EXPERIMENTAL CENTRAL NERVOUS SYSTEM STUDIES RELATED TO ANAESTHESIA: CLINICAL IMPLICATIONS

I. ANAESTHESIA AND THE BRAIN STEM RETICULAR FORMATION

II. EFFECT OF REDUCED SENSORY INFLOW ON ANAESTHETIC REQUIREMENTS*

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What a piece of work is a man! how noble in reason! how infinite in faculties! in form
and moving how express and admirable! in action how like an angel! in apprehension
how like a god! the beauty of the world, the paragon of animals!

WILLIAM SHAKESPEARE,
Hamlet, Prince of Denmark,
Act II, Scene II

INTRODUCTION

IN RECENT YEARS, there has been a great deal of interest in the consideration of man as a neurophysiological organism. As far back as we trace human culture, the classic question as to "What is man?" has persistently remained unanswered. New physioneurological insights do not lessen the wonder of man, but rather emphasize it. We have even more reason than Hamlet to exclaim "What a piece of work is a man!" How the physical can generate self-consciousness and acquire the ability to make judgments, to indulge in self-criticism, to be aware of moral values, and to have a desire for beauty is indeed "a piece of work."¹

We, as anaesthetists, therefore, assume a responsibility when we anaesthetize a patient, for we are entrusted with the preservation of this uniqueness of man, during a deliberate, temporary suppression of his consciousness. Quite naturally, then, any knowledge of a neuronal system able to modify our sensory experience and awareness must be of interest and importance to the anaesthetist, for selective modification of sensation is the purpose of the specialty of anaesthesia.

Discovery of the remarkable functional properties of the reticular formation, an extensive central core of grey matter lying adjacent to the principal afferent and efferent pathways in the brain stem, has given rise to new concepts of mechanisms which may be involved in the production of the anaesthetic state.

ANATOMICAL AND PHYSIOLOGICAL CONSIDERATIONS OF THE RETICULAR FORMATION

The "formatio reticularis" is embryologically that mass of cells in the brain stem and spinal cord which is not utilized in the formation of motor roots or sensory

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relay nuclei.² The central core of this neural mass begins in the medulla oblongata, a little above the decussation of the pyramids, and extends cephalad through the pons, the tegmentum of the mid-brain, the non-specific thalamic nuclei, and into the septal nuclei (Fig. 1). The reticular formation is contiguous caudally with the spinal interneuronal substance to the level of the first lumbar vertebrae.³ Cephalically the reticular formation is connected with the non-specific thalamic nuclei, whence fibres radiate via the diffuse thalamic projection system to all parts of the neocortex (Fig. 1).⁴

Anaesthesia and the Reticular Formation

FIGURE 1. Schematic drawing of the brain stem reticular formation. See text for details.

The reticular formation is composed of an interlacing reticulum of cells and fibres. On the basis of variations in cellular size and shape, 98 different nuclei have been identified. Since the reticular formation is composed of multineuronal polysynaptic pathways, conduction time is prolonged, latency of response is long, peak evoked potential is slow,⁵ and the possibility is raised that this system may be easily depressed by anaesthetics.

In contrast, at the brain stem level, classical sensory (lemniscal) pathways are monosynaptic (Fig. 1), and are more resistant to the depressant effects of anaesthetic agents. In this system, transmission is rapid, latency is of brief duration, and peak evoked potentials are rapid. Cortical representation is precise (Fig. 1), and limited to specific sites (post-central gyri).

Nevertheless, the lemniscal and reticular systems (extra-lemniscal) are far from being separated, either functionally or anatomically. Ascending sensory pathways feed important collaterals into the ascending reticular activating system (Fig. 1),^{5,6} and increasing evidence continues to support the hypothesis that wakefulness and consciousness are dependent upon afferent impulses which initiate and sustain an interplay of neuronal activity between other areas of the central nervous system and the brain stem reticular formation.⁷

