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Abstract

Increase of capillary permeability is the chief symptomatic reaction of various pathologic states, especially that of localized inflammation, and this is the characteristic pharmacological properties of histamine at a far smaller concentration than that of any other chemical substances (Lewis, 1927; Crammer and Hele, 1944). There are numerous observations as to the diminishing effect of antihistamines on the flare and wheal caused by histamine and the inhibition by antihistamines of localized accumulation of intravenously injected dyes, such as trypan blue, referable to intradermal injection of histamine (for refs. cf. Loew, 1947; Feet al., 1950). As for the inhibition of capillary permeability by antihistamines, some maintain that this action is limited to the case where such permeability has been increased by histamine (Wells, Morris and Dragstedt, 1946; Netter, 1947; Rigdon, 1949), but no single and decisive conclusion can yet be given.

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**The Action of Antihistamines on the Lymph Formation
and Its Effect on the Action of
Some Lymphagogues***

By

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Increase of capillary permeability is the chief symptomatic reaction of various pathologic states, especially that of localized inflammation, and this is the characteristic pharmacological properties of histamine at a far smaller concentration than that of any other chemical substances (*Lewis, 1927; Crammer and Hele, 1944*). There are numerous observations as to the diminishing effect of antihistamines on the flare and wheal caused by histamine and the inhibition by antihistamines of localized accumulation of intravenously injected dyes, such as trypan blue, referable to intradermal injection of histamine (for refs. cf. *Loew, 1947; Feinberg et al., 1950*). As for the inhibition of capillary permeability by antihistamines, some maintain that this action is limited to the case where such permeability has been increased by histamine (*Wells, Morris and Dragstedt, 1946; Netter, 1947; Rigdon, 1949*), but no single and decisive conclusion can yet be given.

There is the acceleration of lymph formation as another phenomenon of increased capillary permeability. The fact that histamine also shows accelerating action on not only thoracic duct lymph (*Dale and Laidlaw, 1911; Yamasaki, 1939*) but also on leg (*Haynes, 1932*) and cervical lymph flow (*McCarrell and Drinker, 1941*) indicates that such action is closely related to the capillary permeability. Another interesting fact relating to this problem is that a series of substances such as antigen (in sensitized dog), peptone, and sinomenine, possess striking lymphagogic action

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(*Calvary*, 1911; *Heidenhain*, 1891; *Ishiwari*, 1921) as well as the properties of liberating histamine in blood and lymph (*Dragstedt* and *Gebauer-Fuelnegg*, 1932; *Dragstedt* and *Mead*, 1937; *Mayeda*, 1953).

The purpose of the present series of experiments was first, to study what action such antihistamines themselves would have on the flow of thoracic duct and cervical lymph in the dog, and their protein content, and next, to study the action of antihistamines against the lymphagogic effect of histamine, peptone, and sinomenine, in connection to the mechanism of lymph formation, so as to examine the mode of action of antihistamines on the capillary permeability from the directions different from those made to date. In the course of these studies, the experimental results have also offered some important findings regarding the striking antagonism between histamine and antihistamines in the portal circulation and the modes of action of such lymphagogues.

Methods

All the experiments were carried out with morphine-urethane anesthetized dogs after about twenty four hours' fasting. A fine glass cannula was inserted into the thoracic duct at a point just before its flow into the jugular vein and the thoracic lymph that flowed out was collected every five minutes into a graduated cylinder to measure the rate of flow. The collected lymph was decanted at a definite interval to observe its coagulability. The protein content of lymph in every graduate was determined by the *Pulfrich's* dipping refractometer. For the collection of cervical lymph, a dog of over 10 kg weight, with rather a thick neck, was used and either the right or left cervical lymphatic was cannulated low in the neck and its outflow was successively collected every 10 minutes in accordance with the method of *McCarrell* (1939). The dog from which the cervical lymph was collected was given oral dose of 30 to 40 mg/kg of dicumarol three to four days prior to the experiments in order to decrease the coagulability of the lymph, except in the case of experiments with peptone and sinomenine which strongly diminish the coagulability of lymph.

Eck's fistula, performed in some of the experiments, was carried out by the technique of *Tokumitsu* (1921). For the recording of portal blood pressure and the volume of hind limb, descriptions have already been given elsewhere (*Mayeda*, 1954), and the same technique was used for the recording of the venous pressure. Recording of the liver and intestinal volumes was made by the method of *Yamasaki* (1940). The sinomenine hydrochloride used in the present experiment was provided by the courtesy of the Research Laboratories of *Shionogi & Co.*, Ltd. Amagasaki and peptone was *Witte's* product.

Results

Part I. *Action of Antihistamines on the Lymph Formation*

In this section, results of studies on the actions of antihistamines on the rate of flow of thoracic and cervical lymph and their protein content, and on some cardiovascular effects of antihistamines, carried out mainly with Benadryl, are described.

1. *Action of antihistamines on the flow and protein content of thoracic duct lymph, and its coagulability.* Systemic intravenous injection of 1 to 5 mg/kg/30 sec. of Benadryl resulted in transitory decrease of respiratory amplitude, followed by a slight increase. With 10 mg/kg/30 sec. or 15 mg/kg/min. dose, approximately one minute of apnea was followed by a sudden increase of the rate of amplitude of respiration which returned gradually to normal over a period of more than one hour. Repeated injection of Benadryl with 10 to 15 minutes' interval resulted in a gradual increase of the respiration exciting effect at each injection.

The flow of thoracic duct lymph decreased immediately after the injection of 1 to 5 mg/kg of Benadryl. With 10 to 15 mg/kg dose, a transitory acceleration often preceded this decrease, probably a phenomenon referable to the excitation of respiration. The lymph flow decreased to about one-half or less of the rate of flow before injection in the case of 5 to 10 mg/kg dose and its recovery required 1.5 hours or more (figs. 1, 2 and 4). Second injection of Benadryl during the decreased lymph flow resulted in further reduction but when the interval of repeated injections was short, such as 10 to 15 minutes, there seemed to be no marked additional change to the degree of response to the initial dose (fig. 2). Such a fact was assumed to be due to the gradual increase of respiration exciting action, described above, or to the development of acute vascular refractoriness (*Page and Green, 1949*). However, an interval of more than one hour, in such a case, indicated recovery of almost normal responsibility.

