EXPERIMENTAL CENTRAL NERVOUS SYSTEM STUDIES RELATED
TO ANAESTHESIA: CLINICAL IMPLICATIONS
III. EFFECTS OF MUSCLE RELAXANTS ON SENSORY INFLOW*

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I heard him complain "You have wak'd me too soon, I must slumber again."
—"The Sluggard," stanza 1.
Moral Songs by Isaac Watts

REPORTS OF PATIENTS regaining consciousness during surgical anaesthesia continue to occur.¹ In these circumstances anaesthesia usually is maintained by the simultaneous use of curarization, controlled ventilation, and a light general anaesthetic; a lighter plane of anaesthesia can thereby be used and good muscle relaxation achieved. However, the influences which curarizing drugs may exert on central nervous system activity and sensory inflow remain to be determined. It has recently been suggested that curarization augments general anaesthesia by decreasing proprioceptive and pain inflow.² This view receives support from the clinical observation that occasionally at the termination of surgery and anaesthesia a reversal of residual curarization is coincident with the return of consciousness.³

The effects of curare on sensory inflow have previously been studied in acute preparations in the presence of some form of residual local or general anaesthesia. This report, which describes work on unrestrained unanaesthetized animals, free of extraneous drug effects, re-emphasizes the view that muscle relaxants may fail to alter sensory inflow to the cortex or deeper structures in response to various types of sensory input.³⁻⁵

METHODS

1. Somatic Sensory Inflow

In the first series of experiments, the effects of muscle relaxants on somatic sensory inflow were investigated. Intact unanaesthetized cats were used in these experiments. Cortical screw electrodes were placed on the anterior and posterior sigmoid gyri. Subcortical chemitrodes were placed into the left or right postero-ventral lateral nucleus of the thalamus (PVL), the brain-stem reticular formation, the lateral geniculate body and the pre-optic region, according to co-ordinates taken from the Stereotaxic Atlas of Jasper and Ajmone-Manson.⁶ Implantation technique and electrode design was that of Yamaguchi, Ling, and Marczynski.⁷

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In addition, small silver discs were placed about the triceps of the contralateral leg, and the wires were brought forward subcutaneously and then attached to the head piece. The Winchester plug was fixed to the calvarium with dental cement. Recordings were monitored on a Model 6 Grass ink writing E.E.G. machine. Electrical stimulation through a stimulus isolation unit was accomplished with a Grass Model S4 stimulator. Figure 1 shows a lateral X-ray of the cat's skull with the electrodes *in situ*.

FIGURE 1. Lateral X-ray of cat's skull with the cortical screws and subcortical chemitrodes *in situ*.

Experiments were started not earlier than one week after implantation. The cat was placed in a viewing chamber, and behavioural and E.E.G. responses to auditory (whistle blast, loud click), visual (flashing light), and painful stimuli (single eight-volt shock across the triceps) were noted. Each cat served as its own control. Each was paralyzed with intramuscular succinylcholine (2 mg./kg.), intubated with a number 20 portex oral endotracheal tube, and ventilated with room air by means of a Harvard respirator. A Rochester needle was inserted into the saphenous vein for subsequent injection of drugs to be studied. The cat was extubated after the return of spontaneous respiration and muscle tone. Control E.E.G. and electrocardiograms were recorded with various stimuli before the cats were reparable with either intravenous gallamine (2 mg./kg.) or succinylcholine. The cats were then reintubated and after a suitable interval the series of stimuli were repeated. Arterial blood pressure and arterial blood chemistry (Astrup-pH, P_{CO_2} , P_{O_2} , bicarbonate) also were measured.⁸

2. Anaesthetic Requirements Using Muscle Relaxants

The anaesthetic requirements of intravenous pentobarbital with and without drug-induced skeleto-motor paralysis were also studied in similar preparations. Failure to elicit E.E.G. activation either by pain (repeated pin pricks delivered to the skin of the groin area) or by low-voltage-high-frequency stimulation of the brain stem reticular formation (BSRF)⁹ was the criterion used for the establishment of adequate anaesthesia. In control experiments several days prior to tests with muscle relaxants, the BSRF stimulation parameters necessary to elicit E.E.G. activation were determined and found to vary from 3 to 7 v., 200 to 300 c.p.s., and 1 to 2 msec.

To study the influence of a muscle relaxant on anaesthetic requirements, the cats were given gallamine intravenously (2 mg./kg.) and ventilated for some twenty-five minutes. Then, pentobarbital in doses identical to those used in control experiments was given intravenously. Five seconds of electrical stimulation were then followed, after a ten-second pause, by a five-second interval of painful stimuli. The time taken to obtain E.E.G. activation with each stimulus was noted.

