Changes in Airway Resistance Following Intravenously Administered d-Tubocurarine

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VARIOUS investigators have reported bronchial constriction following intravenous curare both in subjects breathing spontaneously[1,2,3] and in subjects with assisted respirations.[4] This bronchial constriction has most commonly been attributed to the liberation of histamine.[5,6]

Other investigators have reported no change in the bronchial diameter following *d*-tubocurarine administration with assisted respirations.[7,8] Still others have reported that a very small percentage of patients who receive *d*-tubocurarine develop bronchial narrowing.[9]

The purpose of our study was to evaluate the effect on airway resistance of *d*-tubocurarine administered intravenously to human subjects as an adjuvant to general anesthesia.

Methods

Twenty-three patients scheduled for elective surgical operations were studied. Weights of the patients varied between 50.8 and 90.4 kg., and the ages, between 21 and 75 years. None of the patients had a history of allergy and all were free from clinical or laboratory evidence of cardiopulmonary disease. Data from patients developing increased secretions during the study period were discarded.

Preoperative medication consisted of pentobarbital, 100–200 mg. by mouth the night before operation and 4 mg./kg. body weight given intramuscularly ninety minutes prior to the induction of anesthesia. Fifteen minutes before inducing anesthesia, atropine sulfate .01 mg./kg. body weight was given intravenously.

A 2.5 per cent solution of thiopental was administered intravenously in 5 ml. increments to a total dose of 4.4 mg./kg. body weight. A translaryngeal injection of 1.5 ml. of 5 per cent hexylcaine hydrochloride facilitated tracheal intubation. A second dose of thiopental equal of the first was administered while the patient breathed oxygen via a face mask. The trachea was intubated, using in all cases the same no. 8 cuffed portex endotracheal tube. A closed anesthetic system was established, and the patient's lungs were ventilated with a Bird Assistor/Controller. The appropriate tidal volume and respiratory rate were determined from the Radford nomogram,[10] and these, along with the peak flow rate for each patient, were kept constant throughout the test period.

Intraesophageal pressure was measured by means of a catheter and balloon.[11] The balloon was filled with 1.5 ml. of helium and the open end of the catheter was attached to a Sanborn differential transducer. All balloons were individually tested for degree of damping and the maximal response time of the system was 0.02 seconds. Similarly constructed systems gave a 100 per cent response up to a frequency of 35 cycles per second when filled with helium. Airway pressure was measured by the same transducer connected to the oral end of the endotracheal tube by a polyethylene catheter. A Lilly pneumotachometer, interposed between the patient's endotracheal tube and the inspiratory-expiratory valves of the circle absorption system measured respiratory flow rates. Respiratory volume was obtained by electrically integrating the respiratory flow rate. Intraesophageal pressure, airway pressure, respiratory flow rate and volume were recorded on a four-channel Sanborn polyviso recorder. Transpulmonary pressure was detected by a Sanborn differential strain gauge as the difference between the airway pressure and the intraesophageal pressure (figs. 1 and 2).

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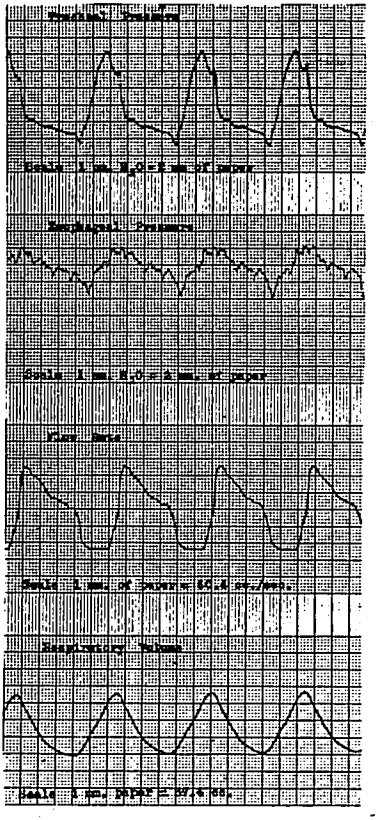

FIG. 1. Representative tracing showing airway pressure, intraesophageal pressure, respiratory flow rate, and respiratory volume.