The protein content of lymph sometimes decreased or increased with the decrease of lymph flow, or was unchanged at others. Such variance did not seem to be essentially related to the difference in the dosage of Benadryl or to the decreased rate of lymph flow. In any case, there were no great changes in the

protein content of blood serum. The coagulability of thoracic duct lymph had a tendency to decrease after injection of over 1 mg/kg of Benadryl and such a decrease was clearly observed for over two hours after injection of 10 mg/kg, the lymph specimen taken around

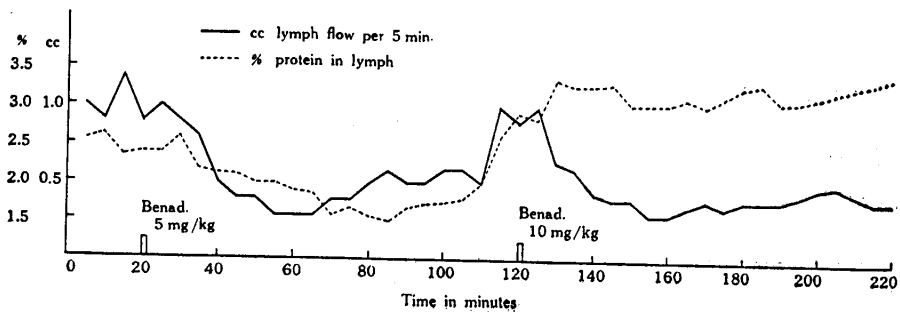


Fig. 1. Effect of intravenous injection of Benadryl on the flow and protein content of thoracic duct lymph. Dog, 5.1 kg female.

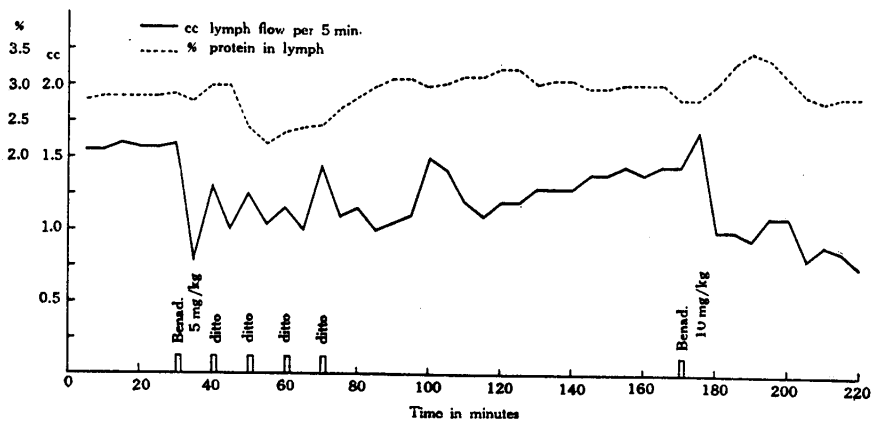


Fig. 2. Changes in the flow and protein content of thoracic duct lymph in a dog receiving intravenously repeated injections of Benadryl with short intervals. Dog, 9.5 kg female.

30 minutes after injection showing complete loss of coagulability for 24 hours.

Injection of Benadryl into portal vein required much longer period until the appearance of the decreasing effect on lymph flow than in the case of systemic injection. In this case, the initial temporary acceleration of lymph flow disappeared together with the acceleration of respiration but the decrease of lymph flow did not seem to be weakened as a whole.

In hepatic artery-ligated dog, the decrease of lymph flow by Benadryl was marked but the initial acceleration was strikingly stronger than in the ordinary cases, accompanied by the strong acceleration of respiration. The same phenomenon was observed

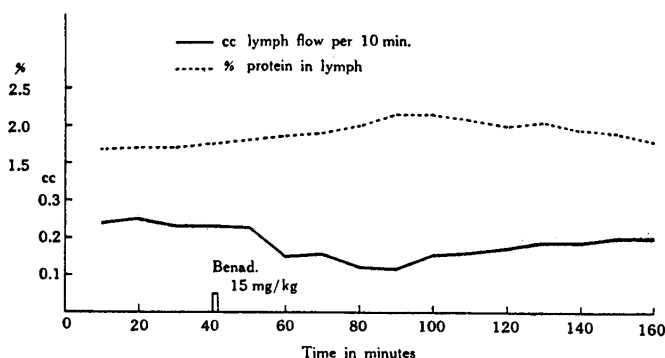


Fig. 3. Effect of intravenous injection of Benadryl on the flow and protein content of cervical lymph. Dog, 12 kg male.

in dog with *Eck's* fistula. These facts suggest that liver plays a rôle in mitigating the initial, violent action of the antihistamine.

These effects were also observed with 3015 RP, 3277 RP, and Pyribenzamine, in a manner similar to that of Benadryl but in a much stronger degree.

2. *Action of Benadryl on the flow and protein content of cervical lymph.* Systemic venous injection of 10 to 15 mg/kg of Benadryl also caused the decrease of flow of cervical lymph for a long period (1.5 hours or more) but the degree of its decrease was slightly less than that of thoracic lymph flow. There was no striking change or only a slight increase in the protein content of lymph (fig. 3). The change in the coagulability of cervical lymph in such cases could not be judged due to the prior administration of dicumarol in dogs.

3. *Action of Benadryl on the circulatory system.* Systemic venous injection of 2 to 10 mg/kg of Benadryl at a comparatively rapid rate (within 30 sec.) caused a temporary but comparatively marked fall in blood pressure followed, in most cases, by a slight hypertension which was generally rather lasting. In the case of repeated injections, the observation of *Winder and Thomas* (1947) that the degree of hypertension after depression of blood pressure

is degraded, was reconfirmed. It was also observed that period of such a fall tended to become longer on repetition of injection. These observations regarding blood pressure may be related to the afore-mentioned phenomenon that the rate of decrease in lymph

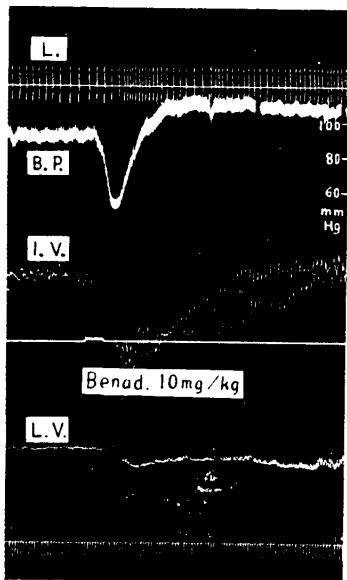


Fig. 4. Dog, 8.5 kg female, morphine-urethane. Effect of Benadryl injected into femoral vein on the lymph flow from thoracic duct (L.: lymph drop), arterial pressure (B.P.), and volumes of small intestine (I.V.) and of liver (L.V.). Time marker: 5 sec. and 1 min. intervals.

flow does not increase on divided doses in proportion to the large dose of total administration. In these cases, also, the reaction type returned to normal after an interval of more than one hour.

The portal pressure showed a slight decrease for a few minutes, up to 30 mm of citrate solution, by 10 mg/kg/30 sec. of Benadryl, slightly after the fall of arterial pressure. When the fall of arterial pressure was striking, blood pressure in jugular vein also showed a slight fall at the same time.

The volumes of liver and small intestines decreased within the 10 minutes extending over the fall of arterial pressure and its subsequent rise (fig. 4). The volume of hind limb increased very slightly coincidentally with the period of hypotension but its later change was generally not striking.

