NEUROPHYSIOLOGICAL STUDIES ON NITROUS OXIDE AND DIETHYL ETHER ANAESTHESIA

BY

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SUMMARY

The spontaneous electrical activities and alterations of the activation threshold of the neo-, palaeo- and archicortical systems were investigated during nitrous oxide and ether anaesthesia. In the neocortical system the threshold for hypothalamic stimulation, induced spindle bursts, recruiting response and thalamic arousal reaction were also examined. The results obtained were as follows:

(a) Nitrous oxide anaesthesia. (1) Changes in the pattern of spontaneous activity were more marked in the neocortex than in the limbic system. Slow waves with increased amplitude appeared in the neocortex but spindle bursts were scarce. The patterns of deep sleep with spikes was not observed in the limbic system. (2) The neocortical system was affected; the thalamocortical reverberating circuit showed impaired activity without any elevation of the threshold of the hypothalamic activating system.

(b) Ether anaesthesia. The changes of electrical activity of the three systems were classified in relation to the depth of ether anaesthesia. During light ether anaesthesia the activation threshold of the hypothalamic activating system was elevated, while that of the reticular neocortex activating system was hardly affected. During deep ether anaesthesia the thresholds of the hypothalamic and reticular activating systems were significantly elevated. Waves of increased amplitude were observed in the hypothalamus, amygdala and hippocampus in contrast to slow waves in the neocortex after prolonged deep ether anaesthesia. High amplitude waves of about 10 c/s appeared in the amygdala and hippocampus at the onset of ether inhalation.

It is well accepted that the reticular activating system plays an important role in the mechanism of e.g. and behavioural arousal (Moruzzi and Magoun, 1949), and various reports have described its responses under the influence of anaesthetics (Arduini and Arduini, 1954; Davis, et al., 1957; Davis, Collins and Randt, 1958; French, Verzeano and Magoun, 1953), hypnotics and tranquilizing drugs (Bradley and Key, 1958, 1959).

Thus, in animal studies French, Verzeano and Magoun (1953) have shown that pentobarbitone exerts its principal effect upon the reticular activating system, tending to depress its electrical activity and to interrupt multisynaptic conduction. Davis and others also have shown similar results, though using different experimental methods. Phylogenetically, the cerebral cortex is divided into three parts: the archicortex (hippocampus) the palaeocortex (pyriform lobe), and the neocortex, each having its own sensory and motor pathway. The sensory pathway of archi-, palaeo- and neocortex is mediated by the posterior hypothalamus, anterior hypothalamus, and nuclei of the thalamus, and the motor pathway is mediated by septal nuclei, amygdala and basal ganglia respectively.

Each cortex and its related nuclei is called respectively the archicortical, palaeocortical and neocortical system; the limbic system consists of the former two systems. Recently it has become clearer that the limbic system plays an important role in autonomic function and emotional behaviour. With regard to consciousness, the neocortex is concerned mainly in alert consciousness while the limbic system is concerned with crude consciousness. Tokizane and his colleagues...
STUDIES ON NITROUS OXIDE AND DIETHYL ETHER ANAESTHESIA

(Kawamura, Nakamura and Tokizane, 1961; Tokizane, Kawamura and Imamura, 1960) investigated the electrical activities of the archi-palaeo- and neocortex with their related subcortical nuclei and concluded that the anterior and posterior parts of the hypothalamus had specific activating effects upon the electrical activities of the paleo- and archicortex respectively, while the reticular activating system was concerning mainly with the neocortex.

Thus, they proposed three different activating systems, namely, the reticular-neocortical, the anterior hypothalamic-palaeocortical, and the posterior hypothalamic-archicortical activation systems.

The purpose of this study was to establish the anaesthetic effects of nitrous oxide and diethyl ether on these three activating systems by monitoring electrical activity at the neocortex (anterior sigmoid gyms, ectosylvian gyri), the palaeocortex (amygdala: representative of the palaeocortex because of the similarity of its e.e.g. pattern to that of pyriform lobe) and the archicortex (hippocampus), and to correlate the experimental results with clinical observations.

