J. Physiol. (1960), **151**, *pp.* 261–271
With 5 *text-figures*
Printed in Great Britain

EFFECTS OF NORADRENALINE AND ADRENALINE ON THE THYROID

BY J. F. MOWBRAY AND W. S. PEART
From the Medical Unit, St Mary's Hospital, London, W. 2

(*Received* 4 *September* 1959)

When Labbé, Tinel & Doumer (1922) first described a patient with a phaeochromocytoma they noticed swelling of the root of the neck in the attacks of sweating, pallor and hypertension. Strombeck & Hedberg (1939) described swelling of the thyroid as at least part of the cause of this increase in neck size.

It has been shown that phaeochromocytomata, in different patients, secrete varying proportions of noradrenaline and adrenaline (von Euler, 1951), and Barnett, Blacket, Depoorter, Sanderson & Wilson (1950) have described swelling of the region of the thyroid in two subjects given infusions of noradrenaline. We have carried out a number of experiments in both man and dogs to study this finding further, with particular reference to the changes in blood flow which occur. A preliminary report of these findings has appeared previously (Mowbray & Peart, 1958).

METHODS

Man

Infusions of noradrenaline and adrenaline were given to fifty-one healthy young adults; forty-nine male and two female. All subjects were at rest on normal diet and infusions were given from 30 to 90 min after their midday meal.

Infusions containing 4 μg/ml. of either noradrenaline or adrenaline in 0·9 % saline were given into an antecubital vein. The infusions were for periods of 30–90 min, and the infusion rate was adjusted so that the systolic blood pressure for most individuals lay between 170 and 190 mm Hg. The dose of both substances required to maintain this lay between 15 and 30 μg/min.

Measurements of blood pressure were made by sphygmomanometer. The measurements of thyroid blood flow were made with a modification of Hensel's heated thermocouple needle (Mowbray, 1959). In this procedure a heated thermocouple is cooled by the tissue blood flow and a reference thermocouple in the same needle compensates for changes in tissue temperature. It was possible to contain the thermocouples and heater in a No. 12 hypodermic needle, which was small enough to be inserted almost painlessly in the thyroid through a small bleb of intradermal procaine solution. Readings of thyroid blood flow were made at 2 min intervals in most subjects, although direct recording of the blood flow has also been used. For this purpose a mirror galvanometer was used for taking spot readings and a DC amplifier with a direct-writing milliammeter for the continuous recordings.

Measurements of the neck circumference were made by sticking a length of tape around the neck and leaving the ends over the front of the neck free. Measurement of the tape plus the gap gave the neck circumference.

Dogs

The dogs used were of a number of breeds weighing about 50–70 lb. (22·7–31·8 kg). Anaesthesia was induced with intravenous sodium thiopentone and was maintained with Nembutal (pentobarbitone; Abbott Laboratories). Laryngeal incubation was carried out, and respiration maintained at a constant rate with a Starling pump. The animals were given heparin 250 u./kg intravenously at the end of the dissection; 100 u./kg was given each subsequent 4 hr.

The thyroids were dissected out and one lobe was used for measurement. There is no isthmus to the thyroid of the dog, and the volume of the isolated lobe was about 1·0 ml. The vessels supplying the lobe were identified and all veins but one were tied; this was cannulated and the effluent blood led through nylon tubing. The drops of blood issuing from the end of this were made to displace a pivoted lever from a reservoir containing saline. The electrical contact between lever and saline was used as input to a Gaddum drop recorder. (The flow was of the order of 30 ml./hr, and it was not necessary to return this to the animal.) A muscular branch of the superior thyroid artery was chosen and cannulated retrogradely so that close intra-arterial infusions of noradrenaline and adrenaline could be given from a constant-rate infusion pump.

Intravenous infusions were given into a femoral vein. Direct recording of blood pressure was made from a mercury manometer attached to a femoral artery cannula.

Measurements of volume change in the thyroid were made by enclosing a lobe in a cylindrical Perspex oncometer and recording with a tambour and writing lever. A change in volume of 0·01 ml., i.e. 1 % of the volume of the lobe, could be easily detected. In order to have confidence in the recordings of volume change it was found necessary to have simultaneous recording of venous outflow. Without this it was difficult to ensure that there was no obstruction to the venous outflow by the oncometer pressing on the veins.