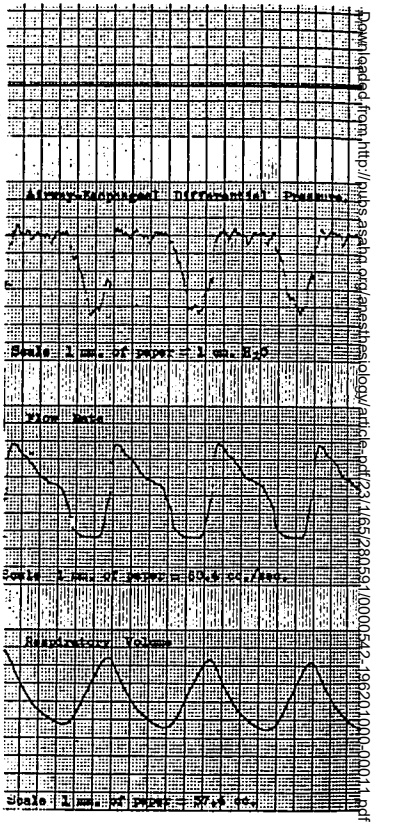

FIG. 2. Representative tracing showing transpulmonary pressure, respiratory flow rate, and respiratory volume.

These elements were recorded thirty and thirty-five minutes after controlled ventilation had been instituted, when a constant anesthetic state was considered in effect. When statistically similar values for airway resistance and static lung compliance were obtained at the thirty and thirty-five minute intervals, *d*-tubocurarine, 0.44 mg./kg., was given intravenously in a single rapid injection. Recordings were then made every five minutes for 4 to 6 recordings. *d*-Tubocurarine, 0.22 mg./kg., was given as before and 2 or 3 more recordings were made. All studies were completed prior to the surgical procedure.

Airway resistance, in centimeters of water per liter per second, was calculated by using the standard formula:

$$R = \frac{A}{B} = \frac{\Delta P}{\Delta Q} \text{ (fig. 3)}$$

R = resistance (cm. H_2O/l./second)

$A = \Delta P$ = change in pressure (cm. H_2O)

$B = \Delta Q$ = change in flow rate (cc./second).

The change in pressure and change in flow rate were measured at the same place and at equal points on the inspiratory and expiratory volume curves. The point on the inspiratory volume curve corresponds to the peak inspiratory flow rate.

Results

Airway resistance values for the 23 patients are shown in table 1. Resistance changes of 7 patients, representative cases of each of group 1, group 2 and group 3, were subjected to more detailed analysis and are listed in table 2.

Patients could be divided into 4 groups on the basis of degree and duration of changes in airway resistance after *d*-tubocurarine administration.

Group 1 consisting of 14 patients, showed a steady small decrease in lung resistance or else a fairly constant lung resistance value. Two examples are shown in figure 4.

The resistance changes in the 4 patients in group 2 were also minimal. Airway resistance first declined followed by an increase which became maximal in fifteen minutes and was resolved by twenty minutes following *d*-tubocurarine administration (fig. 5).

Group 3, consisting of 3 patients, demonstrated the most dramatic airway resistance changes (fig. 6). An increased resistance was evident at five minutes and maximal at

TABLE 1. Airway Resistance Changes in Cm. H_2O/L./Second Following Intravenous *d*-Tubocurarine

