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NEUROPHYSIOLOGICAL STUDIES ON COMA INDUCED BY STIMULATION OF (ESPECIALLY BY MINIMAL NICOTINIZATION INTO) VARIOUS PARTS OF THE BRAIN IN CATS

By

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INTRODUCTION

ISHII, a member of our laboratory, reported in 1944²⁰⁾ that a stitching of the bordering between the pons and the oblongated medulla via inferior colliculus near the midline in monkeys, which was called coma puncture by him, occasionally induced an instantaneous and reversible comatose state. By application of induction currents, ARAKI, TAKETOMO and TODA 1949¹⁾ demonstrated the evidence that this cerebral portion, probably functioning like a switch to the maintenance of the alertness, was seated in mesencephalic central gray matter at the levels of oculomotor and trochlear nucleus in rabbits and cats. YAEONO 1954⁴⁶⁾ executed local administration of minimal dose of nicotine in some parts of the brain for the further research; this procedure had been used by HAYASHI^{21)&42)} in his studies of convulsion, and called "nicotization" by him. YAEONO's study revealed the fact that the minimal nicotization in medial thalamus or substantia nigra as well as in mesencephalic central gray matter occasionally induced comatose state without accompanying any motor phenomena in cats. His study suggests the possibility that many more cerebral portions, in addition to mesencephalic central gray matter, may influence essentially the state of animal's wakefulness.

The purpose of the present study is to obtain exact informations concerning 1) anatomical system of cerebral areas having a distinct relationship to the manifestation of comatose state after the localized application of stimuli or damages, ii) accompanying motor phenomena in such comatose animals and iii) probable basic mechanisms for explaining a series of coma studies in our laboratory. KAZUKI SAKATA⁴¹⁾ who cooperated with me in the recording of electroencephalograms in my experimental animals reported elsewhere on the details of EEG studies. I shall, therefore, only show an outline of EEG changes in this paper.

METHODS AND MATERIALS

Experiments were made on 65 cats, whose body weights ranged from 0.85 to

4.80 kg. Animals are fixed on a hammock in prone position with their limbs hung down naturally. Each limb is connected with a strip to a frame supporting each corner of the hammock, and so is allowed to move freely in the limit of length of the strip. This precaution is important, enabling the animals to assume various bodily movements. Trepanation and installation of CLARKE's stereotaxic instrument (hanging type) are carried out under ether narcosis. A syringe with a needle, one third millimeter in size, has been connected with the electrode holder of the instrument. Undiluted nicotine manufactured by Dr. THEODOR SCHUCHARDT is filled preliminarily in the syringe, and its minimal dose, 0.01 cc is injected through the injection needle into a certain subcortical structure. There is no fear of dropping of nicotine from needle tip without manual pressing of piston because of the high viscosity of nicotine. Insertion of needle and injection of nicotine are done after animal's behaviour and EEG activities ... in the cases outfitted with leading electrodes ... have shown the entire subsidence of narcotic effect of ether. Concerning procedures of the electroencephalography, for instance, selection of the locations where the electrodes are settled, the report of K. SAKATA should be referred to. Exact dosage of nicotine was not so difficult; syringe piston was pushed slowly by hand with some rotating motions. In some cases a small piece of filter paper immersed with nicotine of the same dose, 0.01 cc is stuck on the cortical surface instead of injection, shortly after the cortical surface has been exposed by a small incision of dura mater.

Repeated administrations of nicotine in different locations with certain intervals were often done, twice or more times, on the same animal. Intervals of repetitions were about 2 hours which were enough for animals to recover from striking respiratory alterations (usually tachypnea) and to assume normally active emotional attitudes.

After these schedules of acute experiments have been finished, the animals are put to death by bleeding. According to the common rule, the whole brain is taken out, fixed in absolute alcohol (aethanol), embedded in celloidine, sectioned 20 micra in thickness and stained by means of NISSLE's and myeline sheath staining. Thus locations of nicotization are certified microscopically.

In the tabulation of experimental data, only the name of one structure located in the centre of a necrotic area *, usually forming a small cavity, was labelled as the nicotinized location, though the identification of involved neighboring structures was roughly made in all cases. Anatomical guides were obtained mainly from WINKLER and POTTER (1914)⁴⁵⁾ and NIIMI (1950)³⁶⁾. Reports of JASPER (1949)²²⁾, Mc LARDY (1951)³¹⁾ and others^{39) & 42)} were also referred to.

* In the location of nicotization a homogeneous necrotified mass, one to three millimeters²¹⁾ in outer diameter, was seen. Branches of necrotic mass running along the course of inserted needle or of nerve fibres were usually observed, too. Thus, the organic change often involved more than one structure, particularly in thalamus. On the other hand, nicotine is a corrosive alkaline⁴²⁾ and so probably able to spread...though not yet verified...continually into surrounding tissues until alcohol for fixation stops this expansion. In considering this possibility, the space occupied by injected nicotine would be much more restricted than the size of a histologically proved destruction.

PRELIMINARY STUDY

According to GIRNDT 1932¹³⁾, spontaneous movements, postural reflex, corneal

Table 1. CORRELATIONS BETWEEN DEPTHS OF NARCOSIS AND DISAPPEARANCE OF REFLEXES AND RESPONSES TO EXTERNAL STIMULI ON CATS

depth of narcosis by Girnst	I	II	III	IV	V	VI
reflexes or responses tested						
knee jerks	+	+	+	+	+	+~--
corneal reflex with a piece of gauze	+	+	+	+	+ ~±	-
ear lobe reflex	* ₄ +(or±) +(or±) +(or±) +(or±) + ~± -					
sneezing inducible by stabbing of nasal septum	+	+	+	+	+ ~±	-
flight reflex from heating of nose tip	+	+	+	+	+ ~±	-
vomiting and swallowing reflexes	+	+	+	+	+~--	-
pupillary reflex * ¹	+	+	+	+	+~--	-
flight reflex from pricking of nose tip	+	+	+	+	+~--	-
corneal reflex with cotton wool	+	+	+	+	~± +~--	-
flight reflex from heating of forelimb * ²	+	+	+	+	~± ±~--	-
flight reflex from heating of hind-limb * ²	+	+	+	~± + ~±	-	-
blinking reflex with blowing of examiner's breathing air	+	+	+	~± + ~±	-	-
flight reflex from pricking of tail	+	+	+	+~--	-	-
respiratory stoppage by inhalation of smoke	+	+	+	+~--	-	-
localized piloerection by touch to eyebrows or whiskers * ³	* ₄ +(or±) +(or±) +(or±) +~-- - -					
stiffness against passive movement	* ₄ +(or±) +(or±) +(or±) +~-- - -					
spontaneous movement and meowing	* ₄ +(or±) +(or±) +(or±) +~-- - -					
bodily movement by hand clapping * ³	* ₄ +(or±) +(or) + ~± +~-- - -					
seaching movement for a light moving in front of eye * ³	+(or±) + ~± + ~± ±~-- - -					

*¹ This reflex is usually lost under ether narcosis, but remains positive sometimes through the course of narcosis with amobarbital sodium (isomital).

*² This sometimes turns from negative to positive with repetition of examination.

*³ They tend to become indistinct by repetitive examinations.

*⁴ In rare cases this is negative without any narcosis.

reflex and many sorts of spinal reflexes of animals would disappear successively in this order, with the progress of narcosis. For the purpose of obtaining more details in this respect, various kinds of reflexes or responses to environmental ... mainly external ... stimuli were examined repeatedly through the progress of narcosis with ether, hexobarbital sodium (auropan) or amobarbital sodium (isomital) on 5 cats more than 2 kg in weight. Table 1 indicates the results of this study. In the stage where spontaneous movements and postural reflexes entirely were lost, other various reflexes remained positive, especially flight movements against smell stimuli, against mechanical stimuli to mouth, tongue, gum, pharynx or esophagus and against pain stimuli to skin, particularly in the areas innervated by trigeminal nerve. These responses have a tendency to be lost in a definite order, as shown in table 1, and so are of use for our purpose. I should like to classify the general responsiveness of animals by the criteria consisting of combinations of these reflexes and responses, routinely used in clinical examinations into four stages, as follows.

1) Normal wakefulness or intact responsiveness is equivalent to the first degree of the depth of narcosis by GIRNDT. The animal shows no abnormalities of spontaneous movements, postural reflex and searching movements after abrupt changes of circumstances etc*.

2) Slight stupor or unresponsiveness of the first degree (I) is equivalent to the state ranging from the second degree to the light stage of the fourth degree of the depth of narcosis by GIRNDT. Postural reflexes are lost. The animal responds well to pain stimuli, smell stimuli and stimuli to intestinal mucosa, but shows diminished spontaneous movements or inadequate searching movements etc*.

