

Neuromuscular and Electromyographic Studies in Man: Effects of Hyperventilation, Carbon Dioxide Inhalation and d-Tubocurarine

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The effects of hyperventilation and of carbon dioxide inhalation on neuromuscular transmission, integrated electromyographic (IEMG) activity and on the action of *d*-tubocurarine were studied in patients during anesthesia and operation. The twitch response of the adductor pollicis muscle to supramaximal ulnar nerve stimulation was increased by hyperventilation and decreased by breathing 10 per cent CO₂. The neuromuscular blocking action of *d*-tubocurarine was decreased by hyperventilation and increased by 10 per cent CO₂. Both sets of results were attributed to induced changes in arterial pH and P_{CO₂}. The IEMG activity of the oblique-transversus group of abdominal muscles was not affected by inhalation of 10 per cent CO₂ but was decreased by hyperventilation. This latter effect, which was not due to hypocapnia but appeared to be reflex in nature, may be responsible for the clinically observed abdominal muscle relaxation seen with hyperventilation.

ALTHOUGH HYPERVENTILATION of the lungs of anesthetized patients is a common clinical practice, the effects on muscle relaxation and the neuromuscular blocking agents are not well defined. The effects of hyperventilation have not always been adequately separated from the effects of induced changes in pH and P_{CO₂}. Abdominal muscle relaxation produced by hyperventilation has been reported in man¹ and attributed in part to removal by hypocapnia of the respiratory drive. Downes² however reported that in the rat, inhibition of the contraction of the rectus abdominus muscle in response to electrical stimulation of the tail

was attributable to hyperventilation rather than hypocapnia. Although it has been demonstrated in laboratory animals that pH and P_{CO₂} may affect the action of the neuromuscular blocking agents, the magnitude and direction of effect are not yet agreed upon.³⁻⁹ In man, Dundee¹⁰ reported that hyperventilation modified the dose of *d*-tubocurarine required for abdominal surgery while Scurr,¹¹ and Gray and Fenton¹² reported cases of carbon dioxide retention simulating curarization.

The present study was undertaken to determine the effects of hyperventilation and of carbon dioxide inhalation on (1) neuromuscular transmission, (2) integrated electromyographic (IEMG) activity, and (3) the action of *d*-tubocurarine.

Methods

Forty-two patients were studied before or during operation. Most of the patients received atropine or scopolamine (0.4-0.6 mg.), secobarbital or pentobarbital (50-100 mg.) and/or meperidine (30-100 mg.) for pre-anesthetic medication. Anesthesia was usually induced with thiamylal sodium and maintained with nitrous oxide, supplemented by thiamylal, meperidine or trichlorethylene. Tracheal intubation, when necessary, was accomplished following topical lidocaine anesthesia (5 ml. of 4 per cent) or following the use of intravenous succinylcholine (20-40 mg.). The results in the patients who received succinylcholine did not differ from those in patients intubated during topical anesthesia.

Neuromuscular transmission was studied by the following technique: The patient's hand was carefully fixed in place on a molded

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TABLE 1

	pH	Twitch Height	IEMG Activity
10 Per cent CO ₂	↓	↓	0
Hyperventilation	↑	↑	↓
Hyperventilation with 10 Per cent CO ₂	↓	↓	↓

↑, increased; ↓, decreased; 0, unchanged.

plaster armboard which prevented gross movements. A supramaximal stimulus from a Grass stimulator (model SC4) was applied to the ulnar nerve at the wrist by means of 25 gauge needle electrodes placed subcutaneously. Twitch responses were elicited with square pulse stimuli of 110–150 volts for 0.3 msec. duration delivered at a rate of 18/minute. The resulting adduction of the thumb (attributable predominantly to the adductor pollicis) activated a force displacement transducer (Grass FT-03). The output of the transducer was amplified and recorded on a polygraph. The amplitude of this tracing (twitch height) was used as a measure of neuromuscular response in a given patient. Each patient served as his own control. The twitch height can be modified by changes in the nerve, muscle, neuromuscular junction, or any combination of these sites. No attempt was made in these experiments to determine the site(s) of action. Studies along these lines are in progress.

