NEUROPHARMACOLOGY OF PROCAINE.\* † ‡ §. II. CENTRAL NERVOUS ACTIONS

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Clinical sanction for using intravenous procaine solution in the treatment of chronic pain syndromes does not constitute validation for the several interpretations which have been offered regarding its sites and mode of action. Functional activity in various elements of the peripheral nervous system may be suppressed, it is true, by dosages of procaine of from 10 to 100 mg. per kilogram of body weight. There is, however, little evidence that the clinical response to the procaine unit of 4 mg./kg. is a resultant of conspicuous alterations in function of the peripheral nervous system (1).

Using electrophysiologic techniques, a study of procaine actions has been made at two important functional levels within the central nervous system: the spinal cord and the brain stem. Results of the present experiments indicate that procaine will modify certain aspects of central nervous activity yet leave intact the capacity for functional activity in receptors, peripheral neurons, autonomic synapses, and various effector systems. More specifically, the present experiments have revealed the following drug actions:

1. A graded depression of activity in monosynaptic and multineuronal units at the level of the spinal cord, the more complex polysynaptic circuits being most susceptible to procaine.

2. A vulnerability of strychnine-induced hyperactivity to procaine dosages which do not interfere with normal reflex activity.

3. A selective action on descending inhibitory influences from the brain-stem reticular formation, without equivalent blockade of descending facilitatory systems which influence the motoneuron.

These procaine actions occur independently of secondary effects due to hypoxia and within dose ranges comparable to clinical use. The implications of these results are of significance when considered in the light of modern neurophysiologic theory of pain mechanisms.

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EXPERIMENTAL METHODS

SPINAL CORD ACTIVITY. Electrophysiologic studies of the simplest spinal reflex pathways were made in Dial®-urethane anesthetized cats, acutely spinal animals (D₀-D₁₂) under light barbiturate anesthesia, and one animal decerebrated under ether. The classical dorsal root-ventral root preparation was used (2). Pairs of stimulating electrodes were applied to a dorsal root of the lower lumbar or sacral segments and the electrical discharge in a corresponding isolated and severed ventral root was led from bipolar recording electrodes, amplified, and recorded through a cathode-ray oscilloscope. Barely threshold single-shock stimuli of 0.1 to 0.5 millisecond duration and 0.2 to 1.0 volt were used. In some experiments, two shock-stimuli of just threshold intensity and the same pulse duration were variably timed so as to obtain direct facilitation or inhibition of the motoneuron response, as well as inhibition of a multisynaptic reflex discharge following an unconditioned reflex discharge. The spinal cord preparation was covered after laminectomy with warmed mineral oil to a depth of several centimeters, so as to maintain it at a steady temperature of approximately 38 C. and in good condition for many hours. In a few experiments, continuous artificial respiration was given and continuous blood pressure recordings were made. In other experiments, the differential effects, in the same animal, of the intravenous administration of procaine upon neuro-effector transmission to skeletal muscle (nerve-muscle preparation), a two-neuron reflex (knee jerk), and a prototype of multisynaptic reflex arcs (flexor reflex) were compared. Dogs under light Nembutal® anesthesia and acutely spinal animals maintained with artificial respiration were used. The electromyographic set-up described in another paper was used (1). The effects of intravenous procaine administration upon hyperirritable spinal reflexes and strychnine convulsions were observed, as well as the influence of procaine upon decerebrate rigidity.

