WHAT is anaesthesia? Is it failure of the brain to receive impulses from sensory stimuli; a failure of arriving sensory impulses to pass on into storage; or a failure of arriving sensory impulses to evoke effect? Are there levels of anaesthesia where all three of these failures take place and other levels at which they can be fractionated?

Not very long ago the answer seemed simple to the physiologist who would have replied that anaesthesia is caused by a deafferentation of the brain. In laboratory experiment this concept would appear to be borne out because surgical deafferentation of the brain at the collicular level results in an animal that cannot immediately be aroused (Bremer, 1935).

However, during the past decade there has been a growing recognition among neurophysiologists that the great systems within the brain have different major functions, all having some bearing on the problem of consciousness. That these individual functions can be differentially studied by the appropriate use of anaesthetic agents is one of the most promising potentials for research in this field.

The outstanding contribution that fundamentally changed all previously held concepts of the physiology of consciousness was the observation of Moruzzi and Magoun (1949) that repetitive excitation of the reticular formation in the central core of the brain stem induced e.e.g. arousal. The later expansion of this initial discovery and its implications for the states of vigilance and sleep form the subject of another chapter in this volume, but for those interested in anaesthesia it immediately became clear that loss of consciousness was likely to be caused more by blockade of the afferent systems in the central core than by deafferentation of the lateral classical sensory paths.

Electrolytic lesions confined to the reticular formation result in long lasting coma (French and Magoun, 1952; Lindsley et al., 1950), whereas lesions sparing the midline structures, but intercepting the classical sensory pathways in the brain stem, do not affect the sleep–waking cycle. Early experiments clearly indicated some role of this system in the reversible blockade produced by anaesthesia (French and Magoun, 1952; French, Verzeano and Magoun, 1953; King, 1956; King, Naquet and Magoun, 1957). These studies showed that single impulses entering by sensory nerves reached the cortex serially—first by the fast conducting specific pathways and then 8 to 12 m.sec later by the more slowly conducting central route. Transmission in this latter route was shown to be extremely vulnerable to barbiturate narcosis.

An example from the visual system is shown in figure 1 in which the average of several responses is depicted. This computer technique—which has been described elsewhere (Barlow, 1957)—was used because the waveform of single responses could not be detected in the background e.e.g. activity of the unanaesthetized animal. The short latency response that travels up the classical pathways is present in both the lateral geniculate nucleus and the visual cortex in the normal animal and persists at this level of anaesthesia. The response that follows 12 m.sec later comes from the reticular formation and bypasses the geniculate nucleus. It is abolished by the barbiturate.

As this work unfolded, some of the paradoxes that had plagued the electrophysiologist began to find their explanation. One was the general experience that, as already seen, a clear-cut electrical response to peripheral stimulation could be
SOME EFFECTS OF ANAESTHESIA ON THE BRAIN

Figure 1

Waveform of averaged responses to a flash computed in 1 m.sec steps.

Left, above: Cortical responses from implanted electrodes in an unanaesthetized cat showing initial surface-positive (downward) deflection beginning at 12 m.sec after the flash. Development of surface-negative wave broken into by another surface positive wave beginning 24 m.sec after flash.

Left, below: Simultaneous recording from lateral geniculate nucleus. Only the primary response is seen, the second having presumably travelled from the reticular formation by an extrathalamic route to the cortex.

Right, above: Pentobarbitone anaesthesia induced in the same cat abolishes all but the primary response, the principal site of action of the barbiturates being in the reticular formation.

Right, below: The envelopes of the averaged cortical responses, with and without anaesthesia have been superimposed for contrast. Note longer latency with barbiturate.


recorded from the cortex even in relatively deep barbiturate anaesthesia. In fact, in this condition, the response could be more clearly seen because the background e.e.g. potentials were now depressed. With the elucidation of the role of the ascending influence from the reticular formation, it became clear that the latter, obtunded by the barbiturate, depressed the background e.e.g. to a degree that the relatively unaffected classical systems were now thrown into prominence.

