A STUDY OF THE BRONCHOCONSTRICTOR AND HYPOTENSIVE ACTIONS OF CURARIZING DRUGS *

CHARLES M. LANDMESSER, M.D.

Philadelphia, Pa.

Received for publication December 20, 1946

NUMEROUS reports on the clinical use of curare preparations have described their classical blocking effect on the myoneural junction. A significant number of these reports have mentioned the occurrence of an undesirable and often dangerously sudden side reaction in certain patients to whom curare is administered (1, 2, 3, 4, 5). This side reaction manifests itself as a form of respiratory difficulty, sometimes accompanied by cyanosis (5) or a rapid fall of blood pressure (4). The respiratory embarrassment is described as not being the result of paralysis of the muscles of respiration but of spasm of these muscles or of the larynx or bronchi (4, 5). An increased resistance to inflation of the lungs by manual pressure on the breathing bag has been noted in anesthetized patients given curare (4, 5). In certain cases, relief of this respiratory spasm has followed when the depth of anesthesia has been increased or when additional curare has been injected, and for this reason the reaction has been attributed by some (4, 5) to a reflex mechanism in lightly anesthetized patients. The true nature of this side reaction to curare administration and the mechanism involved, however, are not understood.

In reports on animal experimentation (1, 3, 6, 7, 8), a reaction to curare administration similar to that occurring in man has been described. Cole (6) reported temporary cyanosis in dogs following large doses of intocostrin (Squibb) despite the use of artificial respiration through an endotracheal tube. He stated that the greater amount of force required to raise the chest wall during artificial respiration suggested bronchiolar or intercostal muscle spasm. West (7) reported that animals whose general musculature is not noticeably weakened by curarine may be seized with respiratory embarrassment leading to cyanosis and thence rapidly to fatal asphyxia. He stated that rats and guinea pigs given curarine make pawing movements at their throats, as they do when given histamine, and their respirations suggest bronchial spasm. By performing experiments upon the perfused lungs of guinea pigs he found that curarine produced measurable bronchoconstriction only when given in high concentrations in contrast to histamine

* Prize winning essay in contest sponsored by The American Society of Anesthesiologists, Inc., 1946.

which caused profound constriction in high dilutions. Subsequently, Alam and co-workers (9) found that curare injected intravenously liberated considerable quantities of histamine from muscle tissue in dogs, and that this histamine circulated in the blood in a physiologically active form. The initial injection of curare liberated the greatest quantity of histamine; subsequent doses failed to have as marked an effect in raising the histamine titer of the blood, the amount diminishing progressively as the supply of histamine in the tissues became depleted. They suggested that the bronchoconstriction evoked by curare and noted by West (7) might be caused by liberated histamine. Evidence suggesting that curare may liberate histamine from the body tissues in man has been reported recently by Comroe and Dripps (10), who found that intracutaneous and intra-arterial injections of curare produced typical histamine-like wheals and flares.

In the present study, the bronchoconstrictor and hypotensive actions of curare and curariform drugs have been investigated and compared with the reactions produced by peptone solutions and histamine in dogs in order to determine: (a) the regularity and extent of these responses; (b) the relationship of myoneural block to these secondary actions of curarizing drugs; (c) the mechanism by which these secondary effects are produced; and (d) the effects of antihistamine agents, pyribenzamine hydrochloride (11, 12, 13, 14, 15, 16) and benadryl (16, 17, 18, 19), upon them.

METHOD

Successful experiments were conducted on 44 dogs, ranging in weight from 4.0 to 11.0 Kg. (average 8.5 Kg.). The sex distribution was almost equal.

The dogs were prepared for the measurement of bronchial caliber as follows: without preoperative medication, they were anesthetized with ethyl ether for the preliminary surgical procedures involving cannulation of the trachea and isolation of the left external jugular vein, left carotid artery, and right vagus and phrenic nerves through a midline incision of the neck. Anesthesia was then discontinued and the animals were transferred from the operating table to a Drinker-Murphy infant resuscitator adapted for the registration of bronchoconstriction in dogs by the plethysmographic method described by Jackson (20). This method measures the amount of air moved in and out of the chest during each respiratory cycle; if the rate and force of artificial respirations are kept constant by such a resuscitator, alterations in the record are considered to be due to changes in the caliber of the bronchi and bronchioles. This is true when all spontaneous movements and changes in tone of the respiratory muscles are abolished. To accomplish this, a spinal state was produced in these animals by the injection of 5 to 10 cc. of 95 per cent ethyl alcohol into the cisterna magna and brain stem. Subsequent experimental procedures were conducted on them as un-

anesthetized spinal animals in whom artificial respiration was maintained by the resuscitator.

Blood pressure was recorded from a mercury manometer connected to a cannula inserted into the left carotid artery, a rigid tube about the artery protecting it from compression by the resuscitator cuff surrounding the dog's neck. The drugs used in these experiments were injected intravenously through fine plastic tubing (inserted centrally far enough into the left external jugular vein to prevent compression by the resuscitator cuff), and were immediately washed in with 1 to 2 cc. of physiologic saline solution.