BRAIN STEM RETICULAR FORMATION. Under Dial-urethane intraperitoneal anesthesia (0.3–0.45 cc./kg.) the lightly anesthetized cat was tracheotomized and its head was firmly secured in a stereotaxic instrument. A hind leg was immobilized by skeletal fixation of the femur, with the foot free-hanging or fastened to the animal board. A regular and reproducible knee-jerk response was elicited every one to three seconds, and this response was recorded, after suitable amplification, as an EMG record from a Grass electro-encephalograph. Stereotaxic coordinates for the specific descending inhibitory and facilitatory reticular formation of the brain stem and pons were determined using a bipolar stimulating electrode (3). Parameters of stimulation used were 0.2 to 10 v., 0.1 to 1.0 msec., and frequency ranges of 10 to 100 stimuli per second. Voltage was measured oscillographically at intervals without movement of the indwelling electrodes. A control record was obtained showing inhibitory or facilitatory influences upon the
Fig. 1. Procaine effect on monosynaptic and multisynaptic reflex response; dorsal root-ventral root preparation: Acutely spinal animal (cat), high cervical section, maintained on artificial respiration ($R_{ao}V_{ao} = 1.5$ L./min.). Sample oscillograph records, $t_1$, $t_2$, as indicated in figure 3.
knee jerk from a short period of reticular formation stimulation. The effect of procaine administration upon these responses was then recorded. Visible inhibition or facilitation of the knee jerk occurring with reticular formation stimulation was a more sensitive index of minimal effects than the EMG records that were obtained. In these lightly anesthetized animals, respiratory depression and peripheral vascular collapse did not occur, and the condition of the animals remained good for many hours.

Results

Spinal Cord Activity. Activity in Simplest Spinal Reflex Pathways; Oscillographic Studies. The oscillographic pattern of ventral root responses to dorsal root stimulation was recorded in lightly anesthetized animals. A short, 0.1 to 0.5 msec., threshold stimulus to a dorsal root in the lower lumbar or sacral segment of the spinal cord elicits, after a latency of 1.5 msec. or less, a prominent initial spike followed by an irregular discharge elevation of 10 to 15 msec. duration. The height of the initial spike and the amplitude of the prolonged after-discharge can be used as measures of (1) intensity response in two-neuron (monosynaptic) circuits, and (2) intensity response of multineuron (polysynaptic) reflex discharges which involve interneuronal neurons of the spinal cord. Consistent results were obtained following intravenous doses of procaine from 4 to 20 mg. per kilogram.

Fig. 2 A.
The characteristic pattern of the ventral root response following procaine was a depression of both the monosynaptic and polysynaptic potentials without apparent selectivity. This result is illustrated in figure 1. The results of experiments using 5 and 20 mg./kg. doses of procaine are graphically summarized in figures 2 and 3. There was no qualitative difference between the response in the intact anesthetized cats and the acutely spinal animals. Artificial respiration was maintained and continuous blood pressure records were made throughout the course of some experiments. A graphic record of one such study is shown in figure 4. The changes in electrical events following intravenous procaine administration would seem to occur independently of secondary effects due to hypoxia. In several instances, 5 and 10 mg./kg. doses of procaine resulted in a depression of activity of comparable duration, but the reduction in amplitude of the ventral root response was always greater with the larger dosage of procaine.

In experiment DR/VR VI (2-8-51) the effect of short-lasting hypoxia upon the monosynaptic and multineuronal discharges was ob-
erved (fig. 4). These changes consist in an enhancement of the two-neuron response and depression of multisynaptic internuncial discharge (4, 5). The ventral root response to hypoxia of short duration is qualitatively different from the procaine effect. The procaine depression of both monosynaptic and multisynaptic potentials is more comparable to the progressive depression of monosynaptic and polysynaptic reflex discharges which is caused by the barbiturates and other anesthetic agents (4, 6, 7). The interpretation has been made with regard to these preparations that synaptic transmission is blocked

by increasing the stability of the motoneuron, so that normally effective synaptic potentials fail to initiate an impulse. The procaine effect is significantly different from the selective depression of multineuronal reflex discharges without alteration in the two-neuron response which follows the administration of mephenesin (3, 8), or the depressant effect of the relatively specific anticholinergic compounds TEAC and Banthine® upon monosynaptic responses, without alteration in multisynaptic reflex discharge (9).
In other experiments (DR/VR IX, 23–8–51; DR/VR X, 21–9–51; DR/VR XIII, 26–9–51; and DR/VR XIV, 29–9–51) a two-stimulus reflex preparation was studied, using paired pulse generators and two pulse stimuli with a variable pulse separation from 0.5 to 5 msec. apart. In this way, ventral root recordings of an unconditioned motoneuron response, a facilitated motoneuron response, an inhibited motoneuron response, an unconditioned and an inhibited multineuronal response could be obtained. Analysis of the records of these experiments failed to indicate significant differential effects following the injection of procaine over the general depressant effects upon both monosynaptic and multineuronal reflex discharges which have already been described.