3) Semicomatose state or unresponsiveness of the second degree (II) includes the deep stage of the fourth degree and the light stage of the fifth of the GIRNDT's depth of narcosis. Postural reflexes, seaching movements and others*, as above mentioned, spontaneous movements, meowings** and arrest of respiratory movements inducible by stimulation of air tract are completely lost. Nociceptive reflexes from pain stimuli to skin are partially lost, especially in the body parts below neck. Sneezing after stimulation of nasal septum, flight reflex from pain stimuli to nose tip or its surrounding and corneal reflex remain constantly intact.

4) Comatose state or unresponsiveness of the third degree (III) equals the deep stage of the fifth degree and the sixth degree of the GIRNDT's scale. Nearly

* In normal cats, searching movements of eye balls following a moving electric lamp (related to visual perception), movements of ear lobes, whiskers or head in response to hand claps or imitated meows by examiner (related to auditory perception), body movements or piloerection in response to a light touch on skin or pile of any body portion with only one exception of ear lobes (mainly related to superficial sensation) and transitory stoppage of respiratory movements after inhaling the smoke of tobacco (related to sensibility of air passages including nasal mucosa) are promptly evoked. I examined routinely whether these responses were inducible or not, in addition to other reflexes.

** Monotonous violent meows were rarely heard, especially in cases of rage-like agitation after nicotization. Same phenomenon is also inducible by electric or mechanical stimulation of sciatic nerve in mesencephalic cat (cat whose brain stem has been sectioned at the rostral end of the mesencephalon).

all sorts of reflexes and responses above mentioned are not present. Corneal reflex, ear lobe reflex and pupillary reflex are positive in some cases and negative in others. Tendon reflexes, e. g. knee jerks are usually intact.

Each stage of this classification would represent, in gross, the normal and intact functioning of the whole central nervous system (1), partial loss of cerebral and cerebellar functions (2), or total loss of their functions accompanied by a slight (3) or severe (4) impairment of brain stem functions.

RESULTS

Table 2. DISTURBANCE OF RESPONSIVENESS AND ACCOMPANYING MOTOR PHENOMENA IN CASES OF NICOTINIZATION IN VARIOUS PARTS OF THE BRAIN ON CATS

(Mark C means nicotine-induced coma,
S nicotine-induced semicoma and
X no marked disturbance of responsiveness.)

structure in which nicotine was injected	induced motor effects		no distinct motor effects
	complete generalization	incomplete generalization or localization	
amygdala proper	C	S X	/
fornix	C	X	/
pre- and posteruciate gyri	X	S XXX	/
CL & Pc of intra-laminar nuclei	C	S X	/
substantia nigra	/	C X	/
centre median de Luys	/	C S S	/
mesencephalic CG	C C C	C C C	C S
septum pellucidum	S	X X	X
lateral gyrus	S	S	X
anterior nuclei of thalamus	S	S	S
nucleus caudatus	/	S S	X
globus pallidus	/	X X	/
nucleus lateralis hypothalami	/	S S	X
nucleus parataenialis & stria medullaris thalami	C X	/	S
lobus medialis of cerebellum	X	/	X
rostral end of CG * ¹	C	C C	C C C
anterior cingulate gyrus	C	C S	C C C
n. dorsomedialis thalami	/	X	X
ectosylvian gyrus	/	X	S
pulvinar thalami	/	X X	C X
medioventral portion of capsula interna	C	/	C S
stria olfactoria & surrounding structures	/	C	C C
RA & RM of midline nuclei of thalamus	S	/	S X X
n. ventralis anterior of thalamus	/	/	X X
Re & surrounding structure * ²	X	/	S X
posterior suprasylvian gyrus	C	/	/
preamygdala	S	/	/
commissura anterior	S	/	/
tractus Meynerti	X	/	/
n. proprius pedunculi cerebri	X	/	/
VPM of thalamus	/	S	/
nucleus ruber	/	X	/
lobus paramed. of cerebellum	/	X	/
hippocampus	/	/	C
posterior sylvian gyrus	/	/	S
mesencephalic FR near decussatio Meynerti	/	/	S
orbital gyrus	/	/	X
corp. quadr. anticum	/	/	X

*¹ The rostral end of this structure towards the mediodorsal portion of posterior hypothalamus is uncertain.

*² This group includes RE of Jasper and the pars ventromedialis of nucleus laminaris.

The disturbances of the general responsiveness towards environmental changes, which have been observed after the minimal application of nicotine in various parts of the cat's brains, are summarized in table 2. Thirty six animals which fell in irreversible apnea during experiments are omitted from this table. Some illustrative cases in our experiments will be shown in the following.

Case 31-F (Fig. 1*, showing the lesion due to the first injection). The animal took a somewhat restless attitude immediately after the injection of nicotine. But she fled promptly from pinch of nose tip with a hemostatic forceps (KOCHER's type). Rage-like movements, associated with irregular and increased respiration rate, moderate mydriasis and frequent meowings, began 10 sec. after nicotine injection. One minute and a quarter a. n. (abbreviation of the words "after nicotine injection");

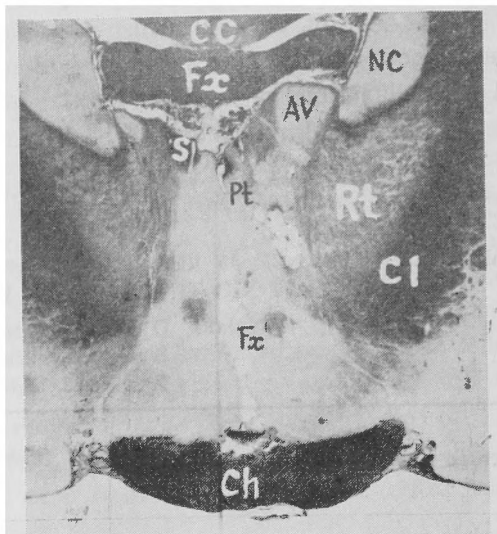


Fig. 1 Cat 31-F

Electrocorticograms, taken during and immediately after the insertion of needle, showed low voltage fast activities. They increased in amplitude after nicotine injection. Moderate or high voltage fast waves were recorded in both occipital regions.

* ABBREVIATIONS (used in the tables and figures of this paper)

AD nucleus anterior dorsalis. AM nucleus anterior medialis. AV nucleus anterior ventralis. Br. conj. brachium conjunctivum. CA commissura anterior. CC corpus callosum. CG substantia grisea centralis (periaqueductal). Ch chiasma nervorum opticorum. CI capsula interna. CL nucleus centralis lateralis of intralaminar nuclei. CM centre médian de Luys. CQA corpus quadrigeminum anticum. D.M. decussatio Meynerti. En nucleus entopeduncularis. Flp fasciculus longitudinalis dorsalis. FR formatio reticularis. Fx fornix. GCA gyrus cinguli anterior. GI ganglion interpedunculare. GL corpus geniculatum laterale. GSS gyrus suprasylvius. HL habenula lateralis. LP pars intermedia of pulvinar (NIMI) or posterior lateral nucleus (RANSON). LV nucleus lateralis ventralis (NIMI) or LV (JASPER). MD nucleus medialis dorsalis thalami. NC nucleus caudatus. NPC nucleus proprius pedunculi cerebri. NPH nucleus hypothalamicus posterior (This structure has no distinct bordering, particularly backwards on the rostral end of mesencephalic central gray matter; man could hardly mark such a border-line). N.R. nucleus ruber. Nucl. IV nucleus trochlearis. Pe nucleus paracentralis of intralaminar nuclei. Ped pes pedunculi cerebri. Pf nucleus parafascicularis. Put putamen. RA nucleus reuniens arcuatus (NIMI). RCC radiatio corporis callosi. Re nucleus reuniens (RANSON) or nucleus paramedianus (NIMI). RM nucleus reuniens medianus (NIMI) or a structure including nucleus rhomboides and nucleus centralis medialis. Rt nucleus reticularis of thalamus. S stria medullaris thalami. SP septum pellucidum. TGu tractus GUDDENI. THI tractus habenulointerpedunculare (MEYNERT). TMT tractus mammillothalamicus (VIC D'AZVER). TO tractus opticus. Tr. M. tractus MEYNERTI, same structure as THI. VA pars anterior lateralis of ventral nucleus (NIMI) or nucleus ventralis anterior (JASPER). VPL pars posterior lateralis of ventral nucleus (NIMI) or nucleus ventralis posterolateralis (JASPER). VPM pars posterior medialis of ventral nucleus (NIMI) or nucleus ventralis posteromedialis (JASPER). ZI zona incerta.

same in the following descriptions), responses to pinch of nose tip became negative. Clonic twitchings began at this time in both eye lids. Clonic convulsion of four limbs and piloerection were observed one minute and three quarters a. n. Rigidity was proved in tail 3 minutes a. n. This convulsion, associated with striking mydriasis, continued to 5 minutes a. n., though the disappearance of seizure activities of electrocorticogram (ECG) occurred 6 minutes a. n. Immediately after the cease of this convulsion, all extremities were flaccid and meows were elicited by rubbing tail with examiner's hand. Thirteen minutes a. n. the animal struggled against tip of lighted cigarette approaching to nose tip, ear lobe or hind limb on either side. Location of nicotinization is in nucleus parataenialis and stria modularis thalami (Fig. 1). Besides them, the lesion due to the injection of nicotine is extended to nucleus anterodorsalis (confirmed in sections more caudad to figure 1).