Radioactive measurements

Measurements of the uptake of radioactive ^{131}I during infusions of noradrenaline were made in two human subjects, and in one with adrenaline. In a further two subjects measurements of the blood level of radioactive protein-bound iodine (PBI) were made during infusion.

A dose of 20 μc of ^{131}I as iodide was given intravenously. Measurements of the activity of the thyroid were then made for a basal period of 90 min. After this time it was possible to extrapolate the curve for the next half hour with reasonable accuracy, during which time a standard infusion was given. In all cases this was sufficient to raise the systolic blood pressure to 180–190 mm Hg. Counting was continued for a further 30 min.

On the day following an injection of ^{131}I the subjects were given a further 30 min infusion and peripheral venous blood was taken before and after this for estimation of the radioactive PBI level.

In one dog, after an injection of 500 μc of ^{131}I given 24 hr previously, measurement was made of the radioactive PBI level in the blood issuing from the thyroid vein during basal periods and with infusions of noradrenaline.

RESULTS

Man

In forty-three out of forty-four subjects given noradrenaline noticeable increase in size of the thyroid occurred. This began within 5 min of starting the infusion and persisted during its course. After stopping the noradrenaline infusion most of the swelling disappeared within 15–20 min, but some detectable swelling was present in a number of individuals for up to 24 hr. The mean increase in neck circumference was 1·3 cm and the largest 4·0 cm.

None of eleven subjects given adrenaline showed any increase in size of the thyroid.

In three of the subjects given noradrenaline a bruit was heard over the thyroid in the course of the infusion. For this reason it was thought that the increase in size might be due to an increase in blood flow. This is in accord with an observation on a patient with a phaeochromocytoma during an attack (Davis, Peart & van't Hoff, 1955).

TABLE 1. Effect of intravenous noradrenaline and adrenaline on thyroid blood flow in three human subjects

	Systolic B.P.			Change in thyroid blood flow (%)	
Subject	Basal	Ad.	NAd.	Ad.	NAd.
1	112	169	180	−11%	+26%
2	120	174	198	− 5%	+34%
3	104	206	171	−12%	+36%

Use was then made of the needle to measure the blood flow in the thyroid of one of us (W.S.P.) during a noradrenaline infusion. It was found that there was a considerable increase in blood flow, which returned to normal rapidly when the infusion was stopped. One subject then had measurements made with an infusion of adrenaline and a slight decrease in flow was noted.

In a further three subjects comparisons were then made of the effect of noradrenaline and adrenaline on the blood flow, with comparable blood pressure changes and closely similar dosage rates. Table 1 shows the means of the results obtained on these subjects. It will be seen that these confirm the initial findings. However, the increase in thyroid size outlasts the increase in flow by many hours, and thus the latter cannot be the only factor accounting for the increase in size.

Dogs

We were thus led to carry out the experiments in dogs where intra-arterial injections could be made and accurate measurement of volume made. Attempts to repeat on dogs the effects found in man were at first unsuccessful. It was found that either a decrease in flow or very little change occurred with intravenous infusions of both noradrenaline and adrenaline (Fig. 1*a*). However, these changes occurred, as will be seen, with only moderate elevations of blood pressure.

The possibility was therefore considered that the changes might be due to a greater increase in perfusion pressure, i.e. general blood pressure, assuming that noradrenaline was not a potent vasoconstrictor in the thyroid. The effects of intra-arterial infusions of noradrenaline and adrenaline were therefore studied (Fig. 1*b*).

