CHLORPROMAZINE: REVIEW AND INVESTIGATION AS A PREMEDICANT IN ANESTHESIA

Allen B. Dobkin, M.D., Richard G. B. Gilbert, M.B.
K. I. Melville

Dimethylaminopropyl-N-chlorophenothiazine hydrochloride was developed as a result of systematic studies by workers in France directed to find a phenothiazine derivative with greater central depressant action than promethazine. This drug appears to have great value in anesthesiology. This communication reports laboratory and clinical data in which this substance, known by the generic name chlorpromazine, was evaluated as a premedicant drug for general and regional anesthesia.

Prior to employing chlorpromazine in clinical anesthesia, the authors investigated the pharmacological and the physiological effects of chlorpromazine in animals and in normal human volunteers in order to supplement the data of Courvoisier (1) and of Laborit (2, 3). In reported studies (4-6), chlorpromazine was found to be as safe as the commonly used narcotic and sedative drugs, and at the same time it appeared to have several attributes which would facilitate the induction and the maintenance of what Little and Stephen graphically have described as combined anesthesia or modern balanced anesthesia (7). On the basis of preliminary data, it seemed desirable to extend the controlled studies in order to avoid what Griffith recently pleaded against in his paper, "The Abuse of Drugs in Anesthesiology" (8), and what Beecher has condemned editorially in "Anesthesia and the Old-Time Shotgun Prescription" (9). The added purpose of this cautious approach was to avoid acute lethal toxicity which may have resulted from combining chlorpromazine with the cardiotoxic drugs noted by Calesnick et al. (10) and Hewer (11) which are employed daily by anesthesiologists.

Chemistry

Chlorpromazine is available commercially as the hydrochloride. In Europe and Canada it is known as largactil, R.P. 4560, and M & B 2378 and in the United States as Thorazine® and 2601A SKF. It has the following structural formula:

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The molecular weight is 355.3, and the melting point is about 195 C. It is a near white crystalline powder, with a slightly pungent odor. The powder and the solution are sensitive to light. It is soluble in water 1:2.5 ml., and in methyl alcohol, ethyl alcohol, and chloroform. It is insoluble in benzene and ether.* The 2.5 per cent aqueous solution is clear and has a pH of 5.3 to 5.6. In normal saline, this aqueous solution becomes milky in greater volumes than 10 ml. It remains clear in 5 per cent Demerol®. 1 per cent morphine, 0.05 per cent atropine, and 10 per cent procaine.

**Toxicity**

Clinical experience shows that there appear to be no disturbing side effects or toxicity with prolonged use in man if a dose of 150 mg. daily by mouth, or 50 mg. daily intramuscularly, is not exceeded. Local irritation is avoided with intramuscular administration if 0.5 per cent aqueous solution is injected deeply into the gluteal or the biceps muscle. Intravenous administration must be given in less than 0.25 per cent solution by slow injection to avoid local irritation and cardiovascular and respiratory depression (6). The single lethal dose in animals varies from 15 to 75 mg. per Kg., depending on species and route of administration. Daily subcutaneous injection of 20 mg. per Kg. for one month in dogs causes no mortality. Studies on absorption and excretion indicate that chlorpromazine undergoes very marked degradation in the body, as only traces have been found in the blood and the urine (1).

**Pharmacology**

In animal studies, Courvoisier (1) reported that chlorpromazine induces somnolence, locomotor difficulties, and central depression. The intensity of these effects increases in direct proportion to dosage. These actions form the basis for its clinical trials in psychiatry and anesthesiology.

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Investigation of Chlorpromazine

Effect on Central Nervous System

The normal human subject (6) becomes drowsy and relaxed after an intravenous injection of 15 to 25 mg. of chlorpromazine. This effect lasts from 4 to 6 hours. The manic psychotic patient (12, 13) becomes lethargic, and assaultive behavior ceases. These patients become easily accessible and respond immediately and relevantly to questions even if disturbed during sleep. However, they appear to lack spontaneous interest in their environment. In the acute and the chronic alcoholic (14), poststoloholic psychomotor agitation accompanying withdrawal does not occur. The nausea and the vomiting produced by disulfiram are suppressed, and the patient becomes drowsy and calm and may fall asleep.

In the electroencephalogram (6), the pattern of the normal awake subject is changed to a sleep pattern, but the subject is aroused easily. Table 1 summarizes data on the effect of chlorpromazine on the human EEG. The data on the resting records taken immediately prior to the test were normal in each of these cases.

The effect on acetylcholine release from cat cortex was studied by the authors in the laboratory of Prof. F. C. MacIntosh (15), in the following manner: The test cat is anesthetized, using ethyl chloride spray on a gauze inhaler mask followed by ethyl ether. Tracheotomy is then performed and 1 mg. of atropine given intravenously. Anesthesia is maintained via the trachea, using 4 per cent ethyl ether in air delivered by a Connell anaesthesiometer (16). The skull over one hemisphere is removed and a flap of dura mater is raised. A lucite cup of 1 ml. volume is placed on the exposed surface of the cortex and sealed over a gyrus with stopcock grease. Into this receptacle, acetylcholine is collected. Eserine solution 1:10,000 is placed in this receptacle to prevent destruction of the acetylcholine. The assay cat is also anesthetized with ethyl-chloride-ether sequence and then maintained by a single intravenous injection of 80 mg. per Kg. of chloralose. Complete abdominal evisceration is then performed. A carotid artery is cannulated for direct blood pressure recording. Sensitivity of the assay cat is tested with 5 to 10 millimicrometers of acetylcholine. If sensitivity is low, eserine solution is administered. Acetylcholine collection and assays are carried out by the cat blood pressure technique described by MacIntosh and Perry (17). It was found that chlorpromazine almost completely suppressed acetylcholine release from the cat's cortex in doses of 30 mg. per Kg.

The preceding studies therefore were extended to determine the effect of a single intravenous dose of 25 mg. of chlorpromazine on acetylcholine release from human frontal cortex of patients with long-standing schizophrenia unresponsive to clinical therapy. Neurologists believe that these behavioral disturbances may be related to disturbances in acetylcholine synthesis and release from the cerebral cortex (18-21). Eight patients undergoing prefrontal lobotomy (McKenzie
TABLE I

