PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

The Action of Pituitary Extracts upon the Kidney

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PHILOSOPHICAL TRANSACTIONS.

I.—*The Action of Pituitary Extracts upon the Kidney.*

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Introduction.

It was noticed in 1901 by R. Magnus and Schäfer* that intravenous injection of pituitary extract may be followed by a marked increase in urine flow, accompanied by expansion of the kidney. This appeared the more remarkable, since the effect of the extract is to cause contraction of the systemic arteries, including those of the alimentary canal, a contraction only inferior to that produced by the active material of suprarenal extract; and it was to have been anticipated that the same effect would be produced upon the kidney vessels, leading to a diminution or suppression of urine. As will appear from the sequel, this effect does, in fact, sometimes occur as a primary result of the injection of pituitary extract, but even when this is the case it is, in the majority of instances, succeeded by prolonged dilatation of kidney vessels accompanied by marked diuresis.

It has been our aim in the present investigation to follow up the line of research indicated by the observations of Magnus and Schäfer, and to endeavour definitely to determine how far this diuretic action is constant, with which part of the pituitary body it is related, whether it is a function of the substance which raises the blood-pressure and is only an indirect effect of this rise, or whether it is due to a substance which exerts a specific effect upon the renal blood-vessels and kidney cells, and in the latter case whether it is possible to isolate this material and exhibit its action independently.

Methods.

We have experimented upon rabbits, dogs, and cats. The animals were anæsthetised either with ether or with chloroform or with a mixture of chloroform and absolute alcohol (nine parts chloroform to one part absolute alcohol),† the anæsthetic being given at first in a box and by the nostrils, but subsequently in all cases through a tracheal tube, with artificial respiration by a pump. Animals which are fully anæsthetised in this way are perfectly motionless, and it is possible to use an oncometer without any fear that the results will be disturbed by reflex or

* 'Phys. Soc. Proc.,' in 'Journ. Physiol.,' vol. 27, p. ix.

† Schäfer and Scharlieb, 'Roy. Soc. Edin. Trans.,' 1906, vol. 41.

spontaneous movements. The apparatus used for the anæsthetic included a three-way stop-cock so arranged as to render it possible to pump into the lungs a definite and readily adjusted mixture of pure air and air saturated with the anæsthetic vapour, and to maintain the requisite proportion for any reasonable time. In many cases, in order to avoid the risk of cardiac inhibition produced by the anæsthetic, a small dose of atropine sulphate, never exceeding 1/50 grain, was injected hypodermically; this dose had no material effect upon the kidney secretion, while enabling the anæsthetic to be administered with much greater ease and confidence.*

The urine was collected either from fine cannulas tied into the ureters or from a glass tube inserted into the bladder by a suprapubic incision, the bladder wall being securely tied round the cannula. The latter was of such a length as would enable it to penetrate to the base of the bladder, and was furnished with lateral orifices as well as a terminal opening. As an additional precaution, to ensure the instant drainage and collection of the urine as soon as it passed into the bladder from the ureters, a few strands of lamp-wick were passed into the cannula and allowed to project from its open end into the bladder cavity. The opposite end of the cannula was connected with a fine indiarubber tube, the free end of which was fixed over a pneumatic (or electric) drop-counter some inches below the bladder level, so that there could be no possibility of any accumulation of urine within the bladder. This method of collecting the urine proved far superior to that of inserting cannulas into the ureters, the one which we at first used, for by the latter method the operation is more severe, and in small animals there is a risk of blockage of the ureter cannulas by kinks, clots, and other kinds of obstructive; these considerations led us ultimately to abandon the ureter cannulas and to adopt the more natural and more simple method of bladder drainage above described. Even under these circumstances the operative procedure and the effect of the anæsthetic combined frequently produced suppression of urine flow, so that in some experiments this part of the record is negative throughout. But in many cases in which the suppression due to operation and anæsthetic was present, the action of the kidneys was restored on administering pituitary extract (figs. 11, 16, 17, and 20); after having been once thus set going the secretion was not, as a rule, again suppressed.†

The other operative procedures consisted in the insertion of artery and vein cannulas and the inclusion of one kidney in an air-oncometer. The kidney volume was recorded by an Albrecht piston recorder. In a few experiments the changes in volume of a loop of intestine were also registered in a similar manner. The artery cannula was connected with a mercurial manometer. A fine cannula was tied in

* *Cf.* SCHÄFER and SCHARLIEB, *op. cit.*

† The urine of both ureters was collected in most cases, and no separate record was taken of the amount flowing from each one. It is a familiar fact to those who are accustomed to this kind of experiment that a kidney in an oncometer may yield no secretion. But in such case the total amount given off is not materially lessened, for the untouched kidney does the work of both.

cats and rabbits into the external jugular, in dogs into the saphenous vein; to it fitted a glass syringe of 4 c.c. capacity. In no instance could more than this small amount of the Ringer solution in which the extracts were dissolved be injected, and in many cases only 1 c.c. or 2 c.c. were employed. The syringe and its contents were always warmed to the temperature of the body before use, and the intravenous injection was performed slowly, so that from half a minute to one minute might be occupied with the injection of 4 c.c.; the solution thus became mixed with a large proportion of blood as it entered the circulation. Without such precautions, in small animals and especially in rabbits, the injection of even so inconsiderable an amount of salt solution as 4 c.c. may produce a distinct, although quite temporary, increase of urine. This is easily distinguishable from the pronounced effect of pituitary extract, but nevertheless we desired to eliminate it as completely as possible. In many cases a preliminary injection of the same amount of Ringer solution as was to be administered with the pituitary extract was given previously as a control.

We are indebted to Messrs. Burroughs and Wellcome for a supply of material for this investigation. Without their aid it would have been impossible to carry the research through, and we desire to record our obligation to them for the trouble they have taken to meet our requirements. We have used almost exclusively the pituitary of the ox, but have tested our results by experiments with glands from other animals (dog, cod) without finding any noticeable difference so far as the effects upon blood-pressure and kidney function are concerned.

Structure of Pituitary Body in Relation to the Activity of Extracts.

The pituitary body of the ox has the general shape and size of a large cob-nut. As received by us the glands were invested by a strong fibrous covering derived from the dura mater. When this is dissected off and a cut is made into the glandular substance the two lobes of the gland are easily distinguished, the smaller posterior lobe being for the most part imbedded in and ensheathed by the larger anterior lobe, the two bearing a relation to one another something similar to that of the cortex and medulla of the suprarenal body.

If a sagittal cut be made through the middle of the gland the relations of the two lobes are evident; still better in stained microscopical sections. It is noticeable that in the ox there is a curved transverse cleft (intraglandular cleft) separating the lobes from one another except near the circumference of the gland. Owing to the existence of this cleft it is very easy to shell out the posterior lobe from its attachment to the anterior, and to obtain the two parts separately. When thus separated and divested of adhering connective tissue the posterior lobe is found to be relatively small, not weighing more than a few grains, and to obtain a fair amount of this part (which contains all the active substances of pituitary extract) for investigations of a chemical nature it is necessary to deal with a large number of

glands at a time, although for purely physiological tests no great quantity is required. On the other hand, a relatively large amount of the anterior lobe substance is yielded from each gland, but only quite exceptionally have we found the extracts of this to be possessed of any active properties, and we, therefore, assume that, as may easily happen, there has in these cases been a *post-mortem* infiltration of the active material into the anterior from the posterior lobe.

That the activity of the extract so far as the heart and blood-vessels are concerned is confined to the posterior lobe was determined by HOWELL; our results, as will be seen, extend these observations to the diuretic effect. This is the more remarkable, because the anterior lobe is very obviously of glandular structure, being composed of masses of epithelial cells which here and there surround a lumen or line a cyst-like cavity, and which have numerous large sinus-like blood-vessels ramifying amongst them. The posterior lobe, on the other hand, is composed mainly of a tissue which resembles nerve grey matter, with many glia cells and, according to some authorities, a few nerve fibres and some scattered nerve cells; it consists, in fact, to all appearance of neuroglia with, perhaps, some nerve tissue, as the mode of its formation from the floor of the third ventricle might lead one to expect. There is, however, a layer of vascular epithelial tissue covering the part of the lobe where it abuts on the intraglandular cleft before noticed, the more superficial cells being arranged somewhat like the cells of a columnar epithelium. This epithelial layer passes at the edges of the intraglandular cleft into continuity with the epithelial tissue of the anterior lobe—of which, in fact, it appears to be an extension; it probably belongs to the hypophysial part of the gland, and the intraglandular cleft—which is not present in all animals—is also wholly hypophysial.* The cleft itself is occupied by a small amount of glairy fluid,† which is probably secreted by the cells which bound the cleft. It is difficult to determine whether there is any difference in activity of an extract made from the anterior layer of the posterior lobe, which includes this epithelial structure, and from the middle and the posterior parts of the lobe where there is apparently nothing but neuroglial tissue. All that can be said on this point is that we have obtained a very active extract from the part of the posterior lobe which is furthest removed from the epithelial layer and the intraglandular cleft, so that the production of an active substance seems not to be bound up with the presence of epithelium in that lobe.‡

* VINCENT and OSBORNE, 'Brit. Med. Journ.,' 1900, vol. 1, p. 38. KUPFFER believes, however, that the glandular structure of the posterior lobe is developed from the infundibulum ('Ges. f. Morph.,' München, 1894).

† W. W. HAMBURGER ('Amer. Journ. of Physiol.,' 1904, vol. 9, p. 294) has investigated this fluid physiologically, and finds it to be destitute of activity. HAMBURGER states that saline extracts of the anterior lobe produce a depressor effect, which is not repeated with subsequent injections. We have not obtained this result.

‡ A similar result was obtained by SWALE VINCENT and OSBORNE (*op. cit.*), so far as concerns the action of the extract upon blood-pressure.

The material which we have employed for the preparation of extracts consists of the posterior lobes of many glands, spread out in a thin layer upon glass and dried at the temperature of the atmosphere of the room. The dry substance is pulverised and kept in a dry stoppered bottle; thus preserved it appears to retain its active properties for months and even years. The extract which we have used has been made by taking one part by weight of the dry material, boiling it with 100 parts of RINGER'S solution and filtering. This solution, which we term the 1-per-cent. aqueous extract, may be kept from day to day and used little by little, if the precaution is taken of boiling it up again and plugging the neck of the flask in the usual manner with burning cotton wool, before putting it away. We have also used saline extracts of the dried material which had been previously extracted with absolute alcohol or with ether, but obtained no diminution of activity after these reagents, nor did the materials which they extracted yield to RINGER'S solution, after evaporation of the alcohol or ether, any physiologically active substance.* Nor, as has already been

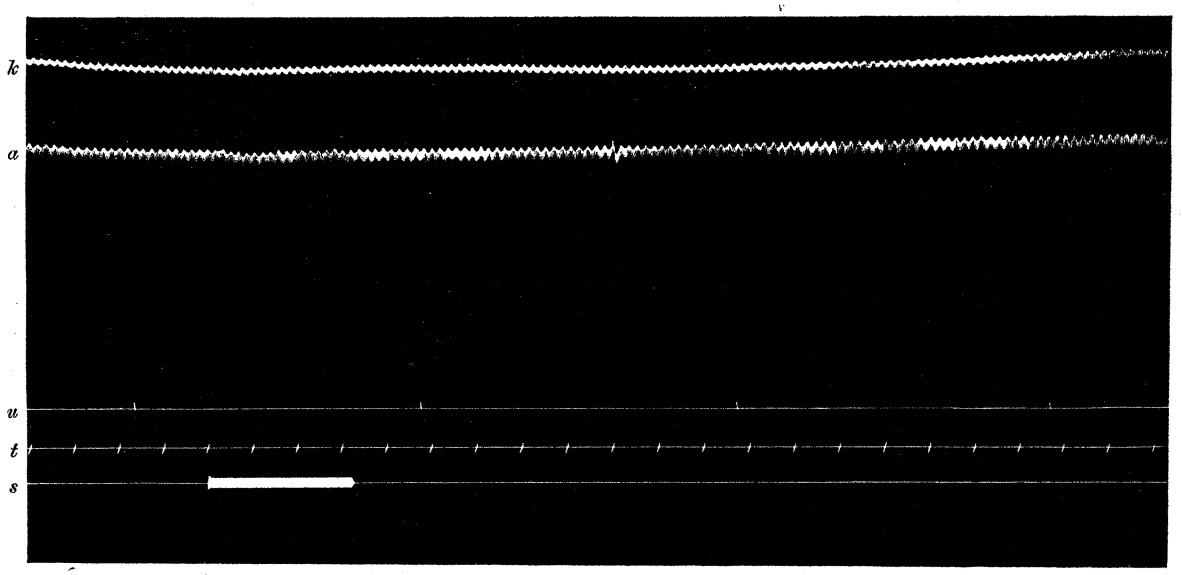

FIG. 1.—Cat. At the place marked by the signal 4 c.c. of a 1-per-cent. boiled aqueous extract of the anterior lobe of the pituitary of the ox was injected into the jugular vein. Notice the entire absence of effect as compared with that produced by the extract of posterior lobe (fig. 2). *a*, arterial pressure; *k*, kidney oncograph; *u*, urine flow and abscissa of blood-pressure; *t*, time in 10 secs.; *s*, signal.† (Reduced to $\frac{2}{3}$rds.)

stated, were we able in the vast majority of cases to prove the existence of any active material in extracts of any kind made from the anterior lobe alone; in the rare

* A contrary result which was yielded in some earlier experiments was perhaps due to the alcohol which was used not having been completely anhydrous. At any rate, in none of our later experiments, in which we have been more alive to this possible source of error, have we obtained positive results with the materials which alcohol and ether extract from the gland.