Patient No.	Age (years)	Wt. (kg.)	Amount *d*-Tubo. (mg.)	Resistance ($\Delta P/Q$) in Cm. H_2O/L./Second										
				Time in Minutes from *d*-Tubocurarine Injection								Time in Minutes from 2nd *d*-Tubo. Inject.		
				0	0	5	10	15	20	25	30	5	10	15
1	48	60.3	30	7.34	7.35	7.31	7.15	8.08	8.20	—	—	9.10	8.93	—
2	35	59.4	27	—	5.04	6.22	6.34	6.88	6.90	—	—	7.08	11.07	9.74
3	37	62	27	6.58	6.89	6.54	6.30	6.46	6.50	—	—	6.80	6.66	—
4	43	67	33	—	11.44	10.95	11.12	10.32	10.46	10.82	10.50	10.85	11.09	—
5	68	54	24	8.58	8.14	8.71	8.86	8.69	9.55	—	—	7.42	7.56	—
6	73	79.4	36	19.28	19.43	19.82	18.83	19.38	19.37	19.47	—	18.53	19.13	—
7	50	57	24	7.80	7.55	7.55	7.75	7.10	7.11	7.14	—	6.28	4.83	—
8	41	64	30	—	10.25	10.16	10.23	10.11	10.20	—	—	10.06	8.93	—
9	66	68	30	7.89	7.84	7.35	7.14	7.09	7.00	—	—	6.97	6.93	—
10	57	68	30	—	5.82	6.09	5.12	5.38	5.02	4.95	—	7.35	5.04	—
11	69	90.4	39	8.70	9.00	8.53	8.25	7.26	8.64	7.60	—	7.94	7.63	7.80
12	68	79.8	36	6.42	6.15	5.98	4.78	4.23	4.17	4.23	—	3.89	6.42	—
13	41	66.2	30	—	9.08	8.27	7.91	7.34	7.16	—	—	6.84	6.67	—
14	68	66	30	9.11	8.56	8.39	8.15	8.10	6.91	6.88	—	7.64	8.02	—
15	61	71.2	33	10.32	10.47	11.94	11.85	10.91	10.61	—	10.91	12.74	12.52	12.52
16	21	65.3	30	4.13	3.72	3.67	4.85	4.88	3.40	—	—	3.37	5.20	
17	48	78.0	36	10.40	9.57	9.22	10.79	11.02	9.51	9.63	—	—	—	—
18	27	81.6	36	12.65	12.40	11.70	12.65	12.49	11.36	—	—	11.34	11.21	10.78
19	75	57.2	24	7.93	7.79	7.59	10.98	10.49	—	—	—	—	—	—
20	64	83.9	36	15.42	14.95	18.71	18.12	16.41	15.84	—	—	15.11	15.51	—
21	65	59.9	30	8.68	8.71	20.27	23.5	23.3	—	—	—	—	—	—
22	52	50.8	21	10.63	10.67	11.10	11.02	8.02	—	—	—	7.47	11.01	—
23	58	83.9	36	—	7.04	5.03	5.22	9.53	14.94	15.76	—	15.75	16.10	—

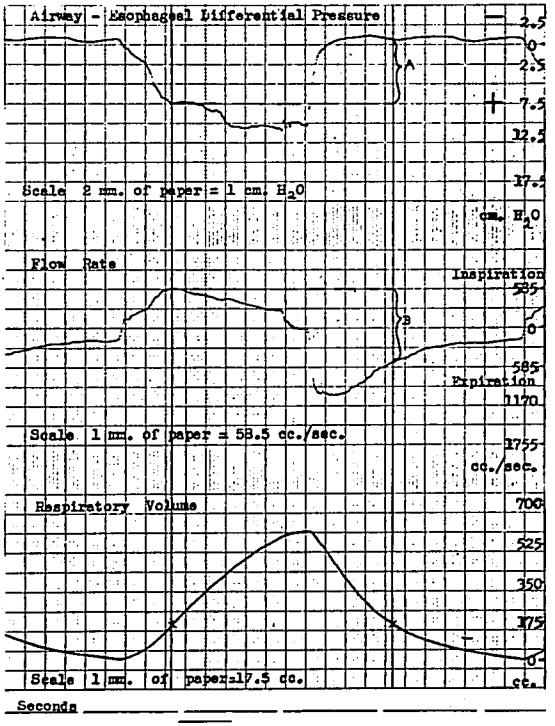

FIG. 3. Patient tracing showing transpulmonary pressure, respiratory flow rate, and the respiratory volume. Resistance (cm. H_2O/l./second) of the lung is computed as the change in transpulmonic pressure ($A = \Delta P$) (cm. H_2O) divided by the change in flow rate ($B = \Delta Q$) (liters/second).