UNANESTHETIZED HEALTHY SUBJECTS—EFFECT ON ELECTRO-ENCEPHALOGRAM

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Wt. (lbs.)</th>
<th>Ht. (in.)</th>
<th>Chlorpromazine IV. Dose (mg.)</th>
<th>Continuous Recordings After Chlorpromazine</th>
<th>Effect of Hyperventilation (in sitting posture)</th>
<th>Pharyngeal Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26</td>
<td>157</td>
<td>69</td>
<td>140</td>
<td>Large amount of rhythmic 6/sec. slow waves which appeared over both frontal and temporal regions combined with some 13-14/sec. sleep spindles</td>
<td>Slightly more effect, suggestive of cerebral ischemia accompanied by hypotension, dizziness and faintness</td>
<td>No abnormality</td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>147</td>
<td>69</td>
<td>90</td>
<td>Continuous picture of 3-4/sec. slow waves chiefly over vertex in frontal and central areas</td>
<td>High-voltage irregular 1.5-2/sec. slow waves over both frontal and temporal regions, accompanied by blurring of vision and faintness</td>
<td>No abnormality</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>154</td>
<td>69</td>
<td>50</td>
<td>Continuous picture of sleep patterns consisting of random slow waves and low-voltage sharp waves maximum in the central vertex position</td>
<td>No change in the EEG, but the patient felt very dizzy. Later, slow waves appeared suddenly on several occasions</td>
<td>No abnormality</td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>115</td>
<td>65</td>
<td>50</td>
<td>Low voltage 5-6/sec. slow waves and occasional sleep spindles indicative of a state of persistent drowsiness</td>
<td>Produced moderate 4-5/sec. slow-wave response accompanied by tachycardia, hypotension and faintness</td>
<td>No abnormality</td>
</tr>
<tr>
<td>5</td>
<td>27</td>
<td>148</td>
<td>71</td>
<td>25</td>
<td>Continuous sleep pattern showed typical irregular 3-4/sec. slow waves with spindles at 12-14/sec. with reversal of voltage in the central vertex position</td>
<td>No abnormality induced. Prestigmine, caffeine and sodium benzoate, and tension induced no change</td>
<td>No abnormality</td>
</tr>
<tr>
<td>6</td>
<td>57</td>
<td>150</td>
<td>67</td>
<td>25</td>
<td>No sleep pattern. Large amount of low-voltage fast-frequency waves probably due to tension state</td>
<td>No change</td>
<td>No abnormality</td>
</tr>
<tr>
<td>7</td>
<td>70</td>
<td>150</td>
<td>67</td>
<td>35</td>
<td>Drowsiness with typical changes consisting of 5-7/sec. irregular slow waves. Occasional low-voltage fast activity typical of sleep spindles. These patterns disappeared when the patient was aroused by noise or when spoken to</td>
<td>No change</td>
<td>No abnormality</td>
</tr>
</tbody>
</table>

* Data taken from Dobkin et al. (6).
procedure) for schizophrenia were investigated. Acetylcholine assay on cat blood pressure was carried out on the tissue removed before and after the administration of the chlorpromazine. Slight depression of acetylcholine release occurred in the majority of these subjects.

Marthé Vogt (22) has studied the effects of narcotic and anesthetic drugs on the sympathin (adrenalin and noradrenalin) content of the hypothalamus. She found that some drugs, when acting over a period of at least three hours, caused a fall in the concentration of the cat's hypothalamic sympathin. This fall was not found unless the drugs also stimulated the adrenomedullary secretion by their central action. The reverse, however, did not hold, and occasionally there was adrenalin secretion without depletion of hypothalamic sympathin. She also found that asphyxia lowered hypothalamic sympathin, provided that the asphyxia was severe enough to cause considerable medullary secretion. Adrenal denervation to prevent medullary secretion did not interfere with the depleting action of drugs on the sympathin in the hypothalamus. In the dog, ether and morphine reduced the concentration of noradrenalin in the hypothalamus and in the midbrain. Chlorpromazine had no effect on the sympathin content of the hypothalamus. Neither did it antagonize the stimulation of the hypothalamus produced by morphine as measured by a loss in hypothalamic sympathin, or by the secretion of adrenal medullary amines (23).

The effects of the convulsant drugs strychnine, picrotoxin, and metrazol® were not suppressed by chlorpromazine (6). However, Courvoisier (1) was able to antagonize convulsions induced by nicotine and nikethamide.

Conditioned-reflex responses in maze-trained rats were altered by chlorpromazine. The drug induced lethargy and the rats disregarded rewards for running the maze (24).

The use of chlorpromazine with anesthetic agents indicates that chlorpromazine induces general mild depression of all vital organs (6). This effect appears to be additive to all forms of narcotics, relaxants, and anesthetic drugs in both animals (1) and man (6).

Rouchy, Boyd and others (25–28) reported the powerful antiemetic action of chlorpromazine. This effect was found to be of excellent clinical value (6, 29–31).

**Peripheral Nervous System**

Sympathetic: 1 to 2 mg./Kg. induces a widespread depression of the sympathetic nervous system in man, as evidenced by bilateral Horner's syndrome, marked warming of the extremities, and orthostatic hypotension.

Parasympathetic: parasympathetic block of some degree is evident. Clinically, there is depression of salivary and gastric secretion (6). Hutcheon (32) has demonstrated the inhibition of salivary secretion
induced by infusion of carbachol in anesthetized dogs by related pheno-
thinazine derivatives. Inhibition of the acetylcholine induced contrac-
tions of the isolated guinea pig ileum and lengthening of the refractory
period of the isolated rabbit auricles as measured by the decrease in
the maximal rate of stimulation also have been demonstrated.

Antihistaminic effect was reported to be weak (1).

No block occurs at the myoneural junction (6), either of the com-
petitive type as represented by d-tubocurarine, or of the depolariz-
ing type as represented by decamethonium. Clinically, however, there
is considerable motor weakness as measured by the dynamometer.
This effect lasts several hours and is proportional to the dosage. The
site of action for this effect may be in the caudal portion of the reticular
activating system. Topical anesthetic effect has been reported (6).

Possible Site of Action in the Nervous System. In 1945, Gellhorn
(33) reported the close relationship between the reticular formation
in the brain and control of the sympathetic nervous system. Recent
studies by Magoun (34-38) have brought to the fore the important
role of the reticular formation of the brain stem in regulating the
background activity of the remainder of the central nervous system.
This formation lies parallel with the long afferent and efferent neural
system. It receives connections from both of them, and exerts in-
fluences of its own at higher and lower levels. Its cephalic influences
upon the cerebral hemispheres provide the substrate of a state called
wakefulness upon which most higher functions of the nervous system
depend. Its caudal influences upon spinal levels contribute to optimum
motor performance. The medial reticular formation appears to con-
trol the central excitatory state, in both a facilitatory and a depressing
manner.

French et al. (39, 40) showed that all sensory paths to the cortex
deliver collaterals into this subcortical activating mechanism and
mediate arousal through it. They further demonstrated a differential
block of ascending conduction in this central arousing mechanism by
pentobarbital or ether. Arduini and Arduini (41) tested the effect of
depressant and excitant drugs upon the activity in the central brain
stem and in direct sensory paths to the cortex. They compared their
findings with the results of interfering with the metabolism of the brain
and found that hypoglycemia induced by sodium pentobarbital, ether,
chloralosane, sodium cyanide, and insulin all reduced potentials in
the medial reticular formation. On the other hand, metrazol and
strychnine produced a striking augmentation of these potentials. These
studies show the great susceptibility of the reticular formation of
the brain stem to anesthetic and depressant drugs. They noted that
ascending conduction in the medial brain stem is reduced or abolished
by depressant drugs while sensory pathways continue to transmit
afferent impulses to the cortex without impairment. These effects
are duplicated by interfering with brain metabolism with induced
hypoxia and hypoglycemia, while conduction in the reticular formation is enhanced by the convulsant drugs.

