# HYPOTHERMIC POTENTIATION OF CENTRALLY INDUCED CARDIAC IRREGULARITIES

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ALTERATIONS in cardiac rate and rhythm constitute one of the most serious complications encountered during hypothermia. Although most of the emphasis on the factors involved in the production of such alterations has been focused on intrinsic myocardial processes (1) the important role of reflexogenic factors has been examined clinically with specific reference to cardiac alterations observed during various neurosurgical procedures (2). The latter study has suggested that activation of central reflex mechanisms concerned with the control of cardiac rate and rhythm are facilitated during hypothermia in a manner similar to cold potentiation of somatic (3–5) and autonomic (6) reflex activity.

In view of the increasing application of hypothermic technique to neurosurgical problems, further examination of the mechanisms and control of cardiac irregularities of central origin was carried out in laboratory animals. In the present experimental series information was obtained relating to the site of integration of certain cardiac reflexes, their hypothermic potentiation, and pharmacological agents of significance in preventing or controlling them.

## METHODS

Experiments were performed on over 30 cats initially anesthetized with ether to permit introduction of a tracheal cannula and other operative procedures. These included exposure of the brain stem following suction-ablation of the overlying cerebellum. At the conclusion of these procedures skin margins and pressure points were infiltrated with procaine (1 per cent). The animals were then permitted to recover, paralyzed with succinylcholine (saline infusion) and artificially ventilated.

Electrical stimulation of diencephalic and brain stem sites was accomplished by means of a 0.5-mm. concentric electrode oriented in a three-dimensional manipulator. All stimulating sites were checked by either gross or histological examination. In most instances electrocardiograms were recorded on a clinical Grass electroencephalographic

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unit although a Cambridge portable electrocardiographic unit was also utilized.

Hypothermia was induced by packing the previously shaven animals in ice, body temperatures being recorded with a rectal thermocouple. Pharmacological agents were administered through an indwelling femoral catheter and consisted of chlorpromazine, sodium pentothal, dibenamine, atropine, procaine, succinylcholine and *d*-tubocurarine.

## Results

*Electrocardiographic Alterations Induced by Brain Stem Stimulation.*—The fact that stimulation of the basal diencephalon and brain stem is capable of inducing a variety of cardiac irregularities is well