† The letters have the same significance in all the tracings, except in fig. 4, where the time tracing is marked in minutes.

instances where such activity was shown there is every reason to believe it was the results of *post-mortem* diffusion from the posterior lobe during the time a consignment of glands was being collected and forwarded to us.* This negative effect of aqueous extracts of the anterior lobe† as contrasted with the positive effect produced by

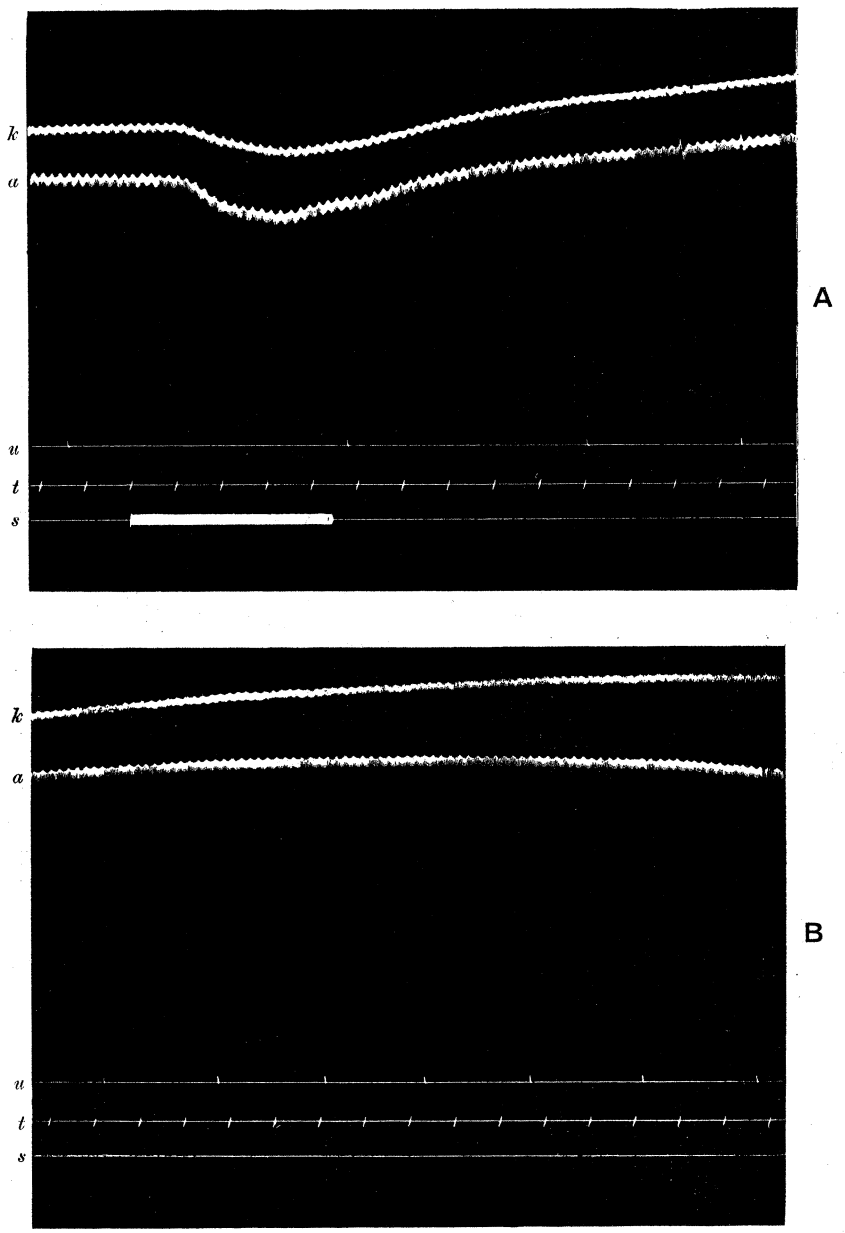

FIG. 2.—Cat. Continuation of the tracing shown in fig. 1. The signal marks the intravenous injection of 4 c.c. boiled aqueous extract of posterior lobe. (Reduced to $\frac{2}{3}$rds.)

This tracing is a continuous one; for exigencies of space it has been cut into two parts, A and B.

* To prevent putrefaction, a little chloroform was always added to the bottle in which the fresh glands were collected, but this was of course eliminated in the drying process.

† So far as we are aware, no observer has obtained active extract from the anterior lobe (except

similar extracts of the posterior lobe is well illustrated by figs. 1 and 2. In the tracings shown in fig. 1, in which the uppermost curve is that described by the oncograph, and the second the curve of blood-pressure, 4 c.c. of a 1-per-cent. boiled aqueous extract of anterior lobe was injected into the jugular vein (of the cat). This produced no noticeable effect. Ten minutes later, during the period marked by the signal in fig. 2, the same amount of a 1-per-cent. boiled aqueous extract of posterior lobe was injected. The effect upon the kidney volume, blood-pressure, and urine-flow are all well marked, although the prolonged diminution of blood-pressure and kidney volume which immediately resulted from the injection are not usually characteristic of a first injection of infundibular extract.

Effects of Intravenous Injection of Infundibular Extract.

Before considering in detail the effect which aqueous extract of the posterior lobe produces upon the kidney secretion it is necessary to draw attention to its peculiar effects upon the heart and blood-vessels. That it produces a general constriction of arterioles leading to considerable elevation of blood-pressure was determined by Oliver and Schäfer.* Howell† confirmed this result, and showed that it is confined to extracts of the posterior lobe. He further found that the elevation of blood-pressure occurs in spite of the fact that the heart may be markedly inhibited and the pulse far slower during the action of the extract; he determined this inhibition to be a peripheral effect, since it continues even with the vagi cut. But the most interesting fact observed by Howell is the immunity which a first dose of any magnitude‡ confers, so that if a second dose is injected intravenously within a given time—about 30 to 60 minutes, depending upon the amount of active material used for the first injection—no second rise of blood-pressure or accompanying cardio-inhibitory effect is produced. The results obtained by Howell were confirmed by Schäfer and Vincent.§ In many cases the rise of blood-pressure which is characteristic of the first injection of pituitary extract is preceded by a slight fall of pressure. When a second and succeeding doses are given within the period of immunity the effect of these doses is not negative, but a well-marked fall of blood-pressure is produced, far greater as a rule than that which is produced by aqueous decoction of other glandular organs. Schäfer and Vincent concluded from their experiments that there are two substances contained in the aqueous extract having opposite effects (pressor and depressor) upon the blood-vessels, but that with the first injection

Hamburger, whose results have already been referred to). The view expressed by Masay that the active agent of the secretion is formed by the epithelial tissue of the gland seems to be based upon purely anatomical considerations ('Ann. d. l. Soc. Roy. d. Sci. Méd. et Nat. de Bruxelles,' vol. 12, 1903).

* 'Journ. Physiol.,' 1895, vol. 18.

† 'Journ. of Exper. Medicine,' 1898, vol. 3.

‡ A very small dose, *e.g.*, 1 c.c. of a 1-per-cent. extract, does not usually produce immunity, and the repetition of the dose is followed by a rise in blood-pressure, but less than that caused by the first dose.

§ 'Journ. Physiol.,' 1899, vol. 25.

the depressor substance is overpowered by the pressor, while with subsequent injections these conditions are generally reversed, although the depression which is the most marked phenomenon of the second and subsequent doses may be succeeded by a slight and gradual rise of pressure. The facts relating to the heart and blood-vessels recorded by the before-mentioned observers have been also observed in our experiments. We have not found the cardiac inhibition to be a constant phenomenon;* sometimes it is absent altogether with the doses of pituitary which we have employed, and often it is so slight as almost to escape observation. Most commonly it does not come on at the same moment as the rise in blood-pressure, but its advent may be delayed for some seconds or even for a minute or more; it is frequently preceded by a period of cardiac acceleration. In all these respects the effect of the active substance or substances of pituitary extract has a certain resemblance to that of suprarenal extract. Nevertheless the substances are undoubtedly different, for with pituitary extract both the vascular contraction and the cardiac inhibition are much more prolonged, and the latter is seen even after section of the vagi; moreover, the immunity to a repeated dose is quite characteristic of pituitary. Nor is pituitary extract a general excitant of such muscle and gland substance as is innervated by the sympathetic, as is the case with suprarenal extract. And although we find that the active material is dialysable through parchment paper (Schleicher and Schüll tubes) the extract of pituitary does not yield a crystallisable body such as that known variously as epinephrin, adrenalin, hemisine, etc., when subjected to the operation of methods similar to those used for obtaining the active material of suprarenal medulla.† Finally, the action upon the kidney of the two extracts is entirely different, for whereas suprarenal strongly contracts the renal vessels, and produces shrinkage of the kidney and cessation of urine, the main and characteristic effect of pituitary extract upon the organ is to produce dilatation of its vessels and increase of urine, although this condition may be preceded by a temporary one in which the urine is diminished or arrested, with or without a temporary shrinkage of the kidney. A typical tracing from the rabbit is given in fig. 3, where the result of injecting 1 c.c. of a 10-per-cent. extract is shown, and may be compared with the effects produced upon blood-pressure, kidney volume and urine by intravenous administration of suprarenal extract (fig. 4, from the cat).

Since the extract produces a notable rise of general arterial pressure in consequence of its effect upon the systemic arteries—which is comparable in magnitude, if the dose be sufficient, to that caused by suprarenal—it might at first sight appear as if the diuresis were due entirely to this rise of pressure, the kidney vessels either not participating in the general contraction or giving way after a short interval, and allowing a passive dilatation. With such a condition as this there would be an increased flow of blood under enhanced pressure through the kidney vessels, conditions

* *Cf.* SCHÄFER and VINCENT, *op. cit.*

† H. H. DALE, private communication.

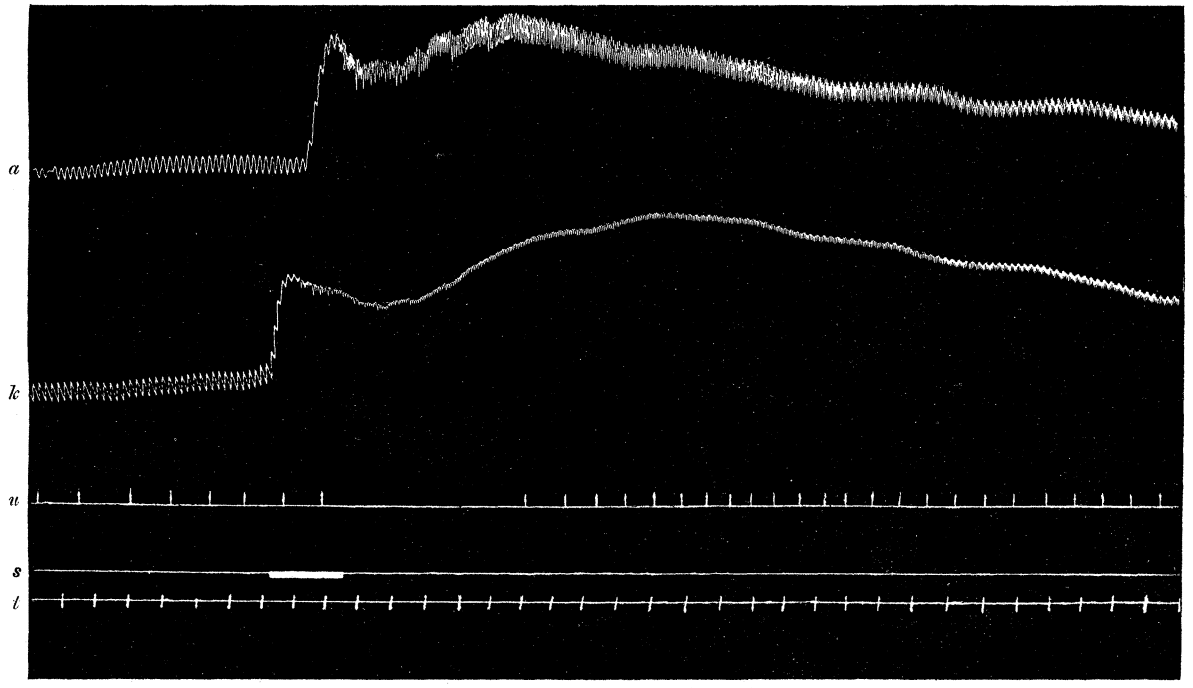

FIG. 3.—Rabbit. Male, weight 2200 grammes, ether, curari, artificial respiration, cannulas in carotid, jugular, and both ureters, kidney in oncometer. Effect of a "first" injection of 1 c.c. of a 10-per-cent. aqueous extract of infundibular pituitary. (Reduced to $\frac{2}{3}$rds.)