The integrated electromyogram (IEMG) of the oblique-transversus group of abdominal muscles was obtained by inserting needle electrodes (two standard 22 gauge 1½ inches long metal needles) between the iliac crest and costal margin. The needles were advanced until they were felt to penetrate muscle; the distance between the needles was approximately 10–20 mm. A 25 gauge metal hypodermic needle placed subcutaneously served as the ground electrode. The electrical activity was measured with an Offner EMG integrating amplifier and recorded on an Invengineering polygraph utilizing Offner components. Except for the recorder used,

the technique is similar to that originally described by Fink.¹³

A modified Boyle's anesthesia machine with an Ohio Chemical model 20 CO₂ absorber in the circle system was used. A nonbreathing system (Sierra nonbreathing valve 268–50) was used for trichlorethylene administration, 10 per cent CO₂ inhalation, or hyperventilation of 15 liters/minute. When hyperventilation of 16–25 liters/minute was carried out, the circle system was utilized. The system permitted a change from the nonbreathing to circle system or back within 3 seconds. From 0.1 to 0.3 mg./kg. of 0.3 per cent *d*-tubocurarine was injected to produce an 80 per cent or greater depression of twitch height.

Ventilation was measured with a Wright ventilometer or a Collins Spirometer. Brachial artery blood samples were analyzed for pH and P_{CO₂} with an Ingold pH electrode and modified Severinghaus P_{CO₂} electrode or by the Astrup technique.

Results (Table 1)

Effects of Hyperventilation and of 10 Per Cent Carbon Dioxide on Twitch Height. In preliminary experiments it was observed that the twitch response was not affected by depth of anesthesia (changes in surgical stimulation or concentration of anesthetic agents) unless the patient was so lightly anesthetized that he could move his thumb. Movement of the thumb could easily be detected by a change in the baseline of the twitch output recording. It was also noted that thiamylal could increase the twitch height approximately 5 per cent and this agent was avoided once the experiment was started.

After establishing a steady level of twitch response in 10 patients with spontaneous respiration, 10 per cent carbon dioxide was added to the inhaled mixture for 10 minutes. There was no change in twitch in 3 patients. In 7 patients twitch height decreased (10–33 per cent) during 10 per cent carbon dioxide inhalation and returned to or toward control when the CO₂ was discontinued (fig. 1A). In 3 of these 7 patients a dose of meperidine sufficient to produce apnea was given and the patient was then manually ventilated at 6

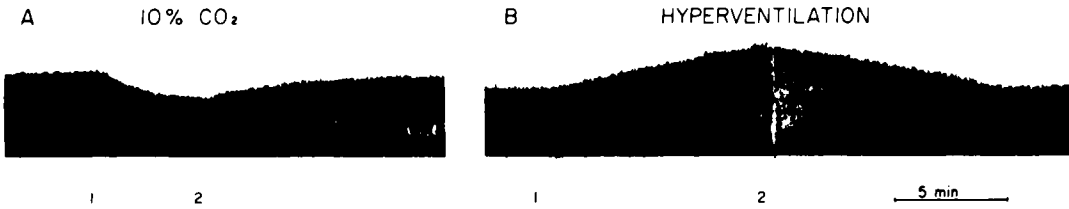


FIG. 1. Effect of 10 per cent CO_2 inhalation and hyperventilation on twitch response. Panel A: inhalation of 10 per cent CO_2 started at 1 and discontinued at 2. Panel B: hyperventilation (25 liters/minute) started at 1 and discontinued at 2.

liters/minute with and without 10 per cent carbon dioxide. The decrease in twitch response with 10 per cent carbon dioxide was similar to that seen during spontaneous ventilation.

