

ANESTHESIOLOGY

THE JOURNAL OF

THE AMERICAN SOCIETY OF ANESTHESIOLOGISTS, INC.

Volume 18

MARCH-APRIL, 1957

Number 2

THE EFFECTS OF NITROUS OXIDE ON RESPONSES EVOKED IN THE BRAIN STEM BY TOOTH STIMULATION

FREDERICK P. HAUGEN, M.D., AND RONALD MELZACK, Ph.D.

THE present study is part of a long-term investigation of the nervous mechanisms subserving the pain process. The tooth pulp has been selected as a recognized source of the sensation of pain, and potentials evoked by stimulation of the tooth pulp in cats have been traced into the trigeminal root (1) and the midbrain and thalamus (2). The areas of the midbrain responding to tooth pulp stimulation have been differentiated into five functional groups (fig. 1) on the basis of anatomical locations, response latencies, and behavior during repetitive stimulation with various frequencies. The purpose of this report is to describe the effects of nitrous oxide inhalation on responses evoked in each of these five areas. This anesthetic agent was selected because it is a well-recognized analgesic in concentrations having ample oxygen to obviate hypoxia, and it can be administered and withdrawn from the animal without the delay noted with the fat soluble agents or the barbiturates.

Physiological studies of the anesthetic state have received great impetus from the recent demonstration by Magoun and his associates (3) of a centrally located area in the brain stem which appears to be essential to the maintenance of the conscious, alert state and which has been shown to be particularly sensitive to depressant drugs. Using auditory and sciatic stimulation, French, Verzeano, and Magoun (4) have shown that ether or pentobarbital sodium blocked impulses propagated through the *reticular system*, while the lateral sensory pathways continued to conduct with unimpaired intensity. They attribute

Read before the annual meeting of the American Society of Anesthesiologists, Kansas City, Missouri, October 10, 1956, and accepted for publication November 6, 1956. Dr. Haugen is in the Department of Surgery, Division of Anesthesiology, University of Oregon Medical School, Portland, Oregon. Dr. Melzack is Research Fellow, Department of Surgery, University of Oregon Medical School, supported by a fellowship from the Commonwealth Fund, New York, New York. This investigation was supported in part by a research grant (B308C) from the National Institute of Neurological Diseases and Blindness, National Institutes of Health, and by a grant-in-aid from the Tekronix Foundation, Portland, Oregon.

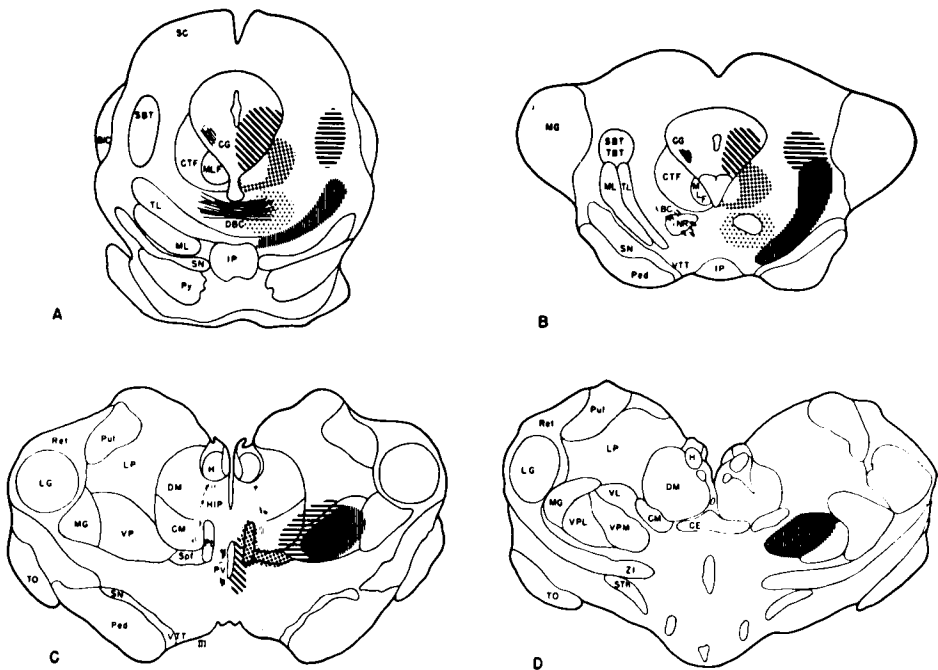


FIG. 1. Tooth pulp projections at selected brain stem levels in the cat. Shaded areas on the right side indicate the sources of potentials which were studied with the *nitrous oxide-oxygen* mixture. The relevant structures are shown on the left side for each level. Abbreviations:

