising once we realize that anaesthetics are apparently able to block transmission across a synapse much more readily than conduction along a nerve fibre (Larrabee and Posternak, 1952), and that the reticular formation is characterized by its multineural or multisynaptic organization, so that impulses have to pass one synapse after another, in contrast to the few encountered by an impulse ascending to the lateral pathway.

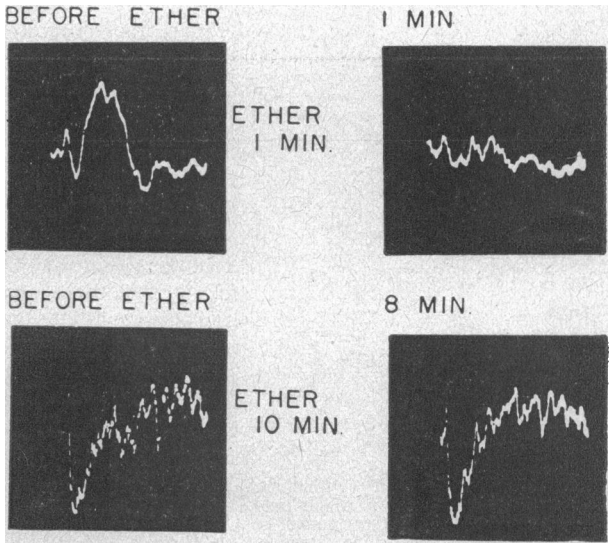


FIG. 13.—Oscilloscope records from the brain stem of a monkey. Effect of ether on evoked auditory responses in the reticular formation (upper records) and in the lateral lemniscus (lower records). (From French *et al.*, 1953.)

Anaesthesia-like Conditions Produced by Injections of Drugs into the Cerebral Ventricles of Unanaesthetized Animals

The structures which on excitation cause arousal and on injury loss of wakefulness and which apparently are selectively blocked in anaesthesia are situated close to the midline, lining the walls of the third ventricle and of the upper end of the aqueduct. If the loss of consciousness in anaesthesia is the result of a selective action on these structures, should it then not be possible to produce the anaesthetic state by injecting anaesthetics into the cerebral cavities ? Such injections I have made, but I have to confess *not* as the result of such logical considerations as they should have been. What happened was as follows.

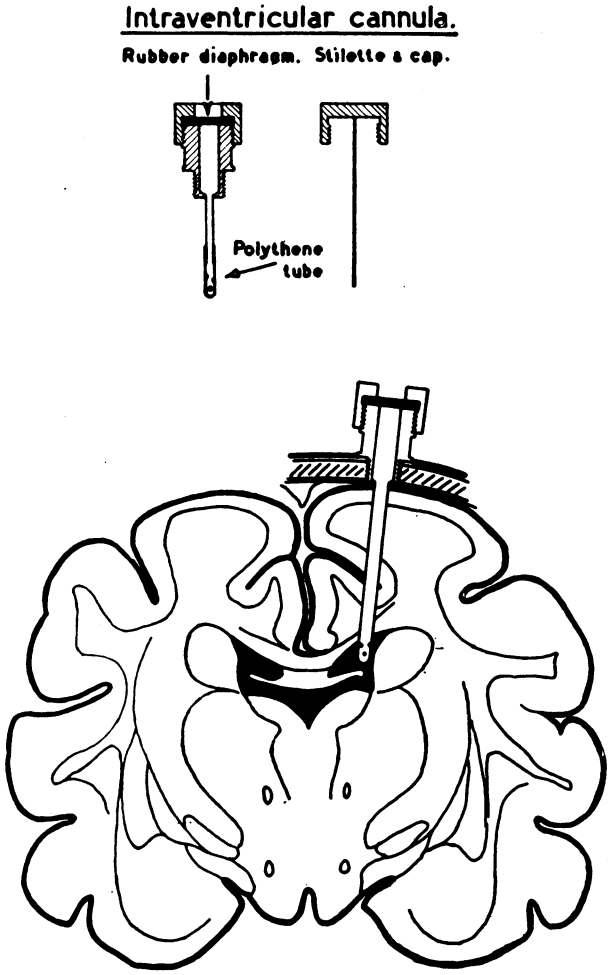


FIG. 14.—Diagram illustrating method of injecting substances into the lateral ventricle of the cat's brain through a Collison cannula screwed into the skull. (From Feldberg and Sherwood, 1953.)

About five years ago, Dr. Sherwood and I started experiments in which we injected drugs into the cerebral ventricular system of the cat. A cannula was permanently implanted into the skull with its tip lying in the lateral ventricle. A diagram of the implanted cannula is shown in Fig. 14. Injections could be made through the rubber diaphragm in the unanaesthetized cat without the animal being aware of it.