Hyperventilation (15–25 liters/minute) for 10 minutes increased the twitch height (20–50 per cent) in 8 patients (fig. 1B) and had no effect in 2 patients. Upon return to the control level, 3 of the 8 patients whose twitch height increased during hyperventilation were hyperventilated with 10 per cent carbon dioxide. A fall in twitch height occurred in all three.

d-Tubocurarine, Carbon Dioxide and Hyperventilation. In preliminary experiments it was observed that a dose of *d*-tubocurarine which produced any perceptible depression of twitch response if repeated even 1–2 hours later usually produced a greater effect. Since the effect of the second dose of *d*-tubocurarine was greater than the first dose, and by a variable degree, it was not possible to compare the effect of the same dose of *d*-tubocurarine in a given patient with and without hyperventilation (15–25 liters/minute) or 10 per cent carbon dioxide. Instead 8 patients received a

dose of *d*-tubocurarine which produced an 80 per cent or greater depression of twitch height (0.1–0.3 mg./kg. *d*-tubocurarine). Respiration was assisted at the control frequency and volume and a recovery curve slope established. The patients were then hyperventilated or inhaled 10 per cent CO_2 for 10 minutes. Although it appeared that hyperventilation increased and 10 per cent carbon dioxide decreased the recovery curve slope, the magnitude of change was sometimes small and we could not be sure of the results (fig. 2, 2–3). In an attempt to increase the magnitude of change, *d*-tubocurarine was given after the patient inhaled 10 per cent carbon dioxide for 10 minutes. After establishing a recovery curve slope the 10 per cent carbon dioxide was discontinued and the patient hyperventilated. The reverse experiment was also performed; hyperventilation for 10 minutes prior to curare followed by 10 per cent carbon dioxide after a recovery curve slope was established. In addition, after *d*-tubocurarine was given and a recovery curve slope established, 10 per cent carbon dioxide inhalation and hyperventilation were alternated. Regardless of the sequence of acidosis and

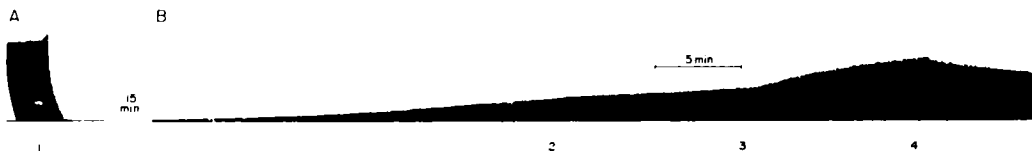


FIG. 2. Effect of 10 per cent CO_2 inhalation and hyperventilation on response to *d*-tubocurarine. Panel A: *d*-tubocurarine (0.3 mg./kg.) injected at 1 during spontaneous respiration. Panel B: 15 minutes later. Recovery curve slope established during manual ventilation. At 2 10 per cent CO_2 added to inhaled mixture. A slight decrease in slope may be observed. At 3 the carbon dioxide was discontinued and the patient hyperventilated (25 liters/minute). At 4 hyperventilation discontinued and 10 per cent CO_2 added to inhaled mixture.

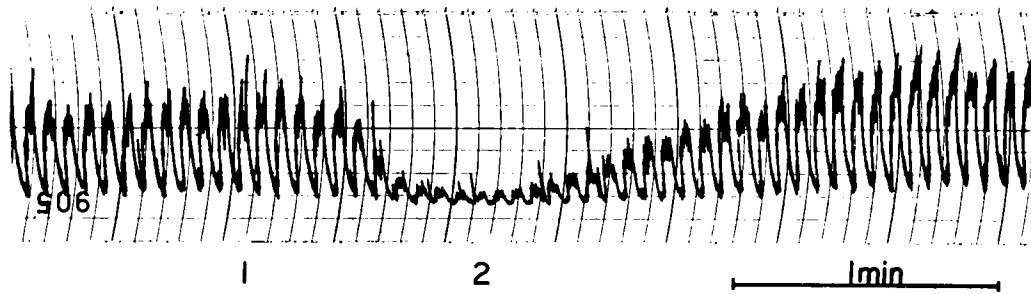


Fig. 3. Effect of hyperventilation on IEMG. At 1 hyperventilation (15 liters/minute) started. At 2 hyperventilation discontinued.