TABLE 2. Airway Resistance Changes in Cm. H_2O/L./Second of Representative Cases from Groups 1 to 3

	Patient No.	Time in Minutes																			
		0		0		5			10			15			20			25			
		Mean	S.D.	Mean	S.D.	Mean	S.D.	S.E.	Mean	S.D.	S.E.	Mean	S.D.	S.E.	Mean	S.D.	S.E.	Mean	S.D.	S.E.	
Group 1	4	—	—	11.44	.40	10.95	.50	.32	11.12	.32	.26	10.32	.40	.27	10.46	.21	.23	10.82	.25	.24	
	6	19.28	.24	19.43	.32	19.82	.51	.30	18.93	.29	.22	19.38	.60	.34	19.37	.13	.17	19.47	.77	.44	
	13	—	—	9.08	.07	8.27	.30	.24	7.91	.28	.22	7.34	.25	.20	7.10	.33	.19	—	—	—	
Group 2	18	12.65	.28	12.40	.42	11.70	.23	.20	12.65	.12	1.8	12.49	.30	.23	11.36	.14	.18	—	—	—	
	17	10.40	.13	9.57	.25	9.22	.33	.21	10.79	.52	.41	11.02	.60	.45	9.51	.11	.33	9.63	.09	.52	
Group 3	19	7.93	.25	7.79	.24	7.59	.59	.37	10.98	.34	.24	10.49	.55	.31							
	21	8.68	.32	8.71	.41	20.27	1.58	.89	23.5	.77	.50	23.3	1.31	.79							

Level of significance: A difference between two mean values of twice the Standard Error indicates a level of significance equal to $P = .05$ (one time in twenty would the difference arise by chance).

ten minutes. Patient 21, despite intravenous isoproterenol, epinephrine, and hydrocortisone still had clinical signs of bronchial constriction eighteen hours after the study. Patient 19, some four hours after the study, had subjective difficulty in inspiring although adventitious sounds were not present in the lung fields and tidal and minute volumes were adequate.

One patient in whom airway resistance changes did not fit into any of the previous groups has been designated group 4 (fig. 7).

Scattergrams comparing age, weight, and total *d*-tubocurarine with the degree of airway resistance changes failed to show any correlation.

Discussion

Changes in intrapleural pressure are accurately reflected by changes in intraesophageal pressure regardless of patient position.[12,13,14] In preliminary work we have demonstrated that the relative change in esophageal pressure between inspiration and expiration for any one individual was independent of the patient's position. Because of these findings and because of the greater ease in handling supine anesthetized patients all patients were supine when studied.

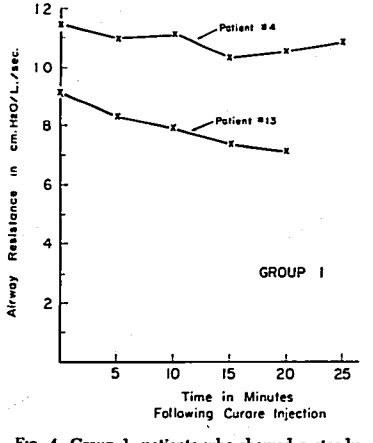

FIG. 4. Group 1, patients who showed a steady small decrease in lung resistance or a fairly constant lung resistance value.

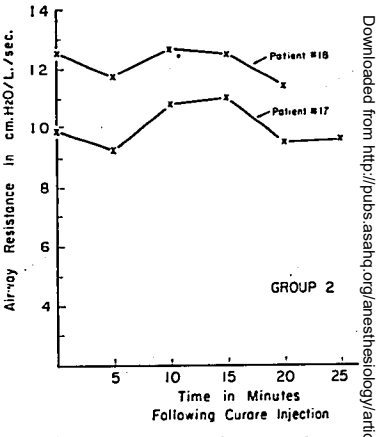

FIG. 5. Group 2, patients showing a decrease followed by an increase in resistance, maximal by fifteen minutes and resolved by twenty minutes, following *d*-tubocurarine administration.