METHOD

Experiments were performed on forty-two cats weighing 2.5–3.5 kg, anaesthetized initially with ether to permit insertion of a tracheal cannula and other operative procedures, including venepuncture and exposure of the brain. When the animals had recovered from anaesthesia, they were paralyzed with tubocurarine and the lungs artificially ventilated.

For recording and stimulating the subcortical structures, concentric needle electrodes, insulated except at the tips were inserted into various parts of the brain by means of a stereotaxic apparatus (Todai-Noken type) with the aid of the atlas of Jasper and Ajmone-Marsan (1956). Silver ball biopolar electrodes, 2 mm apart were used for cortical recording. An electronic stimulator (Nihon-Koden MSE 2) and 12-channel ink-writing electroencephalograph (Sanei Model EG-125) were used for electrical stimulation and recording respectively. A stimulating frequency of 100 c/s, pulse width 1 m.sec, was used throughout.

Electrical activity was recorded from the anterior and posterior hypothalamus, caudate nucleus, centromedian nucleus, amygdala, hippocampus, anterior sigmoid and ectosylvian gyri, and midbrain reticular formation. The locations of inserted electrode tips were checked histologically after the experiments.

The threshold for arousal reaction was determined by electrical stimulation of the respective activating system (activation of the anterior hypothalamic-palaeocortical system by anterior hypothalamic stimulation; activation of the posterior hypothalamic-archicortical system by posterior hypothalamic stimulation; and activation of the reticular-neocortical system by reticular stimulation) before and 30 minutes after the administration of anaesthetics. Furthermore, the effects of anaesthetics on the threshold of spindle bursts in the anterior sigmoid gyrus by stimulation of the caudate nucleus, of recruiting responses in the anterior sigmoid gyrus by stimulation of centromedian nucleus and of neocortical arousal reaction by thalamic (centromedian nucleus) stimulation were also determined.

At least 2 hours were allowed for the effect of the initial ether anaesthesia to disappear before experimental data were recorded. Anaesthetic gases were delivered from an anaesthetic machine with a Rotameter and Copper Kettle recalibrated for these experiments. Eighty per cent nitrous oxide and 3–4 per cent (for light anaesthesia) or 6–8 per cent (for deep anaesthesia) ether vapour in oxygen were administered using a non-rebreathing valve and artificial ventilation.

RESULTS

The electrical activities of various parts of the brain showed different patterns during nitrous oxide, and light or deep ether anaesthesia.

Nitrous Oxide Anaesthesia.

The administration of nitrous oxide was usually accompanied initially by the appearance in the neocortex of spontaneous spindle bursts and later by high amplitude slow waves at 2–4 c/s. In the amygdala (palaeocortex) there was an initial increase in activity which later changed to patterns of drowsiness or sleep depending on the depth of anaesthesia.

The e.e.g. of the hippocampus (archicortex) is, contrary to other nuclei, characterized by regular
slow waves of 1.5–5 c/s before anaesthesia. This is called the hippocampal arousal pattern. These slow waves became fast after anaesthesia and changed to patterns of drowsiness or sleep.

However, spiky waves which indicate strongly depressed activity of the amygdala or hippocampus and appear in deep barbiturate anaesthesia were not observed.

The changes recorded in the thalamic nuclei were similar to those in the neocortex. On the other hand, the hypothalamus and reticular formation showed only slight changes. Usually, these depressed patterns were easily activated into arousal patterns by electrical stimulation of related subcortical nuclei.

The electroencephalographic patterns during nitrous oxide anaesthesia show that nitrous oxide depresses the neocortex more than the amygdala or hippocampus.