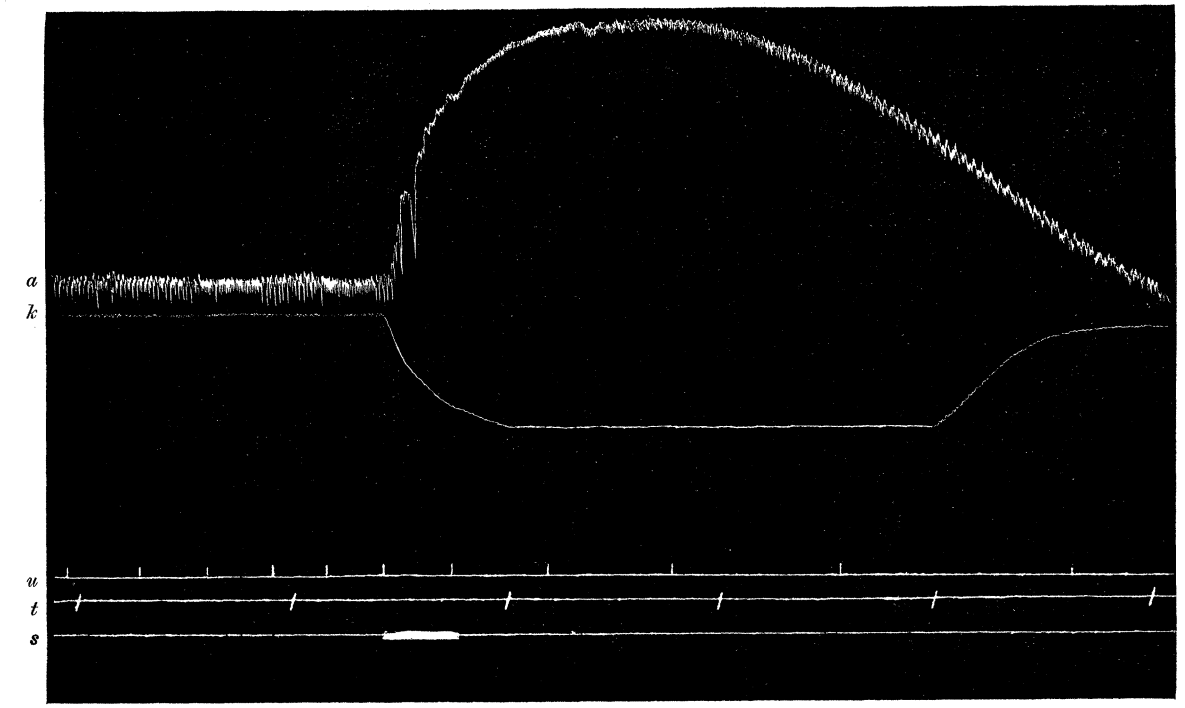

FIG. 4.—Cat. Female, weight 2500 grammes, chloroform + alcohol, artificial respiration. *a*, blood-pressure; *k*, kidney volume; *u*, urine flow; *t*, time in one-minute intervals; *s*, signal. Effect of intravenous injection of 0·0002 gramme hemisine dissolved in 4 c.c. RINGER'S solution. (Reduced to $\frac{2}{3}$rds.)

which are known to favour or even to produce diuresis. But although this may partly account for the diuresis which follows the first dose of the extract, it cannot be the sole cause; for with repeated doses which occasion not a general rise, but a fall of blood-pressure, due to general arterial dilatation, the diuretic effect is still very marked (fig. 5), although usually somewhat less than with the first injection. The immunity to a second dose which is characteristic of the pressor and cardio-inhibitory effects does not therefore extend to the effect upon the kidney, which seems to indicate that this is due to a different chemical substance.

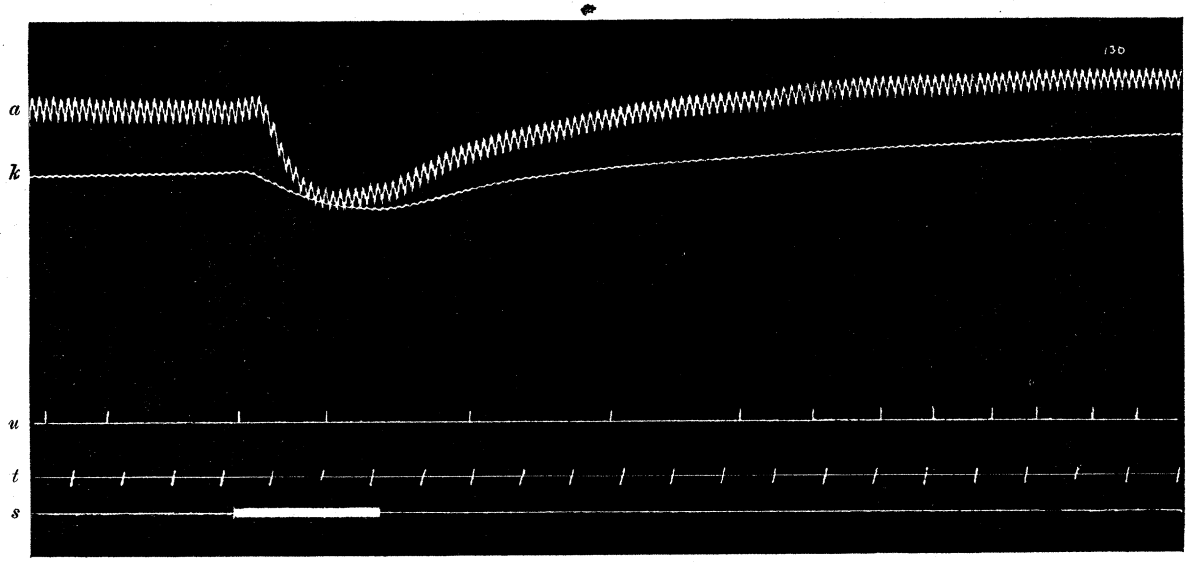

FIG. 5.—Cat. Male, 2700 grammes, atropine sulphate, ether, artificial respiration. Effect of a "repeat" dose of 4 c.c. of a 1-per-cent. aqueous extract of infundibular pituitary. (Reduced to $\frac{2}{3}$rds.)

Moreover, even with the first injection the diuresis continues long after the blood-pressure has returned to the level from which it originally started, and even after it has ultimately fallen, as is often the case, below the original level; in other words, the diuretic effect is prolonged long after the general vascular effect has passed off. The vascular effects, and the effects upon urine secretion of two successive injections of 2 c.c. of 1-per-cent. extract of posterior lobe are exhibited in the accompanying tracing from the cat (figs. 6 and 7); the interval between the two injections was 15 minutes. In the tracings shown in figs. 8, 9, and 10, the dose was only 1 c.c. and the interval between the first and second doses was 40 minutes. The diuresis is increased by the second dose, although there is no appreciable rise of blood-pressure.

The dilatation of the kidney vessels is shown by the expansion of that organ within the oncometer. Although coming on gradually, it often proceeds to such an extent as to far exceed the limits of excursion of the piston recorder (fig. 11). And although after a time there is a tendency for the kidney to regain its original volume, it often falls considerably short of this, showing that there has been an accumulation of lymph

within the organ. It may be that the exit of lymph by the efferent lymphatics is partly interfered with by the mechanical conditions associated with the inclusion of the kidney in the oncometer.

The diuretic effects are most constant in the cat, in which animal the operative manipulations are all easy, and it is usual to obtain a steady flow of urine; moreover, the period of latency between the injection of the extract and the responsive flow of urine is as a rule short. Out of numerous (more than 40) experiments upon

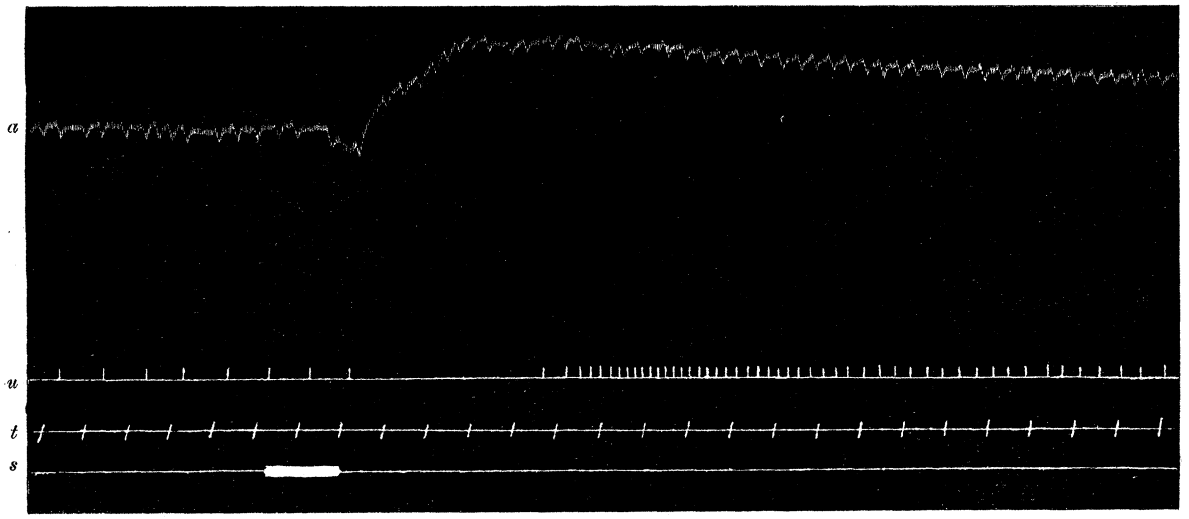

FIG. 6.—Cat. Female, 2100 grammes, atropine sulphate, ether, urine from bladder, lettered as before, kidney volume not recorded. Effect of intravenous injection of 2 c.c. of a 1-per-cent. aqueous extract of infundibular pituitary. In this animal 4 c.c. of the same solution had been injected into the stomach about half an hour previously, but produced no appreciable effect. (Reduced to $\frac{2}{3}$rds.)

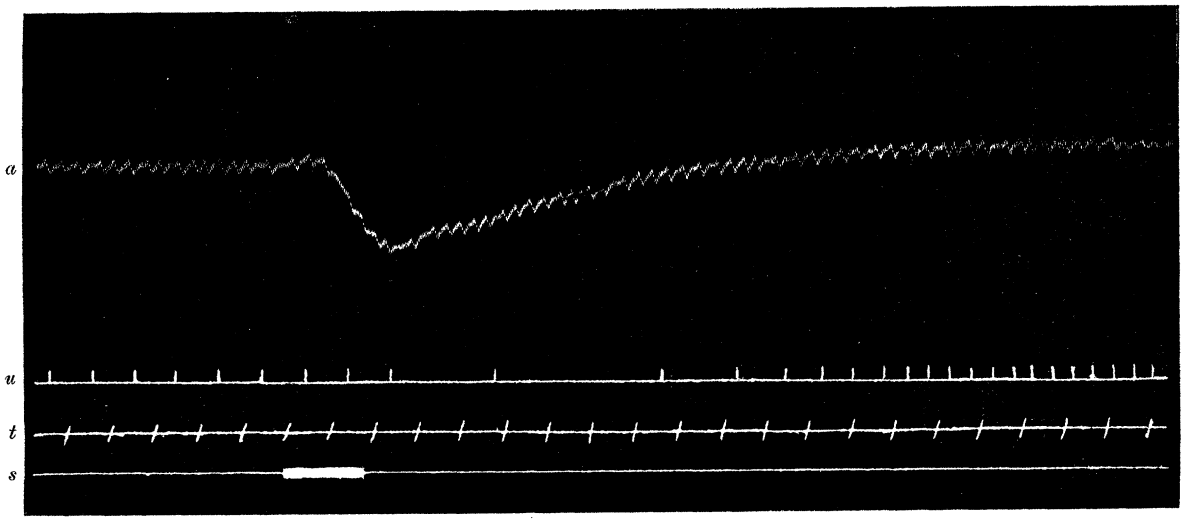

FIG. 7.—Tracing from the same animal as that shown in fig. 6, showing the effect of a second dose of 2 c.c. of a 1-per-cent. aqueous extract of infundibular pituitary administered 15 minutes after the first. (Reduced to $\frac{2}{3}$rds.)