The curarizing preparations studied were: intocostrin, Squibb (20 units/cc.); d-tubocurarine chloride, Squibb (20 units/cc.); curarine chloride, a Wellcome Research Laboratories brand of d-tubocurarine chloride (20 mg./cc.); dihydro-beta-erythroidine hydrobromide, Merck (75 mg./cc.); and quinine methochloride, Merck (10 mg./cc.). The effects of these agents upon bronchial caliber and blood pressure were compared with the effects of substances known regularly to produce bronchoconstriction and hypotension by different mechanisms: (a) histamine, (b) peptone, known to release preformed histamine from stores in the body (21, 22, 23), and (c) mecholyl, a parasympathomimetic drug. The preparations and concentrations employed were: histamine acid phosphate (1.0 mg./cc.), peptone, Witte, or bacto-protone, Difco (10 per cent aqueous solutions), and mecholyl chloride (0.1 mg./cc.). In some of the experiments, these drugs, as well as the curarizing agents, were injected after the administration of a parasympatholytic drug (atropine sulfate) or an antihistaminic drug (pyribenzamine, Ciba, or benadryl, Parke Davis) to determine whether the actions of curare and curariform drugs on the bronchi and blood pressure might involve a cholinergic or histaminic mechanism.*

To record the state of curarization of each dog throughout the course of each experiment, the phrenic nerve was stimulated electrically by platinum electrodes connected to a Harvard inductorium. During this procedure the resuscitator motor was stopped briefly so that the degree of respiratory excursion produced by the diaphragmatic response could be recorded. Likewise, to determine the degree of atropinization and the effect of curarization upon the vagus nerve, this nerve was stimulated and the degree of cardio-inhibition and bronchoconstriction was recorded.

RESULTS

1. *Effects of Stimulation of the Vagus and Phrenic Nerves and of Administration of Mecholyl and Histamine:*

The degree of cardio-inhibition and bronchoconstriction produced by stimulation of the right vagus nerve, the amplitude of respiratory

* The author gratefully acknowledges the generosity of the companies which supplied the drugs used in this study.

excursion produced by the diaphragmatic response to stimulation of the right phrenic nerve, and the extent of bronchoconstriction and hypotension produced by administration of mecholyl and histamine were determined in each animal prior to the injection of a curarizing agent or peptone. Regularly, stimulation of the right vagus nerve inhibited the heart and constricted the bronchi; stimulation of the right phrenic nerve produced a respiratory excursion; and administration of mecholyl and histamine in total dosages of 0.01 mg. and 0.1 mg., respectively, each produced distinct bronchoconstriction and hypotension. These responses to stimulation of the vagus and phrenic nerves and to administration of mecholyl and histamine could be repeated in each animal without decrement. They did not interfere with one another nor did they alter the responses to subsequent administrations of any of the curarizing agents or peptone solutions.

2. *Effects of Curarizing Agents:*

(a) *Intocostrin:* * In initial dosage of 2 units per kilogram, this drug evoked distinct bronchoconstriction and hypotension in each of 5 dogs. The effects of this initial dose on the bronchi and blood pressure resembled those of mecholyl and histamine in all essential respects, but repeated doses of the same size had progressively less effect on the bronchi and blood pressure, while the effects of mecholyl and histamine remained essentially unchanged. Subsequent larger doses of intocostrin occasionally elicited greater bronchoconstrictor and hypotensive effects than had the repeated smaller doses, thus demonstrating the phenomenon of "dose-to-dose refractoriness" described by Dragstedt (23) for peptone. In addition to its effects on the bronchi and blood pressure, the initial dose of intocostrin partially or completely abolished the responses to stimulation of the vagus and phrenic nerves; repeated doses increased the depth of curarization when it was incomplete.

(b) *d-Tubocurarine:* * When tested as intocostrin was, in initial dosage of 2 units per kilogram, and in subsequent larger dosage, this drug produced in 7 of 10 dogs responses indistinguishable from those described for intocostrin.

In the remaining 3 dogs, there was less hypotensive effect and no bronchoconstriction occurred; in 2 there was an actual increase in the amplitude of respiratory excursions, despite a typical curarizing effect on the vagus and phrenic nerves and normal responses to mecholyl and

* The potency of intocostrin solution in terms of units is based on the activity of a standard preparation of which 1.0 mg. is the equivalent of 1 unit of potency. The unit terminology is preferred since standardization by weight really has no significance as there is appreciable variation in activity per unit weight between different specimens of curare. The author is indebted to Dr. H. Sidney Newcomer, Medical Director, E. R. Squibb & Sons, for this information.

* There is slight variation in activity per unit weight between different samples of this drug, 1 unit of which is equivalent to approximately 0.16 mg.