In order to simulate conditions met clinically where paralysis follows loss of consciousness, pentobarbital was first given intravenously at 5 mg. per minute until light anaesthesia was achieved. The threshold for BSRF arousal was next determined using a stimulus of minimal voltage at 200 c.p.s. and 1 msec. pulse duration. The threshold current in milli-amperes was measured with a Hewlett Packard a.c. current probe and a Tektronix RM 565 oscilloscope. Gallamine was then given intravenously, and after a ten-minute waiting period arousal threshold was again determined by electrical stimulation of the BSRF or by painful stimulus (pinching the skin with surgical forceps).

3. Vagal Stimulation

The effects of vagal stimulation in cats given paralyzing doses of muscle relaxants (decamethonium, curare, gallamine, succinylcholine) also were studied. The left vagus nerve in the neck was isolated, a femoral artery and vein were cannulated, and the E.E.G., blood pressure, and electrocardiographic effects of five seconds of vagal stimulation (5 v., 20 c.p.s., 1 msec.) were recorded.

Muscle relaxants were given intravenously in doses used clinically; succinylcholine (1 mg./kg.), gallamine (2 mg./kg.), decamethonium (0.1 mg./kg.) and d-tubocurarine (0.3 mg./kg.).

At the conclusion of each series of experiments, electrode positions were verified histologically.

RESULTS AND DISCUSSION

1. Slow-frequency, high-voltage activity usually dominates the E.E.G. recording of the quiet, drowsy, resting cat. Figure 2 illustrates this pattern. Suitable stimulus of the BSRF changes this pattern to fast low voltage activity—so-called E.E.G. activation—which is typical of the conscious alert animal. Alerting also was readily accomplished by either auditory, visual, or painful stimuli, whose time-locked responses are evident on all channels (Fig. 2). The normotensive, normocarbic ($P_{CO_2} = 40$ mm. Hg), unanaesthetized cat paralyzed with gallamine or

FIGURE 2. Effects of muscle relaxants on somatic sensory inflow. L-APSG = left anterior posterior sigmoid gyrus; R-APSG = right anterior posterior sigmoid gyrus; R-PVL = right postero-ventral lateral nucleus of thalamus; R-BSRF = right brain stem reticular formation.

succinylcholine and ventilated with room air failed to produce any patterns of E.E.G. deactivation for periods lasting from 30 to 60 minutes. Instead, relatively fast, low-voltage E.E.G. activity persisted, and the E.E.G. responses to various parameters of painful stimulation remained unchanged (Fig. 2). This observation suggests, but certainly does not prove, that sensory inflow to the brain stem and cortex is unaltered by muscle relaxants, a hypothesis that gains support from clinical reports in which patients have remembered distinct episodes of consciousness during surgery. Some of these patients have complained of suffering excruciating pain and yet were unable to move during their operative procedures.⁸

That neither consciousness nor pain perception is altered by muscle relaxants per se also has been indicated by studies in conscious human volunteers.^{4,5} Additional anaesthesia with nonhypoxic concentrations of nitrous oxide in the presence of muscle relaxants is not always able to totally obtund consciousness,¹⁰ nor is the addition of hyperventilation to this combination always adequate for surgical anaesthesia.^{11,12} Furthermore, it has been shown that in man the visual evoked cortical response during surgical anaesthesia is intact and is not altered in the presence of succinylcholine paralysis.¹⁸

Nitrous oxide and other anaesthetic gases are known to suppress afferent evoked potentials in the reticular formation preferentially over those in the postero-ventral lateral nucleus of the thalamus.^{14,15} It has been suggested that hyperventilation also disturbs transmission in the reticular formation.^{16,17}

The combination of nitrous oxide and hyperventilation usually leads to a deactivated or synchronous pattern of the E.E.G.¹⁸ It is this differential early

suppression of the reticular formation which seems clearly allied to the loss of consciousness.¹⁹ Recent reports have suggested that the limbic system and particularly the hippocampus is important for the conscious state with special reference to memory of the event.²⁰ Thus it seems that the muscle relaxants by themselves do not initially alter painful, auditory, or visual afferent inflow and do not change the alerted pattern of the E.E.G.

2. It has been suggested that anaesthesia and electrocortical synchronization may be facilitated in the presence of anti-cholinergic skeleto-motor paralysis. In one report electrocortical synchronization occurred frequently after one half hour or longer in paralyzed, ventilated cats.²¹ We have also shown that the de-afferented animal requires significantly less anaesthesia than intact animals in order to achieve the same degree of central nervous system depression.²² The possibility that a reduction of proprioceptive drive as the result of paralysis might decrease afferent inflow sufficiently to reduce anaesthetic requirements was examined in this phase of our study.

