THE ABSORPTION OF ADRENALIN AFTER INTRA-TRACHEAL INJECTION.*

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In order to subject a living organism to the systemic action of any soluble substance, it is obvious that the substance must first reach the circulating fluids of this organism; from the lymph and blood streams the drug then may pass into the tissues and exert its effect. The main routes available for bringing any substance into contact with the tissues are as follows: (1) by introduction into the gastro-intestinal canal; (2) by subcutaneous, intramuscular, intravenous, or intraspinal injection; (3) by inunction through the skin; and (4) through the respiratory tract.

Of these routes the first two are most frequently employed in human therapeutics and in the laboratory. Inunction is used only exceptionally at the present time, and practically the only drug administered through the skin for its systemic action is mercury.

The respiratory route also is not utilized to any extent, except for purely local effects, when it is desired to incorporate a drug. Syphilis was occasionally treated by allowing the patient to inhale the sublimated metal, but this method was never extensively employed because of the impossibility of judging the dose. Local affections of the respiratory passages, for example, laryngitis, bronchitis, and bronchiectasis, are treated by allowing the patient to inhale the vapors of boiling water to which various substances (creosote, eucalyptol, opium preparations, etc.) have been added. Experimentally the respiratory passages are practically not utilized when a drug is to be administered for its general action.

* A preliminary report was published in the Proceedings of the Pharmacological Society (*Jour. Pharm. and Exper. Therap.*, 1914–15, vi, 608).

Among the relatively few experimenters who have used the intratracheal method for this purpose we may mention Külbs,[1] who injected rabbits repeatedly for a number of days with adrenalin, introducing the hypodermic needle into the trachea through the skin of the neck. He observed cough after the injection, and twice an animal died a few minutes after the injection, from pulmonary edema. In those animals which survived the injections, which were given every day or every other day for 22 to 78 days, the total amount being 3.4 to 14 cc. of adrenalin, he found the same macroscopic and microscopic alterations, though of smaller extent, which he obtained after intravenous injection of adrenalin.

Ephraim[2] in a series of papers reports the results of endobronchial treatment of chronic bronchitis and asthma in the human subject. Various drugs, including adrenalin, were introduced as a fine spray into the bronchi, often through a bronchoscope. The effects obtained were chiefly local; even after the bronchial administration of 1 mg. of adrenalin by means of a nebulizer, he obtained no definite rise of blood pressure. In a dog, however, the same method yielded a powerful rise of blood pressure when a large amount, 2 mg., was used.

The failure of Ephraim to obtain a rise of pressure after the administration of 1 mg. of adrenalin endobronchially in the human subject is perhaps attributable to the method. Ephraim himself observed in rabbits that the spray of a colored solution from a nebulizer, even when introduced into the trachea, did not reach the bronchi, the vapor being precipitated near the point of application. In the same way the endobronchial spray of adrenalin was possibly precipitated in the larger bronchi so that only negligible amounts reached the alveolar region where, as we shall show, the absorption is best.

That even colloids can be absorbed with rapidity when injected intratracheally is shown by Ishioka.[3] Ishioka sensitized guinea pigs by the subcutaneous injection of human serum and after 12 to 15 days injected 0.05 to 0.1 cc. of human serum into the trachea of these animals with the object of producing an anaphylactic pneumonia. He observed the milder anaphylactic symptoms in the majority of his experiments, but in two instances acute death with the typical lung picture resulted.

The absorptive capacity of the supratracheal respiratory passages does not concern us here; references concerning the effect of inhaled substances will be found in the papers by Ephraim.

Our own experiments will show that the intratracheal injections of adrenalin are rapidly absorbed even under disadvantageous conditions and exert a systemic effect, and also that this method may be of value therapeutically when a rapid action on the heart is desired.

[1] Külbs, *Arch. f. exper. Path. u. Pharm.*, 1905, liii, 150.

[2] Ephraim, A., *Deutsch. med. Wchnschr.*, 1911, xxxvii, 2079; 1912, xxxviii, 1453.

[3] Ishioka, S., *Deutsch. Arch. f. klin. Med.*, 1912, cvii, 500.

Methods.