It has been shown that 75 per cent of the total lung resistance is due to resistance to air flow offered by the tracheobronchial tree.[15] This is the segment that can be rapidly changed either passively, by collapse of the lung due to a pneumothorax, or actively, by chemical substances such as histamine, acetylcholine, or adrenalin. Small changes in the diameter of the bronchioles cause marked alterations in resistance in accordance with Poiseuille's Law which relates resistance to the reciprocal of the fourth power of the radius.

Nitrous oxide, 5 per cent carbon dioxide in oxygen [15] or 100 per cent oxygen for periods up to ten minutes [7] has no effect on airway resistance. Atropine constricts and lengthens bronchioles in dogs.[7]

Since all the factors affecting lung resistance except the bore of the tracheobronchial airways were kept constant, and since lung compliance also remained unchanged, any change in lung resistance following the administration of *d*-tubocurarine must have been due to a change in the tracheobronchial diameter.

The values given in table 1 for lung resistance at zero minutes are considerably greater than the commonly given values of 1.2–3.5 cm.

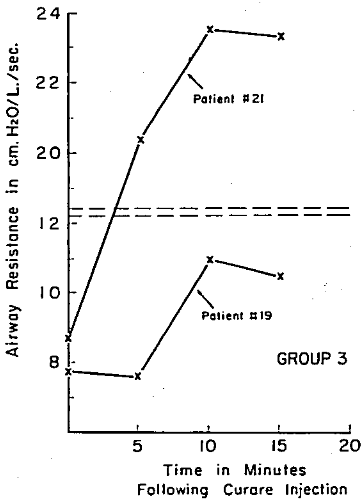

FIG. 6. Group 3, patients who demonstrated a marked change in pulmonary airway resistance following the intravenous administration of *d*-tubocurarine.

of water per liter per second for individuals respiring spontaneously.[16] In an attempt to explain this disparity lung resistance was measured in 2 patients before and after tracheal intubation. Both patients were breathing spontaneously and in both cases the lung resistance was doubled following tracheal intubation.

The degree of change in resistance caused by the endotracheal tube depends predominantly upon the difference between the diameter of the endotracheal tube and the diameter of the portion of the airway which it replaces. The endotracheal tube would most likely increase the lumen of the airway at its most narrow area, the glottis, but would decrease the lumen of the airway in the trachea. The latter effect would be the most prominent and an increased airway resistance would be expected.

The possibility also exists that the presence of the endotracheal tube in the larynx and trachea might reflexly cause bronchial constriction and hence an increase in airway resistance.

In addition, during these experiments respiration became passive on the patient's part and changed in nature from negative pressure breathing to positive pressure breathing. Air entering the tracheobronchial tree had to exert sufficient transmural pressure to overcome the elastic resistance of the lung tissue which was no longer opposed by the active outward movement of the chest wall and diaphragm. Also the diameter of the bronchi are narrowest at the onset of positive pressure inspiration as the lung is in the resting expiratory position.[16, 18]

Although the flow rate was kept constant during the studies on any one patient and an attempt was made to keep the actual flow rate within a physiological range [17] any increase in flow rate above the patient's normal flow rate would give a higher resistance value than would be expected in paitents breathing spontaneously.

One or any combination of these factors could be responsible for the initial high resistance values seen in the study patients.

The greatest number of patients were in group 1 and these showed a steady small decrease in lung resistance or else a fairly constant lung resistance value. In this group the administration of *d*-tubocurarine did not affect the lung resistance (fig. 4).