| | |
|---|---------------------------------------|
| BC—brahium conjunctivum | Pul.—pulvinar |
| BIC—brahium of the inferior colliculus | PV—periventricular area |
| CE—n. centralis | Py—pyramidal tract |
| CG—central grey | Ret.—reticular substance |
| CM—n. centrum medianum | SBT—spino-bulbo-thalamic tract |
| CTF—central tegmental fasciculus | SC—superior colliculus |
| DBC—decussation of the brahium conjunctivum | SN—substantia nigra |
| DM—n. dorsalis medialis | Spf.—n. subparafascicularis |
| H—habenula | STH—n. subthalamicus |
| HIP—habenulo-interpeduncular tract | TBT—trigemino-bulbo-thalamic tract |
| IP—n. interpeduncularis | TL—trigeminal lemniscus |
| LG—lateral geniculate | TO—optic tract |
| LP—n. lateralis posterior | VL—n. ventralis lateralis |
| MG—medial geniculate | VPL—n. ventralis posterolateralis |
| ML—medial lemniscus | VP—n. ventralis posterior |
| MLF—medial longitudinal fasciculus | VPM—n. ventralis posteromedialis |
| NR—red nucleus | VTT—ventral tegmental nucleus of Tsai |
| Ped.—peduncle | ZI—zona incerta |
| Pf.—n. parafascicularis | |

the differential block to the multiple synapses in the medially placed reticular pathway, in contrast with the fewer synapses in the main ascending lateral sensory tracts. Similarly, Arduini and Arduini (5) found that potentials in the reticular system show a markedly greater susceptibility to alteration by metabolic changes and by depressant and excitant drugs than potentials in direct afferent pathways. Finally, procaine has been shown to have a demonstrable effect on activity in

the reticular system (6). These studies strongly suggest that the modification of neural transmission through this system is of major importance in the production of the anesthetic state.

It is well known among anesthesiologists that during induction of anesthesia a stage is reached in which the patient retains auditory perception after the ability to perceive painful stimulation is lost. Anesthetic drugs, then, seem to have an apparent selectivity for the neural mechanisms subserving pain perception at dosages that may leave other perceptions relatively unaffected. In the present investigation an attempt is made to study the effects of analgesic mixtures of nitrous oxide and oxygen on responses in the medial and lateral pathways in the cat brain stem evoked by stimulation of a pain source.

METHOD

In 50 cats, under ether anesthesia, a dental drill was used to expose the dentine of the two upper canine teeth for electrical stimulation. Burr holes were then made in the calvarium to permit the passage of a recording electrode to either midbrain or thalamic structures. After completion of all surgery, *d*-tubocurarine chloride was given intravenously, and the animal maintained on artificial respiration with room air for forty-five minutes before observations were made.

Single electrical rectangular pulses, generally of 0.5 msec. duration and suprathreshold intensity, were used to stimulate the tooth pulp through bipolar wire electrodes. The stimuli were synchronized with a Tektronix oscilloscope sweep; evoked potentials were observed with a conventional differential amplifier and oscilloscope system, and photographed with a manually triggered Grass camera.

A bipolar concentric electrode (22 gauge shell, 30 gauge inner shaft, with a tip separation of 1–2 mm.) was used for subcortical exploration. When potentials suitable for study were observed, nitrous oxide and oxygen were administered to the animal for five minutes in concentrations that at all times supplied at least 20 per cent oxygen, and usually contained between 30–40 per cent oxygen as determined by a Beckman analyzer.*

Electrode positions were controlled stereotaxically and all recording points were checked by histologic sections with Nissl stain and cut in the Horsley-Clarke plane.

RESULTS

On the basis of anatomical locations as well as response latencies, the brain stem potentials evoked by tooth pulp stimulation have been differentiated into five discrete groups (figs. 1 and 2). Two of the areas in which evoked potentials were observed (the trigeminal lemniscus

* Unpublished observations made in this laboratory have shown that this concentration of nitrous oxide and oxygen given to the normal cat produces a lethargic state in which the animal seems to be aware of his surroundings but is slow to respond to stimuli.

and the trigemino-bulbo-thalamic tract) correspond with the "classical" main sensory ascending pathways. The remaining three (the dorsal secondary trigeminal pathway, the ascending path in the central grey, and the reticular formation) lie within the medially located, polysynaptic area that is broadly referred to as the "reticular system" (3, 4). These areas, which are homologous with brain stem pathways activated by stimulation of limb afferents (7), were studied from the mid-collicular to the thalamic levels of the brain stem.