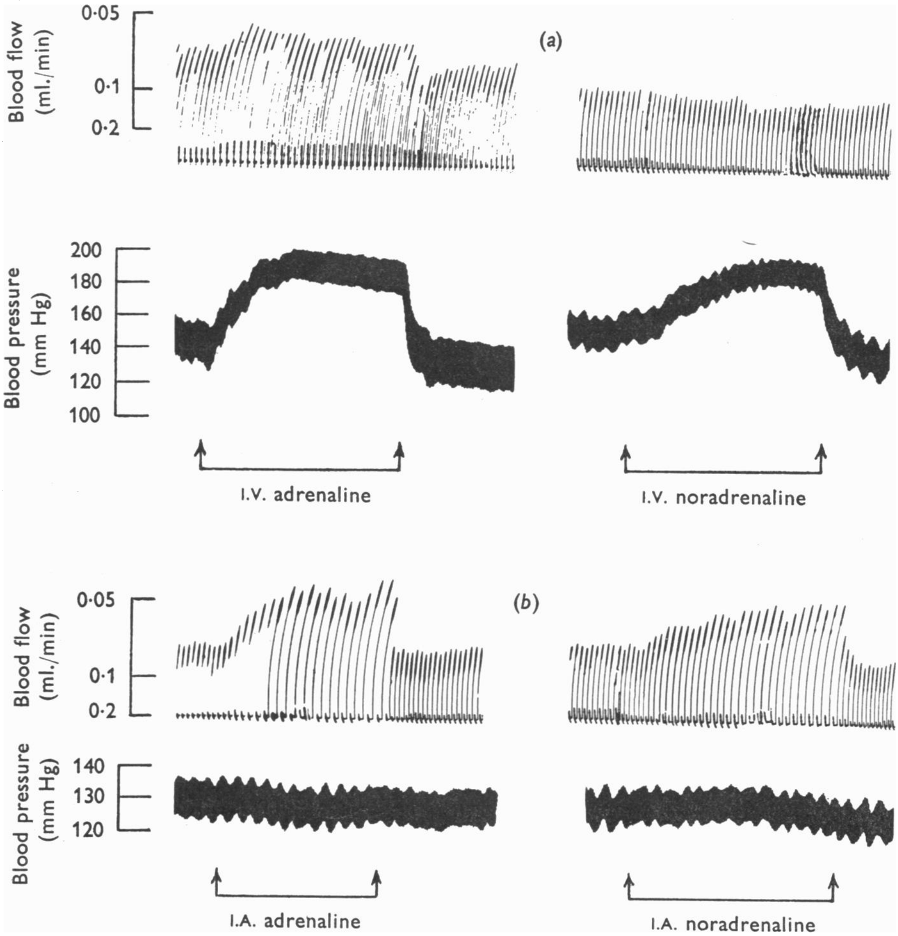

Fig. 1*a*. Effect of intravenous noradrenaline and adrenaline on thyroid blood flow in the dog. *b*. Effect of intra-arterial noradrenaline and adrenaline on thyroid blood flow in the dog.

It was found that adrenaline in all doses which were tried (0·01–1 μg/min) was constrictor, and produced a decrease in flow. In fact, with large doses the blood flow through the gland almost ceased.

Noradrenaline in large doses (0·1 μg/min) was also constrictor, but it was observed that at the start of the infusion, before the full effect was attained, there was often a transient increase in flow. With smaller doses it was found that a rate of about 0·01 μg of noradrenaline per minute would produce a vasodilation in the thyroid in the three dogs studied in this way (Fig. 2).