FIG. 1. Effects of curarine chloride: curarine chloride (0.5 mg./Kg.) produced bronchoconstriction and hypotension (C), and partially abolished responses to vagus and phrenic nerve stimulations (A, B, D, E); a repeated dose had less effect on the bronchi and blood pressure (F), but further abolished responses to vagus and phrenic nerve stimulations (G, H); an increased dose (1.0 mg./Kg.) then had greater effect on the bronchi and blood pressure (I) demonstrating the phenomenon of "dose-to-dose refractoriness," and almost completed the abolition of responses to vagus and phrenic nerve stimulations (J, K); this dose, repeated, and a subsequent larger (2.0 mg./Kg.) dose each failed to produce any further effect on the bronchi or blood pressure (L, M), though they completed the abolition of responses to vagus and phrenic nerve stimulations (N, O); peptone (20 cc.) then produced relatively slight bronchoconstriction and hypotension (P) demonstrating the phenomenon of crossed "desensitization" between curarine chloride and peptone; bronchi and blood pressure still reacted normally to mecholyl (0.01 mg.) and histamine (0.1 mg.) (Q, R).

histamine. This same solution of d-tubocurarine evoked typical bronchoconstriction and hypotension subsequently in other dogs. It is probable, therefore, that these 3 animals exhibited the same type of spontaneous refractoriness to d-tubocurarine that Dragstedt has described for peptone (23).

(c) *Curarine chloride:* In initial dosage of 0.5 mg. per kilogram, and in subsequent larger dosage, this drug elicited in 1 dog responses indistinguishable from those described for intocostrin and d-tubocurarine. Exemplifying the effects of each of the curare preparations tested, these typical responses to curarine chloride are illustrated in figure 1. In 1 other dog, 1 mg. per kilogram of this drug produced such severe bronchoconstriction and hypotension when given initially that the animal could not be saved by repeated doses of epinephrine. In each of 2 other dogs, 2 mg. per kilogram of this drug injected initially produced complete bronchoconstriction and severe hypotension which also were fatal.

Two other dogs were spontaneously refractory to the bronchoconstrictor and hypotensive effects of curarine chloride in initial dosage of 2 mg. per kilogram; this same solution and dosage proved fatal to subsequent animals, as described previously. The responses of these 2 refractory animals were indistinguishable from those of the spontaneously refractory dogs to whom d-tubocurarine was given, except that the degree of curarization produced by this dose of curarine chloride was greater than that produced by the initial injection of 2 units per kilogram of d-tubocurarine.

(d) *Dihydro-beta-erythroidine:* This was given initially in dosage of 2 mg. per kilogram to each of 9 dogs. In no case was there any trace of bronchoconstriction; in 4 there was an actual increase in the amplitude of respiratory excursions. Hypotension occurred in 8 of these dogs, but it was of less degree than that produced by any of the curare preparations; in 1 dog there was no fall of blood pressure. Subsequent similar doses had progressively less effect on the bronchi and blood pressure if these had been affected at all by the initial dose. The effects of this drug on the bronchi and blood pressure were similar to those of d-tubocurarine and curarine chloride in spontaneously refractory animals, but 6 of the 9 dogs given dihydro-beta-erythroidine showed typical bronchoconstrictor and hypotensive responses to the subsequent injection of intocostrin, d-tubocurarine, or peptone (see section 6). This drug produced a curarizing effect on the vagus and phrenic nerves which was of the same order as that of the curare preparations, and each of the dogs in whom it was tested responded normally to mecholyl and histamine both before and after its administration. It appears, therefore, that dihydro-beta-erythroidine does not possess the property of causing bronchoconstriction or severe hypotension when given even in fully curarizing dosage to dogs under the conditions of these experiments. Typical responses to this drug are illustrated in figure 2.

FIG. 2. Effects of dihydro-beta-erythroidine: dihydro-beta-erythroidine (2 mg./Kg.) produced no bronchoconstriction and only slight hypotension (C), though it almost completely abolished responses to vagus and phrenic nerve stimulations (A, B, D, E); bronchi and blood pressure still reacted normally to mecholyl (0.01 mg.) and histamine (0.1 mg.) (F, G); atropine (2.0 mg.) (H) abolished responses to mecholyl (0.01 mg.) (I) without altering the effects of histamine (0.1 mg.) (J); d-tubocurarine (2 units/Kg.) produced typical bronchoconstriction and hypotension (K); a repeated dose had no significant effect on bronchi and blood pressure (L), but an increased (5 units/Kg.) dose then produced slight bronchoconstriction and hypotension (M) demonstrating the phenomenon of "dose-to-dose refractoriness"; peptone (20 cc.) then produced relatively slight bronchoconstriction and hypotension (N) demonstrating the phenomenon of crossel "desensitization" between d-tubocurarine and peptone.

(e) *Quinine methochloride:* This drug was tried in only 2 dogs because it appeared to be the weakest curarizing agent of the series and to have no advantages over the others. In a dosage which produced only partial curarization (10 mg./Kg.), it elicited definite bronchoconstriction and hypotension. As with the other curarizing drugs, repeated doses had progressively smaller effects on the bronchi and blood pressure while increasing the depth of curarization, and they did not alter the responses to mecholyl or histamine.

