THE SECRETION OF SWEAT. Part II. The effect of vaso-constriction and of adrenaline.

By J. N. LANGLEY and K. UYENO, M.D., *Tokio.*

(*From the Physiological Laboratory, Cambridge.*)

CONTENTS.

In Part I(1) it was mentioned by one of us that injection of 0·1–0·15 c.c. of Ringer's fluid into the pad of a cat's foot usually, but not always, causes more secretion of sweat than injection of adrenaline ·001–·1 p.c., and that adrenaline so injected causes a more or less long lasting depression in the response of the glands to pilocarpine. The explanation of the effect of adrenaline solution appeared to be that the fluid in which the adrenaline was dissolved caused the secretion, and that the vaso-constriction produced by adrenaline itself caused the decrease in response. The results however might be taken as showing that adrenaline has both a secretory and an inhibitory action on the gland cells, the inhibition being usually dominant. Since this theory would tend to bring the action of adrenaline on the sweat glands into line with its action on other tissues, we have compared in further experiments the effect of injecting Ringer's fluid with that of injecting adrenaline, and have investigated the effect of vaso-constriction. Considerable attention to detail is unfortunately required in order to arrive at a definite conclusion.

The experiments were made on cats of various ages. As a rule the animals were anæsthetised with C.E. mixture, but in order to make certain that the anæsthetic did not affect the results, some were made on animals decerebrated and only anæsthetised before decerebration and a few on "spinal" animals. The adrenaline and other solutions injected were usually warmed to body temperature, but in the few experiments in which the fluids were injected at room temperature the results were the same. The solutions were injected into the subcutaneous fat tissue,

usually into the pad from the front, occasionally also into one of the toes; the amount injected was usually 0·1–0·15 c.c., occasionally 0·2 c.c., a larger amount was only injected for special purposes. Since all four feet secrete, several observations can be made on any one animal. As a rule the cat was placed lying down on its side and unfastened. It was placed on a warmed surface, and the feet were wrapped in warm cloths. For quick recognition of the secreting parts, it is convenient to mark the right limbs and the inner surface of each. The secretory surfaces were examined with the aid of a lens whether the secretion was obvious to the eye or not.

The stock adrenaline solution was 0·1 p.c. Both Parke, Davis' and Burroughs and Wellcome's adrenaline chloride preparation were used; in each the adrenaline salt is in a faintly acid medium and contains either chloretone or chloroform; we have not noticed any distinct difference in their action. From these, solutions of ·01 and ·001 p.c. were made by diluting with cold Ringer's fluid. The amount injected was only warmed immediately before injection. A few experiments were made with crystallised adrenaline dissolved in a minimal amount of dilute hydrochloric acid, with results similar to those produced by the commercial preparations.

The secretion caused by fluids.

In the experiments referred to in Part I, Ringer's fluid caused secretion in a considerable majority of the experiments. The experiments were made in the late spring and the summer months, and chiefly on half-grown cats. We obtained a fairly similar result up to the end of January. During February and March the result was different. In 16 experiments in which Ringer's fluid or adrenaline or both were injected into the pads of two or more feet no secretion was obtained in 12; in some of these both sciatic nerves were cut. In two (both spinal cats) Ringer's fluid caused a slight secretion, in one it caused a trace. In one both Ringer's fluid and adrenaline caused a slight secretion, the former rather more than the latter. The difference in excitability was probably due, in part at any rate, to the animals having been older in the later experiments. In this and the succeeding section we refer, unless otherwise mentioned, to the experiments made up to the end of January.

The following fluids, in addition to Ringer's fluid and adrenaline ·001 to ·75 p.c. were found to be capable of causing secretion when injected into the pad of the foot. Adrenaline solution in which the adrenaline had been destroyed by warming it with a trace of alkali, distilled water,

Ringer's fluid with four times the normal percentage of salts, barium chloride ·1 to 1 p.c. dissolved either in Ringer's fluid or in distilled water, 1 p.c. calcium chloride, amyl nitrite, 1 p.c. sodium nitrite, and pituitrin (Allen and Hanbury's preparation). The secretion when produced varies greatly in time of visible beginning, amount and duration. It may be obvious in a second or two, or not be visible to the eye for several minutes. With Ringer's fluid the secretion may last any time from five minutes to an hour. The secretion caused by adrenaline lasted usually 5 to 10 minutes, but in the experiments in Tables I and II in which ·01 or ·001 p.c. caused a moderate secretion it lasted 15 to 20 mins.

The number of experiments made with most solutions were insufficient to allow any strict comparison of their relative secretory effect. Amyl nitrite in one case caused a very copious secretion—helped no doubt by the increased blood flow—but with a certain decrease of excitability it had no effect, though pilocarpine still caused a moderate secretion. Hypertonic salt solution caused less secretion than Ringer's fluid with which it was compared. Barium chloride 0·1 to 1 p.c. had about the same effect as Ringer's fluid, sometimes more sometimes less. Calcium chloride 1 p.c. in two experiments caused a slight secretion only, but in these barium chloride 1 p.c. also had only a slight effect. Pituitrin once caused no secretion, once a slight secretion, and once a free secretion. In experiments in March, pituitrin caused a slight secretion when Ringer's fluid did not (2 exps.); histamine ·1 p.c. caused a slight secretion, 1 p.c. caused none; eserine ·5 p.c. (1 exp. in each case) and ergotoxine phosphate ·1 p.c. (2 exps.) caused none.

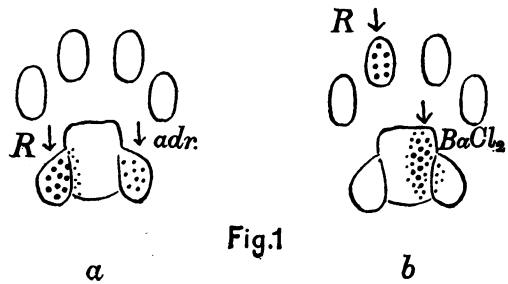

Fig. 1. Restriction of the secretion (when produced) to the injected area.

