myocardium fails to contract following left coronary artery ligation. Consequently, as a result of the combined occlusion of the sinus and a left coronary ramus, dynamic conditions are created, such that there should be a sizable blood flow from non-occluded coronaries through their capillary beds into the large veins and then by Thebesian and arterioluminal vessels into the heart cavities.

If the peripheral coronary artery is closed (not allowed to bleed) it is believed that no adequate anatomical circuit exists to route this venous blood through the capillary bed of the occluded coronary, whereas if the peripheral coronary is opened a portion of this blood is routed in retrograde fashion from the venous system through the capillary bed of the occluded artery. Since ligation of the cardiac veins does reduce considerably the normal left coronary inflow and does not prevent failure of contraction in a myocardial area whose normal blood supply has been acutely removed, such a procedure cannot be regarded as a method of choice for encouraging the blood supply to a potentially infarcted area.

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Inhibitory Action of Narcotics on the Histamine Contraction of Plain Musculature.

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As was first shown by Besredka[1] narcosis may prevent fatal anaphylactic shock in guinea pigs. This effect of the narcotic is not due to its action on the central nervous system as presupposed by Besredka, but is probably attributable to its peripheral action on the bronchial musculature (Farmer[2]). In *in vitro* experiments I[3] was able to demonstrate that narcotics (urethane, chloralose) inhibit anaphylactic contraction of sensitized uterine strips of guinea pigs without inhibiting desensitization of the muscle.

Dale's[4] theory of anaphylaxis assumes that anaphylactic contraction of plain musculature is caused by liberated histamine or "histamine-like" substances. In my experiments (l. c.) anaphylactic con-

1 Besredka, *Ann. de l'Inst. Pasteur*, 1907, **21**, 957.

2 Farmer, *J. Immunol.*, 1937, **32**, 195.

3 Farmer, *J. Immunol.*, 1937, **33**, 9.

4 Dale, *Lancet*, 1929, I, 1179, 1233, 1285.

traction of the uterine strips was prevented through the inhibitory action of the narcotics on the histamine contraction of plain musculature (Saito,[5] Katz[6]).

Several authors[7] have shown that narcotics cause loss of tonus of excised strips of plain musculature (bronchi, intestine, uterus, ureters). This loss of tonus probably explains why histamine fails to cause contraction of plain musculature in the presence of narcotics. The following experiments were undertaken: (1) to compare the inhibitory action of narcotics belonging to various chemical groups on the histamine contraction of plain musculature; and (2) to ascertain the effect of substitution of radicals within these groups.

Method. Young female guinea pigs, weighing between 225 and 315 g, were used as test animals. They were fed a diet consisting of carrots, lettuce and oats. The animals received their last feeding 18 to 24 hours prior to the experiment and were killed by a blow on the head and bled by severing the carotids. Immediately after killing the animal, a piece of ileum about 15 cm long was excised and kept in an oxygenated Ringer's solution of 38° to 39°C. The experiment was carried out by suspending vertically a strip of approximately 2.5 cm length in an oxygenated bath solution of 38° to 39°C. The suspended strip was attached to a lever with a writing point and the muscular actions were recorded on a slowly revolving kymograph. The bath solution was either 50 cc Ringer's solution or 50 cc narcotic solution. The Ringer's solution was made up as follows: NaCl 9.0 g, KCl 0.40 g, $CaCl_2$ 0.24 g, $MgCl_2$ 0.005 g, $NaHCO_3$ 0.5 g, dextrose 1.0 g, distilled water ad 1000 cc. The dextrose and $NaHCO_3$ were added shortly before using the solution. All chemicals were of "tested purity." Water was redistilled in a glass still. The narcotic solution was prepared by dissolving the narcotic in Ringer's solution.

Control experiments. The controls were carried out by suspending an intestinal strip in 50 cc Ringer's solution. After 8 to 10 minutes 0.5 cc of a 1×10^{-6} histamine phosphate (Parke, Davis) solution was added to the bath. In this concentration (1×10^{-8}) histamine causes very marked contraction of the strip.

Narcotic experiments. Eight to 10 minutes after suspension of

[5] Saito, *Z. f. ges. exp. Med.*, 1924, **41**, 570.

[6] Katz, *Arch. f. exp. Path.*, 1929, **141**, 366.

[7] Trendelenburg, *Arch. f. exp. Path.*, 1912, **69**, 79; Redonnet, *Arch. Internat. d. Pharmacody e. d. Therap.*, 1925, **30**, 322; Gruber, *J. Pharm. and Exp. Ther.*, 1926-27, **30**, 149; Fromherz, *Arch. f. exp. Path. u. Pharm.*, 1933, **173**, 78; Frey, *Arch. f. exp. Path. u. Pharm.*, 1931, **159**, 163; Mercier, Krijanovsky and Paganelli, *C. R. soc. biol.*, 1937, **121**, 463.

the intestinal strip in the narcotic solution (50 cc) 0.5 cc of a 1×10^{-6} histamine phosphate solution was added. If contraction took place, a new strip was suspended in a stronger narcotic solution and increasing amounts of histamine were added to the bath. The procedure was repeated, fresh strips and fresh narcotic solutions being used, until a narcotic concentration was elicited which completely inhibited contraction of an intestinal strip after addition of 315 γ histamine phosphate (end concentration of the histamine 1.58×10^{-5}). The concentration of this narcotic solution is designated as the "inhibiting concentration" in the tables. It was felt that addition of an amount of histamine so greatly in excess of that used in the control experiment tended to eliminate variations in the response of individual strips.