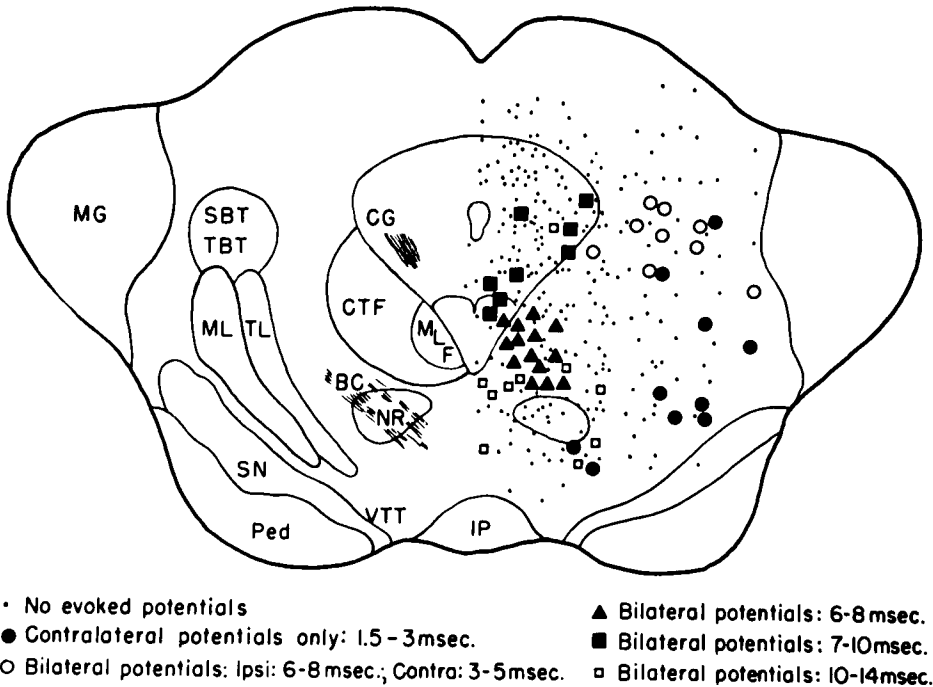


FIG. 2. Points at which potentials were evoked by tooth pulp stimulation: drawn from projected histological sections of the mid-collicular level. The effects of nitrous oxide analgesia were recorded for all evoked potentials shown in the cross section. The latency characteristics of the potentials are indicated for each point.

Figures 3, 4 and 5 illustrate the effects of nitrous oxide-oxygen on evoked midbrain and thalamic potentials are typical for each of the five pathways. Each picture represents ten superimposed oscilloscope tracings in order to indicate the amplitude range in samples of ten successive responses.

(1) *Trigeminal lemniscus* (TL); homologue: medial lemniscus (ML). The potentials recorded from this area were elicited by stimulation of the contralateral tooth only, and had a latency of 1.5-3 msec. Five minutes of the nitrous oxide and oxygen mixture produced no demonstrable change in these responses (fig. 3). Responses evoked by contralateral tooth stimulation only, with the same latency and

wave-form characteristics, were also observed in nucleus ventralis posteromedialis (n. VPM) of the thalamus (fig. 5). Here again, the analgesic mixture had only a negligible effect on the evoked potentials (fig. 4).

(2) *Trigemino-bulbo-thalamic tract* (TBT); homologue: spino-bulbo-thalamic tract (SBT). Responses were observed in this pathway following stimulation of both ipsilateral and contralateral canine