Grossly speaking, motor effects elicited in my experiments** consisted not merely of tonic spasms, but also of phasic movements; the latter were not always associated with rigidity. Such motor effects propagated in some cases all over the body ... complete generalization ..., in some other cases not entirely over the whole body ... incomplete generalization ..., and in still other cases to no other body parts than a certain restricted part ... localization Among the cases of the complete generalization of motor effects, unresponsiveness II or III were observed in cases of the nicotinization on lateral gyrus, and in praeamygdala, septum pellucidum, commissura anterior, anterior nuclei of thalamus, nucleus caudatus, amygdala proper and nucleus centralis lateralis of intralaminar nuclei, as well as in nucleus parataenialis (shown here). Commonly the nicotinization of these structures, unless the complete generalization of motor effects took place, did not result in any marked disturbance of responsiveness. In cases of the nicotinization of other structures, responsiveness was sometimes impaired noticeably without any motor effect or with the incomplete

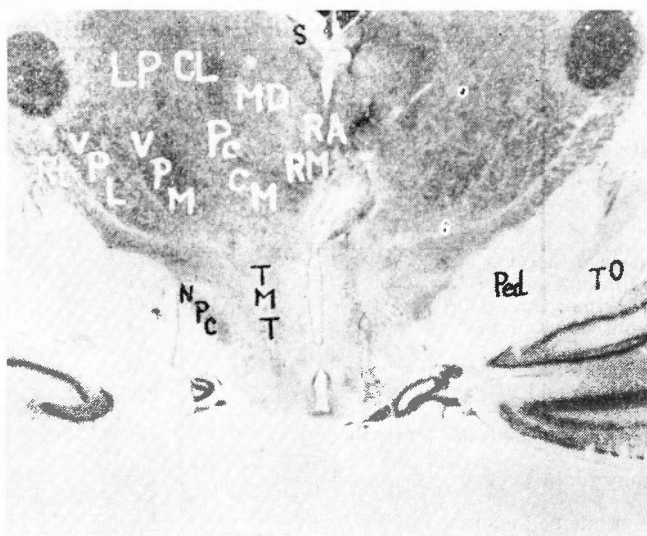


Fig. 2 Cat 29-D

No marked changes of ECG were recorded immediately after insertion. Shortly after nicotinization fast waves, especially in the occipital region, dominated; moderate voltage fast waves appearing during comatose state diminished in amplitude after spontaneous meowings had been initiated.

** Non-convulsive movements, for instance, (i) unrhythmic movements usually of voluntary or emotional nature or (ii) impulsive, reflectoric movements of short duration are not represented by this nomenclature.

generalization or the localization of motor effects.

Case 29-D (Fig. 2, showing the locus of the first injection). The animal struggled against finger touch on nose tip after inserting syringe needle. Tachypnea and mydriasis began 30 sec. a. n. Corneal reflex, either direct or consensual, was lost 2 minutes and a half a. n. Animal did not respond to pricking of nasal septum 4 min. and 20 sec. a. n.; at this time, twitchings of only one ear lobe, on the same side as injection, had been lasting for about 6 minutes, beginning 2 min. a. n., and no responses were provable after pinches of four extremities and tail. The animal avoided a pinch of nose tip 12 min. a. n. incompletely. Meowings were inducible by pricking of nose tip, ear lobes or four limbs 15 min. a. n. Thus in this case unresponsiveness III with the latency of 2 min. and a half lasted 9 min. and 25 sec. Nicotine was found to have been injected in a portion a little ventral to nucleus reuniens medianus (N_{RM}) or to nucleus centralis medialis (J_{ASPER}), corresponding to the mediodorsal part of nucleus posterior hypothalami.

In most cases of the nicotization in olfactory stria and its vicinity, anterior cingulate gyrus, rostral end of central gray matter or mesencephalic central gray matter, unresponsiveness III occurred independently of the presence or absence of motor phenomena. The comatose state without any accompaniment of motor

Table 3. LOCATIONS OF NICOTINIZATION IN CASES OF INDUCED UNRESPONSIVENESS III (COMA) AND ACCOMPANYING MOTOR EFFECTS

structure where nicotine was applied	incidence of unresponsiveness III	accompanied motor effects		
		no motor effects (Group 1)	localized or incompletely generalized motor effects (Group 2)	completely generalized motor effects (Group 3)
stria olfactoria	3/3	2/2	1/1	0
hippocampus	1/1	1/1	0	0
pulvinar thalami	1/4	1/2	0/2	0
ventromedial part of capsula interna	2/3	1/2	0	<u>1/1</u>
				Fig. 4 or Table 6
gyrus cinguli anterior	5/6	3/3	1/2	<u>1/1</u>
rostral end of central gray matter	6/6	3/3	2/2	<u>1/1</u>
		Table 5	Fig. 2	Table 6
gyrus suprasylvius posterior	1/1	0	0	<u>1/1</u>
				Table 6
amygdala proper	<u>1/3</u>	0	<u>0/2</u>	<u>1/1</u>
				Table 6
septum pellucidum	<u>1/4</u>	<u>0/1</u>	<u>0/2</u>	<u>1/1</u>
stria medullaris thalami	<u>1/3</u>	<u>0/1</u>	0	<u>1/2</u>
				Fig. 1
Pe & CL of intralaminar nuclei	1/3	0	<u>0/2</u>	<u>1/1</u>
mesencephalic CG	7/8	1/2	3/3	<u>3/3</u>
		Table 5		Table 6
substantia nigra	1/2	0	1/2	0
centre médian de Luys	1/3	0	1/3	0

Note 1. The ratios of the cases showing completely generalized motor effects are underlined.

2. In 2 cases where nicotine was injected each in pulvinar or internal capsule --- in the latter case generalized motor effects were accompanied ---, the destruction due to injection extend to nucleus reticularis thalami. It may have been possible that the involvement of this nucleus was the chief cause of the induced coma. The number of such cases is too small to permit the definite conclusion.

phenomena was also found in few cases of the nicotization in pulvinar, ventromedial portion of internal capsule or hippocampus. Motor effects after the nicotization in centre médian de Luys or substantia nigra showed usually incomplete generalization. Some of them accompanied comatose state. Concerning the interrelation between responsiveness and the extension of accompanying motor phenomena, table 2 and 3 should be referred to.

Here is my important problem as to whether the occurrence of motor effects paralleled the impairment of responsiveness. Table 2 explains this problem clearly. Among the 23 cases of the complete generalization of motor phenomena, incidence of comatose state amounts to 47.8 per cent (11 cases). Incidence of comatose state was 23.1 per cent (9 cases) among the 39 cases of the incomplete generalization and the localization of motor phenomena, and 34.3 per cent (12 cases) among the 35 cases of no motor effects***. It appears highly probable that complete generalization has a tendency to make the occurrence of comatose state easier. In 6 cases, 26% of the cases of complete generalization, however, responsiveness was hardly impaired. I suppose, therefore, that the occurrence of comatose state is more closely related to the location of the administration of nicotine, than to the coexistence of induced general convulsion.

Case 61-B (Fig. 3, the seat of the second injection). After insertion of needle no marked behavioral changes were observed. The attitude also was not altered after injection. Meowing was easily induced by touch on tail. Corneal and pupillary reflexes, 3 minutes a. n., and ear lobe reflex, 4 m. a. n., were completely positive. About that time clonic convulsion came on first in the forelimb of the opposite side to injection, although the animal was able to avoid heating of forelimbs. The convulsion was altered to slight rigidity 12 m. a. n. Fourteen minutes a. n. fibrillary twitchings appeared in the hind limb of the same side as injection, and marked rigidity in other three extremities. Muscles of masticatory were also stiff 17 m. a. n.

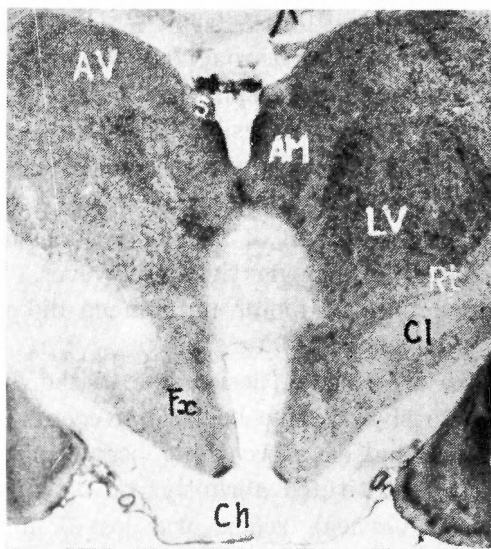


Fig. 3 Cat 61-B

ECGs were not taken. Concerning the changes of responsiveness and the location of injection the protocol presented in text should be referred to.

