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THE LACK OF CEREBRAL EFFECTS OF *d*-TUBOCURARINE *†

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WITH the commercial availability* in recent years of purified and properly standardized preparations of curare, there has been an increasing field of therapeutic usefulness for this interesting pharmacologic agent. The recent acceptance of intocostrin by the Council on Pharmacy and Chemistry (1) for inclusion in New and Nonofficial Remedies has stimulated further clinical and experimental investigation of curare. Scores of published reports are now available concerning the use of curare for the modification of therapeutic metrazol or electroshock convulsions, in the treatment of tetanus, in a variety of spastic, dystonic and choreiform states, as a diagnostic aid in myasthenia gravis, in the facilitation of bronchoscopic and esophagoscopy procedures, and as an adjuvant in surgical anesthesia. With regard to its use in anesthesia, curare is usually employed in combination with inhalation and intravenous agents, but it has occasionally been used in conjunction with preanesthetic medication only (2, 3). In a few instances, curare has been given without additional medication of any type, especially in infants and children (2). Of immediate concern to the patient and the anesthetist is the question whether curare has any central depressant or analgesic properties. Ever since Brodie stated in 1812 that "woorara acts on the brain" and Claude Bernard (4) in 1865 published his classical proof of the peripheral locus of action of curare on skeletal muscle, this question has been the subject of pharmacologic speculation. Although most anesthesiologists are of the opinion that curare is not an analgesic or anesthetic, some believe the drug to

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possess central depressant properties in addition to its peripheral paralyzing action on skeletal muscle.

Experimental work on animals with regard to the action of curare on the central nervous system has been more extensive than definitive. The older literature contains sporadic references to the central effects of curare but the value of these reports is limited by lack of refined methods of investigation. Indeed, a number of the earlier studies revealed an excitatory or convulsant effect of curare on the cerebrospinal axis (5a-g). Inasmuch as crude preparations were employed, it is impossible to know whether the stimulatory action was due to the same principle causing neuromuscular paralysis.

With regard to more modern experimentation, no unanimity of opinion exists as to the central properties of curare. Feitelberg and Pick (6) reported that crude curare extracts abolished the cortical potentials in frogs independently of paralysis of myoneural junctions. Pick and Unna (7) repeated these experiments with purified substances (*d*-tubocurarine chloride, dihydro- β -erythroidine hydrochloride) and found inhibition and suppression of the electrical activity of the frog brain, but their evidence is not convincing. Pick and Feitelberg (8) also found that curare as well as dihydro- β -erythroidine decreased the heat production in certain parts of the brain of cats, independently of any peripheral action. Fegler (9), employing crude curare preparations in anesthetized dogs, concluded that curare first stimulated and then depressed respiration by an influence on the respiratory center independent of its peripheral effect. Girden (10), employing conditioned response techniques in dogs with bilateral extirpation of the cortical auditory areas, believed his results to indicate that curare caused complete unconsciousness or amnesia, but the evidence leaves much to be desired. This investigator (11), however, later reported that in dogs receiving erythroidine the central nervous system was capable of mediating learning whether muscular paralysis was partial or complete. McIntyre and his associates (12) claimed that a variety of electro-encephalographic signs of central depression was produced in the dog by doses of *d*-tubocurarine insufficient to abolish respiratory movements, and concluded that the alkaloid possessed central depressant effects useful in anesthesia. It is not clear whether the barbiturates, conjointly administered, may have been responsible in part for the results obtained or whether some degree of hypoxia may have occurred.

In contrast to the experimental data suggesting that curare-like agents depress central mechanisms, some reports indicate that these drugs are either without central effect or may actually cause excitation. Girden (13) found that dihydro- β -erythroidine hydrobromide caused no disturbance of normal electro-encephalographic activity in dogs and monkeys, provided proper artificial respiration was given. This finding is supported by the observations of Toman and Smith

(14) who could detect no electro-encephalographic changes in dogs given full paralyzing doses of *d*-tubocurarine chloride and adequate artificial respiration. Eccles (15), extending his definitive studies of the depressing effect of curare on skeletal muscle end-plates (16) and autonomic ganglion cells (17a, b), could demonstrate no depressant action of curare on synaptic transmission in the spinal cord. Indeed, a slight facilitating effect was observed. Euler and Wahlund (18), employing both curare extract and curarine in cats, found central vasomotor and respiratory stimulation to occur from intracisternal injection, and a strychnine-like effect on spinal reflexes and even convulsions from lumbar subarachnoid administration.