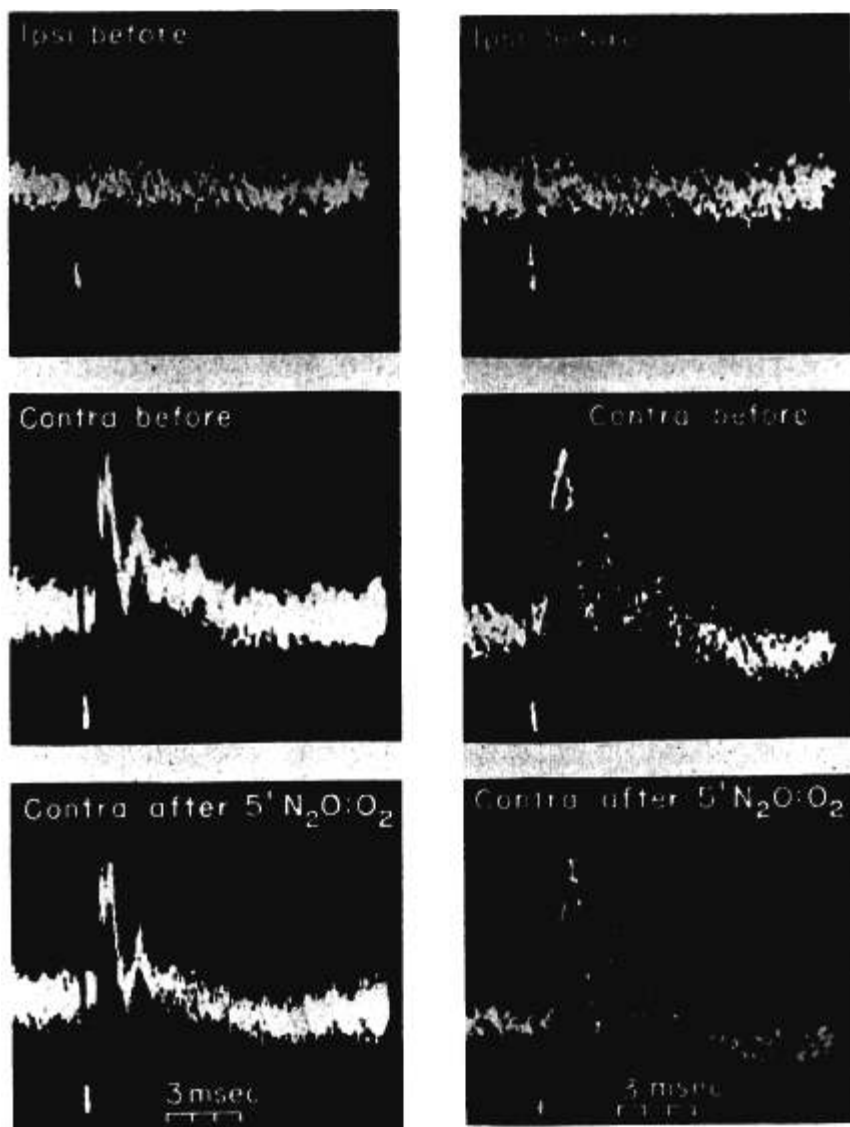


FIG. 3 (left). Evoked potentials in the *trigeminal lemniscus*. Contralateral potential only; negligible amplitude change after *nitrous oxide-oxygen* inhalation.

FIG. 4 (right). Evoked potentials in *n. VPM* (nucleus ventralis posteromedialis). Contralateral potential only; negligible amplitude change after *nitrous oxide-oxygen* inhalation.



FIG. 5. Histological section of the posterior thalamus. The arrow (●) points to the source of evoked fast, contralateral potentials at the thalamic level, shown in figure 4. The nucleus has been identified as *n. VPM*.

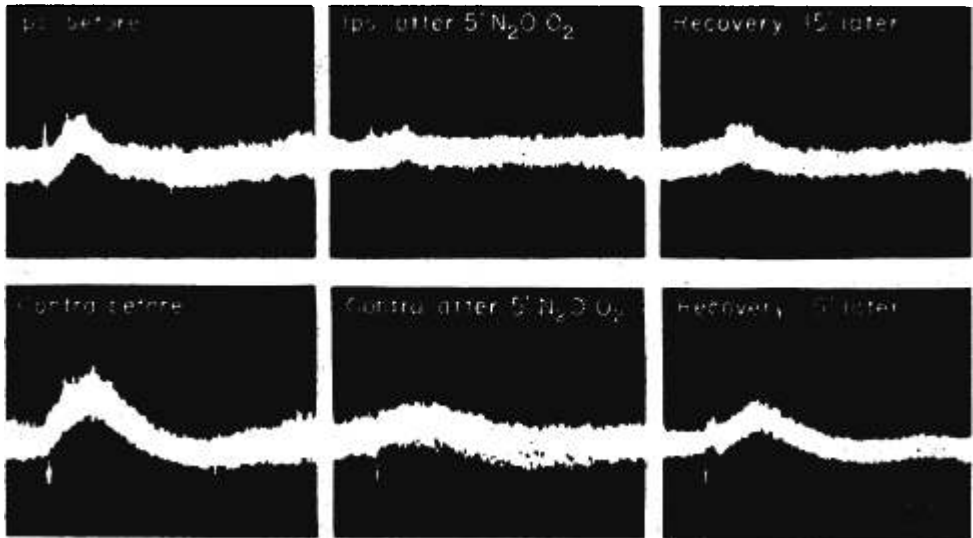


FIG. 6. Evoked potentials in the *trigemino-bulbo-thalamic* path. Bilateral potentials; decreased amplitude after *nitrous oxide-oxygen* inhalation; recovery.

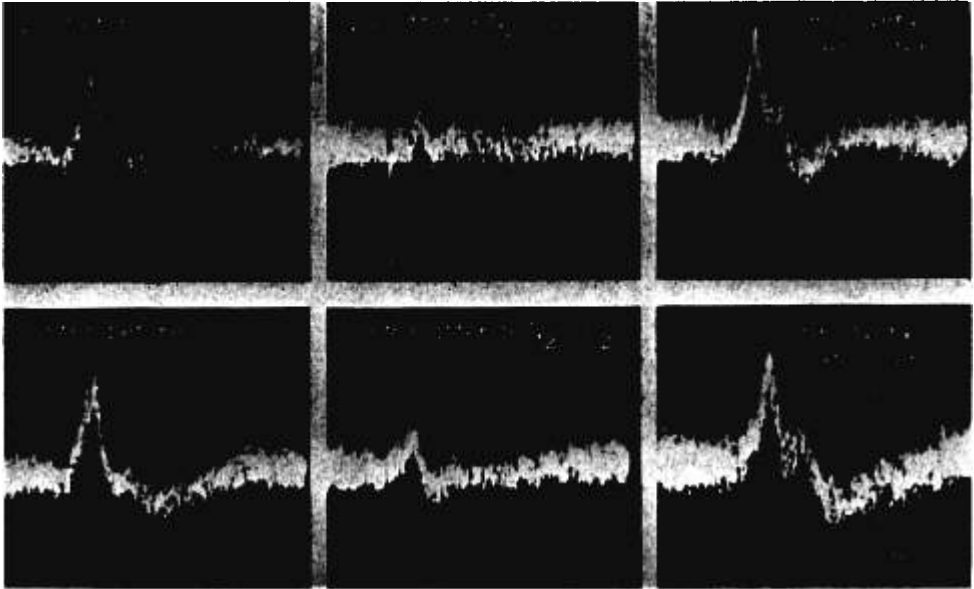


FIG. 7. Evoked potentials in *n. VP* (nucleus ventralis posterior). Bilateral potentials; decreased amplitude after *nitrous oxide-oxygen* inhalation; recovery.