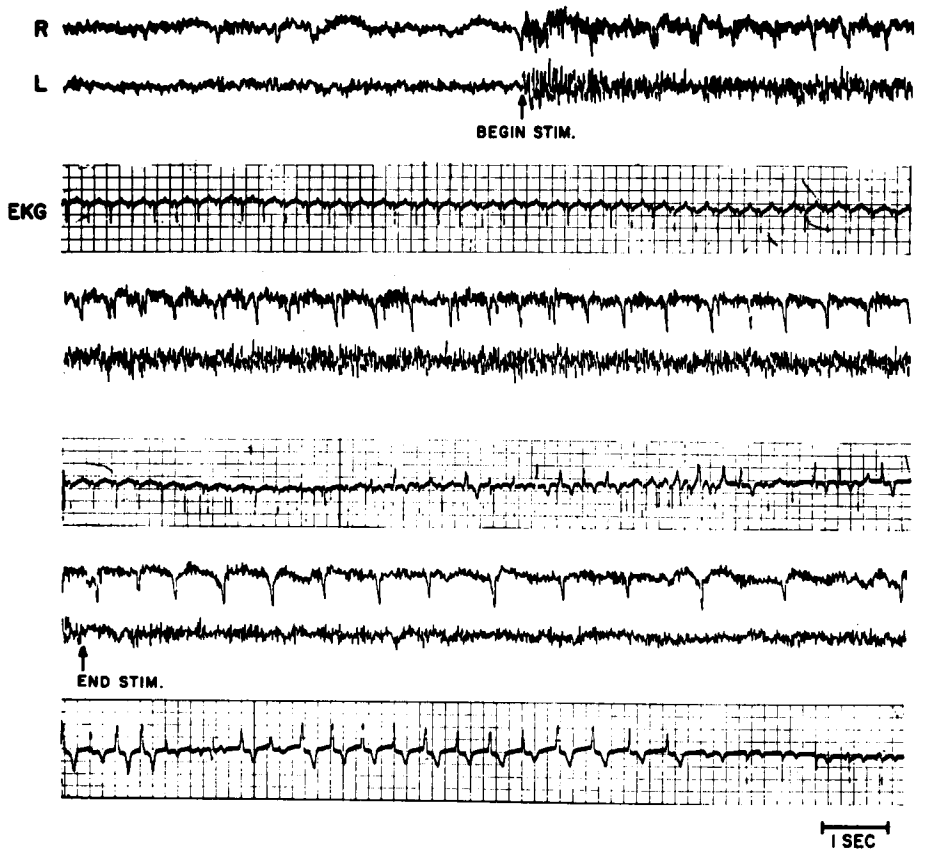


FIG. 1. Continuous recording of electrocortical and electrocardiographic alterations produced by stimulation of lower mesencephalic reticular system (200 c.p.s.; 0.2 msec.; 5 volts). In this illustration electrocardiographic changes commenced during stimulation and persisted for many seconds afterwards. Such changes as these were the most frequently observed. R and L—right and left bipolar sensorimotor cortical leads. (Appearance of cortical spikes during and after brain stem stimulation encountered also in previous studies has not been adequately explained (33).)

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established (7–9). Recently attempts have been made to dissociate poststimulation alterations from those occurring during stimulation (10). The former were reported to be abolished by vagotomy whereas the latter were unaffected or made worse. These results were entirely confirmed in the present investigation. In particular, however, it was noted that cardiac irregularities, consisting of ventricular extrasystoles, bradycardia, T-wave and P-wave changes were induced in widespread regions of the brain stem and basal diencephalon capable of behaviorally and electrographically "alerting" the animal. An example of these effects is shown in figure 1 during and after cessation of stimulation of the medial pons. It should be pointed out that in unanesthetized, normothermic preparations it was often difficult to

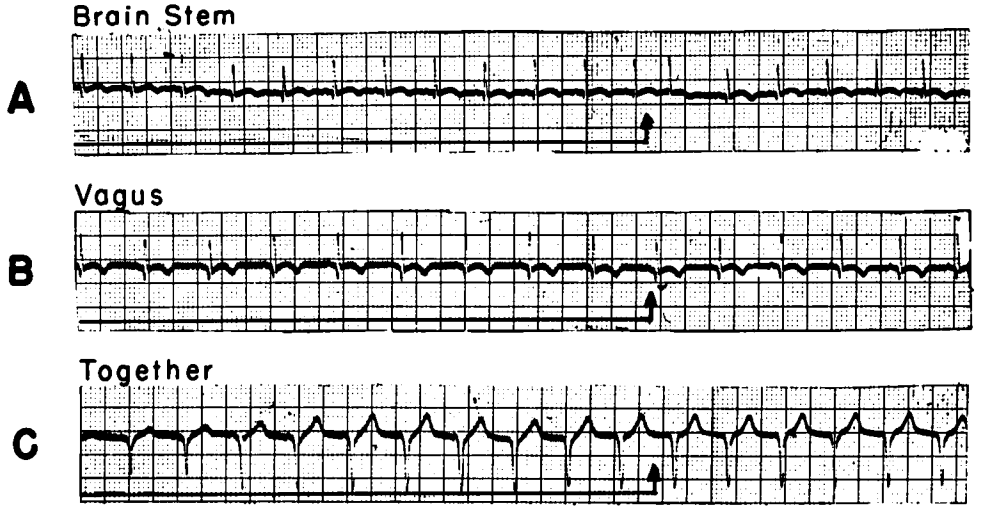


FIG. 2. Effect of combined vagal, brain stem stimulation. Arrows indicate end of 5-second stimulation. A, subliminal stimulation of lower mesencephalic reticular system (100 c.p.s.; 0.2 msec.; 8 volts). B, subliminal stimulation of distal end of cut vagi (25 c.p.s.; 0.2 msec.; 2 volts). C, A and B together.

