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EMOTIONAL ANTIDIURESIS IN THE AUTOTRANSPLANTED KIDNEY

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Theobald & Verney (1935) showed that an emotional inhibition of a water diuresis in dogs was mediated by a humoral mechanism. Rydin & Verney (1938) concluded that an emotional inhibition of a water diuresis was mediated by the posterior pituitary antidiuretic hormone (ADH); they were of the opinion that adrenaline played no part in emotional antidiuresis. O'Connor & Verney (1942) abolished or greatly diminished the emotional inhibition of a water diuresis by removing the posterior pituitary of dogs. O'Connor (1945) found that section of the supraopticohypophyseal tracts reduced or abolished the release of ADH. Subsequently, O'Connor & Verney (1945) analysed, in greater detail, the mechanisms involved in an emotional antidiuresis as evoked by a faradic stimulation in the dog. In normal dogs with an established water diuresis, they found three different responses: (1) an immediate, short-lasting inhibition returning to the previous diuretic flow within 10 min; (2) an inhibition of slow onset continuing much longer and returning to the previous diuretic level 30–60 min later; (3) a combination of these two responses.

Removal of the posterior pituitary abolished or markedly diminished the slow and prolonged antidiuresis in response to a faradic stimulus. Denervation of both kidneys and adrenals abolished the immediate, short-lasting inhibition and a slow, prolonged inhibition always occurred. The operative procedure did not interfere with the typical antidiuretic response to intravenous adrenaline which was identical with the immediate short-lasting antidiuresis sometimes resulting from an emotional stimulus. It was not possible to deduce whether the abolition of the short-lasting antidiuresis was the result of the denervation of the adrenals or of the kidneys. Finally, O'Connor & Verney (1945) observed that in dogs with denervated kidneys and adrenals but with intact pituitaries, an intravenous injection of adrenaline given 30 sec before

the faradic stimulus abolished the prolonged antidiuresis. They concluded that adrenaline inhibited the release of ADH. The interference with the release of the antidiuretic hormone, by adrenaline, was studied further by Duke & Pickford (1951) who found that, on some occasions, adrenaline prevented the acetylcholine-release (ACh) of ADH although, less frequently, adrenaline potentiated the ACh effect or had no effect at all.

In this paper are presented some observations on the emotional antidiuresis evoked by faradic stimulus in dogs with kidneys autotransplanted to the neck. Such a preparation offers two important advantages in such a study, namely, a truly denervated kidney, and a minimal dead space with little or no delay in urine collections due to the direct catheter drainage from the pelvis of the kidney (Dempster, 1950). The 'neck' kidney responds to a faradic stimulus at the height of a water diuresis in a manner indistinguishable from a normal kidney (Dempster & Joekes, 1953). Failure to confirm O'Connor & Verney's finding (1945) of the suppression of ADH release in response to faradic stimulation by intravenous adrenaline immediately prior to the stimulus, led to a further study of this problem.

MATERIALS AND METHODS

The observations were made on greyhounds. The details of the methods used have already been described (Dempster & Joekes, 1953, 1954). Pure laevorotatory adrenaline was used in doses of 15, 40 and 80 μg/ml. made up in 0·9% NaCl and was injected intravenously at the peak of a water diuresis. Dihydroergotamine (Sandoz) was used in 1 mg doses diluted 1 : 10 with 0·9% NaCl. The posterior pituitary extract used was 'Infundin' (Burroughs Wellcome); doses ranged from 0·1 to 4 mU. Urine was collected at intervals ranging from 1 to 5 min. Faradic stimulation was applied via two electrodes placed subcutaneously in the flank. Water, in doses of 1 l., was given over a period of 5 min.

Renal arteriograms. Other dogs were used in acute experiments, in which 2·5 ml. Thorotrast was injected into the carotid artery to which was anastomosed the renal artery of the transplanted kidney. One single exposure was made at 70 sec following the injection of adrenaline and about 2 sec after starting the Thorotrast injection. The transplanted kidneys were not placed subcutaneously, but remained exteriorized during the arteriographic procedure. Pentobarbitone (Nembutal) anaesthesia was used (30 mg/kg).