In view of the clinical effects noted with chlorpromazine in animals and in man, it would appear that its primary effect involves reducing the stimuli which reach the medial reticular formation, inducing a state of motor depression at the spinal level, and annulling the state of wakefulness by cephalic influences upon the cerebral hemispheres, while permitting normal sensory and cerebration responses. The normal cortical release of acetylcholine and the peripheral release of sympathin (adrenalin and noradrenalin) seem to be involved in these effects.

**TABLE 2**

**UNANESTHETIZED HEALTHY SUBJECTS—METABOLIC STUDIES**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Wt. (lbs.)</th>
<th>Ht. (in.)</th>
<th>Study Before Drug</th>
<th>Study After Drug</th>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>Rate of Resp. (min.)</td>
<td>Oxygen Consump. (cc./min.)</td>
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<tr>
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<td>151</td>
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<td>42</td>
<td>154</td>
<td>68</td>
<td>13</td>
<td>190</td>
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<tr>
<td>10</td>
<td>46</td>
<td>145</td>
<td>60</td>
<td>17</td>
<td>300</td>
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<tr>
<td>Averages</td>
<td>33</td>
<td>150</td>
<td>67</td>
<td>17</td>
<td>248</td>
</tr>
</tbody>
</table>

* Data taken from Dobkin et al. (6).

**Effect on Metabolism**

In animal studies, a reduction in cerebral oxygen uptake of up to 20 per cent occurred. This effect lasted at least six hours after a single subcutaneous dose of 10 to 20 mg. per Kg. (1). In man (6), there is no significant change with doses up to 2 mg. per Kg. Table 2 summarizes duplicate studies of the effect on metabolism of a premedicant dose of chlorpromazine on 10 healthy males.

**Effect on the Blood Pressure and on the Heart**

The Blood Pressure: Following an intravenous dose of 1 mg./Kg. in a normal man, the blood pressure becomes orthostatic, and usually responds instantly to posturing (6). This effect is due to marked peripheral vasodilatation (5).

The Electrocardiogram: Transient tachycardia sometimes briefly follows intravenous injection of chlorpromazine in the normal man.
An initial sinus arrhythmia is often noted. These are not persistent with continuous medication if the dose is not excessive. Table 3 summarizes the findings in 15 healthy male subjects with regards to the cardiovascular effects of chlorpromazine. In patients under general anesthesia, the injection of chlorpromazine sometimes produces a persistent tachycardia, which may last several hours.

The Cardiac Reflexes: Courvoisier (1) demonstrated that chlorpromazine was more effective than dibenamine\textsuperscript{5}, yohimbine, or 933F in protecting against adrenalin-induced ventricular fibrillation following sensitization of the heart with aconitine nitrate and adenosine phosphate acid in rabbits. Laborit (42) demonstrated that chlorpromazine has a stabilizing effect on the heart during hypothermia, and greatly reduced the possibility of ventricular fibrillation in dogs cooled to low temperatures (below 80 F.). Ripstein also made this observation (43).

Pharmacologically, this effect appeared logical in view of the findings of Levitan and Scott (44) working in these laboratories. They demonstrated the inhibition of chloroform-adrenalin fibrillation by the antihistaminics. Orians showed that the antihistaminics have a quinidine-like effect on myocardial conduction. This partially may explain the protective action (45).

The problem of emergency treatment of serious cardiac arrhythmias has yet to be solved effectively (46) and the anesthesiologist still may be harassed by it most commonly during intrathoracic and intracardiac operative procedures. This problem occurs particularly during cyclopropane anesthesia (47-51) and when anesthesia is supplemented by hypothermia (51-55). Therefore it was considered important to add the premedicant use of chlorpromazine to the many attempts at preventing serious cardiac arrhythmias during anesthesia (56-76).

In testing chlorpromazine as a prophylactic agent against the increased reflex irritability of the heart during anesthesia, an important clinical problem had to be considered. During general and regional anesthesia, it was noted that patients who became hypotensive during the surgical operation resisted the effects of the usual doses of vaso-pressor drugs. This effect extended into the postoperative period. It subsequently was found that posturing, pressure bandages on the legs, or relatively larger doses of pressor amines were required to produce an effective elevation of the blood pressure. Phenylephrine and arterenol were most effective.

Melville (76) showed that chlorpromazine inverts the response to infused catecholamines to a striking degree in pentobarbitalized and morphinized cats and dogs. This effect was less marked if the animals were atropinized, vagotomized, or pithed. Chloroform-epinephrine-induced ventricular fibrillation was averted by protecting the animals with a premedicant dose of chlorpromazine. However, irregularities induced by ouabain and pressor pituitary extract were not prevented.
## Investigation of Chlorpromazine

### TABLE 3

<table>
<thead>
<tr>
<th>Subject</th>
<th>ECG Before Drug (Standard Leads I, II, III)</th>
<th>Vagal Nerve Stimulation (used as a control)</th>
<th>Pupil Response</th>
<th>Mean Arterial Blood Pressure</th>
<th>Heart Rate (20 Min. After Drug)</th>
<th>1 Min. After Drug</th>
<th>Vial Sign 1 Min. After Drug</th>
<th>Averages of 3–6 Min. Readings</th>
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<tr>
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<td>Normal record</td>
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<td>Normal response</td>
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Finkelstein (77) investigated the mechanism of these actions using the cat heart papillary muscle technique of Cattell and Gold and found that chlorpromazine in concentration of 0.1 to 0.5 mg./100 ml. of bathing fluid produced a reversible negative inotropic action on the heart, resulting in 40 to 60 per cent reduction in the contractile force, and 100 to 300 per cent increase in the threshold voltage required to drive the muscle. This indicated marked reduction in myocardial irritability. Low concentrations of chlorpromazine also depressed the automaticity of the heart and greatly reduced the positive inotropic response to the catecholamines.

Most of the commonly used sympathomimetic amines markedly accelerate the sino-auricular rate during cyclopropane anesthesia and may cause progressive disturbances similar to that seen with catecholamines (78-80). The blood-pressure effects of the sympathomimetic amines, with special reference to their antagonism by blocking drugs, have been studied by Melville and others (66-68, 70, 73, 81-86).

In the light of these findings, it was desirable to study both the effect of the catecholamines and the peripheral acting sympathomimetic amines during cyclopropane anesthesia following premedicant doses of chlorpromazine. The numerous factors involved in experimental production of cardiac arrhythmias during cyclopropane anesthesia were reviewed by Meek, in 1941 (87, 88). The theoretical considerations as to their cause, the mechanisms of their production and prevention, and the protective effect of drugs against epinephrine-induced arrhythmias have been inclusively reviewed by Dawes (89). These considerations guided the following experiments.

**Method**

Experiments were conducted on 15 medium size mongrel dogs with an average weight of 10.30 Kg. Electrocardiograms (lead II) were taken with a Sanborn direct writing Viso-cardiette prior to and after premedication; after intervals of 25 per cent (light) and 40 per cent (deep) cyclopropane anesthesia; and continuously prior to, during, and following intravenous injection of test drugs. The stylus of the ECG was under direct surveillance by one of us throughout each experiment. If arrhythmias were seen when the recorder was off, a tracing was recorded promptly.