effect a threshold dissociation between the electrocortical and electrocardiographic alteration when stimulating mid-line ponto-bulbar regions. Although in most instances the "arousal" thresholds were lower than those necessary for producing the electrocardiographic changes, rarely was it possible to elicit electrocardiographic changes without also producing electrocortical activation. This was not true for the hypothermic preparation in which the threshold for electrocortical arousal progressively increased while that for eliciting cardiac irregularities decreased (fig. 5 A and B).

Effects similar to those shown in figure 1 were reproducible throughout the central core of the brain stem reticular system and were generally accompanied by, but not dependent upon, pressor-depressor responses. These results indicate that the brain stem reticular system

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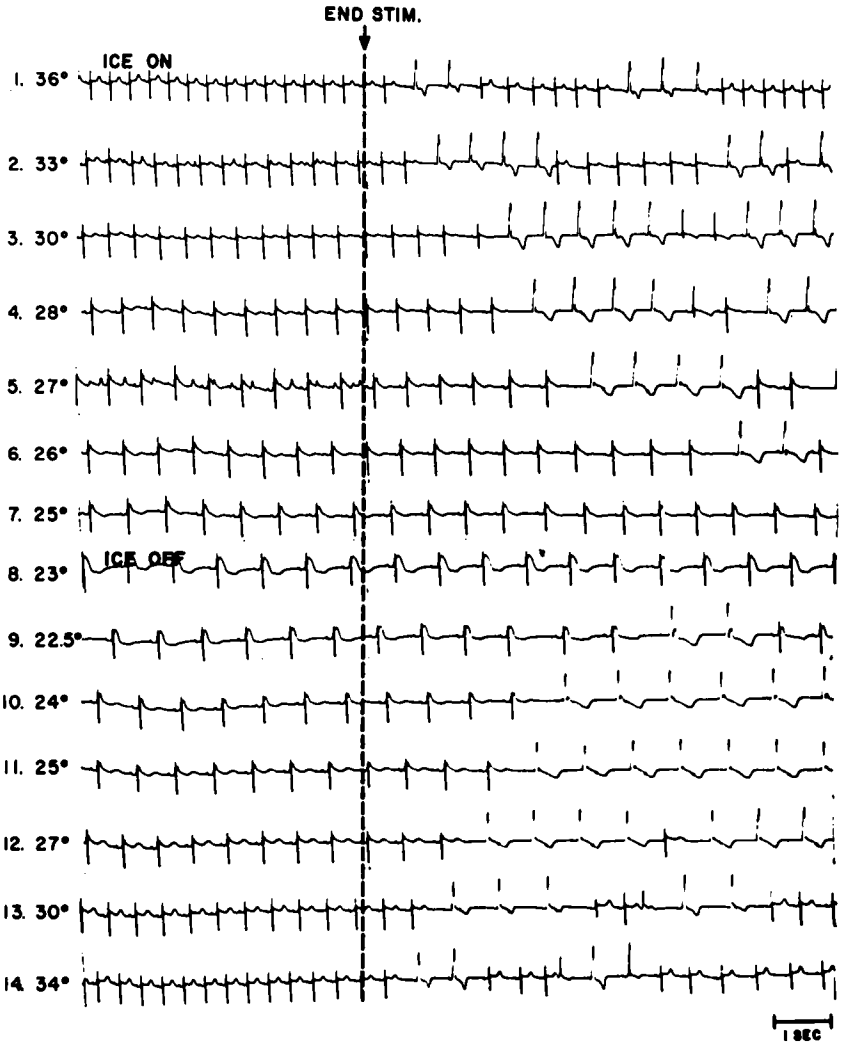


