STUDIES ON CONDITIONS OF ACTIVITY IN ENDOCRINE ORGANS

XXIX. SYMPATHIN E AND SYMPATHIN I

W. B. CANNON AND A. ROSENBLUETH

From the Laboratories of Physiology in the Harvard Medical School

Received for publication March 11, 1933

Stimulation of sympathetic fibers, which deliver impulses to the smooth muscle of tail hairs, leg vessels or the splanchnic area, causes a prolonged rise of blood pressure and other sympathomimetic effects on distant organs which have been either completely denervated or deprived of their sympathetic nerve supply, such as the heart, salivary gland, nictitating membrane, and intestine (see Cannon and Bacq, 1931; Bacq and Brouha, 1932; Rosenblueth and Cannon, 1932; Bacq, 1933). Since the only connection between the denervated structures and the stimulated region was the blood stream, and since the effects failed or were minimized when the stimulated region was excluded from the circulation while the stimulus was active, the conclusion was drawn that a substance, "sympathin," is set free when the smooth muscles are subjected to sympathetic nerve impulses.

Sympathin has the same effects as adrenin on the various test structures mentioned above. In the present research we have found, further, that like adrenin sympathin can cause contraction of the pregnant uterus of the cat, as well as contraction of the spleen and the blood vessels (see fig. 2A). Like adrenin, also, sympathin has its influence increased by a previous injection of cocaine (Rosenblueth and Schlossberg, 1931). A characteristic reaction for adrenin is given by a substance liberated into the aqueous humor of the eye after cervical sympathetic stimulation—presumably sympathin (Bacq, 1931). Moreover, the accelerator substance given off into the saline perfusate from cardiac tissue when responding to sympathetic influence affects test organs as adrenin affects them (Loewi and Navratil, 1926; Lanz, 1928). Because of these various resemblances the inference has been drawn that sympathin may be the same as adrenin. In the present paper we shall present evidence that sympathin is not only different from adrenin, but that there are two sorts of sympathin.

**Sympathin differs from adrenin.** The first evidence that sympathin differs from adrenin appeared when we tested the effects of sympathetic stimulation and adrenin on blood pressure after injecting ergotoxine. In
Fig. 1. Cat, under dial anesthesia, and injected with ergotoxine (5 mgm. per kgm.). Records of carotid blood pressure. Time, half-minutes.

A. Effects of injecting adrenalin (0.5 cc., 1:50,000), and stimulating the lower abdominal sympathetic chains (l.a.s.).

B. After injection of cocaine (7 mgm. per kgm.). Effects of stimulating l.a.s. and of injecting adrenalin during the elevated pressure induced by l.a.s.

C. Effects of injecting adrenalin and of stimulating the hepatic nerves (h.n.s.).
these experiments the animals (cats) were usually anesthetized with dial (0.85 cc. per kgm., by stomach) and the reacting organs were usually sensitized by an injection of cocaine (8 mgm. per kgm.). When in animals thus prepared the severed lower abdominal sympathetic chains (l.a.s.) are stimulated there is a characteristic prolonged rise of blood pressure, lasting 4 or 5 minutes (see Rosenblueth and Schlossberg, 1931). Adrenalin likewise in a sufficiently large dose causes a rise of blood pressure, or an initial brief sharp rise, then a fall and a final long rise, with gradual return to the former level. In studying the action of ergotoxine we found that in order to produce the effects described by Dale (1906) a larger amount is required in an animal under dial anesthesia than in a decerebrate animal—4 mgm. instead of 2 mgm. per kgm. After ergotoxine an intravenous injection of adrenalin causes a sudden fall of blood pressure, followed by a gradual return (see fig. 1A); stimulation of the l.a.s. causes, during the first half-minute, a fall which is quickly replaced by a rise, lasting 8 to 9 minutes or longer (see fig. 1A). If during this rise the nerves are stimulated again or adrenalin is injected, a pure fall results (see fig. 1B). If the hepatic nerves (h.n.s.) are stimulated on the duodeno-hepatic artery the usual effect, after ergotoxine, is a simple elevation of blood pressure, in marked contrast to the drop produced by adrenin (see fig. 1C). The “usual effect” is mentioned, because exceptionally there was a short, slight, initial drop of pressure on stimulating the h.n.s., such as shown in figure 1A and B on stimulating the l.a.s., but in these circumstances the branches to the duodenum were invariably intact. Whether the h.n.s. or the l.a.s. strands were stimulated, increased blood pressure was always associated with a faster heart rate.