After cyclopropane anesthesia was induced, the blood pressure was continuously recorded directly from the right common carotid artery by a mercury manometer and kymograph. On the first 2 dogs premedicated with 1 mg./Kg. of chlorpromazine, arterial blood samples were collected anaerobically for duplicate oxygen and carbon dioxide analyses (modified Van Slyke and Neill method) (90). Samples were collected before and thirty minutes after induction of 25 per cent cyclopropane anesthesia.

The dogs were premedicated intravenously with morphine and atropine (1 mg./Kg. of each) in 2 experiments, and with chlorpromazine (0.5 mg./Kg., 1 dog), (1 mg./Kg., 11 dogs), and (5 mg./Kg., 1 dog).

Ten to fifteen minutes following premedication, anesthesia was induced by
INVESTIGATION OF CHLORPROMAZINE

oxygen-cyclopropane sequence until stabilized at a 25 per cent cyclopropane and 75 per cent oxygen mixture. A specially prepared inhaler mask lined with sponge rubber was used to minimize anatomical dead space. Endotracheal intubation was not used in these studies to eliminate the possibility of reflex cardiac disturbances. In each experiment, the anesthetic mixture was delivered from an anesthetic gas machine by a semiclosed system with circle filter CO₂ absorber provided with fresh soda lime. Gas flows were set at 2 to 3 liters per minute in order to assure a constant cyclopropane-oxygen concentration in the 5-liter rebreathing bag. The pop-off valve was open to prevent positive pressure building up in the system.

![Graph showing effects of premedication with morphine and atropine on a 12.9 Kg. male dog.]

A. Control before premedication—sinus arrhythmia at 90/min.
B. Premedication with 1 mg./Kg. of morphine and atropine intravenously—paroxysmal auricular tachycardia at 230/min. 1. 20 per cent cyclopropane—80 per cent oxygen anesthesia started 25 min. after premedication and maintained for 20 min., followed by the injection of 0.002 mg./Kg. of adrenalin: time zero: paroxysmal auricular tachycardia at 180/min. +15 sec.: paroxysmal auricular tachycardia at 225/min. with runs of ventricular extrasystoles. +75 sec.: paroxysmal auricular tachycardia at 214/min. 2. 20 per cent cyclopropane—90 per cent oxygen anesthesia maintained for a further 5 min., followed by the injection of 0.02 mg./Kg. of adrenalin: time zero: paroxysmal auricular tachycardia at 187/min. +6 sec.: onset of ventricular tachycardia which rapidly changed to ventricular fibrillation, accompanied by abrupt precipitous fall in blood pressure.

With the cyclopropane in 25 per cent concentration, the lid reflex was absent, but intercostal paralysis was not evident in the animals premedicated with chlorpromazine. This may have been due to the stimulation of respiration by this substance reported to occur in animals by Courvoisier (1) but absent in man (6). The 2 dogs premedicated with morphine and atropine developed progressive intercostal paralysis and apnea at this concentration so that it was necessary to carry out the tests using 15 to 20 per cent cyclopropane and assisted respiration. When the anesthesia was deepened to 40 per cent cyclopropane with 60 per cent oxygen, intercostal paralysis and apnea rapidly ensued in all the dogs, and respiration was maintained by rhythmic manual compression of the rebreathing bag. After three to six minutes at this concentration, the blood pres-
Fig. 2. 15.35 Kg. male dog premedicated with chlorpromazine which succumbed after multiple injections of catecholamines.

A. Control before premedication—slight sinus arrhythmia at 150/min.

B. 14 min. after premedication with 1 mg./Kg. of chlorpromazine—slight sinus arrhythmia at 130/min. and absent Q waves. 1. 16 min. after 25 per cent cyclopropane—75 per cent oxygen anesthesia started, injection of 0.002 mg./Kg. of adrenalin: time zero: sinus rhythm at 136/min. + 30 sec.: paroxysmal supraventricular tachycardia at 187/min. + 60 sec.: sinus rhythm at 115/min. with inverted T waves. Note that blood pressure response to adrenalin was inverted. 2. 22 min. after 25 per cent cyclopropane—75 per cent oxygen anesthesia started, injection of 0.002 mg./Kg. of noradrenalin: time zero: sinus rhythm at 136/min. + 6 sec.: auricular fibrillation at 187/min. with ventricular extrasystoles. + 15 sec.: sinus rhythm at 136/min. with inverted T waves. + 75 sec.: sinus rhythm at 115/min. with upright T waves. 3. 29 min. after 25 per cent cyclopropane—75 per cent oxygen anesthesia started, injection of 0.02 mg./Kg. of adrenalin: time zero: sinus rhythm at 125/min. + 6 sec.: supraventricular tachycardia at 187/min. + 9 sec.: supraventricular tachycardia at 240/min. with ventricular extrasystoles. + 12 sec.: auricular fibrillation.

C. + 3 min.: sinus rhythm at 136/min. with inverted T waves. 4. 36 min. after 25 per cent cyclopropane—75 per cent oxygen anesthesia started, injection of 0.2 mg./Kg. of adrenalin: time zero: auricular fibrillation. + 12 sec.: auricular fibrillation with multifocal ventricular extrasystoles. + 78 sec.: auricular fibrillation with multifocal ventricular extrasystoles.

C. + 6 min.: cyclopropane 40 per cent and oxygen 60 per cent maintained for 3 min.—sinus rhythm at 150/min. with inverted T waves. 5. 46 min. after 25 per cent cyclopropane—75 per cent oxygen anesthesia and 8 min. of 40 per cent cyclopropane—60 per cent oxygen anesthesia, injection of 0.02 mg./Kg. of adrenalin:—sinus rhythm at 150/min. → paroxysmal supraventricular tachycardia → ventricular extrasystoles → ventricular fibrillation.
Fig. 3a. 11.7 Kg. female dog premedicated with 5 mg./Kg. of chlorpromazine.

A. Control before premedication—sinus arrhythmia at 120/min.
B. 6 min. after 5 mg./Kg. of chlorpromazine—sinus arrhythmia at 90 min. + 1 min.: similar.
C. 25 per cent cyclopropane—75 per cent oxygen for 20 min.—sinus rhythm at 125/min. with inverted T waves. 1. Injection of 0.4 mg./Kg. of adrenalin: time zero: sinus rhythm at 125/min. with inverted T waves. + 6 sec.: supraventricular tachycardia at 214/min. + 15 sec.: multifocal ventricular extrasystoles. + 6 sec.: ventricular tachycardia at 275/min. + 1 min.: ventricular tachycardia—auricular fibrillation.
C. 3 min. after injection: auricular fibrillation at 360/min. + 45 sec.: similar. + 18 min.: auricular fibrillation at 300/min.
C. 37 min. of 25 per cent cyclopropane—75 per cent oxygen, deepened to 40 per cent cyclopropane—60 per cent oxygen for 6 min. auricular fibrillation with ventricular rate of 140/min. 2. After 8 min. of deep cyclopropane anesthesia, injection of 2 mg./Kg. of neosympheine: time zero: auricular fibrillation with ventricular rate of 160/min. + 24 sec.: auricular fibrillation with ventricular rate of 120/min. + 52 sec.: auricular fibrillation with ventricular rate of 130/min. + 30 sec.: ventricular tachycardia at 250/min.
C. + 6 min.: cyclopropane anesthesia lightened to 25 per cent and maintained for 10 min. —auricular fibrillation with ventricular rate of 320/min. 3. Injection of 1 mg./Kg. of effortil: time zero: auricular fibrillation with ventricular rate of 320/min. (due to persistent effect of neosympheine). + 21 sec.: similar. + 2 min.: paroxysmal supraventricular tachycardia at 300/min. Neo-sympheine produced an adequate pressor response.
sure gradually fell, so that the initial tests at this level were not delayed beyond about six minutes.