*** Twitching of ear lobe was observed in all cases (13 in number) where nicotine was administered hypodermically. Abnormal movements of eye-balls, e. g. nystagmus or strabismus, were often but too irregularly observed to warrant some explanation for the mechanism of their occurrence. These motor phenomena were, therefore, neglected in reviewing experimental data.

Through this entire time course, the animal could avoid the pinch of nose tip or tail, and the heating of both forelimbs. Intermittent hissings were listened to about 24 m. a. n. when generalized fibrillary twichings and the erection of tail were seen. Location of injection was revealed to lie ventrocaudad to the lesion in the case of generalization demonstrated above (case 31-F, Fig. 1). The lesion due to injection extended into nucleus paramedianus, pars ventromedialis of nucleus laminaris (N_{PLM}), Vic d'Azyr's bundle and dorsal part of nucleus dorsomedialis hypothalami.

In one animal whom nicotine was injected directly in the third ventricle (case 50-B), responsiveness was not disturbed throughout the entire course until respiratory movements stopped irreversibly, despite the animal showed generalized tonic spasm. Generally in the animals nicotinized in various structures lying at the levels between nucleus rhomboideus of the thalamus and rostral terminal of the mesencephalon, no remarkable motor phenomena have been observed. Among them, however, there was one exceptional case in which the occurrence of motor phenomena did not coincide in time with that of induced unresponsiveness.

Case 97 (Fig. 4, lesion due to the first injection). Before injection the animal tended to show active bodily movements in response to noisy sounds. Restlessness, mydriasis and deep breathing began immediately after injection. This state was, however, substituted abruptly by an extremely quiescent state one minute and a half a. n. Corneal reflex was lost 3 m. a. n. Reflexive stoppage of respiratory movements against smoke was not to be induced 4 minutes and a half a. n. Vomiting reflex and pupillary reflex were negative up to 6 m. a. n. Rigidity was not certified in any muscles including masticatory. Knee jerks were also lost 8 minutes and three quarters a. n. The animal began to avoid smoke with some difficulty and also to show bodily movements in response to passive movements of limbs about 10 m. a. n. Twelve minutes a. n., however, response to prickings of nasal septum disappeared once more. Following this, fibrillation came on in one forelimb opposite to the side of nicotization. Sixteen minutes and a half a. n., this motor effect was transferred to another fore-limb. Motor effect was propagated to tail

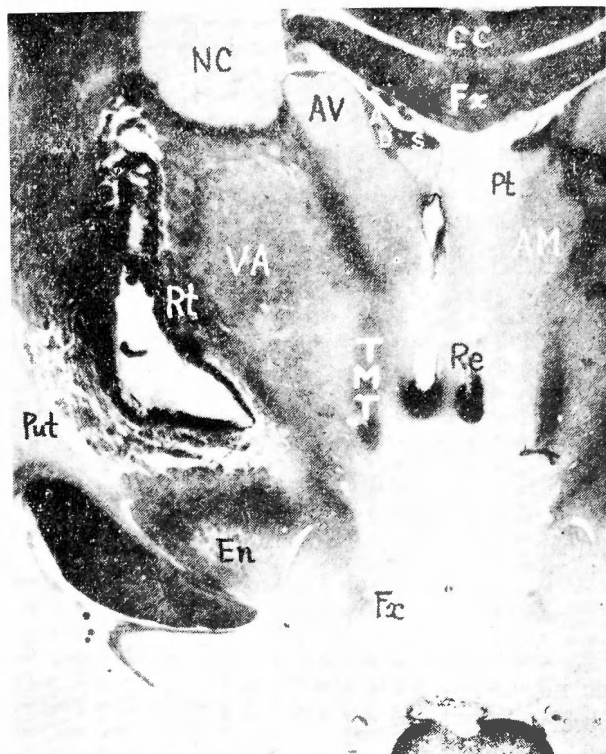


Fig. 4 Cat 97

ECGs were not recorded.

23 m. a. n., and gradually substituted by rigidity in all extremities. Knee jerks and tendon jerks of upper arms ... of either extensor or flexor ... which had been lost at the initial stage of unresponsiveness, became vividly positive during these motor phenomena (18 m. a. n.). Spontaneous struggling movements were seen first ca. 20. m. a. n., and respiratory movements stopped reflectorically by inhalation of smoke. The animal growled continually 55 m. a. n. After all, unresponsiveness III came on first and then motor phenomena occurred and were propagated to the whole body. Lost tendon jerks also returned before the onset of motor effect. Huge necrotified lesion is certified to have included nucleus reticularis thalami, nucleus ventralis posterolateralis thalami and capsula interna. It may have been possible that motor effect was caused by delayed expansion of nicotine into certain surrounding structure. This kind of complex phenomenon was observed in another case, in which nicotine was also applied on posterior suprasylvian gyrus (case 98). In these 2 cases impaired responsiveness had subsided before the onset of motor effects; so it may not be probable that unresponsiveness was due to the same mechanism as the spreading of motor effect.

Electrical stimulations ... in 19 animals bipolarly with rectangular pulse currents, in 21 animals monopolarly with the same currents ... gave rise to inconstant changes in animals' attitudes, particularly in their responsiveness. Sorts of stimulating electrode ... bipolar or monopolar ..., forms and frequencies of currents and duration in which rectangular pulse currents were passed, may be very important factors for any alteration of attitudes. Threshold stimulus to induce some particular behavioral change ranged widely from time to time in almost all cases. In certain portions, however, the result was fairly constant, i. e. a certain degree of disturbance of responsiveness occurred immediately after the stimulation with rectangular pulse currents of low frequencies ... 30 per second in maximum ...; difference of electrode, whether bipolar or monopolar, was negligible within this limit. Locations of stimulation where impaired responsiveness occurred during or immediately after application of currents were not found over the telencephalon, but in nucleus reuniens and in posterior hypothalamus and also in the vicinities of the bordering of central gray matter to reticular formation in the mesencephalon. Unresponsiveness accompanied by generalized motor effects was omitted from this study. I will demonstrate here one of the most typical cases where a certain degree of unresponsiveness was induced not only by electrode and/or syringe needle but also by the injection of nicotine in one location.

Case 70-D-1 (Fig. 5). Bipolar electrode (electrode distance 0.2 mm, outside diameter ca. 0.7 mm) coated in two layers, each layer being of polystyrol and of lacquer, was inserted slowly into nucleus reuniens medianus (in its right half). Response to hand claps or electric lamp moving in front of eyes became negative. Flight movements against pricking of nasal septum or pinch of tail were inconstant. This slight stupor, unresponsiveness II, subsided 10 seconds after insertion. Then, rectangular pulse currents, 3 ps, 4 V, 0.2 msec, were applied. During stimulation, 35 seconds in duration, restlessness or motor effect was not seen at all. Flight

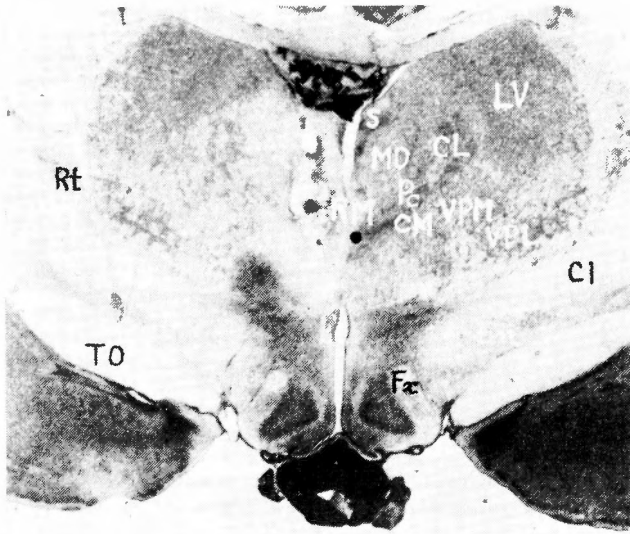


Fig. 5 Cat 70-D-1.