3. *Effects of Peptone:*

Peptone (10 per cent aqueous solution of peptone, Witte, or bactoprotone, Difco) was given initially in total dosage of 4 to 10 cc. to each of 3 dogs. The 10 cc. dose (peptone, Witte) given to 1 of these dogs caused complete bronchoconstriction and severe hypotension, indistinguishable from those responses produced by large (2 mg./Kg.) doses of curarine chloride, and death ensued. In each of the other 2 dogs, peptone initially given in total dosage of 4 cc. (peptone, Witte) and 5 cc. (bactoprotone, Difco), respectively, produced bronchoconstriction and hypotension similar to the corresponding typical effects of curare preparations but tending to be more intense. As with the curare preparations, the same doses had progressively less effect on the bronchi and blood pressure when repeated, and a subsequent larger dose then elicited greater degrees of bronchoconstriction and hypotension than had the repeated smaller doses. This phenomenon of "dose-to-dose refractoriness" was similar to that already described for curare preparations, and, as with them, peptone did not alter the responses to mecholyl or histamine. The effects of peptone differed significantly from those of the curare preparations only in respect to curarization which was lacking after peptone. Typical responses to peptone are illustrated in figure 3.

4. *The Influence of Atropine:*

This drug, given in total dosage of 2 mg., did not modify significantly the bronchoconstrictor or hypotensive effects of intocostrin (1 dog), d-tubocurarine (5 dogs, 3 of which were spontaneously refractory), peptone (1 dog), or histamine (7 dogs), although this dosage regularly abolished the effects of stimulation of the vagus nerve and administration of mecholyl in each of these experiments. It did not interfere with curarization as determined by stimulation of the phrenic nerve. The influence of atropine is illustrated in figure 2.

5. *The Influence of Antihistamine Agents:*

(a) *Pyribenzamine (N'-Pyridyl-N'-Benzyl-N-Dimethylethylene Diamine HCl):* This drug, reported to be an antihistamine agent (11–16), was tested to determine its effect on the bronchoconstrictor and hypotensive actions of the drugs used in this study. In total dosage of 25

FIG. 3. Effects of peptone: peptone (5 cc.) produced bronchoconstriction and hypotension (B); a repeated dose had less effect (C); a larger (10 cc.) dose increased the response (E), but in turn became less effective when repeated (F); a still larger (20 cc.) dose again increased the response (H), demonstrating the phenomenon of "dose-to-dose refractoriness"; peptone had no effect on responses to phrenic nerve stimulations (A, D, G, I); d-tubocurarine (2 units/Kg.) then produced no bronchoconstriction or hypotension (J), demonstrating the phenomenon of crossed "desensitization" between peptone and d-tubocurarine, but almost completely abolished responses to phrenic nerve stimulations (K).

mg., pyribenzamine completely prevented the usual bronchoconstrictor effect of histamine (0.1 mg.) and of d-tubocurarine (2 units/Kg.) in each of 2 dogs (fig. 4). When similarly administered before curarine chloride (0.5 mg./Kg.) in 1 dog, it prevented all but the slightest degree of bronchoconstriction, and in this animal histamine (0.1 mg.) likewise broke through to constrict the bronchi to a similar slight degree. In 1 of the 2 unprotected dogs in whom curarine chloride (2 mg./Kg.) caused complete bronchoconstriction and severe hypotension, prompt administration of pyribenzamine (25 mg.) partially relieved the bronchoconstriction although death from circulatory failure ensued; pyribenzamine was not given to the other dog, and complete bronchoconstriction persisted until death occurred from anoxia. Pyribenzamine (25 mg.) failed to prevent the occurrence of moderate bronchoconstriction following the administration of peptone (peptone, Witte, 5 cc.) in 1 dog. The response which occurred, however, was not typical of those evoked by the same dose of peptone in unprotected animals, and it could be duplicated by the injection of large amounts of histamine (5.0 mg.) even though the action of the usual bronchoconstricting dose of histamine (0.1 mg.) was prevented completely. This suggests that peptone is the most potent histamine-liberating agent in the series of drugs studied.

Pyribenzamine in the dosage used in these experiments had inconsistent effects on the hypotensive actions of histamine, curare, and peptone. In each animal tested, its inhibitory effect on the hypotensive action of curare or peptone paralleled its inhibitory effect on that of histamine, but in none of the animals was hypotension completely prevented; in most of them it was inhibited only slightly, if at all. This indicates that none of the dogs tested with pyribenzamine were spontaneously refractory to curare or peptone, for in unprotected animals this degree of hypotension produced by histamine, curare, or peptone was invariably accompanied by a corresponding degree of bronchoconstriction.

The administration of pyribenzamine (25 mg.) did not alter appreciably the effects of mecholyl on the bronchi and blood pressure, or the responses to stimulations of the vagus and phrenic nerves in any of these dogs; neither did it interfere with curarization.

(b) *Benadryl (Beta-Dimethylaminoethyl Benzhydryl Ether)*: To confirm the effectiveness of pyribenzamine in inhibiting the bronchoconstrictor action of curare by virtue of its antihistamine property, benadryl, also reported to be an antihistamine drug (16–19), was administered in total dosage of 10.0 mg. to each of 3 dogs before the injection of 2 units per kilogram of d-tubocurarine. In each of these dogs, this dose of benadryl had essentially the same antihistamine effect as 25 mg. of pyribenzamine. It prevented the usual bronchoconstrictor action of histamine (0.1 mg.) and d-tubocurarine (2 units/Kg.). Like pyribenzamine, benadryl had little if any inhibitory effect on the

FIG. 4. Influence of pyribenzamine: typical responses to vagus and phrenic nerve stimulations and to mecholyl (0.01 mg.) and histamine (0.1 mg.) administrations were recorded (A, B, C, D); pyribenzamine (25 mg.) then was injected (E); this completely prevented the bronchoconstrictor effects of histamine (0.1 mg.) (G) and d-tubocurarine (2 units/Kg.) (J) without modifying significantly the hypotensive effects of these drugs; it did not prevent responses to mecholyl (0.01 mg.) (F), or to vagus and phrenic nerve stimulations (H, I); responses to vagus and phrenic nerve stimulation (K, L) were partially abolished by d-tubocurarine.

hypotensive action of either of these drugs. One of these dogs failed to exhibit any degree of hypotension following the administration of d-tubocurarine although histamine produced a typical hypotensive response, and this animal therefore must be considered as another example of spontaneous refractoriness to d-tubocurarine.