If, in an animal with brain pithed (under ether), the cervical spinal cord was stimulated after injection of ergotoxine and curare, the blood pressure underwent a marked fall, such as occurs when commercial adrenalin is injected. This effect is due to medulliadrenal secretion, and proves the identical influence of adrenin and adrenalin. The same stimulation after excluding the adrenal glands yields the same sort of record as that of the l.a.s. in figure 1A.

The identity of the effects of l.a.s. and h.n.s. stimulation on blood pressure led us to assume that the cardio-accelerator and blood-pressure raising substance found in blood from the liver, as reported by Cannon and Uridil (1921), is the same as the sympathin given off when smooth muscle in any other area of the body is made to contract. Whether liver parenchyma as such contributes to the product is not yet determined.

Because both sympathin and adrenin influence the heart rate, we decided to make sure whether the difference of their effects on blood pressure could be due to any differences in their cardiac effects. In an animal under dial anesthesia the heart was denervated, the adrenal glands were tied off, the liver nerves were placed on shielded electrodes, the abdomen closed and er-
ergotoxine injected. Stimulation for one minute increased the heart rate from 104 to 148 beats per minute and raised the blood pressure 20 mm. Hg. A few minutes later, 0.4 cc. adrenalin, 1:100,000, uniformly injected during

Fig. 2. Cat, under dial anesthesia, sensitized with cocaine. Top record, spleen volume; lowest, leg volume; middle, arterial pressure. Arrows indicate direction of contraction of spleen and leg. Time, half-minutes.

A. Effects of stimulating h.n.s.
B. Effects of injecting adrenalin (0.5 cc., 1:100,000).
C. After injection of ergotoxine (4 mgm. per kgm.). Effects of stimulating h.n.s.
D. Effects of injecting adrenalin (same dose as in B).

15 seconds, increased the heart rate from 104 to 146 beats per minute, and lowered the blood pressure 34 mm. Hg. It was clear that the difference between the actions of the two agents should be sought in peripheral organs.
It seemed possible that by using organs which can contract or relax in response to sympatic impulses insight might be obtained into the difference between adrenin and sympathin. Accordingly we selected the spleen and the leg (Dale, 1906), registering the spleen changes from an oncometer by means of a tambour (having a very thin rubber membrane) and the leg from a plethysmograph by means of a similar tambour or a float attached to the short arm of a nearly balanced writing lever (see Hoskins, Gunning and Berry, 1916). Dial anesthesia was employed.

Effects of sympathin and adrenin on spleen and leg volume. In figure 2A are shown records of spleen and leg volume and blood pressure when the h.n.s. were stimulated. It is noteworthy that both the spleen and the leg were contracted by the circulating sympathin, and not passively dilated by the increased blood pressure, as Griffith, York and Zachmys (1928) reported,—i.e., except at the start they were contracted in spite of the higher pressure. An injection of adrenalin (0.5 cc., 1:100,000) had similar but larger effects (fig. 2B). Now ergotoxine was given, and artificial respiration was much increased, as suggested by Dale, so that the lungs were definitely hyperventilated. As illustrated in figure 2C, stimulation of the h.n.s. caused, as before, a marked rise of arterial pressure; the spleen underwent no noteworthy change of size, but in accord with the curve of higher pressure the leg was slightly enlarged. When the dose of adrenalin was repeated (fig. 2D), the arterial pressure sharply fell, as in figure 1. There was a slight initial relaxation of the spleen (which was more marked in other experiments), followed by a slight contraction as the pressure was rising. The initial relaxation Dale (1906) had previously recorded. The leg volume did not alter decisively during the blood-pressure drop, but it expanded to a considerable degree in the course of the rise.

When in the experiment just cited ergotoxine was given, the spleen and leg first strongly contracted, simultaneously with the entrance of the blood pressure on the long period of elevation which the drug induces. The spleen promptly relaxed, however, as the pressure continued to rise, whereas the leg remained in the contracted state. The effect of adrenin after ergotoxine can be readily explained by Dale's evidence that ergotoxine produces, as the doses are increased, an increased paralysis of the contractile action of adrenin, leaving its inhibitory action unimpaired. The fall of blood pressure was due, therefore, to lessened peripheral resistance because of vasodilation. The slight contraction of the spleen is explicable as a result of an insufficient dose of ergotoxine, for in other experiments as well we found that an amount of ergotoxine which conditioned a pure fall of blood pressure, after an injection of adrenin, left the spleen still capable of contracting. In the leg, of course, the blood vessels were the affected parts. The large expansion of the leg after adrenalin can reasonably be attributed to relaxation of the vessels innervated by sympathetic vasodilators (see
I.a.s. stimulation, fig. 1A and B). That this expansion occurred only when the blood pressure began to rise implies that the relaxation was more considerable and more prolonged in the limbs than elsewhere, e.g., than in the splanchnic area (see spleen record, fig. 2D). This early constriction in some regions (probably due to incomplete paralysis by ergotoxine), combined with a faster heart and a ready supply of venous blood in the big veins (because of hyperventilation) accounts for the prompt recovery of blood pressure. The foregoing explanation is in accord with the fact that as the doses of ergotoxine are increased, a series of intermediate responses is obtained which progressively unmask a dilator effect as the constrictor action of adrenin becomes progressively less efficient.