Pain fibres en route to specific areas of the sensory cortex also give collateral fibres to the reticular formation and simultaneously contribute to its activation. Unless simultaneous activation of the reticular system is possible, sensory inflow via the classical lemniscal pathways is able to produce only brief reflex activity, instead of the characteristic integrated behavioral response to pain. Once activated, however, the reticular system also propagates sensory input rostrally to all areas of the cortex, although at a much slower rate than the lemniscal system. Thus, an appropriate and integrated response to painful or alerting stimuli is achieved, which is much more complex, thoughtful, and purposeful than the brief initial reflex response.⁸ Recent experimental work^{9,10} has shown that some eighty per cent of the ascending lateral spinothalamic tract fibres end in the reticular formation from whence those impulses can be relayed to the cortex via the diffuse thalamic projection system.¹¹ The remaining twenty per cent continue directly cephalad in the medial lemniscus. Further, *all* sensory modalities have quantitatively large reticular system inputs.^{7,12}

It now appears likely that the brain stem reticular formation represents one of the more important *integrating* structures, if not, indeed, "the master control mechanism in the central nervous system," for additional influences of this system have been demonstrated in the mediation of control of many visceral functions, such as respiration, vasomotor tone, gastrointestinal secretions, temperature regulation, and neuroendocrine output.^{13,14} It extends a critical degree of influence over motor functions concerned both in phasic and in tonic muscular control,^{11 15} and modifies reception, conduction, and integration of all sensory signals to the degree that some are perceived and others are not.¹⁶

Current investigations as to whether or not synaptic mediation within the reticular core is adrenergic, cholinergic, or "serotonergic" have led to conflicting reports.¹⁷⁻²³ Conceivably, all three of these synaptic types (and perhaps others as well) may be present in the brain stem reticular formation, and some localization of their effects has been suggested.^{8,11}

The conceptual importance of the reticular core has increased so greatly that one investigator²⁴ was moved to state, somewhat wistfully, "the cortex has been reduced so low that it is now no more than a conveniently shaped dependency for electrode placements." Another²⁵ enthusiastically proclaimed that the reticular system "is" the central nervous system.

EXPERIMENTAL

A. ANAESTHESIA AND THE BRAIN STEM RETICULAR FORMATION

The pioneer experimental investigations of Bremer²⁶ have provided significant contributions to understanding the nature of anaesthesia, sleep, and wakefulness.

Transection of the spinal cord of cats at cervical one (the *encéphale isolé* preparation) (Fig. 1) produced an "activated" or desynchronized E.E.G., as evidenced by low-voltage, high-frequency electrocortical activity (Fig. 1). In contrast, cats with mesencephalic transection at the superior collicular level of the mid-brain, just caudad to the third nerve nucleus (the so-called *cerveau isolé* preparation), were stuporous (Fig. 1), and exhibited an E.E.G. pattern characterized by high-voltage, slow-wave activity. This is the "deactivated" or synchronized E.E.G. (Fig. 1).

Discrete experimental lesions in the brain stem reticular formation result both in stupor and in E.E.G. "deactivation"; yet lesions abolishing only common somatic sensory pathways of the medial lemniscus neither alter consciousness nor produce "deactivation" of electrocortical activity.^{27,28} Clinically, humans with pathological lesions involving the reticular formation may present in stupor or coma.²⁹⁻³⁰

Failure to regain consciousness after general anaesthesia has been attributed to a failure in reactivating the reticular formation because of persistent "chemical deafferentation."³¹ Reticulo-spinal outflow may modify neuromuscular activity by inhibition of alpha efferent conduction via Renshaw internuncial cells.¹⁵ Alternatively, muscle relaxant blockade of cholinergic gamma efferents to muscle spindles may interrupt proprioceptive inflow to the reticular formation. Thus, in certain instances, as in inadvertent prolonged apnoea secondary to use of muscle relaxants, failure to reawaken, despite cessation of general anaesthesia (a common clinical observation), may in part be related to chemical deafferentation, rather than to the possible central actions of the muscle relaxant.

Sleep can be induced when the thalamic portion of the reticular activating system is electrically driven at a rate comparable to slow frequencies observed during physiological sleep.³² The clinical application of this knowledge has received attention in electronarcosis studies.³³⁻³⁷

Reversible blockade of conduction of cephalic sensory inflow in the reticular activating system is believed to play a major role in the induction of the anaesthetic state,³³⁻⁴⁴ but direct evidence in support of this view has been lacking. Potentials evoked in the medial lemniscus (M.L.) by sciatic stimulation remain unchanged during general anaesthesia, while responses in the reticular activating system (R.A.S.) are obliterated by the anaesthetic.³⁸ (Fig. 1.)