teeth. The contralateral potentials had a latency of 3–5 msec. and the ipsilateral responses 6–8 msec. A decrease in the amplitude of the potentials in this pathway became evident within two minutes of the onset of the administration of nitrous oxide and oxygen and continued until

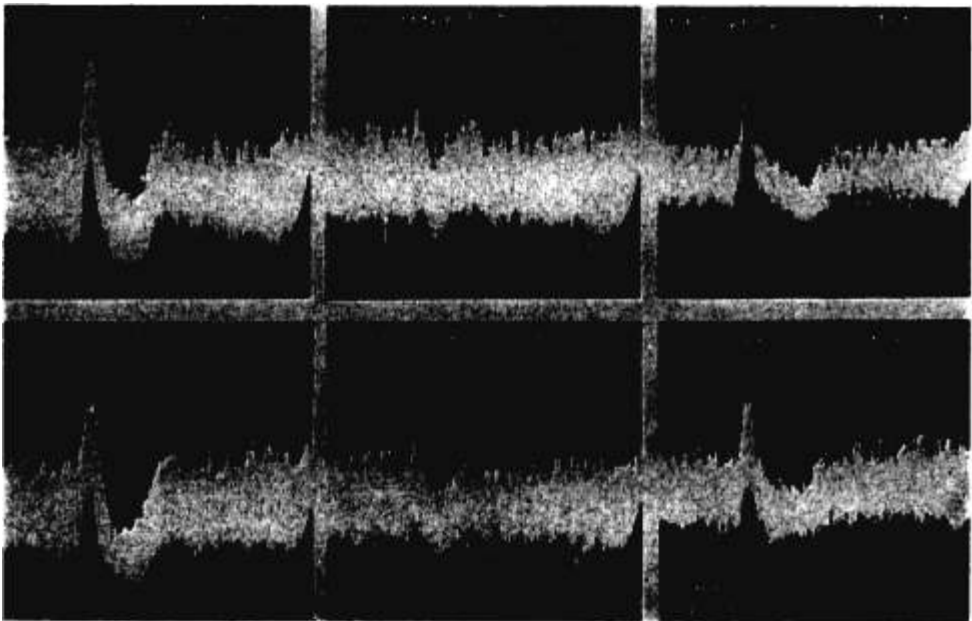


FIG. 8. Evoked potentials in the *central tegmental fasciculus*. Bilateral potentials; decreased amplitude after *nitrous oxide-oxygen* inhalation; recovery.

the agent was replaced by room air after five minutes (fig. 6). The ipsilateral response was usually found to be affected to a greater degree than the contralateral one. Comparable effects (fig. 7) were observed in nucleus ventralis posterior (n. VP) of the thalamus (fig. 10) to which this pathway projects.

(3) *Dorsal secondary trigeminal pathway.* These ascending central tegmental fasciculi (CTF) contained bilateral potentials of 6–8 msec. latency. There is usually enormous activity in this area as evidenced by the contours of the evoked potentials and the concomitant unit activity. The nitrous oxide and oxygen mixture was found to have a profound effect on both the ipsilateral and contralateral poten-