In case the drug was injected into the portal vein, the foregoing circulatory effects were strikingly weakened and became sluggish compared to its systemic venous injection, as was observed by the alternate injections of both methods in the same animal.

Summary :

1. Systemic venous injection of Benadryl caused the decrease of flow of thoracic duct lymph in dogs for 1.5 hours or more. This action was observed in the case of exclusion of liver circulation and the injection of the drug into portal vein, but in these cases, initial temporary acceleration of lymph flow became markedly strong in

the former and such acceleration completely disappeared in the latter. A parallel relationship was found to exist between this initial lymph acceleration and respiratory stimulation. Repeated administration of Benadryl with short intervals caused transitory refractoriness in the effect of decreasing lymph flow. The decrease of lymph flow was also observed with the other antihistamine^s examined.

2. Benadryl also showed decreasing effect on the flow of cervical lymph, although in a lighter degree than in the case of thoracic lymph flow.

3. No definite change was observed in the protein content of lymph after injection of Benadryl, while the protein content in blood serum remained unchanged. However, the clotting time of thoracic duct lymph was extended.

4. Benadryl caused fall of arterial blood pressure, followed by a slight rise of a comparatively long duration; a slight fall of portal pressure, and a transitory decrease of liver and intestinal volumes, i.e. anemia of portal system, also occurred. Repeated injection of Benadryl with short intervals caused extension in the duration of fall in arterial pressure with decreased rate of its secondary rise.

Part II. *Influence of Antihistamines on the Lymphagogenic Effect of Histamine*

Considering the known facts that there are differences of wide variety in the degree of antagonism of antihistamines and histamine with the kinds of organs and their functions, the influence of antihistamines on some vascular effects which might be related to the mechanism of lymphagogenic action of histamine, was examined in order to obtain more detailed informations regarding the main site of the antagonism of these two substances.

1. *Influence of Benadryl on the lymphagogenic effect of histamine on thoracic duct lymph.* Histamine dihydrochloride (hereinafter indicated as histamine) was given into the femoral vein 30 minutes after the injection of 10 mg/kg of Benadryl. As can be seen from the representative data given in figure 5, the lymphagogenic action of 0.05 to 0.1 mg/kg of histamine on thoracic duct lymph was markedly restricted after Benadryl. Moreover, such action was reversed to the decrease of lymph flow immediately after the injec-

tion of histamine, with attendant almost complete inhibition of histamine action in increasing protein content of lymph and decreasing the protein content of blood serum. Such inhibitory effect of Benadryl weakened gradually with lapse of time but it required

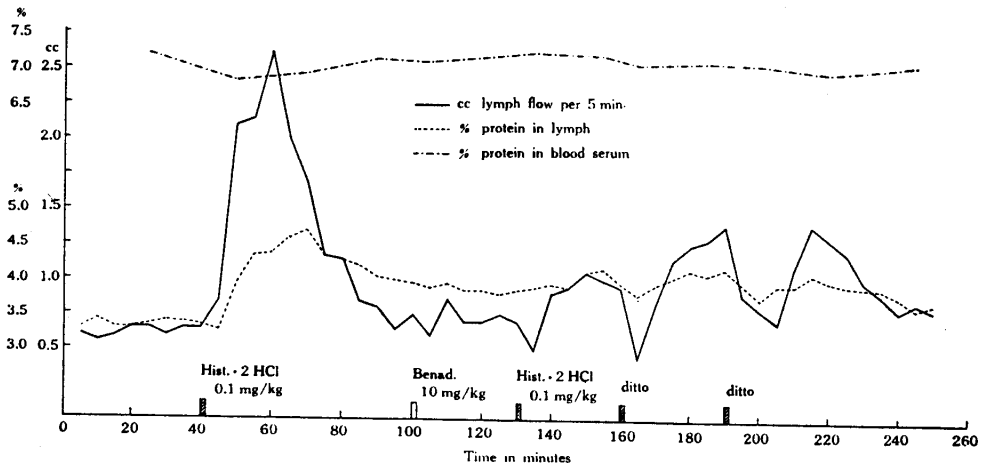


Fig. 5. Effect of intravenous injection of histamine on the flow and protein content of thoracic duct lymph and the protein content of blood serum, before and after Benadryl. Dog, 9.0 kg female.

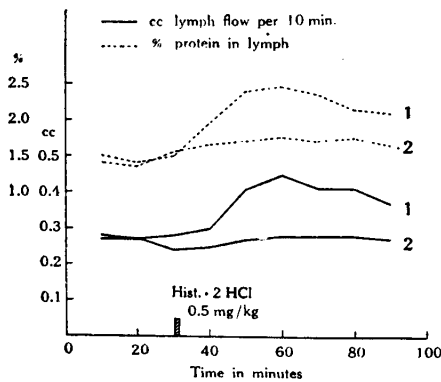


Fig. 6. Effect of intravenous injection of histamine on the flow and protein content of cervical lymph of (1) normal anesthetized dogs and of (2) dogs receiving Benadryl 10 mg/kg 30 min. prior to histamine. Each pair of curves show average of respective 3 experiments.

more than four hours for the complete disappearance of this effect. The marked lymphagogic action of histamine by its 1 mg/kg dose was almost completely suppressed within one hour after injection of 10 mg/kg of Benadryl.

2. *Influence of Benadryl on the lymphagogic effect of histamine on cervical lymph.* The flow of the cervical lymph showed medium increase after a single injection of 0.5 mg/kg of histamine, reached the maximum about 30 minutes after the injection, and returned to normal after more than one hour. This lymph

was also highly proteinized after the injection. Administration of Benadryl 30 minutes before injection of histamine practically suppressed such action (fig. 6) and this suppressive effect was maintained for over two hours. When a hypotension of long duration