Animal experimentation can provide at best only a partial and indirect answer as to whether curare exerts a central depressant or analgesic action in man. Unfortunately, very little direct evidence on human beings has accumulated to elucidate this problem. "Drowsiness" has been subjectively reported after administration of erythroidine, but this symptom is variable (19). Harvey and Masland (20) noted no marked central effect in man from nonparalytic doses of curare extract, but erythroidine frequently produced mental changes (drowsiness, confusion, disorientation). Intocostrin did not alter the therapeutic or electro-encephalographic effects of metrazol-induced convulsions in mental patients (21), and most observers report that prophylactic administration of curare does not necessitate an increase in the dose of metrazol needed for therapeutic convulsions (22a, b).

Pain is a complex psychosomatic experience and a subjective report as to its occurrence is needed. The subjective reports with regard to pain by patients receiving curare for surgical procedures without supplemental general or local anesthesia are not entirely reliable for the reasons that preanesthetic agents causing analgesia and amnesia are usually employed, that the pain modality is variable from patient to patient, that an important factor of hypnosis may operate in the individual incapable of movement, and that emotional stress *per se* may produce analgesia, perhaps by liberation of epinephrine (23).

It, therefore, was thought desirable to obtain the subjective report of a trained observer under the influence of curare alone and not undergoing a surgical procedure. One of us (S. M. S.) volunteered to act as the subject of the following experiment.

EXPERIMENTAL PROCEDURE

The subject was a healthy male adult, 34 years of age, weighing 80 Kg. To facilitate administration of *d*-tubocurarine* and subsequently neostigmine, an intravenous infusion of sterile 0.9 per cent sodium chloride solution was instituted, and the appropriate agents injected *via* the rubber tubing. Continuous recordings of the electro-

* Kindly supplied through the courtesy of Dr. H. Sidney Newcomer, E. R. Squibb & Sons.

encephalogram (standard leads) and the electrocardiogram (lead 2) were obtained throughout the control period, experimental procedures, and postexperimental period. Pulse rate, blood pressure, respiratory rate and character, neurologic signs, psychologic indexes, and sensorium were followed and recorded almost continuously. When verbal contact with the subject was lost, communication was continued as long as possible by means of prearranged signals involving voluntary contraction of such muscles as were not yet completely paralyzed. When paralysis was complete, the subject was instructed to make mental notes of all experiences, and these were dictated to a stenographer immediately upon recovery of intelligible speech. The only objective index of cerebral function which could be followed during complete skeletal muscle paralysis was the character of the electro-encephalogram and its response to pattern vision.

Oxygen was administered early, and shortly thereafter, when the first evidence of respiratory embarrassment was noted, artificial respiration with oxygen was instituted by means of a rebreathing bag, face mask, and carbon dioxide absorbing unit. Adequate pulmonary exchange was maintained at all times. Tracheal intubation was performed for a six-minute period at the height of paralysis in order to obtain evidence on visceral pain. Nasal and oropharyngeal suction was performed as needed. Neostigmine methylsulfate was injected to facilitate emergence from curare-induced paralysis.

RESULTS

An abbreviated chronological outline of the major events in the experiment is as follows:

January 10, 1946

- 2:00 p.m. Electro-encephalographic and electrocardiographic continuous recording started. Control observations made on blood pressure, pulse rate and respiratory rate, neurologic signs, etc. B.P., 130/70; pulse rate, 92; respiratory rate, 16.
- 2:10 Intravenous saline infusion started.
- 2:11 *D*-tubocurarine chloride injected intravenously at a slow constant rate so that 200 units were administered over a fifteen-minute period. Feels "a little bit dizzy and quite a 'glow.'" "A little hard to focus on anything." Weakness in jaw muscles noted. "Hard to talk." Difficulty in swallowing and keeping eyes open. "No unpleasant sensations, legs feel weak."
- 2:18 Upon subject's request, oxygen administration with face mask started. "Can hardly bring teeth together." Complains of residual odor from rebreathing bag. Alpha rhythm in electro-encephalogram prominent and inhibited by pattern vision. Total of 100 units *d*-tubocurarine chloride given. B.P., 130/70; pulse rate, 112; respiratory rate, 16.
- 2:20 Speech no longer possible. Can hear distinctly. Still able to nod head and to move hands slightly, but can scarcely move fingers.