RESULTS

Effect of faradic stimulation at the peak of a water diuresis

Faradic stimulation was applied when the maximal diuresis following a litre of water appeared to have been reached. This occurred about 60 min after the water had been given, by which time about 160 ml. had been excreted. The results are recorded in Table 1.

In all dogs there was an immediate, profound and prolonged inhibition of diuresis. On one occasion with Alice (174 days after transplantation) there was a rapid return of diuresis; the previous diuretic level being reached in 10 min. This result was thought possibly to be related to a high salt diet at that time;

that it was not a permanent change in the behaviour of the kidney was shown by a subsequent standard response 229 days after transplantation.

In Denise there is clear evidence of two components of the antidiuresis—a rapid inhibition with recovery of urine flow in 3 min and then a further inhibition (Fig. 1*c*).

TABLE 1. The effect of faradic stimulation at the peak of a water diuresis. Dogs with single 'neck' kidneys

Dog	Days after transplanting kidney	Urine flow at time of faradic stimulus (ml./min)	Urine flow in consecutive minutes following faradic stimulation (ml./min)	Time after faradic stimulus when 50% of original urine flow regained (min)
Lynda	18	4·0	0·5, 0·3, 0·9, 0·9, 0·6	35
Marcelle	220	3·5	0·1, 0·1, 0·1, 0·1, 0·1	25
	224	5·0	0·2, 0·3, 0·5, 0·5, 1·0	45
Kate	40	4·0	0·1, 0·1, 0·1, 0·1, 0·1	45
Alice	32	5·6	0·1, 0·1, 0·2, 0·3, 0·4	50
	174	3·3	0·1, 0·1, 0·5, 1·0, 1·5	6
	229	3·5	1·0, 0·5, 1·5, 0·8, 0·8	25
Denise*	18	5·0	1·0, 1·0, 4·5, 3·5, 3·0 3·0, 2·2, 3·5, 2·8, 2·0 2·0, 2·6, 2·4, 2·3, 2·0	>20

* Three other results are shown in Fig. 1*a*, *b* and *d* for this dog. These are not given in this table as the faradic stimulus was preceded by adrenaline administration, although the response was similar to that without adrenaline.

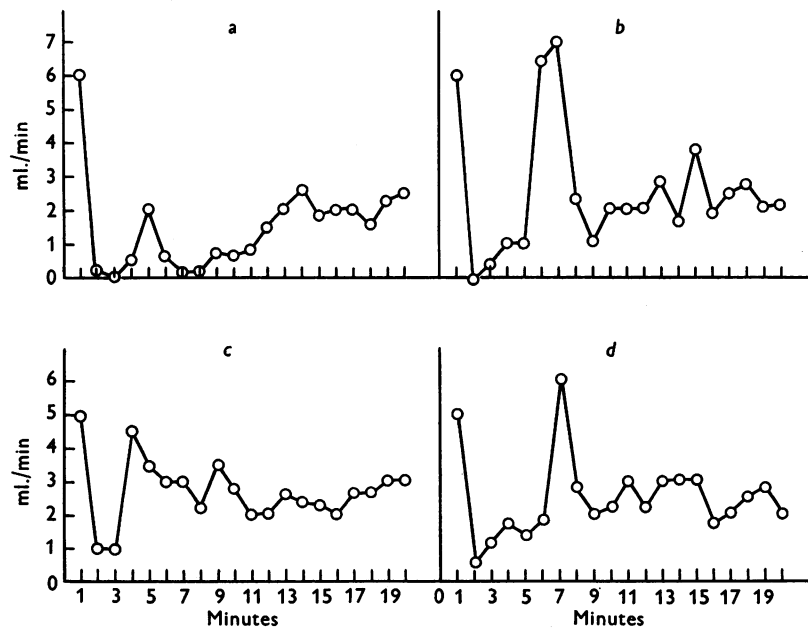

Fig. 1. Denise. The effect of varying doses of adrenaline injected 30 sec prior to a faradic stimulus applied at the peak of a water diuresis. *a*, 15 μg on the 12th post-operative day; *b*, 40 μg on the 15th post-operative day; *c*, the effect of a faradic stimulus without a previous injection of adrenaline (18th post-operative day); *d*, 80 μg on the 19th post-operative day.