Due to wide exposure for the insetion of needle, some slow waves were found in ECGs over left hemisphere before injection. ECGs were not changed by the insertion of needle. Diffuse 3 per second spike-and-wave-like responses, which were of maximal amplitude immediately after turning on the switch and decreased gradually in amplitude, were evoked during repeated stimulations of the black point in this figure with pulse currents, 3 ps, 0.7 V or more, 0.2 msec. These responses were followed by 4-7 ps slow waves of sevral seconds in duration after turning off the switch; at the time of this after-discharge, responsiveness was slightly impaired for ca. 8 seconds. After introducing currents of 60 or 120 ps in frequencies instead of those of 3 ps, low voltage fast waves predominated. Points of stimulation effective in evoking 3 ps spike-and-wave-like responses were found in the areas by 3 mm adove and by 1 mm below the black point. At the seconds experiment on the same day stimulating electrode was inserted in the symmetrical point on the opposite side. ECGs recrded at this time were similar. Unresponsiveness II was also observed.

movements against heating of nose tip was negative for 8 seconds after stimulation. Severity of unresponsivness was not modified by raising up the frequencies of stimuli; besides this, rigidity was observed in both fore-limbs during stimulation with currents of 60 ps and in all four extremities with them of 120 ps. Similar results were obtained with electric stimulation of nucleus reuniens medianus on the opposite side another time on the same day. After the subsequent injection of nicotine in the latter nucleus (through a needle molded in the coating substance of electrode) unresponsiveness with the latency of 2 minutes lasted for 7 minutes and a half. The location of nicotinization lay in centre médian de Luys and its vicinity, a little more lateral than the position of stimulation on the opposite side.

DISCUSSION

Incidence of coma-like unresponsiveness after the injection of nicotine or the application of a small piece of filter paper immersed with nicotine, 0.01 cc in dose in either administration, is extremely high in certain portions (Fig. 6) of the cat's brain (Table 3). Either electrocoagulation with direct current (DC) or injection of olive oil in these structure in order to cause a spot of destruction nearby as large as the necrotified focus due to nicotinization, scarcely affected animal's responsiveness (see Fig. 7). It would seem from this that probable modification of neural functions in cases of nicotine-induced coma is not limited to the restricted

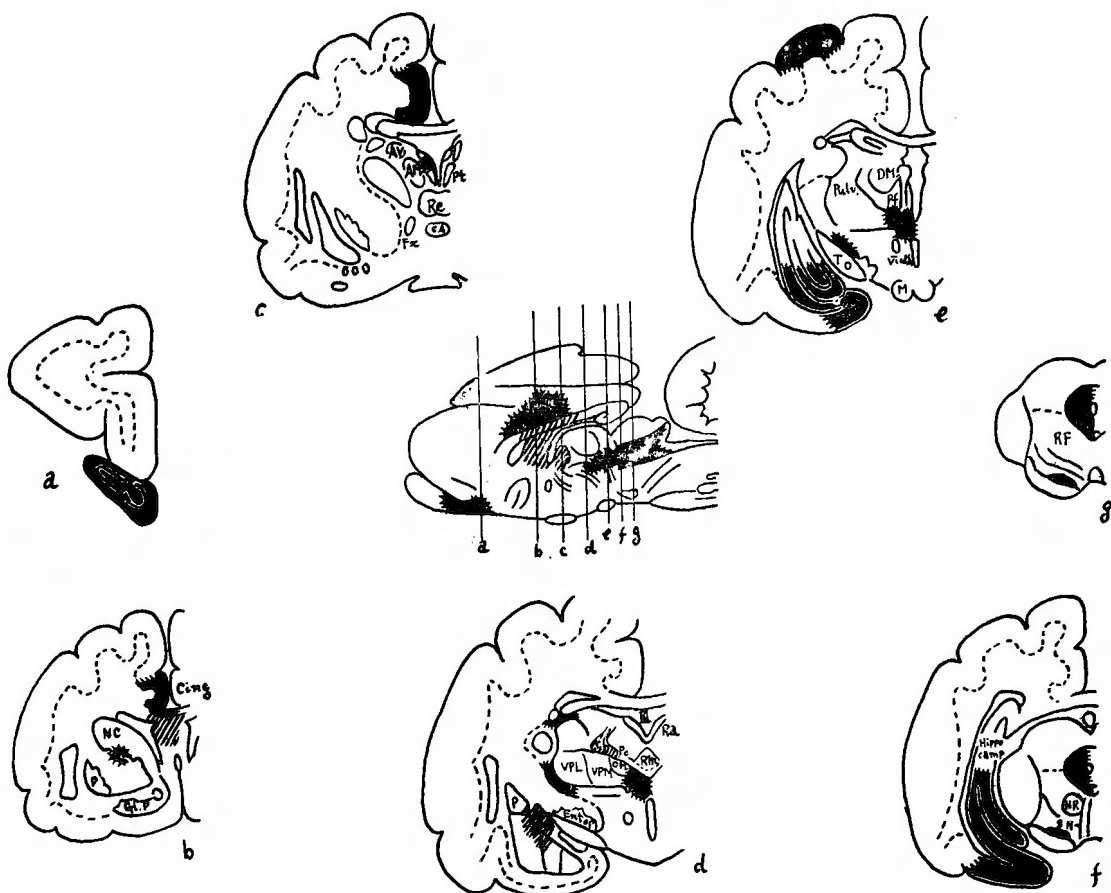


Fig. 6 SCHEMATICALLY ILLUSTRATED LOCATIONS WHERE COMA-LIKE UNRESPONSIVENESS WAS INDUCED BY MEANS OF NICOTINIZATION

Note 1. Black smeared areas are the portions of the group 1 (without accompaniment of motor effects) or that of the group 2 (with accompaniment of slight, i. e. non-generalized motor effects was induced).

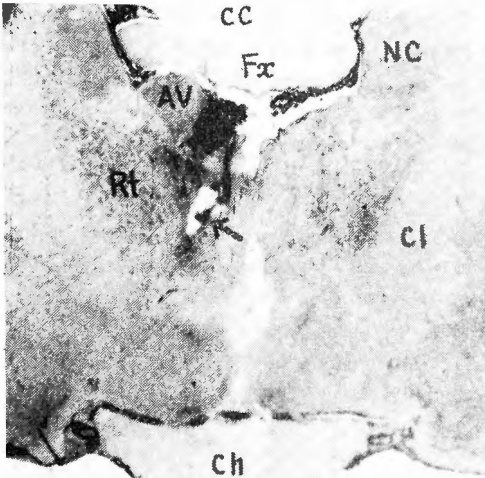
2. The shaded are the structures where coma-like state occurred coincidentally with the general spread of motor effects.

3. Concerning the incidence of induced unresponsiveness, man should refer to Table 3 and 7.

4. Coronal sections a to g correspond to the levels passing (a) stria olfactoria, (b) septum pellucidum, (c) chiasma opticum, (d) infundibulum (in its middle portion), (e) corpus mammillare, (f) substantia nigra and (g) frontal terminal of trochlear nucleus.

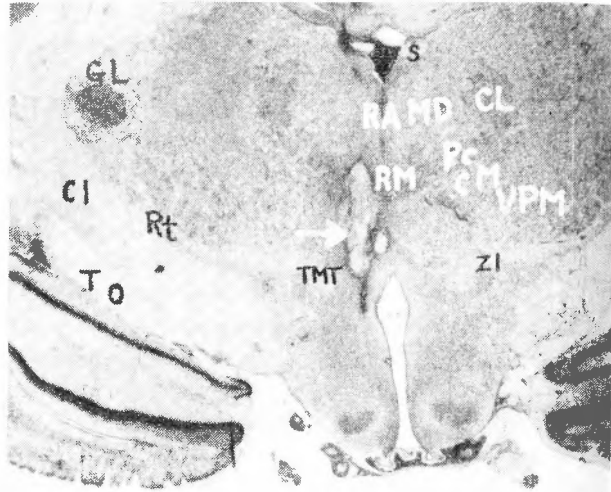
portions in and around the location of nicotine injection, although location is surely one of the important factors for the occurrence of such heavy unresponsiveness. Characteristic findings of EEG activities in my experimental animals (reported by K. SAKATA) were, in general, not slow waves as in cases of brain stem destruction (INGRAHAM, KNOTT, WHEATLEY and SUMMERS 1951¹⁹; MAGOUN 1950²⁸) or in cases of deep narcosis, but fast waves with various amplitudes. This EEG feature was not entirely modified by the location of nicotine injection, the location of leading points as shown in Fig. 8, or the degree of impaired responsiveness. Corresponding to this EEG changes, generalized convulsion (Table 2) or rage-like activation^{5(7)(11)(19) & 32)}

Fig. 7 LESIONS RESULTING FROM VARIOUS WAYS OF DESTRUCTION



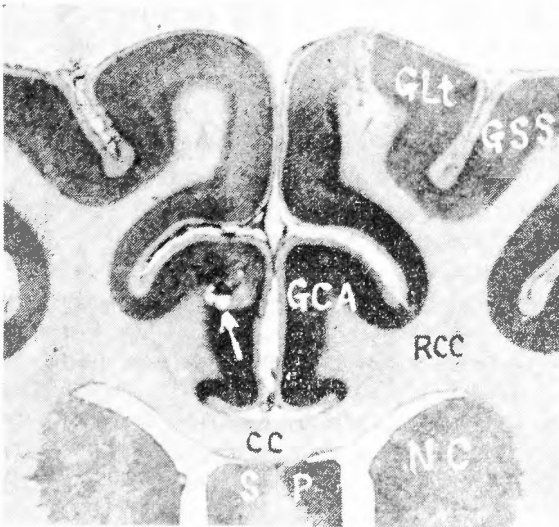
[A] 31-F

Nicotine 0.01cc was injected without dilution. Unresponsiveness III accompanied by general convulsion.