- Respiration more diaphragmatic; manual compression of rebreathing bag begun.
- 2:22 Subject reports by movement of head that the experience is not unpleasant, that he does not want an airway and that he is mentally clear. Total of 150 units *d*-tubocurarine chloride given. B.P., 130/80; pulse rate, 108.
- 2:24 Head movement impossible. Unable to open eyes. Can wrinkle forehead slightly and indicates in this manner, in response to inquiry, that he can see clearly when his eyelids are manually elevated.
- 2:26 Ability to comprehend and answer questions accurately is indicated by correctness of replies when the inquiries are restated in the negative or double negative. Indicates he desires the experiment to continue. Upon request, moves feet and hands slightly. Total of 200 units given. Some spasmodic diaphragmatic movements out of rhythm with artificial respiration. Slight snoring sound on exhalation.
- 2:28 Can distinguish heat from cold, sharp from dull, and can feel pain pinprick.
- 2:30 No further spontaneous respiratory movements. Ability to wrinkle forehead almost gone, but indicates he can hear, see, and feel touch and pain as well as ever. Pupils medium size and equal, and pupillary responses to light and accommodation unaffected. Airway inserted, and subject indicates he feels it. Jaws very relaxed. Color good. Electro-encephalogram unaltered, and alpha rhythm still inhibited by pattern vision when eyelid is passively elevated. Intermittent pharyngeal aspiration started because of accumulating secretions. B.P., 130/70; pulse rate, 100. Subject indicates he desires the next 100 units rapidly, as planned.
- 2:32 Can no longer move feet or hands upon request, and indicates by slight remaining movement of left eyebrow that he is trying to do so. Also signals that he feels all right and that artificial respiration is satisfactory to him. Additional 100 units given rapidly; total 300 units.
- 2:35 Subject indicates he wants another 100 units and that the experience is not unpleasant. Answers to questions are consistent. Signals that diplopia is marked when eyelids are passively elevated and that objects are seen clearly when placed in line of gaze.
- 2:37 Subject signals in answer to inquiries that sensorium is normal, airway is not troublesome, and painful stimuli are felt. Additional 100 units *d*-tubocurarine chloride given rapidly; total 400 units. B.P., 140/80; pulse rate, 112. Electro-encephalogram and electrocardiogram normal.
- 2:42 Ability to signal by slight movement inner aspect left eyebrow almost gone. Indicates he desires the final 100 units, that he is perfectly conscious and that his sensorium is unimpaired.
- 2:44 Additional 100 units *d*-tubocurarine chloride given rapidly; total, 500 units.
- 2:45 Subject now unable to signal response to inquiries, due to complete skeletal muscular paralysis. Endotracheal catheter inserted with ease due to very relaxed pharynx and vocal cords, and artificial