A general "tranquilizing" effect from procaine was noted in restless and lightly anesthetized animals, comparable to the mephenesin result described by Henneman, Kaplan and Unna (3). This tranquilizing effect occurred following as little as 3 to 5 mg./kg. of procaine and seemed to outlast changes in ventral root discharges which were being recorded.

**Spinal Cord Reflex Activity; Electromyographic (EMG) Studies.** Records were obtained comparing a two-neurone reflex (knee-jerk)
and a prototype of the multineuron reflexes (flexor reflex) with neuromuscular transmission (nerve-muscle preparation). A combination of physiologic and electrical stimuli were used to elicit the responses. The recording system was relatively insensitive and of an all-or-none type. The reflex responses in acutely spinal animals were qualitatively the same as the responses which occurred in the lightly anesthetized (Diacephaline) intact animal. The results of these experiments can be summarized as follows:

1. A hierarchy of procaine actions was evident. Monosynaptic and multineuronal reflexes were depressed by smaller doses of procaine than were required to block neuro-effector transmission to skeletal muscle. In turn, a multineuronal circuit (flexor reflex) was more vulnerable to procaine than a two-neuron reflex system, the knee jerk. The results of typical experiments are shown in figures 5, 6, and 7. It would appear that there is a graded sensitivity to procaine of the various reflex units which can be correlated with the complexity of the neuronal circuits involved in the reflex response.

2. A short-lasting, but effective, anti-strychnine action of procaine was demonstrated. This result is shown in figure 6 (sections 4 to 5)
and figure 7 (sections 6 to 9). Hyperreflexia, repetitive firing, and strychnine convulsions were reduced promptly to normal levels of activity after procaine dosages which did not exert an apparent depressant influence upon the baseline reflex activity recorded in monosynaptic and multisynaptic circuits before drug injections. This result would imply that procaine opposes excessive activity in selected internuncial circuits before normal levels of activity in two-neuron reflex circuits and multineuronal pathways are affected.

![Diagram](image)

**Fig. 6.** Differential sensitivity to procaine of two-neurone reflex response and polysynaptic reflex response; procaine-strychnine antagonism. A 7 kg. tracheotomized dog, nembutal anesthesia, 1.0 cc./kg. KJ = knee jerk, right side. FR = flexor reflex, left side. Ephedrine, 50 mg. at 2:45 p.m. Records taken as follows: (1) Control record at 5:30 p.m.; (2) 5:35 p.m., 15 mg./kg. procaine also was given at 5:38 p.m., depressing totally the flexor reflex; knee jerk depressed to approximately 20 per cent of the control record; (3) record at 6:05 p.m., showing recovery; (4) 6:07 p.m., after 0.5 mg. strychnine intravenously; and (5) 6:10 p.m., after 15 mg./kg. of procaine.

**Brain Stem. Specific Reticular Formation; Descending Inhibitory and Descending Facilitatory Systems.** Evidence of procaine effects upon the neuraxis was obtained from experiments that were designed to test the influence of the inhibitory and facilitatory reticular formation of the brain stem upon the knee jerk. Since the specific reticular formation of the brain stem and pons is considered to represent a complex and diffuse multineuronal regulator of descending influences
from the cortex and cerebellum which finally converge upon the moto-
neuron (10, 11, 12), the knee jerk response offers on the motor side a
simple and reliable indicator for judging the activity in this reticular
formation, before and after drug injections. Five satisfactory experi-

