STAGES AND SIGNS OF PENTOTHAL ANESTHESIA:
PHYSIOLOGIC BASIS

B. ETSSEN, M.D., AND II. E. HIMWICH, M.D.

Albany, N. Y.

The recent war has climaxd the extensive clinical use of intravenous pentothal sodium for the production of surgical anesthesia. It is to be expected that the returning surgeone will ask for this type of anesthesia and that the anesthesiologist will use this drug extensively.

The civilian population presents a different problem than that of the members of the Armed Forces in regard to surgical and anesthetic risk. The extremes of age, the poorly nourished, the debilitated and the chronic diseased patients are all unduly susceptible to excessive depression. Some of the guides used at present to ascertain the clinical depths of pentothal anesthesia are the relative degrees of respiratory depression and the presence or absence of a muscular response to a painful stimulus. These are not sharply definitive but indicate only the approximate depth of anesthesia. The lack of a systematic study of the clinical signs is a factor in the failure of recognizing any untoward depression and of preventing excessive depths of anesthesia.

The purposes of this paper are to present a physiologic basis for the classification of the stages and clinical signs of pentothal anesthesia, so that the anesthetist may gain insight into the mechanism, and, more important, a correlation between the degree of cerebral metabolic inhibition and the various anesthetic stages.

A guide to the pattern of the clinical changes is afforded by the suggestion of Hughlings Jackson (1) that the newer phylectic and higher anatomic portions of the brain regulate and control the older and lower areas and, when the function is depressed in a newer layer, the cerebral part immediately below assumes dominant control. Although the cerebral components are integrated in such a manner that the brain acts as a single organ, it is known that to some extent there is an allocation of specific functions to different cerebral areas. Recent work indicates

* From the Departments of Anesthesia and Physiology and Pharmacology, Albany Hospital and Albany Medical College, Union University, Albany, New York.
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‡ Present address, Chemical Warfare Service, Medical Division, Edgewood Arsenal, Maryland.

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that the functional organization of the brain consists of five phyletic layers (2, 3), each of which is a seat of activities similar to those disclosed by a series of progressively descending surgical transactions of the neuraxis.

Before presenting the detailed description of the clinical stages and signs of pentothal anesthesia, we feel that it will be of aid to outline the underlying physiologic mechanisms so that the reader may be better able to appreciate the deviations caused by pentothal.

The physiologic basis, in brief, may be divided into two parts: first, the symptoms and signs allocated to each layer of the normal unanesthetized brain, and second, an examination of the metabolic rates of the various parts of the brain as well as the influence of barbiturates upon brain metabolism.

![Diagram of the brain](attachment://brain_diagram.png)

**Fig. 1.** Representation (transverse section) of the brain disclosing the five phyletic areas: 1. cerebral hemispheres; 2. subcorticodiencephalon; 3. midbrain; 4. pons and upper medulla; 5. medullary centers.

**Neuro-anatomic Allocation**

Figure 1 illustrates the organization of the brain according to the phyletic pattern. The layers are numbered in order, beginning with the most newly acquired cerebral hemispheres and ending with the oldest, the medulla oblongata. The pattern of activities for each layer pertinent to the subsequent discussion on pentothal anesthesia is presented.

1. **The Cerebral Hemispheres.**—The cerebral hemispheres contain the most discriminating analyzers for the appreciation of the environment as well as the centers for the finest coordination of motor activities. Consciousness, defined for the present study as awareness of the environment, depends largely on this phyletic layer.

2. **The Subcorticodiencephalon.**—The second phyletic layer, the subcorticodiencephalon, is composed of several parts; chief among them are the thalamus, hypothalamus and subcortical motor nuclei.
thalamus, a relay station for sensory impulses, transmits most of them to the cerebral hemisphere but is, itself, an organ of crude awareness. It lacks the fine analyzers resident in the cerebral cortex. An example of the function of this lower sensory center is afforded by a painful stimulus, which cannot be interpreted accurately in regard to the site of application or the character of the instrument producing the pain. The hypothalamus, in which resides the fight or flight patterns for the organization of the bodily resources in emergencies, contains centers for the sympathetic and parasym pathetic nerves. The sympathetic activities are usually predominant over the parasympathetic in this portion of the brain. The visceral or autonomic organs of the body including those of the cardiorespiratory system are, in part, influenced by these centers. The subcortical motor nuclei are mainly responsible for stereotyped movements in contrast to the "spontaneous" activities of the motor areas in the cerebral hemispheres.