FIG. 3. Hypothermic potentiation of centrally induced cardiac irregularities. "End stim." indicates cessation of a 5-second stimulus to upper pontine reticular system (200 c.p.s.; 0.5 msec.; 10 volts). Note that during progressive hypothermia irregularities are delayed but more persistent when developed. At 25 C. no effect is produced by stimulation but irregularities reappear during initial rewarming despite continued temperature drop (22.5 C.).

can be viewed as the site of integration of a wide variety of afferent drives capable of affecting vago-sympathetic centers controlling cardiac rate and rhythm.

Participation of both vagal and sympathetic elements in the production of the arrhythmias was demonstrated by physiological and pharmacological means. Whereas subliminal stimulation of either the brain stem reticular system or vagi *individually* was ineffective (fig. 2 A and B) in producing cardiac irregularities, the latter were readily induced by *combined* stimulation (fig. 2 C).

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The fact that it is generally not possible to dissociate "descending" somatic effects from respiratory and cardio-vascular effects by bulbar reticular stimulation (12–14) or hemodynamic from electrographic alterations by stimulation of the ascending activating system (15) is now well established. On the basis of these studies the clinical observations become explicable in terms of an activation of this diffuse system by afferent drives from certain "trigger" sources; for example, circle of Willis aneurysms or other pathological processes contiguous to basal

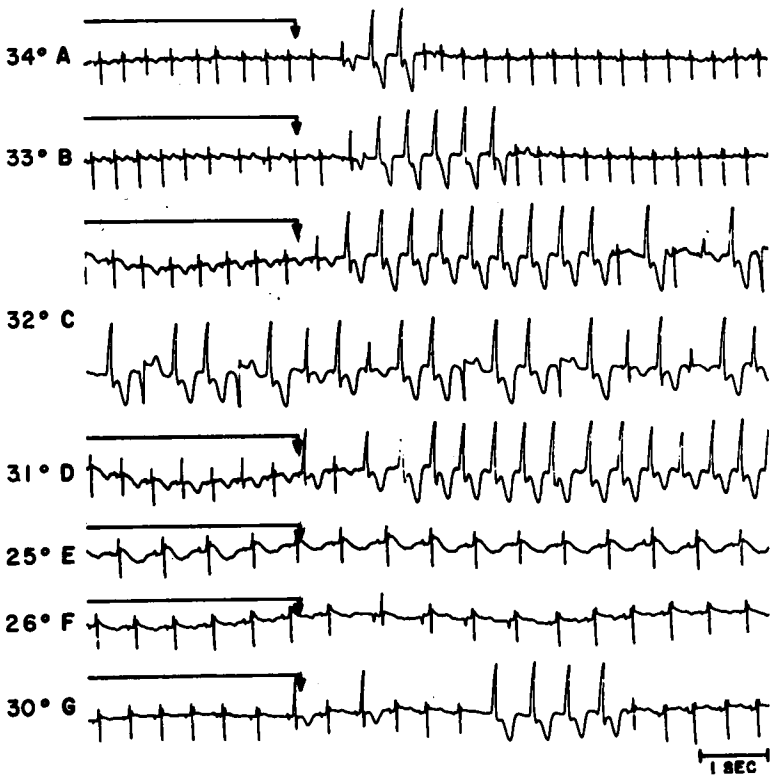


FIG. 4. Hypothermic potentiation of cardiac irregularities induced by a stimulus to the mesencephalic reticular system (100 c.p.s.; 0.5 msec.; 9 volts). Arrow indicates end of a 5-second stimulus. Note facilitation of irregularities at 32 C., abolition at 25 C. and reappearance during rewarming.

or brain stem structures. Reproduction of cardiac irregularities in the laboratory preparation by controlled reticular stimulation thus provides a convenient method for testing the effects of various agents on the centrally induced cardiac alterations.