Amongst the various drugs and ions we injected, we found three which produced anaesthesia or sleep-like conditions (Feldberg and Sherwood, 1954, 1957). They were adrenaline, noradrenaline, and $CaCl_2$. An anaesthetic or soporific effect of these three substances had been observed before (Bass, 1914 ; Marinesco, Sarger, and Kreindler, 1929 ; Leimdorfer and Metzner, 1949 ; Leimdorfer, 1950). Fig. 15 is from a film we took and shows the condition produced in a cat about half an hour after an intraventricular injection of 50 μg. of adrenaline. The animal could be turned on its back or lifted by its front or hind legs without it struggling. The eyes were closed most of the time, but when disturbed the cat stared with open, apparently unseeing, eyes. It reacted slowly, if at all, when pricked with a pin. The condition resembled that of light anaesthesia.

Adrenaline, noradrenaline, and $CaCl_2$ are neither anaesthetics nor hypnotics. This made me wonder what would happen if the latter were injected intraventricularly. Would they also produce an anaesthesia-like condition ?

I tried barbiturates, urethane, $MgCl_2$, chloral, and chloralose (Feldberg, 1958). With the exception of chloral, they are all used as anaesthetics in animal experiments. But the amounts I injected intraventricularly were so small—a few milligrams or less—that they would not have affected wakefulness if given intravenously.

Unfortunately, the barbiturates proved unsuitable because they are soluble in strong alkali only, and I did not want to inject strong alkaline solutions into the brain cavities. However, I could dissolve at a *p*H of about 8 very small amounts, and when injected intraventricularly they often, though not always, produced sleep or an anaesthesia-like condition. Urethane produced only sleep, not anaesthesia. The cats could always be aroused, but when they were then left undisturbed they curled up again and went to sleep. On the other hand, intraventricular injections of a few milligrams of $MgCl_2$, chloral, or chloralose produced anaesthesia-like conditions which lasted for one to three hours.

The first effect produced by all these substances was hyperphagia accompanied or followed by ataxia. The effect occurred even with doses too small to produce sleep or anaesthesia—for instance, 0.2 mg. of chloralose

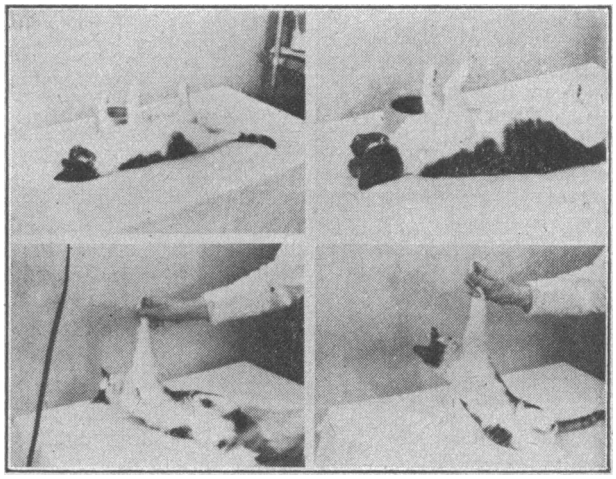


FIG. 15.—Anaesthesia-like condition in a cat produced by 50 μg. of adrenaline injected into the lateral cerebral ventricle. About half an hour after the injection. (From a film made by Feldberg and Sherwood, 1959.)

was sufficient, and after the larger doses it happened again when the cats came round from their sleep or anaesthesia. It was always a striking picture.

Immediately after the injection, when placed in its cage, the cat would rush to the meat-pot, swaying and stumbling, if already ataxic, and then, unable to stand or sit, would lie on its belly, and with its head shaking or rocking would voraciously devour the whole pot of meat, or even more. Sometimes, while still eating, the cat would be overcome by anaesthesia, and the head would just drop into the meat-pot or on to its rim. I remember that one cat, immediately after the intraventricular injection of 2 mg. of chloralose, crawled to the meat-pot and just had time to put its head into it before falling asleep.

If the cats were offered both meat and milk, they usually went for the meat; several cats, however, preferred milk. In a few cats there was compulsive biting and gnawing of inedible objects—a proffered pencil, a piece of wood lying in the cage, or, less appreciated, electrode leads attached to the cat.