As with pyribenzamine, benadryl did not interfere with curarization as determined by stimulation of the phrenic nerve. It differed from pyribenzamine, however, in appearing to be less specifically antihistaminic. As well as inhibiting the usual bronchoconstrictor effect of histamine (0.1 mg.), it inhibited this response to mecholyl (0.01 mg.) and to stimulation of the vagus nerve. As with histamine, there was little if any inhibitory effect on the hypotensive action of mecholyl, and the cardioinhibitory response to stimulation of the vagus nerve was not modified significantly. This anticholinergic effect of benadryl was neither as strong nor as lasting as its antihistaminic effect; the usual bronchoconstrictor action of mecholyl (0.01 mg.) and of stimulation of the vagus nerve returned within a short while but that of histamine (0.1 mg.) remained inhibited.

Because benadryl appeared to be a less specific agent than pyribenzamine when tested in these experiments in the dosage required to protect the bronchi from the action of histamine, further experiments were not done with this drug. The effectiveness of antihistamine drugs, however, in preventing the bronchoconstrictor action of curare, even though they had little if any inhibitory effect on the hypotensive action of either this substance or histamine itself, was confirmed.

6. *Crossed "Desensitization":*

The data so far presented are compatible with the hypothesis that curare preparations (intocostrin, d-tubocurarine, and curarine chloride) cause liberation of physiologically effective amounts of histamine when injected even in mildly curarizing dosage in dogs. Quinine methochloride apparently acts similarly. Peptone appears to have a similar action, although it fails to exert any curarizing effect. Two phenomena lend support to this conception, viz., the already described progressive loss of effect on the bronchi and blood pressure when the initial dose of any one of these drugs is repeated, and, as will be described, the phenomenon of crossed "desensitization" when one of these drugs is followed by another. Both could be attributed to exhaustion of tissue stores of histamine.

Crossed "desensitization" could be produced reciprocally between peptone and the various curare derivatives, as well as among the latter themselves, regardless of which agent was given first. After the responses of the bronchi and blood pressure had been relatively exhausted by repeated administrations of one agent, the subsequent administration of another agent failed to produce the usual bronchoconstriction and hypotension even though typical responses to injections of mecholyl

and histamine still occurred at this time. The crossed "desensitization" produced by peptone against the curare derivatives was usually more complete than that produced by the latter against peptone; in this respect, as well as in others already presented, peptone appeared to be a more potent histamine liberator than the curare derivatives. Crossed "desensitization" was produced between intocostrin and peptone (two experiments), d-tubocurarine and peptone (four experiments), curarine chloride and peptone (one experiment), peptone and intocostrin (two experiments), and peptone and d-tubocurarine (two experiments). Examples are shown in figures 1, 2 and 3. Similar attempts with dihydro-beta-erythroidine showed no trace of crossed "desensitization" to the bronchoconstrictor and hypotensive effects of intocostrin (one experiment), d-tubocurarine (three experiments), or peptone (two experiments), even when dihydro-beta-erythroidine was given to the point of full curarization, as illustrated in figure 2. This also was true of quinine methochloride, which, when given in repeated doses to the point of complete curarization, failed to prevent the appearance of characteristic bronchoconstrictor and hypotensive effects from d-tubocurarine in each of the 2 dogs in which it was tried.

DISCUSSION

The bronchoconstrictor and hypotensive actions of curare preparations (intocostrin, d-tubocurarine, and curarine chloride) have been demonstrated in this study. The similarity of the effects of these drugs to those of histamine upon the bronchi and blood pressure is apparent. The administration of an antihistamine agent, pyribenzamine or benadryl, has inhibited regularly the bronchoconstrictor response in both cases; the hypotensive effect of the curare preparations and of histamine has not been inhibited by antihistamine agents as effectively, if at all. The only striking difference between the effects of the curare preparations and those of histamine upon the bronchi and blood pressure is that, while repeated doses of histamine produce essentially constant degrees of bronchoconstriction and hypotension, repeated doses of curare evoke progressively diminishing bronchoconstrictor and hypotensive responses. Furthermore, it is apparent from this study that the effects of peptone upon the bronchi and blood pressure are essentially the same as those of the curare preparations. In other words, curare and peptone each appears to cause bronchoconstriction and hypotension through a histamine mechanism which is most active with the initial administration of either of them and which becomes progressively exhausted with repeated administrations.