3. The Midbrain.—The midbrain contains several motor nuclei, including those of the third and fourth cranial nerves, which control all but one of the external ocular muscles. A portion of the nucleus of the third cranial nerve, the Edinger-Westphal nucleus, gives rise to the tonic constrictor impulses to the pupils. The activity of this nucleus is responsible for the constriction of the pupil to light and inhibition of this center is a cause of pupillary dilation in response to pain (4). The phylogenetically oldest type of pain center, according to Walker (5) is found in the midbrain. Such a center is consistent with our observations that a painful stimulus can reflexly influence the respiratory rate and the size of the pupil even when the thalamus and cerebral cortex are suppressed. A part of the nucleus of the fifth nerve is also situated in this layer.

4 and 5. The Pons and the Medulla Oblongata.—The pons contains the sixth cranial nerve and portions of the nuclei of the fifth and seventh nerves, the afferent and efferent pathways of the corneal reflex. All the other cranial nerves as well as the vital centers for the control of respiration and blood pressure reside in the medulla oblongata.

Biochomic Aspects

Metabolic studies of excised cerebral tissues corroborate this phylectic concept. In the dog, cat and rat the various parts of the brain have been found to possess characteristic metabolic rates. (6, 7, 8). The rostral areas, such as the cerebral cortex and basal ganglia, exhibit the fastest rate, while the medulla oblongata possesses the slowest one. Quastel has shown that barbiturates inhibit cerebral oxidations (9). Other work on excised cerebral tissue reveals that the metabolic depression occurs according to a phylectic pattern, the cerebral cortex being the part of the brain which suffers the greatest metabolic inhibition (8). These in vitro results could not be applied directly to the living organism because of the high dosage required to inhibit cerebral metab-
lism and, therefore, necessitated an extension of these observations to the intact animal. Cerebral metabolism was found to be retarded by pentothal both in the monkey (10) and the dog (11), but it required experiments on man to determine the phyletic arrangement. This was made possible because of an asymmetric venous return from the brain in man (12, 13). The cortical component usually appears predominantly in one of the two internal jugular veins, while the other vein drains most of the blood from the basal ganglia. This division of blood does not apply to the more caudal portions of the brain which are equally represented in both internal jugular veins. In every instance pentothal anesthesia induced a depression of cerebral metabolic rate and in a characteristic manner: Cortical oxidations are depressed earlier and more profoundly than those of the rest of the brain. This depression is a progressively descending phenomenon, which may finally envelop the entire brain (14). The correlation between the metabolic depression of the brain and the clinical symptoms produced by pentothal is one of the main issues of this paper.

Method

Observations are made on nonpremedicated and nonoperative patients, who were anesthetized with the intravenous administration of pentothal sodium, 1 per cent solution. A needle communicating with a two-way stopcock was inserted into the antecubital vein, permitting the injection of pentothal in one of two different ways: either by syringe or by the intravenous drip method. The initial injection was slow irrespective of the source of pentothal and varied with each patient. The solution was allowed to run at such a rate as to obtain any required level of depression and retain it over a given period. If it was desired to lighten the plane of anesthesia after the initial injection had been made, the administration of pentothal sodium was slowed or stopped. For increasing depths, the injection of the solution was continued or accelerated.

Observations of the clinical signs were made on the patient in both the resting state and during the various stages of anesthesia. These signs were observed in a definite orderly fashion, first noting the eyelid tone, the absence or presence of the eyelid reflex, then eliciting the corneal reflex. The size of the pupils, the position of the eyeballs and their movements were also observed. Respiratory activity was then recorded, including rate and amplitude. Deep tendon reflexes were next elicited, particularly the knee and ankle jerk. The sign of Babinski and flight or withdrawal were noted.

Responses to various types of painful stimulation were next evoked: first, touch; second, slight pressure; third, light pain as elicited by pin prick; fourth, moderate pain by clamping the skin with a padded clamp; fifth, severe pain by clamping the skin with an unshielded forceps; and, sixth, pressure on the supra-orbital nerve. A time interval was per-
mitted to elapse between each observation in order to avoid the ana-
leptic effect of pain. The responses to nocuous stimuli were used as
an aid in differentiating the various stages but were intended to simu-
late the various types of pain caused by surgery. All of these observa-
tions were made at each stage of anesthesia, which was maintained by
an appropriate rate of flow of pentothal.