![Graph showing differential sensitivity to procaine of two-neurone reflex response and polysynaptic reflex response; procaine-strychnine antagonism. An 8.1 kg. tracheotomized dog, acutely spinal at C8, artificial respiration. Short-lasting areflexia following transection, 4.5 cc. 2% ephedrine subcutaneously at 3:35 p.m. KJ = knee jerk, right side. FR = flexor reflex, left side. Records taken as follows: (1) Control record, 5:15 p.m.; (2) 5:14 p.m.; (3) 5:16 p.m.; (4) 5:24 p.m., showing recovery; (5) Control record, 6:30 p.m.; (6) 6:31 p.m., after 1 mg. strychnine intravenously; (7) 6:33 p.m., heavy black line in records (7) and (8) indicates spontaneous activity, record (7) showing the end of a 30-second convolution; (8) 6:35 p.m., after 12.5 mg./kg. procaine, and (9) 6:37 p.m.]

ments were completed, lasting from 300 to 650 minutes each, during
which time an average of 5 injections of procaine and more than 90
separate periods of electrical stimulation of the reticular formation
were carried out. Intravenous injections of procaine were made at a
rate of 5 to 10 mg./kg./minute, through a dose range of 4 to 40 mg./kg.

**Knee Jerk Response.** A 4 mg./kg. dose of procaine exerted an imperceptible effect, or a minimal and short-lasting influence, upon the indicator reflex. The period of knee jerk depression was less than five minutes in all of these instances. Doses of procaine of 5 to 25 mg./kg.

**Fig. 8.** Selective procaine blockade of inhibitory (**—**) influences from brain stem reticular formation without equivalent blockade of facilitatory (**+**) influences upon the motoneurone. Experiment (**—**) on 28–12–51, stereotaxic coordinates: P_{6}V_{5}L_{4} (R), 10 v., 10 msec., 40 stimuli/second. Experiment (**+**) on 12–1–52, stereotaxic coordinates: A_{8}V_{5}L_{4} (R), 6.7 v., 10 msec., 40 stimuli/second. Tracheotomized cats, dial-urethane narcosis. EMG recordings. KJ = knee jerk. On and Off of RF stimulation indicated by dots below each record.

usually resulted in suppression of the reflex response with a decreased amplitude of the EMG record. In most cases, a sufficient time interval was allowed for recovery of the knee jerk to pre-injection levels before the effects of procaine upon the knee jerk response to reticular formation stimulation were assessed.
Reticular Formation Stimulation; Inhibition of Knee Jerk. The most striking result of any of the experiments which were carried out was the consistent and reproducible effect observed after injections of procaine. There was a variable period during which blockade of the descending inhibitory influences from reticular formation stimulation was manifest. The completeness of the blockade and its duration could be related in a general way to the procaine dosage. Four mg./kg. of procaine resulted in a 50 per cent or more blockade of reticular formation inhibition of the knee jerk response, an effect lasting for eleven minutes in one experiment (EMG I, 27–12–51). In another experiment (EMG V, 12–1–52), 8 mg./kg. of procaine was followed by an estimated 80 per cent blockade of descending inhibitory influences upon the knee jerk, as measured by the amplitude of the EMG record, with recovery to the pre-injection control amplitude of reflex response at fourteen minutes after the procaine injection. In this same animal, 15 mg./kg. of procaine resulted in a complete block of inhibitory reticular formation influences upon the knee jerk at seven minutes following the completion of the injection. The suppression of inhibition was still evident at fourteen minutes following procaine injection and recovery of amplitude of the knee jerk response was complete at twenty minutes following injection. This result is illustrated in figure 8. A 25 mg./kg. dose of procaine (EMG VII, 6–2–52) exerted blocking effects which were measurable for twenty-one minutes following the completion of the injection.