cats in which the natural urine flow was satisfactory, we never failed to obtain the diuretic effect. In all cases, second and subsequent injections, although generally causing a fall of blood-pressure, were followed by an accelerated flow of urine, often preceded, as with the first injections, by a temporary diminution of flow (figs. 7 and 12). The kidney almost invariably shows an increase of volume with both first and

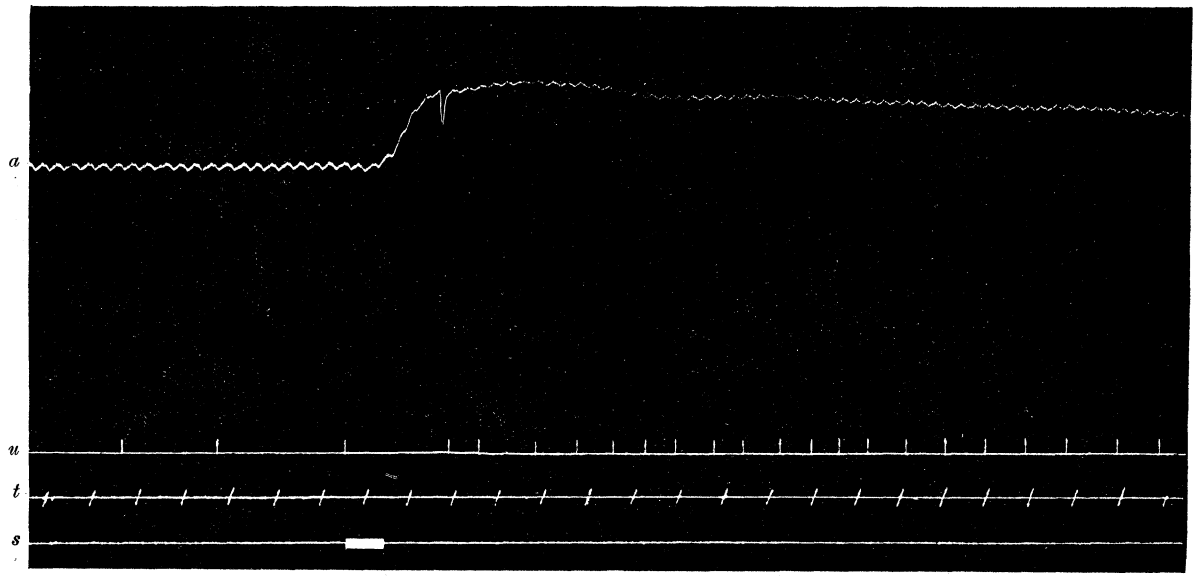

FIG. 8.—Cat. Female, 2100 grammes, atropine sulphate, ether, urine from bladder, no oncometer. Effect of injecting 1 c.c. of a 1-per-cent. aqueous extract of infundibular pituitary into jugular vein (4 c.c. had been injected into the stomach about 15 minutes previously, but without producing any appreciable effect). Notice the rise of blood-pressure, without preliminary fall, and the marked increase of rate of urine flow, without preliminary arrest, and commencing about 20 seconds after the injection. (Reduced to $\frac{2}{3}$rds.)

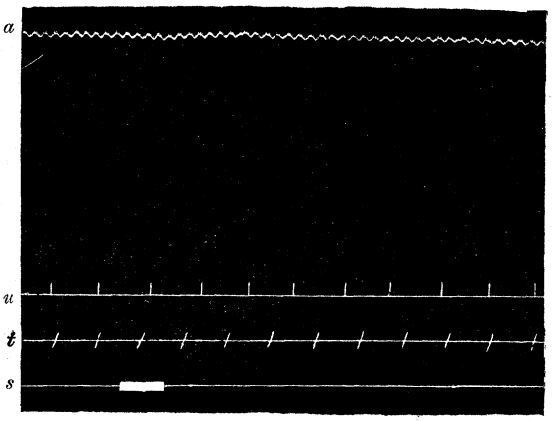

FIG. 9.—Part of the same tracing as that shown in fig. 8, taken 35 minutes later. The rate of flow of urine is still rapid, although the blood-pressure has fallen to below the original level. At the point marked by the signal 1 c.c. of RINGER'S solution was injected into the jugular vein. This had no appreciable effect on the rate of flow of urine, and scarcely any on the blood-pressure. (Reduced to $\frac{2}{3}$rds.)

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subsequent injections, but this is often preceded by a temporary decrease (figs. 2, 5, 11, 12 from cat; fig. 16 from dog). When the fall in blood-pressure produced by the

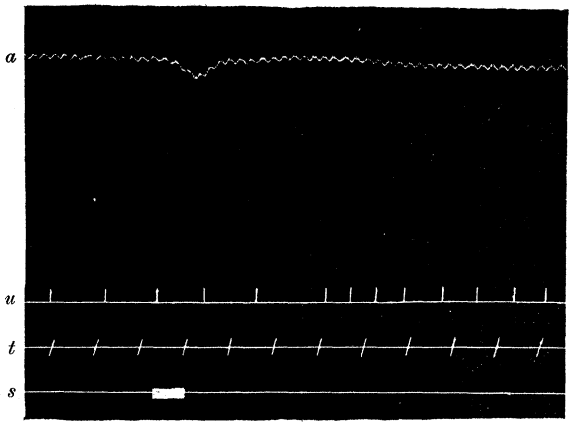

FIG. 10.—Part of the same tracing five minutes later. At the point marked by the signal a repeat dose of 1 c.c. of the same 1-per-cent. aqueous extract was injected into the jugular vein. Notice the slight fall of blood-pressure caused by the injection and the marked increased rate of urine flow, commencing after a latency period of about half a minute, the blood-pressure being considerably lower than it was prior to the first injection. (Reduced to $\frac{2}{3}$rds.)

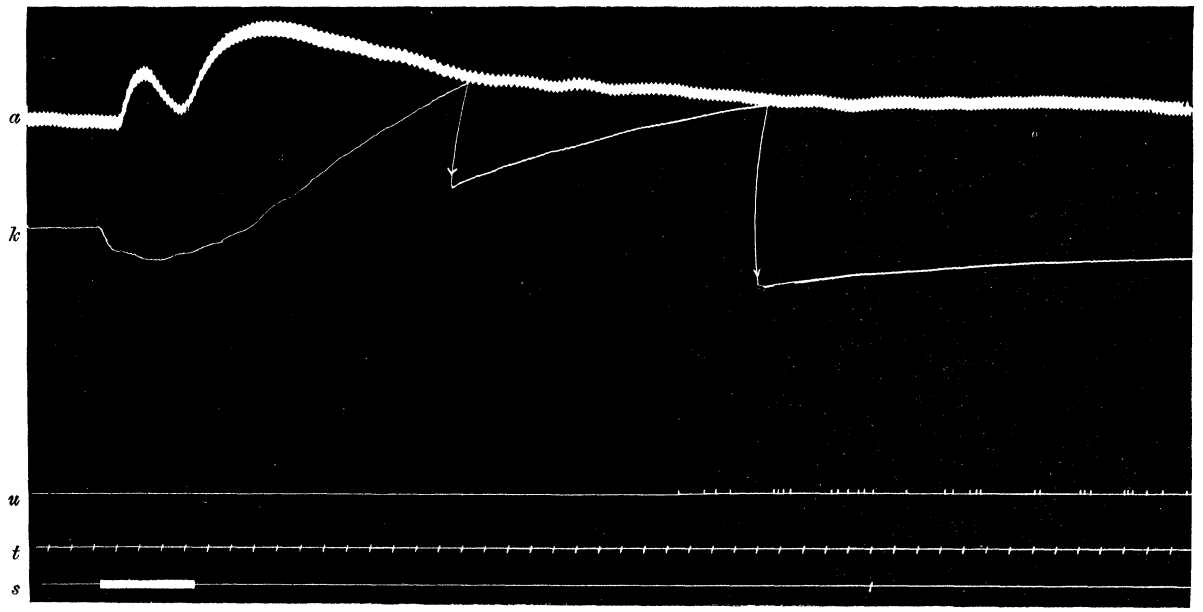

FIG. 11.—Cat. Female, 3000 grammes, atropine sulphate, ether, urine from bladder. Effect of intravenous injection of 4 c.c. of a 1-per-cent. aqueous extract of dried infundibular pituitary. (This had been previously exhausted by absolute alcohol.) No urine was being secreted before the injection, but a free flow began about $4\frac{1}{2}$ minutes after. Notice the preliminary shrinkage of the kidney, followed by enormous dilatation. The arrows indicate artificial lowering of the oncograph lever, which was rising above its recording limit. The last part of the oncograph tracing therefore represents a far greater expansion than the level of the tracing would appear to indicate. (Reduced to $\frac{2}{3}$rds.)

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"repeat" dose is well marked, the temporary decrease in volume is also very distinct (fig. 5); here the effect is probably mainly a passive one. It is always followed by expansion. It is possible that this also is in part passive, the kidney vessels not participating in the contraction of the arterial system in general. But as a rule the curve of kidney volume does not run exactly parallel with that of blood-pressure, and especially it continues to rise long after the blood-pressure has begun to fall. If only a very small dose is given in the first instance, *e.g.*, 1 c.c. of a 1-per-cent. extract, the second dose may show not a fall of blood-pressure, but a rise; less, however, than that caused by the first dose. Nevertheless, the diuresis may be quite as well or even

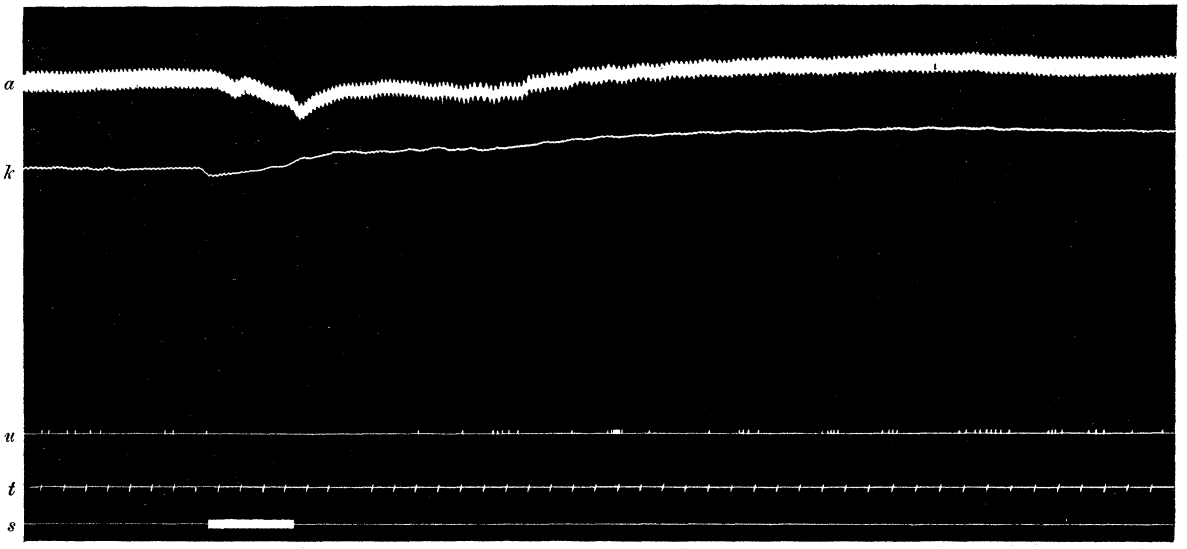

FIG. 12.—Effect of second injection of 4 c.c. of the same 1-per-cent. extract of infundibular pituitary, administered half an hour after the first dose. The kidney being still greatly expanded, the effect of the second dose upon this is less marked than usual. There is a slight fall in blood-pressure, followed by a slight but prolonged rise, and a marked increase in the rate of flow of urine, the drops of which are in this animal delivered in groups, corresponding probably to rhythmic contraction of the ureters. (Reduced to $\frac{2}{3}$rds.)

better marked. This is exemplified in figs. 13 and 14 which represent the effects in a cat of two successive doses of 1 c.c., with an interval of nine minutes between the two doses.

A prolonged injection of 50 c.c. of a very weak aqueous extract (1 in 10,000 Ringer) was found (one experiment in the cat) to cause a gradual rise of blood-pressure (from 74–106 mm. Hg) with expansion of kidney and increased flow of urine, all which phenomena were maintained at a high level during the duration of the inflow, which lasted for several minutes, and continued for a considerable time after the injection had ceased. No doubt these effects were partly due to the salt solution, but it was previously ascertained that 10 c.c. of the 1 in 10,000 extract also had a marked effect, far more than the same quantity

of ordinary Ringer solution; *e.g.*, raising the blood-pressure from 78–92 mm. Hg, although the injection was spread over $1\frac{1}{2}$ minutes, and there must consequently have been a very free dilution with blood.