In those experiments in which cerebral blood flow determinations
were made, needles with stilts were inserted into both internal jugular
veins and the femoral artery with the aid of procaine for the local con-
trol of pain. The stilts were removed and blood samples were col-
lected simultaneously from the three vessels in the nonanesthetized
subjects and during the various stages of pentothal anesthesia. Blood
flow determinations were made according to the method of Kety and
Schmidt (15). The cerebral blood flow when multiplied by the cerebral
arteriovenous oxygen difference (16, 17) yielded cerebral metabolic
rate.

**Clinical Signs and Stages of Anesthesia**

In order to obtain a fast induction and surgical anesthesia, pentothal
is usually administered rapidly and in a strong concentration. The
erlier stages are then telescoped and may be missed, but the full gamut
of the signs of intravenous pentothal anesthesia are best seen when this
drug is given slowly in a dilute solution. However, irrespective of the
method of injection and concentration of the drug, the clinical signs re-
main consistent for any given stage (18).

Although some of the pharmacologic actions of pentothal may not be
influenced by the depression of cerebral oxidations, as, for example,
a transitory respiratory depression occurring in the earlier phases, in
most instances the clinical signs are related to the metabolic inhibition
and may be segregated into four stages conforming, in general, to a
definite pattern. It must be realized, however, that the changes do not
take place in an abrupt, step-wise manner, but develop gradually from
one stage to the next. Infrequent variations are not presented in the
following clinical picture. The reader is referred to figure 2 for the
correlation of stages and neuroanatomic allocation and figure 3 for
various clinical signs observed in each stage.

**Stages of Anesthesia**

The progress of pentothal anesthesia is divided into four stages. The
third stage, named surgical anesthesia, is composed of three planes.

*Stage I. Clouded Consciousness.*—The functions ascribed to the
highest phyletic layer, the cerebral cortex, are moderately depressed
throughout this stage. Environmental contact and performance of
voluntary motor activities are impaired. Euphoria is a characteristic
manifestation. The patient may still respond to questions but the
### Stages and Signs of Pentothal Anesthesia

<table>
<thead>
<tr>
<th>Stage</th>
<th>Anesthesia</th>
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<th>Brain</th>
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<tr>
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<td>Slight depression</td>
<td>Cortex to Moderate depression of Cortex</td>
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<td></td>
<td>Loss of</td>
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<td>Discrimination</td>
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<td>Impairment of</td>
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<td></td>
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<td>Contact</td>
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<tr>
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<td>Loss of</td>
<td>Predominant control by subcortex</td>
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<td></td>
<td></td>
<td>Consciousness</td>
<td></td>
<td></td>
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<tr>
<td>III</td>
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<td>Hypoactivity</td>
<td>Moderate depression of subcortex</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>to Painful</td>
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<td></td>
<td></td>
<td>Stimulus</td>
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<tr>
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<td>Loss of</td>
<td>Predominant control by midbrain</td>
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<td>Somatic Response to Pain</td>
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<td>Plane II</td>
<td>Deep Surgical</td>
<td>Loss of</td>
<td>Moderate depression of midbrain</td>
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<td></td>
<td></td>
<td>Visceral Response to Pain</td>
<td></td>
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<tr>
<td>Plane III</td>
<td>Impending Failure</td>
<td>Fall in</td>
<td>Moderate depression of Pons</td>
<td></td>
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<td></td>
<td></td>
<td>Pulse Pressure</td>
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</table>

*Fig. 2. A correlation between the stages of pentothal anesthesia and the outstanding clinical signs and their neuro-anatomic allocations.*

The character of the answer reveals depression of cortical control. Fine discrimination is impeded; an increased sensitivity to touch and pain appears in the lowest portion of this stage.