All the experiments were performed during the fifteen to sixty minutes after a stable level of 25 per cent cyclopropane anesthesia was attained. This permitted the equilibration of the anesthetic drug in the dog, and avoided the blocking of adrenalin effect due to prolonged cyclopropane anesthesia (91). The following drugs were tested: l-epinephrine 0.1 per cent (Suprarenin® bitartrate) and l-arterenol 0.1 per cent (Levophed® bitartrate monohydrate);* phenylephrine 1 per cent (Neo-synephrine® hydrochloride); M-1-36 1 per cent (effortil), obtained from Ingelheim (Germany) (92); methoxamine hydrochloride 2 per cent (Vasoxyl®); methamphetamine hydrochloride 2 per cent (Methedrine®);

Fig. 3b. Effect of premedication with chlorpromazine (1 mg./Kg.) and large dose of adrenalin during deep cyclopropane anesthesia. 1. 15 min. of 25 per cent cyclopropane—75 per cent oxygen—sinus arrhythmia at 65/min. 2. 6 min. of 40 per cent cyclopropane—60 per cent oxygen—partial heart block. 3. Injection of 0.4 mg./Kg. of adrenalin: time zero: partial heart block. + 6 sec.: partial heart block. 4. + 27 sec.: paroxysmal ventricular tachycardia. 5. + 60 sec.: complete A-V dissociation. 6. + 9 sec.: multifocal ventricular extrasystoles. 7. + 42 sec.: paroxysmal ventricular tachycardia. 8. + 65 sec.: ectopic auricular focus with inverted T waves. 9. + 3 min.: sinus rhythm at 100/min. with inverted T waves. 10. + 7 min.: ectopic auricular focus.

ephedrine hydrochloride 5 per cent; and mephentermine sulfate 1.5 per cent (Myamine® sulfate);† and laboratory pituitary preparation containing 10 pressor units and 0.5 oxytocic unit per ml. (referred to in figure 10 as "pitressin").

All drugs were administered by rapid injection into an exposed femoral vein. The doses of drugs selected in these experiments were chosen according to previous reports on equipressor effects (78, 93, 94) and with reference to the findings in clinical anesthesia (6).

**Results**

*Effect with Morphine and Atropine:* Figure 1 shows the response of a dog to an intravenous injection of 0.002 mg./Kg. of adrenalin following premedication with 1 mg./Kg. of each of morphine and atropine and maintained for twenty

*Supplied by Sterling Winthrop Research Institute.
†Supplied by Wyeth, Inc.
minutes under 20 per cent cyclopropane anesthesia. The subsequent intravenous injection of 0.02 mg./Kg. of adrenalin produced the usually observed rapid rise in blood pressure which is reversed abruptly to a precipitous fall accompanied by ventricular fibrillation.

**Effect with Chlorpromazine:** Therapeutic doses of adrenalin produced a fall in blood pressure without changing the cardiac rhythm (fig. 2[1] and fig. 4, upper). Large doses, which are frequently lethal, produced an elevation in blood pressure but failed to produce ventricular fibrillation during general anes-

![Image](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931678/)

**Fig. 4.** 1. Effect of premedication with 1 mg./Kg. of chlorpromazine and 25 per cent cyclopropane-75 per cent oxygen anesthesia at 2 dose levels of adrenalin.

Upper A. 15 min. anesthesia (10.6 Kg. female dog) 0.002 mg./Kg. of adrenalin. 1. time zero: sinus arrhythmia at 120/min. 2. + 1 min.: sinus rhythm at 125/min. with inverted T waves. Note inverted blood pressure response.

Upper B. 24 min. anesthesia 0.25 Kg. male dog 0.2 mg./Kg. of adrenalin. 1. time zero: sinus arrhythmia at 107/min. 2. + 6 sec.: paroxysmal auricular tachycardia with ventricular extrasystoles. 3. + 12 sec.: ectopic auricular beats. 4. + 40 sec.: paroxysmal auricular tachycardia at 230/min. with ventricular extrasystoles. 5. + 80 sec.: similar at 136/min. and slight notching of T waves. 6. + 3 min.: sinus arrhythmia at 107/min. as at time zero. Note inverted blood pressure response.

II. Effect of premedication with 1 mg./Kg. of chlorpromazine and 25 per cent cyclopropane-75 per cent oxygen anesthesia at 2 dose levels of noradrenalin.

Lower A. 15 min. anesthesia 15.3 Kg. male dog 0.002 mg./Kg. of noradrenalin. 1. time zero: sinus arrhythmia at 75/min. 2. + 1 min.: sinus arrhythmia at 60/min. 3. + 4 min.: sinus arrhythmia at 80/min. Note significant pressor response.

Lower B. Same dog. 0.02 mg./Kg. of noradrenalin. 1. time zero: sinus arrhythmia at 78/min. 2. + 1 min.: idioventricular rhythm at 63/min. 3. + 1 min.: sinus bradycardia or ectopic auricular focus. 4. + 3 min.: sinus bradycardia or ectopic auricular focus. 5. + 2 min.: nodal rhythm at 80/min. This dose produced a good pressor response.
thesia with cyclopropane in a concentration of 40 per cent (fig. 3a[1]). During general anesthesia using cyclopropane in 40 per cent concentration, one of 12 dogs developed ventricular fibrillation following 0.02 mg./Kg. of adrenalin (fig. 2[5]). In the remaining 11 dogs, doses as high as 0.4 mg./Kg. of adrenalin failed to produce ventricular fibrillation (fig. 3b).

Noradrenalin in dose of 0.002 to 0.2 mg./Kg. invariably produced an adequate rise in the blood pressure without seriously disturbing the cardiac rhythm (fig. 2[2] and fig. 4, lower).

Neo-syneprine in doses of 0.25 to 1 mg./Kg. produced an adequate rise in blood pressure in light and deep anesthesia without seriously disturbing the cardiac rhythm (fig. 3a[2], fig. 5, fig. 8).

Fig. 5. I. Effect of premedication with 1 mg./Kg. of chlorpromazine and 25 per cent cyclopropane-75 per cent oxygen anesthesia at 2 dose levels of neo-syneprine.