(*a*) Secretion was caused by injecting 0·1 c.c. of Ringer's fluid into the lateral side pad of a foot and a minute later by injecting 0·1 c.c. of 0·1 p.c. adrenaline into the medial pad. The maximal secretion (about 5 minutes later) is shown diagrammatically.

(*b*) Secretion 5 minutes after injecting 0·1 c.c. barium chloride 1 p.c. into the antero-lateral part of the mid pad, and 0·1 p.c. Ringer's fluid into one toe.

The secretion produced by each of the fluids is more or less strictly confined to the injected area (cp. Fig. 1). If 0·1 c.c. is injected into the middle of the pad (mid pad) no secretion is caused in the small lateral eminences (side pads) except it may be with nitrites. In no case does

injection into the pad cause secretion in the toes, or injection into one toe cause secretion in any other part of the foot.

When a secretion has been caused by injecting Ringer's fluid, a second injection in the same area causes usually less secretion and may cause none. The result depends upon the initial excitability of the glands and upon the degree of decrease of excitability in the interval, due to decreased circulation and cooling of the feet and to fatigue. But there is usually some decrease of response as the direct result of the injection (cp. p. 213). Since the secretion with all the fluids is local, observations on the effect of more than one fluid can be made on the same foot. But there is a limitation to this method, since some solutions, though only causing secretion in the injected area, depress the response to pilocarpine outside the injected area. This will be referred to later.

The secretory effects of all the fluids is prevented by previous injection of a small amount of atropine. The amount we have injected has varied from 1 to 5 mgms. of atropine sulphate. The suppression of the action of barium chloride is noteworthy, since on unstriated muscle, the point of action of barium chloride is held to be the general muscle substance and not the receptive substance. The result tends to show that $BaCl_2$ has no direct secretory action. The secretion caused by fluid is not due to mechanical stimulation of the nerve filaments by stretching them, since the injection of air does not, so far as we have seen, cause secretion, and since Ringer's fluid may cause secretion in denervated glands (cp. Part I, p. 118). The fluid must have a direct action on the gland cells. It would appear that the glands, if readily excitable, secrete at once when there is excess of fluid around them, whether the fluid is hypotonic or hypertonic.

Ringer's fluid, up to 100 c.c. injected intravenously at a time after pilocarpine when the secretion is slow causes a slight increase only. We have not tried this at the beginning of an experiment when the excitability is greater.

Relative amount of secretion caused by Ringer's fluid and by adrenaline.

In 11 experiments (including those on which Part I was based but omitting the three in which pilocarpine caused no secretion or only a trace) adrenaline was injected and not Ringer's fluid, it caused secretion in 6 (3 with ·1 p.c. secretion slight; 2 with ·01 p.c. one secretion slight, the other moderate; 1 with ·001 p.c. secretion moderate). In three experiments Ringer's fluid was injected and not adrenaline, and it caused secretion in two.

Ten experiments were made in which Ringer's fluid was injected into

the mid pad of one foot, and adrenaline into the mid pad of the opposite foot and in which Ringer's fluid caused a secretion (Table I). The secretion varied in amount from copious to very slight. In 4 of these adrenaline caused no secretion, in 4 it varied from a mere trace to a slight secretion, in 2 it caused a moderate secretion and distinctly more than Ringer's fluid. In one of these two, the result was not constant for though Ringer's fluid caused only a slight secretion in the mid pad, a subsequent injection into a toe of the same foot caused a free secretion. In the other experiment (·001 p.c. adrenaline was injected) a suspicious fact was that the fore foot became redder on injection instead of paler. Assuming that there was no error in making up the solutions in this experiment, the result shows that adrenaline injected into one foot may occasionally cause distinctly greater secretion than Ringer's fluid injected into the foot of the opposite side. But the fact that when Ringer's fluid was injected both into the fore and hind foot, it caused a somewhat different amount of secretion in three out of four experiments suggests that the greater effect of adrenaline than of Ringer's fluid in Exps. 9, 10 may have been due to a difference either in the excitability of the glands or to the experimental conditions.

TABLE I. Injection into the mid pad of different feet.

	Ringer's fluid	Adrenaline	p.c. of adrenaline
1.	Rt. fore, copious	L. fore, none	·001
	L. hind, „	Rt. hind, very slight	·01
2.	L. hind, slow but copious	Rt. hind, slight	·1
3.	L. fore, good > hind	Rt. fore, very slight	·1
	Rt. L. hind, good, at end L. > R.	—	
4, 5.	Rt. fore, moderate	L. fore, none	·1
6.	Rt. fore, slight to moderate	L. fore, none	·001
		Rt. hind, none	·1
7.	Rt. fore, very slight	L. fore, none	·1
8.	Rt. hind, very slight	L. hind, slight	·001
		L. fore*, trace	·1
9.	L. fore, very slight	Rt. fore, moderate	·1
	Rt. hind, slight	L. hind, moderate	·001
10.	L. fore, very slight†	Rt. fore, moderate‡	·001
	L. hind, none‡	Rt. hind, moderate	·001

* In R. fore $BaCl_2$ 1 p.c. caused a moderate secretion.

† Adrenaline ·001 p.c. subsequently injected caused no secretion. Ringer's fluid subsequently injected into the toes of the hind feet caused a good secretion.

‡ The pad became redder instead of paler.

It seemed probable that the excitability of the two side pads of one foot would vary less in excitability than the mid pads of different feet so that experiments were made in which Ringer's fluid was injected

into one side pad and adrenaline into the other side pad of one or more of the feet. The results are given in Table II.

TABLE II. Injection of ·1 or ·15 c.c. into the lateral and medial side pad of the same foot.