**Stage II. Hypersensitivity.**—The stage of hypersensitivity begins with a loss of consciousness when the patient is no longer aware of his environment. The functions of the cerebral cortex are suppressed and the second layer is now the highest one remaining in function, although it, too, is under slight depression. This depression applies particularly to the hypothalamic activities and those of the subcortical motor nuclei,
and it is for this reason that the excitement described by Guedel in the second stage of ether anesthesia (19) is not observed with pentothal. The thalamus is deprived of most of its modalities except that of pain. A painful stimulus, however, will elicit a hyperactive response exemplified by exaggerated and inappropriate movements of the arms and legs. These involuntary reactions subside immediately after the stimulus is withdrawn.

**Stage III. Surgical Anesthesia.**—The stage of surgical anesthesia is divided into three planes: (a) light, (b) moderate, and (c) deep. They are characterized by alterations in responses to pain, whether muscular, pupillary or respiratory, as well as changes of eyeball movements.

**Plane I. Light surgical anesthesia.**—With the beginning of the first plane the response to a painful stimulus becomes diminished. For example, even the application of a clamp to the skin can evoke only a slight movement of a leg or an arm. For this reason it is believed that minor surgical procedures may be performed here. At this time not only are the cerebral hemispheres suppressed but also the second phyletic layer, though still functional, is depressed deeper than in the second stage.

**Plane II. Moderate surgical anesthesia.**—In the second plane, muscular response to a painful stimulus is abolished but pupillary dilatation and respiratory changes are still evoked on application of a clamp to the skin. The suppression of the second phyletic layer accounts for the failure of somatic or muscular reactions to painful stimuli, and the midbrain, though somewhat depressed, still acts as the highest remaining functional level. The persistence of the pupillary and respiratory responses may be attributed to a midbrain pain center (5). From this center impulses emanate to the Edinger-Westphal (third) nucleus, thus inhibiting its tonic constrictor effect upon the pupil. When the patient is not stimulated the pupils are constricted and do not react to light.

**Plane III. Deep surgical anesthesia.**—As muscular responses to pain have ceased in the previous plane, the distinguishing signs of Plane III are the loss of pupillary and respiratory reactions to various stimuli, because the lowest pain center becomes increasingly depressed with the other midbrain mechanisms.

**Stage IV. Impending Failure.**—All visible responses to pain have previously disappeared, but the estimation of the depth of narcosis is aided by an evaluation of pulmonary and cardiovascular function. The predominant signs of the fourth stage are extreme depression of respiration and diminution of pulse pressure. The onset of pupillary dilatation frequently observed may be ascribed, in part, at least, to anoxia. Although the pons and medulla are not free of sensible metabolic inhibition, they are the highest active cerebral regions. This stage must be regarded as a warning sign that further progression in the depth of anesthesia would suppress the vital centers and lead to the dangerous fifth stage of medullary failure.
STAGES AND SIGNS OF PENTOTHAL ANESTHESIA

SIGNS OF PENTOTHAL ANESTHESIA

<table>
<thead>
<tr>
<th>STAGES OF ANESTHESIA</th>
<th>PUPIL SIZE</th>
<th>PUPIL REACT. TO LIGHT</th>
<th>PUPIL REACT. TO PAIN</th>
<th>EYEBALL ACTIVITY</th>
<th>EYELID TONE</th>
<th>CORNEAL REFLEX</th>
<th>RESP. MUSCLE REACT. TO PAIN</th>
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<td>4+</td>
<td>4+</td>
<td>VOL.</td>
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<td>4+</td>
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<td>4+</td>
<td>4+</td>
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<td>4+</td>
<td>4+</td>
<td>4+</td>
<td>O</td>
<td>0</td>
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<td>3+</td>
<td>3+</td>
<td>3+</td>
<td>SLIGHT</td>
<td>2+</td>
<td>4+</td>
<td>DIM</td>
<td>1+</td>
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<td>To 0</td>
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<td>2+</td>
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**Fig. 3.** The series of clinical signs are correlated with the four stages of pentothal anesthesia.

SIGNS OF ANESTHESIA

The series of progressive changes of the clinical signs during the various stages of pentothal anesthesia are presented in figure 3.

**Pupil Size.**—The size of the pupil gradually becomes smaller with increasing depth of anesthesia and is constricted in the second and third planes of the third stage. The absence of earlier dilatation of the pupil may be attributed to depression of the hypothalamic mechanisms (20) though the pupil may be dilated when anoxia supervenes.