Effect of adrenaline preceding faradic stimulation at the peak of a water diuresis

Fig. 1 shows the effect of varying doses of adrenaline given intravenously 30 sec prior to the faradic stimulation. In (*a*) 15 μg, in (*b*) 40 μg, and in (*d*) 80 μg adrenaline were given. It will be seen that the expected inhibition of a water diuresis was in no way interfered with. Adrenaline preceding faradic stimulation in Marcelle, Alice and Claude similarly did not prevent a slow and prolonged antidiuresis.

TABLE 2. Effect of 'Infundin' injected intravenously at the peak of a water diuresis. Dogs with single 'neck' kidneys

Dog	Days after transplanting kidney	Urine flow at time of injection (ml./min)	Minimum urine flow reached (ml./min)	Urine flow in consecutive minutes after injection (ml./min)	Dose of 'Infundin' (mU)
Marcelle	178*	4·6	1·0	—	0·6
	179*	4·0	0·6	—	1·0
	181*	5·2	1·6	—	2·0
	182*	4·0	0·5	—	2·0
	183	4·6	0·9	2·5, 2·5, 2·4, 1·7, 1·2 1·1, 0·9, 1·1, 1·0, 1·0	4·0
	184	4·4	0·6	3·2, 2·2, 1·8, 0·8, 0·8, 0·6, 0·6, 0·6, 0·8, 0·8	1·0
Denise	8	6·0	0·4	3, 1·5, 3, 2·5, 1·0, 1·0, 1·0, 0·5, 0·4, 0·5	1
	10	5·0	1·8	2·2, 2·2, 1·8, 3·5, 3·8 3·0, 3·0, 2·5, 2·1, 3·2, 1·8, 2·8, 2·5, 2·5, 2·2	1
Claude	3	7·0	1·25	4, 3·5, 3·5, 2·8, 2·8 2·2, 2·4, 1·25, 1·4, 1·4	1

* Urine was collected at 5 min intervals.

Effect of 'Infundin' at the peak of a water diuresis

'Infundin' in doses ranging from 0·1 to 4·0 mU was given intravenously at the peak of a water diuresis.

Table 2 shows the results obtained from single 'neck' kidneys. The minimum urine flow occurred at 6, 7, 8 and 9 min respectively after the injection of 'Infundin', on four occasions. In one dog, Denise, at 10 days, a rather flat curve showed the minimal flow at 3 min. The decline of diuresis was gradual compared with that seen with adrenaline, although a fall to about 50% of the original value occurred in the first minute. The recovery of 50% of the original diuretic flow occurred in periods varying from 40 to 120 min.

Effect of adrenaline at the peak of a water diuresis

At the peak of a water diuresis 15, 40 or 80 μg adrenaline solution was injected intravenously. Table 3 shows that in seventeen experiments in three dogs, each with a single 'neck' kidney, a constant pattern of inhibition of diuresis resulted. A rapid decrease of urine flow occurred, usually maximal in

the second minute, with a rapid return to the previous diuretic level; in most instances within 5 min. Fig. 2 shows typical responses in Denise to 15, 40 and 80 μg adrenaline. These results are virtually identical with those recorded by

TABLE 3. Effect of adrenaline injected intravenously at the peak of a water diuresis