	Secretion caused by Ringer's fluid	Secretion caused by adrenaline	p.c. of adrenaline
1. R. fore	Good	Trace	·01
R. hind	Copious	Good but brief	·001
L. hind	Copious	Slight to moderate	·001
2. R. fore	Moderate	None	·001
L. fore	Moderate	Slight, brief	·1
L. hind	—	None	·001
L. hind (in opposite side pad)	—	Slight, brief	·1
3. R. fore	Slight	? trace	·001
L. fore	Slight	Slight	·1
4. R. fore (Ringer in both side pads)	Good	—	
L. fore	Good	Trace, very slow	·01
R. hind	Very slight	None	·001
L. hind (Ringer in both side pads)	Moderate to good	—	
5. R. fore	Slight	None	·1
6. R. fore	Good	Good > Ringer	·001
L. fore (adr. injected first)	Very slight	None	·001
R. hind	None	None	·0001
7. L. hind (adr. injected first)	? trace	Moderate to good	·01
R. hind „ „	Trace to slight	Moderate	·01
R. fore	Trace	None	·001
L. fore	Moderate	None	·1

The results are much the same as in the experiments in which the fluids were injected into the pads of the opposite feet. Usually Ringer's fluid had a distinctly greater effect than adrenaline, but this was not the case in all the feet in Exps. 6 and 7. There are several causes which might produce this result.

1. In the numerous experiments in which we have injected a *small* amount of pilocarpine subcutaneously in the body region, or locally into the feet, we have nearly always found some difference in the amount of the secretion in different feet and in different parts of the same foot. The stimulus to the glands by fluid is very near the threshold, so that a small difference in excitability (or in experimental conditions) makes a considerable difference in the result of injecting it. The differences we have found are sufficient to account for the result in Exp. 6.

2. In these experiments the direction of the aperture of the needle was not noticed. If it is directed upwards, the fluid passes mainly towards the dermis. If it is directed downwards, the fluid passes mainly to the deeper tissue around the bases of the glands, and this may be sufficient to account for a difference in the amount of secretion.

3. In the experiments in Table II in which adrenaline caused a

greater secretion than Ringer's fluid it was injected first. It is possible that in some cases its vaso-constrictor effect may spread to the opposite side of the pad and thus reduce the excitability below the threshold of stimulation by Ringer's fluid.

In February and March we made a number of experiments to determine the effect of conditions (2) and (3), but, as we have mentioned earlier, Ringer's fluid and adrenaline either caused no secretion or caused so little as to be useless for our object.

Reviewing the results of the comparative experiments, it may be doubted whether the method can give completely decisive results, for though it is certain that the excitability of the glands varies in some cats in different parts of the secretory surface, it does not seem possible to determine the degree of difference before injecting the fluids to be compared.

It is of some significance that the secretion caused by ·001, ·01 and 1 p.c. adrenaline is not very different, but on the whole secretion is rather greater and is commonly of longer duration with ·001 p.c. The fact is not easily reconcilable with adrenaline itself causing a secretion. The fact which we think is decisive is that already mentioned in Part I, viz. the restriction of the secretion to the area injected. In none of the experiments referred to above, or to be referred to later, did adrenaline cause secretion outside the injected area. When a small amount of pilocarpine is injected into the mid pad of one foot, its secretory effect spreads to the side pads and then to the toes without causing secretion in any other foot. The depressive action of adrenaline on the response to pilocarpine—the details of which we consider presently—also spreads beyond the injected area. We have seen that ·001 p.c. adrenaline usually causes a little more secretion locally than ·1 p.c. If adrenaline itself caused secretion it is, we think, inevitable that a ·1 p.c. solution would diffuse, or be carried by blood vessels, into the surrounding area sufficiently to make a ·001 p.c. solution and so would cause secretion outside the injected area. We have made a few experiments only with solutions stronger than ·1 p.c.; in one of these ·75 p.c. adrenaline caused secretion and it was strictly local. It follows, we think, that the secretion which adrenaline solution causes in the injected area is due to the fluid in that area, and not to the adrenaline.

The decrease of secretion caused by local injection of adrenaline.

It is clear that adrenaline will tend to reduce secretion of sweat both because it causes great reduction of the blood supply to the glands and

because the decreased blood supply leads to a lower skin temperature. Knauer and Billigheimer(2) found in patients suffering from spontaneous sweating that adrenaline stopped the sweating for a considerable time. Billigheimer(3) adopting Dieden's view of the presence of inhibitory fibres in the posterior roots attributed the action of adrenaline to its stimulating these nerve fibres. It has been shown in Part I that the posterior roots do not inhibit sweating; so that if adrenaline stimulates inhibitory nerve fibres, they must belong to the sympathetic system. Billigheimer's conclusion was based on the following observations. Into patients he injected pilocarpine on one day, and pilocarpine sometime after adrenaline—on an average 15 to 20 minutes—on another day. He found that the beginning of the secretion was later in the latter case by a time varying from 2 to 20 minutes. He considered that the retarding action was not due to vaso-constriction, since this in some cases had passed off before the pilocarpine was injected. This argument overlooks that though the vaso-constriction had passed off the skin would probably not have recovered the normal temperature. In his experiments 1 mg. of adrenaline was injected sub-cutaneously, so that the amount reaching the sweat glands through the circulation would be very small. Thus on Billigheimer's hypothesis the supposed inhibitory nerve fibres must be very responsive to adrenaline, but when he injected adrenaline after pilocarpine he did not find that it had any retarding action, *i.e.* by this method there was no evidence of inhibitory action.

The experiments mentioned earlier in this paper show that in most cases adrenaline causes decidedly less secretion than does Ringer's fluid, so that it must lessen the secretory response to the stimulus set up by the fluid in which it is dissolved. In order to determine more accurately the degree of depressive action of different concentrations of adrenaline, experiments were made in the following way—Ringer's fluid, or adrenaline of a given percentage, was injected into the mid pad of one foot, and adrenaline of another percentage into the mid pad of the opposite foot. When the secretion caused by Ringer's fluid (if any) had ceased or was only slight (about half an hour later) 1–2 mgms. of pilocarpine were injected sub-cutaneously in the upper abdominal region and the relative degree of secretion in the two feet, and in the different parts of the same foot noted.

The effect of Ringer's fluid varied considerably, sometimes it had a marked depressive effect. An example of this has been given in Part I, Exp. 4, p. 116. In this the secretion caused by Ringer's fluid though fairly free was brief, *i.e.* the excitability of the gland was not great.

Sometimes there was no appreciable depressive effect. An example of this is given in Exp. 1 below. In this the excitability of the glands was high. In general it has appeared that the greater the excitability, the less the depressive action of Ringer's fluid. Adrenaline in all concentrations from ·001 p.c. upwards causes a considerable decrease in the response of the injected area to pilocarpine, but ·001 p.c. has constantly at some stage a less effect than ·01 p.c. An example is given in Exp. 1.