There was evidence that this blockade of descending inhibitory influences via the reticular formation is not absolute but reversible by changes in stimulus intensity. A 3.5 volt increase in stimulus strength overcame completely, for example, a total procaine blockade of knee jerk inhibition from reticular formation stimulation in one experiment (EMG VIII, 6–2–52).

Reticular Formation Stimulation; Facilitation of Knee Jerk. A procaine blockade of descending facilitatory influences could not be introduced by the knee jerk depression which follows large dosages of procaine comparable to, or larger than, the concentrations required to block descending inhibitory influences were used. Marked depression of the knee jerk followed the injection of 20 to 40 mg./kg. of procaine, but the facilitatory response was still obtained. A typical result is shown in figure 8. In this experiment (EMG II, 29–12–51), what appeared to be maximal facilitation was recorded at twenty-five minutes following the injection of 25 mg./kg. procaine, although an 80 per cent reduction in amplitude of the knee jerk response was evident at this time. Supramaximal stimuli without voltage alteration were used in these experiments and electrode positions were not altered during the course of a single testing procedure. The limitations of the recording technique make it impossible to say whether or not a minimal blockade of facilitation does actually occur. An obscurity
is introduced by the knee jerk depression which follows large dosages of procaine, for the facilitatory response did not always equal the pre-injection control record for the indicator reflex. This suggests one or a combination of three possible explanations: (1) a curariform action of procaine, depressing the facilitatory response and masking it, (2) monosynaptic reflex arc suppression by procaine and depression of the facilitatory response at the level of the motoneuron, and/or (3) a partial blockade of descending facilitatory influences from the reticular formation.

In these experiments, both ipsilateral and contralateral reticular stimulation were carried out. Sufficient crossing of the descending facilitatory and inhibitory influences from the brain stem RF has been demonstrated at bulbar and spinal levels for bilateral influence to be exerted (24). Rigidity of the decerebrate state was abolished in several animals by procaine infusions, but this effect was observed only as a part of laboratory demonstration experiments and quantitative dose response records of these results were not obtained.

In summarizing these results, a preferential blockade of multi-neuronal inhibitory influences from the ventro-medial RF of the brain stem was observed following procaine infusion. A significant effect upon descending facilitatory pathways from the reticular formation could not be demonstrated.

The experimental results following procaine injection are in contrast to the non-selective depression of both inhibitory and facilitatory brain stem RF mechanisms by mephenesin (3, 8, 10). Using this inter-neuronal blocking agent, a persistence of some inhibitory influence from the reticular formation has been demonstrated at a time when the abolition of facilitatory responses was complete. The preferential blockade of the inhibitory reticular formation system by procaine is of interest, also, when it is contrasted to recent studies of morphine action (13, 14). The analysis of respiratory patterns in unanesthetized dogs, before and after morphine injection, and morphine studies in animals with an isolated respiratory center, have led Hoff and Breckenridge to the interpretation that the morphine effect upon respiration is exerted through a depression of multineuron arc discharges, with a preferential selection of suppressor mechanisms at cortical and sub-cortical levels, releasing from check the facilitatory systems. Also of interest is a discussion by Tomans and Davis (15) in considering the basic mechanisms of action of the local anesthetics. It is well known that these agents may be convulsants. Tomans and Davis suggest that since conduction block rather than depolarization is the important factor in alteration of threshold with the local anesthetics, a threshold-raising drug might cause epileptiform seizures by a selective depression of inhibitory systems in the central nervous system.

A few experiments were carried out testing the effects of atropine and TEAC upon the specific inhibitory and facilitatory systems of the
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brain stem reticular formation. The anti-acetylcholine compounds atropine and TEAC, 1 mg./kg. and 5 mg./kg. respectively, were ineffective in blocking either inhibitory or facilitatory influences upon the motoneuron response under these testing conditions.

Discussion

The present experiments reveal significant patterns of procaine action within the neuraxis at spinal cord and brain stem levels. Since the peripheral effects of procaine would appear to be negligible at the clinical dose range (1), the demonstration of internuncial blocking actions invites discussion of a neurophysiologic frame of reference which might be useful in explanation of the clinical response to dilute procaine infusions in certain cases of pain.