*Hypothermic Potentiation.*—The effects of hypothermia and subsequent rewarming on the cardiac alterations induced by brain stem stimulation are characterized in figures 3, 4 and 5. The following points are emphasized as regularly induced events. Immediately after application of the ice and during the period when a rapid fall in body

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temperature occurs, brain stem stimulation previously minimally effective (figs. 4 A and 5 A) induces maximal alterations (fig. 3, *3–5*; fig. 4) often leading to sustained arrhythmias (fig. 5 C). The latter were spontaneously irreversible but could be effectively blocked in all instances by administration of additional succinylcholine (10–25 mg./kg.) (fig. 5 D). Other observations of interest included those relating to the transition periods. Whereas a hypothermic stage might be reached during which previously effective stimulation became sub-

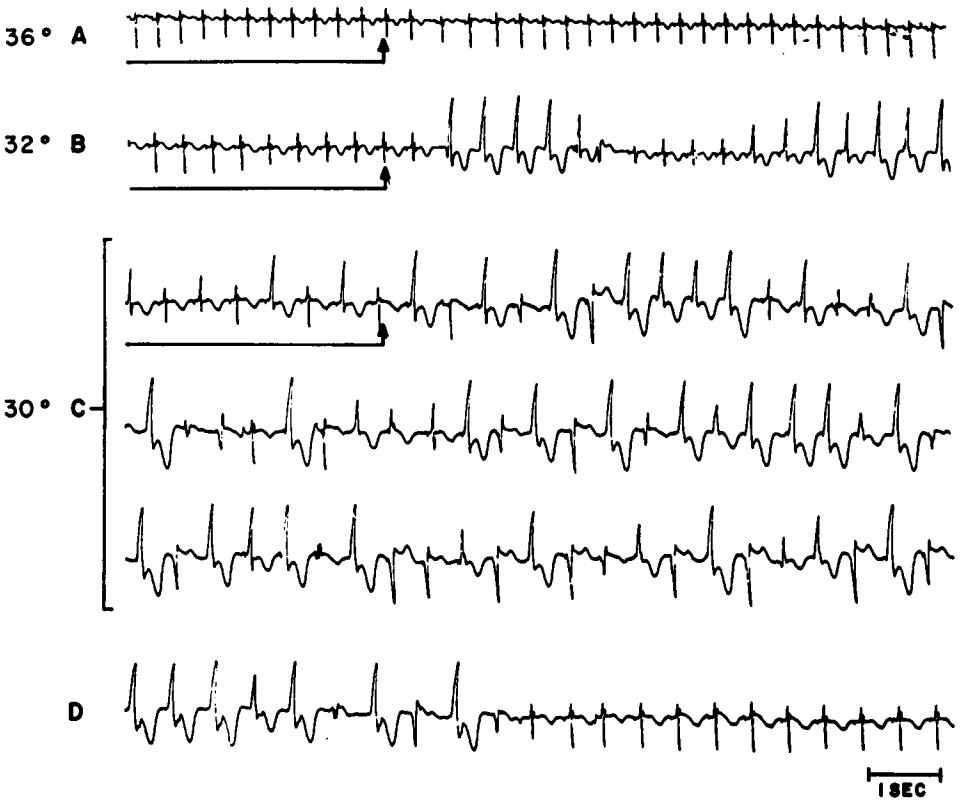


FIG. 5. Blocking action of succinylcholine. Same experiment as that shown in figure 4, during another run. At 30 C. stimulation induced marked, persistent irregularities as shown in continuous record (C). D, 1½ minutes later, begins 20 seconds after administration of 25 mg./kg. succinylcholine chloride.

liminal (fig. 3, *7–8*; fig. 4 E), this was reversed during rewarming despite the fact that in the initial rewarming period *body temperature continued to fall* (fig. 3). Recognition of this "hysteresis-like pattern" during hypothermia has been previously noted with nociceptive activation of the ascending reticular system (11).