Sympathin from the liver region, unlike adrenin, caused a rise of general arterial pressure. This rise resulted from acceleration of the heart and from vasoconstriction. We found that a plot of the heart rate runs closely parallel with the curve of heightened blood pressure. Associated with the larger volume output from the heart, however, there is vasoconstriction; the spleen, for example, would have been passively distended (see beginning of the spleen record, fig. 2A), if it had not contracted in response to sympathin. In the leg the passive dilation was not considerable,—in some records it did not occur. Some constriction, therefore, must have occurred in the vessels of the leg, but certainly there was no active vasodilatation in that region.

The difference between the actions of adrenin and of sympathin from the liver region, as manifest in the blood pressure, appeared then to lie in a difference in their ability to affect sympathetic vasodilator systems. Further evidence in favor of this suggestion is presented in figure 3. In an animal under dial anesthesia and sensitized by cocaine, a minimal dose of adrenalin (0.1 cc., 1:200,000) was injected intravenously; it caused a contraction of the denervated nictitating membrane and a dilation of the denervated leg (fig. 3A). In figure 3B are the records obtained when the h.n.s. were stimulated; the leg, instead of dilating, was markedly contracted, i.e., an amount of sympathin having less effect than the adrenalin on the membrane had quite the opposite effect on the leg volume.

In the experiments hitherto described sympathin was obtained by stimulating structures (the smooth muscles of the liver and the tail) which in the main were contracted by sympathetic impulses. It seemed possible that if sympathin could be derived from structures inhibited by such impulses it might have a different effect. The volume changes of peripheral organs which may either contract or relax, confused as they are by the ups-and-downs of blood pressure, make the results too complicated to be easily and clearly judged. We turned away from these methods, therefore, and determined to use as indicators smooth-muscle organs which are exclusively contracted or relaxed by adrenin (and therefore do not require ergotoxine
to separate the responses), which are not much if at all affected by blood-pressure changes, and which can be readily recorded. The nictitating membrane (n.m.) has already proved to have an admirable sheet of smooth muscle which, when denervated, registers quite conveniently its contraction under the influence of adrenin or sympathin. As a structure the body of which relaxes under adrenin, we tried the urinary bladder, but found it, when supporting a column of fluid, a disorderly and relatively insensitive organ. Finally we tested the non-pregnant uterus, which, in the cat, relaxes when adrenin is injected into the blood stream (Dale, 1906; Cushny, 1906), and found it a satisfactory and delicate means of registering inhibition.

Contrasting effects of sympathin from different sources on the non-pregnant uterus and on the nictitating membrane. In experiments on the non-pregnant uterus we learned that certain precautions are necessary. Although dial anesthesia does not wholly prevent responses, it may diminish them; consequently the preliminary preparations (e.g., inserting a tracheal cannula, cutting the right cervical sympathetic strand, baring the duodeno-hepatic nerves and the right splanchnics, tying off the adrenal glands, exposing the uterus and releasing the nictitating membrane) were made under ether anesthesia and then, after the carotid artery on the left side had been tied and the right carotid temporarily clamped, the dorsal part of the brain was destroyed by means of a stylet passed through the foramen magnum (see Elliott, 1912). Although artificial respiration was not always required it was, as a rule, now started. During the pithing the vertebral arteries below the wings of the atlas were pressed upon and held for several minutes,
to permit clots to form over the damaged cerebral vessels. As soon as the vertebrais were released the clamp was removed from the right carotid in order to renew the supply of blood to the n.m. that was to be used. From this time onward anesthesia ceased, and if there were movements which disturbed the records a small dose of curare was given. As to the uterus, the entirely quiescent non-pregnant organ is most responsive; if it is subinvolved or highly active, it is not so sensitive. Asphyxia has a lasting depressive influence and therefore must be avoided; similarly a low blood pressure is deleterious; favorable conditions are a pressure above 90 mm. Hg and a slight hyperventilation of the lungs.