Another paradox had arisen from the discovery of Derbyshire, et al. (1936), and the later studies of Forbes and Morison (1939) that as barbiturate anaesthesia deepened, a "new" late response developed about 80 to 100 m.sec after the first one. The latter they named "the secondary discharge", for the anaesthetic hid from them the midline conducted response that has just been described. They showed this late response to follow an ascending route distinct from the lemniscal pathway and to enter the internal capsule from the subthalamus. Originally demonstrated in the somatic system, the secondary response of long latency evocable in barbiturate narcosis has since been demonstrated in the...
visual system and is probably general to all sense modalities (fig. 2) (Brazier, 1954a, b, c; Brazier, 1957). In the case of electrical stimulation of the somatic system, Forbes and his group (1939) described the secondary discharge as a generalized response recordable all over the cortex. In the visual system, with flash as the stimulus, no such generalization has been found. Secondary responses to retinal illumination have so far been detected only in the visual cortex (Brazier, 1957).

Usually described as being a "new" response brought in by the anaesthetic, the secondary response is nevertheless present in the unanaesthetized animal where it has a latency of 50–55 m.sec. Its amplitude is, however, usually so much less than that of the on-going e.e.g. activity that some technique (such as has been applied in figure 3) needs to be used for the averaging of
several responses, with the omission of potentials unrelated to the flash. The secondary response can also be detected by this means in chloralose or ether anaesthesia, but the phenomenon of its enhancement is essentially a feature of barbiturate action, a release from inhibition of a long latency path by suppression of the reticular pathway for short latency responses.

The long-latency secondary response of Forbes can be brought out, magnified or decreased by appropriate manipulation of the anaesthetic level, not only at the cortex (Forbes et al., 1949) but also in the hypothalamus and brain stem (Feldman and Porter, 1960).

This observation led to the suggestion that at a certain stage of narcosis the barbiturate might be blocking an inhibitory ascending system whose removal unleashed the secondary response in a long-latency pathway (Brazier, 1954b, c; Purpura, 1955). This effect is not only demonstrable in responses recorded directly from the exposed cortex of animals, but can be seen in recordings from scalp electrodes on man (see, for example, figure 4).

Evidence for an ascending inhibitory, as well as an ascending excitatory influence from the reticular formation began to accumulate from several sources. The micro-electrode studies of Machne, Calma and Magoun (1955) and Magoun (1958) clearly indicated an inhibitory component. In terms of cortical responsivity, the action of deepening barbiturate anaesthesia can therefore be viewed as a U-shaped curve. Concurrently with depression of the early transmission from the reticular formation there is release from inhibition in the extralemniscal system travelled by the Forbes response which therefore grows in amplitude. On increasing the anaesthetic the excitatory process too becomes depressed and eventually the cortex becomes unresponsive.

If, as it seems justifiable to propose, nonspecific ascending systems rather than the lateral pathways are involved in the sensation of pain, then one might perhaps expect some exacerbation of sensation at very light levels of induction by barbiturates. In an early study Tucci et al. (1949) found that when thiopentone was given intravenously very slowly in man, the first stage (before loss of consciousness) was marked by blurring of speech without change of respiration, eyelid tone or pupils, though with a slight but definite hyperactive response to peripheral stimulation. At this stage the e.e.g. shows only high voltage fast activity (fig. 5) and none of the slow waves usually associated with impaired consciousness, and since, in this period, there is no analgesia it is tempting to relate this fact to the finding in animals of an exaggerated cortical response to stimulation.

In connection with the suggestion of an extra-

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**Fig. 4**

Responses to flash recorded from the scalp in the occipital region of normal man during intravenous infusion (4 flashes at 1 per second flash rate).

*Above:* With normal saline.

*Below:* With dilute thiopentone.
Changes in the electroencephalogram of a human subject at deepening levels of thiopentone anaesthesia.

Lower right: The horizontal line represents the duration of 1 sec, the vertical line the deflection for 100 μV.


lemniscal route for pain, there is electrophysiological evidence from the work of Livingston, Haugen and Brookhart (1954) that stimulation of pain receptors in the tooth pulp evokes responses in the midbrain reticular substance. Responses in this region are also evoked by stimulation of the slowly conducting gamma-sized fibres of peripheral nerve which are thought to convey pain (Collins and O'Leary, 1954). Both of these effects can be abolished by anaesthesia, whether induced by barbiturates, ether or nitrous oxide (Haugen and Melzak, 1957).