Using the method already described, a comparison was made between two groups of cats, infused intravenously with pentobarbital respectively in the absence and in the presence of drug-induced motor paralysis. Figure 3 shows the typical deactivated hypersynchronous E.E.G. pattern of a cat after the infusion of 5 mg./kg. of pentobarbital. At this dosage of pentobarbital, the cat still can be readily alerted either by a painful stimulus or by electrical stimulation of the brain stem reticular formation. However, with increasing doses of pentobarbital (12 mg./kg.) an end point is reached where E.E.G. activation can no longer be elicited by the same stimuli (Fig. 3). A comparison of the doses of pentobarbital needed to produce the same degree of central nervous system

FIGURE 3. Effects of muscle relaxants on anaesthetic requirements.

TABLE I
INTRAVENOUS PENTOBARBITAL
End Point in mg./kg.

Cat	Non-paralyzed		Paralyzed	
	BSRF Stim.	Pin prick	BSRF Stim.	Pin prick
A	7.0	8.4	8.5	7.0
B	13.0	7.2	11.6	7.2
C	15.5	8.9	13.3	6.7
D	14.5	9.1	12.7	9.1
Average	12.5	8.2	11.5	7.5

depression with and without muscle relaxants is given in Table I. In the non-paralyzed cats an average dose of 12.5 mg./kg. of pentobarbital is needed to prevent E.E.G. arousal to electrical stimulation, whereas approximately the same dose of pentobarbital (11.5 mg./kg.) is required to produce the same effect in the presence of muscle relaxants. Similarly, the alerting response to pin-pricks is not significantly different in the two groups ($+ < 0.01$), though it is lost at a lower dosage of pentobarbital than the response to electrical stimulation. Thus neuromuscular blockade does not alter anaesthetic requirements in the cat, at least in the induction phase of anaesthesia.

Additionally, the threshold current (in milliamperes) needed to elicit brain stem arousal in cats under light intravenous pentobarbital anaesthesia was investigated. After intravenous gallamine, the pentobarbital-induced deactivated E.E.G. did not change and the electrical threshold for arousal remained the same (Fig. 4). Neuromuscular blockade does not appear to alter anaesthetic requirements in the early maintenance of pentobarbital-induced anaesthesia.

Reports describing electrocortical synchronization after the use of muscle relaxants have stressed that changes in the E.E.G. are not readily seen until after an hour or even three hours of controlled ventilation. Our observations

FIGURE 4. Effects of muscle relaxants on anaesthetic requirements.

were always made after less than one hour of exposure to muscle relaxants, and it may well be that as time elapses, anaesthetic requirements may become reduced.

It is generally agreed that neuromuscular fatigue promotes sleep,²³ and that proprioceptive afferents may act as powerful alerting stimuli.²⁴ However, with the cat supine and comfortable, there is already a considerable decrease in proprioceptive drive. In this instance muscle relaxants may not produce any further significant reduction in proprioceptive inflow.

In some circumstances, decreased sensory input may be stressful.²⁵ Full muscle paralysis and automatic ventilation of the lungs may also constitute a stress. Nevertheless, our cats so treated needed the same induction dose of pentobarbital as the control group. It is possible that this stressful situation may mask any soporific properties of reduced proprioceptive drive. However, this mechanism does not explain why there is no change in anaesthetic requirements when a muscle relaxant is given to a cat which is already under light surgical anaesthesia. In these circumstances proprioceptive inflow is minimal and a further reduction using a muscle relaxant should add little to the existing degree of afferent deprivation. Nevertheless, it is a common clinical observation that the reversal of curarization (by an "atropine-neostigmine" sequence) at the conclusion of anaesthesia and surgery often coincides with the return of consciousness, spontaneous ventilation, and motor activity. It has been suggested that spontaneous ventilation and wakefulness are closely interrelated.²⁶

3. The fact that the effects of reflex vagal stimulation are potentially harmful during clinical anaesthesia²⁷ led to the third phase of our investigation. Stimulation of the left vagus nerve in the restrained, unsedated cat produced bradycardia with only slight blood-pressure changes. Table II shows that similar

TABLE II
VAGAL STIMULATION
5 v., 20 c.p.s., 1 msec., for 5 sec.

	Before stim.		After (no sig. B.P. change)	
	E.C.G. (H.R./min.)	systolic B.P.(mm.Hg)	E.C.G. (H.R./min.)	per cent change
Control	220	114	170	23
Succinylcholine	270	120	210	22
Decamethonium	228	98	168	26
Gallamine	280	108	280	0
D-Tubocurare	198	84	198	0
D-Tubocurare (9 v.)	198	84	174	12

results during vagal stimulation were obtained in the normotensive, normocarbic, ventilated cat after paralysis with either decamethonium or succinylcholine. However, vagal stimulation in cats treated with gallamine had no effect on either heart rate or blood pressure. The administration of d-tubocurare alone caused a precipitous fall in blood pressure which was reversed with intravenous phenylephrine. Vagal stimulation (5 v.) in this cat produced no additional observable cardiovascular effect. Increasing the stimulator voltage to 9 v, produced slight bradycardia after d-tubocurare, but was without effect in the gallamine-treated preparations.