The uterus was approached through a mid-line incision. If the urinary bladder was obstructive, it was emptied. The right uterine horn was tied in two places near the ovary, cut between, and then freed from its membranous attachment by a slit which avoided the attendant blood vessels but severed the nerves. A needle, thrust through the base of the horn and held in a clamp, provided a fixed point. The thread used to tie the horn served to attach it (via pulleys) to a writing lever. The long slender uterine muscle was thus pulled directly upward into a vertical position; in order to keep it moist it was surrounded by a small, waxed, cardboard cylinder, closed below and nearly closed above by wet absorbent cotton.

As noted, the right n.m. was deprived of its sympathetic supply by severance of the cervical sympathetic strand. In order to give the membrane free play the eyelids were cut midway and some neutral oil was dropped on the eyeball. A serrefine clipped to the free edge of the membrane attached the connecting thread; the cat's head was held rigidly in such position that the smooth muscle pulled directly downward the short end of the writing lever.

Cocaine was invariably used to sensitize the reacting organs. At times it caused contracture of the uterus, but then a small injection of adrenin produced partial relaxation and increased the responsiveness.

The two main sources of sympathin in this series of experiments were the liver and the splanchnic area. Experience with many animals has left the impression that the results are much more marked, whichever the source, if the animal has recently been fed and preferably is well advanced in the digestion of a meal of protein food.

In figure 4 are shown the records of the n.m. (upper) and the uterus (lower) in their responses to stimulation of the h.n.s. (A) and the right splanchnic nerves (B). Note that when the liver region was the source of sympathin, though the n.m. contracted, the uterus did not relax (cf. fig. 3A and B, also); and when the gastro-intestinal tract, mainly, was the source, both organs responded characteristically. Occasionally this difference was not so clear, but in all such cases the duodenal fibers of the duodeno-hepatic nerves were intact. Figure 4D illustrates a relaxation of the
uterus caused by stimulation of these fibers, and caused also (fig. 4C) by exciting the splanchnic nerves and by injecting adrenin. Now the fibers to the duodenum, which are distributed to the smooth muscle of the gut wall, were severed. Repetition of the stimulations resulted in the usual

![Image](http://ajplegacy.physiology.org/)

**Fig. 4.** Upper record, n.m. with cervical sympathetic cut; lower record, denervated non-pregnant uterus. Arrows indicate contraction. Time, half-minutes.

A and B, cat under dial and cocaine; other records (another preparation), cat with brain pithed under ether, and injected with cocaine and curare.

A. Effects of stimulating h.n.s.

B. Effects of stimulating right splanchnic nerves (adrenals tied off).

C. Effects of stimulating splanchnic nerves (adrenals tied off), and injecting adrenalin (0.3 cc., 1:200,000).

D. Effects of stimulating duodeno-hepatic nerves.

E. After severance of duodenal nerves. Effects of stimulating h.n.s.

difference—contraction of the membrane without relaxation of the uterus when the h.n.s. were stimulated (fig. 4E), and the typical reaction of both organs when the current was applied to the splanchnics.