Upper A. 21 min. anesthesia. 9.40 Kg. male dog 0.25 mg./Kg. neo-syneprine. 1. time zero: regular rhythm from ectopic auricular focus. 2. +6 sec.: sinus arrhythmia. 3. +24 sec.: sinus arrhythmia with ventricular extrasystoles. 4. +4 min.: sinus arrhythmia. 5. +3 min.: regular rhythm. Note moderate pressor response.

Upper B. 32 min. anesthesia. 8.55 Kg. male dog 1.0 mg./Kg. neo-syneprine. 1. time zero: auricular paroxysmal tachycardia. 2. +9 sec.: sinus arrhythmia. 3. +36 sec.: sinus arrhythmia at a faster rate. 4. +5 min.: auricular paroxysmal tachycardia at 250/min. Note marked pressor response.

II. Effect of premedication with 1 mg./Kg. of chlorpromazine and 25 per cent cyclopropane-75 per cent oxygen anesthesia at 2 dose levels of effitol.

Lower A. 21 min. anesthesia. 8.55 Kg. male dog 0.25 mg./Kg. effitol. 1. time zero: sinus arrhythmia at 107/min. 2. +15 sec.: paroxysmal supraventricular tachycardia at 260/min. 3. +1 min.: unchanged. 4. +8 min.: unchanged. Note inverted pressor effect.

Lower B. Same dog. 46 min. anesthesia 1.0 mg./Kg. of effitol. 1. time zero: sinus tachycardia at 106/min. 2. +9 sec.: paroxysmal auricular tachycardia at 250/min. 3. +1 min.: paroxysmal auricular tachycardia at 300/min. 4. +20 min.: sinus rhythm at 105/min. Note inverted pressor response and marked tachycardia.
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Effortil in dosage of 0.25 to 1 mg./Kg. produced a fall in blood pressure during light and deep anesthesia, accompanied by a prolonged supraventricular tachycardia (figs. 5 and 8). After prolonged anesthesia, a moderate elevation of pressure may occur (fig. 3a[3]).

Methedrine in dosage of 2.5 mg./Kg. during light and deep cyclopropane anesthesia produced a significant rise in blood pressure without seriously affecting the cardiac rhythm (figs. 6 and 9).

**Fig. 6.** I. Effect of premedication with 1 mg./Kg. of chlorpromazine and 25 per cent cyclopropane–75 per cent oxygen anesthesia. 9.90 Kg. male dog. 2.5 mg./Kg. methedrine. 22 min. anesthesia. 1. time zero: sinus rhythm at 140/min. with inverted T waves. 2. +3 sec.: similar. 3. +30 sec.: similar at 150/min. 4. +2 min.: ectopic auricular foci. 5. +8 min.: similar. 6. +15 min.: similar. Note adequate pressor response.

II. Effect of premedication with 1 mg./Kg. of chlorpromazine and 25 per cent cyclopropane–75 per cent oxygen anesthesia.

A. 9.40 Kg. male dog. 0.25 mg./Kg. vasoxyl. 18 min. anesthesia. 1. time zero: sinus arrhythmia at 78/min. 2. +3 sec.: similar. 3. +9 sec.: similar. 4. +36 sec.: similar. 5. +7 min.: sinus arrhythmia at 140/min. Note poor pressor response.

B. 10.5 Kg. male dog. 1.0 mg./Kg. vasoxyl. 38 min. anesthesia. 1. time zero: sinus arrhythmia at 108/min. 2. +3 sec.: ectopic auricular focus. Rate 126/min. 3. +9 sec.: similar. 4. +4 min.: similar. 5. +7 min.: sinus tachycardia at 187/min. Note good pressor response.

Vasoxyl in dosage of 1 to 2 mg./Kg. during light and deep cyclopropane anesthesia produced a slight to moderate rise in blood pressure without significant effect on the cardiac rhythm (figs. 6 and 9).

Ephedrine in large dosage (5 mg./Kg.) produced an elevation in blood pressure during light anesthesia (fig. 7) but enhanced the subsequent possibility of adrenalin-induced ventricular fibrillation (noted in 2 experiments). In view of this, and tachyphylaxis with ephedrine, no studies were carried out with deep anesthesia.
Wyamine® in doses of 1 to 5 mg./Kg. lowered the blood pressure during light and deep cyclopropane anesthesia. Cardiac rhythm is not affected seriously.

Pituitary extract in doses of 20 pressor units administered during deep cyclopropane anesthesia and low blood pressure produced a substantial pressure response without deteriorating the cardiac status (fig. 10).

There was no significant change in the oxygen content and the carbon dioxide content in the 2 animals checked.

Fig. 7. I. Effect of premedication with 1 mg./Kg. of chlorpromazine and 25 per cent cyclopropane-75 per cent oxygen anesthesia. 9.9 Kg. male dog. 5 mg./Kg. ephedrine. 30 min. anesthesia. 1. time zero: sinus arrhythmia at 170/min. 2. +6 sec.: sinus arrhythmia. 3. +27 sec.: sinus arrhythmia. 4. +1 min.: sinus arrhythmia. 5. +1 min.: sinus arrhythmia. Note moderate pressor response with very large dose of ephedrine.

II. Effect of premedication with 1 mg./Kg. of chlorpromazine and 25 per cent cyclopropane anesthesia. 10.2 Kg. male dog. 1 mg./Kg. wyamine. 31 min. anesthesia. 1. Control before premedication: sinus rhythm at 125/min. 2. time zero: similar with inverted T waves at 125/min. 3. +6 sec.: similar with inverted T waves at 113/min. 4. +30 sec.: similar with inverted T waves at 113/min. 5. +30 sec.: similar with inverted T waves at 160/min. 6. +2 min.: similar with inverted T waves at 136/min. 7. +1 min.: similar with inverted T waves at 160/min. Note inverted pressor effect.

Comments

Chlorpromazine provides significant protection against adrenalin-cyclopropane arrhythmias. However, the pressor effect of adrenalin is inverted when therapeutical doses are employed. Neo-synephrine, norepinephrine, methedrine and vasoxylin in decreasing order of effectiveness produce pressor effects in larger than therapeutic doses without serious cardiac effects. The pressor response to wyamine and effortil is inverted. The pressor response to ephedrine is very weak. Pressor pituitary preparation induces an adequate pressor response without the serious effect on the heart usually seen during cyclopropane anesthesia.
Effectiveness as Premedication

Chlorpromazine may be effective in premedication through the following activities: it produces sedation in the normal, in the excited psychotic, and in the alcoholic patient; it depresses conditioned reflexes and reflexes which may be mediated by acetylcholine, adrenalin, or histamine; it dries salivary secretions; it depresses gastric secretion and motility; it depresses nausea and vomiting of central and of drug-induced origin. Protection against epinephrine-induced irritability of the heart during clinical anesthesia is evident. The depression of the sympathetic nervous system facilitates induction of hypothermic and hypotensive states if these are desired.

Cohen and Beecher (95) have reviewed and studied the use of narcotics in preanesthetic medication. They disagree with the commonly expressed aim of premedication with narcotics: to "lower the
Fig. 9. Effect of premedication with 1 mg./Kg. of chlorpromazine and 40 per cent cyclopropane—60 per cent oxygen anesthesia.