The source of the pituitary extract appears to be immaterial. Fig. 15 shows the effect of injecting 4 c.c. of a 2-per-cent. solution of the whole pituitary gland* of a cod fish. It is obvious that the effects upon kidney, blood-pressure, and urine flow are similar to those of injecting extract of ox pituitary. The diuretic action,

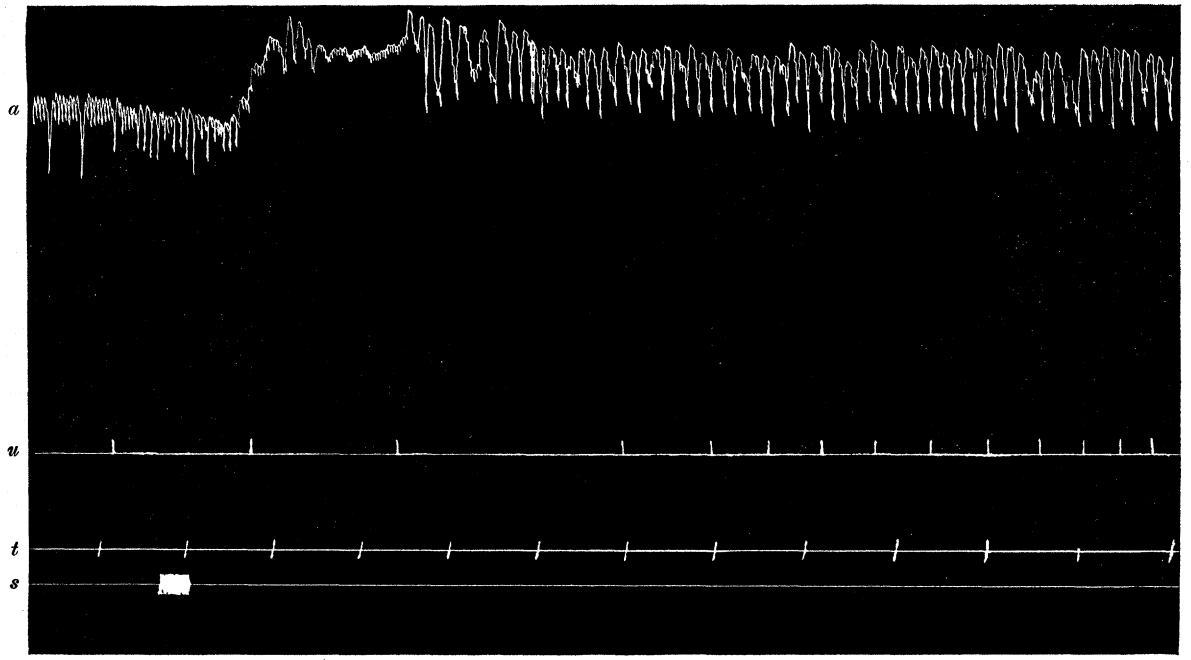

FIG. 13.—Cat. Female, 3800 grammes, chloroform, no atropine, urine from bladder, no oncometer. Effect of a first injection of 1 c.c. of a 1-per-cent. aqueous extract of infundibular pituitary. Notice the rise of blood-pressure with, at first, an increase of pulse-rate, but subsequently a diminution; also the increased rate of urine flow, commencing 50 seconds after the injection and preceded by a diminished rate. (Reduced to $\frac{2}{3}$rds.)

therefore, as well as the vascular effects, are probably produced by extracts of the pituitary glands of vertebrata generally.

The effects in the dog, although often very well marked, are not as constant as in the cat. Out of 19 experiments in which the urine flow was recorded, 12 gave an increase as the effect of the first injection; in the remaining 7 cases the first injection was followed by diminution of flow. On the other hand, in 14 out of the 19, the subsequent injections produced an increase, and in only 5 was the opposite result obtained.

* The material used was probably in the main the hypophysial part, so that, viewed as an extract of the active or neural part of the gland, the percentage is doubtless far less than 2 per cent.; hence the relatively small effect on blood-pressure. Nevertheless the effects on the kidney and urine are very distinct.

As in the cat, the diuresis is, with few exceptions, preceded by temporary diminution or arrest of flow, lasting in some instances for several minutes. The flow when once started is generally very rapid and persists long after the vascular effects of the injection have disappeared. As with other animals, the flow of urine, which may have been suppressed by the anæsthetic and operative proceedings, is often started freely by the first dose of pituitary extract. This is well shown in fig. 16, which represents a typical result in the dog.

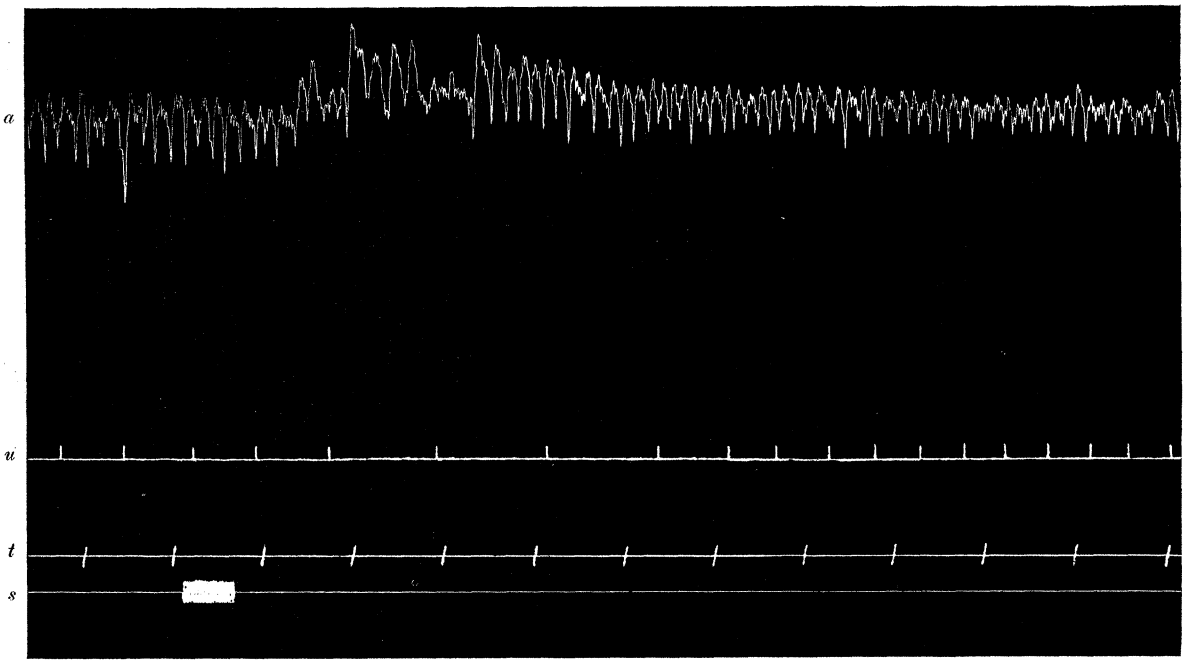

FIG. 14.—Part of the continuation of the same tracing as is shown in the previous figure. The signal marks the administration of a second dose of the same aqueous extract nine minutes after the first dose. Notice the relatively small additional rise of blood-pressure and the marked increase in rate of flow of urine, coming on, in this instance, one minute after the injection and preceded by a period of diminished rate. (Reduced to $\frac{2}{3}$rds.)

The effects upon kidney volume in 13 recorded cases in dogs were as follows :—

Result of first injections ... Increase in 9 cases (preceded in most by a slight contraction). Decrease in 4 cases.

Result of second injections ... Increase in 11 cases (preceded by slight contraction). Decrease in 2 cases.

Although the results are more variable in the dog than in the cat, especially as regards first injections, nevertheless, when the diuretic effect is produced, it is often of a very striking character, the urine almost pouring from the cannula. And this result may be obtained with a very small dose of the extract, as was the case with the tracing shown in fig. 16.

In the rabbit the diuresis and increase of kidney volume produced by a first

injection of pituitary extract (see fig. 3) are nearly as constant as in the cat, but the effects of second injections are less constant.

The effects upon urine flow in 19 experiments on rabbits were as follows :—

Result of first injections ... Increase in 16 cases. Decrease in 2 cases. No effect in 1 case.

Result of second injections ... Increase in 7 cases. Decrease in 5 cases. (No second dose given in the remaining 7 cases.)

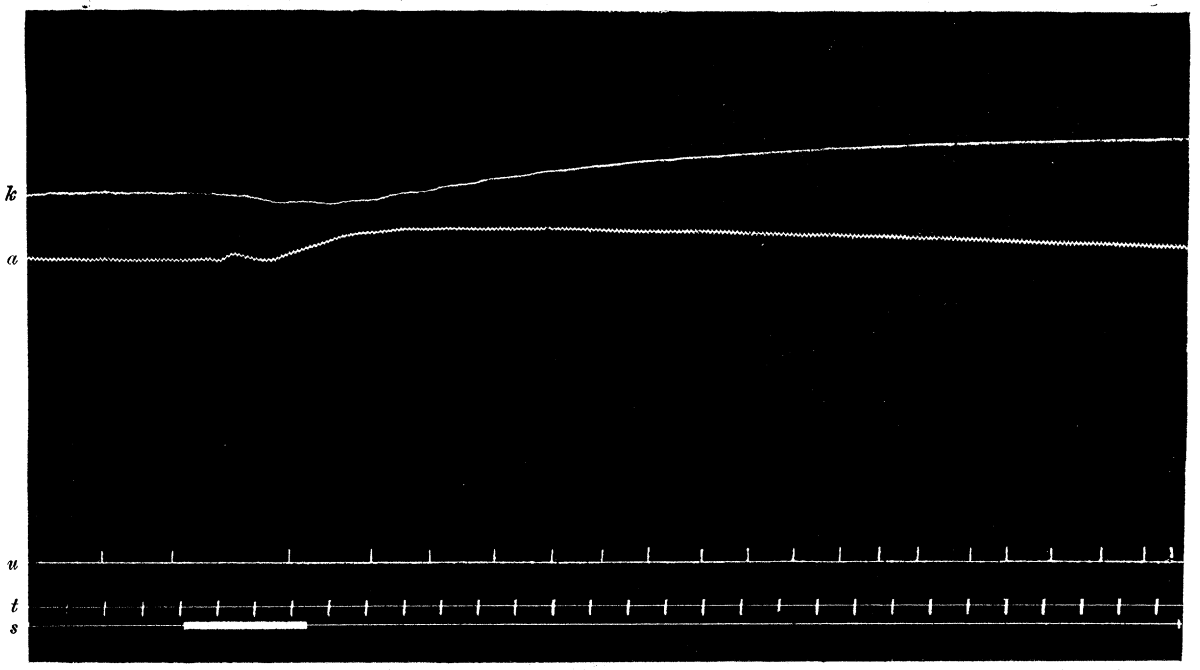

FIG. 15.—Cat. Female, 1750 grammes, chloroform + alcohol, no atropine, urine from bladder, left kidney in oncometer. Effect of injecting 4 c.c. of a 2-per-cent. boiled aqueous extract of fresh (not dried) cod's pituitary into jugular vein. Notice the gradual but distinct rise of blood-pressure and subsequent fall to normal; the shrinkage and subsequent expansion of the kidney, and the increased rate of flow of urine, commencing 50 seconds after the beginning of the injection and preceded by a diminished flow. (Reduced to $\frac{2}{3}$rds.)

The effects upon kidney volume in 19* recorded cases (rabbit) are as follows :—

Result of first injections ... Increase in 14 cases (generally preceded by slight decrease). Decrease in 5 cases.

Result of second injections ... Increase in 3 cases. Decrease in 4 cases. (No second dose given in the remaining cases.)

* Although the number is the same as that of the recorded cases of urine flow, some of these refer to different experiments and the correspondence is accidental. For in some experiments the kidney was not placed in an oncometer, and the flow of urine only was recorded, whilst in others in which the kidney volume was recorded no urine at all was secreted (either naturally or as the result of the extracts) throughout the experiment, so that only the effects of blood-pressure and kidney volume could be investigated.