The striking results illustrated in figure 4 challenge interpretation. In order to make clear our points, we shall number them: 1. Either
adrenin or synthetic adrenalin acts as an excitatory agent for some smooth muscles and an inhibitory agent for others. 2. The differential action of adrenin, then, does not reside in the hormone; nor does the differential action of sympathetic nerve impulses reside in different types of impulses. 3. There is no reason for assuming different types of smooth muscle—e.g., muscle for inhibition in the wall of the gastro-intestinal tract and muscle for contraction in the neighboring arterioles; indeed, smooth muscle may be inhibited by one set of nerves and contracted by another set. 4. Since the differential factor is not found in adrenin nor in different kinds of muscle fibers, we are driven to conclude that a peculiar agent exists inside some muscle cells which modifies adrenin so that they are made to shorten and another agent in other cells, modifying adrenin, causes them to lengthen. 5. The fact that sympathetic nerve impulses have the same action as adrenin has led to the supposition that the impulses liberate a substance which is like adrenin if not identical with it; but any such substance must necessarily be altered, as adrenin itself must be altered, in order to produce opposite effects in different cell groups. 6. An analysis of the action of adrenin and of nerve impulses on smooth muscle led Rosenblueth (1932a, b) to the hypothesis (consistent with his experimental results) that a substance $A$ from the outside (adrenin, e.g.) or $M$ (a local product dependent on the number of nerve impulses in the stimulus) unites in the cell with another substance $H$, thus making a combination $AH$ or $MH$ which evokes a response proportional to the amount formed. As records of the intestine and the non-pregnant uterus prove, the conception is quite as applicable to inhibition as it is to excitation; consequently $H$ must be regarded as either $I$ (inhibitory) or $E$ (excitatory), and the combination, after nerve stimulation, for example, would be $ME$ in a contracting muscle and $MI$ in a relaxing muscle. 7. Sympathin is defined as the chemical mediator of sympathetic nerve impulses, $ME$ or $MI$, which in the cell induces the typical response, contraction or relaxation, and which, escaping from the cell into the blood stream, induces effects elsewhere in organs innervated by the sympathetic. These effects, as shown in figure 4, are only excitatory when the sympathin comes from structures which are only excited to action by the nerve impulses (hepatic nerves, see p. 564); they are both excitatory and inhibitory when the sympathin comes both from the contracted blood vessels and the inhibited muscular walls of the intestine; and when both effects are present, as sometimes in the stimulation of duodeno-hepatic nerves, severance of the duodenal branches, which excludes the source of the inhibitory sympathin, results in a change from the double effect to that caused by the excitatory sympathin alone (see fig. 4D and E). 8. From the foregoing facts and illustrations we feel justified in concluding that there are two kinds of sympathin, sympathin $E$ (excitatory) and sympathin $I$ (inhibitory).
There are experiments which do not fit into this interpretation. Brinkman and Van Dam (1922) and also Lanz (1928) have published records indicating that the substance coming away from the heart on stimulating the cardiac accelerators causes stoppage of rhythmic gastric or intestinal contractions, a positive agent having an inhibitory effect. These experiments were performed, however, by perfusing salt solution through the organs, and that may have altered the sympathin—perhaps by removing the differential feature, E, and leaving an undifferentiated agent resembling adrenin. In the cat's heart sympathetic impulses not only have a positive action in accelerating the beat, but a negative action in relaxing the coronary arteries. The former of these two sources of sympathin is probably much more extensive than the latter, i.e., sympathin E from the heart muscle might be expected to be much more abundant than sympathin I from the coronaries. When the cardio-accelerator strands from the right stellate are stimulated, in a cat under dial and cocaine, the n.m. contracts in a striking fashion, and the uterus relaxes (see fig. 5A). These results can be repeatedly obtained. If the stimulus is reduced, the n.m. still responds, but the uterus does not (fig. 5B). Now an injection of adrenin, which causes a fair replica of the smaller record of the n.m., induces a sharp relaxation of the uterus (fig. 5C). These results can be readily explained on the reasonable assumption that the selected weak stimulus was capable

Fig. 5. Upper record, right n.m. with cervical sympathetic cut; lower record, denervated non-pregnant uterus. Arrows indicate contraction. Time, half-minutes. Cat under dial and cocaine.

A. Effects of stimulating right cardio-accelerator fibers (C-a) 20 seconds, coil distance 8.0 cm.
B. Same as A, but stimulation for 10 seconds, with coil distance 9.0 cm.
C. Effects of injecting adrenalin (0.05 cc., 1:100,000).
of liberating enough sympathin E from the heart but not enough sympathin I from the coronary arteries, to be effective. That the uterus was sufficiently sensitive to respond is shown by the effects of adrenin. The conclusions indicated are that sympathin E and I are different from each other and also different from adrenin.

These conclusions have interesting bearings on the views expressed by Langley (1921) regarding the action of sympathomimetic and parasympathomimetic drugs. He assumed a chemical combination between adrenin, for example, and receptive substances in the responding cells. These substances were supposed to belong to two classes—those which cause contraction and those which cause relaxation. Langley's receptive substances would correspond to the substances E and I here postulated. He did not develop his views in relation to the transmission of nerve impulses. In accordance with the evidence reviewed above a further step may be taken. The similarity of the action of sympathin E and I (resulting from nerve stimulation) to the action of adrenin, and the similarity of the chemical reaction of sympathin to the reaction of adrenin (Bacq, 1931) indicate that a substance similar to adrenin is produced when sympathetic impulses affect smooth muscle. This is in harmony with the idea expressed by Elliott (1904). It differs from that idea in adding the evidence which now exists that this adrenin-like substance becomes differentiated for positive and negative action. As argued by Rosenblueth, the substance M must unite with H in the cell in order to become effective, and the experiments here reported separate H into E and I.

The question may be asked, why ME, which induces contraction in the cell where it originates, does not induce contraction when it enters a cell inhibited by sympathetic nerve impulses? And similarly, why MI, entering a contractile cell, does not cause inhibition? One can only speculate on answers to these questions. Possibly the I in the naturally inhibited cell offsets or neutralizes the action of intrusive ME, and likewise the E in the naturally excited cell might be imagined to oppose the action of intrusive MI. Thus foreign MI, but not foreign ME, could influence inhibited cells, and foreign ME alone excited cells. Or conditions may be such that ME and MI cannot penetrate the cells which they do not affect. Unfortunately we are not able to offer evidence on this point.