Exp. 1. Ringer's fluid was injected into the right fore foot and adrenaline ·001 p.c. into the left. Adrenaline ·01 p.c. was injected into the right hind foot, and Ringer's fluid into the left. In each case the injection was 0·15 c.c. into the mid pad. Half an hour after the injection, when the secretion caused by Ringer's fluid had all but ceased, 2 mgms. of pilocarpine were injected sub-cutaneously in the abdominal region. The secretion was almost at once copious in the pads which had been injected with Ringer's fluid, it began a little later in the ·001 p.c. adrenaline mid pad, and none was visible in the ·01 p.c. adrenaline mid pad in 3 mins. The state 3 mins. from the injection of pilocarpine is represented in Fig. 2 *a*, *b*, *c*. The secretion in the mid pad injected with ·001 p.c. adrenaline continued, that in the mid pad injected with ·01 p.c. reached its maximum in 8 mins. (Fig. 2 *c'*) and stopped in about 15 mins. The side pads and toes secreted freely in all, but less in the foot in which ·01 p.c. adrenaline had been injected than in the others.

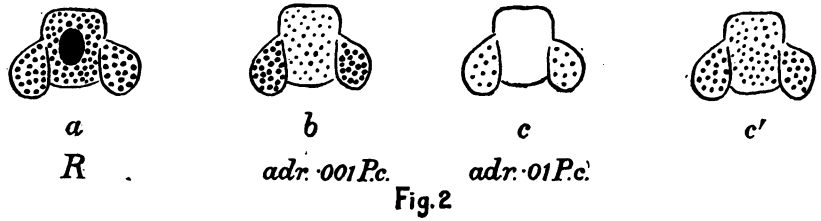

Fig. 2

Fig. 2. Secretion caused in 3 mins. by pilocarpine injected sub-cutaneously in the abdominal region half an hour after injecting the mid pads with (*a*) Ringer's fluid, (*b*) ·001 p.c. adrenaline, (*c*) ·01 p.c. adrenaline respectively.

c'—secretion in *c*, 8 mins. after injecting pilocarpine.

When ·001 p.c. adrenaline is injected into the mid pad and excitability is slight, the slight secretion caused at first by pilocarpine may stop in about 10 mins. and begin again in a further 15 to 20 mins., or there may be no secretion for 25 to 30 mins.

The depressive action of ·01 and of ·1 p.c. adrenaline differs only slightly. In the given conditions pilocarpine may cause secretion, or fail to cause it both in the mid pad injected with ·01 p.c. adrenaline and in that injected with ·1 p.c. Whether there is secretion or not depends mainly at any rate on the excitability of the glands. When there is a difference however it is in favour of the ·01 p.c. adrenaline mid pad. When excitability is high, even ·75 p.c. adrenaline locally injected does

not prevent pilocarpine injected in the body region from causing secretion. The fact goes far to show that adrenaline has no direct inhibitory action.

On the other hand there is a marked difference in the outspread of the depressive action beyond the injected area. This is usually slight with ·01 p.c. adrenaline and generally extensive with ·1 p.c. With the latter either the side pads or the two mid toes or both may fail to secrete on injecting 1–2 mgms. of pilocarpine sub-cutaneously elsewhere: the outer and inner toes are the much less affected (cp. Fig. 3).

The effect on the middle toes is obviously conditioned by the course of the arteries to them. The arteries run under the mid pad, a little on either side of the mid line. Thus, on injecting adrenaline into the mid pad, the adrenaline diffusing to these arteries will be of higher concentration than that diffusing to the arteries of the inner and outer toes. Further, if the injection is made deep in the tissue of the pad, undiluted

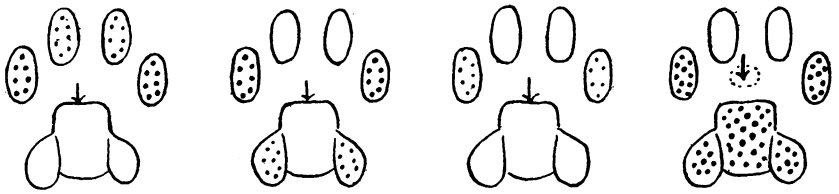

Fig. 3.

Fig. 4.

Fig. 3. Different areas in which no secretion is caused by sub-cutaneous injection of 1–2 mgms. pilocarpine in the abdominal region half-an-hour after injecting about ·15 c.c. ·1 p.c. adrenaline in the mid pad.

Fig. 4. Secretion after injecting ·1 p.c. adrenaline mid-way between the pad and the toes.

adrenaline may reach the vessels. In our experiments we think that if the latter event occurred, it occurred only occasionally, since injection of ·01 p.c. adrenaline in the same way as that of ·1 p.c. rarely had any marked differential action on the toes, and ·01 p.c. is sufficient to cause strong local arterial contraction. If ·1 p.c. adrenaline is injected sub-cutaneously half way between the pad and the toes and then pilocarpine injected elsewhere, the decrease of response is great in the middle toes and slight or not appreciable on the rest of the secretory area (cp. Fig. 4). If the decrease of response in the middle toes is due entirely to local contraction of the arteries, it is proof that adrenaline has no direct inhibitory action. It is possible however that some is absorbed by the arteries and is carried to the toes.

When pilocarpine causes no secretion in the first 10 minutes in a mid pad which has been injected with ·01–·1 p.c. adrenaline, it causes

none later. If ·1 c.c. of pilocarpine ·1 to 1 p.c. is injected into the mid pad itself secretion is sometimes obtained although it is not obtained by injecting 1–2 mgms. sub-cutaneously elsewhere, *i.e.* the strength of the stimulus is a factor in the occurrence or non-occurrence of a secretion. The injection of pilocarpine must, however, not be delayed too long, for at the end of an experiment lasting 1½–2 hours, it is common to find that local injection of even 1 p.c. pilocarpine causes no secretion in the adrenaline area and but a slight secretion elsewhere.