These results indicate that the "pseudoanesthetic" action of moderately severe cold (23–26 C.) on central synaptic systems reflexly linked to vago-sympathetic neurons is presumably readily reversed by changes in afferent bombardment such as occur during the initial

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stages of the rewarming process. A similar reversal may be effected at these temperatures by increasing stimulus intensity, an event, however, likely to induce profound cardiac irregularities.

*Prevention and Control.*—Reference has already been made to the effects of moderately high doses of succinylcholine on centrally induced cardiac irregularities (fig. 5 D). Previous studies from this laboratory have defined the mode of action of this agent on cardiac arrhythmias (16). It has also been shown that this agent even in extraordinarily high doses is without central blocking action (17). This factor

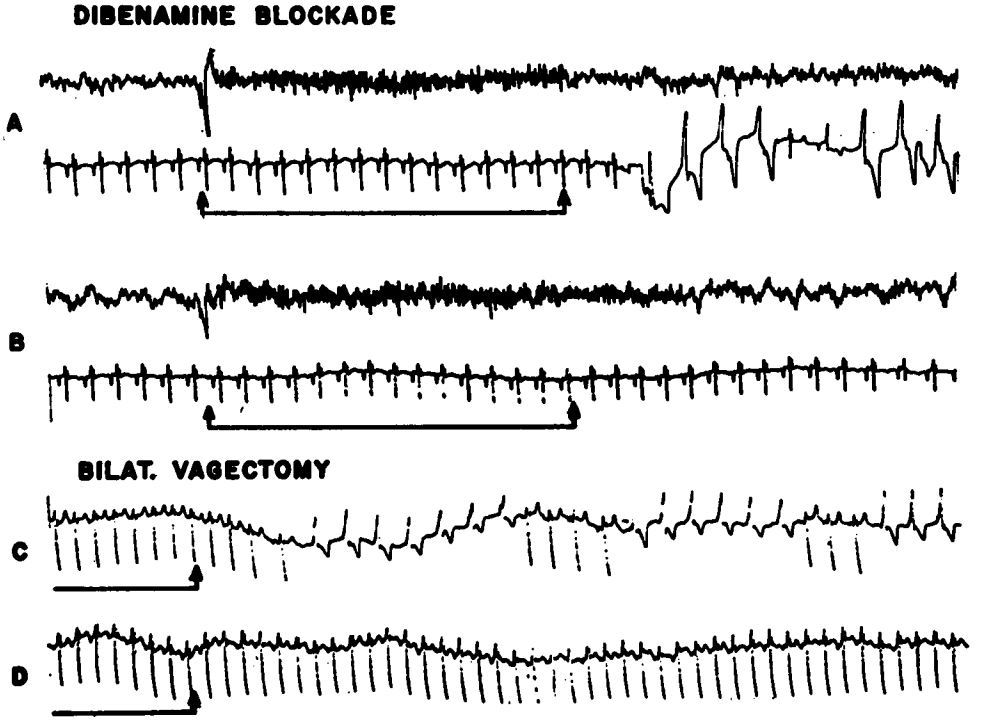


FIG. 6. Components involved in the production of cardiac irregularities by mesencephalic stimulation. A, electrocorticogram (upper trace) and electrocardiogram (lower trace). Arrow indicates duration of brain stem stimulation. Abolition of irregularities by dibenamine 10 mg./kg. C, D, another experiment. Arrow indicates end of a 5-second brain stem stimulus. C, before and D, after bilateral vagectomy. Irregularities occurring *after* stimulation were always permanently abolished by vagectomy (10).

plus its controllability, which is conferred by virtue of its rapid hydrolysis, thus provides a safe and powerful pharmacological tool for preventing cardiac irregularities of the kind noted above. It is of interest to note that succinylcholine has recently also been found to abolish ether-epinephrine induced cardiac arrhythmias (18).