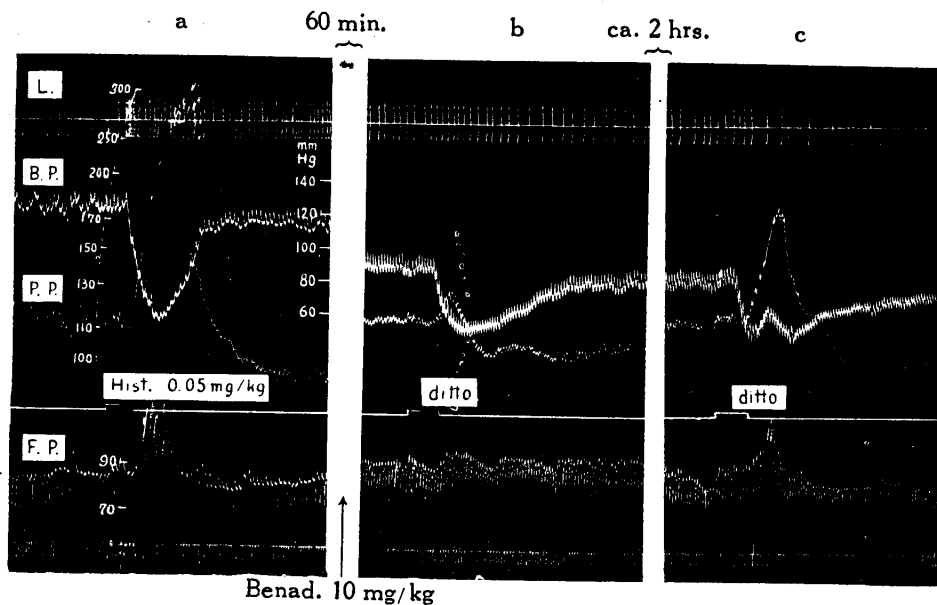


Fig. 7. Dog, 7.6 kg female, morphine-urethane. Effect of histamine injected into femoral vein on the lymph flow from thoracic duct (L.: lymph drop), arterial (B.P.) and portal blood pressure (P.P.) and femoral venous pressure (F.P.), (a) before and (b, c) after Benadryl. At arrow, 30 min. before b, Benadryl was injected. Hist. refers to histamine dihydrochloride. Scales for portal and femoral venous pressures are indicated in mm of 10 per cent sodium citrate solution.

had been caused by the injection of 2.5 to 3 mg/kg of histamine in multiple divided doses during one hour, the augmentation of cervical lymph flow was much more marked but the protein percentage of lymph decreased agreeing with the results of *McCarrell* and *Drinker* (1941).

3. *Influence of Benadryl on the actions of histamine on circulatory system.* Reports still remain small regarding the influence of antihistamines on the vascular effects of histamine, other than that on arterial blood pressure.

The observations on the effect of 0.05 to 0.1 mg/kg of histamine given 30 minutes after the injection of 10 mg/kg of Benadryl showed that a partial inhibition occurs on the fall of arterial blood pressure

by histamine, in a degree distinguishable from tachyphylaxis (Karady, 1936). In contrast to the small degree of effect on the fall of arterial blood pressure, the rise of portal pressure by histamine was markedly inhibited for a long period, more than two hours after the injection of Benadryl. Jugular venous pressure rises with a small

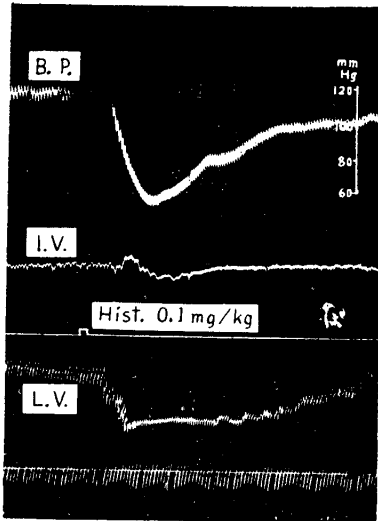


Fig. 8. Dog, 7.5 kg female, morphine-urethane. Effect of histamine injected into femoral vein on the arterial blood pressure (B.P.) and volumes of intestine (I.V.) and of liver (L.V.), 30 min. after Benadryl. Hist. refers to histamine dihydrochloride.

dose of histamine and falls with a large dose. These actions were completely arrested by pretreatment with Benadryl. Figure 7 also indicates that, besides such effects, Benadryl is antagonistic to the lymph flow acceleration of histamine.

Intestinal volume increased a few minutes after temporal decrease by histamine but liver volume showed a rather simple swelling. After administration of Benadryl, the volume increase of these organs were arrested, or rather, the liver volume inversely showed marked decrease (fig. 8). Hind leg volume underwent transitory decrease immediately after administration of histamine and then turned to increase. Inhibitory effect of Benadryl was also apparent in these changes.

Summary :

1. Pretreatment with Benadryl markedly suppressed the accelerating action of histamine on flow of thoracic duct lymph and increase of its protein content, and under the action of Benadryl the lymph flow immediately after the injection of histamine decreased.

2. Benadryl practically suppressed the accelerating action of histamine on cervical lymph flow and increase of its protein content.

3. Benadryl failed to show marked antagonism against fall of arterial blood pressure by histamine but did markedly suppress the rise of portal pressure, and increase of intestinal and hind limb volumes caused by histamine. Liver volume became smaller after injection of histamine following that of Benadryl.

Part III. Influence of Antihistamines on the Lymphagogic Effect of Peptone

Some workers (*Markowitz and Mann, 1931*) deny the essential rôle of liver in the acceleration of thoracic duct lymph flow by

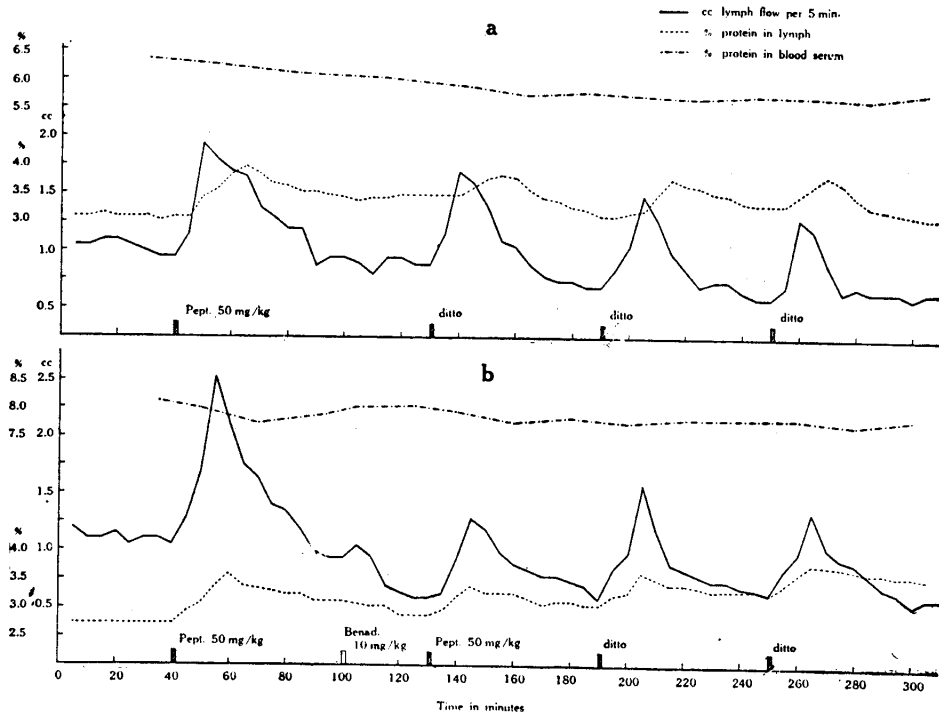


Fig. 9. Effect of intravenous injection of peptone on the lymph flow from the thoracic duct and the protein content of lymph and blood serum. Upper graph (a) shows gradual decrease in response to peptone on repetition of the injection; lower graph (b) shows slight inhibitory influence of Benadryl on the peptone effect. Dogs, a, 6.4 kg male; b, 7.3 kg male.

peptone but many maintain that the action is caused chiefly by the increase of plasma filtration under liver congestion (*Starling, 1893; Abe, 1919; Petersen, Jaffé, Levinson and Hughes, 1923*). It is known that the amount of histamine in plasma increases during peptone shock (*Dragstedt and Mead, 1937; Dragstedt, Mead and Eyer, 1938*), and it has been confirmed in dogs that most of such histamine is liberated in the liver (*Holmes, Ojers and Dragstedt, 1941; Mayeda, 1954*). In the present series of experiments, examinations were

made on the degree of antagonism of Benadryl against the lymphagogic and vascular effects of peptone.