When 1–2 mgms. of pilocarpine are injected first in the abdominal region, and the secretion is fairly free, the effect of injecting adrenaline ·01–·1 p.c. into the mid pad is to stop the secretion in it gradually but permanently. Adrenaline ·001 p.c. may also stop the secretion, but if it does it usually begins again in 20–30 mins. When the secretion caused by pilocarpine has become slow, the secretion may be stopped in a few seconds by injecting adrenaline. The depressive effect of the injected solutions can also be shown by stimulating the posterior tibial nerve or the lumbar sympathetic, but if gland excitability is high, the stimulus should be weak.

Some experiments were made in order to determine whether the depressive effect of adrenaline was greater as its action was more prolonged. In these 1 to 2 mgms. of pilocarpine were injected sub-cutaneously in the body region 5 mins. after ·1 p.c. adrenaline had been injected into the mid pad of one foot, and 25–30 mins. after it had been injected into the mid pad of the opposite foot. It was found that when a secretion was obtained on the mid pad, either there was rather more in that on which adrenaline had acted for the shorter time, or that there was a trifling secretion in this and none in the other pad. In one experiment a ·75 solution of "crystallised adrenaline" was used, and pilocarpine 1 p.c. was injected locally into the pads. Injected 9 mins. after the adrenaline it caused a slow but fairly good secretion in the mid pad—which died out in about 15 mins.—a slight secretion in the side pads, and a free secretion in the toes. Injected 20 mins. after the adrenaline into the other mid pad, it caused a slight secretion only. This was the maximum difference obtained; in the other experiments the difference though distinct was slight. There is then a slight decrease of excitability during the action of adrenaline.

On the theory that the depressive action of adrenaline is caused by vaso-constriction the facts given above would be accounted for as follows: Adrenaline causes strong contraction of the arteries in the injected region and thus greatly reduces the blood supply. The production of a secretion

by pilocarpine after adrenaline depends upon the excitability of the glands, the concentration of the pilocarpine and on the degree to which the blood flow around the glands is reduced. Thus 1–2 mgms. of pilocarpine injected sub-cutaneously elsewhere than in the foot will cause secretion if the excitability is above a certain level, but not if it is below this level. Secretion in some cases can still be produced by injecting ·1 c.c. of 1 p.c. pilocarpine locally because the stimulus is stronger. Adrenaline ·001 p.c. causes less arterial contraction than ·01 or ·1 p.c. and the contraction is less prolonged. Thus a given amount of pilocarpine causes more secretion after ·001 p.c. adrenaline than after ·01 or ·1 p.c. and as the contraction lasts a shorter time, the secretion which has been stopped by ·001 p.c. may begin again. The arterial contraction produced by ·01 p.c. adrenaline is approximately maximal, so that ·1 p.c. can cause little more, and the depressive action of the two is nearly the same in the injected area, the diffusion in the surrounding area, in sufficient concentration to cause strong contraction, will however be more extensive with ·1 p.c. than with ·01, so that its depressive effect on secretion will be more extensive. The common absence of effect of 1 p.c. pilocarpine when injected 1½–2 hours after ·1 p.c. adrenaline is due to the protracted vaso-constriction and consequent progressive decrease of excitability.

This explanation makes some assumptions as to the extent and duration of the reduction in blood supply. Before passing to the observations made to test these assumptions we may mention briefly the result of some experiments on the degree of depressive action of other solutions. Barium chloride 1 p.c., though it has usually about as much secretory effect as Ringer's fluid, has after a time a marked depressive effect on excitability. When 1 to 2 mgms. pilocarpine are injected sub-cutaneously elsewhere than in the foot about half an hour after local injection of 1 p.c. barium chloride, it does not as a rule cause any secretion in the injected area. The depressive effect, unlike that of ·1 p.c. adrenaline rarely extends to any obvious degree, beyond the injected area; in two cases only the two mid toes secreted less than the others and than the side pads. It may be presumed that 1 p.c. barium chloride has a gradual depressive action on the gland cells. Calcium chloride 1 p.c. in the two experiments tried had a similar depressive action. Pituitrin (Allen and Hanbury's preparation) was injected locally in the strength in which it is sent out. Five experiments were made, in none had it any appreciable depressive action, the secretion indeed in three of the experiments was rather freer in the injected area than elsewhere. One experiment only was made with

each of the following solutions; the results were: considerable depressive action—chloretone ·4 p.c., alcohol 30 p.c., amyl nitrite after causing profuse secretion, histamine 1 p.c. Slight depressive action—lactic acid ·01 p.c., sodium carbonate ·1 p.c., acetyl-choline ·1 p.c., ergotoxin phosphate ·1 p.c. in rather strongly alkaline solution. Little or no depressive action—barium chloride ·1 p.c., eserine salicylate ·5 p.c., histamine ·1 p.c.

Vascular changes. Clamping of blood vessels.

Changes in the tint of the skin of the foot caused by local injection. The changes in the colour of the skin of the foot caused by injecting locally ·1–·15 c.c. of adrenaline do not at first sight seem consonant with the degree of restriction of blood supply to the glands required in order to account for its depressive action. A brief pallor is caused by injection of any fluid; this is due to the pressure exercised, for after Ringer's fluid the earlier tint is rapidly regained. After adrenaline ·001 p.c. the primary pallor—confined or nearly confined to the area injected—is of variable duration; often it disappears in a few minutes, sometimes a faint pallor may be seen for half an hour. The tint of the foot seems to depend largely upon the venous pressure; lifting the foot is apt to cause it to become redder. When 0·1 p.c. adrenaline is injected into the mid pad, the pad itself usually remains somewhat paler than the rest of the foot throughout the experiment, but the foot as a whole after a few minutes becomes somewhat flushed and has a faint bluish tinge. The cyanotic tinge is most marked in the two mid toes and is often absent from the inner and the outer toe.