The research was carried out entirely with rabbits, and the chief test substance employed was adrenalin. Adrenalin was chosen because its absorption could be readily detected by recording the blood pressure, and the character and degree of the resultant rise would give some indication of the speed and amount of absorption.

The animals were anesthetized by ether for the operative interferences. These were the insertion of a cannula into the right carotid artery; transection of the trachea with introduction and ligation of a wide glass tube about 2 cm. long into the distal stump so that the respiratory path was free and injection into the trachea easy; in some rabbits the tracheal cannula was inserted as near the thorax as possible and the lower end of the proximal trachea then ligated, thus converting the cervical trachea into a sac from which the absorption of adrenalin could be tested; in a number of experiments both vagi were sectioned in the neck.

The blood pressure was written by a mercury manometer connected with the artery by tubing filled with a half saturated solution of sodium sulphate.

The adrenalin used was generally the commercial solution in 0.1 per cent strength, preserved with chloretone. In some experiments, however, a solution was made from the commercial powder preparation, and this was used with or without the addition of chloretone.

The dose injected varied from 0.15 to 0.03 cc. per kilo of body weight. The maximum dose quoted was occasionally greatly exceeded when adrenalin was injected intramuscularly.

The solutions were injected into the respiratory passages in several ways. Usually the required amount was injected in 4 to 6 seconds from a Record tuberculin syringe into the tracheal cannula. In a number of experiments a filiform catheter was introduced into a bronchus and the solution then driven in by a gentle blast of air. A few times the solution was injected directly into the lung tissue by passing the hypodermic needle through the walls of the chest.

In a majority of the experiments doses of adrenalin were injected repeatedly, not only into the trachea but also into the erector spinæ muscles of the back.

The rabbits were always placed on an electric warming pad to reduce or prevent the loss of body heat.

EXPERIMENTAL RESULTS.

Twenty-three experiments were carried out in the adrenalin series; in ten of these tests both vagi were cut previous to the injection of the drug. The course of the experiments and the characteristic effects will be illustrated by a few typical protocols arranged in tabular form.

All rabbits tabulated were tracheotomized under light ether anesthesia; there was no insufflation of air except in No. 3 (Table I); vagi

were intact, except in No. 8 (Table IV); all injections into the trachea were made with a syringe through the tracheal tube.

TABLE I.

No. of animal.	Color. Sex. Weight.	No. of injection.	Method and site of injection.	Amount of adrenalin per kilo.	Latent period of blood pressure rise.	Blood pressure rise.	Duration of blood pressure rise.	Interval between injections.
				cc.	*sec.*	*mm.*	*min.*	*min.*
3		1	Catheter into bronchus.	0.23	12	64 (104–168)	8	
		2	Trachea.	0.23	—	45 (90–135)	9	9
	Gray ♀	3	"	0.23	6	25 (107–132)	9	10
Vagi intact.	2,210 gm.	4	Erector spinæ muscle.	0.23	No rise in 4 min.			10
		5	Erector spinæ muscle.	0.46	" " " 4 "			4
		6	Trachea.	0.23	7	24 (96–120)	18	4

Killed by medullary puncture after experiment. Lungs showed only a moderate degree of pulmonary edema.

6		1	Tracheal sac.	0.25	52	16 (91–107)	15	
		2	Trachea.	0.25	12	60 (100–160)	—	17
	Gray ♂	3	Tracheal sac.	0.25	No rise in 6 min.			16
Vagi intact.	2,100 gm.	4	Trachea.	0.25	3	40 (62–102)	10	8
		5	Erector spinæ muscle.	0.5	No rise in 7 min.			10
		6	Trachea.	0.25	4	26 (80–106)	7	10

Killed later by medullary puncture. The lower lobes of both lungs showed well marked pulmonary edema; slight in upper lobes.

TABLE II.