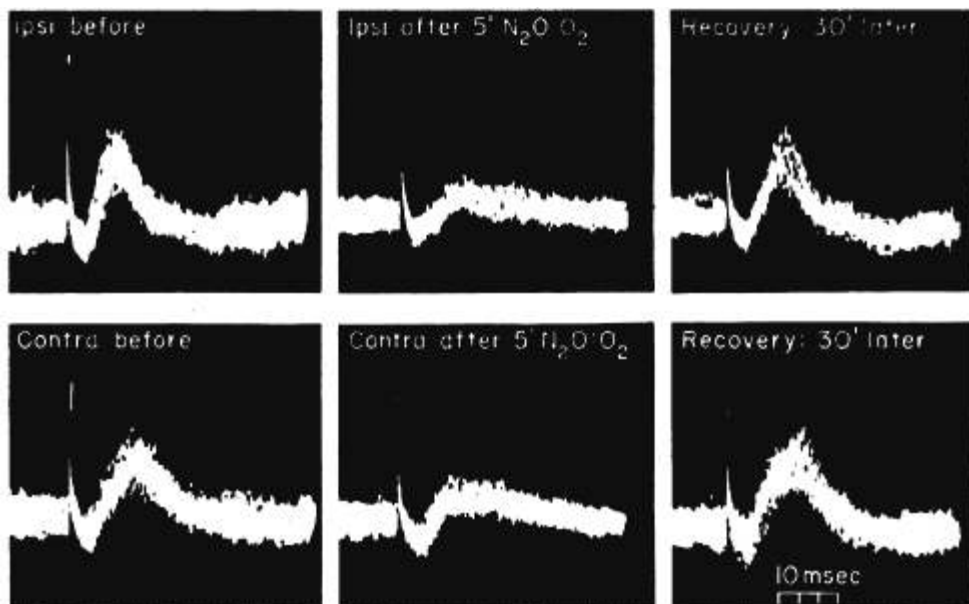


FIG. 9. Evoked potentials in *n. Spf* (nucleus subparafascicularis). Bilateral potentials; decreased amplitude after *nitrous oxide-oxygen* inhalation; recovery.

tials (fig. 8). Similar responses, with comparable latencies and wave forms, were also observed in nucleus subparafascicularis (Spf), shown in histological section in figure 10, and nuclei parafascicularis (pf) and nucleus centrum medianum (CM). The effect of nitrous oxide and oxygen on evoked responses in nucleus subparafascicularis is definite (fig. 9), but usually not as marked as in the pathway.

(4) *Central grey (CG).* Responses evoked by tooth pulp stimulation were also observed in the intermedio-lateral portion of the central grey. The responses were bilateral and the latencies were 7–10 msec. Potentials from this path in the central grey could also be traced into the periventricular grey (PV) of the thalamus. The nitrous oxide and oxygen mixture had a relatively small but consistent diminishing effect on the amplitude of potentials in this area (fig. 11).



FIG. 10. Histological section of the posterior thalamus. Arrow (○) points to a source of potentials from *n. VP*: contralateral: 3–5 msec.; ipsilateral: 6–8 msec. (fig. 7). Arrow (▲) points to the source of bilateral potentials of 6–8 msec. from *n. Spf* (fig. 9).

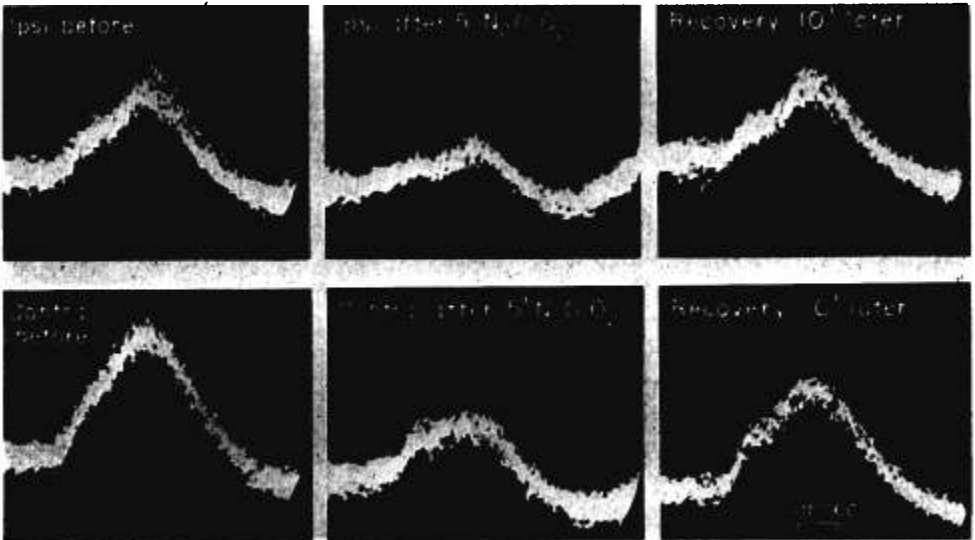


FIG. 11. Evoked potentials in the *central grey*. Bilateral potentials; decreased amplitude after *nitrous oxide-oxygen* inhalation; recovery.

(5) *Reticular formation.* Between these areas of positive identifiable wave form and latency, responses of varying latencies, usually 10–15 msec. were recorded. The nitrous oxide and oxygen mixtures usually produced a definite decrease in the amplitude of the potentials in this area and occasionally eliminated the response completely (fig. 12). In figure 12 the contralateral reticular potential is preceded by a small lemniscal response which remained undiminished.