These observations suggest that in the cat depolarizing muscle relaxants offer no protection to vagal stimuli. Clinically, the vagolytic effects of gallamine in man are well known, and it has been shown that gallamine has profound vagolytic activity.²⁸ In contrast, vagal blockade with d-tubocurarine in man is not as evident, although in this study d-tubocurarine seems to offer some antagonism to vagal stimulation in the cat in the presence of phenylephrine. With increasing doses of d-tubocurarine a fall in blood pressure of surgical patients is occasionally seen and is usually attributed to either ganglionic blockade or histamine release. The pulse rate is not uniformly raised as it is with gallamine. Thus any "protective" action against vagal stimulation in curarized man is probably small.

SUMMARY AND CONCLUSIONS

Muscle relaxants do not appear to alter the effects of afferent inflow in the cat and do not initially change the activated E.E.G. That this is probably the case in man has been borne out by clinical reports of patients being awake during their surgery.

The induction dose of pentobarbital which is sufficient to depress E.E.G. and behavioural arousal in response to two different types of stimuli was found to be approximately the same in "normal" cats and in cats treated with paralyzing doses of muscle relaxants. The threshold stimulation for brain stem arousal was found to be the same in a lightly anaesthetized cat with and without skeleto-motor paralysis. With the techniques described, we have not been able to demonstrate convincingly that clinical doses of muscle relaxants by themselves initially contribute more than neuromuscular paralysis to the anaesthetic state in the cat. Whereas a slight decrease in proprioceptive drive is no doubt achieved this seems to play little if any role during the induction and early maintenance of anaesthesia. The possibility that this role may be greater during the emergence from anaesthesia when muscle paralysis is reversed with neostigmine and the initiation of spontaneous ventilation is being currently investigated.

Experiments with the cat indicate that muscle relaxants, with the exception of gallamine, do not protect against the effects of vagal stimulation. The clinical use of gallamine in man lends support to these findings.

RÉSUMÉ

Nous avons poursuivi des expériences sur des chats intacts non anesthésiés à l'aide d'électrodes fixées dans le cortex sur les gyri antérieur et postérieur. Des chémitrodes subcorticales ont été placées dans le noyau latéral postéro ventral gauche ou droit du thalamus, dans le corps géniculaire latéral, dans la région pré-optique et dans la formation réticulée de la substance cérébrale.

Nous avons étudié, à l'aide de cette préparation d'un chat, les effets des myo-résolutifs sur la conduction de la sensibilité somatique. Nous avons également étudié, sur des préparations semblables, les quantités requises de pentobarbital donné par voie veineuse selon que l'animal avait reçu ou non des médicaments paralysant la musculature squelettique; nous avons fait de même en ce qui con-

cerne les effets de la stimulation vagale chez des chats paralysés par des myorésolutifs (décaméthonium, d-tubocurare, gallamine, succinylcholine).

D'après nos résultats, il ne semble pas que les myorésolutifs puissent changer les effets de la conduction afférente de la sensibilité chez le chat, et ils ne changent pas, en premier lieu, le tracé électroencéphalographique. Des observations cliniques faites chez des malades éveillés au cours de la chirurgie nous laissent croire qu'il en est probablement ainsi chez l'homme.

L'induction avec une dose de pentobarbital suffisante pour déprimer le tracé électroencéphalographique et prévenir le réveil en réponse à deux types différents de stimulations, s'est avérée à peu près la même chez les chats "normaux" que chez les chats "paralysés" par des myorésolutifs. Le seuil de stimulation pour l'éveil de la substance cérébrale a été le même chez le chat sous anesthésie légère avec ou sans paralysie musculaire.

Cette technique ne nous a pas permis de démontrer de façon convaincante que des doses cliniques de myorésolutifs de fait pouvaient produire autre chose, chez le chat anesthésié, qu'une paralysie neuromusculaire. Bien qu'il existe une légère diminution de la sensibilité proprioceptive, cela n'a que peu ou pas d'influence sur l'induction et le début du maintien de l'anesthésie. Nous essayons d'établir s'il est possible que les myorésolutifs jouent un rôle plus grand au cours de l'élimination des agents anesthésiques alors que la paralysie musculaire est renversée avec de la néostigmine et que la respiration spontanée reprend.

Chez le chat, nous pouvons affirmer que les myorésolutifs, à l'exception de la gallamine, n'assurent aucune protection contre les effets de la stimulation vagale. Chez l'homme, l'usage clinique de la gallamine confirme ces résultats.

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