**DISCUSSION.** The foregoing observations and inferences are related in an important way to a variety of questions concerned with the physiology of smooth muscle, the action of ergotoxine, the nature of inhibition, and others. We shall comment briefly on these questions.

**The action of ergotoxine.** The responses to stimulation of the h.n.s. and to adrenin, after ergotoxine, have been discussed above (see p. 562). There remain to be considered the effects produced by stimulating l.a.s. As already stated, these effects are the same as those produced by stimulation
of the cervical spinal cord (with adrenals absent). Since that stimulation involves all the sympathetic vasoconstrictor and vasodilator systems of the body, just as adrenin does, we should expect the result on blood pressure to be the same as that caused by adrenin. In fact, however, stimulation of the cord causes, after a brief initial fall (due to unimpaired vasodilators), a prolonged rise of pressure, whereas adrenin causes a fall followed merely by a return to the previous level (fig. 1A). If M (the substance locally produced) is identical with A (adrenin) the failure of adrenin to make the blood pressure rise after ergotoxine cannot be due to blockage of action of AE, since MF (i.e., sympathin F) is effective. Also it cannot be explained as a necessary consequence of extreme contraction of the vascular smooth muscle established by ergotoxine, since sympathin E causes a rise. Further, it is not reasonable to assume a change in the nature of E, since M unites with E and A should be able to do likewise. The possibility is suggested that ergotoxine alters the nature of adrenin, perhaps as it enters the cell, in such manner that it no longer combines effectively with E. Clearly this action of ergotoxine could not be uniform, for, as already mentioned, the drug has different degrees of effect in different organs (cf. spleen volume and blood pressure, fig. 2B). An alternative possibility is that M is not identical with adrenin. Evidence on these suggestions is lacking.

Inhibitory action of sympathin I. In their first account of sympathin Cannon and Bacq (1931) reported an inability to produce inhibition of the stomach and intestines. Although the stomach and intestines had been denervated for a week, "a magnificent erection of the tail hairs," with, no doubt, contraction of the caudal vessels, caused no lessening whatever of the motions of the gastro-intestinal tract. Here was an activity which required for its inhibition sympathin I, and they were attempting to influence it with sympathin E! Recently Bacq (1933) has reported that stimulation of the peripheral ends of the severed sciatic nerves results, after about two minutes, in a cessation of the movements of the denervated intestine. In the muscle vessels of the legs, caused to relax by sympathetic stimulation (cf. Hoskins, Gunning and Berry, 1916; cf. fig. 1) sympathin I would be produced, which would explain the inhibition of the intestinal rhythmic contractions. The inhibition of the contractions of an isolated intestinal loop by means of salt solution passing over another loop inhibited through its nerves, as described by Finkelman (1930), can be similarly explained.

Sympathetic vasodilators. Burn (1932) has stated that the "Cannon school" has rejected the evidence for existence of sympathetic vasodilator fibers. Hoskins and his collaborators (1916) showed that with nerves intact adrenin causes active dilatation in limb muscles; Hartman and a collaborator (1917) confirmed this testimony; and it was further corroborated by Gruber (1918). All three investigators just named were former associates of
this laboratory. The results which they reported were publicly accepted by Cannon (1929) four years ago. Further proof of sympathetic vasodilators was obtained during the present investigation in the fall of arterial pressure when adrenin was injected after ergotoxine (fig. 1A, confirmatory of Dale, 1906), in observations that increasing doses of adrenin under these conditions produced falls which fitted a hyperbolic curve (cf. Rosenblueth, 1932a), in the drop of blood pressure at the start of stimulating l.a.s. after ergotoxine (fig. 1A and B), in the expansion of the leg while the blood pressure was still low from adrenin after ergotoxine (fig. 2D), and in the expansion of the leg after a minimal dose of adrenin, such as would cause a fall of arterial pressure (fig. 3A). The evidence for existence of sympathetic vasodilators has seemed to us for years to be thoroughly convincing. The distribution of sympathetic vasodilators is, however, obscure. The evidence of Hoskins, Gunning and Berry (1916) points toward their existence in skeletal muscle. Our observations confirm this view (see in fig. 1A and B the decided fall of blood pressure on stimulating the l.a.s.). Dale (1913) generalized their presence to the splanchnic area. Probably some vasodilator fibers are present, since stimulation of the splanchnics after ergotoxine and exclusion of the adrenals may evoke a fall of blood pressure. This drop is, however, minimal (see e.g., Dale’s records; our results were similar) as compared with the relatively large drop obtained from stimulating the l.a.s. and a still greater drop from stimulating the cervical spinal cord. If, then, sympathetic vasodilators distribute mainly to skeletal muscle, as seems probable, one of the results of general excitation of the sympathico-adrenal system, such as occurs, for example, in emotion, will be a redistribution of blood with an increased flow in muscles, a condition eminently favorable to action.