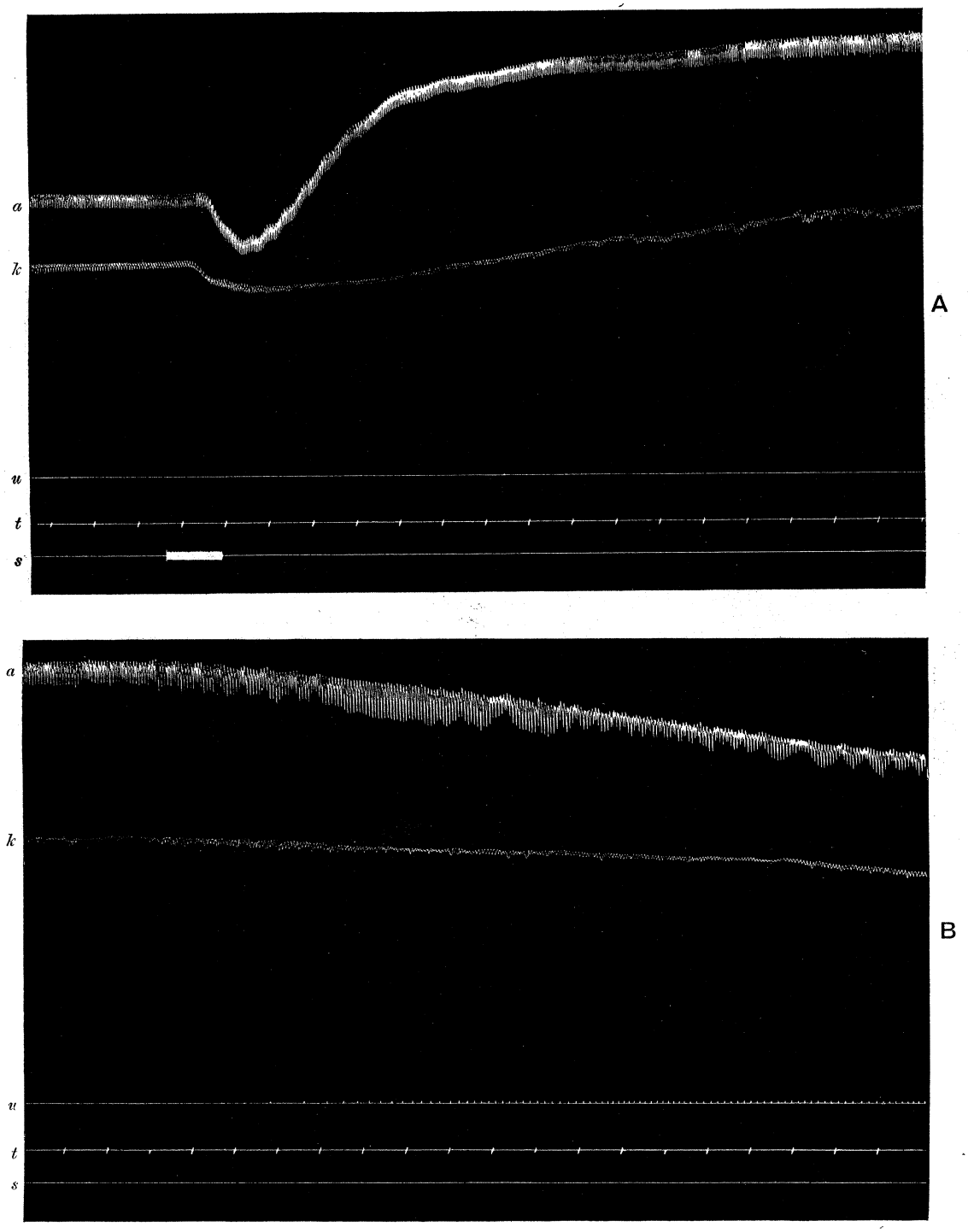

FIG. 16.—Dog. Female, 7500 grammes, atropine sulphate, ether, left kidney in oncometer, urine from bladder. Effect of injecting into the saphenous vein 2 c.c. of an aqueous extract of infundibular pituitary of ox, made by boiling one part of the fresh glandular substance with 100 parts of RINGER'S solution. The tracing is a continuous one; for exigencies of space it is cut into two parts, A and B. Notice the preliminary fall of blood-pressure, followed by a rapid rise (from 125 mm. to 175 mm., and then a gradual ascent to 220 mm. Hg), the preliminary shrinkage of the kidney, followed by prolonged expansion, and the very rapid flow of urine, commencing $3\frac{1}{2}$ minutes after the injection of the extract. In this animal no urine was being secreted prior to the administration of the extract. (Reduced to $\frac{2}{3}$rds.)

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One of the most interesting facts in connection with the action of pituitary extract is the prolonged period of latency which sometimes—especially in the dog and rabbit, less often in the cat—intervenes between the intravenous injection and the effect upon the secretion of urine. This is most marked where there has previously been a suppression of urine, in which case several minutes may elapse before the effect on the urine shows itself, although the effects upon blood-pressure and kidney volume are at once manifested. Figs. 17, 18, and 19 show such a result, but with blood-pressure and urine flow alone registered. The kidneys and ureters were left untouched in this instance and the urine was collected by a drainage tube tied into

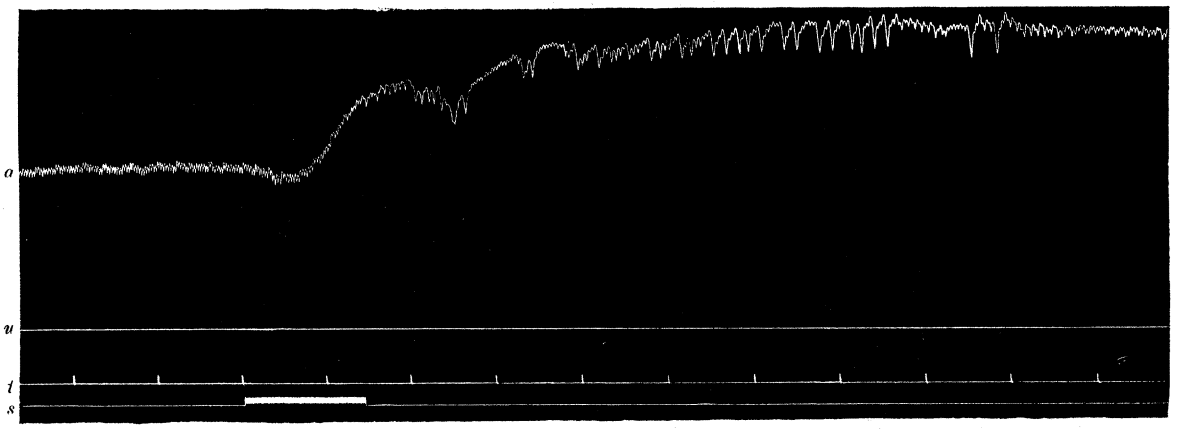

FIG. 17.—Rabbit. 2300 grammes, ether, no atropine, urine tube in bladder, no oncometer. The signal marks the time of injection of 4 c.c. boiled 1-per-cent. aqueous extract of infundibular pituitary into the jugular vein. Notice the slight preliminary fall, followed by a rapid rise of blood-pressure; the pulse-rate at first more rapid, but afterwards slower from cardiac inhibition. No urine was being secreted prior to the administration of the extract, but a free flow was started seven minutes after (see next tracing). (Reduced to $\frac{2}{3}$rds.)

the bladder. At the place marked by the signal in fig. 17, 4 c.c. of a 1-per-cent. aqueous extract of infundibular lobe was injected into the jugular vein. This at once caused the characteristic rise of blood-pressure and cardiac inhibition shown. The pressure remained at a high level for some minutes and then gradually fell to the level shown in fig. 18, which is a part of the same tracing, taken seven minutes after the injection, and just at the time when the flow of urine commenced. The tracing shown in fig. 19 was taken three minutes after the last one, a second dose of 4 c.c. having been administered in the interval. The rate of flow of urine—about 1 drop per second—is extremely fast, especially for the rabbit, and the kidney secretion was doubtless for the time at its maximum; subsequent injection of caffeine produced no increase. Fig. 16 shows a long latency in the dog, here the interval between the injection and the first appearance of the secretion was about three and a-half minutes.

We do not find the diuretic effect of intravenous injections of pituitary extract to be proportionate to the amount given. The difficulty of carrying out quantitative

experiments is extreme, but the general impression we have formed is that, within certain limits, we often obtain a more marked result from a small dose than from a large one. This may very well be due to the circumstance that larger doses have

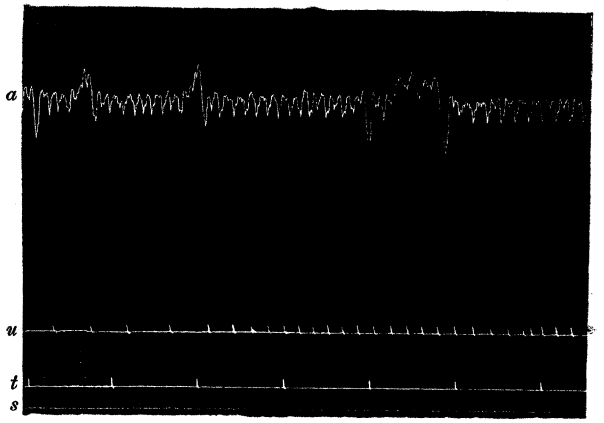

FIG. 18.—Continuation of the tracing shown in the last figure, taken seven minutes after the injection, and showing the commencing rapid secretion of urine. (Reduced to $\frac{2}{3}$rds.)

a greater tendency than small doses to involve the kidney vessels in the general vascular constriction. And the differences which we have observed in the dog and rabbit, as compared with the cat, may be connected with the relative excitability of their renal vessels when exposed to the action of the extract. Thus the

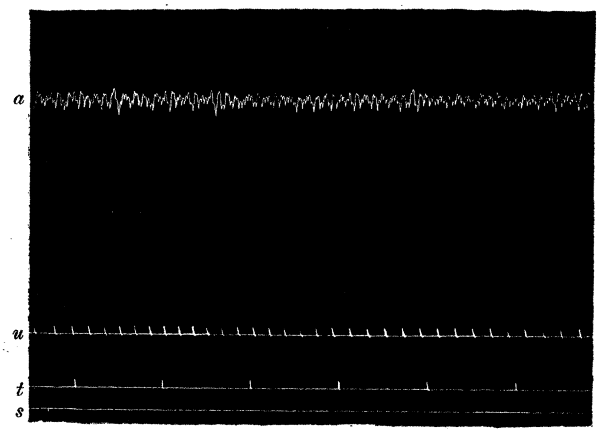

FIG. 19.—Continuation of the tracings shown in figs. 17 and 18, taken three minutes after that shown in the last figure. In the interval a second dose of 4 c.c. of the same extract had been given. This caused the slight rise in the average blood-pressure shown, but little if any acceleration of urine, which was already flowing at a very fast rate. (A subsequent dose of caffeine citrate also caused no further acceleration.) (Reduced to $\frac{2}{3}$rds.)

extraordinarily well-marked effect which is shown in the tracing reproduced in fig. 16 was obtained in a dog weighing 7500 grammes by a dose of only 2 c.c. of a 1-per-cent. extract made from the fresh pituitary. Assuming that in the process

of drying this loses two-thirds of its weight, the amount of extract used would represent only two-thirds of a cubic centimetre of the 1-per-cent. extract of the dried gland which we have usually employed. The same thing is illustrated in other tracings (figs. 8, 10, 13, 14), which all show a marked result of small doses. On the other hand, where we have obtained a diminution of urine, as has sometimes been the case in dogs and rabbits, we have generally used larger doses (4 c.c. of a 1-per-cent. extract of the dried gland). In these animals, also, even if the extract produces diuresis with the first two or three doses, a frequently-repeated administration is apt eventually to produce decrease or arrest of urine. On the other hand, in the cat this condition is much more difficult to produce, each successive dose being responded to by an increase of rate of flow, even when a considerable number are given at intervals of a few minutes (fig. 5). The fact that within certain limits the kidneys are more responsive to a small than to a large dose of the extract is in consonance with the view that the pituitary produces a secretion which is discharged into the blood and subserves a diuretic function. For, with so small a gland, it is impossible to suppose that a large amount of secretion could be produced, and a constant small production would appear from our results to be more effective in this respect than the introduction into the blood of a larger proportion of the active material.

Effects of Injecting Pituitary Extract Hypodermically.

We have made four experiments (on cats) to determine whether the physiological and especially the diuretic effects of the extract could be obtained by hypodermic injection. In each case we injected 4 c.c. of the 1-per-cent. aqueous extract under the skin of the chest or hind limb, usually distributing the injection over more than one region. In one case only were all the ordinary effects apparent. These showed themselves 53 minutes after the injection in the form of a gradual expansion of the kidney, accompanied by a slight rise of blood-pressure and with at first a temporary decrease of urine, followed by marked increase of rate of flow (three times the original rate). These effects lasted some minutes and gradually passed off. In one other case there was an expansion of the kidney with slight increase of urine (one-third faster), but the blood-pressure at the time was not recording, in consequence of the formation of a clot in the artery cannula. These effects began about 25 minutes after the injection. In a third experiment there appeared a rise of blood-pressure, accompanied by kidney expansion, soon after the injection, but no urine was flowing during this experiment, and since the effect was so soon manifested, it is possible that some of the injection passed at once into a vein. In the fourth case no effect was observable as the result of the hypodermic injection. But that some physiological effect had been produced was evidenced by the result of an intravenous injection an hour and a-half after the hypodermic. This caused, not the rise of pressure

characteristic of a first injection, but the fall characteristic of a second injection, so that, at any rate, the substance producing immunity (see p. 7) had been absorbed.*

Effects of Injecting the Extract into the Stomach, and of Subjecting it to Peptic and Tryptic Digestion.