Dog	Days after transplanting kidney	Urine flow at time of injection (ml./min)	Urine flow in consecutive minutes after the injection (ml./min)	Dose of adrenaline injected (μg)
Marcelle	176	5·6	0·6, 0·3, 1·0, 3·5, 4·5, 5·0	80
	185	4·0	1·7, 0·1, 0·4, 2·5, 3·2, 4·0	40
	186	4·0	1·0, 0·1, 2·5, 2·6, 4·5, 5·0	40
	228	3·8	1·0, 0·3, 1·2, 3·0, 3·0, 4·0	40
	229	4·0	0·5, 0·5, 1·0, 4·5, 5·5, 5·5	15
	234	5·0	0·5, 0·2, 0·7, 4·4, 5·0, 5·0	15
Alice	255	3·0	0·5, 1·5, 2·0, 4·0, 3·0, 3·0	80
	256	3·1	0·5, 0·2, 0·4, 1·5, 3·0, 3·0	80
	257	4·0	0·8, 0·3, 1·5, 4·0, 4·0, 3·8	40
	261	3·0	0·6, 0·6, 1·6, 3·0, 3·2, 3·0	40
	263	4·0	1·0, 0·8, 2·2, 3·0, 3·0, 3·6	15
Susan	3	3·0	1·4, 0·6, 1·2, 1·2, 2·0, 2·2	80
	6	3·5	2·5, 1·5, 1·0, 0·4, 0·8, 2·5	40
	8	4·0	1·8, 0·1, 0·8, 3·0, 4·0, 4·5	15
Denise	10	7·0	3·2, 3, 6, 8·2, 7·0	15
	12	6·0	1·0, 2·1, 5·1, 5·1, 4·8	40
	14	5·6	0·3, 1·0, 4·0, 4·2, 4, 4·7	80

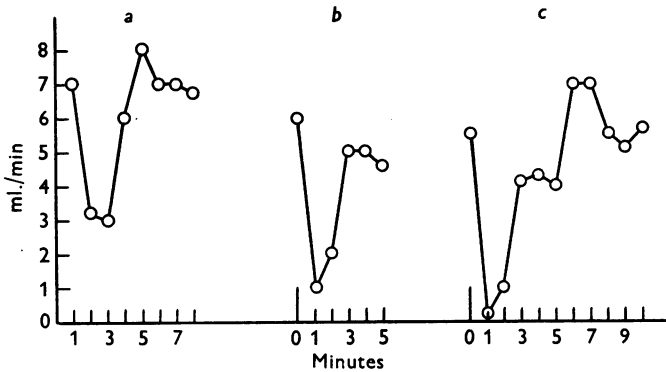

Fig. 2. Denise. The effect of adrenaline injected intravenously at the peak of a water diuresis: *a*, 15 μg; *b*, 40 μg; and *c*, 80 μg.

Pickford & Watt (1951) in dogs with normal kidneys. Pl. 1 shows arteriograms of one 'neck' kidney following the intravenous injection of adrenaline in varying doses. There is considerable intrarenal constriction affecting the whole arterial tree. Similar results were obtained in three other transplanted kidneys.

Effect of dihydroergotamine tartrate (DHE) on the adrenaline inhibition of a water diuresis

Just prior to the expected peak of a water diuresis 1 mg of DHE was injected intravenously, without affecting the urine flow significantly. After an interval of time, varying from 5 to 20 min after the DHE administration, 80 μg adrenaline was injected intravenously.

Table 4 shows that, in four dogs each with a single 'neck' kidney, DHE abolished the adrenaline inhibition of a water diuresis.

TABLE 4. The blocking action of 1 mg dihydroergotamine tartrate on the effect of 80 μg adrenaline at the peak of a water diuresis

Dog	Days after transplanting kidney	Time interval between DHE and adrenaline (min)	Urine flow at time of adrenaline injection (ml./min)	Urine flow in consecutive minutes after adrenaline injection (ml./min)
Alice	257	20	4·4	3·0, 4·5, 4·5, 4·0, 3·5, 4·0
	261	15	4·0	4·0, 3·8, 3·2, 3·0, 3·2
	263	10	2·4	4·0, 3·0, 3·0, 3·0, 3·0
Marcelle	184	6	3·8	3·8, 3·2, 4·0, 4·4, 4·0
	234	5	3·2	3·5, 4·2, 4·0, 4·0, 4·0
Susan	1	10	3·5	3·8, 3·0, 2·2, 3·0, 3·0
Lynda	7	10	3·3	4·0, 4·2, 3·7, 2·9, 3·0

Effect of DHE preceding a faradic stimulus at the peak of a water diuresis

At the peak of a water diuresis, 1 mg DHE was injected intravenously and was followed by faradic stimulation after an interval varying from 6 to 30 min.

Table 5 shows the results obtained from three dogs with single 'neck' kidneys. In Lynda and Marcelle, the inhibition of a water diuresis following faradic stimulation showed a relatively slow decline with the maximum depression at 6 and 7 min; this is similar to the results obtained in Marcelle and other dogs following an injection of 'Infundin' (Table 2). Alice showed an inhibition similar to that when no DHE had been given (Table 1); the degree of inhibition, however, was less.