In rats and cats, small bilateral electrolytic lesions close to the wall of the hypothalamus lead to hyperphagia and obesity (Hetherington, 1941; Anand and Brobeck, 1951a, 1951b). On the other hand, lesions placed more laterally in the hypothalamus completely inhibit the food intake, so that the animals would die of starvation if not fed by tube. The lateral lesions abolish also the hyperphagia produced by the more medially placed lesions. Fig. 16 illustrates the sites of such lesions in

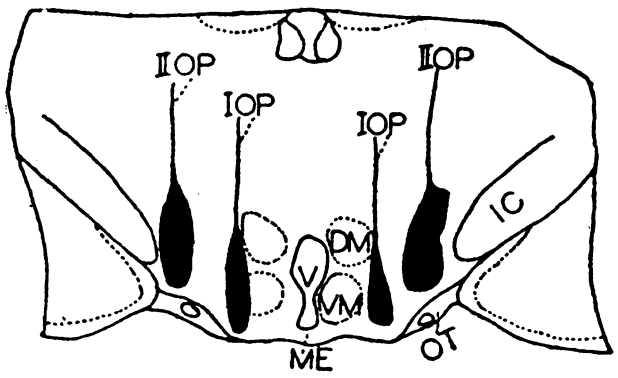


FIG. 16.—Diagram of a cross-section of a rat's brain stem. The black areas represent bilateral lesions in the hypothalamus; the dorsal prolongations represent electrode tracts. The medial lesions (I OP) induced hyperphagia and obesity. Feeding disappeared after the production of the lateral lesions (II OP). DM and VM = nucleus hypothalamicus dorso- and ventromedialis; V = third ventricle; ME = median eminence; OT = optic tract; IC = internal capsule. (From Anand and Brobeck, 1951b.)

the rat's brain. According to Anand and Brobeck, the lateral areas must be regarded as the actual feeding centres responsible for the central hunger reaction and the urge to eat, whereas the ventro-medial nuclei exert an inhibitory influence on these feeding centres. Bilateral lesions between the two areas also remove the inhibitory control and produce hyperphagia.

The anaesthetics when injected intraventricularly impinge on these medially situated nuclei, and, by "anaesthetizing" them, remove the inhibitory control over the feeding centre, thus producing the urge to eat.

Hyperphagia can apparently also occur when the anaesthetics reach the brain via the blood-stream, provided that anaesthesia does not supervene too quickly. At least, I found this so with chloralose. To produce full anaesthesia in a cat one usually injects 70 to 90 mg./kg. intravenously. When I injected intravenously only 10 mg./kg., the cats began to eat immediately after the injection, although they had been well fed before, and continued to eat vigorously and without interruption for 10 to 20 minutes and then drank milk or water for another few minutes. While eating and drinking they became very ataxic.

To come back, however, to the anaesthesia-like condition. When deeply under, the cat can be turned on its side or back, and it remains in this position. The nictitating membranes are relaxed, the pupils are narrow and slit-like, the eyes are mostly closed. The respiration is slow, sometimes very slow, and the heart rate shows strong sinus arrhythmia which is characteristic for sleep. In addition, each substance may produce specific effects which are also seen when the substance is given by the intravenous route. For instance, a characteristic feature of intravenous chloralose anaesthesia is the hyperexcitability. When a cat is under chloralose anaesthesia, tapping its foot causes a strong twitch of the leg, and a sudden noise or banging at the operating-table may result in vigorous jerking. The same hyperexcitability is found after intraventricular chloralose. This suggests that it is due to a subcortical action of chloralose, at structures close to the wall of the ventricles or aqueduct. One thinks of the descending reticular formation. The hyperexcitability is actually so strong and persistent after intraventricular chloralose that it would be difficult to perform operations in this condition.

And, finally, what about the E.E.G.? Would we record the typical synchronization so characteristic for sleep and anaesthesia; the high-voltage slow waves, the spindle bursts?

For some other purpose Professor Malcolm (1958), together with Mr. Gold, had developed a beautiful little radio-transmitter which a cat can carry on its back without apparent discomfort. Fig. 17 shows this transmitter strapped on to a cat. The cat had a burr-hole made in the skull so that a microelectrode could be lowered into the superficial layers of the cortex; the electrode was connected to the transmitter, and the E.E.G. could be picked up in another room and photographed. For our purpose, the cat also had an implanted cannula for intraventricular injections.