The state of the circulation in the sub-cutaneous tissue was investigated by cutting through the fat tissue of the pad parallel with the surface. After injection of ·1 p.c. adrenaline, the fat tissue in which the glands are imbedded was white, and there was hardly any oozing of blood from it in the course of 30–60 secs., but blood flowed from the skin edges of the cut. After injecting ·001 p.c. adrenaline there was also pallor of the fat tissue, but the oozing of blood from it was generally distinctly more than after ·1 p.c. adrenaline. The restriction of the circulation around the glands caused by ·1 p.c. adrenaline was very protracted; it was present when the pad was cut 1½ hours after the injection. Thus the tint of the skin not only does not show the degree of restriction of blood supply to the deeper tissue, but may suggest a free blood circulation in it when there is little or none. We take the explanation of the slightness of the pallor commonly produced by ·001 adrenaline to be that the capillary network immediately beneath the epidermis in the

injected area can be supplied with blood from the surrounding area, although the small arteries running to it through the fat and glandular tissue are fairly strongly contracted. The flushing and bluish tint caused by ·1 p.c. adrenaline may naturally be attributed to its causing contraction of small veins and causing it outside the area of injection. The pallor caused by most of the other solutions was not great (one or two were injected into pigmented feet) and was roughly proportional to their depressive action.

Effect of adrenaline on the vessels of the sub-cutaneous tissue of the rat and on the ear of the rabbit. Donegan(4) found that adrenaline ·0001 p.c. locally applied caused complete contraction of superficial veins. Those he mentions which concern us are the internal and external saphena veins. These are larger than the veins of the foot and although there is no reason to suppose that the smaller veins react differently, it seemed worth while to make certain of this and to compare the effect on them of the solutions we had used. Our observations were made on the sub-cutaneous small veins of the rat and on the veins of the ear of the rabbit.

The rats were anæsthetised, ·1 to ·2 c.c. of the solutions was injected under the skin. In a variable time the skin was incised, turned back and the state of the blood vessels in the sub-cutaneous tissues noted. Adrenaline ·1 and ·01 p.c. caused complete pallor. The veins as well as the arteries were completely, or almost completely, constricted; these effects lasted for an hour or more, the only marked difference noted in the action of the two solutions was that a larger area was affected by ·1 p.c. than by ·01 p.c. adrenaline. Adrenaline ·001 p.c. caused distinctly less pallor, the arteries were contracted but the veins remained obvious, often slight return of the normal tint began in about half an hour. The pallor caused by 1 p.c. $BaCl_2$ and 1 p.c. $CaCl_2$ was less than that caused by ·001 p.c. adrenaline, and varied in the different experiments, sometimes $BaCl_2$ and sometimes $CaCl_2$ had the greater effect; the arteries and veins, except perhaps the smallest, remained distinct, but the contraction produced was prolonged. Pituitrin and ·1 p.c. acetyl-choline on the other hand caused pallor and contraction of the arteries, but not of the veins, ergotoxine ·1 p.c. caused slight pallor, and histamine ·1 p.c. none.

In the rabbit's ear a drop of adrenaline ·1 p.c. injected near one of the lateral veins caused complete contraction of the vein at the spot —an effect not caused by Ringer's fluid—and small areas of contraction could thus be obtained in adjoining spots. On injecting rather more adrenaline, contraction of a long stretch of the vein was obtained and stagnation of part of the capillary circulation, the central artery re-

maining obvious. It may be noted that this effect of adrenaline is much greater than can be obtained by stimulation of the cervical sympathetic.

The results just described are in general features like those deduced above as occurring in the deeper tissue of the cat's foot. Adrenaline ·001 p.c. caused less complete, less protracted and less extensive contraction than ·1 p.c.; the latter caused complete contraction of the small veins, and there was little difference in the effect of ·01 and ·1 p.c. adrenaline except in extent in the area affected. But in most cases the effect on the vessels appeared to be greater than on those of the cat's foot, for in the foot pilocarpine obviously sometimes makes its way to the glands after local injection of ·1 p.c. adrenaline since injected elsewhere it may cause secretion; ·01 p.c. adrenaline does not cause venous congestion, and pituitrin causes but slight pallor. Possibly pituitrin has a slight secretory effect. Adrenaline ·1 p.c. injected into the gum caused pallor lasting more than two hours; here, as in the sub-cutaneous tissue of the cat, there was no cyanosis.

Effect on secretion of clamping the blood vessels. It is known that by stimulating the sympathetic nerves, secretion of sweat can be obtained after death. Restriction of circulation by adrenaline need not then prevent the fluid in which it is dissolved from causing secretion, and we have seen that adrenaline solution may cause secretion lasting 15 to 20 minutes. In order to determine more exactly the effect of restriction and cessation of circulation upon sweat secretion, we made experiments in which the femoral or common iliac or brachial artery was clamped before or after injecting pilocarpine. One to two mgms. of pilocarpine were injected sub-cutaneously into the abdominal region or ·1 to 1·5 c.c. of ·01 to 1 p.c. pilocarpine were injected sub-cutaneously into the mid pad. Here as in other experiments the results varied more or less obviously with the excitability of the glands.

Clamping the common iliac vein had but a small effect on secretory activity during half-an-hour, the longest time we have tried. The secretion became somewhat but not greatly less than on the opposite side. Clamping the femoral artery centrally of the popliteal branch had a considerably greater effect, but it varied with the condition of the glands. Three experiments were made; in two of them, in which the artery was clamped early in the experiment, secretion continued for the half-an-hour during which the clamp was kept on, but it became slow towards the end of the time. In one of these experiments the feet were unpigmented, the foot on the side with artery clamped remained slightly pink, and on pressing it, the pink tinge slowly returned, so that passage of blood to

the skin was not completely stopped. That blood can slowly pass to the foot after clamping the artery was shown by injecting pilocarpine in the body region (cp. Exp. 2).

Exp. 2. Femoral artery clamped. Ten minutes later 2 mgms. of pilocarpine were injected sub-cutaneously in the abdominal region. A trace of secretion appeared on the pad of the foot ten minutes after the injection. The drops steadily increased in size in the course of the next ten minutes, and formed on the toes.

Since clamping the femoral artery stops all direct supply of blood, it is clear that secretion can go on for a considerable time with a slow circulation and a small oxygen supply. In the third experiment the artery was clamped after other observations; in this case (cp. Exp. 5) the secretion was stopped at once except for a mere trace. The greater effect here was no doubt partly due to lowered excitability and less strong stimulus, but probably the degree to which the blood supply is cut off varies in different cats and varies with the blood pressure.