1. *Influence of Benadryl on the lymphagogic effect of peptone on thoracic duct lymph.* Since it had been found that the action of

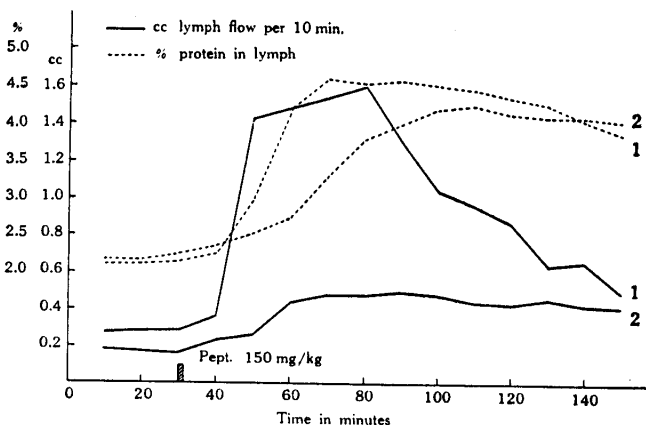


Fig. 10. Effect of intravenous injection of peptone on the flow and protein content of cervical lymph of (1) normal anesthetized dogs and of (2) dogs receiving Benadryl 30 min. before peptone. Each pair of curves represent average of respective 3 experiments.

50 mg/kg of *Witte's* peptone on blood pressure was recoverable and showed comparatively marked effect on thoracic duct lymph, this dose was used in the majority of the present experiments.

At this dose, the lymph flow from thoracic duct was accelerated for about one hour and the maximum value taken every five minutes was 2 to 4 times of that before the injection. In this case, the protein concentration of the lymph also underwent reversible increase attended with a slight decrease of blood serum protein. Repeated injection with an interval of 60 to 90 minutes showed gradual and slight decrease of such responses. Benadryl was injected in a dog in which the first peptone effect had been observed, then the second injection of peptone was given 30 minutes later, followed by the repeated injections of peptone with one hour's interval. The influence of Benadryl was judged by comparative observation of a control animal given similar injections except those of Benadryl. As shown in figure 9, Benadryl diminished these effects of peptone but the degree of such inhibition was clearly smaller compared to the foregoing case of histamine and

that of sinomenine described later. Benadryl did not show substantial influence on the action of peptone in decreasing the coagulability of lymph.

2. *Influence of Benadryl on the lymphagogenic effect of peptone on cervical lymph.* No reports are available as yet on the action of

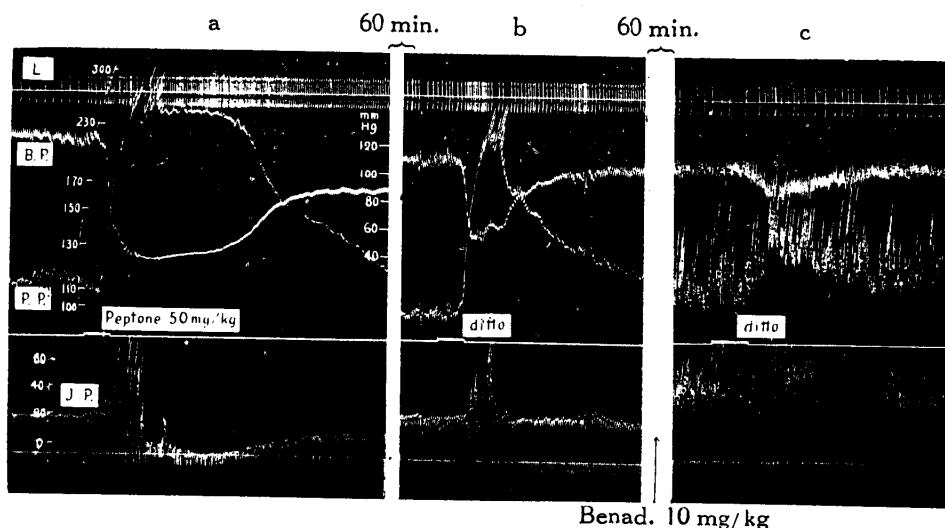


Fig. 11. Dog, 10.2 kg female, morphine-urethane. Effect of peptone injected into femoral vein on the lymph flow from thoracic duct (L.: lymph drop), arterial (B.P.) and portal blood pressure (P.P.) and jugular venous pressure (J.P.), (a, b) before and (c) after Benadryl. At arrow, 30 min. before c, Benadryl was injected.

peptone on cervical lymph flow. In the present series of experiments, the intravenous injection of 150 mg/kg of peptone caused marked lymphagogenic effect and increase of protein content on cervical lymph of dog. At this dose, the effect of subsequent injection of peptone was markedly decreased. In a different dog, the injection of 10 mg/kg of Benadryl 30 minutes before the injection of peptone caused a marked decrease of the effect of peptone in spite of the fact that a larger dose had been used than in the case of thoracic lymph flow (fig. 10). The coagulation time of this lymph was extended by peptone but Benadryl failed to show any apparent influence on this effect.

3. *Influence of Benadryl on the actions of peptone on circulatory system.* The arterial blood pressure fell 80 to 100 mm Hg after the systemic venous injection of 50 mg/kg of peptone and this hypotensive effect returned to preinjection level within one hour.

The jugular venous pressure also decreased proportionally when the fall of arterial pressure was severe, but the portal pressure markedly increased and this increase was more longer lasting than in the case of histamine of equihypotensive dose. These effects all weakened to some extent by repeated injection of peptone. Such effects of peptone were reduced by 10 mg/kg of Benadryl, distinguishable from such weakening of the effect. The rise of portal blood pressure was suppressed only slightly as compared to the case of histamine (fig. 11).