DISCUSSION

The antidiuretic effects of intravenously administered adrenaline, posterior pituitary extract ('Infundin') and faradic stimulation at the peak of a water diuresis have different characteristics. Although variations in sensitivity between normal and 'neck' kidneys may occur, no essential difference in their response to the fore-mentioned antidiuretic influences has been found in our experiments.

Intravenous adrenaline caused an immediate inhibition of diuresis, maximal within 3 min, and returning to the previous diuretic level in 5 or 6 min. This aspect has been studied in the 'neck' kidneys only in our experiments but the

results are virtually identical with those of Pickford & Watt (1951) who used normal dogs. This short-lasting antidiuresis will be referred to as the short component.

'Infundin' caused a relatively slow decline of diuresis, the maximum inhibition usually not occurring before 6 min after the injection. The return of diuresis was variable but diuretic values greater than 50% of the previous diuretic level did not occur earlier than 30 min. Variation of dose from 0·1 to 4 mU affected only the length of time of inhibition but did not alter the rate of decline of diuresis. The slow, prolonged antidiuresis will be referred to as the long component.

TABLE 5. The blocking action of dihydroergotamine tartrate on the effect of faradic stimulation at the peak of a water diuresis

Dog	Days after transplanting kidney	Interval between DHE and faradic stimulus (min)	Urine flow at time of faradic stimulus (ml./min)	Urine flow per minute* in consecutive minutes after faradic stimulus (ml./min)	Comment
Lynda	30	14	6·0	**3·0**, 3·4, 2·6, 1·8, 1·9, 1·5, 1·5, **1·4**, 1·6, 1·8	Slow component only
Marcelle	184	17	4·0	3·1, 2·0, 1·7, 1·3, 1·3, 1·2, **1·1**, 1·1, 1·5, 1·7	Slow component only
	233	6	5·6	5·0, 3·9, 4·4, 3·8, 3·2, **3·0**, **3·0**, **3·0**, **3·0**, 3·2	Slow component only
Alice	255	30	4·2	**1·5**, 2·0, 2·0, 2·0, 2·0, 2·2, 2·5, 2·0, 2·5, 2·5	Both rapid and slow components
	259	15	3·0	**1·0**, 1·2, 2·6, 3·0, 2·0, 2·2, 2·5, 2·0, **1·0**, **1·0**	Both rapid and slow components separated

* The lowest minute flow values are given in black.

Faradic stimulation at the peak of a water diuresis resulted in an inhibition of water diuresis showing an immediate decrease of urine flow similar to that found following intravenous adrenaline and then continued into a prolonged inhibition with a slow return to normal similar to that obtained after an injection of 'Infundin'. In some instances, both in O'Connor & Verney's experiments and our own, a clear biphasic character of the inhibition was apparent (Fig. 1). Thus the characteristic inhibition following faradic stimulation is composed of a short and a long component similar to those described above.

O'Connor & Verney (1945) state: 'We are thus led to the view that the rapid inhibition is the result of vaso-constriction in the kidney and that the slow inhibition is due to the release of an anti-diuretic substance from the posterior lobe of the pituitary.' These authors were unable to determine the exact cause of the vasoconstriction in the kidney. The rapid inhibition was abolished by denervation of the kidneys and adrenals in their experiments. The rapid inhibi-

tion constantly occurs in the 'neck' kidney unless the dog has become accustomed to faradic stimulation. It may thus be argued that the abolition of the rapid component was due to the denervation of the adrenals (the nerve supply was intact in the present work), although denervation of the kidney was inevitably complete. The similarity of the rapid inhibition with that caused by intravenous adrenaline, and the blocking by DHE of the short component due to faradic stimulation and of the inhibition caused by adrenaline, strengthens the conclusion that release of adrenaline mediates the short component of the emotional type of antidiuresis we have studied.