On clamping the common iliac artery we did not find that pilocarpine injected in the body region caused secretion in the foot in the $8\frac{1}{2}$ mins. before unclamping (cp. Exp. 3). The effect produced by clamping the artery, when pilocarpine has been given before clamping, depends mainly upon the excitability of the glands. Exp. 3 shows the result when the excitability is fairly high.

Exp. 3. The left common iliac artery was clamped. Two minutes later 1·5 mgms. of pilocarpine were injected sub-cutaneously in the body region. The artery was unclamped after $8\frac{1}{2}$ mins. during which time there was no secretion; the secretion on unclamping rapidly became copious in all parts of the foot. The foot was wiped, and the artery clamped.

Time after clamping	State of foot
3 mins.	Good secretion on whole of pad, none in toes
5 „	Very slight secretion on pad
8 „	No secretion

On unclamping the artery the secretion in 3 mins. became copious on the pad and slight on the toes. We may note that unless there has been a previous injection into the pad (as in Exp. 5) clamping the artery has more effect in decreasing the secretion in the toes than in the pad.

It will be seen that notwithstanding cessation of the circulation, the secretion went on freely for about three minutes, then rapidly diminished and stopped in about eight minutes. A higher degree of excitability or a larger amount of blood in the limb at the moment of clamping the artery would no doubt allow secretion to go on longer than in this experiment.

On repetition of the clamping, the time required to stop the secretion usually becomes less and less, until it is stopped at once (cp. Exp. 4), and if excitability is low at the beginning of an experiment, clamping may stop it at once.

Exp. 4. Observations had been made on the effect of local injection on the fore foot. The left iliac artery had been clamped for a time sufficient to cause congestion of the foot and a copious secretion produced by injecting ·1 c.c. 1 p.c. pilocarpine into the mid pad. The following observations were then made:

0	mins.	Artery clamped; foot remained red.
5	,,	Secretion stopped.
6	,,	Common iliac vein clamped.
7	,,	No secretion. Artery unclamped. In 3 mins. copious secretion.
12	,,	Artery clamped, vein unclamped. Press the foot, the pallor produced slowly (30 secs.) gives way to a pink tint.
14	,,	Secretion copious.
14½	,,	,, moderate, wipe the foot.
15½	,,	,, very slight.
16	,,	No secretion; foot is a blue red.
20	,,	No secretion. Unclamped artery; secretion copious in 3 to 4 mins.
35	,,	Secretion moderate to good. Clamp artery and wipe foot. No secretion in 6 mins.
41	,,	Unclamp artery. Fairly good secretion in 2 mins.
45	,,	Clamp artery. Trace of secretion in ½ min. which rapidly disappears.
48	,,	Unclamp artery. Moderate secretion in 4 mins.

From these and similar experiments it follows that both adrenaline and clamping the artery stop secretion in a time depending upon the excitability of the glands. When pilocarpine is injected into the pad of the foot a short time after clamping the artery, and whilst the artery remains clamped, the occurrence or non-occurrence of a secretion depends similarly on the gland excitability. If it is fairly high, free secretion goes on for a few minutes, it then diminishes, at first rapidly and then slowly. If excitability is low, there is either no secretion, or there is none for several minutes and then a very slow secretion commences. The explanation of this retarded secretion we shall deal with presently, we may first give an example of an experiment which shows it and which shows the relative effect of restriction of blood supply by adrenaline and by clamping the common iliac artery.

Exp. 5. Ringer's fluid caused no secretion in the mid pads. The common iliac artery was clamped on one side and ·1 c.c. ·1 p.c. adrenaline injected into the mid pad of the opposite side. A few minutes later ·1 c.c. of ·1 p.c. pilocarpine was injected into the mid pad of each foot.

Mins. from pilocarpine injection	Artery clamped. Secretion	Adrenaline in mid pad. Secretion
3	None	None
10	None	Slight on part of mid pad
20	Trace on whole of pad, moderate on toes but unequal	None on mid pad, slight on side pads, good on toes
29	Secretion less	Moderate on toes
30	(Unclamp iliac artery)	
31½	Good	
38½	(Clamp femoral artery)	
42	None	
48½	Trace	Slight on 2nd and 3rd toes
50	(Unclamp femoral), good in a few minutes	

It will be seen that in this experiment, the slight secretion began rather earlier in the mid pad which had been injected with adrenaline than in that in which the blood supply had been stopped by arterial clamping. Although on account of possible variation in excitability no great stress can be laid on the earlier occurrence of secretion after adrenaline, it may fairly be inferred that the effect of adrenaline and of decrease of blood supply is so nearly the same as to leave no room for appreciable inhibitory effect of adrenaline. On the adrenaline side the local vaso-constriction continued and gradually involved the rest of the foot so that the secretion gradually decreased.

There are some minor effects of restriction of blood supply which are worth notice. These chiefly relate to its after effects. When a secretion is going on it sometimes happens that the after-effect of clamping the common iliac artery is to produce a rather freer secretion than on the side the artery of which has not been clamped, and a rather freer secretion than occurred before clamping. So far as we have seen this is only marked when the excitability is low. Exp. 6 is an example.

Exp. 6. Ringer's fluid injected into the mid pads caused no secretion, 1·5 mgms. of pilocarpine injected under the body skin caused a moderate secretion, after this had gone on for 25 mins. the feet were wiped and the left common iliac artery clamped for 6 mins.; during this time there was no secretion on the clamped side. On unclamping the artery, the secretion was rather more than on the opposite side and rather more than it was before clamping. After repeating the clamping and unclamping, ·1 c.c. of ·2 p.c. pilocarpine was injected into each mid pad; the secretion was slow and moderate. The artery was clamped for 15 mins.; a trifling secretion went on for a minute or two only; the foot was pale. On unclamping, the foot became intensely red and the secretion was distinctly greater than on the opposite side and than it was before.