The present report describes the production of clear-cut "barbiturate spindles," and subsequent anaesthesia, not only following intravenous administration of low concentrations of thiopentone (sodium pentothal) but also by the direct application of small quantities of this compound into the brain stem reticular formation (BSRF) of freely moving cats.

Methods

1. Surgical Preparation: Intact Cat with Chronically Implanted Cortical and Subcortical Electrodes and Cannulae

Under intraperitoneal pentobarbital (nembutal) anaesthesia (35 mg./kg.), the cat was placed in a Johnson stereotaxic instrument. The cranium was exposed. The skull was trephined. Small stainless steel screws were placed bilaterally on the cranial dura mater for recording electrocortical activity from the anterior and

posterior sigmoid gyri (A-PSG). Depth recordings were monitored from concentric needle electrodes and from stainless steel "cannulae-electrodes" lowered under stereotaxic guidance⁴⁵ into such predetermined subcortical sites as the brain stem reticular formation (BSRF), and the preoptic region (RPO).

The "cannulae-electrodes" were utilized for applying thiopentone directly into the BSRF and RPO, and for recording directly from the site of drug implantation or injection according to the method of Yamaguchi, Ling, and Marczynski.⁴⁶

Precise electrode and cannulae placements were verified histologically by the method described by Marshall.⁴⁷

Following surgery, several days (usually one week or more) were allowed for recovery from anaesthesia and to ensure the complete metabolism and excretion of the administered pentobarbital. For intravenous (femoral vein) thiopentone administration, the animal was suitably immobilized by draped "mummification." Transitory and gentle manual restraint was used during the application of very small (0.2 mg.) quantities of thiopentone directly into the BSRF or RPO.

2. Basic E.E.G. Patterns

Figure 2 demonstrates typical patterns of "activation" and "deactivation" which are observed in preparations used in this study.

When at rest in a dimly lighted and quiet environment, an E.E.G. record, dominated by spindle bursts with amplitudes up to 500 microvolts (pattern D),

FIGURE 2. Basic E.E.G. patterns in the unanaesthetized cat preparation: A, complete "activation"; D, maximal "deactivation"; B and C, intermediate and progressive degrees of the "deactivating" process.

is noted. In contrast, when alerted (e.g. whistle blast) an electrocortical transition takes place which is manifested by low-voltage, fast activity of varying frequency, amplitude, and duration, the degree of variation being dependent on the type and intensity of the alerting stimulus.

Under such circumstances and experimental conditions it was found convenient to designate four basic types of E.E.G. patterns for the purpose of characterizing and evaluating drug-induced changes in the E.E.G. These E.E.G. patterns are similar to those designated by the letters A, B, C and D by Rothballer.^{17,48} Figure 2 illustrates this system of lettering. Pattern D indicates maximal "deactivation." In contrast, pattern A manifests an E.E.G. pattern of complete "activation," with patterns C and B representing intermediate and progressive degrees of the activating process.

Results and Discussion

Effect of Thiopentone on the Cat E.E.G.

Figure 3 demonstrates the early electroencephalographic changes which are elicited by low doses of thiopentone, even before overt clinical evidence of progressive anaesthesia was apparent. In contrast to the activated pattern of the

FIGURE 3. Note the clear-cut "barbiturate spindles" on cortical leads (R: A-PSG, L: A-PSG) produced by 7.9 mg./kg. of thiopentone injected 16 minutes earlier. Partial deactivation is also observed in the preoptic region (RPO) and the brain stem reticular formation (BSRF). Painful stimulation (lower panel) produces immediate and intense type A E.E.G. activation (in all leads) whose duration parallels that of the stimulus.