alkalosis the recovery curve slope during hyperventilation was greater than during 10 per cent carbon dioxide inhalation in 16 of 22 patients (fig. 2). The magnitude of change in 6 patients was too small to be accurately assessed. In 2 of the 16 patients in whom hyperventilation increased and 10 per cent carbon dioxide decreased the recovery curve slope, hyperventilation and 10 per cent carbon dioxide inhalation prior to the *d*-tubocurarine did not affect twitch height.

Effects of Hyperventilation and of 10 Per Cent Carbon Dioxide on IEMG. In preliminary experiments it was observed that a sudden increase in surgical stimulation could increase IEMG activity while thiomylyl decreased IEMG activity. Therefore, most of the IEMG studies were carried out prior to operation and after a steady level of nitrous oxide, oxygen, trichlorethylene anesthesia was established.

After establishing a constant level of IEMG activity during spontaneous ventilation in 5 patients, 10 per cent carbon dioxide was added to the inhaled mixture for 10 minutes. There was no significant change in the IEMG although ventilation increased. These patients, after a 20–30 minute recovery period, and 5 others were hyperventilated (15–25 liters minute) for 1–10 minutes. A 75 per cent or greater decrease in IEMG activity was observed in every patient (fig. 3). The decrease in activity began within the first 10–30 seconds, while the maximum decrease occurred within 1–2 minutes and persisted as long as the patient was hyperventilated. Discontinuing the hyperventilation produced a return to the control level of IEMG activity

within 1–2 minutes. The time required for return to control did not appear to be related to the duration of hyperventilation. Hyperventilating 6 of these patients (20 minutes later) with 10 per cent carbon dioxide produced changes similar to those seen with hyperventilation alone.

Changes in Arterial pH and P_{CO_2} . The mean arterial pH and P_{CO_2} during spontaneous or assisted respiration at the control frequency and volume were 7.38 (range = 7.35–7.42) and 41 (range = 36–44), respectively. During hyperventilation the pH increased to 7.61 (range = 7.55–7.67) while P_{CO_2} fell to 19 (range = 17–23). Inhalation of 10 per cent carbon dioxide decreased pH to 7.19 (range = 7.13–7.22) and increased P_{CO_2} to 63 (range = 55–76). No attempt was made in these experiments to separate changes in pH from those in P_{CO_2} . For the sake of convenience, however, subsequent comments on acid-base changes will be referred to in terms of pH changes.

Discussion

The twitch response to a supramaximal stimulus was usually increased by alkalosis and decreased by acidosis. That the changes were due to pH effects and not to mode of ventilation was shown by the decrease in twitch when acidosis was produced by hyperventilation with 10 per cent carbon dioxide. A decrease in twitch height with acidosis (5–20 per cent carbon dioxide) has also been reported in the cat by Payne,⁴ Frederickson and Schenk⁵ and Katz *et al.*⁹ Gamstorp and Vinnars,⁶ however, reported that in the rabbit, acidosis did not affect the twitch response to

supramaximal stimuli but did depress the twitch response to submaximal stimuli. They suggested that Payne,⁴ who did not state whether or not his stimulus was supramaximal, might have used a submaximal stimulus and therefore observed a fall in twitch height with acidosis. This suggestion cannot explain the discrepancy in results since a supramaximal stimulus was used in the present study and those of Frederickson and Schenk⁵ and Katz *et al.*⁹ Furthermore, we observed an increase in twitch height with alkalosis while Gamstorp and Vinnars⁶ reported that alkalosis did not affect the twitch response to supramaximal or submaximal stimuli. In addition to the different species studied, Gamstorp and Vinnars⁶ recorded electrical responses while mechanical responses were recorded in the other studies. Since it is known that the mechanical and electrical recording of a muscle contraction may differ,¹⁴ we are currently recording both electrical and mechanical responses to nerve stimulation in an attempt to explain the different results.