These findings are compatible with the theory that curare and peptone each liberates histamine from the body tissues of dogs as reported by Alam and co-workers (9) and by Dragstedt and co-workers (22), respectively. The former group showed that the initial injection of curare liberates the greatest quantity of histamine from the tissues

and that subsequent doses fail to have as marked effect in raising the histamine titer of the blood, the response diminishing progressively as the tissue supply of histamine becomes depleted. Likewise, Dragstedt (23) showed that the initial injection of peptone produces the severest peptone shock, the response to repeated administrations being less severe. Dragstedt (23) showed also that "dose-to-dose refractoriness" occurs with peptone; an increased dose, after progressively diminishing responses to repeated smaller doses, produced a greater degree of response than did the repeated smaller doses. In the present report, this "dose-to-dose refractoriness" has been shown to occur not only with peptone but also with curare, thus further suggesting a similar mechanism through which peptone and curare each evokes bronchoconstriction and hypotension.

To continue the analogy between the bronchoconstrictor and hypotensive actions of curare and peptone, crossed "desensitization" between curare "shock" and peptone shock, and vice versa, has been demonstrated in this study. A similar crossed "desensitization" between anaphylactic shock and peptone shock in dogs has been referred to by Dragstedt (23), the active substance producing the symptoms of anaphylactic shock having been shown to be histamine (24, 25, 26). A plausible explanation of this phenomenon of crossed "desensitization" is that a histamine-liberating mechanism is involved in the production of each of these types of "shock." The explosive mobilization of histamine during the initial "shock" caused by any one of these histamine-liberating agents may well leave the tissues relatively depleted of histamine. There are not sufficient quantities of this substance then remaining in the tissues to be liberated in "shock"-producing amounts when a subsequent histamine-mobilizing agent is administered.

Their activity does not supply the only evidence that curare and peptone each evokes "shock" through a similar mechanism; their inactivity in certain dogs also supports this theory. Dragstedt (23) reported an incidence of 10 per cent spontaneous refractoriness to peptone in a large series of dogs. In the present study, 9 of 44 dogs (20 per cent) demonstrated spontaneous refractoriness to the bronchoconstrictor and hypotensive effects of d-tubocurarine (7 dogs) or curarine chloride (2 dogs), and these dogs were similarly refractory to subsequent administrations of other curare preparations or peptone. None of these dogs was refractory to the myoneural blocking effect of curare or the effects of injected histamine upon the bronchi and blood pressure. Even though such spontaneous refractoriness was more frequent in this series than in that reported by Dragstedt (23), its occurrence suggests that curare, like peptone, elicits bronchoconstriction and hypotension not directly but rather through the mechanism of mobilizing histamine from the body tissues. A certain percentage of dogs appears to be spontaneously refractory to this mechanism regardless of what histamine-mobilizing agent is administered. Since curare appears to be a

weaker histamine-mobilizer than peptone, this may explain why the incidence of spontaneous refractoriness is greater in this series of experiments than in Dragstedt's (23) which concerned peptone only.

The fact that dihydro-beta-erythroidine in initial curarizing dosage does not evoke bronchoconstriction, although it sometimes produces a small degree of hypotension, and does not cross "desensitize" against curare preparations or peptone solutions suggests that this drug does not have the capacity to initiate the histamine-liberating mechanism. Further evidence that this is the case is provided by the observation that dihydro-beta-erythroidine does not produce wheals and flares when injected intracutaneously in man, although curare derivatives do (10).

Although quinine methochloride in initial curarizing dosage produces definite bronchoconstriction and hypotension, it does not elicit such marked responses as do curare preparations or peptone solutions. Its inability to produce any significant degree of crossed "desensitization" against d-tubocurarine suggests that quinine methochloride cannot sufficiently deplete the stores of tissue-histamine to prevent subsequent mobilization of effective amounts of this substance by d-tubocurarine.

The marked degrees of bronchoconstriction and hypotension noted in unanesthetized spinal animals have been observed less consistently in anesthetized patients to whom curare preparations have been administered clinically. Several possible factors may account for this: (1) anesthesia. It has been reported (27, 28, 29) that certain anesthetic agents suppress the release of histamine from the body tissues. It is conceivable that anesthetized patients could be somewhat protected in this way from the histamine-mobilizing action of curare; in unanesthetized spinal animals this action of curare is not suppressed. (2) Reflexes. The detection of any bronchoconstriction which may occur clinically depends upon the recognition of increased resistance to manual inflation of the lungs. Since, in patients, the degree of this resistance depends not only upon the caliber of the bronchi but also upon the reflex tone of the thoracic muscles, the abolition of this tone by curarization would tend to decrease the resistance to inflation of the lungs manually at the same time that the occurrence of bronchoconstriction would tend to increase it. These two opposing influences could prevent the occurrence of any detectable change in the resistance to manual inflation of the lungs, and bronchoconstriction, though present, would go unrecognized. This is not the case in spinal animals since the reflex tone of the muscles already is abolished or greatly reduced before curarization. Severe hypotension also is less likely to occur clinically because vasomotor reflexes would tend to compensate for the hypotensive action of curare. The absence of such reflexes in spinal animals allows the hypotension produced by curare to go uncompensated. (3) Refractoriness. Spontaneous refractoriness to the bronchoconstrictor and hypotensive actions of curare occurs in a certain percentage of

dogs, and it is likely that it may occur similarly in an unknown percentage of patients.