Fig. 18 shows the result of an experiment by Professor Malcolm and myself. A shows the noise level of the

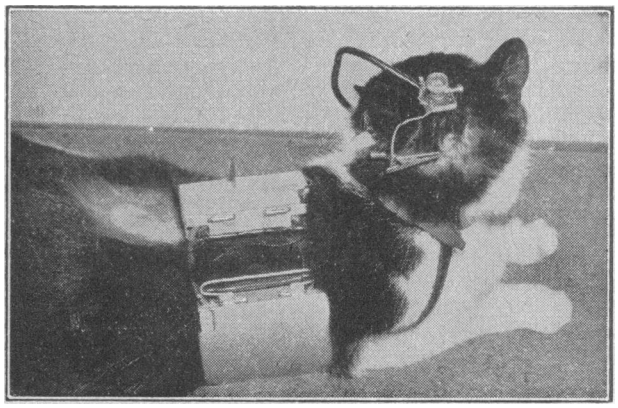


FIG. 17.—Radio-transmitter strapped on to a cat. (From Malcolm, 1958.)

transmitter when not connected to the electrode. B shows the fully desynchronized E.E.G. of the waking cat. Then 2.4 mg. of chloralose was injected intraventricularly. C and D were taken 10 and 20 minutes, E and F 40 minutes, and G 70 minutes after the injection, while the cat was still deeply under and could not be roused to full wakefulness. The E.E.G. shows bursts of typical high-voltage waves. H and J were taken about two hours after the injection. Between H and J, I went into the room where the cat was lying and succeeded in arousing it. She stretched out her forelegs like a cat waking up, and Professor Malcolm at once noted a strong reduction of the E.E.G. activity. The E.E.G. became desynchronized as shown at J. K was taken nearly four hours after the injection. The cat was awake. The E.E.G. fully desynchronized. This record was taken during the stage where the ventromedial nuclei of the hypothalamus were apparently still "anaesthetized" because it was taken while the cat lapped up a full pot of milk.

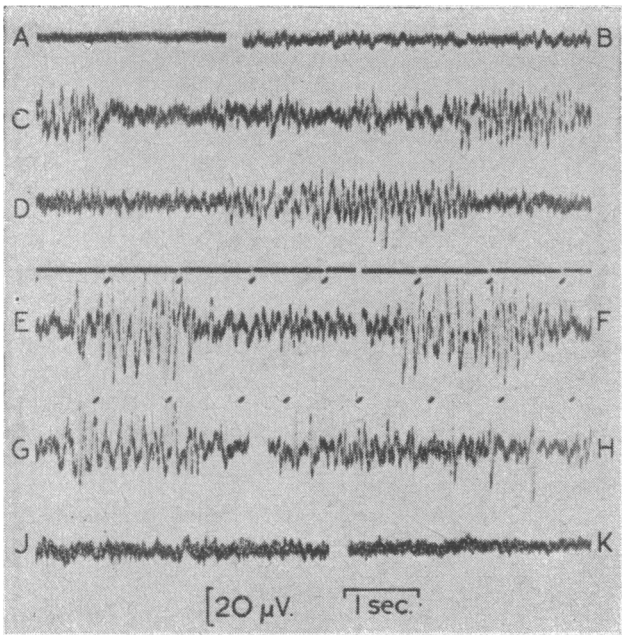


FIG. 18.—Records taken from a microelectrode in the superficial layer of the cerebral cortex of a cat with the radio-transmitter shown in Fig. 17. A, noise level; B, E.E.G. before, and C to K at various times after, an injection of 2.4 mg. of chloralose into the lateral cerebral ventricle of a 3-kg. cat. For details see text. (From Feldberg and Malcolm, 1959.)

With this experiment I have come to the end of my attempt to present a physiological approach to the problem of consciousness, or unconsciousness, and of the neural basis of the anaesthetic state. I have tried to show how this problem has developed over the past 25 years, and how essential it has been for this development that the clinician, the physiologist, the pharmacologist, and the anatomist have shared their experience.

Summary

It is not so long ago since neurologists supposed that consciousness was exclusively a function of the cerebral cortex, and that the loss of consciousness from cerebral haemorrhage was caused by general cerebral anaemia. Yet removal of the cerebral hemispheres does not lead to loss of consciousness but to a condition of idiocy. And there is abundant clinical evidence that disturbances of consciousness are associated not with lesions of the cerebral cortex but with lesions of the diencephalon and perhaps of the rostral parts of the mesencephalon. These findings are in accord with the conclusions arrived at by the physiologist.

Bremer started from the hypothesis that sleep is the result of deafferentation—that is, of suppression of the impulses which usually reach the cerebral cortex. He showed in cats that after transverse section of the brain at mid-collicular level the head of such a cerveau isolé behaved as if it were asleep, and its E.E.G. showed the typical high-voltage slow-wave pattern. However, the cerebral cortex receives the signals in anaesthesia as they travel up the ascending pathways. Bremer's concept of deafferentation thus required additional interpretation.