As already reported by Kawamura and Nakamura (1963), nitrous oxide anaesthesia also evoked sinusoidal waves of 3–8 c/s in the optic tract, lateral geniculate body and lateral gyrus during photic stimulation. Furthermore, dissociation of the e.e.g. activity shown by the neocortical “arousal” and limbic “drowsy” patterns; was frequently observed. Figure 1 shows typical e.e.g. tracings during nitrous oxide anaesthesia.

**Ether Anaesthesia**

3–4 per cent.

Administration of this concentration for 30 minutes or more led to the changes in the e.e.g. tracing shown in figure 2, I. The fast waves of the amygdala decreased in frequency, while the regular slow waves of the hippocampus observed before ether administration were replaced by lower amplitude irregular slow waves on which fast waves were superimposed. The neocortical
High amplitude waves induced in the limbic system by prolonged deep ether anaesthesia. Note overall increased amplitude and frequency. For abbreviations, see fig. 1.

The effect of electrical stimulation (horizontal bars) of the anterior hypothalamus, posterior hypothalamus, and reticular formation, on the high amplitude waves of the limbic system, during deep ether anaesthesia (right). Electrical stimulation does not influence the patterns. The left-hand column shows the threshold voltages before ether anaesthesia. For abbreviations, see fig. 1.
Electrical activity at the onset of ether inhalation. High amplitude waves appeared in the amygdala and hypothalamus. Superimposed fast activity was also observed in the hippocampus. For abbreviations, see fig. 1.

**Fig. 5**
Electrical activity at the onset of ether inhalation. High amplitude waves appeared in the amygdala and hypothalamus. Superimposed fast activity was also observed in the hippocampus. For abbreviations, see fig. 1.

E.g. also showed slowing of its frequency. The stage characterized by these e.g. patterns, with moderate pupil dilatation, may be tentatively called light ether anaesthesia.

6–8 per cent.
Tracing II in figure 2 was obtained after the additional administration of 6–8 per cent ether for 30 minutes subsequent to the stage of light ether anaesthesia; the stage of deep ether anaesthesia associated with widely dilated pupils. The dominant waves in the neocortex in this stage were of high amplitude, the frequency slowing to 1–2 c/s. The amygdala showed similar changes, the frequency slowing to about 5 c/s, with an increase in amplitude. In eighteen of twenty-two records studied, this pattern was replaced by characteristic trains of high amplitude waves at 15–16 c/s. The hippocampus, however, showed a fast wave pattern with randomly occurring spiky waves which later changed to high amplitude wave trains of 10–12 c/s in seventeen out of twenty-two instances. An example is shown in figure 3. These high amplitude wave trains in the amygdala or hippocampus, or in both, seemed to occur more frequently after prolonged anaesthesia and after repeated electrical stimulation, but some cats did not show these patterns in spite of deep ether anaesthesia or repeated electrical stimulation.

During this stage anterior or posterior hypothalamic stimulation, or reticular stimulation did not influence the waves even with high voltages (fig. 4). Furthermore, they were not accompanied by postconvulsive depression, abnormal movement of the limbs, eyelids or eyes. The high amplitude waves were also observed in the amygdala and hippocampus at the onset of ether anaesthesia, but these were transient, and the frequencies as well as amplitudes decreased as anaesthesia deepened (figs. 5, 6). The initial frequencies were 12–13 c/s in the amygdala and 7–9 c/s in the hippocampus.

**Fig. 6**
High amplitude waves in the hippocampus observed at the beginning of ether inhalation. For abbreviations, see fig. 1.

**Effect of anaesthesia upon the activation threshold.**
The thresholds for arousal reaction, evoked spindle bursts, and recruiting responses, were determined by electrical stimulation of the respective activating system before and 30 minutes after the administration of 80 per cent nitrous oxide, 3–4 per cent and 6–8 per cent ether in oxygen.
Activation of the anterior hypothalamic-paleocortical system by anterior hypothalamic stimulation.

As indicated by Tokizane et al. (1960), high frequency electrical stimulation (100 c/s, 1 m.sec) of the anterior hypothalamus elicits low amplitude fast waves in the amygdala.