Following ventilatory control, all patients had a relatively high airway resistance. In most cases this resistance decreased quickly to a constant resistance value. However, in some cases there was a period of rapid adaptation to positive pressure ventilation but a prolonged period of small but constant decrease in the airway resistance. The time referred to as 0 minutes in tables 1 and 2, 30 minutes after ventilatory control had been established, was the time when two resistance values were statistically similar. Those patients in group 1 who showed a steady small decrease in lung resistance may still have been in this adaptive phase.

d-Tubocurarine, through its parasympathetic ganglionic blocking properties, may have blocked the stretch reflex of the vagi, thereby increasing the diameter of the bronchioles.[18] Widdicombe [19, 20] showed that these stretch receptors were located in the bronchioles. Under positive pressure ventilation intravenous acetylcholine or histamine caused a bronchoconstriction by increasing the frequency of dis-

charge and shortening of the time of onset of discharges from these slowly adapting stretch receptors.[18] Dawes' [18] work indicates that the afferent arm of this reflex is via the vagi nerves. Guyton [21] has shown that curare is able to block impulse transmission over the vagus nerve through parasympathetic ganglionic blockade and by so doing can obtund this reflex.

With the loss of this reflex, passive distention of the bronchioles would then cause a lowering of resistance by increasing the total lung volume.[22]

An explanation of the changes in airway resistance seen in the patients comprising group 2 (fig. 5) can be given by examining the three known actions of curare: ganglionic blockade, neuromuscular blockade, and histamine release. The important observations here are: (1) the sudden rise in resistance, (2) the small magnitude of the rise although statistically significant and, (3) the rapid return to a pre-elevation resistance value.

It is unlikely that ganglionic blockade could be responsible for a rise in resistance as such a blockade would have to involve the sympathetic ganglia leaving parasympathetic ganglionic transmission intact.[21, 23] No evidence exists for sympathetic ganglionic blockade by *d*-tubocurarine in doses of the magnitude used here. Also parasympathetic ganglia are paralyzed with much smaller doses and Guyton has shown that the vagi are particularly sensitive to this block.[21]

This pattern can be attributed to the neuromuscular blocking effect of curare. The normal peak action of *d*-tubocurarine is five to ten minutes after administration. Following the injection of *d*-tubocurarine the tone of the intercostal muscles and the diaphragm is lost, and the intrapleural pressure (intraesophageal) rises from a negative value to close to zero. The elastic property of the lung unopposed by the tone of the diaphragm and intercostal muscles, tends to collapse it towards the hilum narrowing the bronchial tree and perhaps even entirely collapsing scattered terminal segments. This then raises the resistance to airflow until by the adaptive mechanisms already described the previous resistance level is attained.

The above explanation is not adequate to explain the resistance changes that occurred in

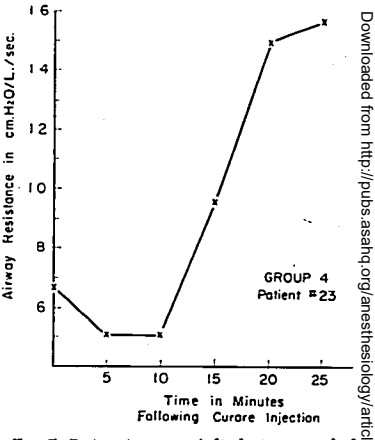

FIG. 7. Patient in group 4 displaying a marked rise in resistance probably secondary to an excessive amount of endobronchial mucus.

the patients in group 3. The resistance changes in these patients were of greater magnitude and were more prolonged than those changes that occurred in the patients of group 2 (fig. 6).

We believe that the resistance changes that occurred in group 3 patients are the result of histamine uptake by the end-organs related to the tracheobronchial tree. As was previously mentioned, the release of endogenous histamine has been implicated as the cause of many "histamine like reactions" that occur following *d*-tubocurarine administration. No measurement of blood histamine was made on these patients, but we have shown that *d*-tubocurarine is capable of elevating blood histamine under similar test conditions. We have also shown that at the time of the "histamine like reaction" there is a drop in the blood level of histamine probably due to the uptake of histamine by the various effector cells.[24]