FIGURE 4 An activated E.E.G. can still be elicited by painful stimulation after the I.V. administration of 10-30 mg./kg of thiopentone in the intact cat. In contrast, similar stimulation fails to alter "barbiturate spindles" after 35 mg/kg thiopentone I.V. In partially deactivated preparations given low doses of thiopentone (4 mg/kg and 11 mg/kg, for cord transected, and cord and cervical sensory root transected preparations respectively), drug-induced E.E.G. deactivation remains unchanged in the presence of painful trigeminal stimulation.

control tracing, the slow intravenous administration of thiopentone (7.9 mg./kg.) induces isolated bursts of spindle activity (barbiturate spindles), which are particularly clear-cut in the cortical leads. Our studies indicate that barbiturate spindles produced by low concentrations of this anaesthetic agent are readily reversed by various types and intensities of afferent sensory inflow. Painful stimulation (Figs. 3 and 4) of the paws results in reversion to an "activated" pattern, even after the intravenous administration of 10-30 mg./kg. of thiopentone. In this circumstance, concomitant behavioural arousal is also observed. In contrast slightly higher concentrations (35 mg./kg.) elicit a persistently "deactivated" E.E.G., whose "spindles" continue, regardless of repetitive painful stimulation. Clinically, the animal is anaesthetized. Further, it now appears likely that reticular formation conduction is blocked and reticulocortical transmission depressed since the E.E.G. remains "deactivated."

These observations suggest that thiopentone may inhibit activity of the brain stem reticular formation, and thus produce sedation, sleep, and ultimately anaesthesia. This effect on the brain stem reticular formation gains support from studies in which small concentrations of thiopentone (0.2 mg.) were applied through implanted cannulae directly into the reticular formation of the brain stem. Progressive behavioural inactivity, eventually followed by surgical anaesthesia, with an associated "deactivation" of the cortex and the brain stem reticular formation were observed. This is similar in every respect to the responses (E.E.G. and behavioural) which were observed following the intravenous administration of much larger doses of this compound. Sham stimulation or the application of normal saline in volumes comparable with those used for direct drug application and adjusted to the same pH as the thiopentone solution failed to alter the behaviour or control E.E.G. activity of the same test animal.

In clinical practice the intravenous administration of thiopentone is usually carried out at such a rate that surgical anaesthesia is reached within one to two minutes. Thus, the classical signs and stages of anaesthesia cannot be detected. However, it has been shown by Etsten and Himwich,⁴⁹ who studied the effects of thiopentone in man, that when this compound is given slowly in a 1 per cent solution, the pattern of evolution of the central nervous system depression was similar in many respects to that seen with other anaesthetic agents. Characteristic changes in the E.E.G. pattern during thiopentone narcosis in man have been noted by many workers.⁵⁰⁻⁵² With only minor variations there is general agreement between various investigators as to the pattern of these E.E.G. changes and their relation to the depth of anaesthesia.

Although intravenous thiopentone reaches the central nervous system rapidly, Brodie⁵³ did not find any selective localization of the drug in different parts of this organ. Since the concentration of the drug in the plasma and cerebrospinal fluid is approximately the same, the depth of anaesthesia is dependent on and varies with the blood barbiturate level. However, this relationship is not a simple linear one, since Brodie⁵⁴ and Dundee⁵⁵ have shown that *acute tolerance* develops to the narcotic effect of thiopentone.

This demonstrated susceptibility of BSRF to depression by the direct application of very small quantities of thiopentone to this subcortical site in freely moving cats with chronic electrode implants does not rule out the possibility that other central sites might play a role in the development of surgical anaesthesia. We have been able to induce anaesthesia and E.E.G. deactivation by the application of 0.5 mg. of thiopentone into the RPO. Yamaguchi *et al.*⁴⁶ have induced sleep, and correlated high-voltage, slow-wave electroencephalographic activity in cats, following the application of very small quantities of acetylcholine into the RPO.