The activity of *d*-tubocurarine was decreased by alkalosis and increased by acidosis. Since *pH* changes affect twitch height in the absence of *d*-tubocurarine it was not possible in the present experiments to separate the relative effects of *pH* on *d*-tubocurarine and on twitch height. *pH* does affect *d*-tubocurarine because *pH* changes modified the recovery curve slope even in the few patients whose twitch height was not affected by acidosis or alkalosis.

Most of the studies of the effects of *pH* on *d*-tubocurarine in other species are in agreement with our results. Kalow,³ Payne,⁴ Gamstorp and Vinnars,⁷ Johansen and Osgood,⁸ and Katz *et al.*⁹ found in the frog, cat and rabbit that *d*-tubocurarine was more active during acidosis (respiratory or metabolic) and less active during alkalosis (respiratory or metabolic). Kalow³ explained the effect of *pH* on *d*-tubocurarine in terms of changes in ionization of the two hydroxyl groups of *d*-tubocurarine. He markedly altered the percentage of hydroxyl groups ionized by changing the *pH* from 6.7 to 8.7. Increasing the *pH* increased the percentage of hydroxyl groups ionized and decreased the action of *d*-tubo-

curarine, while decreasing the *pH* decreased the percentage of hydroxyl groups ionized and increased the action of *d*-tubocurarine. Although *pH* changes of 2 units could sufficiently alter hydroxyl group ionization to account for Kalow's results, factors other than hydroxyl group ionization may be required to explain the results of studies in which smaller changes in *pH* were produced.⁴⁻⁹ Katz *et al.*⁹ questioned whether the changes in ionization of the hydroxyl groups (pK_a 's of 8.1 and 9.1) produced by *pH* changes of 0.3-0.4 units were sufficient to account for the marked changes in *d*-tubocurarine activity. Utting¹⁵ recently stated that changing the *pH* only 0.11 unit (from 7.1 to 7.21) produced a sudden and considerable fall in plasma concentration of *d*-tubocurarine. In addition, Utting¹⁵ found that decreasing *pH* by adding carbon dioxide to the inspired gas mixture did not affect the plasma concentration of *d*-tubocurarine. Finally, although dimethyl tubocurarine differs from *d*-tubocurarine only by two methoxy (CH_3O) groups substituted for the two hydroxyl groups and therefore does not undergo *pH* dependent changes in ionization, the action of dimethyl tubocurarine in the cat is affected by *pH* changes^{4,9} (acidosis decreases and alkalosis increases activity of dimethyl tubocurarine). Other factors which may be involved include *pH*-induced changes in calcium ionization, sodium ion flux, enzyme activity, blood flow or the physical state of the receptor substance.

The magnitude of effect of *pH* on *d*-tubocurarine in this study is smaller than seen in studies of other species and is of minimal clinical significance. This may be related to the speed, magnitude or time of change of *pH*. It was pointed out in our previous study in the cat⁹ that it was difficult to interpret the effect on *d*-tubocurarine of *pH* changes produced by hyperventilation or 10 per cent carbon dioxide because of the time required to change *pH*. A dose of sodium carbonate which increased *pH* an average of 0.36 units was injected in 10-20 seconds and produced clearcut results. The more slowly this dose was injected the less clearcut the results. Gamstorp and Vinnars⁷ pointed out that metabolic alkalosis and acidosis produced