Bouhuys and co-workers [25] have shown that hexamethonium given to asthmatic patients prior to histamine aerosol inhalation completely prevents the bronchoconstriction which normally results. These workers have also shown that adrenalin aerosol inhalation prior to the histamine aerosol modifies the bronchoconstric-

tion. Atropine also diminishes the bronchoconstrictor response.[26] This work adds strength to the proposition that the bronchoconstriction induced by histamine is mediated through a neurogenic mechanism or reflex.[25] Ganglion cells are known to exist in the bronchial walls and are, like the stretch receptors, approximated to preganglionic vagal fibers.[27] Herxheimer [28] has shown that hexamethonium protected guinea pigs against anaphylactoid and histamine induced shock. Curry [29] demonstrated the protective effect of hexamethonium on histamine and methacholine actions in man. It has been suggested that a function disorder of autonomic nervous structures in the bronchial walls may be of importance in the pathogenesis of bronchial asthma as well.[25]

We can offer no evidence as to the underlying mechanism of the reaction. Whether any of the previously mentioned conditions were present in our patients cannot be proven from these studies. Our patients, however, had no clinical evidence of cardiopulmonary disease and none had any history of allergy.

It is also possible that *d*-tubocurarine may directly sensitize the end-organs in certain individuals, although evidence for or against such a mechanism does not exist. The possibility that the individuals in this group had a latent hypersensitivity to histamine or were latent asthmatics cannot be excluded. Any degree of bronchial obstruction before histamine release by curare, such as edema of the bronchial endothelium, hypertrophy of bronchial smooth muscle, and endobronchial mucus, would accentuate the effect of bronchial narrowing by histamine, as resistance is inversely proportional to the fourth power of the radius.

The resistance changes seen in patient 23 (fig. 7) cannot be explained adequately. The onset of the rise is too late to be explained by histamine release, and the magnitude is too great to be from neuromuscular blockade of the chest wall and diaphragmatic muscles. A mucus plug or increasing narrowing of the bronchioles from retained mucus gives a similar picture.

Twenty of the 23 patients received a second dose of *d*-tubocurarine, and table 1 shows that airway resistance changes were quite varied. Few conclusions can be drawn as the study-time interval following the second dose of *d*-tubocurarine was too short to allow any pattern in resistance changes to develop. Increases in airway resistance of a magnitude comparable to resistance changes seen in group 3 patients, however were observed (patient 2). Secondary airway resistance changes showed no correlation with the primary changes.

Summary and Conclusions

The effect on pulmonary airway resistance of a .44 mg./kg. body weight dose of *d*-tubocurarine administered as a single intravenous injection has been evaluated. Twenty-three patients free of cardiorespiratory disease and having no history of allergy comprised the study group.

An elevated airway resistance resulted in 4 cases. In 4 instances the elevation was minimal and was considered to be due to the passive collapse of bronchioles resulting from the paralysis of the intercostal and diaphragmatic muscles.

In 3 instances the elevated airway resistance was believed to be due to histamine uptake by effector end-organs located in bronchial walls. It is suggested that the histamine release was produced by intravenous *d*-tubocurarine.

Two patients had airway resistance changes which were not considered directly related to *d*-tubocurarine administration.

No correlation between age, weight, or total *d*-tubocurarine and type or degree of airway resistance change existed.

This investigation was reported in part at the New York State Fourteenth Postgraduate Assembly in Anesthesiology, 1960, and was done in partial fulfillment of requirements for Master of Science degree from the University of Minnesota. Supported by Research Grant H-1983(C6) from the United States Public Health Service.

References

1. West, R.: Pharmacological study of derivatives of two specimens of tube-curare, Arch. int. pharmacodyn. 56: 81, 1937.
2. —: Action of curarine on respiration. Lancet 1: 432, 1938.
3. Harvey, A. M., and Marsland, R. L.: Actions of curarizing preparations in human, J. Pharmacol. Exp. Ther. 73: 304, 1941.
4. Landmesser, C. M., Converse, J. G., and Harmel, M. H.: Quantitative evaluation of