No. of animal.	Color. Sex. Weight.	No. of injection.	Method and site of injection.	Amount of adrenalin per kilo.	Latent period of blood pressure rise.	Blood pressure rise.	Duration of blood pressure rise.	Interval between injections.
				cc.	*sec.*	*mm.*	*min.*	*min.*
7		1	Trachea.	0.12	2	50 (100–150)	6	
		2	"	0.12	4	39 (88–127)	12	9
	Gray ♂	3	Erector spinæ muscle (left).	0.6	3	43 (99–142)	20	13
	1,610 gm.	4	Trachea.	0.12	8	21 (98–119)	10	21
Vagi intact.		5	"	0.12	5	25 (95–120)	12	15
		6	Erector spinæ muscle (right).	0.28	No rise in 8 min.			14
		7	Trachea.	0.12	3	24 (92–116)	21	8
		8	"	0.24	10	10 (102–112)	5	20

Killed later by medullary puncture. Lungs collapsed well and showed only a moderate degree of pulmonary edema.

8		1	Trachea.	0.21	6	64 (114–178)	15	
Vagi cut.	White ♀ 2,365 gm.	2	"	0.21	10	30 (110–140)	6	18
		3	"	0.21	8	16 (116–132)	9	8
		4	Erector spinæ muscle.	0.42	No rise in 4 min.			15

Pink fluid poured from trachea 13 min. after first dose. About 5 min. after last injection, blood pressure fell abruptly, convulsions, death. Lungs showed marked pulmonary edema.

TABLE III.

No. of animal.	Color. Sex. Weight.	No. of injection.	Method and site of injection.	Amount of adrenalin per kilo.	Latent period of blood pressure rise.	Blood pressure rise.	Duration of blood pressure rise.	Interval between injections.
				cc.	*sec.*	*mm.*	*min.*	*min.*
4		1	Erector spinæ muscle (left).	0.23	14	34 (106–140)	4	
		2	Jugular vein.	0.23	At once.	43 (107–150)	10	9
Vagi intact.	Gray 2,160 gm.	3	Trachea.	0.23	8	20 (110–130)	10	9
		4	Erector spinæ muscle (right).	0.23	No rise in 2 min.			11
		5	Trachea.	0.23	10	10 (100–110)	3	2
		6	Erector spinæ muscles.	0.23	No rise.			

After last injection foam and pink fluid poured from trachea (marked pulmonary edema).

A study of these typical protocols as given in Tables I, II, and III shows with clearness all the points we wish to emphasize, and they will now be considered in detail.

Latent Period.—The latent period elapsing between injection and the onset of the blood pressure rise varied between 2 and 38 seconds, but usually was less than 10 seconds; the general average of all first injections was 13 seconds. Repeated injections exerted no uniform effect on the length of the latent period. Thus in Experiment 7 the first dose of 0.12 cc. of adrenalin per kilo injected into the trachea surely reached a physiologically effective concentration in the blood within 2 seconds, for after that interval the blood pressure began to rise. The seventh injection of the same dose in the same place, 80 minutes later, exerted a blood pressure effect after a latent period of only 3 seconds, in spite of the fact that the animal had received intratracheally and intramuscularly in the interval between the two injections mentioned 1.24 cc. of adrenalin per kilo, divided into five doses. A still more striking example of the speed of absorption is

given in Experiment 8. In this experiment the vagi had been cut before administering the adrenalin, and the first dose of 0.21 cc. per kilo into the trachea caused a pulmonary edema of such an extent that foam and pinkish fluid poured from the tracheal cannula. Nevertheless, a repetition of the same dose in the same place a few minutes later exerted a good blood pressure effect after a latent period of only 10 seconds. In this instance the area available for absorption was undoubtedly reduced considerably by the pulmonary edema, yet the speed of absorption was still rapid. All the tabulated protocols show a similar rapid absorption after intratracheal injections.

The latent period or speed of absorption was not apparently affected by the amount of adrenalin injected; for example, in Experiment 3 the intrabronchial injection of 0.23 cc. per kilo by means of a catheter showed a latent period of 12 seconds before the blood pressure began to rise. In Experiment 7, on the other hand, a much smaller dose per kilo, 0.12 cc., injected into the trachea gave a blood pressure effect after a latent period of only 2 seconds.