greater changes in the action of *d*-tubocurarine than respiratory acidosis and alkalosis due to the more rapid shift in *pH*. They also found a greater magnitude of effect with 20 per cent carbon dioxide than with 10 per cent carbon dioxide. Because of the cumulative effect observed with *d*-tubocurarine, repeated injections at varying *pH*'s could not be meaningfully compared. Instead we determined the effect of changes in *pH* on the recovery curve slope. Changing the *pH* prior to the injection of *d*-tubocurarine and maintaining acidosis or alkalosis for the duration of action of *d*-tubocurarine might have brought forth a greater effect of *pH*. This was attempted in preliminary experiments by giving alternate patients 0.2 mg./kg. of *d*-tubocurarine at *pH* 7.2, 7.4 and 7.6 and comparing the magnitude and duration of neuromuscular block. The variation in biological response from patient to patient at the same *pH* was too great to permit interpretation of small numbers of patients. Smith *et al.*¹⁶ studied the interaction of halothane and *d*-tubocurarine on twitch response by analyzing blood concentrations of halothane and *d*-tubocurarine at selected twitch heights. From plasma concentration-effect curves plotted for each drug as well as for the combination, isobolograms were constructed and used to determine the interaction of halothane and *d*-tubocurarine. This technique of analysis could provide quantitative data on the interaction of *pH* and *d*-tubocurarine on neuromuscular transmission.

The clinical observation which prompted these studies concerned the apparent muscle relaxation produced by hyperventilation. Hyperventilation-induced alkalosis increased twitch response and decreased the action of *d*-tubocurarine and cannot explain hyperventilation-induced relaxation. However, the marked decrease in abdominal muscle IEMG activity produced by hyperventilation appears adequately to explain the clinical observation. Gray and Reese¹ attributed the hyperventilation-induced abdominal relaxation to a combination of hypocapnia and inhibition of the Hering-Breuer reflex. The former is unlikely since hyperventilation with 10 per cent carbon dioxide, which results in hypercapnia, also

decreases abdominal muscle IEMG. The rapid decrease in activity with hyperventilation and the rapid recovery of activity upon cessation of hyperventilation suggest a reflex mechanism of action. It has been shown in the rat that contraction of the rectus abdominus muscle evoked by electrical stimulation of the tail is inhibited by hyperventilation.² The inhibition was attributed to hyperventilation rather than hypocapnia.

Summary

The integrated electromyographic (IEMG) activity of the oblique-transversus group of abdominal muscles and the twitch response of the adductor pollicis muscle to supramaximal ulnar nerve stimulation were studied in patients during anesthesia and operation. Twitch height was increased by hyperventilation and decreased by 10 per cent CO₂. The neuromuscular blocking action of *d*-tubocurarine was decreased by hyperventilation and increased by 10 per cent CO₂. These results were attributed to changes in *pH* and P_{CO₂}. The IEMG activity was not affected by 10 per cent CO₂ inhalation but was decreased by hyperventilation with or without 10 per cent CO₂. The decrease in IEMG activity was therefore attributed to hyperventilation rather than to changes in *pH* or P_{CO₂}. These results suggest that the clinically observed muscle relaxation produced by hyperventilation is not due to changes in *pH* or P_{CO₂}, an effect on neuromuscular transmission, or the neuromuscular blocking agents. A reflexly mediated decrease in abdominal muscle tone is proposed to account for the observation.

References

1. Gray, T. C., and Rees, R. J.: Role of apnoea in anesthesia for major surgery, *Brit. Med. J.* **2**: 891, 1952.
2. Downes, H.: Hyperventilation and abdominal reflex inhibition in the rat, *ANESTHESIOLOGY* **24**: 615, 1963.
3. Kalow, W.: Influence of *pH* on ionization and biological activity of *d*-tubocurarine. *J. Pharmacol. Exp. Ther.* **110**: 443, 1954.
4. Payne, J. P.: Influence of carbon dioxide on neuromuscular blocking activity of relaxant drugs in cat, *Brit. J. Anaesth.* **30**: 206, 1958.
5. Frederickson, E. L., and Schenk, E. A.: Response of neuromuscular junction prep-