Before anaesthesia, the threshold for activation of the amygdala was 1 to 2 volts. During inhalation of nitrous oxide in 19 cats, there was an average increase in threshold of only 7 per cent. In contrast, in the 12 cats anaesthetized with ether concentrations of 3–4 per cent and 6–8 per cent in oxygen the activating thresholds were increased by 38 and 105 per cent respectively. The activation pattern elicited in the amygdala by anterior hypothalamic stimulation usually did not outlast the period of stimulation.

An example during nitrous oxide anaesthesia is shown in figure 7.

Activation of the posterior hypothalamic-archicortical system by posterior hypothalamic stimulation.

High frequency electrical stimulation of the posterior hypothalamus produces regular slow waves, indicative of arousal, in the hippocampus (Green and Arduini, 1954).

Before anaesthesia, the threshold voltage ranged from 1 to 2 volts. After the administration of nitrous oxide, the average threshold increase in 19 cats, was only 7 per cent, whereas threshold elevations of 53 per cent (15 cats) and 167 per cent (17 cats) were observed during light and deep ether anaesthesia respectively. Figure 8 illustrates the finding during light ether anaesthesia in one experiment.

As reported by Murphy and Gellhorn (1945), high frequency posterior hypothalamic stimulation can activate the neocortex as well as the hippocampus. During nitrous oxide anaesthesia, the activation threshold was little changed in 10 cats.

On the other hand, there was elevation of the activation threshold by 193 per cent (9 cats) during deep ether anaesthesia. The threshold voltages for hippocampal arousal waves were usually lower than those required to evoke low amplitude fast waves in the anterior sigmoid gyrus, when both tests were performed on the same animal.

Effects on spindle bursts induced by stimulation of the caudate nucleus.

Induced spindle bursts are elicited in the an-
terior sigmoid gyrus by single shock stimulation of the caudate nucleus (or other thalamic nuclei involved in the diffuse projection system). Before anaesthesia the threshold voltages for caudate stimulation ranged from 1 to 2.5 volts. After 30 minutes inhalation of nitrous oxide in 15 cats the thresholds were elevated by 106 per cent. Such a high elevation of the threshold voltage was not observed during light ether anaesthesia, which in 11 cats was associated with an average increase in threshold of only 10 per cent. One example of induced spindle bursts during light ether anaesthesia is shown in figure 9. During deep ether anaesthesia, however, induced spindle bursts were markedly depressed, stimulation as high as 10 volts being sometimes ineffectice; the threshold voltages were increased on average by 35 per cent in 10 cats in this stage of anaesthesia.

Effect of recruiting responses in the anterior sigmoid gyrus evoked by stimulation of centromedian nucleus.

The threshold voltage for these responses before anaesthesia ranged from 1 to 3 volts. After nitrous oxide anaesthesia the threshold was elevated by 94 per cent. Light ether anaesthesia did not raise the recruiting thresholds, but deep ether anaesthesia elevated the threshold by an average of 111 per cent in 12 cats. Figure 10 illustrates the determination of recruiting threshold during light ether anaesthesia.

Threshold voltage for spindle bursts induced in the anterior sigmoid gyrus by stimulation of the caudate nucleus did not show a definite increase during light ether anaesthesia. For abbreviations, see fig. 1.

![Figure 9](https://example.com/figure9.png)

**Fig. 9**
Light ether anaesthesia did not alter recruiting threshold in the anterior sigmoid gyrus evoked by stimulation of the centromedian nucleus. For abbreviations, see fig. 1.

![Figure 10](https://example.com/figure10.png)

**Fig. 10**
Light ether anaesthesia did not alter recruiting threshold in the anterior sigmoid gyrus evoked by stimulation of the centromedian nucleus. For abbreviations, see fig. 1.
Arousal threshold of the neocortex by thalamic stimulation.

The neocortical arousal reaction can be elicited by high frequency stimulation of nuclei involved in the diffuse thalamic projection system.