The exact route of the Forbes response still remains to be charted, though it appears mainly to follow the extrathalamic branch of the ascending system from the brain stem that has been identified electrophysiologically by Starzl, Taylor and Magoun (1951a). Even less clearly understood is the vertex response found in man when consciousness is obtunded, either by natural sleep or by anaesthetic agents. This transient change in the e.e.g., named by its discoverers (Davis et al., 1938) the “K Complex”, is also apparently related to the conscious state by a U-shaped curve, being absent in the waking state and in deep anaesthesia, and present only at the onset of sleep or in light narcosis (fig. 6).

The enhancement of a response by an anaesthetic agent would seem paradoxical according to concepts of some of the earlier investigators who viewed the brain as having only excitatory activity, and inhibition as being merely an absence of excitation. Modern physiology teaches us that inhibition is an active process of neurones discharging and sending impulses to impinge on other neurones, creating in them a state of hyper-
polarization that effectively inhibits their discharge. This information about inhibition in the central nervous system was first obtained for neurones in the spinal cord (Renshaw, 1940; Eccles, 1957), but has since been demonstrated in the brain (Phillips, 1956).

Thus when some potent agent, such as an anaesthetic, reaches the brain there are two active processes upon which it can act: excitatory systems and inhibitory systems. In the unanaesthetized brain there would appear to be an effective balance between excitation and inhibition which may be regarded as part of the fine degree of homeostasis maintained in the normal state.

In the light of modern knowledge there can be little doubt that it is the ascending activating influence of the brain stem reticular system on cortical excitability that is impaired by most anaesthetics. The cortical e.e.g. signs of arousal that follow high frequency stimulation of the reticular system fail to appear in anaesthesia (Arduini and Arduini, 1954; King, 1956) (fig. 7). The finding that anaesthetic agents prevent arousal of the cortex, not only to peripheral stimulation but also to direct reticular stimulation, would indicate that the vulnerable locus of blockade is not at the synapse where collaterals from the specific sensory pathways enter the reticular core but beyond this point (Starzl, Taylor and Magoun, 1951). In fact, at a level when the animal is anaesthetized, respon-
**EFFECT OF NEMBUTAL ON E.E.G. AROUSAL**

**AROUSAL BY OLFATORY STIM.**

Control

2 mg/K

10 mg/K

**AROUSAL BY RETICULAR STIM.**

Control

2 mg/K

10 mg/K

10 mg/K

Stim. V

X2

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**FIG. 7**

The electroencephalographic arousal effect in a rabbit and the depressing effect on it of increasing doses of pentobarbitone. The black horizontal lines indicate the period of stimulation in each case. From: Arduini and Arduini (1954), *J. Pharmacol. exp. Therap.*, 110, 76.

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**FIG. 8**

Responses to flash recorded in the reticular formation in the same cat with different anaesthetic agents. Latencies to the peak of the wave are indicated. (Averages of 50 responses.)
ses to sensory stimulation can be recorded from the reticular formation (whether the agent be barbiturate, ether, chloralose or tribromethanol) (fig. 8).

At an earlier period, the ascending pathways in the reticular substance of the mesencephalic brain stem were thought to be entirely polysynaptic and to be composed only of neurones with short axons. The work of Scheibel and Scheibel (1958) on the intimate neuronal structure has more recently revealed the presence also of cells with long axons (both ascending and descending) that run almost the full length of the midbrain core. Whether or not these long fibres subserve the ascending extrathalamic route to the internal capsule, in contrast to the polysynaptic route through the midline thalamus (Starzl and Magoun, 1951; Starzl, Taylor and Magoun, 1951a, b), remains to be clarified but, if it be granted that synapses are the most probable locus of anaesthetic action (Bremer, 1937), several different sites of action are available to these drugs. The site of lowest threshold for one agent may not be the same as for another.