O'Connor & Verney (1945) found that intravenous adrenaline (15–40 μg) 30 sec prior to faradic stimulation abolished the slow component of emotional antidiuresis. They concluded that adrenaline prevented the release of ADH. This must imply that adrenaline release cannot mediate the rapid component of an emotional antidiuresis if it is followed, as is agreed, by the slow component. It may be argued, however, that faradic stimulation releases simultaneously adrenaline and ADH, and adrenaline inhibition of ADH release would then not obtain. This possible apparent contradiction does not, however, arise in our arguments as we were unable to confirm the finding that adrenaline given immediately prior to faradic stimulation abolished the slow component.

O'Connor & Verney (1945), while believing that the rapid component was dependent on renal vasoconstriction, did not determine whether the cause was nervous or humoral. The arteriograms in the present work further support the belief that the antidiuretic action of relatively large amounts of adrenaline is due to generalized renal vasoconstriction as suggested by Pickford & Watt (1951).

It is therefore concluded that in autotransplanted kidneys an emotional inhibition of a water diuresis, as resulting from a faradic stimulation, is mediated first by adrenaline causing an immediate, short-lasting inhibition and then by ADH resulting in a prolonged inhibition, of slower onset, the last effect being masked by the adrenaline effect.

These conclusions differ from those of O'Connor & Verney (1945) because of our finding that, in the autotransplanted kidney, adrenaline did not prevent the appearance of the slow component of an emotional antidiuresis. As the autotransplanted kidney appears to react like the normal kidney in all other aspects of antidiuresis, it is considered probable that these conclusions apply to normal kidneys also.

SUMMARY

1. Using dog kidneys autotransplanted to the neck, observations have been made on the nature of the emotional inhibition at the peak of a water diuresis; inhibition was produced by faradic stimulation, and by intravenous injections of adrenaline and 'Infundin'.

2. Adrenaline injected 30 sec prior to faradic stimulation had no effect on the immediate profound inhibition usually observed after such stimulation.

3. Arguments are presented for the belief that the emotional inhibition of a water diuresis induced by faradic stimulation is mediated first by adrenaline and then by the posterior pituitary antidiuretic hormone. This chain of reactions results in an immediate, profound and short-lasting inhibition followed by an inhibition of slower onset and prolonged in character.

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REFERENCES

DEMPSTER, W. J. (1950). Observations on the behaviour of the transplanted kidney in dogs. *Ann. R. Coll. Surg. Engl.* **7**, 275–302.

DEMPSTER, W. J. & JOEKES, A. M. (1953). Diuresis and antidiuresis in the autotransplanted kidney in dogs. *Quart. J. exp. Physiol.* **38**, 11–24.

DEMPSTER, W. J. & JOEKES, A. M. (1954). Functional studies of kidneys autotransplanted to the neck of dogs. *Acta med. scand.* **147**, 99–118.

DUKE, H. N. & PICKFORD, M. (1951). Observations on the action of acetylcholine and adrenaline on the hypothalamus. *J. Physiol.* **114**, 325–332.

O'CONNOR, W. J. (1945). The effect of section of the supraoptico-hypophyseal tracts on the inhibition of water diuresis by emotional stress. *Quart. J. exp. Physiol.* **33**, 149–161.

O'CONNOR, W. J. & VERNEY, E. B. (1942). The effect of removal of the posterior lobe of the pituitary on the inhibition of water diuresis by emotional stress. *Quart. J. exp. Physiol.* **31**, 393–408.

O'CONNOR, W. J. & VERNEY, E. B. (1945). The effect of increased activity of the sympathetic system in the inhibition of water diuresis by emotional stress. *Quart. J. exp. Physiol.* **33**, 77–90.