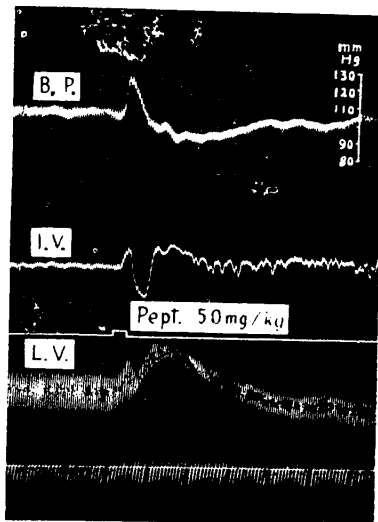


Fig. 12. Dog, 7.5 kg female, morphine-urethane. Effect of peptone injected into femoral vein on the arterial blood pressure (B.P.) and volumes of intestine (I.V.) and of liver (L.V.) in a dog receiving Benadryl before 30 min.

Intestinal and hind limb volumes increased after temporary decrease by peptone but the liver volume markedly increased immediately. Benadryl effected a definite suppression on such increasing effect on liver and hind limb volumes but there was no occurrence of the reversal of liver volume toward decrease, as in the case of histamine, and the degree of such suppression was in no means marked (fig. 12).

Foregoing observations indicate that the actions of peptone on the circulatory system, especially on the portal circulation, is less affected by Benadryl than that of histamine.

Such facts suggest the possibility of some relationship of these observations with the foregoing view that the action of peptone on the lymph flow from thoracic duct resists Benadryl than that of histamine.

Summary :

1. The lymphagogic effect on thoracic duct lymph and increase of protein content of the lymph by peptone were weakened by pretreatment with Benadryl but only slightly.

2. Suppressive effect of Benadryl on the action of peptone on cervical lymph flow and its protein content was more marked than that on thoracic duct lymph.

3. Benadryl effected a definite degree of suppression on the fall of arterial blood pressure, rise of portal blood pressure, and increase of liver volume by peptone, but the degree of suppression of the two latter effects of peptone was far more incomplete than the suppression of similar actions of histamine by Benadryl.

Part IV. *Influence of Antihistamines on the Lymphagogenic Effect of Sinomenine*

The lymphagogenic action of sinomenine on dog thoracic duct was first found by *Ishiwari* (1921) who isolated this alkaloid, and was later confirmed by many other workers (*Nagase*, 1923; *Kosuge*, 1923; *Itô*, 1940; *Kobayashi*, 1942). Recently, one of the authors, *Mayeda* (1953, 1954), observed that, whereas peptone caused liberation of histamine from dog liver, sinomenine caused the liberation of it chiefly from the skin. These observations have prompted the present studies on sinomenine because of the interesting assumption that there is apparently a difference in the mechanism of histamine liberation by peptone and sinomenine.

1. *Influence of Benadryl on the lymphagogenic effect of sinomenine on thoracic duct lymph.* Administration of 1 to 3 mg/kg of sinomenine hydrochloride (hereinafter indicated as sinomenine) into femoral vein resulted in a marked increase of thoracic lymph flow and protein content of the lymph, the outflow of the lymph taken every five minutes reached a maximum of about four times that of the control. These increases were accompanied by the attendant decrease of blood serum protein, as in the case of the foregoing two substances. The change of the lymph flow returned almost to normal after 30 to 60 minutes but the increased content of the protein continued far longer. The lymph obtained during a definite period after the injection of sinomenine was markedly less coagulable or incoagulable, as in the case of peptone. Since such actions of sinomenine are tachyphylactic, more pronounced than in the case of peptone, the influence of Benadryl was judged by comparing the results with two groups of dogs each, one group given sinomenine 30 minutes after the injection of Benadryl and the other only sinomenine.

These experimental results have shown that the lymph acceleration from thoracic duct caused by 1 to 3 mg/kg of sinomenine is almost completely suppressed by pretreatment with 10 mg/kg of

Benadryl and this is the point that clearly differs from that of peptone. However, the increase of protein content of the lymph caused by sinomenine is not completely eliminated by Benadryl although the beginning of the increase is somewhat retarded and

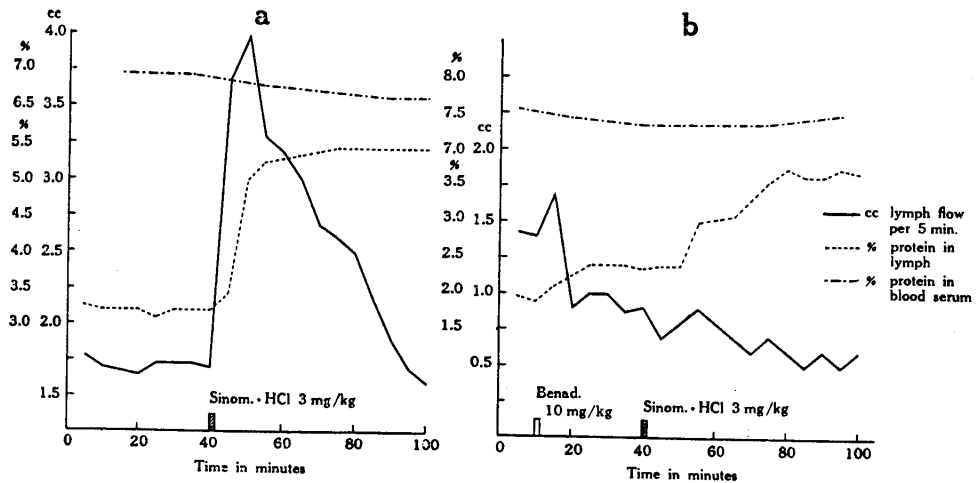


Fig. 13. Effect of intravenous injection of sinomenine on the lymph flow from thoracic duct and the protein contents of lymph and blood serum, in (a) normal and (b) benadrylized dogs. Each graph represents average of respective 2 experiments.

the degree of increase is considerably reduced. The decrease of serum protein content was also restricted to comparable degree (fig. 13). The decrease of coagulability did not seem to be modified by Benadryl. Three administrations of Benadryl in 15 minutes' interval, for a total of 30 mg/kg failed to influence the foregoing effects of sinomenine any further. The insufficient suppression of the increase of lymph protein content by Benadryl was similarly observed in dogs with complete ligation of periportal lymphatics or with *Eck's* fistula so that these effects of sinomenine are probably not related to the hepatic mechanism of lymph formation.

2. *Influence of Benadryl on the lymphagogic effect of sinomenine on cervical lymph.* The cervical lymph flow was markedly accelerated for over one hour by 3 mg/kg of sinomenine and its protein content showed a more lasting increase. The injection of 10 mg/kg of Benadryl resulted in somewhat more pronounced suppression of the lymphagogic effect and increase of protein content by sinomenine, than in the case of peptone.

3. *Influence of Benadryl on the action of sinomenine on circulatory system.* Systemic injection of 1 to 3 mg/kg of sinomenine caused a marked fall of arterial blood pressure. The portal blood pressure rose definitely after the fall of arterial pressure began but the degree of such rise was far weaker than that in the case of peptone in a dose that shows the same degree of the fall of arterial blood pressure. Although the change of pressures in jugular and femoral veins was related to the strength of the fall in arterial blood pressure, such change was not generally marked (fig. 14). Considerable tachyphylaxis was observed in these effects, as in lymphagogic action.