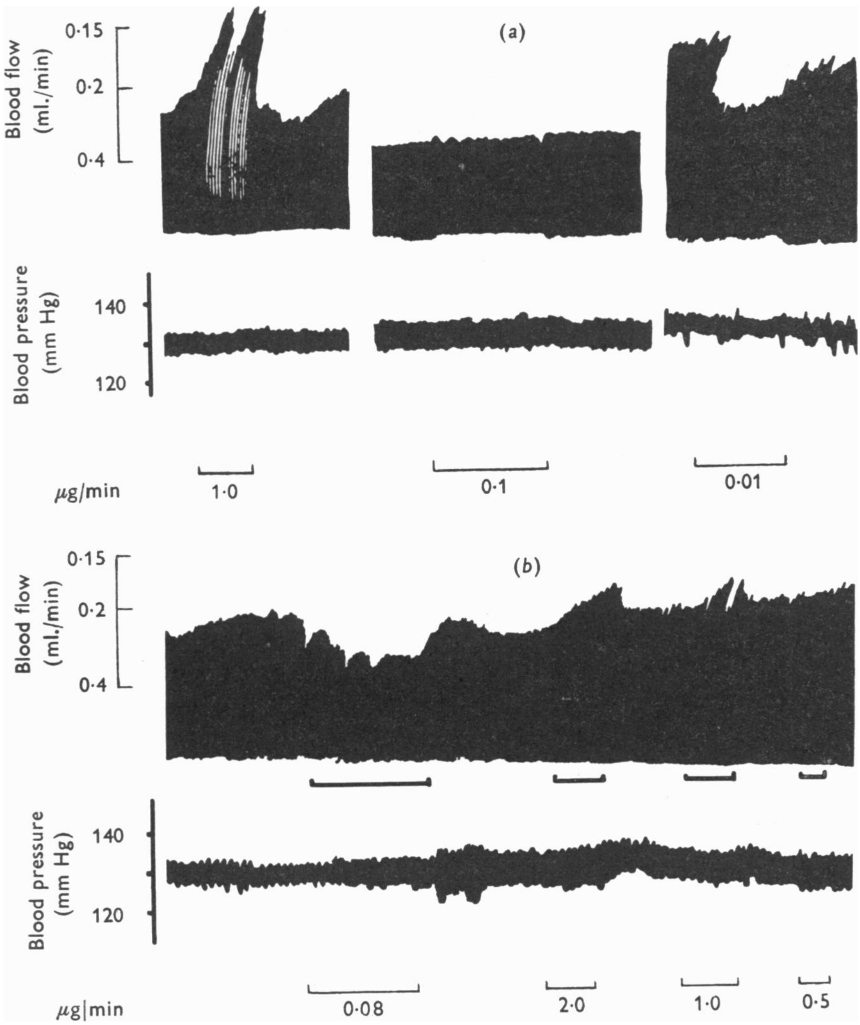

Fig. 2. Effect of intra-arterial noradrenaline on thyroid blood flow in the dog.

Since noradrenaline is known to be released at the majority of sympathetic nerve endings, it was considered possible that cervical sympathetic stimulation might produce an increase in flow. However, electrical stimulation of the common vagosympathetic trunk with an induction coil produced no significant change in thyroid blood flow in four dogs, although contraction of the nictitating membrane was produced, showing the efficacy of the stimulation.

It has not been possible to show whether the increase in flow with intravenous noradrenaline is due to a small vasodilating dose reaching the gland,