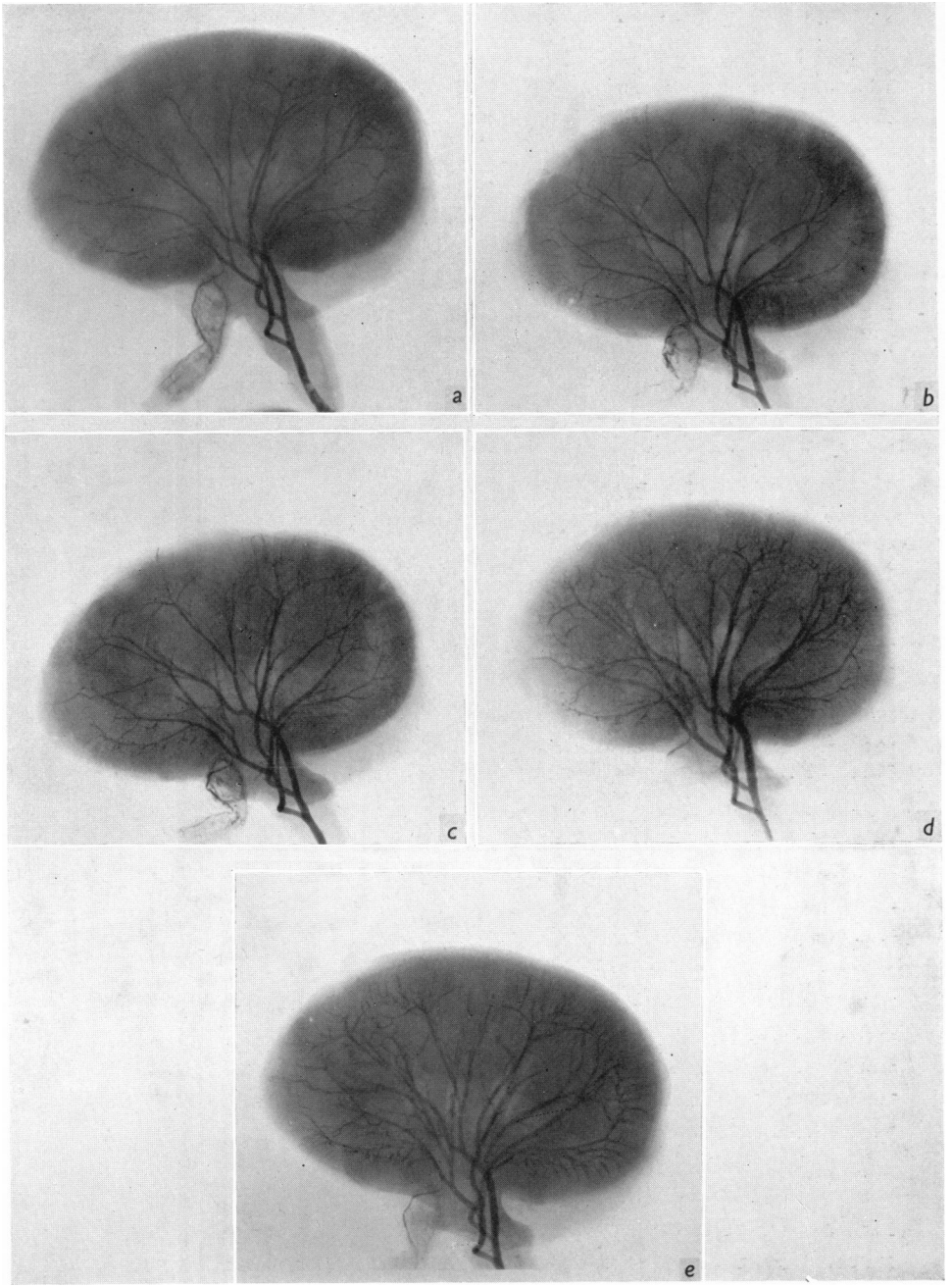
PICKFORD, M. & WATT, J. A. (1951). Comparison of some of the actions of adrenaline and noradrenaline on the kidney. *Quart. J. exp. Physiol.* **36**, 205–212.

RYDIN, H. & VERNEY, E. B. (1938). The inhibition of water diuresis by emotional stress and by muscular exercise. *Quart. J. exp. Physiol.* **27**, 343–374.

THEOBALD, G. W. & VERNEY, E. B. (1935). The inhibition of water diuresis by afferent nerve stimuli after complete denervation of the kidney. *J. Physiol.* **83**, 341–351.

EXPLANATION OF PLATE

Arteriograms of a transplanted kidney at 70 sec following an intravenous injection of adrenaline. *a*, 15 μg; *b*, 40 μg; and *c*, 80 μg; *d* and *e*, controls before and 10 min after the adrenaline experiments. It will be seen that the whole intrarenal vascular system is affected by adrenaline.



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