Quantitative Absorption.—The quantitative absorption cannot be definitely established, yet the blood pressure rises obtained after the various injections furnish some indication of the amount of adrenalin absorbed. Examination of the absolute values of the blood pressure rises in mm. of mercury obtained after successive injections of the same dose of adrenalin in the same place, the lung passages for example, shows that the blood pressure effect in general decreases with the number of injections. Thus in Experiment 7 five doses of 0.12 cc. of adrenalin per kilo were injected into the trachea, the time intervals varying between 9 and 34 minutes if the interpolated intramuscular injections are included. The blood pressure rises after these five tracheal injections were 50, 39, 21, 25, and 24 mm. In Experiment 8 the successive decrease of effect is more pronounced. In this experiment 0.21 cc. of adrenalin per kilo into the trachea at intervals of 8 to 18 minutes gave the following rises of blood pressure: 64 ,30, and 16 mm. In this animal, however, the vagi had been sectioned previous to the first injection of adrenalin, and after the first dose a marked pulmonary edema developed during which fluid poured from the tracheal cannula. The presence of so much fluid decreased the absorptive area available, and in addition diluted the adrenalin with a colloidal

solution, rendering absorption still slower, yet in spite of this the speed of absorption was not appreciably delayed, the latent period being 10 and 8 seconds, but the amount absorbed, as judged by the pressure rises, showed practically 50 per cent decreases.

This decrease in effectiveness in causing a blood pressure rise shown by successive tracheal injections is in accord with the observations of Meltzer and Auer[4] that adrenalin diminishes absorption from the tissues. These authors demonstrated, among other facts, that the intravenous injection of adrenalin delays the absorption of strychnine or fluorescein from the subcutaneous tissue, and also that repeated intramuscular injections give a decreasing blood pressure effect, due to diminished absorption.

It will be noticed on examining the tables that all injections of adrenalin into the trachea gave some blood pressure effect; in other words, that some absorption took place even under unfavorable circumstances. A comparison was therefore made between the absorptive capacity of the lung and that of the erector spinæ muscles. The erector spinæ muscle was chosen because this thick mass of muscle is composed of fine fibers not separated into coarse fasciculi, like the glutei for example, and in addition is surrounded by a dense fascia which exerts pressure upon the injected substance, thus facilitating absorption. Injection into this muscle has been shown by Meltzer and Auer[4] to be practically equivalent to an intravenous injection.

The experimental test gave important results. It clearly appeared that the injection of several doses of adrenalin into the lung passages reduced the absorption from the erector spinæ muscles to such a degree that even double the intratracheal dose given intramuscularly did not enter the circulation in sufficient amount to affect the blood pressure; nevertheless, another injection of the original dose of adrenalin into the lungs promptly entered the circulation in sufficient concentration and amount to cause a blood pressure rise (see Experiments 3, 6, 7, and 4). This fact appears with especial clearness in Experiment 3. In this test the rabbit received three doses each of

[4] Meltzer, S. J., and Auer, J., *Tr. Assn. Am. Phys.*, 1904, xix, 207; *Jour. Exper. Med.*, 1905, vii, 59. Auer and Meltzer, *ibid.*, 1911, xiii, 328.

0.23 cc. of adrenalin per kilo into the lung, the time consumed being about 29 minutes. Each injection gave a rise of blood pressure (64, 45, and 25 mm.). Then the same dose was injected intramuscularly, but no blood pressure rise occurred in 4 minutes. The dose was then doubled and 0.46 cc. per kilo was injected into the other erector spinæ muscle, but again no blood pressure rise followed. 4 minutes later the original dose of 0.23 cc. was injected into the lung passages and after a latent period of 7 seconds the blood pressure began to rise and reached an absolute value of 24 mm. of mercury.

The failure to obtain a blood pressure effect from an intramuscular injection of adrenalin under the conditions mentioned is, however, not absolute. If the dose administered intramuscularly is increased sufficiently, enough adrenalin will be absorbed to cause a blood pressure rise. This is illustrated in Experiment 7. Two lung injections of 0.12 cc. of adrenalin each had been injected in about 22 minutes. Then five times the dose (0.6 cc. per kilo) was injected intramuscularly; after a latent period of 3 seconds the blood pressure rose 43 mm. That there was, nevertheless, a definitely diminished absorption from this large intramuscular injection is shown by the fact that the rise of blood pressure, 43 mm., is even less than that caused by the first lung injection of only one-fifth the dose, which latter raised the pressure 50 mm. Subsequent injections of adrenalin into the lungs all gave rises of blood pressure, but an interpolated intramuscular injection of double the pulmonary dose gave no blood pressure effect. The amount absorbed from the muscles had fallen below the level of a physiologically effective dose.