B EFFECT OF REDUCED SENSORY INFLOW ON ANAESTHETIC (THIOPENTONE, CHLORPROMAZINE) REQUIREMENTS

Partially paralysed patients with reduced sensory inflow require a lower concentration of drug to induce anaesthesia than normal patients. Although this clinical observation is commonly noted verbally among anaesthetists, we have not been

able to find a documented report which attempts to explain these observations. It has been reported that quadriplegics may require only 100 mg. of thiopentone for induction of anaesthesia, whereas an individual of the same weight having a similar surgical procedure requires 500 mg.⁵⁶ In addition, patients with high spinal analgesia (T2-T4) require very low concentrations of sodium pentothal for sleep sedation,⁵⁷ and paraplegics (with no cross-tolerance to central depressant agents) require less drug for induction and maintenance of anaesthesia. Observations made in these partially deafferented patients have revealed that there was no anaemia, amyloidosis, hypoproteinaemia, debilitation, or other conditions known to increase the susceptibility of these patients to the depressant effects of administered anaesthetic agents.

We have, therefore, endeavoured to evaluate the effect of experimental reductions in sensory inflow on anaesthetic requirements.

Methods

1. Preparations Studied

(a) Controls (intact). This preparation is identical to that described previously. This animal then acts as its own control for the three subsequent test preparations made by:

(b) Transection of cervical spinal cord at C8-T1, and

(c) Transection of all cervical sensory roots (cervical dorsalectomy). This surgical technique for transection of spinal cord (at C8-T1) and the cervical sensory roots is similar to that described earlier.^{58 59}

(d) Further deafferentation is achieved by partial trigeminalectomy, in which the roots of maxillary and mandibular branches of trigeminal nerve are transected extra-cranially, as reported by Ling and Foulks.⁵⁸ In this preparation, olfactory (I), optic (II), ophthalmic division of trigeminal (V), and vestibular and auditory (VII) nerves remain intact, as are the motor components of all cervical spinal nerves. This preparation exhibits good cardiovascular status, maintains spontaneous respiration, and may be maintained two to three months if suitable precautions are observed and adequate nursing care provided.

2. Criteria of Anaesthesia

Thiopentone (sodium pentothal) and chlorpromazine (largactil) were administered through a polyethylene catheter inserted percutaneously into the femoral vein. The level of anaesthesia was assessed by observing the electrical activity of the cortex and subcortex, the responses to audiogenic and painful stimulations, and the time needed for recovery. Failure to demonstrate either behavioural arousal or to maintain persistent E.E.G. "deactivation" following painful stimuli was used as the criterion of effective surgical anaesthesia. Recovery time was measured from the onset of surgical anaesthesia to the first evidence of E.E.G. "activation" to a painful stimulus.

Results and Discussion

Effect of Reduced Sensory Inflow on Anaesthetic Requirements in the Cat

All observations reported have been repeated a number of times in several different preparations.

The concentrations of drug which induced effective anaesthesia in intact cats and in cats with various degrees of reduced sensory inflow are illustrated in Table I.

TABLE I
EFFECT OF REDUCED SENSORY INFLOW ON ANAESTHETIC REQUIREMENTS
IN THE CAT

Cat	Drug			
	Thiopentone		Chlorpromazine	
	Dose (mg./kg.)	Recovery time (minutes)	Dose (mg./kg.)	Recovery time (minutes)
Controls	35	4	10	13
Transection C ₈ -T ₁	11	6	6	25
Transection C ₈ -T ₁ and cervical sensory roots	4	15	1.5	40

In the intact cat (control) an average intravenous dose of 35 mg./kg. of thiopentone was necessary to induce effective anaesthesia. Following transection of the spinal cord of this cat at the C₈-T₁ level, the intravenous concentration of thiopentone needed to produce a similar effect was reduced to 11 mg./kg., while only 4 mg./kg. was required in the presence of transection of both the spinal cord and the cervical sensory roots. Unmistakable reductions (Table I) in the effective concentration of chlorpromazine were observed as afferent inflow was progressively reduced by these surgical deafferentation procedures. Significantly, the markedly reduced dosages of chlorpromazine (1.5 mg./kg.) and thiopentone (4.0 mg./kg.) which were sufficient to produce deactivation and anaesthesia in the deafferented preparations (cord and cervical sensory root transections) were also associated with marked prolongation of recovery time (Table I) (40 and 15 minutes for chlorpromazine and thiopentone respectively), as compared with the corresponding controls (recovery times of 13 and 4 minutes).