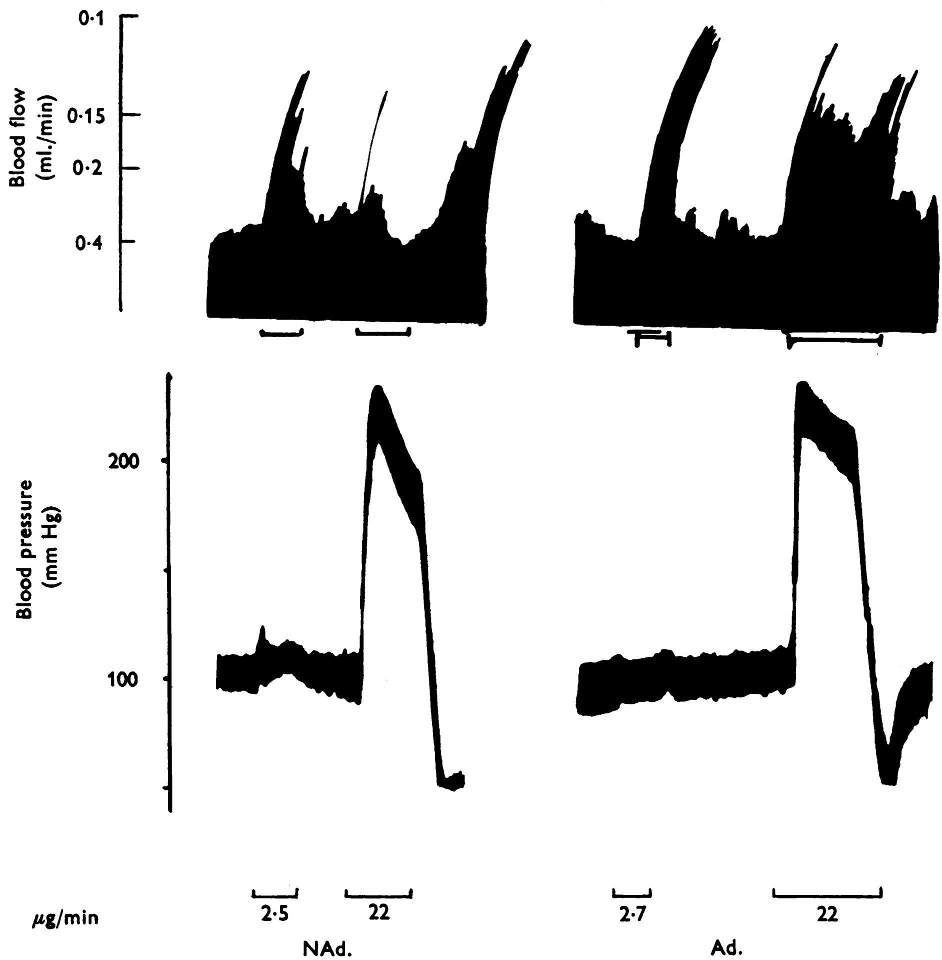

Fig. 3. Effect of large and small doses of intravenous noradrenaline (NAd.) and adrenaline (Ad.) on thyroid blood flow in the dog.

or merely to an increase in perfusion pressure. However, adrenaline in all doses (1–60 μg/min) given intravenously produced a decrease, but the large dose of noradrenaline (over 10 μg/min) increased the flow (Fig. 3). As the small dose did not do so it would seem most likely that an increase in perfusion pressure is the important factor. The same experiment carried out in man produced an identical result (Fig. 4).

Attempts to show a change in size of the dog thyroid during the infusion produced variable results. In one animal increases in size of up to 30 % were shown with noradrenaline, but in three other animals decrease in size of the order of 2–3 % occurred during infusion of noradrenaline and adrenaline.

Since it was considered possible that the increase in flow with noradrenaline might be associated with a change in function, attempts were made to measure functional changes during infusions.

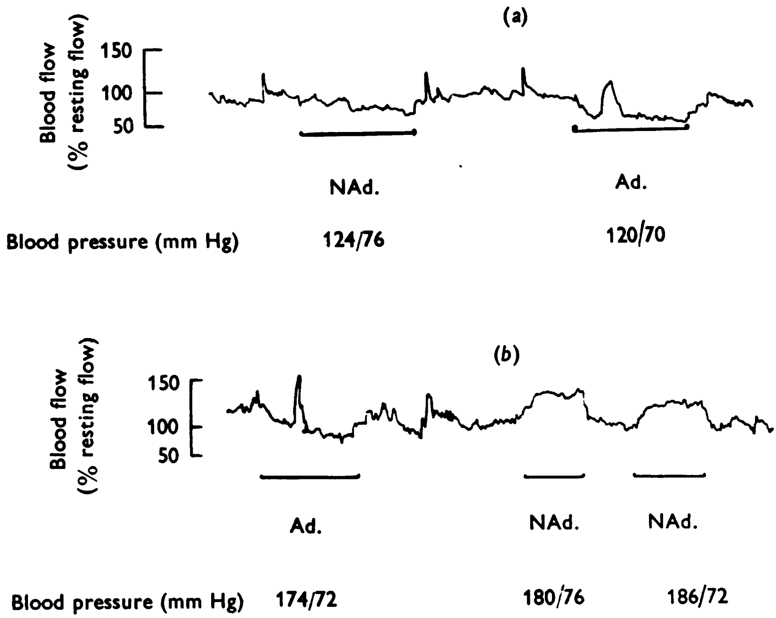

Fig. 4. Effect of large and small doses of intravenous noradrenaline (NAd.) and adrenaline (Ad.) on thyroid blood flow in man. (The upward spikes are artifacts due to swallowing.)

Radioactive studies

Studies were made in man of the effects of noradrenaline and adrenaline infusions on the uptake of ^{131}I and blood level of PBI, as already described. Figure 5 shows typical uptake curves obtained and Table 2 the PBI levels. The normal curve also shown in Fig. 5 flattens out after 90 min and it is possible to extrapolate the curve over the next 30 min. It will be seen that there is no detectable change in either parameter with infusions of noradrenaline. Again no change was found with adrenaline infusions. The blood levels of radioactive PBI were also not significantly altered during infusion of noradrenaline and adrenaline.