- 2:48 respiration continued through it. B.P., 130/84; pulse rate, 120. Eyelids manually opened. Alpha rhythm of electro-encephalogram inhibited by pattern vision (object held in line of gaze). Subject stated upon recovery that he was "clear as a bell" all this period.
- 2:51 Neostigmine methylsulfate, 0.5 mg., intravenously. Endotracheal catheter removed, face mask reapplied. B.P., 130/100; pulse rate, 100.
- 2:55 Neostigmine methylsulfate, 0.5 mg., intravenously. B.P., 138/84; pulse rate, 96.
- 2:56 Subject can now contract muscles of medial aspect left eyebrow. Communication thus being reestablished, he signals that he can hear and see normally, and that painful stimuli are felt.
- 2:59 Subject indicates he wants more neostigmine. Considerable nasal and oropharyngeal secretion, and aspiration performed frequently. Lacrimation also prominent, and sweating increased.
- 3:00 Neostigmine methylsulfate, 0.5 mg., intravenously. First evidence of returning respiratory movement. Subject able to raise eyebrows feebly. B.P., 140/90; pulse rate, 80.
- 3:02 Weak respiratory movements; rate, 30. Unable to move hands or feet upon request, and signals he is attempting to do so. Color vision tested and found to be unimpaired.
- 3:05 Indicates in response to inquiry that he wants more neostigmine and that atropine is not needed.
- 3:06 Respiratory effort becoming more prominent. Extremities still completely paralyzed. Muscle of eyelids and forehead much more active. Can open eyes with difficulty. Neostigmine methylsulfate, 0.5 mg., intravenously. B.P., 140/80; pulse rate, 72.
- 3:08 Ability to wrinkle forehead has returned. Lips can be moved slightly. No intestinal symptoms from neostigmine. Aspiration now applied almost continuously. (The subject's desire for almost continuous aspiration was most intense, as reported later. He was asked questions periodically concerning his comfort and fortunately was asked at this time whether there was something he desired which had not yet been done. A most vigorous wrinkling of the forehead indicated an affirmative answer. Only by a series of many questions was it disclosed that accumulating secretions were most annoying and that more frequent aspiration was desired.)
- 3:10 Sweating prominent. Aspiration needed almost constantly. Spontaneous respiratory movements stronger. Cannot move eyes or open mouth. Diplopia present. B.P., 120/80; pulse rate, 80.
- 3:14 Subject indicates that he is uncomfortable when artificial respiration is even briefly discontinued. More neostigmine not wanted at present. Can move his feet slightly, but not hands. Can move tongue but cannot speak.
- 3:18 Subject indicates he still desires artificial respiration and oxygen. Unintelligible vocalization. Can move his shoulder girdle and extremities but cannot raise hands or flex fingers. Spontaneous respiration improving.
- 3:20 Signals his desire for more neostigmine.
- 3:21 Neostigmine methylsulfate, 0.5 mg., intravenously.

- 3:25 Spontaneous respirations improved (200-300 cc. each). Diaphragmatic excursions fair but some residual intercostal paralysis. Speech is weak and slurred, but now intelligible. Wants aspiration frequently but does not desire any atropine. B.P., 130/80; pulse rate, 80.
- 3:30 Can move arms and legs, but cannot make a fist or elevate head from the bed. Speech is clearer. "I probably could get by without artificial respiration but still want it."
- 3:35 Can now open eyes more easily, but prefers to keep them shut. Can cough weakly but unable to swallow. Respiratory assistance still desired. Movements of hands and feet more adequate. "Will be glad when I can swallow." Prefers aspiration catheter to be passed through nose rather than mouth because of gagging sensation.
- 3:40 Still unable to elevate arms or legs from the bed. No complaints. B.P., 120/70; pulse rate, 88.
- 3:50 Artificial respiration stopped. Subject can now swallow with difficulty. Aspiration applied intermittently. Speech still slurred. B.P., 110/84; pulse rate, 80.
- 4:05 Muscle power returning slowly. No more diplopia. Aspiration still employed. After conference with the subject, neostigmine methylsulfate, 0.5 mg., given intravenously, slowly, B.P., 110/80; pulse rate, 70.
- 4:20 Progressive improvement. Can elevate head from pillow.
- 4:35 Neostigmine methylsulfate, 0.5 mg., intravenously, slowly. Aspiration discontinued. Talking freely. Describing the experience.
- 4:50 With assistance, subject is able to sit up on edge of bed. Complaints of dizziness. Complete subjective report dictated.
- 5:10 Complaints of weakness, slight soreness of throat (from tracheal intubation).
- 5:25 Feels both drowsy (for first time) and "uneasy." Slight nausea. Prefers to lie down.
- 5:35 Nausea has subsided. Able to stand unassisted. Legs feel heavy and weak. Shuffling gait. B.P. (sitting), 105/80; pulse rate, 80.
- 6:00 Progressive improvement. (Skeletal muscle weakness persisted throughout the evening.)