After the injection of 10 mg/kg of Benadryl, the hypotensive effect caused by 1 mg/kg of sinomenine seemed to be somewhat reduced but no apparent influence was observed on the intensive fall caused by 3 mg/kg of sinomenine. The rise of portal blood pressure caused by 1 mg/kg of sinomenine was completely suppressed, or rather, was reversed to a fall (fig. 15), although the same caused by 3 mg/kg of sinomenine was largely restricted. The changes of other venous pressures were also arrested by pretreatment with Benadryl.

Sinomenine caused initial increase followed by decrease of liver volume but the intestinal volume rather decreased immediately. After Benadryl administration, the increase of liver volume caused by 3 mg/kg of sinomenine was reduced to a certain degree, but that caused by 1 mg/kg of sinomenine was reversed to shrinkage. These observations are similar to the case of antagonism between Benadryl and histamine described before. The intestinal volume also decreased even after Benadryl. The action of sinomenine in increasing the hind limb volume is stronger than those of histamine and peptone, corresponding to the strength of the fall of arterial blood pressure. This action was incompletely suppressed by Benadryl.

4. *Influence of Benadryl on the cutaneous reaction of sinomenine.* Intracutaneous injection of sinomenine in man and dog caused flare and wheal, weaker but indistinguishable from those caused by histamine. Injections of 0.05 cc each of normal saline containing gradient concentration of sinomenine and histamine were made intradermally to the skin of a shaved back of dogs and after 15 minutes the area of the wheals thereby formed were

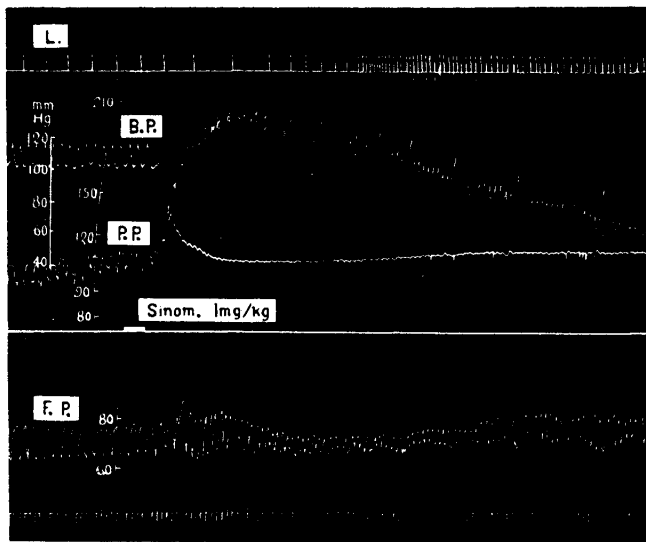


Fig. 14. Dog, 7 kg male, morphine-urethane. Effect of sinomenine on the lymph flow from thoracic duct (L : lymph drop), arterial (B.P.) and portal blood pressure (P.P.) and femoral venous pressure (F.P.) in a normal anesthetized dog.

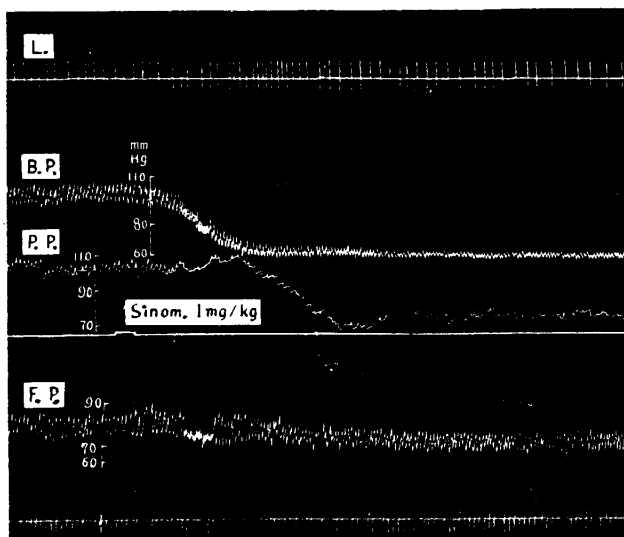


Fig. 15. Dog, 7.9 kg male, morphine-urethane. Effect of sinomenine on the lymph flow (L : lymph drop), arterial (B.P.) and portal blood pressure (P.P.) and femoral venous pressure (F.P.) in a dog treated with Benadryl 10 mg/kg 30 min. prior to sinomenine.

measured planimetrically by tracing the outline of the wheal on a thin paper. The areas obtained are shown in figure 16, with the area of a wheal caused by 1 : 8,000 of histamine as 100, together with the size of the wheal caused by the combination of 1 : 1,600 of

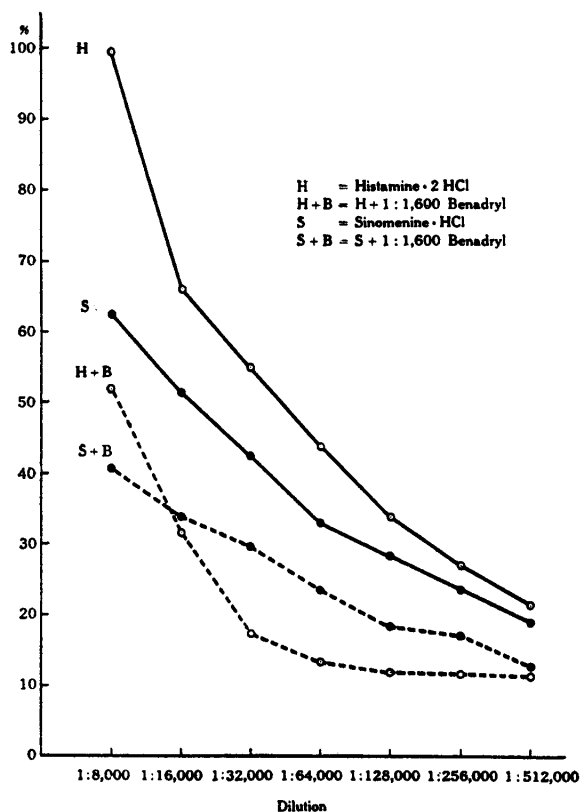


Fig. 16. Influence of Benadryl on the cutaneous reaction of sinomenine and histamine. Dimension of the wheal induced by 0.05 cc normal saline containing sinomenine or histamine in indicated dilution is plotted as percentage of that of 1 : 8,000 histamine dihydrochloride.

Benadryl in such a solution, at various concentrations of the two substances. These results indicated that the wheal caused by sinomenine is considerably reduced by the action of Benadryl although not as distinct as that caused by histamine. The skin area from which the wheal caused by sinomenine has disappeared was immune to sinomenine for a definite length of time but injection of

histamine in this area caused a wheal of the same size as that on normal skin.