**Pupillary Reaction to Light and Pain.**—The pupillary reaction to light disappears in the second plane of the third stage when the Edinger-Westphal nucleus is obtunded. The dilatation with pain fails to occur in the third plane of the third stage, probably because of depression of the midbrain pain center.

**Eyeball Activity.**—Eyeball movements become involuntary in the second stage, and even in the first plane of the third stage some slight activity is present. Then, in the lower part of the second plane and in the third plane, the eyeballs become fixed and centrally placed. The loss of movement can be explained by a depression of the median longitudinal bundle and the nuclei of the third and fourth cranial nerves.

**Eyelid Tone.**—The eyelid tone gradually recedes in conformity with skeletal muscle tone throughout the body.

**Corneal Reflex.**—The corneal reflex exhibits a greater inconsistency than any of the other signs, perhaps because of its association with pain centers situated in three different phyletic layers. Thus, this reflex...
may disappear in the second stage or in the first and the second planes of the third stage. It is not invariably absent, however, until the third plane is attained, when the three top phyletic layers are obtunded.

Effect of Pentothal on Respiration.—Respiratory activity must be considered separately throughout the four stages. Respiratory arrest may take place in any of the last three stages, and, therefore, need not be indicative of the actual depth of anesthesia. Apnea occurring in the upper levels of anesthesia is usually temporary but in the later stages becomes prolonged because the respiratory centers are then deprived of their metabolic support. This phenomenon of respiratory arrest in light anesthesia may be avoided by a slow and gradual intravenous administration of pentothal and then the pattern of breathing becomes more consistent with the degree of metabolic inhibition of the brain. An apparently normal respiratory rate and rhythm persist until the second plane of the third stage and at that time a diminution of amplitude and an increase in rate are observed.

Breathing, which becomes still more rapid and shallow in the third plane, may give rise to apnea which, however, is the usual occurrence in the fourth stage. In the second and third planes of the third stage and in the fourth stage the pulmonary exchange is so depressed that arterial oxygen is reduced (21, 22). Thus, in the deeper stages anoxic anoxia is added to the existing histotoxic anoxia and, therefore, the brain labors under a double handicap.

Muscular Reaction to Pain.—The muscular responses to all kinds of pain are unchanged in the first stage but are hyperactive in the second when the second phyletic layer is dominant. All reflex movements become minimized in the first plane with depression of the second layer. When the functions of this cerebral area are entirely suppressed, skeletal muscular reactions fail completely.

Pulse.—The pulse rate is altered by pentothal only when anoxia or carbon dioxide accumulation supervenes and at that time the rate increases.

Blood Pressure.—The blood pressure will fall frequently in the lighter stages of anesthesia and especially during rapid induction. This phenomenon, however, is usually transient. There are often slight variations in the systolic and diastolic pressure, but a fall in pulse pressure is characteristic of the fourth stage.

Discussion

We have shown that the stages of pentothal anesthesia possess diagnostic signs which represent a descending neuroanatomic allocation with deepening anesthesia. The earliest clinical changes are associated with depression of the cerebral hemispheres and the latter ones with the lower phyletic areas of the brain.

This conclusion, drawn from clinical observations, receives support from cerebral metabolic studies. Because of the asymmetric cerebral
venous return (12, 13), it is possible to distinguish between the cerebral hemispheres and the rest of the brain. In a series of 5 patients (14), whose brain metabolism was studied before and during anesthesia, the metabolic rate as calculated from one internal jugular vein was higher than the other in the resting individual. The average value of the higher rate is 3.9 cc. of oxygen per 100 Gm. of tissue per minute and for the lower is 2.7 cc. of oxygen per 100 Gm. of tissue per minute. If it is true that the higher figure includes the metabolism of the cerebral hemispheres, it is also true that the cerebral cortex is most depressed in pentothal anesthesia (8, 11, 14). For example, in subject 1, the cerebral metabolic rate as calculated from the right internal jugular vein, presumably carrying the cortical return, was decreased from 4.2 to 2.4, a difference of 1.8 while on the left the fall, although significant, was only 0.5, from 2.6 to 2.1. In Case 2, the cerebral metabolic rate