Burn’s (1932) explanation of the fall of arterial pressure at each step in a progressive removal of the sympathetic ganglionic chains (B. Cannon, 1931), as due to operative stimulation of vasodilators, seems to us to have little warrant. First, why selective stimulation of vasodilators rather than vasoconstrictors? Again, the fall of pressure, attributed by B. Cannon to interruption of tonic vasoconstrictor impulses, was not recovered from for at least 24 hours. Burn’s view would require stimulation of the vasodilators during this time. Langley (1900) testified that “on section of all or the great majority of sympathetic nerves to tissues paralytic effects may be observed in a few seconds.” Our experience is in accord with Langley’s. In accord with it, also, are the observations of Forbes and Cattell (1924) and of Adrian (1930) that after severance of a motor nerve galvanometer records fail to show any impulses passing in the isolated fibers after a period measured in seconds. The vasodilation from section of a limb nerve can be explained as a result of abolition of vasoconstrictor tone, and the slowly regained vasoconstriction as a result of restoration of intrinsic tone in the contractile muscles of the vessel walls.
The relation of sympathin I to theories of inhibition. From the evidence presented in figure 4 it is clear that only a structure contracted and inhibited by sympathetic impulses becomes the source of both contractile and inhibitory humoral agents. Unfortunately we have not been able to devise, in the living animal, an experiment in which pure inhibition of smooth muscle is caused by sympathetic impulses—blood vessels are always present and are contracted by the impulses, so that not only sympathin I is discharged but also sympathin E. The simple, positive evidence of the existence of sympathin I, apart from E, we have not obtained. The result illustrated in figure 4F, however, proves that when the inhibited elements are excluded from stimulation the inhibitory humoral action disappears, leaving only the excitatory. And Finkelman’s experiment, previously mentioned, supplies direct corroborative testimony to the separate existence of an inhibitory substance given off from smooth muscle when the muscle is inhibited by sympathetic impulses.

That a substance is produced by nerve impulses which causes inhibition both directly and indirectly may have an important bearing on theories of inhibition. Especially would this be true if, as Howell (1925) has suggested, “inhibition is fundamentally the same process in all tissues,” because other theories (drainage, interference, anabolism, etc.) would thereby be supplanted. The chief support for the humoral or chemical theory of inhibition, cited by Howell, was that offered by Loewi’s (1921) “vagal substance,” evoked when the heart is inhibited by vagal impulses and capable of inhibiting a second heart when applied to it. It is an attractive and logically reasonable idea that parasympathetic as well as sympathetic fibers should liberate one kind of substance when they cause excitation and another kind when they cause inhibition, and that the substance causing inhibition (e.g., the “vagus stuff” of the heart) should cause inhibition elsewhere, but not excitation (i.e., not contraction of the stomach). Brinkman and van Dam (1922), however, have reported that the inhibitory “vagal stuff” from the heart of one frog induces contraction of the stomach of another. Although, as Howell remarks, their records are not convincing, their results are in agreement with results of other investigators. Thus, Engelhart (1931) found that after the ciliary body and the iris had been contracted by oculomotor impulses, the aqueous humor had a new, markedly inhibitory action on the tortoise heart. And Bain (1932) has reported that fluid perfused through vessels of the tongue, while they were being relaxed by stimulation of the lingual nerve, acquired properties which made it excitatory to rabbit intestine. These results do not fit into a general concept of excitatory and inhibitory substances. It is possible, of course, that the highly unstable “vagal stuff” loses differential features first of all, before further breakdown. Public speculation at this stage, however, is futile.

Some further implications. The evidence for the existence of two sub-
stances, sympathin E and I, resembling adrenin in action, but differing from it in discriminative relations to excitatory and inhibitory effects, suggests the possibility of so modifying adrenin by chemical means that it too might be used in a discriminative manner. Thus adrenin E, if made, could be used to stimulate the heart, contract blood vessels, etc., without inhibiting the digestive process. And adrenin I could be employed to relax spasm of the bronchioles or alimentary canal, for example, without raising arterial pressure or increasing blood sugar. Such possibilities render important the attempt to obtain modified forms of adrenin.