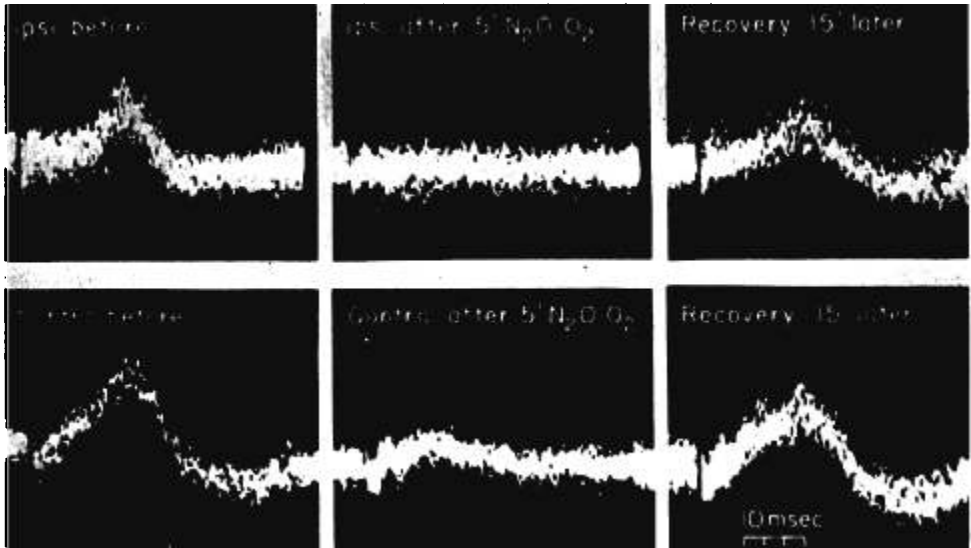


FIG. 12. Evoked potentials in the *reticular formation*. Bilateral potentials; decreased amplitude after *nitrous oxide-oxygen* inhalation; recovery. Note the small lemniscal response preceding the reticular potential evoked by the contralateral tooth.

DISCUSSION

The major assumption in the present investigation is that stimulation of the tooth pulp is capable of eliciting pain in the conscious animal. An earlier study from this laboratory (1) has shown that the tooth pulp of the cat is supplied with myelinated, small-diameter fibers having undifferentiated terminals. These fibers resemble, anatomically and physiologically, the smaller fibers of the *A* group of the cat's saphenous nerve which have been associated with "fast" pain in studies by Gasser (8), Zotterman (9), and others (10). This does not rule out the possibility that sensations other than pain may be subserved by these sensory units and that low levels of electrical stimulation or other types of stimuli might elicit sensations of touch and pressure. However, the suprathreshold levels of stimulation used in the present study are capable of eliciting pain in the conscious human; †

† To obtain a reasonable level of magnitude for stimulation, the senior author and Dr. W. K. Livingston submitted themselves to electrical stimulation of newly placed amalgam fillings of their teeth. The sensation produced by stimuli of the same parameters used in this experiment was judged as being slightly above the pain threshold level.

and, since the chronaxie of the tooth pulp fibers in the cat closely resembles that of the tooth pulp fibers in man (1), it is reasonable to assume that such stimulation would give rise to pain in the test animal. It is therefore of interest that a concentration of nitrous oxide and oxygen which can markedly diminish the perception of pain in man can also produce such consistently depressing effects on the pattern of potentials evoked in the midbrain of the cat by tooth pulp stimulation.

It is noted that the lemniscal response is not perceptibly altered by the nitrous oxide. This finding is consistent with the observation by Magoun and his associates (4) that the lemniscal potentials elicited by sciatic and auditory stimulation are unaffected by anesthetic drugs. In fact, the contralateral potentials conveyed by the lemniscal tracts reach the thalamus and are transmitted on to the cortex with undiminished amplitude even under the deepest anesthesia (4). The significance of this observation, which also holds true in the case of tooth pulp stimulation, is not clear; but it does seem to suggest that activation of the cortex by these direct pathways is not the essential element in the perceptual process.

In contrast to the lack of effect of the nitrous oxide on transmission in the lemniscal tract, there is a significant depression of the evoked ascending potentials recorded from each of the other four areas, which we believe may contribute to the neural substrates of the perceptual process. The depressing effect of the nitrous oxide is seen to be greatest on the potentials in the reticular formation whose latencies of response (10–14 msec., fig. 2) were longest. This observation seems consistent with those reported by French, Verzeano, and Magoun (4). They interpreted their observations as suggesting the possibility that anesthetic agents exert their maximal depressing effect on neuronal chains having the greatest number of synapses. However, Magoun (11) has recently pointed out that this hypothesis might require further qualification, since King (12) has demonstrated that some drugs which are known to act on multi-neuronal chains, such as mephenesin, do not impair conduction in the reticular system. This might suggest a selectivity of drug action rather than a generalized synaptic effect. This suggestion of selectivity is supported by the fact that the responses evoked by tooth pulp stimulation in the contralateral trigemino-bulbo-thalamic path (homologue of the spino-thalamic path) are significantly depressed by the nitrous oxide mixture even though the latency of these responses approximates that observed in the lemniscal system.

The possibility of some selective action of the nitrous oxide mixture is also suggested by its effects on the responses recorded in the dorsal secondary trigeminal pathway (of the CTF) and in the central grey. The drug does not abolish responses in these ascending pathways but it markedly depresses them. The presence of these two pathways,

lying within the "reticular activating system" (3, 4) and separate from the classical sensory pathways (trigeminal lemniscus and trigemino-bulbo-thalamic path), has been discussed in an earlier paper (2).