The polysynaptic nature of some of the components of the mesencephalic brain stem is supported by the pharmacological evidence that, at recording sites more rostral than those used for figure 8, and impairment of sensorily evoked responses by barbiturates and by ether becomes apparent (French, Verzeano and Magoun, 1953; French and King, 1955; King, 1956; Killam,

![Fig. 9](https://example.com/fig9.png)

**Fig. 9**

Responses to flash recorded in the centre median in the same cat with different anaesthetic agents. (Averages of 50 responses.)
Killam, and Shaw, 1957; King, Naquet and Magoun, 1957). Chloralose, up to doses of about 30 mg/kg, on the contrary, does not suppress the reticular response at any level of the brain stem.

Moving up to the level of the diencephalon one finds responses in the centre median and the intralaminar cell groups of the thalamus at anaesthetic doses of barbiturates, chloralose and tribromethanol, but not with ether (fig. 9).

These nonspecific nuclei* of the thalamus and the caudate nucleus have a characteristic electrical sign by which their function can be tested. Electrical excitation by slow pulses of any one of these nuclei evokes a surface negative response on the cortex that slowly grows in amplitude during the first few pulses. This is a response, in the upper layers of the cortex, of the dendrites on to which the projections from the nonspecific thalamus make synaptic connection. This characteristic response was discovered by Dempsey and Morison (1942) and named by them the "recruiting response".

Recruiting responses, present in the awake animal (Evarts and Magoun, 1957), are abolished when it is alerted by stimulation of the reticular formation (Moruzzi and Magoun, 1949) and, conversely, become intensified with impairment of consciousness. These responses behave as

*These intralaminar groups include the following nuclei: parafasciculus, limitans, paracentralis, centralis lateralis.

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**Fig. 10**

An example of the fast-frequency bursts (35-40 c/s) evocable in the amygdaloid complex of unanaesthetized man during distressful episodes.

though depression of activity in the reticular formation resulted in a release of the mechanism for their production.

In studies of recruiting responses under different pharmacological conditions, King (1956) has shown them to be augmented by barbiturates and chloralose, and depressed by ether. Again the different action of ether becomes apparent. From King's experiments and from those from which figure 9 is drawn, one would conclude that ether, alone of the agents mentioned, was exerting a major depressant effect at the level of the midline thalamus.

The above review of the relative vulnerability of various sites that sensory impulses may pass through en route to the cortex has been concerned almost entirely with anaesthetic levels that more closely parallel those used in modern surgery than the heavy degree of central nervous system depression used in earlier years. When the experimental animal is taken to these deeper levels, depression of activity can be demonstrated even in the specific relay nuclei of the thalamus (King, 1956) and is especially conspicuous when the recovery cycles of these centres are tested.

Any review of this nature is bound, at present, to be a review of work in progress. Not only are the lines of research discussed here in need of further extension, but two of the questions asked in the opening paragraph are as yet almost untouched by investigators. Some anaesthetic agents used clinically suggest that their effect is essentially an impairment of storage or memory and not of sensation. Are the sites of blockade stations on the route to perception or to storage? Search for a prime focus of their action in the hippocampal regions of the brain seems worth while, and is currently being undertaken.

Is the action of some agents one on "affect" rather than on sensation ("I still feel my pain but it doesn’t bother me any more")? With the recent unravelling of the role of the limbic system in the life of the emotions (MacLean, 1955a, b) some of these older rhinencephalic structures may prove to be sites of action of narcotics.

The consideration of "affect" lay, until recently, in another realm of discourse, but in recent years even this has yielded to the electrophysiologist. An electrical sign, apparently peculiar to the amygdala, has been shown (by implanted electrodes in man) to be evoked by emotionally distressing situations (Brazier, 1959) (fig. 10). The sign consists of bursts of 35 to 40 per second potentials in the amygdala which resemble rather closely those seen in animals in the stress of avoidance conditioning in which the animal must learn to escape a shock. Although the animal cannot report its distress during these episodes, as does the man, the analogy seems justifiable. This phenomenon has yet to be examined in relation to the anaesthetic state.

In the exploration of the action of anaesthetics on the central nervous system there are still many frontiers to challenge the pioneer, in addition to those mentioned in this brief review.

ACKNOWLEDGMENTS

The computer analyses in the work reported here were made possible through the co-operative programme of the Brain Research Institute at the University of California, Los Angeles, and the Center for Communication Sciences at the Massachusetts Institute of Technology.

REFERENCES