Figure 3 illustrates the transition from an activated to a deactivated state and demonstrates the type B spindle burst E.E.G. activity which follows intravenous administration of this compound in low doses (7.9 mg./kg.). After large doses of thiopentone (10-30 mg./kg.) are injected, a type C E.E.G. pattern appears (Fig. 4). E.E.G. "activation" and associated behavioural arousal to painful stimulation are still observed, but these effects fail to make their appearance in the presence of type D E.E.G. deactivation induced by the administration of 35 mg./kg. of thiopentone. In preparations with cord transections and in those in which additional cervical sensory root transections have been performed, painful stimulation of cutaneous areas supplied by the intact portions of the trigeminal nerve fails to activate the synchronized spindle activity induced by low doses (11 mg./kg. and 4 mg./kg.) of thiopentone (Fig. 4), doses which did permit behavioural arousal and E.E.G. activation in animals with intact sensory pathways.

In one cat with cord transection at C₈-T₁, cervical dorsalectomy, and partial trigeminalectomy, the concentration of thiopentone required to produce surgical

anaesthesia was reduced to 3 mg./kg., as compared with its own control of 39 mg./kg. in the intact state. Of interest also was the very prolonged recovery time of 240 minutes in this deafferented preparation as compared with only 4 minutes for the much larger dose of anaesthetic in the intact preparation.

SUMMARY AND CONCLUSIONS

The reticular formation is an extensive central core of grey matter, which interrelates with the principal afferent and efferent pathways through synaptic connections in the medulla oblongata, pons, and tegmentum of mid-brain. Some aspects of the anatomy and physiology of this subcortical area have been described.

Thiopentone administered intravenously elicits E.E.G. "deactivation" and surgical anaesthesia. The same effects are induced when thiopentone is applied directly in minute quantities into subcortical sites (brain stem reticular formation, preoptic region) of intact freely moving cats, with in-dwelling "cannulae-electrodes."

Preliminary studies have indicated that reduced sensory inflow (e.g. as observed with quadriplegia and high spinal analgesia) plays a significant role in decreasing the concentrations of pharmacological agents required for sedation and clinical anaesthesia. In intact animals, chlorpromazine and thiopentone induce anaesthesia (as reflected in the E.E.G. responses to audiogenic and painful stimulations and in the duration of recovery time) only with doses of the order of magnitude of 10 mg./kg. and 35 mg./kg. respectively. In the spinal preparation similar anaesthetic effects are achieved with lower concentrations of each compound, and *even lower* concentrations (chlorpromazine 1.5 mg/kg. and thiopentone 4.0 mg./kg.) suffice in preparations in which both spinal section and cervical dorsalectomy have been performed.

These observations also emphasize the potential hazard of overdosage with central nervous system depressants in patients with decreased sensory inflow.

Further studies of the effects of various anaesthetic agents on the electrical activity of cortical and subcortical sites are currently being conducted.

Man's neurophysiological uniqueness is entrusted to us during anaesthesia. We, as anaesthetists, must preserve it well, by our judicious use and management of central nervous system depressant drugs—for, indeed, "What a piece of work is a man!"

Nous avons fait des études expérimentales sur l'anesthésie et la substance réticulée du cerveau; en second lieu, nous avons étudié l'effet de la diminution sensorielle sur les exigences anesthésiques.

Le pentothal administré par voie veineuse amène la "déactivation" de l'E.E.G., et l'anesthésie générale. On produit les mêmes effets lorsqu'on dépose du pentothal en quantité minime dans les régions sous-corticales de chats normaux en liberté, porteurs d'"électrodes-canulés."

Des études préliminaires ont montré qu'un influx sensoriel diminué joue un

rôle important en diminuant la concentration requise des produits pharmaceutiques utilisés pour la sédation et pour l'anesthésie clinique.

Ces observations mettent en lumière les dangers de doses exagérées de produits qui dépriment le système nerveux central chez des sujets à l'influx sensoriel diminué.

L'entité neurophysiologique de l'homme nous est confiée devant l'anesthésie. Nous, anesthésistes, devons la conserver intacte, en nous servant judicieusement et habilement des produits qui dépriment le système nerveux central, car en vérité, "quelle merveille qu'un homme"!

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