SUBJECTIVE REPORT

(Certain aspects of the patient's subjective experiences are included in the preceding protocol.) The subject remained acutely conscious throughout the experiment and memory was unimpaired. At no time was there any evidence of lapse of consciousness or clouding of the sensorium. This statement is based particularly on the fact that at intervals of a minute or less, during the period when communication with the subject was impossible, various statements were made, questions asked, stimuli presented, objects placed in the line of gaze and so forth, on which the subject was requested to report when speech returned. In each instance, the report was accurate in all details and properly oriented as to temporal sequence. Indeed, several occurrences which were forgotten or unrecorded by the experimenters were

recalled by the subject. Visual acuity and color sense were not affected. Vision was handicapped only by diplopia and the inability to focus on anything that was not directly in line of gaze. The eyes remained passively shut most of the time. Hearing and smell were unimpaired. Indeed, it seemed to the subject that hearing was more acute than normal and remarks whispered at a distance of 20 feet were heard distinctly. Taste sensation was not examined.

Pain, touch, and other modalities of cutaneous sensation remained normal throughout. Tracheal intubation caused much less discomfort than was anticipated. Although the passage and presence of the endotracheal catheter was unpleasant, the sensation was not intolerable and was not perceived as real pain. This suggests that the pain usually attending such a procedure, when the pharynx and larynx are not sufficiently anesthetized locally, is largely secondary to reflex muscle spasm. When such reflex spasm is prevented by curare, only mucosal sensation contributes to the uncomfortable experience and this is not intense. A desire to cough was felt only during the maneuvers of intubation and extubation, and not while the tube was in place. Inflation of the cuff caused no sensation. The tube was felt in the trachea more at the lower end than at the level of the vocal cords.

The subject reported that sensations of "shortness of breath" and "choking" existed at certain times during the period of paralysis. The "shortness of breath" is of interest because it occurred in the presence of adequate pulmonary ventilation and oxygenation. ("I felt that I would give anything to be able to take one deep breath. The period of a few seconds taken for the tracheal intubation seemed unusually long, and I was awfully glad when artificial respiration was resumed.") The dyspnea appeared to be related somewhat to the rate and character of the artificial respiration, and disappeared when smooth rhythmical pressure on the rebreathing bag (inspiration) alternating with slow even release (expiration) was employed at a rate of 24 per minute. The usual rate (18 to 20 per minute) was unsatisfactory to the patient, as was also sudden release (expiration) of pressure on the bag. Why the sensation of shortness of breath should be relieved by increasing the usual rate of artificial respiration is unknown. Smith (2) has observed the same phenomenon in patients with partial respiratory paralysis resulting from high spinal anesthesia. It is tentatively suggested that a feeling of inadequacy of respiratory movement may occur, despite normal oxygenation and extensive passive thoracic excursions, if curare paralysis prevents the normal pattern and sequence of kinesthetic impulses which ordinarily arise from an actively contracting respiratory musculature.

The "choking" sensation was reported as being due to secretions accumulating in the throat, and only repeated aspiration served to decrease it but not to abolish it entirely. Apparently the inability to swallow secretions accumulating in the pharynx may give rise to a

sensation of choking independent of any interference with a patent airway.

MEANS OF COMMUNICATION

The method adopted for communicating with the curarized subject after speech was absent or no longer intelligible was to have the patient respond in the affirmative to a particular inquiry by moving whatever muscle group was still capable of being contracted. Shortly after respiratory paralysis occurred, the only muscles capable of being voluntarily contracted were those of the forehead. Ability to contract the medial aspect of the left eyebrow (procerus muscle?) was the last to disappear, and the first to reappear upon recovery. In order to test the reliability of the subject's answers and to ascertain whether automatism was operating, the questions presented were first phrased in the positive and then in the negative. No discrepancies or errors were disclosed in any of the subject's responses. Once muscle paralysis was complete, communication with the subject was no longer possible. It was not anticipated that curare would leave consciousness and sensorium entirely unaffected. Had this been known, means of communicating with the patient during complete muscular paralysis would have been arranged, as follows: (1) the inhibition of alpha rhythm of the electro-encephalogram by pattern vision, the patient focusing or not focusing on an object in the line of gaze, depending on the answer intended; (2) the constriction of the pupil by focusing on an object in the line of vision; (3) the appearance of a burst of action potentials, recorded through needle electrodes aseptically implanted in the easily accessible end-plate region of the abductor pollicis, occurring when an attempt at voluntary abduction of the thumb is made by the subject in order to indicate an affirmative answer to an inquiry.