- arations to changes in oxygen and CO₂, Fed. Proc. 18: 463, 1959.
6. Gamstorp, I., and Vinnars, E.: Studies in neuromuscular transmission; influence on neuromuscular transmission of alkalosis and acidosis, Acta. Physiol. Scand. 53: 142, 1961.
 7. Gamstorp, I., and Vinnars, E.: Studies in neuromuscular transmission; influence of changes in blood pH and carbon dioxide tension on the effect of tubocurarine and dimethyl tubocurarine, Acta. Physiol. Scand. 53: 160, 1961.
 8. Johansen, S. H., and Osgood, P. F.: Influence of hypercarbia on the activity of neuromuscular blocking agents in the cat, Acta. Pharmacol. 19: 212, 1962.
 9. Katz, R. L., Ngai, S. H., and Papper, E. M.: The effect of alkalosis on the action of the neuromuscular blocking agents, ANESTHESIOLOGY 24: 18, 1963.
 10. Dundee, J. W.: Influence of controlled respiration on dosage of thiopentone and d-tubocurarine chloride required for abdominal surgery, Brit. Med. J. 2: 893, 1952.
 11. Scurr, C. F.: Carbon dioxide retention simulating curarization, Brit. Med. J. 1: 565, 1954.
 12. Gray, T. C., and Fenton, E. S. N.: Carbon dioxide retention simulating curarization, Brit. Med. J. 1: 820, 1954.
 13. Fink, B. R.: A method of monitoring muscle relaxation by the integrated abdominal myogram, ANESTHESIOLOGY 21: 178, 1960.
 14. Inman, V. T., Ralston, H. J., Saunders, J. B. de C. M., Feinstein, B., and Wright, E. W., Jr.: Relation of human electromyogram to muscular tension, Electroenceph. Clin. Neurophysiol. 4: 187, 1952.
 15. Utting, J.: pH as a factor influencing plasma concentrations of d-tubocurarine, Brit. J. Anaesth. 35: 706, 1963.
 16. Smith, N. T., Bellville, J. W., and Cohen, E. N.: Interaction of halothane and d-tubocurarine on skeletal muscle in the cat, Pharmacologist 5: 276, 1963.

HALOTHANE AND ETHER During 25 neurosurgical procedures general anesthesia was maintained by alternating halothane and halothane-ether azeotrope mixture every hour for a total of 99 hours. Both drugs were given in a concentration of 1 per cent. The tendency to hypotension was less pronounced during anesthesia with azeotrope. Preceding halothane anesthesia did not predispose to hypotension during anesthesia with the azeotropic mixture. (*Clementson, H. J.: Halothane and Halothane-Ether Azeotrope as Alternating Anesthetics, Danish Med. Bull. 11: 119, 1964.*)

SPINAL HEADACHE Of 251 patients subjected to spinal anaesthesia, 34 complained of postoperative headache. Diamox was very effective against headache in cases with elevated cerebrospinal pressure, moderately so in cases with normal pressure and little so in cases with lowered pressure. This agent tended to cause a transient rise of spinal pressure lasting 45 to 50 minutes followed by a persistent fall. (*Hiki, T., and others: Therapeutic Use of Diamox for the Headache Caused by Spinal Anaesthesia, Japanese Red Cross Med. J. 15: 236, 1963.*)

TRANSABDOMINAL SPINAL In order to prolong or improve the effect of spinal or general anesthesia for abdominal surgery, spinal tap was performed through the second or third anterior vertebral space during operation. Combination with ordinary spinal anesthesia was preferred when the effect of spinal anesthesia was limited to a narrower area than expected or was not maintained for completion of the surgical procedure. (*Arima, J.: Transabdominal Spinal Anesthesia, J. Japanese Surg. Soc. 63: 683, 1962.*)