Results. Twenty-one narcotics, belonging to 6 different chemical groups, were examined. Seventy-two guinea pigs were used and 196 individual experiments were carried out. The results of these experiments, which were very uniform, are summarized in Tables I-IV. Furthermore, the inhibiting effect of ephedrine sulphate on the histamine contraction of intestinal musculature was determined in the above described manner. In a concentration of 1:400 ephedrine sulphate completely inhibits contraction of an intestinal strip after addition of 315 γ histamine. The inhibiting effect of this ephedrine sulphate concentration was designated as 1 and the inhibiting effects of the various narcotic solutions were compared with it.

TABLE I.
Inhibiting Action of Barbiturates on the Histamine Contraction of Intestinal Musculature.

Substance				Inhibiting concentration	Inhibiting effect compared with Ephed. Sulph. = 1
Diethyl	barbituric	acid	(Veronal)	1:400	1.0
*Ethylisopropyl	"	"	(Ipral "acid")	1:500	1.25
*N-Butylethyl	"	"	(Neonal "acid")	1:2000	5.0
Isoamylethyl	"	"	(Amytal)	1:4000	10.0
Phenylethyl	"	"	(Luminal)	1:1000	2.5
Na-Diethyl	"	"	(Sodium-Veronal)	1:80	0.2
Na-Isoamylethyl	"	"	(Sodium-Amytal)	1:2000	5.0
Na-Phenylethyl	"	"	(Sodium-Luminal)	1:80	0.2
Diallyl	"	"	(Dial)	1:500	1.25
*Allylisopropyl	"	"	(Alurate)	1:1000	2.5
*Isobutylallyl	"	"	(Sandoptal)	1:2000	5.0

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TABLE II.
Inhibiting Action of Urethanes on the Histamine Contraction of Intestinal Musculature.

Substance	Inhibiting concentration	Inhibiting effect compared with Ephed. Sulph. = 1
Ethylurethane	1:66	0.165
n-propylurethane	1:133	0.33
n-butylurethane	1:400	1.0
Phenylethylurethane	1:2000	5.0
Trichlorourethane	1:1000	2.5

TABLE III.
Inhibiting Action of Sulfones on the Histamine Contraction of Intestinal Musculature.

Substance	Inhibiting concentration	Inhibiting effect compared with Ephed. Sulph. = 1
Sulfonal	1:200	0.5
Trional	1:400	1.0

TABLE IV.
Inhibiting Action of Chloretone, Paraldehyde, Morphine, on the Histamine Contraction of Intestinal Musculature.

Substance	Inhibiting concentration	Inhibiting effect compared with Ephed. Sulph. = 1
Trichloroisobutyl alcohol (Chloretone)	1:1000	2.5
Paraldehyde	1:100	0.25
Morphine hydrochloride	1:400	1.0

As shown by these tables, all of the examined narcotics exercise a marked inhibiting action on the histamine contraction of intestinal musculature. The suspended intestinal strips showed very pronounced relaxation, which was not overcome by addition of histamine. It is interesting to note in this connection that morphine hydrochloride showed the same inhibiting action on histamine contraction, although it does not prevent fatal anaphylactic shock in guinea pigs. As demonstrated by Trendelenburg (l. c.) it has a marked relaxing effect on excised bovine bronchial musculature.

Substitution of aliphatic radicals with increasing C-atoms enhances the relaxing and inhibiting action of narcotics. Substitution of a phenyl group or halogenation have the same effect (see Tables I, II, III).

In Table V the pH of a number of inhibiting narcotic solutions are registered. As seen from this table the pH of the narcotic solution is not the cause of its inhibiting action. Although the concentration of an inhibiting ethylurethane solution is approximately 30

times as great as the concentration of an inhibiting phenylurethane solution their respective pH are 8.6 and 8.7. Furthermore, the pH of an inhibiting ethylurethane solution is the same as that of the Ringer's solution (8.6). However, the hydrogen ion concentration of a narcotic solution can exert a certain effect on its inhibiting action. As shown in Table I sodium veronal, sodium amytal, and sodium luminal which are all decidedly alkaline (Table V) have a smaller inhibiting effect than the corresponding acids. This is in accordance with the observations of Gruber (l. c.) who found that increasing the pH of the bathing fluid heightened the tonus of the tissues, whereas a decrease in the pH brought a fall in tonus.

TABLE V.
pH of Various Inhibiting Narcotic Solutions.

Substance	Inhibiting concentration	pH
Ringer's solution	—	8.6
Ethylurethane	1:66	8.6
Phenylethylurethane	1:2000	8.7
Veronal	1:400	7.3
Sodium Veronal	1:80	9.3
Amytal	1:4000	8.0
Sodium Amytal	1:2000	8.9
Luminal	1:1000	8.2
Sodium Luminal	1:80	9.3
Dial	1:500	7.0
Sulfonal	1:200	8.7
Trional	1:400	8.6
Chloretone	1:1000	8.4
Paraldehyde	1:100	7.5

Summary. (1) Narcotics belonging to various chemical groups inhibit the histamine contraction of plain musculature (intestinal strips of guinea pigs). (2) This inhibiting action of the narcotics can be enhanced by (a) substitution of aliphatic radicals with increasing C-atoms; (b) substitution of a phenyl group; and (c) halogenation. (3) The described inhibitory action is probably due to the relaxing effect of narcotics on plain musculature.