There is little reason to question the basic assumption of peripheral nerve axonology that the procaine action at a molecular level is related to conduction block, without notable change in membrane potential, rather than depolarization (16, 17). The central nervous system correlates of this generalization can only be inferred at the present time in the absence of direct evidence.

The basic mechanisms involved in the selective action of anesthetics on synapses and axons have been studied by Larrabee and Posternak (18), using an isolated synaptic system. Two general hypotheses have been advanced for the selective action of anesthetics: (1) A specific drug effect upon synapses (2) equivalent depression of axonal and synaptic irritability, a selective drug action resulting from the relatively small "factor of safety" in transynaptic excitation as compared to axonal conduction.

These hypotheses of synaptic and axonal blockade suggest interesting theoretical possibilities: (1) The relief of pain might occur on the basis of a highly discriminative synaptic or neuronal blockade occurring in cellular masses considered as essential to the perception of pain. (2) A mass-action type of relatively indiscriminate depression might be produced, involving the total input-output performance of the central and peripheral nervous systems, but with central nervous effects dominant because of increased vulnerability based on complex interneuronal organization. Even at this point in a theoretical discussion, it should be emphasized that there is no reason to consider these possibilities as mutually exclusive:

1. In terms of the so-called "specificity" theory, the neuro-anatomic substrate for pain might be said to consist of specially adapted receptor endings and fibers subserving the sensation of pain with an ascending relay in the anterolateral tracts, ending in the thalamus. The concept of pain mechanisms which evolves from such an interpretation of sensory physiology requires that pain shall be thought of as a physical quantum, measurable in terms of stimulus intensity or body
response. There is evidence that an hypothesis of drug actions confined within such a frame of reference would be inconsistent with fact (11, 19–26). Were one to hold to the "specificity" theory, the control of pain by selective drug action or ablative neurosurgical procedure should be notable for its predictability once the critical points in the neural sequence had been identified. The essential neuro-anatomic links have not been demonstrated within the limits of the classical sensory pathways, at least, and the common denominator of drug action which is crucial to the elimination of pain is still no more than a hypothetical possibility. Only death or loss of consciousness can give absolute assurance of relief from pain. Significantly, the classical sensory pathways are functionally intact and available to peripheral stimuli during anesthesia (22), although pain perception is gone. A long record of neurosurgical failures in the effort to achieve permanent relief from pain by ablative techniques is another impressive critique of the specificity concept.

2. Release from the static and rigid confines of the specificity concept required, first, anatomic-physiologic demonstration of a neural basis for a departure. An experimental basis was provided by Lorente de Nó (27). Subsequently, in a discussion of pain mechanisms, the "internuncial pool" concept was presented by Livingston (19). Current extensions of a unifying concept of neurophysiologic actions have focused upon a common reticular relay in the medial brain stem, the so-called "activating system" (11, 12, 20, 22, 28–31). Thus there are two pathways for the sensory input: (1) The well-defined classical pathways (visual, auditory, visceral and somatic sensory) with precise localization in the specific cortex. Electrical impulses recorded laterally in lemniscal and primary sensory areas are characterized by short latencies, spike-like appearance, segregation of responses into discrete pathways, little or no attenuation on repetitive stimulation, and localized cortical distribution. (2) A diffuse afferent collateral system, the common reticular relay, extending the length of the neuraxis from the lower border of the pons to the ventromedial thalamus, and into which an extensive input of sensory impulses passes. Potentials recorded medially exhibit long latencies, wave-like configuration, lack of modality segregation, inter-action and attenuation of succeeding responses on multiple stimulation, and diffuse cortical distribution.