We have been surprised to note how similar the patterns of response obtained by tooth pulp stimulation are to those elicited by stimulation of the sciatic, the superficial radial and the infraorbital nerves: the five areas that respond to tooth pulp stimulation also respond to activation of each of these peripheral nerves comprising fibers of many different sizes. It has also been surprising how similar the effects of nitrous oxide are on the evoked potentials from the tooth and the other peripheral nerves (7, and unpublished observations). It is reasonable to assume that the process of sensory perception takes place at some level above the midbrain, and that all five of these areas transmit afferent potentials which may contribute to the impulse patterns from which the sensory experience is derived. The fact that a considerable portion of this complex pattern survives after the administration of nitrous oxide precludes an identification of the whole pattern with any particular perception, such as pain. Rather, it would seem that the part of the pattern most closely related to pain is that portion which is abolished under the influence of the nitrous oxide mixture. Such an assumption would be strengthened if it could be shown that the same concentration of nitrous oxide administered to a normal cat receiving tooth pulp stimulation can prevent the cat from responding to the noxious stimulus. Investigations using psychological techniques to correlate the behavior of the cat with analgesic levels of anesthesia will be attempted in future studies in this laboratory.

SUMMARY

The purpose of this investigation was to study the effects of nitrous oxide-oxygen inhalation on potentials evoked in the brain stem of cats by tooth pulp stimulation. Fast contralateral potentials in the trigeminal lemniscus were not diminished in amplitude. However, the amplitude of responses in the trigemino-bulbo-thalamic path, the dorsal secondary trigeminal pathway, the central grey, and the reticular formation was significantly diminished.

A selective action of drugs, rather than a generalized synaptic effect alone, is suggested by the finding that the contralateral responses in the trigemino-bulbo-thalamic path were significantly affected by the nitrous oxide mixture, even though their latencies approximated those of the lemniscal tract.

The results show that a considerable portion of the complex pattern of midbrain potentials evoked by stimulation of the tooth pulp survives after the administration of the gas mixture. This suggests that the part of the pattern most closely related to pain perception is that portion which is abolished.

ACKNOWLEDGMENT

The authors wish to acknowledge gratefully the advice and encouragement given by Dr. W. K. Livingston throughout this work, and the technical assistance of Mr. John Friend.

REFERENCES

1. Brookhart, J. M., Livingston, W. K., and Haugen, F. P.: Functional Characteristics of Afferent Fibers from Tooth Pulp of Cat, *J. Neurophysiol.* **16**: 634 (Nov.) 1953.
2. Kerr, D. I. B., Haugen, F. P., and Melzack, R.: Responses Evoked in the Brain Stem by Tooth Stimulation, *Am. J. Physiol.* **183**: 253 (Nov.) 1955.
3. French, J. D., Verzeano, M., and Magoun, W. H.: Extralemniscal Sensory System in Brain, *A. M. A. Arch. Neurol. & Psychiat.* **69**: 505 (April) 1953.
4. French, J. D., Verzeano, M., and Magoun, W. H.: Neural Basis of Anesthetic State, *A. M. A. Arch. Neurol. & Psychiat.* **69**: 519 (April) 1953.
5. Arduini, A., and Arduini, G.: Effects of Drugs and Metabolic Alterations on Brain Stem Arousal Mechanism, *J. Pharmacol. & Exper. Therap.* **110**: 76 (Jan.) 1954.
6. Peterson, C. G.: Neuropharmacology of Procaine; Central Nervous Actions, *ANESTHESIOLOGY* **16**: 976 (Nov.) 1955.
7. Stotler, W. A., and Kerr, D. I. B.: Experimental Investigation of the Somesthetic Afferent Systems of the Brainstem, *Anat. Rec. (supp.)* **121**: 418 (Feb.) 1955.
8. Gasser, H. S.: Pain-producing Impulses in Peripheral Nerve, *A. Research Nerv. & Ment. Dis., Proc.* (1942) **23**: 44, 1943.
9. Zotterman, Y.: Touch, Pain and Tickling; Electro-physiological Investigation on Cutaneous Sensory Nerves, *J. Physiol.* **95**: 1 (Feb.) 1939.
10. Maruhashi, J., Mizuguchi, K., and Tasaki, I.: Action Currents in Single Afferent Nerve Fibers Elicited by Stimulation of Skin of Toad and Cat, *J. Physiol.* **117**: 129 (June) 1952.
11. Magoun, H. W.: Ascending Reticular System and Anesthesia, *Neuropharmacology*. New York, Josiah Macy, Jr. Foundation, 1955, pp. 145-161.
12. King, E. E.: Differential Action of Anesthetic and Multineuronal Blocking Agents upon EEG Arousal and Recruitment Responses Evoked from the Brain Stem, *Fed. Proc.* **13**: 375 (March) 1954.

NOTICE OF THE ANNUAL MEETING

The American Society of Anesthesiologists, Inc.

October 14-18, 1957

Los Angeles, California