ELECTRO-ENCEPHALOGRAM

The control electro-encephalogram was within normal limits in all respects. The left fronto-occipital lead which was recorded almost continuously throughout the experiment was of dominant alpha type. Blocking by pattern vision was practically complete. No significant alteration in amplitude, frequency, or percentage time alpha occurred even at the height of skeletal muscle paralysis; blocking of the alpha rhythm by pattern vision was normal as long as the stimulus object was maintained in the line of gaze (fig. 1). Neostigmine administered to facilitate recovery was without effect on the electro-encephalogram.

ELECTROCARDIOGRAM

The control electrocardiogram was within normal limits. No significant changes other than those secondary to changes in heart rate occurred (fig. 1) until the administration of neostigmine which pro-

duced a slight prolongation of PR interval from the control value of 0.16 seconds to a maximum of 0.19 seconds.

CARDIOVASCULAR SYSTEM

D-tubocurarine chloride exerted no untoward effect on the cardiovascular system. Blood pressure and pulse rate fluctuations were inconsequential. Despite the complete and generalized muscular flaccidity, venous return and cardiac output were apparently adequate (the subject remained supine throughout the experiment). Skin color was

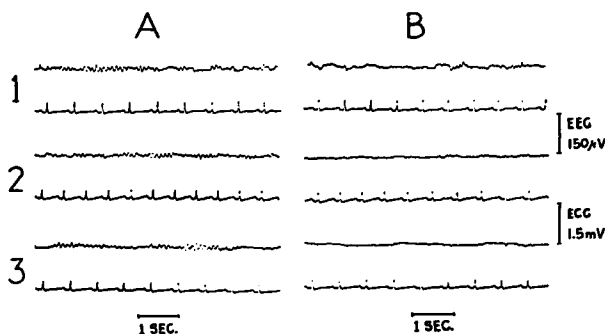


FIG. 1. Top tracing in each record is the electro-encephalogram (fronto-occipital lead); lower tracing, the electrocardiogram (lead II). A, eyes closed; B, one eyelid held open. Horizontal line, 1 second. Vertical lines, 150 microvolts (electro-encephalogram) and 1.5 millivolts (electrocardiogram). 1. Control record, 2:02 p.m., during saline infusion. 2. Record at height of curare paralysis, 2:45 p.m. 3. Record during recovery following neostigmine, 3:05 p.m.

good at all times. Unexpectedly, repeated intravenous doses of neostigmine had little effect on the cardiovascular indexes observed, and atropine was not required.

RESPIRATION

Adequate pulmonary ventilation and oxygenation were maintained at all times so that hypoxia would not be a complicating factor. Oxygen was administered early. Artificial respiration with oxygen was instituted at the first sign of respiratory insufficiency and continued until late in the emergence period, when the subject volunteered that mechanical assistance be terminated. During the period of complete respiratory paralysis, different types and rates of artificial respiration were tried. A rapid rate (24 per minute) with slow smooth expiration seemed to give the patient the most satisfaction. Inasmuch as full

communication with the subject was not possible, this fact was not made known until the experiment was over. Consequently, despite adequate oxygenation and pulmonary exchange, the subject unhappily experienced some "shortness of breath" an undue amount of the time. The significance of the observation has been commented upon above.

D-TUBOCURARINE DOSAGE

A total dose of 500 units of *d*-tubocurarine chloride was given intravenously over a period of thirty-three minutes. The last 300 units were given within a period of twelve minutes in three 100-units doses, each of which was injected rapidly. Complete respiratory paralysis occurred when approximately 200 units (2.5 units per Kg.) had been administered. Thus, an amount of *d*-tubocurarine chloride was given which was two and one-half times that required for complete paralysis of respiration and adequate for complete skeletal muscular paralysis. Despite this large dosage, no discernible change was observed in the electro-encephalogram, electrocardiogram, psyche, mentality, memory, or sensory modalities. No objective or subjective evidence of central depression or stimulation by curare could be detected.