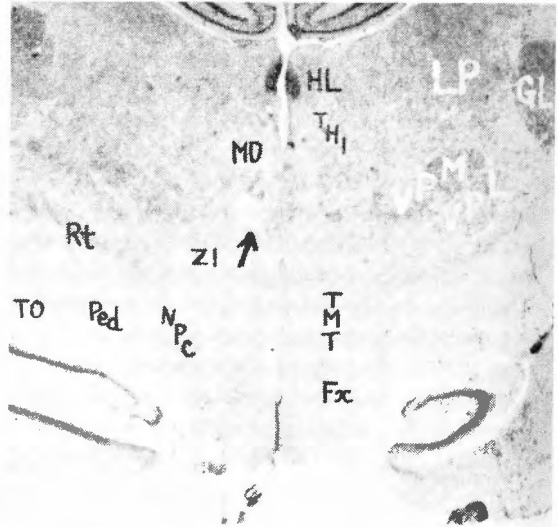
[B] 33-I'

DC current, 2 mA, was applied for 10" through a monopolar electrode with positive polarity in its apex. Responsiveness was not impaired.



[C] 53-G

Olive oil, 0.02 cc was injected. Spontaneous movements increased after the insertion of syringe needle. After injection, for which it took ca. 10", there was no impairment of responsiveness.



[D] 53-F

Olive oil 0.02cc was injected. Repeated meowings occurred after insertion of needle. No remarkable impairment of responsiveness was found after injection for which it took ca. 5 sec.

(Table 4) was observed most often besides the changes of responsiveness. I can conclude, therefore, that nicotinization tends to evoke diffuse excitation of the central nervous system.

Table 4. BEHAVIORAL ACTIVATION ACCOMPANIED OR NOT ACCOMPANIED BY UNRESPONSIVENESS IN CASES OF INTRACEREBRAL NICOTINIZATION

location of nicotine applied	incidence of behavioral activation	number of unresponsiveness III (without apnea) accompanying activation
hippocampus	3/3	1
nucleus lateralis hypothalami	3/3	0
anterior cingulate gyrus	6/7	5
stria olfactoria and surrounding structures	3/4	2
nucleus reunions medianus (N _{11MT})	3/4	0
amygdala proper	3/4	0
anterior nuclei of thalamus	2/3	0
medioventral portion of capsula interna	2/3	2
pulvinar thalami	4/6	1
gyrus lateralis	2/4	0
pre- and posteruciate gyri	3/6	0
orbital gyrus	1/2	0
ectosylvian gyrus	1/2	0
lobus medialis of cerebellum	1/2	0
lob. paramed. of cerebellum	1/2	0
mesencephalic central gray matter	3/8	2
centre médian de Luys	1/3	0
nucleus parataenialis and stria medullaris thalami	1/3	1
posterior hypothalamus *	1/3	0
nucleus caudatus	1/3	0
globus pallidus	2/3	0
rostral end of central gray matter	2/9	1
fornix and septum pellucidum	1/6	0
posterior suprasylvian gyrus	1/1	1

Note 1. Besides the cases compiled in this table, similar behavioral activation was observed in each one case of nicotization in the following structures; anterior sylvian gyrus, commissura anterior, praeamygdala, corpus quadrigeminum anticum or mesencephalic reticular formation.

2. So far as we observed, there were no cases of behavioral activation after nicotization in nucleus dorsalis medialis, nucleus ventralis anterior, nucleus ventralis posteromedialis, nucleus paramedianus and its surrounding structures, nucleus paracentralis, nucleus centralis lateralis, tractus habenulointerpeduncular, nucleus proprius pedunculi cerebri, substantia nigra or nucleus ruber.

3. Relating to the incidences of activation, fatal cases are also included.

* Herein are included medioventral portion of nucleus posterior hypothalami and nucleus supra-mammillaris.

Extension of convulsive motor effects suggesting widespread excitement of large parts of the brain, however, was not always associated with heavy unresponsiveness (Table 2, 4). Occurrence of comatose state following foregoing rage-like excitation that had been characteristic in cases of nicotization in any part of the rhinencephalon was also not so common (Table 4). Thus I can not assume that expansion of the whole brain may be the main reason for coma-like unresponsiveness in majority of my experiments. As a matter of fact, coma-like unresponsiveness in most cases of nicotization in olfactory stria, anterior cingulate gyrus, hippocampus, rostral end of central gray matter, ventromedial portion of internal capsule or pulvinar was not accompanied by motor phenomena in any musculature. I should like to designate such a type of coma as coma of the first group. On the other hand, almost all animals nicotized in centre médian de Luys, substantia nigra and mesencephalic central gray matter showed some motor effects which were not extended over the whole body; some of these animals lost responsiveness completely. According to LLOYD 1941²⁶, brain stem facilitatory system (RHINES and

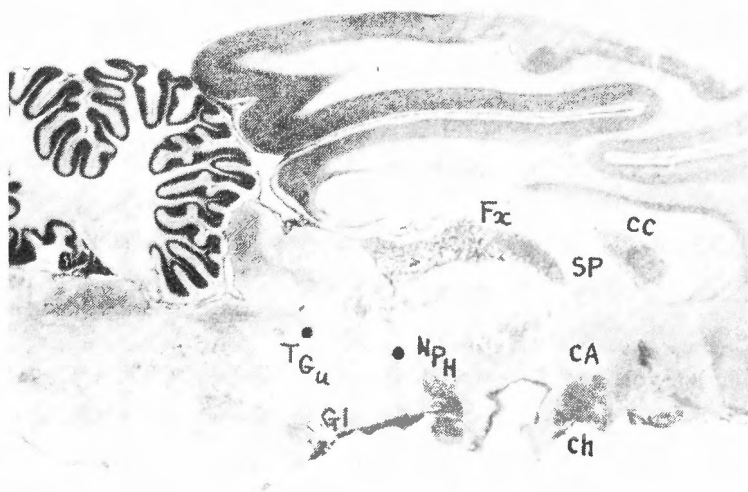
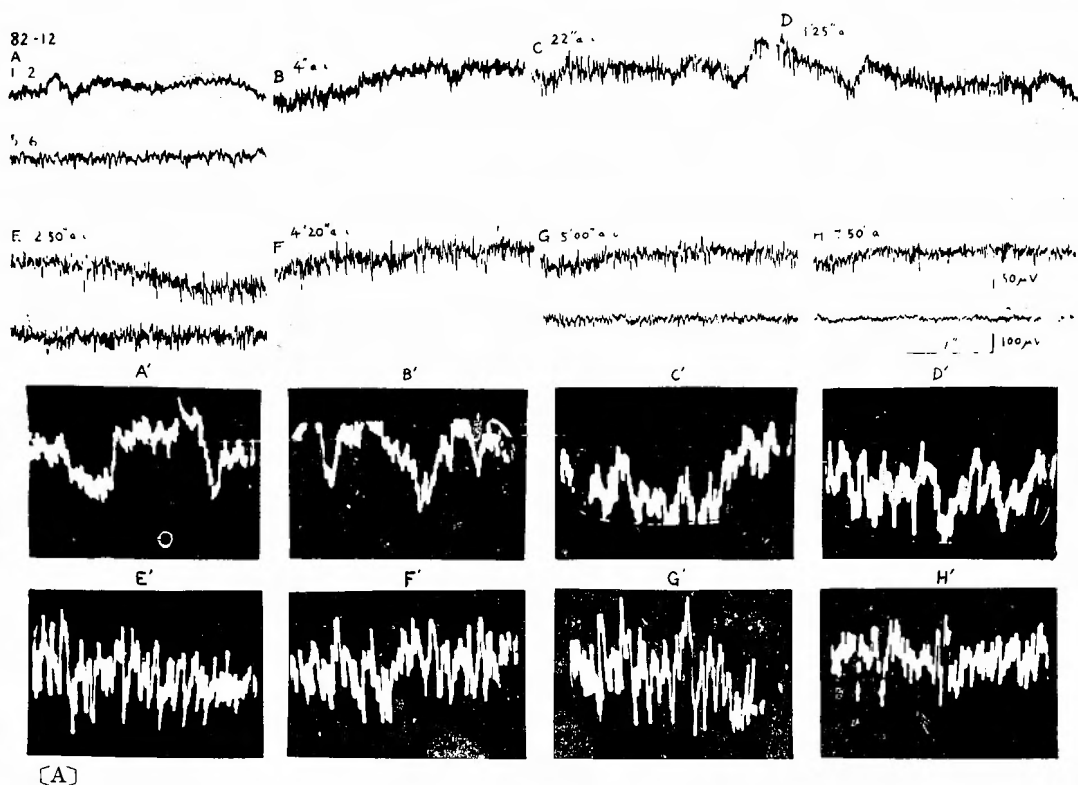


Fig. 8 Cat 82

A-H; ECGs obtained by using a pen-writing apparatus. Each lower tracing of the two line records A, E, G, and H shows sudcortical eletrograms—bipolar—led from tow points, the one being in the reticular formation at the level of red nucleus and the other 4 mm caudad to the former (black spots in Fig. 8(B)). Each upper tracing of the two line records and remaining single line records, i. e. B, C, D or F are coricograms led with phonograph's needles fixed at frontal and caudal terminals of the cortex on dural membrane. Times checked on the upper corners mean time having passed after nicotinization.