Stimulation of the centromedian nucleus was effective with 0.75–3 volts before anaesthesia. Nitrous oxide increased the threshold voltages by 58 per cent in 19 cats. Ether produced elevations of 9 and 176 per cent (13 cats) in light and deep anaesthesia respectively. Hippocampal arousal waves were also elicited by centromedian stimulation. Furthermore, deeper ether anaesthesia produced a decrease in the duration of activation in the neocortex and hippocampus. Arousal patterns of the cortex during deep ether anaesthesia were high amplitude less fast waves instead of low amplitude fast waves. Figure 11 shows an example of these patterns during deep ether anaesthesia.

Arousal reaction of the neocortex by reticular stimulation.

The anterior sigmoid gyrus was activated by reticular stimulation at 0.5 to 1.5 volts before anaesthesia. Nitrous oxide elevated the threshold voltage by 38 per cent in 19 cats. During light and deep ether anaesthesia there were increases by 24 per cent (15 cats) and 192 per cent (13 cats) respectively. Figure 12 shows an example of threshold elevation during light ether anaesthesia. The activation patterns during deep ether anaesthesia were also high amplitude less fast waves compared with low amplitude fast waves which were observed during light ether anaesthesia. Hippocampal arousal waves tended to decrease in frequency as anaesthesia deepened.

Summarizing the results obtained in this study (figure 13), it is seen that there are well defined differences between the effects of nitrous oxide and ether upon neocortical (left anterior sigmoid gyrus), palaeocortical (amygdala), and archicortical (hippocampus) systems. Nitrous oxide depressed the neocortical system, especially the thalamocortical reverberating circuit, but did not depress the hypothalamic activating system. Light ether anaesthesia depressed the limbic system but not the neocortical system; deep ether anaesthesia depressed all of these systems.

DISCUSSION

The results obtained by simultaneous observation of the pattern changes and elevation of the threshold voltages in the present experiments indicate that the effects of nitrous oxide anaes-
Diagrammatic representation of the effects of nitrous oxide, and light and deep ether anaesthesia, upon the hypothalamic activating system, induced spindle bursts, recruiting responses, and the reticular activating system. For abbreviations, see fig. 1.

Besides reticular and posterior hypothalamic activation, the present experiments relating to neocortical function include the study of induced spindle bursts, recruiting responses and thalamic arousal reaction. Since the former two responses were depressed strongly during nitrous oxide anaesthesia, this may indicate that nitrous oxide has a greater effect on the thalamocortical reverberation circuit than on the neocortex itself. During nitrous oxide, higher voltage was required for recruiting responses by centromedian nucleus stimulation than was required to arouse the neocortex by the same stimulation. Such observations are compatible with the hypothesis that the mechanisms involved in recruiting responses and thalamic arousal reaction are different. The anaesthetic state produced by nitrous oxide might be due to a decreased activity of the reticular formation, and also due to a functional depression of the thalamocortical circuit.

During light ether anaesthesia, while hypothalamic activation was considerably affected, the thalamic diffuse projection system (induced spindle burst or recruiting response) was little influenced. The reticular activating system was depressed.

The data presented could offer an explanation for the clinical use of nitrous oxide with ether. The results summarized in figure 13 indicate that light ether anaesthesia combined with nitrous oxide might produce general elevation of the threshold voltage of the various activating systems.
istic regular slow waves for several years (Green and Arduini, 1954). Torii and Kawamura (1960) recently reported a parallelism between hippocampal activity and blood pressure. In the present experiments, electrical activity of the hippocampus and the activation thresholds showed considerable change by ether inhalation.

High amplitude waves in the amygdala have been observed at the onset of ether inhalation, as reported by Tokizane (1958) and Naquet (1954). Liberson (1954) induced high amplitude waves of 4-6 c/s in the hippocampus by blowing tobacco smoke into the nostrils.