bronchoconstrictor action of curare in anesthetized patient, preliminary report, ANESTHESIOLOGY 13: 275, 1952.
5. West, R.: Pharmacology and therapeutics of curare and its constituents, Proc. Roy. Soc. Med. 28: 565, 1934–5.
6. —: Action of curarine on respiratory mechanisms, J. Physiol. 91: 437, 1938.
7. Kilburn, K.: Dimensional responses of bronchi in apneic dogs to airway pressure, gases and drugs, J. Appl. Physiol. 15: 229, 1960.
8. Cole, F.: New lethal dose of curare with some observations on the pathology produced by large doses, ANESTHESIOLOGY 7: 190, 1946.
9. Griffith, H. R.: Physiological and clinical actions of curare, Anesth. Analg. 25: 45, 1946.
10. Radford, E. P., Jr., Ferris, B. G., and Kriete, B. C.: Clinical use of nomogram to estimate proper ventilation during artificial respiration, New Engl. J. Med. 251: 877, 1954.
11. Mead, J., Mellroy, N. B., Silverstone, N. J., and Kriete, B. C.: Measurement of intraesophageal pressure, J. Appl. Physiol. 7: 491, 1955.
12. Fry, D. L., Stead, W. W., Ebert, R. V., Lubin, R. I., Wells, H. S.: Measurement of intraesophageal pressure and its relationship to intrathoracic pressure, J. Lab. Clin. Med. 40: 664, 1952.
13. Cherniak, R. M., Farhi, L. E., Armstrong, B. W. and Proctor, D. F.: Comparison of esophageal and intrapleural pressure in man, J. Appl. Physiol. 8: 203, 1955.
14. Marshall, R., and Dubois, A. B.: Viscous resistance of lung tissue in patients with pulmonary disease, Clin. Sci. 15: 473, 1956.
15. Butler, J. B., Caro, C. G., Alcala, R., and Dubois, A. B.: Physiological factors affecting airway resistance, J. Clin. Invest. 39: 584, 1960.
16. Butler, J.: Mechanical properties of lung, Brit. J. Dis. Chest 54: 118, 1960.
17. Mead, J., and Whittenberger, J. L.: Physical properties of human lungs measured during spontaneous respirations, J. Appl. Physiol. 5: 779, 1953.
18. Dawes, G. E., and Comroe, J. H., Jr.: Chemoreflexes from heart and lungs, Physiol. Rev. 34: 167, 1954.
19. Widdicombe, J. G.: Respiratory reflexes from trachea and bronchi of cat, J. Physiol. 123: 55, 1954.
20. —: Respiratory reflexes excited by inflation of lungs, J. Physiol. 123: 105, 1954.
21. Guyton, A. C., and Reeder, R. C.: Quantitative studies on autonomic actions of curare, J. Pharmacol. Exp. Ther. 98: 188, 1950.
22. Marshall, R.: Physical properties of lungs in relation to subdivisions of lung volume, Clin. Sci. 16: 507, 1954.
23. Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, ed. 2. New York, Macmillan Co., 1955, p. 604.
24. Westgate, H. D., Schultz, E. A., and Van Bergen, F. H.: Urticaria and angioneurotic edema following *d*-tubocurarine administration, ANESTHESIOLOGY 22: 288, 1961.
25. Bouhuys, A., Jonnason, R., Lichtneckert, S., Lindell, S. E., Lundgren, C., Lundlin, G., and Ringquist, T. R.: Effects of histamine on pulmonary ventilation in man, Clin. Sci. 19: 75, 1960.
26. Michelson, A. L., Hollander, W., and Lowell, F. C.: Effect of 5-hydroxytryptamine (serotonin) on respiration of nonasthmatic and asthmatic subjects, J. Lab. Clin. Med. 51: 57, 1958.
27. Kuntz, A.: The Autonomic Nervous System, ed. 4. Philadelphia, Lea & Febiger, 1953, p. 184.
28. Herxheimer, H.: Bronchoconstrictor agents and their antagonists in intact guinea pigs, Arch. pharmacodyn. 106: 371, 1956.
29. Curry, J. J., Fuchs, J. E., and Leard, S. E.: Effects of dihydroergocornine on pulmonary response to methacholine and histamine in subjects with bronchial asthma, J. Clin. Invest. 29: 439, 1950.