A'-H'; subcortical electrograms by means of BROWN tube occillograph obtained with the same subcortical electrode as in A-H.

Both superficial and subcortical electrograms show fast waves which seem somewhat synchronized in subcortical occillograms (E', F' and G'). These fast activities decreased in amplitude, particularly in the subcortex in the course of time. Fast waves of increased amplitudes after nicotization did not completely disappear (G' and H'). Responsiveness was impaired to the degree II immediately after injection, and later to the degree III (Table 6). The lesion due to injection involved dorsal portion of mesencephalic central gray matter, commissura posterior and the fourth layer of colliculus superior.

MAGOUN 1949⁴⁰⁾; MAGOUN 1950²⁸⁾) which strengthens the functioning of corticospinal path, evokes usually no or only little motor phenomena by itself. This may be responsible in part for partial motor effects in these cases. Coma-like state, accompanied by partial or restricted motor effects is designated as coma of the second group.

By coma of the third group, is meant coma-like unresponsiveness accompanied by total extension or generalization of motor effects. In some cases of this group, motor effects came on shortly after recovering from unresponsiveness which was not accompanied by any marked movements (Table 5 and case 97 presented above in text). In other cases of this group various motor phenomena were remarkably blocked for varying periods of time, during comatose stage (Table 5); the block sometimes resembles so-called seizure stoppage (DONDEY and SNIDER 1955⁸⁾). After recovering from comatose state various motor phenomena in nicotinized cats were, in general, strengthened by sensory stimulation except in comatose stage.

In the literature existence of suppressor area in anterior cingulate gyrus (BAILEY et al. 1944³⁾; WARD 1948⁴⁴⁾; LENNOX and ROBINSON 1951²⁴⁾) and posterior suprasylvian gyrus (BARKER and GELLHORN 1941⁴⁾; GELLHORN 1947¹²⁾) have been well known. The effect diminishing motor phenomena or vigilance of animals have been reported in case of stimulation of hippocampus (Mc LEAN 1954³²⁾; PASSOUANT, GROS, CADILLAC and VLAHOVITCH 1954³⁸⁾), "rostral portion of mesencephalic central gray matter"... somewhat caudad to the analogous area in the present study ... (HESS, W. R. 1948¹⁶⁾). Induction of sleepy state (HESS, Jr. 1949¹⁷⁾; HESS, W. R. 1948¹⁶⁾), electronarcosis (GUALTIEROTTI, MARTINI and MARZORATTI 1949¹⁴⁾) and experimental petit mal-like attack (HUNTER and JASPER 1949¹⁸⁾) with stimulation of thalamus were also reported respectively. It is not easy to compare our comatose state after nicotization with those behavioral changes reviewed here, especially from the view-point of neuronal mechanisms. Three possibilities of mechanism may, however, be taken into consideration for our induced coma; 1) impairment of physiological patterning of impulses related to waking state due to the excessive excitement arising in the location of nicotization, 2) exhaustion of the motor neuron system after non-physiological excitement or 3) some kind of physiological blocking effect initiated in the nicotinized location, such as inhibition (DUSSEY de BARENNE

Table 5. DIMINUTION OF MOTOR EFFECTS.....MAINLY OF EVOKED ONES.....DURING UNRESPONSIVENESS III ON NICOTINIZED CATS

case number	location of nicotization	motor effects seen before onset of unresponsiveness III	latent time of unresponsiveness	time elapsing until end of comatose state (after nicotization)	motor effects during unresponsiveness	motor effects after arousing from unresponsiveness	other remarks
30-G	rostral end of CG-Vic Azyr's bundle, ZI, VPM, CM etc.	generalized clonic convulsion occurred with foregoing unresponsiveness (lt 3'30"; dt 12') ---comprized in table 1, 3 & 7	33' (not comprized in table 1, 3 & 7)	37'	motor effects disappeared for a definite period of time (33'-47' a. n.)	clonic convulsion same as that seen before onset of unresponsiveness	
82	dorsal portion of CG-colic. sup. & commiss. posterior	generalized shivering	8'	17'	motor effects disappeared and entire body was flaccid (2'-12' a. n.)	generalized shivering	unresponsiveness II, instead of III, when (2'-8' a. n.) motor effects stopped
97	n. reticularis thal-ventro-medial portion of capsula int.	none	2'45"	9'45"	none	total march of clonic convulsion initiated in an upper limb opposite to side of nicotization (16'15"-45' a. n.)	tendon jerks were lost for some minutes
98	posterior suprasylvian gyrus (19-S)	rigid in one upper limb opposite to side of nicotization	8'	30'	none	total march of twitching from one lower limb opposite to side of nicotization occurred 50' a. n.	tendon jerks were lost during and after comatose state
96-D	posterior portion of lateral gyrus neighboring area 19-S	none	(1'30")	(4')	none	total march of clonic convulsion from 10 minutes to 18 a. n.	unresponsiveness II instead of III

Note. In each case where nicotization was done in pulvinar, tractus habenulointerpeduncularis (MEYNERI), or septum pellucidum, it took a very long time ranging from 12 to 54 minutes to bring about motor effects. They were by no means generalized and not accompanied by unresponsiveness. Except for these and other cases comprized in upper table, motor effects induced by nicotization began always by 10 minutes after nicotization.

and WARD 1937⁹⁾) or suppression (BARKER and GELLHORN 1941¹⁰⁾; DUSSEY de BARENNE and Mc CULLOCH 1941¹⁰⁾) of descending impulses reaching final motor neurons in anterior horn of the spinal cord or in cranial nerve nuclei.

The recovering time of the "extinction" after cortical excitement (DUSSEY de BARENNE and Mc CULLOCH 1941¹⁰⁾) or of the depression of activities, immediately after spinal transection (LIDDEL 1934²⁵⁾; Mc Cough 1934³⁰⁾) ... called as spinal shock ... has been reported to be only several minutes in cats. Generalized diminution of motilities including knee jerks in cases of my studies is of longer duration. Providing the extinction was the main cause of the diminution of motilities in my cases, some hyperexcitative manifestation, e. g. convulsive movements, raging attitude or others would have foregone commonly before the development of this hypomotility. We could not prove complete parallelism between unresponsiveness and generalization of motor effects. Due to this discrepancy, the second possibility is highly improbable.

The dominant pattern of EEG activities in nicotinized cats is composed of fast waves, as above mentioned. This change is brought about properly in group 1 or 2, both associated with no or little spontaneous and/or induced motor phenomena. By using microelectrode, MORUZZI 1953³⁵⁾ ascertained the possibility that the inhibitory mechanism of medial reticular formation results in no particular motor counterpart in spite of co-existence of convulsive activities on the motor cortex. In my cases no movements due to nociceptive reflexes took place through the entire course of coma-like unresponsiveness (see our definition in the preliminary experiments). Nociceptive reflexes are chiefly flexor reflexes of polysynaptic character, which are constantly inducible by any nociceptive stimuli, such as pain stimuli, in normal cats. Recent reports (KLEYNTJENS, KOIZUMI and BROOKS 1955²³⁾; BROOKS and KOIZUMI 1956⁶⁾) have emphasized the fact that polysynaptic reflexes are "inhibited" by mesencephalic stimulation. Thus my results may also be related to the similar mechanism of inhibition*. In some cases of comatose animals after nicotization tendon jerks were completely lost, usually on both sides (Table 6). KLEYNTJENS, KOIZUMI and BROOKS 1955²³⁾ showed the fact that spinal monosynaptic reflexes, knee jerk or other stretch reflexes were facilitated in most cases, but "inhibited" in some cases by the stimulation of mesencephalic reticular formation, especially by using strong stimuli (voltages).

Several signs, such as marked EEG activation, respiratory acceleration** and others suggest that the effect of nicotization is very severe. Similar unresponsiveness without accompaniment of any convulsive movement, however, took

* HUGBARTH et al. recently reported that stimulation of the mesencephalon induced always the blocking effect on ascending conduction of sensory impulses¹⁵⁾.