Blockade of cardiac synapses by adrenolytic or anticholinergic agents must also be considered. In the case of cardiac irregularities of central origin the site of blockade (that is, central, cardiac ganglionic or receptor sites) must be carefully evaluated. This can be

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facilitated by simultaneous recording of electrocortical activity as shown in figure 6 A and B. Dibenamine is capable of transiently abolishing the cardiac effects of reticular stimulation through peripheral blockade of the sympathetic component but does not affect the electrocortical response to reticular stimulation. Similar effects are obtainable with chemical (atropine) or surgical vagotomy (fig. 6 C and D), although the former may also have a central blocking action (19).

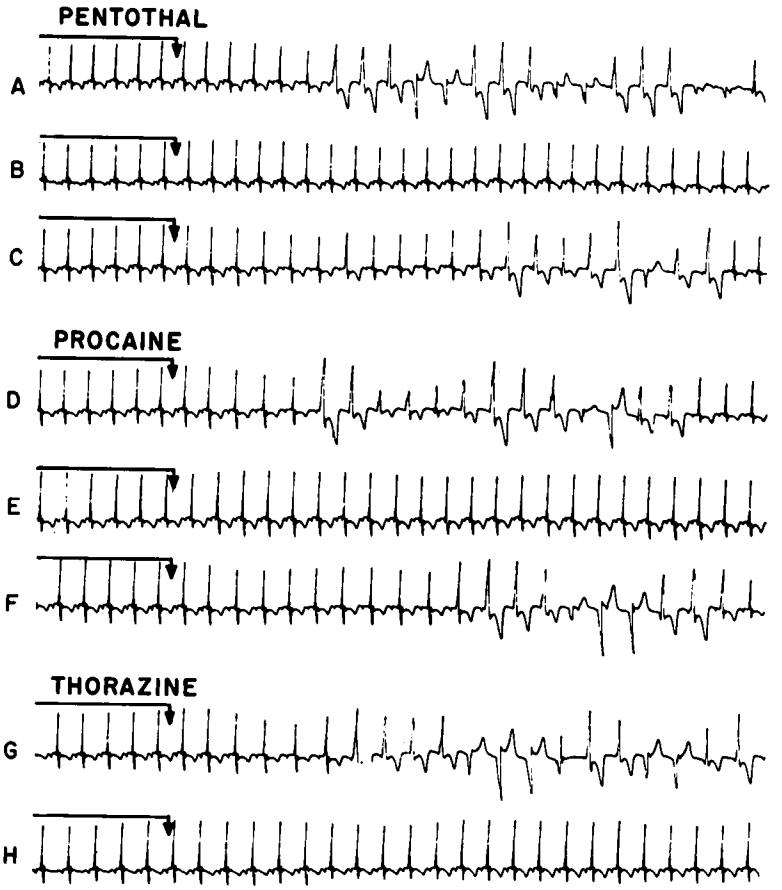


FIG. 7. Effects of various "blocking" agents on centrally induced cardiac irregularities. In all instances arrows indicate end of 5-second stimulus to dorsomedial pontine reticular system. A, control; B, two minutes later after 8 mg./kg. sodium Pentothal, intravenously; C, recovery of responsiveness 16 minutes later; D, control; E, one minute after 1 cc. 2 per cent procaine solution, intravenously; F, recovery 12 minutes later; G, control; and H, five minutes after 2.5 mg./kg. chlorpromazine, intravenously.

Agents which exclusively depress central reticular interneurons are of primary importance in preventing various afferent drives from reflexly engaging vago-sympathetic elements. Barbiturates in low doses are highly effective (fig. 7 A–C) but also depress general reticular activity (20, 21). On the contrary, chlorpromazine (2–5 mg./kg.) appears to selectively block the induction of cardiac irregularities (fig.

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7 G and H) by central sympathetic depression (22) without significant effect on reticulo-cortical activation thresholds following sciatic or reticular stimulation, as demonstrated in the unanesthetized-curarized cat (23).