In some experiments the conditions were still further varied by preceding the lung injections of adrenalin by intramuscular and intravenous injections of the same substance. Experiment 4 is one of this type. The adrenalin dose was always 0.23 cc. per kilo. After an intramuscular and an intravenous injection, absorption of adrenalin from the lung was by no means prevented, the blood pressure rising 20 mm. after a latent period of 8 seconds. A subsequent intramuscular dose, however, produced no blood pressure rise within 2 minutes. Another lung injection even now caused a definite rise of pressure.

These experiments definitely show that, under the conditions

mentioned, absorption from the lungs occurs with doses of adrenalin which are ineffective when injected intramuscularly.

There was no definite relationship to be observed between the amounts of adrenalin injected into the lungs and the resultant blood pressure rise. The same dose per kilo often produced widely different rises in different animals, and smaller doses often caused greater elevations of pressure than larger ones. Table IV illustrates this and demonstrates in addition that the amount of adrenalin injected played no part.

TABLE IV.

		gm.			*mm.*
No. 5	Vagi intact.	1,650	0.3 cc. per kilo (0.5 cc.)	4 sec. latent period.	33 rise (107–140)
" 7	" "	1,610	0.12 cc. per kilo (0.2 cc.)	2 " " "	50 rise (100–150)
" 8	" cut.	1,980	0.25 cc. per kilo (0.5 cc.)	18 " " "	30 rise (114–144)
" 13	" "	1,790	0.25 cc. per kilo (0.4 cc.)	18 " " "	82 rise (116–198)

Blood Pressure.—The duration of the blood pressure elevation was usually less than 10 minutes; if only the effects of the first tracheal injections are considered the average is 6 minutes. Subsequent injections, however, often showed a definitely longer duration of the elevation. An illustration of this effect will be found in Experiment 7.

The character of the rise varied somewhat; it was usually more or less abrupt, the maximum being reached within 30 seconds. In other instances the maximum elevation was reached in about 1 minute. The abruptness of the rise seemed to bear some relation to the number of preceding injections, the slope becoming less steep with succeeding doses. This, however, was by no means true of all experiments, for in some all intratracheal injections gave sharp rises of pressure. Vagus pulses were often observed, but their occurrence was not as frequent as when the adrenalin is administered intravenously or intramuscularly.

In a number of experiments abrupt and profound drops of blood pressure were noted. These occurred without any warning during the maximum pressure elevation, the pressure falling within a few

seconds to 20 mm. and even less. These drops lasted from 30 to 160 seconds, and were not necessarily fatal. In some instances a number of these profound drops occurred, recovery of the blood pressure taking place spontaneously after a series of convulsions. When these drops occurred, they were always associated with more or less pronounced signs of pulmonary edema. The significance of this phenomenon will be discussed in a later paper.

Site of Absorption.—In order to obtain some information regarding the site of absorption of the injected drug, a few experiments were made with intratracheal injections of India ink or suspensions of lampblack in an extremely dilute gum arabic solution. Doses of 0.3 cc. per kilo of body weight were injected slowly by syringe into the tracheal cannula. 10 seconds after the injection the medulla was destroyed by puncture, and the lungs and trachea were immediately excised and examined. The three experiments carried out gave concordant evidence: the posterior and diaphragmatic surfaces of the lower left lobe always showed a large number of discrete and confluent, irregular black spots varying from about 2 to 5 mm. in diameter. The surfaces of the other lobes showed only a few or no spots, and these were confined largely to the posterior surfaces near the hilus of the right lower and right middle lobes.

On sectioning the lungs through the trachea and bronchi, the larger part of the left lower lobe was found to be a black mass containing foam and some fluid. The right lower and right middle lobes near the hilus also contained an amount of pigment which was greater than would be expected from the surface indications. The upper lobes and the median lappet showed a few spots in the body of these divisions.