Magoun and his associates suggest that the central core of the brain stem subserves a specialized function since collaterals from each of the four great afferent systems pervade its structure. A notable lack of segregation of discrete sensory modalities within the area has been observed. Also, all sensory systems which feed into it do so diffusely throughout its extent. High frequency stimulation of peripheral receptors effects an electrical desynchronization of it (21), a result that is comparable to the desynchronization of electrocortical activity.
following direct high frequency stimulation of the system and parallel to the arousal from sleep, or alerting to attention, described by Moruzzi and Magoun (28). This area of collateralization in the reticular formation, the so-called "alerting system," provides additional substrate for a dynamic concept of integrated nervous actions. It has important implications relative to such reactions as the awareness of sensation, arousal to wakefulness, and alerting to attention (31). It has significant implications, clearly, with reference to pain mechanisms and the control of pain.

A new concept of anesthesia was recently formulated by French, Verzeano and Magoun (22) on the basis of experiments which were devised to examine contrasting features of potentials conducted via the two routes under various states of wakefulness and of sleep induced with barbital or ether. Impulses propagated over the medial system were blocked after the administration of ether or pentobarbital sodium. Laterally conducted impulses reached the sensory cortex with unimpaired, or even augmented intensity. The evidence suggests that the central brain stem system has a multisynaptic interneuronal organization which makes it more susceptible to anesthetic blockade than the polysynaptic lateral pathways. It was concluded by these authors that depression of activity in such areas participates to a considerable degree in the production of the anesthetic state. The reduction or block of impulses conducted through the medial brain stem common reticular relay, and a reversible state of anesthesia, were considered as comparable to the permanent unresponsiveness of animals with electrolytic lesions in the central cephalic brain stem (29).

A similar frame of reference is useful when considering the mode of action of procaine. A concept of the nervous system which stresses a transactional point of view and the interneuronal systems which give it unity in space and time (20) provides a basis for interpreting the clinical results following dilute intravenous procaine administration. At least in part, procaine must exert its beneficial influence upon pain through altering activity in a variety of interneuronal relays within drug vulnerable areas of the neuraxis. The results of present experiments demonstrating procaine actions upon multisynaptic systems in the spinal cord and brain stem provide incomplete but concrete support for such an explanation.

**Summary**

Using electrophysiologic techniques, a study of procaine actions has been carried out in lightly anesthetized and acutely spinal animals at two levels in the central nervous system: (1) the spinal cord, and (2) the brain stem.

Under the conditions of these experiments, a differential vulnerability of certain central nervous system elements to procaine has been
demonstrated. The procaine effects which were demonstrated in these experiments are as follows:

1. A selective action at the spinal cord level upon synaptic processes of increasing complexity. Neuro-effector transmission to skeletal muscle was found to be more resistant to procaine than the two-neuron reflex arc. The knee jerk, in turn, was more resistant to procaine than the flexor reflex.

2. A vulnerability of strychnine-induced hyperactivity to procaine dosages which did not interfere with normal reflex activity.

3. A selective action on inhibitory descending influences from the brain stem reticular formation without equivalent blockade of descending facilitatory influences from the brain stem which influence the motoneuron.

Central procaine effects were elicited following doses of procaine approximately the clinical procaine unit of 4 mg./kg. Spinal cord and brain stem actions of procaine were evident following dosages which on a mg./kg basis of comparison did not block functional activity of the various elements within the peripheral nervous system.

In the light of current interpretations of pain mechanisms which stress the multisynaptic interneuronal organization of the nervous system, this evidence suggests that procaine effects upon drug vulnerable reticular relays must be a factor in the control of pain, in those instances where dilute intravenous procaine infusion is effective.

REFERENCES

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ERRATUM

In Part I of the above article, published in the September Issue, the legend which appeared beneath figure 2 is incorrect. The legend should read "Fig. 2. Procaine neuromuscular blockade. Curare-like action of procaine, anti-procaine action of epinephrine. 2.5 kg. cat, Nembutal anesthesia, 0.6 cc/kg. Isometric responses of gastrocnemium to sciatic nerve stimulation, rate of stimulation, one stimulus per two seconds. Ipsilateral femoral artery injections."