It is important to understand the mechanism whereby curare may cause bronchoconstriction and hypotension since these reactions can occur when this drug is administered intravenously to patients for the production of muscular relaxation (1, 2, 3, 4, 5). The present study indicates that it may prove feasible to prevent these complicating and sometimes dangerous side reactions either by employing curarizing drugs which are relatively incapable of mobilizing histamine from the tissues (as appears to be the case with dihydro-beta-erythroidine), or by administering prophylactic doses of an antihistamine drug, such as pyribenzamine or benadryl, before the intravenous administration of curare preparations.

Evidence is presented suggesting that when the administration of curare to unprotected animals does produce bronchoconstriction and hypotension, these effects may be ameliorated by prompt treatment with an antihistamine drug. Although these drugs appear to be much less effective in combating the hypotension than the bronchoconstriction caused by curare in unanesthetized spinal dogs, their clinical trial for the treatment of curare "shock" would seem more rational than attempts to relieve this condition by the various methods so far suggested by others: (a) the injection of more curare or the administration of more anesthetic (4, 5); (b) the administration of parasympatholytic drugs (3); and (c) the administration of epinephrine (2) which would be contraindicated if curare were being used in conjunction with cyclopropane anesthesia (30).

Summary

In unanesthetized spinal dogs in whom artificial respiration through a tracheal cannula was maintained by a Drinker-Murphy infant resuscitator adapted to record bronchial caliber by the plethysmographic method of Jackson, the following experiments and results were obtained.

1. Intocostrin, d-tubocurarine chloride, curarine chloride, and quinine methochloride, when administered intravenously in curarizing dosage, caused bronchoconstriction and hypotension. Quinine methochloride was the least potent of these drugs in these respects. Dihydro-beta-erythroidine hydrobromide, except for its slight hypotensive effect, failed to produce these responses even though it was a satisfactory curarizing agent.

2. Peptone, when administered intravenously, produced peptone shock characterized by bronchoconstriction and hypotension. This was similar to but usually more severe than curare "shock."

3. The prophylactic administration of an antihistamine agent, pyribenzamine hydrochloride, inhibited the bronchoconstrictor response to curare but had little if any inhibitory effect on the hypotensive response; it inhibited the responses to peptone similarly but less com-

pletely. The inhibitory effect of pyribenzamine on curare "shock" was confirmed with another antihistamine agent, benadryl.

4. In evoking bronchoconstriction and hypotension, curare preparations and peptone solutions not only produced a "dose-to-dose refractoriness" to themselves, but also produced varying degrees of crossed "desensitization" against one another. There occurred a certain incidence of spontaneous refractoriness to each.

5. The results obtained in this study substantiate the theory that curare preparations and peptone solutions administered intravenously elicit bronchoconstriction and hypotension through the liberation of histamine from the body tissues.

6. This study suggests that it may prove possible to avoid the complicating bronchoconstrictor and to a lesser extent the hypotensive action of curare either by employing curarizing drugs which, as was the case with dihydro-beta-erythroidine in spinal dogs, do not have bronchoconstrictor or severe hypotensive actions, or by prophylactically administering an antihistamine drug, such as pyribenzamine or benadryl, before the intravenous injection of a curare preparation. The most rational treatment of these side reactions to curare when they do occur in unprotected subjects would appear to be the prompt administration of an antihistamine drug.

REFERENCES

1. West, R.: Intravenous Curarine in the Treatment of Tetanus, Lancet 1: 12–16 (Jan.) 1936.
2. Harvey, A. M., and Masland, R. L.: Actions of Curarizing Preparations in the Human, J. Pharmacol. & Exper. Therap. 73: 304–311 (Nov.) 1941.
3. Cullen, S. C.: Clinical and Laboratory Observations on the Use of Curare During Inhalation Anesthesia, Anesthesiology 5: 166–173 (Mar.) 1944.
4. Whitacre, R. J., and Fisher, A. J.: Clinical Observations on the Use of Curare in Anesthesia, Anesthesiology 6: 124–130 (Mar.) 1945.
5. Holaday, D. A.: Nitrous Oxide-Cyclopropane-Curare Anesthesia; A Review of 200 Cases, Anesthesiology 7: 426–440 (July) 1946.
6. Cole, F.: A New Lethal Dose of Curare, with some Observations on the Pathology Produced by Large Doses, Anesthesiology 7: 190–197 (Mar.) 1946.
7. West, R.: The Action of Curarine on the Respiratory Mechanism, J. Physiol. 91: 437–446 (Jan.) 1938.
8. West, R.: The Pharmacology and Therapeutics of Curare and its Constituents, Proc. Roy. Soc. Med. 28: 565–578 (Mar.) 1935.
9. Alam, M.; Anrep, G. V.; Barsoum, G. S.; Talaat, M., and Weininger, E.: Liberation of Histamine from the Skeletal Muscle by Curare, J. Physiol. 95: 148–158 (Feb.) 1939.
10. Comroe, J. H., Jr., and Dripps, R. D.: The Histamine-like Action of Curare and Tubocurarine Injected Intracutaneously and Intra-arterially in Man, Anesthesiology 7: 260–262 (May) 1946.
11. Mayer, R. L.; Huttrer, C. P., and Scholz, C. R.: Antihistaminic and Antianaphylactic Activity in Vitro and in Vivo of some Alpha-aminopyridyl Derivatives, Federation Proc. 4: 129 (Mar.) 1945.
12. Rennick, B.; Chess, D.; Hays, H. W.; Mathieson, D.; Mayer, R. L., and Yonkman, F. F.: The Antianaphylactic and Antihistaminic Activity and Toxicity of N'-pyridyl-N'-benzyl-N-dimethylethylenediamine HCl, Federation Proc. 4: 133 (Mar.) 1945.
13. Yonkman, F. F.; Chess, D.; Mathieson, D., and Hansen, N.: The Antihistaminic Action of N'-pyridyl-N'-benzyl-N-dimethylethylenediamine HCl (63C) in Relation to Salivation, Retraction of the Nictitating Membrane, Mydriasis, Lachrymation and Blood Pressure in Cats, Federation Proc. 4: 143 (Mar.) 1945.