In ten instances (cat) we injected the extract into the stomach in doses of from 2 c.c. to 20 c.c. of the 1-per-cent. aqueous solution. In four cases there was food in the stomach at the time; in the remaining six the stomach was empty, the animal having fasted 24 hours. In none of these ten experiments was any very definite physiological effect observed, although one or two showed a slight rise of blood-pressure (30 or 40 mm. Hg) and expansion of kidney and slight increase of urine. In all a subsequent intravenous administration produced the usual results of a first injection, but in some it was modified by a preliminary fall of blood-pressure more marked than usual (fig. 20). Apparently, therefore, there is little, if any, absorption of the active substances, but some absorption of the immunity conferring material from the stomach. These results are not due to destruction of the active matters by gastric juice, for the extract can be digested with artificial gastric juice for 24 hours without losing its diuretic activity when neutralised and injected into a vein. But the effect on blood-pressure is somewhat modified by such digestion, the rise of pressure produced no longer exhibiting the prolonged character which is characteristic of a first injection, and the preliminary fall being more marked than usual (fig. 21).

We have also determined that digestion with trypsin during 18 hours does not destroy the active principles, having obtained (in the cat) the usual effects on the blood-pressure, kidney volume and urine by intravenous injection of the neutralised digest. In the case of one such digest the result (on two cats) was complicated by an extraordinary fall of blood-pressure, the diuretic effect being deferred for two minutes. The result may have been due to the presence of products of digestion of proteid substances in the fluid, or possibly to some accidental contamination; it was only yielded by this sample.

Effects of Oxidating and Reducing Agents.

In four instances (cats) we employed a 1-per-cent. aqueous extract, to which half its bulk of a solution of hydrogen peroxide had been added. After the mixture had been well shaken up it was allowed to stand for a few minutes at the room

* A similar result was obtained by testing Case 3 with intravenous injection one hour after the hypodermic. Cases 1 and 2, which were tested by intravenous injection one hour and ten minutes after the hypodermic, both gave, besides the usual effect of a first injection, a marked preliminary fall preceding the rise of blood-pressure, and a marked preliminary contraction preceding the prolonged expansion of kidney, followed by the usual diuresis. It is probable that in these two cases the immunity had partly passed off.

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temperature, and then evaporated down to its original bulk by boiling. Intravenous injection of this solution produced in the first case a slight fall of blood-pressure with expansion of kidney and marked increase of urine; in the second case a slight rise of blood-pressure with contraction of the intestine and increase of urine (kidney volume not recorded); in the third case a fall, followed by a slight rise of blood-pressure with expansion of kidney and increase of urine; and in the fourth case also a slight rise of blood-pressure with expansion of kidney (but no urine was secreted during the whole course of this experiment).* In all cases, therefore, there was

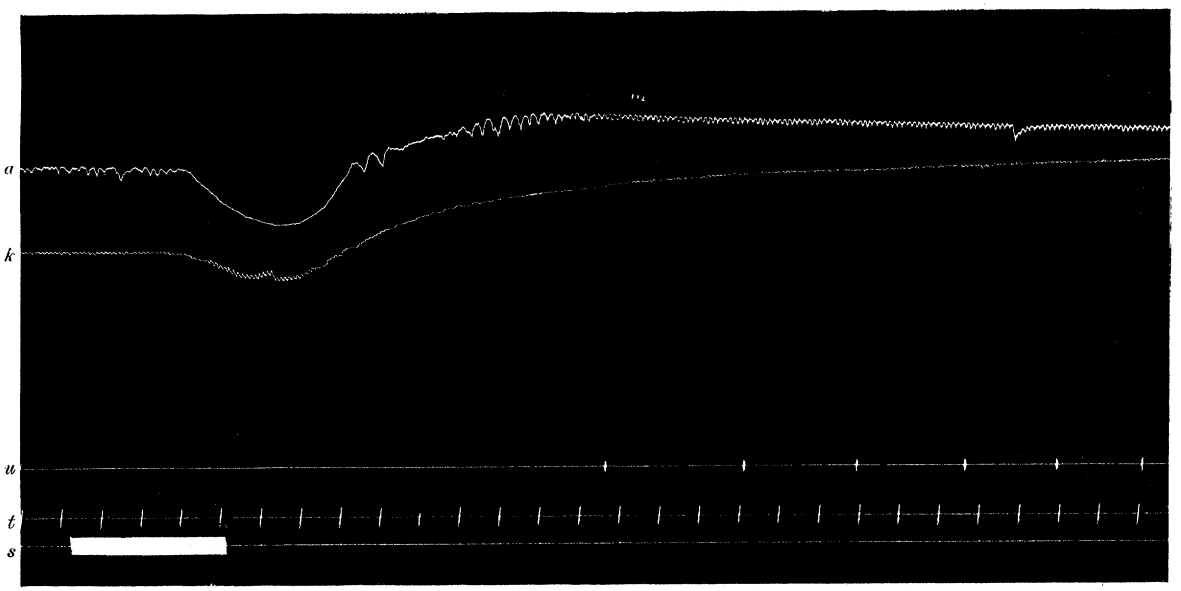

FIG. 20.—Cat. Male, 2800 grammes, no atropine, chloroform + alcohol, left kidney in oncometer, urine from bladder. The animal had fasted 24 hours, and 1¼ hour before had received an injection of 20 c.c. of a 1-per-cent. boiled aqueous extract of infundibular pituitary into the stomach. This produced very little effect: a slight rise of blood-pressure and slight dilatation of kidney, but caused no flow of urine. The signal marks the injection of 4 c.c. of the same extract into the jugular vein. Notice the marked preliminary fall of blood-pressure, followed by prolonged rise; the preliminary shrinkage of the kidney, followed by prolonged expansion. After a latency of about two minutes a flow of urine commenced and was continued for a long time without further intermission. (Reduced to ⅔rds.)

expansion of kidney, and in three increase of urine—in one case out of the four, with a fall of blood-pressure, and in the remaining three cases, with only a *slight* rise (in one preceded by a fall). It would, therefore, appear that treatment with hydrogen peroxide tends to destroy the blood-pressure raising constituent of the extract without affecting that which acts upon the kidney. This furnishes further evidence of the independence of the substance which stimulates renal activity from that which produces rise of general arterial pressure.

On the other hand, reducing agents appear to have no influence upon any of the

* The blood-pressure in this animal was very low throughout (about 50 mm. Hg).

active constituents of the extract. In two instances (cat) we obtained marked results of the usual character, *i.e.*, rise of blood-pressure, dilatation of kidney vessels, increased flow of urine, as the result of first injections, temporary fall of blood-

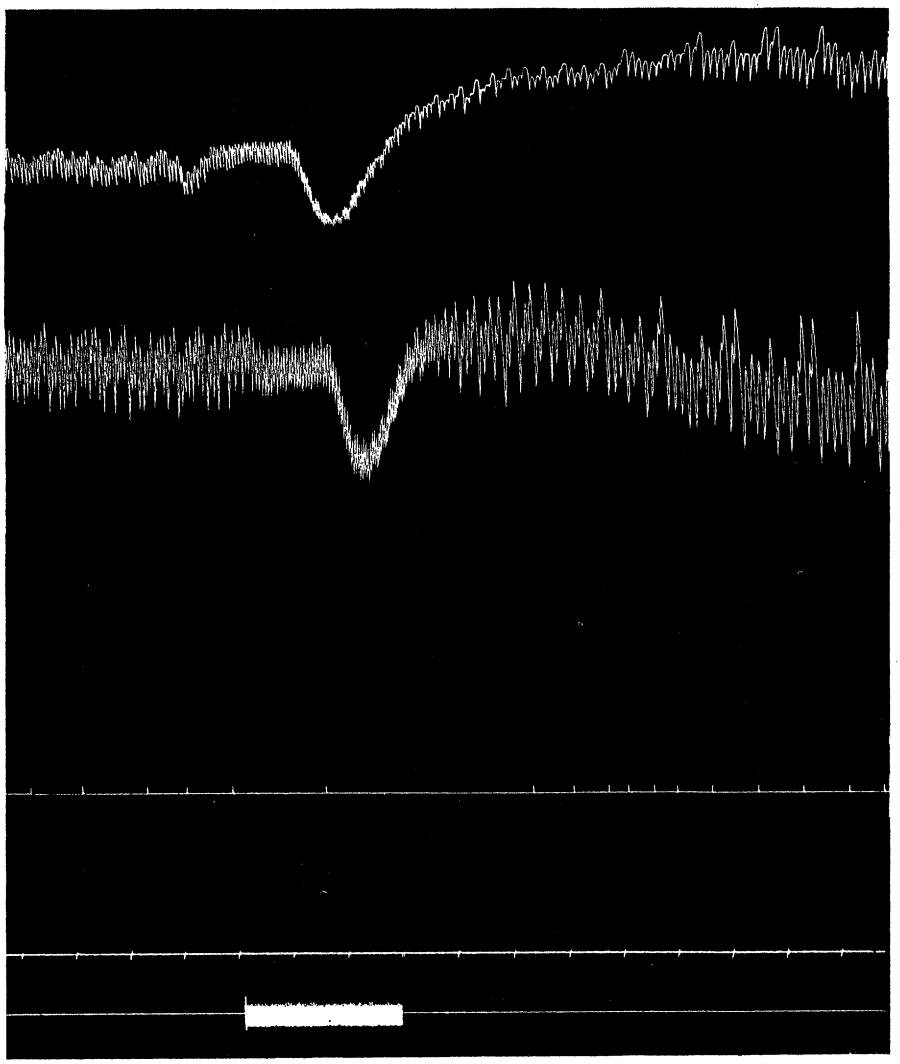

FIG. 21.—Dog. Male, 16,000 grammes, anæsthetised by intravenous injection of laudanum diluted with Ringer. At the place marked by the signal 4 c.c. of a 3-per-cent. extract of infundibular pituitary, which had been digested for three hours with pepsin and hydrochloric acid, and had subsequently been neutralised, was injected into the saphenous vein. Notice the fall of blood-pressure with, at first, increase of rate of heart, followed by decrease; the decrease in kidney volume, followed by steady increase, and the increase in rate of urine flow after a preliminary decrease. (Natural size.)

pressure, dilatation of kidney vessels, and increased flow of urine as the result of second injections of 1-per-cent. aqueous extract which had been subjected to such agencies. In the one case the treatment adopted was to add ammonium sulphide, allow to stand a few minutes, evaporate to dryness on the water bath, and extract the residue with water. In the second case the reducing agent used was zinc

+ hydrochloric acid, the latter being added to the extract in the proportion of 1 per cent.*

Effects of Pituitary Extract upon other Secreting Glands.

We have not noticed that extracts of the pituitary body provoke other glands besides the kidney to secretion. So far as graphic representations are concerned our observations have been confined to the pancreas. Thus in a dog in which the intravenous injection of 4 c.c. of a 1-per-cent. aqueous extract of duodenal mucous membrane of dog which had been treated with dilute hydrochloric acid produced the effect on pancreatic flow which is shown in fig. 22, a similar injection of 4 c.c. of a 1-per-cent. aqueous extract of infundibular lobe caused, along with a large rise in blood-pressure and increased secretion of urine,

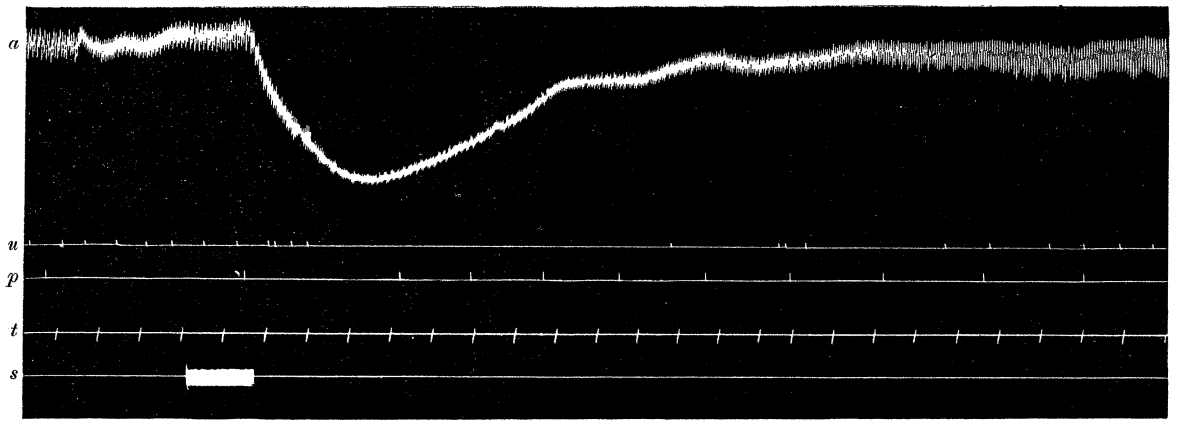

FIG. 22.—Dog. Male, 5450 grammes, morphia acetate ($\frac{1}{2}$ grain), atropine sulphate ($\frac{1}{100}$ grain), cannulas in femoral artery (*a*), in ureter (*u*), in pancreatic duct (*p*), and in saphenous vein. The signal marks the injection of 4 c.c. of neutral saline extract of duodenal mucosa, which had been previously acted on by dilute hydrochloric acid. Notice the great fall of blood-pressure, followed by a gradual rise to, but not above, normal; the diminished flow of urine, followed by a gradual return to normal rate; the greatly increased rate of flow of pancreatic juice. (Reduced to $\frac{2}{3}$rds.)

the diminution in the rate of flow of the pancreatic juice which is exhibited in the tracing shown in fig. 23, a diminution which presently passed into a condition of complete arrest, although the flow was renewed with a further dose of the duodenal extract. On the other hand, the duodenal extract causes, as the same tracing shows, at least temporarily, a diminished flow of urine, an effect which is perhaps correlated with the great fall in blood-pressure which it also produces. We have looked for, but have failed to observe, any increase of sweat secretion in the pads of the cat's foot, nor have we seen an increase of salivary secretion to result from the intravenous

* The mixture was placed in an incubator for some hours. The dissolved zinc was then precipitated by hydrogen sulphide, the solution neutralised with sodium carbonate, filtered, and evaporated down to the original bulk.

injection of pituitary extract. We conclude, therefore, that it acts specifically upon the kidneys and does not directly affect the secretory activity of glands in general.