Summary :

1. Benadryl suppressed the lymphagogic effect on thoracic lymph and increase of its protein content caused by sinomenine, the effect being more completely on the former.

2. Benadryl suppressed the lymphagogic effect on cervical lymph and increase of its protein content caused by sinomenine, more stronger than their suppression in the case of peptone.

3. Fall of arterial blood pressure, rise of portal pressure, and increase of liver and hind limb volume caused by sinomenine were all reduced by pretreatment with Benadryl. When the dose of sinomenine was not extremely large, reversal of the action was observed on the portal blood pressure and liver volume.

4. Benadryl markedly reduced the cutaneous reaction of sinomenine.

Discussion

The direct action of antihistamines on the capillaries had not been well known until *Haley* and *Harris* examined, in 1948, this action by the topical application of a series of such chemicals in rat's capillary bed. They observed by these experiments that antihistamines caused a definite vasoconstriction of precapillary sphincters and assumed that such action might reduce capillary permeability by decreasing the flow through capillary bed and thereby cause diminished extravasation of dyes, India ink, or plasma into the surrounding tissues.

In the present series of experiments, the fact that Benadryl (and also some other antihistamine agents) caused decrease of lymph flow, not only from thoracic duct but also from cervical lymphatics, for a comparatively long period indicates that the decrease of plasma extravasation is caused by vascular mechanism of the whole body. However, it is not possible to determine by the present experimental results alone whether such decrease of capillary permeability is the result of vasoconstrictor effect on precapillary sphincters and/or other vessels (mesoarterioles and arterioles) of peripheral vascular system, or whether such is due to the change of the capillary wall itself. The former, however,

seems more convenient in explaining the following two phenomena. The secondary rise of arterial blood pressure that is observed for a long period of time after injection of antihistamines, although seemingly masked by myocardial depression in the case of a large dose (*Winder and Thomas, 1947*), agrees with the mostly likely view that antihistamines directly affect peripheral vessels (*DeCuyper, 1946; Winder and Thomas, 1947*). The other is the fact that the decrease of lymph formation is not necessarily accompanied by the decrease of its protein content. Such a fact suggests the possibility that reabsorption of water in the venous side of the capillaries (*Starling, 1895/96; Drinker and Field, 1933*) is being carried out freely. The more pronounced decrease of thoracic lymph flow than that of cervical lymph is probably referable to a transient anemia of splanchnic area and the direct cause of such action is possibly the relaxation of sluice muscles located in the hepatic veins (*Simonds and Arey, 1920; Jaffé, 1924*) and not only the vasoconstriction of intestines and spleen (*DeCuyper, 1946*), because distinct counteraction with histamine was observed in this site.

Transient initial acceleration of lymph flow observed after antihistamines is probably due to the accelerated respiration caused by the presso- and chemoreceptive mechanism of these substances (*Winder and Thomas, 1947*). The destruction or inactivation of antihistamines in liver is suggested by the fact that the exclusion of the liver from circulation causes intensification of such accelerating effect and this weakens on injection into portal vein. Since the decrease of lymph flow in these two cases are not so different, the rôle of liver in these cases rather may be the mitigation of a sudden rise of the drug concentration in blood.

The antagonism between histamine and Benadryl was clearly indicated in both lymph flows and in vascular reaction examined, other than arterial pressure. The interaction of the two substances observed in liver circulation is extremely important. Pretreatment with Benadryl not only suppressed the liver swelling effect of histamine but caused a complete reversal action, turning to shrinking. Such histamine reversal, whose site of action is assumed to be in the sluice mechanism of the hepatic veins (*Mautner and Pick, 1929*) is a new type of antagonism of the two substances, not reported to date. The effect of such histamine reversal in portal circulation was clearly observed in thoracic lymph flow,

Very similar effect was observed in comparatively small dose (1 mg/kg) of sinomenine on portal circulation. The lymphagogic action of sinomenine was very clearly inhibited by Benadryl. These facts support the view that practically all the vascular effect of sinomenine is due to histamine it liberates (*Mayeda*, 1953). The similar action of peptone on portal pressure and liver volume is not so clearly inhibited by Benadryl, and the antagonism of the two substances was rather incomplete in the action on thoracic lymph flow.

The above fact may suggest that the liver congestion caused by peptone is due to the liberation of some active principle other than histamine. However, experiments carried out in this laboratory recently by *Nishiyama* (1954) have offered evidences that the marked rise of portal pressure in dog anaphylaxis is hardly inhibited by pretreatment with Benadryl, in spite of marked suppression of the fall of arterial blood pressure. Considering the common fact in these two cases that the majority of liberated histamine originates in the liver, whereas histamine release by sinomenine occurs chiefly in the skin and muscles, it seems most probable that the constriction of hepatic veins is caused by the *Dale's* (1948) so-called "intrinsic" histamine liberated in the cells of reacting tissues rather than by the "extrinsic" histamine transported from other places, as in the case of sinomenine or histamine injection. Such explanations would probably help to understand the reasons why the liver congestion by peptone, and consequently, the increased flow of thoracic lymph largely due to it, receive only a weak inhibitory influence by antihistamines.

The series of foregoing findings show that the antagonism of antihistamines against lymph formation is most clearly indicated in a mechanism chiefly represented by this extrinsic histamine. However, it is true that the antihistamines themselves possess the effect of suppressing plasma filtration that it is possible that such effect would be displayed to a certain extent in a pathologic condition not involving histamine as long as this mechanism is not damaged.

Conclusions

1. Benadryl and other antihistamines examined cause a decrease of thoracic and cervical lymph flow in dogs over a long

period by intravenous injection. From the fact that such effect is not attended by the decrease of lymph protein level and the fact that there is a long lasting secondary rise in arterial blood pressure, such effect is assumed to be due to the decrease of plasma filtration caused by the decreased capillary blood flow by peripheral vasoconstriction but the marked decrease of lymph flow from thoracic duct is in part due to a transient anemia brought about in splanchnic region.

2. Benadryl clearly inhibits the acceleration of thoracic and cervical lymph flow and increase of protein content of the lymph caused by histamine, probably by competition for the same site of action on the precapillary vessels. The reversal of the accelerating effect of histamine on thoracic lymph flow by Benadryl is assumed to have some bearing on the new type of marked counteraction of these two substances in the hepatic sluice mechanism noted for the first time during the present series of experiments.

3. The suppression of the accelerating action of sinomenine on thoracic and cervical lymph flow by Benadryl is marked but that of the accelerating action of peptone on thoracic lymph flow is rather incomplete. The difference in the effect of Benadryl on these two substances was also observed on their action of portal circulation. These facts can be explained by assuming the distinction between the extrinsic and intrinsic histamines as the origin of liberated histamine that affects the hepatic sluice mechanism.

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