The sections of the lung containing the pigment were larger and fuller than those free from it; moreover, they contained more fluid. The distension was greater than the amount of fluid present explained, and apparently was at least partly caused by a mechanical plugging of the bronchioles and infundibular ducts by the pigment. The amount of fluid present in the tissues seemed greater than the amount injected (0.3 cc.), so that perhaps some degree of pulmonary edema also developed.

These experiments with the tracheal injection of pigment suspen-

sions thus indicate that a certain amount penetrates to the alveoli, chiefly of the left lower lobe, within less than 1 minute, and that absorption in all likelihood takes place there.

It might be thought that some absorption could take place from the mucosa of the trachea and the bronchi, and such absorption indeed does take place, at least as far as the tracheal mucosa is concerned. This absorption from the tracheal mucosa is, however, quite slow and the blood pressure rise obtained sets in very slowly. We tested the absorptive power of the tracheal mucosa in the following way. The tracheal cannula was inserted as low as possible in the neck; the upper section of the trachea was then ligated near the cannula, converting it into a sac. Injections of adrenalin were then made into this sac and the blood pressure effect was noted. In the two experiments made the first injection of adrenalin gave each time a slow and gradual rise of pressure, the latent period being respectively 150 and 52 seconds. In the first experiment the blood pressure rise equaled 59 mm. and lasted longer than 15 minutes. In the second experiment (Experiment 6) the first injection into the tracheal sac gave a rise of only 16 mm. of mercury after a latent period of 52 seconds, the rise persisting for more than 15 minutes. A subsequent repetition of the injection gave no blood pressure effect within 6 minutes. The doses of adrenalin injected were respectively 0.3 and 0.25 cc. per kilo.

These experiments show that while absorption of adrenalin does take place from the tracheal mucosa, and therefore probably also from the bronchi and bronchioles, these surfaces play only a subsidiary part as sites of absorption when adrenalin is injected into the trachea.

Section of the vagi in the neck before the intratracheal injection of adrenalin yielded interesting results. These nerves were cut in order to prevent the occurrence of those profound blood pressure drops mentioned previously, on the assumption that they were due to the well known initial effect of adrenalin upon the vagus center. However, these drops still occurred in some of the experiments after section of the vagi, and in addition, pulmonary edema and sudden death were much more frequent than in the series with vagi intact. One intratracheal injection of adrenalin often sufficed to bring on a strong pulmonary edema and even death within a few

minutes. Without entering here into a discussion of all the phenomena observed, it may be said, in general, that section of the vagi produced no noteworthy alteration in the absorptive power of the lung tissue as far as adrenalin is concerned. The variations observed in the vagotomized series fell well within the range of those seen in the normal series, though a percentage reckoning of all intratracheal injections given for the first time, shows that the vagotomized animal exhibited a shorter latent period (10 against 13 seconds), a higher blood pressure rise (56 against 46 mm.), and a longer duration of the pressure elevation (9.5 against 6 minutes). Not much stress, however, should be laid upon averages gained from only twenty-three experiments, especially in this work where pulmonary edema entered as a complicating factor in the vagotomy series.

A number of experiments were also carried out with a 0.1 per cent solution of adrenalin made from the commercial powder, a few drops of concentrated hydrochloric acid being added to the sterile saline to bring about solution. This solution, with or without the addition of chloretone, did not give as good results when injected intratracheally as the solution obtained in the open market; the absorption was slower and the resultant rise of blood pressure less marked.

A few experiments were also carried out with the sodium salt of fluorescein. Solutions of this substance, in 1 or 10 per cent strength, were injected intratracheally, the dose being 0.3 cc. per kilo of body weight. Samples of blood were then taken at regular intervals from the carotid artery, allowed to clot in small test-tubes, and the serum was examined for fluorescence. These experiments also indicated a rapid absorption though not as striking as with adrenalin; after 15 to 30 seconds the blood samples showed the first detectable green fluorescence. This fluorescence rapidly increased at first, then more slowly, reaching a maximum after a number of minutes.

DISCUSSION AND SUMMARY.