The greater secretion on the side on which the artery had been clamped than on that on which it had not, is partly due to the absence of fatigue in the former; in the latter, fatigue is caused by the continued secretion. But the increase of secretion over that before clamping can only be due to the increased blood flow which follows anæmia. The increase does not always occur; this lack of constancy is partly due to the fact that the degree of hyperæmia caused by previous clamping of the common iliac artery for a given time varies in different cats and varies with the blood-pressure. There is another factor which we think influences the result, viz. a slight decrease of excitability during anæmia. Three experiments were made on this point in the following way. The common iliac artery was clamped on one side for 5 mins. and on the other for 30 mins. Two minutes before unclamping the arteries, 2 mgms. of pilocarpine were injected sub-cutaneously in the body region. The

secretion began a little earlier and for 7 to 10 minutes was rather less on the side on which the anæmia had lasted longer. The difference was slight, and except that the results of the three experiments agreed, might have been due to differences of excitability. This factor is probably negligible with short duration of anæmia, but becomes sensible with long duration of anæmia such as is caused by the ·01 to ·1 p.c. adrenaline. It is clear that after brief anæmia, excitability, if decreased, is rapidly regained on re-establishment of the circulation (cp. Exps. 3 to 5). In one experiment the artery on one side was clamped for a quarter of an hour; pilocarpine was injected sub-cutaneously two minutes after unclamping and caused no certain difference in secretion on the two sides.

The fact that local injection of pilocarpine, which provides fluid for the glands, may be prevented by vaso-constriction from causing secretion indicates that a certain amount of oxygen is necessary for secretion, although, as we have seen, this amount is small.

We have said above that clamping the femoral artery did not in our experiments prevent blood passing to the foot. The foot after a time recovered its pink tint. In this case there is some collateral circulation. Some degree of recovery from pallor may occur whilst the common iliac artery is clamped, though the recovery, so far as we have seen, is slight and may be only partial. We take this to be due to the dilatation of capillaries and small vessels occurring in anæmia. Clamping the artery leaves blood in the limb, and when the capillaries dilate blood flows into them from the larger vessels and possibly from capillary areas less affected than those of cutaneous and sub-cutaneous tissues. This, we think, is the explanation of the retarded secretion spoken of above in connexion with Exp. 4. Indication of a similar retarded secretion is sometimes seen when the excitability is higher than it was in Exp. 4. Thus, local injection of pilocarpine whilst the artery is clamped may cause a secretion which stops in a few minutes and some minutes later begins again but is very slow.

From the foregoing account it is seen that the major effects of adrenaline on the response of the glands to pilocarpine can be produced by clamping the arteries and so restricting the blood supply to them, and that the small differences in the effect of restricting the blood supply by the two methods are due to adrenaline causing constriction (of varying intensity) close to the glands, whilst arterial clamping causes constriction at a distance from the glands. We conclude then that the depressive effect of adrenaline on secretion is solely due to its vaso-constrictor action.

It may be noted that none of the facts given in this paper suggest that the longitudinally arranged cells in the outer part of the sweat glands—commonly taken to be unstriated muscle cells of epithelial origin—take any part either in furthering or retarding the secretion of sweat.

Summary.

All aqueous solutions, which are not injurious, tend to stimulate the sweat glands. The stimulating action is weak, so that whether the solutions cause secretion or not depends on the excitability of the glands. In summer, secretion was produced by local injection of Ringer's fluid much more frequently and in much greater amount than in February and March.

The secretory effect of adrenaline was in the great majority of cases markedly less than that of Ringer's fluid. There is little difference between the secretory effect of ·001 p.c. and of ·1 p.c. solution of adrenaline, but generally the secretion (if any) is rather greater and is longer lasting with ·001 p.c. than with ·1 p.c. And the vaso-constrictor effect of ·001 p.c. adrenaline is less than that of ·1 p.c.

Whatever the concentration of adrenaline, its secretory effect is confined to the area in which fluid is injected. Since adrenaline diffuses into the surrounding tissue, as shown by its decreasing the response to pilocarpine, adrenaline has no secretory action. The occasional greater secretion caused by adrenaline than by Ringer's fluid when injected into different regions is due to the different excitability of the areas, or to differences in the level of injection.

Clamping the common iliac artery, and local injection of adrenaline, primarily affect the secretion caused by pilocarpine in the same way. If the excitability of the glands is high, neither stops the secretion at once; if the excitability is low, either stops it in a few seconds. Similarly, if the blood supply is cut off, either by clamping the artery or by local injection of adrenaline, local injection of pilocarpine will cause secretion if the excitability is high and will not cause secretion if the excitability is low. The depressive action of adrenaline is then caused by vaso-constriction and not by direct inhibitory action.

The two methods of restricting the blood supply differ in that adrenaline ·01 to ·1 p.c. causes long lasting vaso-constriction of peripheral origin so that the blood supply of the glands is kept minimal. Clamping the artery leaves blood in the tissues so that a certain amount can still pass to the glands. The glands can secrete when there is a very

small blood and oxygen supply, but some supply of oxygen is necessary for continued secretory activity.

On unclamping the artery of a hind limb, there is, as is known, flushing of the skin more or less in proportion to the duration of the anæmia, the increased blood flow tends to cause a freer secretion than occurred before the clamping. This may be counterbalanced by the slight progressive decrease of excitability occurring during anæmia. Up to the limit of duration of anæmia tried—about half an hour—the excitability is rapidly recovered on re-establishment of the circulation.

A drop of adrenaline ·1 p.c. locally injected into the ear of the rabbit causes local contraction of the veins. When injected in rather greater amount it causes extensive venous contraction and stagnation in part of the capillary area. Adrenaline ·1 p.c. locally injected into the foot causes a bluish flush of the skin, due to contraction of the small veins, as well as of the arteries. The fat tissue in which the glands are imbedded become, however, almost bloodless. Thus the state of the dermal capillaries does not necessarily show the state of the sub-cutaneous capillaries.

Adrenaline causes much greater contraction of the veins in the rabbit's ear than is caused by stimulating the cervical sympathetic nerve.

Pituitrin and some other vaso-constrictor substances when injected into the foot appeared to produce insufficient vaso-constriction to seriously influence secretory activity.

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