The highly puzzling change in the response of the cat’s uterus—from inhibition of the non-pregnant to contraction of the pregnant organ, when subjected to sympathetic impulses or adrenin—has not received appropriate attention. Alterations of nerve impulses and muscle fibers are quite improbable, and it is unnecessary to assume that they occur. The shift could be accounted for if the physiological readjustments which accompany pregnancy should include a change from the substance I to the substance E in the smooth-muscle cells. Since the shift seems to be restricted to uterine smooth muscle, it possibly has a local origin, perhaps the agency which brings about the enlargement of the uterus and the lengthening of its muscle fibers and the thickening of the uterine wall.

**SUMMARY**

Sympathin differs from adrenin, because after ergotoxine sympathin evoked by stimulation of hepatic nerves (h.n.s.) causes a primary rise of arterial pressure followed by a fall to the former level (fig. 1C), whereas adrenin has quite the contrary effect (fig. 1A).

Because stimulation of the h. n.s. resembles stimulation of the lower abdominal sympathetic strands (l.a.s.) in causing a rise of arterial pressure after ergotoxine (fig. 1A and B), the pressor agents (i.e., sympathin) from the two regions, are assumed to be identical.

The difference between the actions of adrenin and of sympathin on arterial pressure is not due to different influences on the heart rate (see p. 560); it is therefore attributable to effects on peripheral structures.

Both sympathin (from the liver region) and adrenin cause contraction of leg and spleen volumes (fig. 2A and B). After ergotoxine the elevation of arterial pressure due to sympathin is accompanied by only slight expansion of the leg (fig. 2C); the fall of pressure due to adrenin is accompanied by a marked expansion of the leg (fig. 2D)—apparently a difference of effects on vasodilator systems.

Confirmation: a minimal dose of adrenin causes contraction of the denervated nictitating membrane (n.m.) and an increase of leg volume (fig. 3A); sympathin from the liver region having even less effect on the n.m. causes marked decrease of leg volume (fig. 3B).
With the denervated n.m. and the denervated non-pregnant uterus as indicators respectively of excitatory and inhibitory sympathomimetic humoral agents (e.g., adrenin), the h.n.s. and the splanchnics were stimulated. Splanchnic stimulation (adrenals excluded) causes contraction of the n.m. and relaxation of the uterus; stimulation of the h.n.s. causes contraction of the n.m., but not relaxation of the uterus (fig. 4A and B). If duodenal fibers are included with the h.n.s., relaxation occurs (fig. 4D); but when these fibers are severed, only contraction occurs (fig. 4E).

Stimulation of the cardio-accelerator nerves causes strong contraction of the n.m. and some relaxation of the non-pregnant uterus (fig. 5A); with a reduced stimulus the n.m. contracts, but the uterus does not relax—not because insensitive, for adrenin evoking an equal contraction of the n.m. evokes a marked uterine relaxation (fig. 5B and C).

The foregoing results are explicable on the assumption that two kinds of sympathin are produced,—sympathin E, excitatory, produced by structures stimulated, and sympathin I, inhibitory, produced by structures inhibited by sympathetic impulses. Thus the liver region, stimulated, gives rise to sympathin E; and the gastro-intestinal tract, with vessels stimulated and walls inhibited, produces both E and I (see p. 566). Thus the heart muscle discharges E, while the coronary arteries discharge a less amount of I; when the sympathetic stimulation is decreased, therefore, E remains effective and I does not.

In the discussion the results here reported are considered in their relation to the action of ergotoxine, to the existence of sympathetic vasodilators, to theories of inhibition, and to certain pharmacological and other implications.

BIBLIOGRAPHY

1933. Ibid., cviii, 211.
Brinkman, R. AND E. Van Dam. 1922. Pflüger's Arch., cxxvi, 66.
Cannon, B. 1931. This Journal, xvii, 592.
Cannon, W. B. AND Z. M. Bacq. 1931. This Journal, xvi, 392.
Cannon, W. B. AND J. E. Urüdil. 1921. Ibid., lviii, 353.
Dale, H. H. 1906. Ibid., xxxiv, 163.
1913. Ibid., xlvi, 291.
1912. Ibid., xliv, 376.
Engelhart, E. 1931. Pflüger's Arch., cxvii, 220.
Finkelman, B. 1930. Ibid., lxx, 145.
Gruber, C. M. 1918. This Journal, xlv, 302.
1921. The autonomic nervous system. Cambridge.
Loewi, O. 1921. Pflüger's Arch., cixxix, 239.
Loewi, O. and E. Navratil. 1926. Ibid., ccxiv, 678.
Rosenblueth, A. 1932a. This Journal, ci, 149.
1932b. Ibid., cii, 12.