In the preceding pages we have submitted evidence which shows that a simple intratracheal injection of a solution in a normally breathing rabbit penetrates within a few seconds to the alveoli, chiefly those of the left lower lobe; that absorption is rapid and well maintained;

and that the procedure may be repeated effectively a number of times even with a substance like adrenalin which decreases absorption. It was also shown that absorption of adrenalin from the lung could be obtained at a time when double the dose given intramuscularly exerted no blood pressure effect whatever, and that absorption could still take place after the development of pulmonary edema, when there was an undoubted dilution of the injected solution with a serum-containing liquid and when a diminution of the absorptive field had occurred.

The solution injected, after reaching the alveoli, is probably largely taken up by the capillaries of the pulmonary veins. This is indicated by the great rapidity with which an intratracheal injection of adrenalin may cause a rise of blood pressure. In numerous instances, for example, the pressure began to rise less than 5 seconds after the completion of an injection, equaling and even surpassing in rapidity of effect an intramuscular injection. Absorption by the lymphatics probably plays a secondary part, an assumption rendered all themore likely if we consider that lymph nodes are interpolated in the lymphatic pulmonary path, where the bed of the lymph stream becomes greatly widened and the current slowed.

Injection into the lungs, however, offers another advantage due to the vascular arrangement of the absorbing field which could be of value therapeutically. Absorption of liquids injected into the lung probably takes place largely through the capillaries of the pulmonary veins; to a slight extent possibly through the capillaries of the bronchial veins which empty partly into the pulmonary veins, partly into the azygos veins; and probably some absorption occurs also through the lymphatics. By far the larger proportion of the absorbed material will thus be rapidly delivered to the left auricle and then to the left ventricle. At each succeeding systole, as long as absorption continues, a fraction of the drug will be driven into the coronary arteries and be able to affect the musculature of the cardiac pump. This fact ought to render the procedure of intratracheal injection a valuable method when it becomes imperative to stimulate a suddenly failing heart as promptly as possible by drugs of the digitalis group.

Intratracheal injection is perhaps better under the conditions mentioned than the intravenous route, for the surface veins cannot

always be entered with promptness and certainty even under fairly normal conditions, and in cases of cardiac weakness the difficulties will be measurably increased, while an intratracheal injection can be carried out with ease. Moreover, it is legitimate to expect that some absorption will take place from the lung alveoli as long as the heart-lung circulation persists, no matter how feebly, and that thus some of the drug will reach the heart to act on this structure itself more promptly perhaps than when the drug is administered successfully through surface veins. As far as the intramuscular route is concerned, we have shown that the intratracheal injection of adrenalin gives prompt though diminished absorption at a time when double the dose intramuscularly exerts no blood pressure effect whatever.

The technical difficulties of giving an intratracheal injection in animals are slight. Tracheotomy as practised by us in the present series of experiments is not necessary, for the injection may be given into the intact trachea without exposure of the trachea. The hypodermic needle is inserted through the skin about 1 cm. below the larynx in a slanting caudad direction; the entrance of the needle into the trachea is readily felt. The injection should not be so rapid that the injected solution fills the entire tracheal lumen, but it should flow down the sides of the trachea. If the lumen is entirely filled, an expiration may drive some of the injected liquid into the larynx causing cough. In our experiments each injection of about 0.5 cc. consumed approximately 5 seconds.

In the human subject no data are available as far as our knowledge goes, but *a priori* it would seem that an intratracheal injection is almost as simple as in the lower animals. The free hypodermic needle could be inserted into the tracheal lumen immediately below the cricoid cartilage. The needle itself should preferably be connected with the syringe by a short length of rubber tubing to minimize the danger of breaking the needle by a sudden move of the patient. The amount of the solution should not be too small, so that at least a fraction of it may reach the alveoli as promptly as possible; 3 to 5 cc. probably would suffice.

Insertion of the needle in the locality mentioned would puncture the isthmus of the thyroid, but this is of no significance, especially when the procedure is employed in cases of cardiac failure where the

gravity of the condition would warrant incurring much heavier risks than a slight bleeding from the thyroidal isthmus.

In conclusion it may be said that the incorporation of drugs by intratracheal injection, while not as generally applicable as other methods, nevertheless has advantages which warrant its use also in human therapeutics.