I. 10.5 Kg. male dog. 2 mg./Kg. vasoxyl. Deep anesthesia stable for 5 min. 1. Control (25 per cent cyclopropane anesthesia); slight sinus arrhythmia at 100/min. 2. time zero: similar. 3. + 18 sec.: ectopic P waves. 4. + 1 min.: auricular fibrillation and slight depression of ST segment. 5. + 3 min.: sinus rhythm; marked Q waves; marked ST segment depression. Note good pressor response.

II. 9.90 Kg. male dog. 2.5 mg./Kg. methedrine. Deep anesthesia stable for 6 min. 1. 4 min. deep anesthesia—ectopic auricular focus. Ventricular rate at 215/min. 2. time zero: marked sinus arrhythmia; inverted T waves. 3. + 12 sec.: unchanged. 4. + 1 min.: unchanged. 5. + 1 min.: unchanged and more rapid rate. 6. + 1 min.: unchanged and more rapid rate. Note good pressor response.

III. 10.2 Kg. male dog. 5 mg./Kg. wyamine. Deep anesthesia stable for 6 min. 1. time zero: sinus rhythm at 93/min. 2. + 1 min.: P wave changed indicating slightly ectopic auricular pacemaker. 3. + 3 min.: sinus rhythm at 136/min. Note inverted pressor effect.
metabolic rate' so that 'anesthesia will be easier' (96, 97). They do not believe that the metabolic rate is lowered by them or that their use would be a sound procedure. They conclude that, unless pain is present, there is no need for a narcotic in preanesthetic medication, and feel that adequate premedication is achieved with atropine and a barbiturate.

Griffith also feels that morphine, codeine, and Demerol can be replaced by barbiturates in premedication. However, he stresses that the dosage easily is underestimated in children and overestimated in the geriatric patient. An adequate dose is a critical factor if prolonged psychic trauma is to be avoided. In the words of Bourne, "The purpose of premedication in anesthesia is to obtund, to obfuscate, and to obnumbulate." That is, the patient must not arrive in the operating room in a state of agitation and aware of the preparations for anesthesia and operation.

In an attempt to determine whether chlorpromazine alone would produce the desired effect of premedication in clinical anesthesia, 12 patients were first studied to determine the effect of a single intravenous premedicating dose of chlorpromazine on the vital signs (table 4). No significant alterations were observed. A preliminary series of 164 patients were then observed by a method similar to that described by Cohen and Beecher, in order to permit valid comparison of our observations with those on morphine and atropine, pentobarbital and atropine, and atropine alone, which they reported. The patients in this study were males, and varied in age from 18 to 78 years. Except for slight variation, the average patient received 150 mg. of chlorpromazine by mouth the evening preceding surgery, and 50 mg. of chlorpromazine by deep intramuscular injection administered 1 hour preceding induction of anesthesia. No other drugs were ad-

Fig. 10. Effect of premedication with 1 mg./Kg. of chlorpromazine and 40 per cent cyclopropane—60 per cent oxygen anesthesia. 15.35 Kg. dog. 20 pressor units of pituitrin. Deep anesthesia stable for 6 min. 1. Control: auricular fibrillation, ventricular rate of 180/min. 2. + 6 sec.: auricular fibrillation—varying ectopic pacemaker. 3. + 2 min.: sinus rhythm with ventricular extrasystoles. 4. + 8 min.: sinus rhythm. Note that cardiac status was not affected by the pituitrin and a good pressor response was obtained.
### TABLE 4

**Unanesthetized Patients—Effect of Premedication**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Ht. (in.)</th>
<th>Wt. (lbs.)</th>
<th>Disease</th>
<th>Study 1, and 1/2 Hour Before Drug</th>
<th>Study 2, and 1 Hour After Drug</th>
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<tr>
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<td></td>
<td></td>
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<td></td>
<td>Pulse</td>
<td>Blood Pressure</td>
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<td>(min.)</td>
<td>(mm. Hg)</td>
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<td>1</td>
<td>24</td>
<td>66</td>
<td>138</td>
<td>Post-traumatic Neurosis</td>
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<td>170</td>
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<td>110/70</td>
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<td>130/80</td>
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<td>142</td>
<td>Peptic ulcer</td>
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<td>66</td>
<td>154</td>
<td>Bilat. ing. hernia</td>
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<td>120/78</td>
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<tr>
<td>Average</td>
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<td>67</td>
<td>154</td>
<td>Post-traumatic Neurosis</td>
<td>75</td>
<td>130/76</td>
</tr>
</tbody>
</table>

* Data from Dobkin et al. (6).
ministered for premedication. Upon arrival in the operating suite, the anesthesiologist asked the patient 9 direct, neutrally phrased questions, expecting a “yes” or “no” answer. These questions were as follows:

1. Are you comfortable?  Yes  No
2. Are you worried?    Yes  No
3. Are you tense?      Yes  No
4. Are you unusually happy?  Yes  No
5. Are you unusually sleepy?  Yes  No
6. Is your stomach upset?  Yes  No
7. Did you vomit?      Yes  No
8. Do you feel tired?   Yes  No
9. Do you see double?   Yes  No

The responses were recorded at the time of questioning. In a lateral column, the anesthesiologist recorded his own opinion as to the patient’s mental state by circling or checking the following points:

- Was the patient:
  1. Comfortable
  2. Worried
     Apprehensive
  3. Excited
     Relaxed
  4. Happy
     Euphoric
     Serene
  5. Drowsy
     Wide awake
  6. Talkative
  7. Nauseated
  8. Able to raise eyelids
  9. Able to hand grip firmly

The majority of these patients received Pentothal® and a muscular relaxant for induction, and were maintained with nitrous oxide and oxygen (1:1), with supplemental doses of pentothal and relaxants, as required. A small number of these patients received spinal analgesia. Data relative to the adequacy of premedication and the character of induction were noted in each case. Postoperatively, these patients were questioned further for information to reveal amnesia and their impression of the anesthetic induction. The postoperative course was closely followed and recorded. Table 5 summarizes the data relative to the premedicant value of chlorpromazine as determined in this study.