NEOSTIGMINE DOSAGE

A total of 3.5 mg. of neostigmine methylsulfate was injected intravenously in divided doses (seven 0.5 mg. doses) over a period of 102 minutes. Emergence from curariform paralysis was considerably accelerated by neostigmine through its well-known anticholinesterase action and perhaps also by a direct effect on skeletal muscle (24). The order of recovery of function of muscle groups was the reverse of the order of paralysis. No skeletal muscle fasciculations were seen. The electro-encephalogram was not altered by neostigmine. Despite the rather large dose of neostigmine employed, no significant cardiovascular or visceral effects occurred and atropine was not required. The subject reported that he experienced no desire to urinate or defecate and no sensations of increased intestinal activity. The only recorded muscarinic responses to prostigmine were secretory and pupillary. Lacrimal, salivary, nasopharyngeal, and sweat gland secretions were enhanced and the pupils were constricted.

COMMENT

From the evidence presented, it would appear that curare does not possess central stimulant, depressant or analgesic properties. In a normal subject not undergoing operation, a dose of *d*-tubocurarine chloride at least two and one-half times that required to cause complete respiratory paralysis failed to alter the electro-encephalogram, or to impair consciousness, memory, or sensorium. Significant effects on systems other than skeletal muscle were also absent.

Neostigmine given in fairly large dosage greatly facilitated re-

covery from the curare-induced paralysis. Although 3.5 mg. of neostigmine methylsulfate was given intravenously within a period of less than two hours, no significant muscarinic action on the gastrointestinal tract, urinary bladder or cardiovascular system was observed, and atropine was not required. Curare is usually considered to have no direct blocking action on smooth muscle cells. Perhaps this point is worthy of reexamination. Gross and Cullen (25) found that therapeutic amounts of curare in dogs caused relaxation of the smooth muscle of the small intestine; Pichard and Luco (26) reported that erythrina extracts caused depression of autonomic cholinergic effector cells in cats, and Mautner and Luisada (27) presented evidence that curare may cause an inhibition of the peripheral effects of the vagus nerve. Whether in the subject reported here the large dose of *d*-tubocurarine may have modified the response of smooth muscle to neostigmine either directly or by a depressant action on parasympathetic ganglia cannot be stated with certainty. (Curare is known to depress autonomic ganglia.) The stimulant effect of neostigmine on the constrictor of the pupil and on secretory glands was abundantly evident. Neostigmine had no discernible central effect on the nervous system, and the electro-encephalogram was not altered.

D-tubocurarine chloride was the curare preparation employed. It is not appropriate here to discuss the chemistry of the curare alkaloids but it should be mentioned that there is the possibility that different curare preparations may have slightly different pharmacologic effects. Whether this would apply to the central nervous system is not known; but, until further information is available and from the point of view of practical application of the observations recorded in the above experiment, it may be assumed that the other curare alkaloids used clinically do not cause central depression or analgesia.

It is suggested that if curare is to be used properly as an adjuvant in anesthesia, its inability to depress the central nervous system be kept clearly in mind. Curare does not cause analgesia or obtund consciousness. Its sole action of value in anesthesia is to produce skeletal muscular relaxation by a peripheral paralytic effect on endplates of skeletal muscle cells. The suggestion is therefore advanced that curare not be used alone in surgical procedures but that it be employed only as an adjuvant with agents capable of relieving pain and of obtunding consciousness. This suggestion holds not only for adults but also for young children in whom a painful experience, even though not reportable to the physician, may constitute a serious psychic trauma. Failure to appreciate the limitations of curare may bring this very valuable agent into undeserved disrepute.

SUMMARY

A dose of *d*-tubocurarine chloride two and one-half times that necessary for complete respiratory paralysis and adequate for complete

skeletal muscular paralysis was given intravenously over a period of thirty-three minutes to a healthy trained adult observer not undergoing operation. Inasmuch as no changes occurred in the electro-encephalogram, consciousness and sensorium, or in any aspect of higher central nervous system function, it is concluded that *d*-tubocurarine chloride has no significant central stimulant, depressant or analgesic action. Attention is called to the importance of this observation for the proper use of curare as an adjuvant in anesthesia.

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