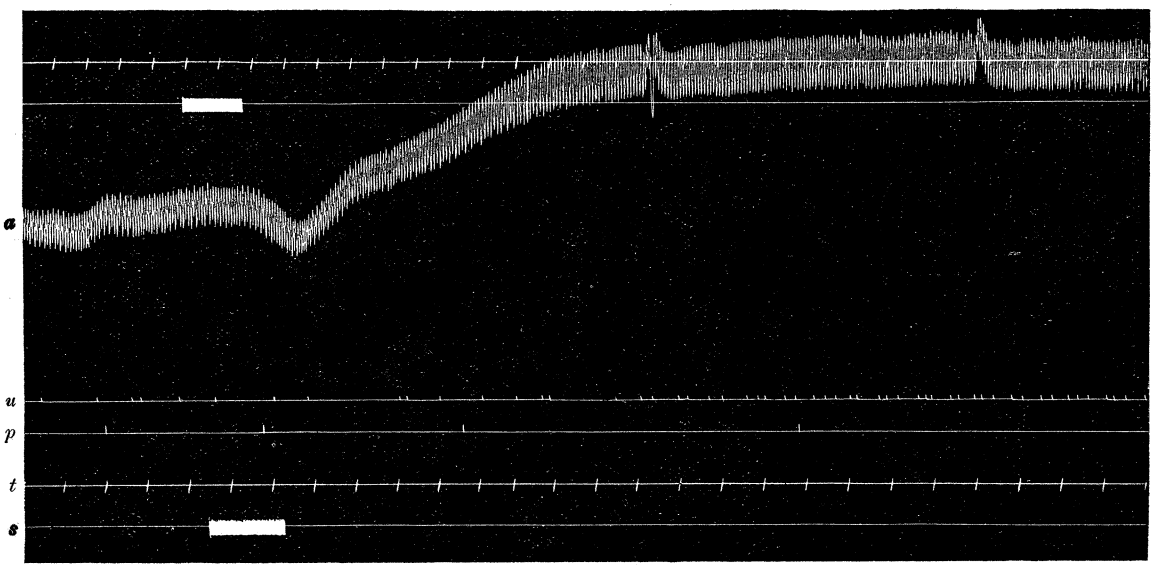

FIG. 23.—Continuation of previous tracing, showing the effect of injecting, 10 minutes later, 4 c.c. of a 1-per-cent. boiled aqueous extract of infundibular pituitary into the saphenous vein at the place marked by the signal. Notice the slight preliminary fall, followed by a great rise of blood-pressure (but without cardiac inhibition), the great increase in rapidity of urine flow, and the diminished rate of flow of pancreatic juice resulting from the injection. (Reduced to $\frac{2}{3}$rds.) The upper time- and signal-lines belong to another tracing.

General Conclusions.

Besides the pressor and depressor constituents of extract of the infundibular part of the pituitary body this organ yields a substance soluble in water and not destroyed by boiling, which acts specifically upon the kidney, producing along with dilatation of the renal vessels an increase of secretion from the tubules, and even causing a flow if the secretion, from the operative procedures or the anæsthetic, happen to be suppressed. The effect obtained from intravenous injection of only 1 c.c. of a 1-per-cent. extract of the dried glandular substance may be as marked as that of such an actively diuretic substance as caffeine citrate. But the one or two grains of caffeine citrate which are required to produce active diuresis represent a vastly greater amount of material than that of the diuretic constituent in 1 c.c. of a 1-per-cent. extract of the gland. The diuretic activity of the substance formed by and contained within the gland must therefore be far greater than that of any diuretic in the pharmacopœia. Assuming that the pituitary is an internally secreting gland, these results render it probable that the main purpose of its secretion is ancillary to the function of the renal organs. The effect of its extract both upon the vascular system generally and upon the renal vascular system in particular is to

produce those conditions which are most favourable to renal activity. And even when these vascular conditions are not fulfilled—for example, when there is a general fall of blood-pressure with no increase, but even a shrinkage of kidney volume—we still obtain a diuretic action, thus indicating a specific stimulation of the renal epithelium.

The circumstance that in a relatively small proportion of experiments, especially in dogs, we fail to obtain diuresis, and the further circumstance that when the diuretic effect is observed it is often preceded by a period during which the secretion is diminished, or temporarily arrested, does not invalidate the view of the function of pituitary secretion which we put forward. For the extracts contain both vaso-constrictor and vasodilator constituents, and it is easy to understand that in some animals the vasoconstrictor may overpower the vasodilator in acting upon the renal vessels; indeed, this is, in many cases, the usual result at the beginning of their joint action. This would naturally lead to a diminished secretion of urine as long as the constriction of renal vessels lasts (as in the case with the constriction and arrest of urine produced by suprarenal extract), and for that period at least the extract would be anti-diuretic rather than diuretic. But the main or diuretic effect is so pronounced that it is hardly possible to regard the preliminary diminution—which occurs in some, but not in all, cases—as of the same physiological importance. We have no right to assume that the internal secretion which is passed by the cells of the gland into the blood is, so far as the relative amounts of the several active constituents are concerned, the same as the extracts we make by boiling the gland substance, and we can conceive that by variations in the delivery of these active constituents the gland may exert a controlling influence upon the renal functions, both by the effects of its secretion upon the vascular system in general, as well as by a direct influence exerted by one of its constituents upon the renal cells and upon the renal circulation in particular.

The parallelism in development, structure and functions between the suprarenal capsules and the pituitary body is, to a certain point, a striking one. Both exist in all vertebrates. Each consists of two parts, of which the one is a highly vascular epithelium, the other of neuro-ectodermic origin. In neither the suprarenal nor the pituitary do extracts from the epithelial, and more obviously glandular portion, produce any physiological effect, whereas the parts of neuro-ectodermic origin yield highly active substances, which in both cases exert a remarkable influence upon the heart and arteries. Here the parallelism ends. Whereas extract of suprarenal medulla has an excitatory influence upon the terminal mechanism of sympathetic fibres in general, this is not the case with that of the pituitary medulla. For although this also excites contraction of arteries and affects the heart (usually, but not always, in the direction of inhibition) it combines with this a specific effect upon the kidneys. The blood-vessels of this organ are influenced by pituitary extract differently from those of the rest of the body, while the renal cells appear to be

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specifically stimulated to secretion. It is not easy to understand, in view of the entire absence of activity in extracts of the epithelium, why so close an anatomical relationship should be found between glandular epithelium and secretory neuro-ectoderm, both in the pituitary and in the suprarenal capsules of most vertebrates, unless the two kinds of tissue possess also some physiological connection. It may, however, be conjectured that in the epithelial part of each organ the material which is to furnish the active agent of the secretion passes through certain stages of formation, and that its production is merely completed in the neuro-ectodermic part, in which part alone the full activity of the secretion is acquired.

Other Views regarding the Functions of the Pituitary Body.

Two other views have been prominent regarding the possible functions of the pituitary. The one supposes that it furnishes an internal secretion analogous to that of the thyroid, and that it may act vicariously for the last-named gland. This opinion has been supported by experiments in animals, in which the thyroid has been removed, and from cases of cachexia thyreopriva in man.* In certain of these cases alterations have been noticed in the epithelial part of the pituitary body, and there have been described in it the development of cysts or vesicles occupied by fluid, which is said to resemble the "colloid" of the thyroid vesicles. But, in view of the fact that such cyst-like cavities occur normally in the pituitary, and further that many other organs besides the pituitary undergo alterations in character after thyroidectomy, one would hesitate to accept this evidence as sufficient to support the theory. In any case, whether true or not, the function which this view ascribes to the pituitary would be confined to the epithelial tissue of the gland, and could have nothing to do with the infundibular part, in which alone the active agents which influence the circulation and renal secretion are found.

The second view supposes the pituitary body to have some ill-defined influence upon the nutrition and growth of the extremities and especially of the bones. It is based upon the fact that, as was first noted by Marie, the condition of acromegaly or gigantism is frequently found to be associated with tumours of the pituitary body.† The character of the tumours which have been found has varied greatly, and certainly in most cases their ultimate effect must have been to destroy the normal tissue; but whether this was preceded or not by a condition of the gland which was characterised by simple hypertrophy cannot be affirmed. Assuming that the internal secretion of the pituitary exerts some influence upon the growth of bones, it is not known whether the changes which occur have been produced by an increase in the secretion or by its abolition.‡ And a similar remark applies to this theory as to the other one, viz., that whether true or not of the epithelial portion of the gland, it would not invalidate the conclusion which is indicated by our experiments, that the internal secretion of the infundibular portion is ancillary to the functions of the renal organs.

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* Rogowitsch, 'Ziegler's Beiträge,' 1889, vol. 4; Stieda, *ibid.*, vol. 7; Schönemann, 'Virchow's Archiv,' vol. 129; Boyce and Beadles, 'Journ. of Path.,' vol. 1, where other literature of the subject is referred to.

† 'Rev. de Médecine,' 1886 and 1890, with Marinesco, 'Arch. d. Méd. Exp.,' 1891. Other literature is given by Thom ('Archiv f. Mikr. Anat.,' 1901, vol. 57).

‡ Arnold ('Virchow's Archiv,' vol. 135) and Ponfick (71 Versamml. Deutsch. Natur. u. Aerzte, 1899) point out that cases of acromegaly occur without affection of pituitary, and that most of the recorded cases of pituitary tumour have not been attended by symptoms of acromegaly.

In view of the probability that this is actually the purpose of this internal secretion, it will be of interest to know whether diabetes, and especially diabetes insipidus, is associated with hypertrophy of the pituitary. Cases of tumour of pituitary have been recorded* in which polyuria was a prominent symptom, but the condition of the posterior lobe has not been specially noted, and the polyuria may have been merely an accidental complication. The point is one for future observation and will no doubt receive the attention of clinicists.†

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* *E.g.*, by BYROM BRAMWELL, in 'Clinical Studies,' vol. 4, Part 4, July, 1906.

† We have not thought it necessary to comment at length upon the views of CYON ('PFLÜGER'S Archiv,' various papers, 1898 to 1902), who rejects the internal secretion theory of the pituitary, and regards it as a centre from which the vascular supply of the brain is influenced through the thyroid body. For it is clear that the results which he obtained from electrical and mechanical stimulation of the exposed gland can be explained on the supposition that the stimuli which he used caused an increased discharge of internal secretion into the blood stream, where it produced the usual result of the extract upon the heart and blood-pressure. It is of course possible that endings of afferent nerves within the organ may have been stimulated in his experiments, in which case the usual results upon heart and blood-pressure of exciting such nerve-endings would be produced. The same remark applies to the experiments of MASAY (*op. cit.*), who also exposed and stimulated the gland, but offers a different explanation of the results, viz., that they are due to a discharge of internal secretion which stimulates afferent fibres in the walls of the blood-vessels, and in this way produces its effects reflexly through the medulla upon the heart and arteries. But this cannot be a sufficient explanation of the effects of the introduction of the secretion into the blood, for it is known that the effects of the extract are obtained even with the isolated arteries and heart (SCHÄFER and OLIVER, *op. cit.*; CLEGHORN, 'Amer. Journ. Physiol.,' vol. 2, 1899). BIEDL and REINER (PFLÜGER'S Archiv,' vol. 2, p. 23, 1898), who also repeated CYON'S experiments, failed to obtain similar effects.

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