High amplitude rhythms in the limbic system also appeared during deep anaesthesia. Domino (Domino and Ueki, 1959a, b) described similar effects with various anaesthetic agents, but they were of a temporary nature during light anaesthesia. In the present experiments, high amplitude waves of this type were observed, but there were other high amplitude waves in the deeper stages, which lasted as long as ether was administered. These were not accompanied by postconvulsive depression of the e.g. or abnormal movements of the body, and disappeared without any augmentation in the period of recovery from anaesthesia.

The definite meaning of this kind of wave remains unknown at this time, but it is thought to be due to the depression of the hypothalamic activating system.

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REFERENCES


ETUDES NEUROPHYSIOLOGIQUES DE L'ANESTHESIE AU PROTOXYDE D'AZOTE ET A L'ETHER DIETHYLIQUE

SOMMAIRE

Les activités électriques spontanées et les altérations du seuil d'activation des systèmes neocortex, paleo- et archicortical ont été examinées au cours d'anesthésies au protoxyde d'azote et à l'éther. Dans le système neocortical le seuil de stimulation hypothalamique, l'induction d'accès fusiformes, la réponse par sommation et le réveil thalamique ont aussi été examinés.
Voici les résultats obtenus:

(a) Anesthésie au protoxyde d'azote:
1. Les changements du genre d'activité spontanée étaient plus marqués dans le néocortex que dans le système limbique. Dans le néocortex apparaissaient des ondes lentes d'amplitude croissante, mais les accès fusiformes étaient peu nombreux. L'image de sommeil profond avec ondes en pointe n'a pas été observée au niveau du système limbique.
2. Le système néocortical était atteint; le circuit de résonnance thalamocortical montrait une activité détériorée sans aucune élévation du seuil du système d'activation hypothalamique.

(b) Anesthésie à l'éther:
Les variations de l'activité électrique des trois systèmes ont été classées suivant le degré de profondeur de l'anesthésie à l'éther. Au cours de l'anesthésie légère à l'éther de seuil d'activation du système d'activation hypothalamique était élevé, pendant que celui du système d'activation du néocortex réticulaire était à peine modifié. Au cours de l'anesthésie profonde à l'éther les seuils des systèmes hypothalamique et réticulaire étaient considérablement élevés. On a observé des ondes avec amplitude accrue dans l'hypothalamus, les amygdalas et l'hippocampe contrastant avec les ondes basses du néocortex après une anesthésie profonde à l'éther. Dans les amygdalas et l'hippocampe apparaissaient au début de l'inhalation d'éther des ondes élevées de 10 cps environ.

NEUROPHYSIOLOGISCHER UNTERSUCHUNGEN WÄHREND DER LACHGAS- UND DER DIÄTHYLÄHER-NARKOSE

ZUSAMMENFASSUNG

Im Verlauf von Lachgas- und Diäthyläther-Narkose wurde die spontane elektrische Aktivität und die Veränderungen der Aktivierungsreizschwelle des Neokortex, Palaeokortex und Archikortex untersucht. Im neokortikalen System wurden außerdem die Reizschwelle für hypothalamische Reizung, induzierte Spindelausbrüche, Wiedererregbarkeit und thalamische Aufweckreaktion untersucht. Es wurden folgende Ergebnisse erzielt:

(a) Lachgasnarkose:
1. In der Neokortex waren die Veränderungen im Stromkurvenverlauf der spontanen Aktivität ausgeprägter als im limbischen System. In der Neokortex traten langsamen Wellen mit gesteigerter Amplitude auf, Spindelausbrüche waren selten. Im limbischen System wurden Abläufe wie beim tiefen Schlaf mit steilen Ausschlägen nicht beobachtet.
2. Das neokortikale System war ebenfalls betroffen, das thalamokortikale Rückfluss-System zeigte eingeschränkte Aktivität ohne Anhebung der Reizschwelle des hypothalamischen Aktivierungssystems.

(b) Äthernarkose:

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Further details may be obtained from Professor J. F. Nunn, Department of Anaesthesia, The University of Leeds.