14. Yonkman, F. F.; Hays, H. W., and Rennick, B.: The Protective Action of N'-pyridyl-N'-benzyl-N-dimethylethylenediamine HCl (63C) against Horse Serum Anaphylaxis in Dogs, Federation Proc. 4: 144 (Mar.) 1945.
15. Yonkman, F. F.; Chess, D.; Mathieson, D., and Hansen, N.: Pharmacodynamic Studies of a New Antihistamine Agent, N'-Pyridyl-N'-Benzyl-N-Dimethylethylene Diamine HCl, Pyribenzamine HCl. I. Effects on Salivation, Nictitating Membrane, Lacrymation, Pupil, and Blood Pressure, J. Pharmacol. & Exper. Therap. 87: 256–264 (July) 1946.
16. Friedlaender, S.: Experimental and Clinical Evaluation of Synthetic Anti-histaminic Drugs, Am. J. Med. 1: 174–179 (Aug.) 1946.
17. Loew, E. R.; Kaiser, M. E., and Moore, V.: Synthetic Benzhydril Alkamine Ethers Effective in Preventing Fatal Experimental Asthma in Guinea Pigs Exposed to Atomized Histamine, J. Pharmacol. & Exper. Therap. 83: 120–129 (Feb.) 1945.
18. Wells, J. A., and Morris, H. C.: Observations on the Antagonism of Histamine by Beta-dimethyl Aminoethyl Benzhydryl Ether (Benadryl), Federation Proc. 4: 140 (Mar.) 1945.
19. Wells, J. A.; Morris, H. C.; Bull, H. B., and Dragstedt, C. A.: Observations on the Nature of the Antagonism of Histamine by Beta-Dimethylaminoethyl Benzhydryl Ether (Benadryl), J. Pharmacol. & Exper. Therap. 85: 122–128 (Oct.) 1945.
20. Jackson, D. E.: Experimental Pharmacology and Materia Medica, St. Louis, C. V. Mosby Co., ed. 2, 1939, p. 511.
21. Dragstedt, C. A., and Mead, F. B.: Peptone Shock, J. Pharmacol. & Exper. Therap. 59: 429–436 (Apr.) 1937.
22. Dragstedt, C. A.; Mead, F. B., and Eyer, S. W.: Further Studies on the Mechanism of Peptone Shock, J. Pharmacol. & Exper. Therap. 63: 400–406 (Aug.) 1938.
23. Dragstedt, C. A.: Observations on Spontaneous and Induced Refractoriness to Peptone Shock in Dogs, J. Immunol. 47: 1–6 (July) 1943.
24. Dragstedt, C. A., and Gebauer-Fuelnegg, E.: Studies in Anaphylaxis. I. The Appearance of a Physiologically Active Substance During Anaphylactic Shock, Am. J. Physiol. 102: 512–519 (Nov.) 1932.
25. Gebauer-Fuelnegg, E., and Dragstedt, C. A.: Studies in Anaphylaxis. II. The Nature of a Physiologically Active Substance Appearing During Anaphylactic Shock, Am. J. Physiol. 102: 520–526 (Nov.) 1932.
26. Dragstedt, C. A., and Mead, F. B.: Further Observations on the Nature of the Active Substance ("Anaphylatoxin") in Canine Anaphylactic Shock, J. Immunol. 30: 319–326 (Apr.) 1936.
27. Katz, G.; Frey, C. T., and Frey, L. I.: Action of Diethyl Ether on Histamine Release in Anaphylaxis, Proc. Soc. Exper. Biol. & Med. 42: 716–718 (Dec.) 1939.
28. Katz, G.: The Action of Anesthesia on the Histamine Release in Anaphylactic Shock, Am. J. Physiol. 129: 735–743 (June) 1940.
29. Hennig, G. C.: Reactivity of the Skin: Effect of Anesthesia and Shock on Histamine and Allergic Responses, U. S. Nav. M. Bull. 41: 698–707 (May) 1943.
30. Meek, W. J.: Cardiac Automaticity and Response to Blood Pressure Raising Agents During Inhalation Anesthesia, Physiol. Rev. 21: 324–356 (Apr.) 1941.