This interpretation was provided by the work of Magoun and Moruzzi on the reticular activating system of the brain stem. This system of diffuse aggregation of cells in the central core of the brain stem receives sensory signals from collaterals of all kinds of ascending fibres and sends impulses to practically the whole cortex, desynchronizing its high-voltage slow-wave E.E.G. pattern and alerting the cortex. Arousal, wakefulness, or the conscious state can be expressed in physiological terms as a function of the ascending reticular formation in alerting the cortex.

Lesions in the area of the ascending reticular formation produce sleep-like conditions.

During the stupor of concussion the normal responses to an afferent stimulus in the reticular formation are absent, but those in the lateral ascending pathways remain.

Anaesthetics, even if they act diffusely upon the brain, have a predilection for the reticular activating system; they block the ascending conduction in this medially situated system of the brain stem, whereas the laterally conducted impulses remain unimpaired and reach the cortex.

At first sight the classical observation of Hess that a cat falls asleep on weak low-frequency stimulation of the massa intermedia or the medially situated intralaminar thalamic nuclei does not seem to conform with these findings. Hess's effect appears to be related to the recruiting response of the diffuse thalamo-cortical system. Both effects suggest that we can drive the cortex on stimulation of the medial thalamic nuclei provided we use weak current and a rate of stimulation close to that of the normal slow rhythm of the sleeping brain.

Since the structures which on excitation cause arousal, and on injury loss of wakefulness, and which are selectively blocked in anaesthesia are situated close to the midline lining the walls of the third ventricle and of the aqueduct, it is not surprising that sleep-like and anaesthesia-like conditions are produced with drugs injected into the lateral ventricle. Such effects were produced with adrenaline, noradrenaline, and $CaCl_2$, and also with some anaesthetics ($MgCl_2$, urethane, chloral, and chloralose) injected in amounts far too small to produce such effects on intravenous injection. The immediate effect of the anaesthetics was hyperphagia, probably due to "anaesthesia" of the ventro-medial nuclei of the hypothalamus, which are known to exert an inhibitory influence on the more laterally situated feeding centres.

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According to a British United Press report from Frankfurt, 428 surgeons, 125 dentists, and 30 veterinary surgeons fled from Eastern Germany to the West in the first eight months of this year.

TREATMENT OF IRON DEFICIENCY WITH FERROUS FUMARATE

ASSESSMENT BY A STATISTICALLY ACCURATE METHOD

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It is desirable to know how the new iron preparation ferrous fumarate compares with pre-existing therapies. To commend itself for routine use it should be at least as effective as established drugs, and have fewer or no unpleasant side-effects, as well as being safe. The results reported below show that these requirements appear to be satisfied by ferrous fumarate.

For many years the mainstay of iron therapy has been ferrous sulphate. In 1836, Ashwell, when discussing the treatment of chlorosis, said that the sulphate of iron was "probably the most efficacious and possessed more specific properties than any of the rest." Davidson (1933) urged the use of ferrous sulphate tablets, adequate treatment with which still costs only one penny a week. Gastric symptoms such as epigastric discomfort, nausea, and vomiting have often been reported after its use. In a recent comparative trial the incidence of such side-effects was found to be 13% with ferrous sulphate (O'Sullivan, Higgins, and Wilkinson, 1955). Girdwood (1952) drew attention to a strong psychological intolerance shown by his patients towards tablets of ferrous sulphate, but only when they were coated green. Kerr and Davidson (1958) showed by a double blind trial, however, that unrecognized control pills caused the same incidence of side-effects as did the active iron pills, including ferrous sulphate. Ingestion of an overdose of ferrous sulphate by children who have mistaken the green sugar-coated tablets for sweets has resulted in death (Forbes, 1947; Thomson, 1947) and has been shown to cause pyloric stenosis and fibrous stricture of the pyloric antrum or mid-portion of the stomach (Ross, 1953; Shepherd, 1955). Despite these disadvantages, ferrous sulphate is still accepted as a very effective therapeutic compound.

Many alternative potent preparations of iron have been used in order to avoid undesirable side-effects and dangers to children. Ferrous gluconate, originally recommended by Reznikoff and Goebel (1937), has lately become one of the most popular of iron tablets. These tablets are sugar-coated and relatively cheap, although four times as expensive as ferrous sulphate. The incidence of toxic side-effects has been estimated at 4%, with clinical efficacy similar to that of ferrous sulphate (O'Sullivan *et al.*, 1955). Deaths attributable to overdosage had not been reported by 1955 (Hoppe, Marcelli, and Tainter) and no report of a death resulting from ferrous gluconate has been seen since then. There have been many other effective but even more expensive

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