The extension of this series to premedication for all types of anesthetic procedures is substantiating the early conclusions drawn from this study (6). The various aspects of anesthesiology where the
### TABLE 5a
Premedication Study Table I: Pre-anesthetic State: Comparison of data from Cohen and Beecher with study at QMVH (Preliminary Report)

<table>
<thead>
<tr>
<th>Patients' Answers to Direct Questions</th>
<th>Morphine and Atropine 184 Cases Per Cent</th>
<th>Pentobarbital and Atropine 182 Cases Per Cent</th>
<th>Atropine (Alone) 192 Cases Per Cent</th>
<th>Chlorpromazine (Alone) 164 Cases Per Cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Discomfort</td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>2. Apprehension</td>
<td>32</td>
<td>35</td>
<td>36</td>
<td>25</td>
</tr>
<tr>
<td>3. Excitement</td>
<td>27</td>
<td>34</td>
<td>33</td>
<td>18</td>
</tr>
<tr>
<td>4. Euphoria</td>
<td>7</td>
<td>7</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>5. Sleepiness</td>
<td>17</td>
<td>15</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td>6. Nausea</td>
<td>3</td>
<td>4</td>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>

### TABLE 5b
Premedication Study Table II: Pre-anesthetic State: Comparison of data from Cohen and Beecher with study at QMVH (Preliminary Report)

<table>
<thead>
<tr>
<th>Anesthetists' Own Impression as to Patients' State</th>
<th>Morphine and Atropine 184 Cases Per Cent</th>
<th>Pentobarbital and Atropine 182 Cases Per Cent</th>
<th>Atropine (Alone) 192 Cases Per Cent</th>
<th>Chlorpromazine (Alone) 164 Cases Per Cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Discomfort</td>
<td>9</td>
<td>5</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>2. Apprehension</td>
<td>57</td>
<td>55</td>
<td>62</td>
<td>35</td>
</tr>
<tr>
<td>3. Excitement</td>
<td>16</td>
<td>16</td>
<td>21</td>
<td>9</td>
</tr>
<tr>
<td>4. Euphoria</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>5. Sleepiness</td>
<td>10</td>
<td>10</td>
<td>8</td>
<td>49</td>
</tr>
<tr>
<td>6. Nausea</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>7. Talkativeness</td>
<td>22</td>
<td>24</td>
<td>20</td>
<td>7</td>
</tr>
</tbody>
</table>

### TABLE 5c
Premedication Study Table III: Comparison of data from Cohen and Beecher with study at QMVH (Preliminary Report)

<table>
<thead>
<tr>
<th>Anesthetists' Characterization of Induction with Respect to Premedicating Agent</th>
<th>Morphine and Atropine 184 Cases Per Cent</th>
<th>Pentobarbital and Atropine 182 Cases Per Cent</th>
<th>Atropine (Alone) 192 Cases Per Cent</th>
<th>Chlorpromazine (Alone) 164 Cases Per Cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Smooth—adequate Slow</td>
<td>69</td>
<td>67</td>
<td>64</td>
<td>84</td>
</tr>
<tr>
<td>2. Difficult—Inadequate Stormy</td>
<td>31</td>
<td>33</td>
<td>36</td>
<td>15</td>
</tr>
<tr>
<td>3. Excessive</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1</td>
</tr>
</tbody>
</table>
TABLE 5D
PREMEDICATION STUDY TABLE IV: Comparison of data from Cohen and Beecher with study at QMVH (Preliminary Report)

<table>
<thead>
<tr>
<th>Postoperative Memory of Induction</th>
<th>Morphine and Atropine 184 Cases Per Cent</th>
<th>Pentobarbital and Atropine 182 Cases Per Cent</th>
<th>Atropine (Alone) 182 Cases Per Cent</th>
<th>Chlorpromazine (Alone) 184 Cases Per Cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Pleasant</td>
<td>73</td>
<td>70</td>
<td>73</td>
<td>60</td>
</tr>
<tr>
<td>2. Indifferent</td>
<td>22</td>
<td>27</td>
<td>20</td>
<td>37</td>
</tr>
<tr>
<td>3. Unpleasant</td>
<td>5</td>
<td>3</td>
<td>7</td>
<td>3</td>
</tr>
</tbody>
</table>

TABLE 5E
IMMEDIATE POSTOPERATIVE FOLLOW-UP (24 HRS.) OF PATIENTS PREMEDICATED WITH CHLORPROMAZINE (164 CASES) ALONE

1. Amnesia                          | 7 cases                                  | 4%                                          |
2. Unpleasant memory                | 6 cases                                  | 3%                                          |
3. Urinary retention                | 0 cases                                  | 0%                                          |
4. Urinary incontinence             | 6 cases                                  | 3%                                          |
5. Excessive secretions             | 8 cases                                  | 5%                                          |
6. Excessive diaphoresis            | 0 cases                                  | 0%                                          |
7. Shivering                        | 4 cases                                  | 2%                                          |
8. Postanesthetic hypotension       | 8 cases (below 100 mm. Hg)               | 5%                                          |
                                      | (responded well to Neo-synephrine)       |                                              |
9. Cardiac irregularities           | 0 cases                                  | 0%                                          |
10. Postanesthetic nausea or vomiting| (72 hr. follow up)                       | 2%                                          |
11. Prolonged spinal or sleep       | (4 hrs. + postop.)—14 cases              | 8%                                          |

TABLE 6
SUMMARY OF OBSERVED CLINICAL VALUE OF CHLORPROMAZINE (LARGACTIL) IN ANESTHESIA

<table>
<thead>
<tr>
<th>Excellent</th>
<th>Good—Fair</th>
<th>Contraindicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. General sedation</td>
<td>a. Early occlusive disease</td>
<td>2. Preoperative medication for:</td>
</tr>
<tr>
<td>b. Relief of vascular spasm</td>
<td>b. Chronic indolent ulcers</td>
<td>General anesthesia (add atropine)</td>
</tr>
<tr>
<td>c. Relief of thrombosis</td>
<td>c. Acute embolus</td>
<td>2. Respiratory depression</td>
</tr>
<tr>
<td>d. Relief of gastrointestinal spasm</td>
<td>d. Thrombosis</td>
<td></td>
</tr>
<tr>
<td>e. Relief of genitourinary spasm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Topical anesthesia</td>
<td>a. Psychomotor excitation</td>
<td></td>
</tr>
<tr>
<td>b. Regional anesthesia</td>
<td>b. Alcoholism</td>
<td></td>
</tr>
<tr>
<td>c. Spinal anesthesia</td>
<td>c. Intractable pain</td>
<td>4. Late vascular occlusive disease (except diagnostic)</td>
</tr>
</tbody>
</table>
to obtain: general sedation: | | |
| "belle indifférence" relaxation | d. Chorea and athetoid movements | |
| antiemetic effect | e. Decerebrate rigidity | |
cardiac protection | f. Status epilepticus (?) | |
value of chlorpromazine has been indicated, and where clinical caution in its use may be required, are indicated in table 6. It is important to extend these observations to many thousands of patients for adequate appraisal.

Summary

Studies indicate that chlorpromazine has numerous pharmacological attributes of value to use in premedication for clinical anesthesia. Laboratory and clinical data are presented to indicate this view. In normal humans, chlorpromazine induces a sleeping state from which the subject is aroused easily; renders the subject relaxed, untroubled, and serene; reduces salivary and gastric secretions; reduces alarm responses and reflexes; facilitates induction and maintenance of general and regional anesthesia; and reduces postoperative-management problems with particular reference to postoperative nausea and vomiting.

On the cardiovascular system, large doses induce orthostatic hypotension. Therapeutic doses cause transient sinus arrhythmia and tachycardia. Some protection against cardiac arrhythmias induced during cyclopropane anesthesia by the catecholamines, pressor amines, and pituitrin in dogs is afforded by a premedicant dose of chlorpromazine. The effect of vasopressor drugs on cardiovascular homeostasis in dogs and in man following chlorpromazine premedication is such that much larger doses of the peripheral acting vasopressors are required to correct hypotension.

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