** After hypodermic administration of nicotine, tachypnea...similar as in cases of intravenous administration by OZAKI, ISHIBASHI and WATANABE³⁷⁾...were observed in all animals, and motor effects (MITSUEDA, NAWA and HAMADA 1943³³⁾; SOLLMANN 1948⁴²⁾) under half of the cases. General responsiveness to various external stimuli remained almost intact in all cases until irreversible stopping of respiratory movement. It would follow from this that the systemic action of nicotine, particularly on the musculatures of the whole body, is not primarily important for the development of comatose state after the local administration of nicotine.

Table 6. MOTOR EFFECTS INDUCED BY EXTERNAL STIMULI

case number	location of nicotine applied	unresponsiveness induced by nicotine	time of recovery from unresponsiveness after nicotine	sort of external stimuli effective in evoking motor effects	time when external stimulation was done (after nicotine)	outline of motor effects induced by external stimulation	other remarks
27-C	CG-DM, Flp, Tr. M., Nucl. IV	III	17'40"	somewhat violent pressure to external auditory meatus	55'	tonic-clonic convulsion only of one upper limb opposite to side of nicotine (occurring immediately after stimulation)	no motor effects were induced 30' after nicotine when injection needle was taken out
19-A	Pt-stria medull. thal., AM, AD	II	15'	same as above	20'	generalized tonic-clonic convulsion (occurring immediately after stimulation)	no motor effects were observed before recovering from unresponsiveness knee jerks were normal immediately after cease of convulsion
14-C	FR-br. conj. Flp, D. M., N. R.	II	12'	taking out syringe needle	12'	whirl-like rotation of tail followed by generalized tonic convulsion (occurring 5' after external stimulation)	knee jerks were exaggerated after convulsion no motor effects were induced by pressure to external auditory meatus 35' a. n.
23-D	rostral end of CG, posterior hypothalamus -RM, RA	III	7'	somewhat violent pressure to external auditory meatus	15'	apnea after opistotonos and generalized tonic-clonic convulsion (occurring immediately after stimulation)	
94-B	pre- & posterior lateral gyri	I	/	touching any bodily surface	15'	tonic convulsion was intensified (each time after repetitive stimulations)	generalized clonic convulsion continued from 7' a. n. to 41' tendon jerks were exaggerated
7-C	stratum zonale sept. pelluc.	I	/	passive bending of limbs	6'	generalized tonic-clonic convulsion ending in apnea	four extremities were rigid 3' a. n.

place by means of less severe procedures, e. g. electrical stimulation or mechanical injury such as the insertion of syringe needle in a certain subcortical structure of the same animal, though slight and of short duration. It would be concluded that a certain suppressing mechanism on descending motor paths may contribute mainly to my coma-like unresponsiveness without any convulsive movement or with some diminution of general motor phenomena. The time needed for the full development of comatose state⁴⁶⁾ is about 2 to 8 minutes in cases of group 1 (Table 7), though

Table 7. TIME NEEDED TO DEVELOP UNRESPONSIVENESS III (COMATOSE STATE)---LATENT TIME---AND DURATION OF THAT STATE---DURATION TIME

location of nicotization	incidence of unresponsiveness III *1 (group 1-2-3/ total)	mean time elapsing until unresponsiveness III was certified ---It *2	mean time of duration of unresponsiveness III---dt *2
n. parataenialis & stria medull. thalami	0-0-1/3	1'	7'
mesencephalic CG	1-3-3/8	1'1" (8"-5')	12'40" (7'52"-13'45")
amygdala proper	0-0-1/3	1'30"	13'30"
pulvinar thalami	1-0-0/4	1'30"	4'10"
centre médian de Luys	0-1-0/3	2'	9'30"
rostral end of CG	3-2-1/6	2'8" (10"-4'10")	7'34" (2'-11')
substantia nigra	0-1-0/2	2'30"	16'30"
hippocampus	1-0-0/1	3'	7'
medioventral portion of internal capsule	1-0-1/3	3'	7'
corpus callosum & fornix	0-0-1/5	3'	4'
ant. cingul. gyr.	3-1-1/6	3'14" (1'15"-8')	5'33" (2'45"-6')
olfactory stria	2-1-0/3	4'23" (1'10"-6'20")	5'23" (4'-7'30")
posterior suprasylvian gyr.	0-0-1/1	8'	22'
Pc & CL of intralaminar nuclei	0-0-1/3	15'	8'30"

*1 In terms of fraction the number of cases where comatose state was observed among the total cases nicotinized done in each location, is shown. Cases of apnea are omitted from this table.

*2 The numbers put in brackets indicate the minimal and the maximal time.

it was rather shorter in case of nicotization in mesencephalic central gray matter. The 2-8 minute latent time is quite similar to the latency necessary to the development of cortical suppression (Dusser de BARENNE and Mc CULLOCH 1941¹⁰⁾; GELLHORN 1947¹²⁾). It would seem, therefore, that not only the diminution of motor phenomena but also unresponsiveness itself is caused by some active blocking effect similar to suppression. It would be a most serious problem to give a solution to this question in the near future***.

SUMMARY

Non-diluted nicotine 0.01 cc in dose was injected in or applied on various parts of the brain in adult cats. After this procedure alterations of general responsiveness, one of the most important aspects of so-called vigilance, were examined. The results obtained in my experiments are as follows.

1) It is improbable that the comatose state induced with the local adminis-

*** At the present stage of my studies, such remarkable diminution of motor phenomena and/or coma-like unresponsiveness are not yet clearly explained by a physiological mechanism, such as inhibition.

tration of nicotine results from the systemic effect by absorption, or from the localized destruction at the point of injection.

2) In about half of the animals (47.8%) where convulsive motor effects propagating over the whole body were manifested, coma-like unresponsiveness was observed. In a quarter of the animals (26.0%) of this group, however, responsiveness was hardly impaired. Comatose state was induced, on the other hand, in almost all cases in which nicotine had been administered in certain cerebral portions... olfactory stria, anterior cingulate gyrus, rostral end of central gray matter or mesencephalic central gray matter...; among these animals, there were a considerable number of cases where comatose state was not accompanied by any motor phenomena, including those induced by external stimuli.

3) A rage-like activation was commonly seen in cases nicotinized in the rhinencephalon. Comatose state followed this sort of behavioral change was observed in rather exceptional cases.

4) Considering these results... 2) and 3) ..., it would seem improbable that extinction resulting from the excessive excitement is the main cause of coma-like unresponsiveness.

5) EEG activities in comatose state in my experimental animals, which were reported by my co-worker K. SAKATA elsewhere in detail, are characterized by fast waves. Corresponding to the EEG findings, various hyperirritative motor effects associated with the changes of responsiveness were often found in a restricted part or in larger parts of the body, or over the entire body. It was observed that various motor phenomena including convulsion were often diminished transitionally or a certain period of time by the occurrence of coma.

A reason for such a comatose state without co-existence of hypermotility may be the blocking of the normal functioning of motor pathways. It is interesting that knee jerks on both sides, tested with crude manual taps, were also lost in some animals for a relatively long period, about 30 minutes in maximum.

6) Application of some other means of less severity than nicotine, i. e. mechanical stab or electric stimulation with rectangular pulse currents of low frequencies under 30 per second was also effective to induce the impairment of responsiveness to a certain degree... without any convulsive movements..., although incidence, degree and duration were low and short.

7) It has not yet been certain from my present studies that the striking unresponsiveness induced by local administration of nicotine is caused by physiological function, i. e. "inhibition". It seems, however, that the development of comatose state without any convulsive movements and the diminution of various motor phenomena, either spontaneous or induced, in this unresponsive state, may most probably be due to a suppression on descending paths.

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和文抄録

猫に於ける脳の種々の部位を（特に微量ニコチン注入による）刺戟した際に起る昏睡の神経生理学的研究

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石井節行が猿の青斑核をガラス棒で刺した時に起る無反応状態に就て報告して以来、竹友・戸田が単なる破壊（限局性の）ではなくて刺戟が原因であろう事を明かにし、藪野が中脳を超えて間脳レベルに侵襲を加えても同様な状態が起る事を述べた。そこで更に終脳レベルに至る種々の部位（猫）に、藪野と同様に微量即ち 0.01cc の Theodor Schuchardt の製品であるニコチンを注入又は貼布した際の態度の変化を観察し、又一定の動物では脳波を同時に記録した。脳波所見に就ては共同実験の坂田が既に報告しているので、態度特にその運動効果と無反応状態との相関に就て報告す

る。即ち、昏睡状態を惹起させる為に最も重要な実験上の条件は、痙攣を随伴する事ではなくて何処に注入したかという事であり、従つて少く共痙攣後の困憊がその原因ではないと思われる。昏睡中は痙攣をも含めて種々の運動効果が減退し、例によつては最長30分迄の間も膝蓋腱反射が消失した。一般にはニコチンの注入後種々の運動現象は亢進していると思われるので、この様な昏睡中は積極的な何等かの抑制効果が働いたものと想像される。只、本実験のみでは生理学的な意義を有する inhibition がその本態であるかどうかは知る由もないので、その点の吟味が必要となろう。