<table>
<thead>
<tr>
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<td>62</td>
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<td>2.88</td>
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<td>Control</td>
<td>3.67</td>
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<td>4.22</td>
<td>40</td>
<td>1.7</td>
<td>4.93</td>
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Differences of 0.3 cc. oxygen/100 Gm. tissue/min. for cerebral metabolic rate and 8 cc. blood/100 Gm. tissue/min. are significant.

determined from the right internal jugular vein was diminished by 0.2, an insignificant difference. On the left side, however, which in this patient contained the blood from the cerebral hemispheres, the decline was greater, 2.6. Thus, in each instance the cortex was depressed and in Case 3, for example, the depression went further to include significantly the rest of the brain. In 14 observations of 9 patients the average metabolic rate of the entire brain during anesthesia was 2.1, a reduction of 36 per cent from the average control value of 3.3 (14).

In analyzing the cause for the decrease of brain metabolism during anesthesia we find that the two factors upon which it depends are both reduced; these include cerebral arteriovenous oxygen difference and cerebral blood flow. Table 1 shows that in every instance the fall of blood flow was more profound in the cortex than in the lower parts of the brain. In a total of 18 observations, including those presented in
table 1, the arteriovenous oxygen difference fell twelve times and cortical blood volume decreased thirteen times during pentothal anesthesia. A smaller arteriovenous oxygen difference despite the slower blood flow can be caused only by interference with cerebral oxidative processes. It is also probable that inhibition of cerebral metabolism is one of the factors that determines the fall in cerebral blood flow.

The data presented so far prove that barbiturates depress brain metabolism, but the role played by this depression in the production of anesthesia is not the entire story. The depth of narcosis varies with the metabolic inhibition but its extent is inadequate to explain the entire anesthetic effect. Observations made both on animal and man reveal that some of the clinical signs are out of proportion to the depth of anesthesia. The results of studies with the electroencephalogram showed that sensory impulses reach the cerebral hemispheres, but motor expression is preferentially depressed with barbiturates (23).

It has been shown that the barbiturates have a specific effect in interfering with nervous activity of the hypothalamus (20) and this has been substantiated by our clinical observations, particularly those made during the second stage of pentothal anesthesia. Perhaps the variability in loss of corneal reflex and the specific effect on the respiratory center may also be attributed to interference with nerve function. This does not mean, however, that the histotoxic action of the barbiturates is not a part of the mechanism of narcosis. On the contrary, the order in which the symptoms appear during pentothal anesthesia is evidence for the metabolic factor.

Recent studies have shown that pentothal exerts an inhibition of cerebral cellular oxidation. If the arterial blood is inadequately oxygenated in the lung, however, anoxic anoxia is produced in the course of anesthesia. Depletion of arterial oxygen is frequently observed in the second plane of the second stage and becomes more marked in deeper narcosis (22). It is essential, therefore, to reinforce the respiratory activity with oxygen in order to avoid the anoxic anoxia of the second and third planes. But it must be remembered that the histotoxic anoxia is largely uninfluenced by the improved oxygenation of the arterial blood.

Changes in the deep tendon reflexes were observed during pentothal anesthesia. Increases and decreases were elicited in the various stages. At times there were discrepancies in the reflexes in the two sides of the body. There was no positive correlation with the depth of anesthesia and these reflexes were occasionally hyperactive even in the fourth stage in some patients and yet were absent in the third stage in others.

**Summary and Conclusions**

The clinical signs of pentothal anesthesia have been found to conform to a pattern which consists of four stages of progressively deepen-
STAGES AND SIGNS OF PENTOTHAL ANESTHESIA

ing anesthesia. The following are the characteristic landmarks of the various stages: Stage I, clouded consciousness. Stage II, loss of environmental contact and hypersensitivity to painful stimuli. Stage III, Plane I, light surgical anesthesia. Diminished muscular response to painful stimuli. Stage III, Plane II, moderate surgical anesthesia. Loss of muscular response to pain. Stage III, Plane III, deep surgical anesthesia. Loss of respiratory and pupillary reaction to pain. Stage IV, impending failure. Fall in pulse pressure. The evolution of the signs of clinical significance throughout the four stages is summarized in table 3. The pattern of pentothal anesthesia is the result of a two-fold mechanism: (1) a descending depression of cerebral oxidations starting with the cerebral hemispheres and extending to include the lower parts of the brain, and (2) a specific effect on nerve function exerted in certain cerebral areas.

REFERENCES


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