Of added interest is the fact that parenterally administered procaine exerts a relatively prolonged blocking action on centrally induced cardiac arrhythmias (fig. 7 D–F) although this agent affects both central and cardiac synapses as well as the direct electrical excitability of the myocardium.

## Comment

The foregoing experimental analysis has focused on the factors which require special consideration in those neurosurgical procedures involving inadvertent excitation of afferent systems capable of engaging brain stem circuits which are concerned with the regulation of cardiac rate and rhythm. For this reason little consideration has been given to the alterations in the direct electrical excitability of the myocardium induced by hypothermia. Such information can only be adequately obtained in the denervated heart or isolated myocardial strips. While it has been established that focal cooling of the ventricles during *rapid* ventricular activity (auricular flutter or fibrillation) may induce ventricular extrasystoles and fibrillation (24) the effects of temperature on ventricular fibrillation in the isolated heart are not clearly defined. Fibrillation has been reported to be induced by electrical stimulation at temperatures below 27 C. but not at higher temperatures (25). Opposite effects have also been obtained (26); that is, an increasing tendency to fibrillate with increasing temperatures. Similarly arrhythmias induced in isolated rabbit atria were diminished in rate on lowering the temperature from 37 C. and often ceased at 29 C. only to reappear after rewarming (27). These experimental results suggest that in the intact preparation cardiac alterations are more likely to be induced during hypothermia as a consequence of potentiated reflexogenic mechanisms than from an increased direct myocardial irritability. Indeed, it has recently been shown that the ventricular refractory period is greatly prolonged and there is no significant alteration in diastolic excitability of the ventricle during hypothermia (1).

The fact that direct stimulation of the reticular system of the basal diencephalon and brain stem can experimentally reproduce the various cardiac irregularities observed in clinical situations (2) indicates that many of the alterations occurring in this system of interneurons by physiological, pathological or pharmacological factors may be expressed in cardiac as well as general somato-visceral effects. Thus strychnine activation of reticulo-cerebellar circuits involved in the production of the strychnine tetanus induces cardiac irregularities (28) similar to those evoked by direct electrical stimulation of the brain stem. Recognition of the physiological substrate mediating these ir-

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regularities has facilitated analysis of the effects of agents potentiating as well as those abolishing them. Of clinical significance is the fact that in the unanesthetized-paralyzed cat hypothermia increases the excitability of cardiac reflex mechanisms in a manner presumably similar to its effects on somatic reflexes (3–5). In addition to direct effects of cooling on excitatory synapses, these results may be attributed to a reduction in tonic inhibitory activity which some components of the brain stem reticular system exert on primary afferent (29–30) and efferent (31–32) pathways. This suggests that descending reticular effects of an inhibitory nature are as susceptible to cold blockade as ascending reticular influences (11). In view of this a number of prophylactic measures can be outlined which effectively eliminate cardiac irregularities produced by afferent stimuli arising from certain intracranial "trigger" sites and potentiation of these stimuli by hypothermia. These measures must involve the use of adequate levels of anesthesia supplemented with central or peripheral cardiac synapse-blocking agents similar to those described above. Failure to recognize the necessity of preventing activation of pathological reflex mechanisms affecting cardiac rate and rhythmicity during combined hypothermic-neurosurgical vascular procedures can only result in creating additional hazards especially for the "poor-risk" patient.

## Summary

Experiments carried out on unanesthetized-paralyzed cats indicate that stimulation of diffuse components of the brain stem reticular system from basal diencephalon to bulb reproduces cardiac irregularities similar to those produced during various neurosurgical procedures. These irregularities are markedly potentiated by hypothermia prior to the onset of a cold induced "pseudoanesthetic" state. Pharmacological agents capable of abolishing these irregularities at central or peripheral junctions have been listed. Centrally induced cardiac irregularities can be adequately prevented by judicious use of these and other related agents.

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