As changes in PBI would be shown more rapidly and in much greater degree in the thyroid than in systemic venous blood, an attempt was made

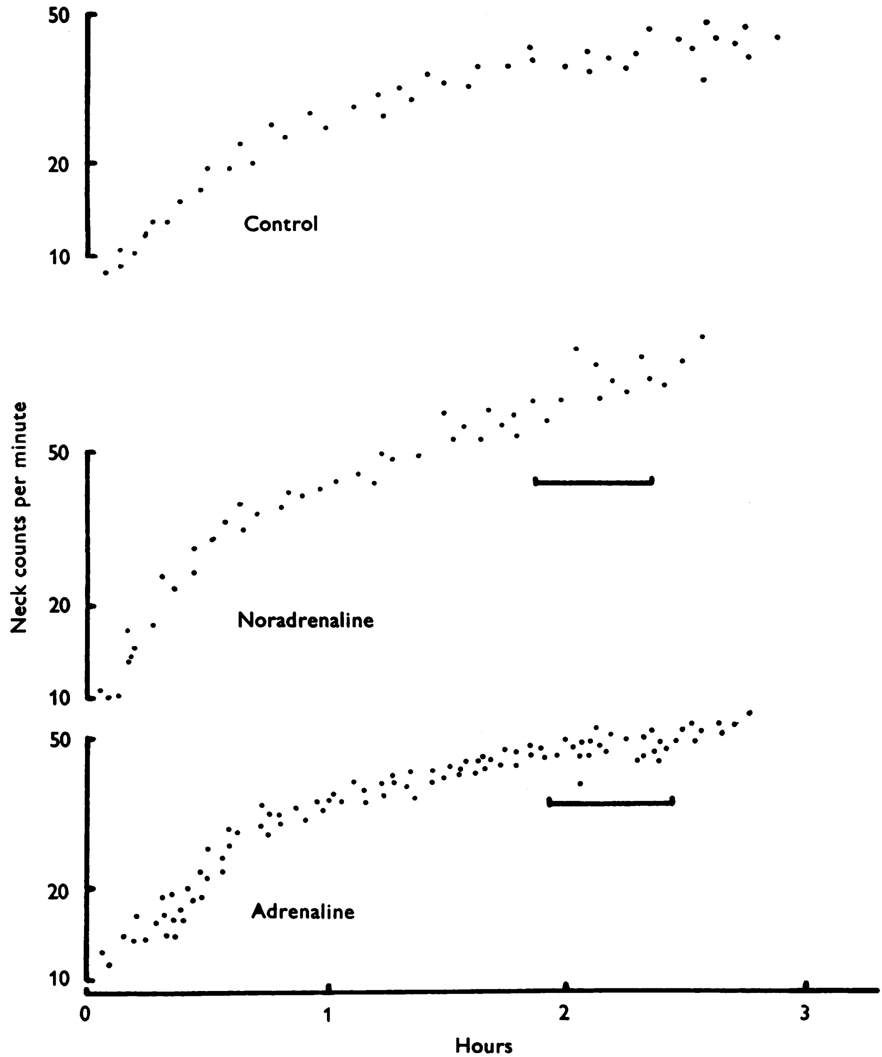

Fig. 5. Thyroid uptake curves following intravenous ^{131}I. The effects of intravenous noradrenaline and adrenaline are compared with a control subject.

TABLE 2. Radioactive protein-bound iodine levels in blood before and after noradrenaline infusion.

Subject	Protein-bound radioactivity (counts/min/15 ml. plasma; and S.D.) Before NAd.	After NAd.
S.T.	13·7 (2·01)	10·9 (1·98)
J.I.R.	16 (2·6)	10 (2·5)

to measure the output of radioactive PBI in the thyroid venous blood of the dog. It was found in the one dog studied that the concentration of activity in the blood fell as the flow rose during intravenous noradrenaline infusions, so that the total output per minute did not differ significantly from the control periods (Table 3).

TABLE 3. Radioactive protein-bound iodine levels in thyroid venous blood of a dog before and during intravenous noradrenaline

		Blood flow (ml./min)	PBI (counts/min/ml. blood; and S.D.)	PBI output (counts/min)
Period 1	Control	0·3	180·4 (7·3)	54
	NAd.	1·1	62·2 (2·8)	68·4
Period 2	Control	0·33	176·3 (7·0)	58·2
	NAd.	0·50	98·4 (3·6)	49·2

DISCUSSION

It has been possible to show an increase in size of the thyroid in only one anaesthetized dog with either intravenous or intra-arterial infusions of noradrenaline. In man swelling of the thyroid is the rule with noradrenaline, but not with adrenaline, and in both dog and man an increase in blood flow was observed. Increase in blood flow cannot be the sole explanation for the increase in size, however, since in the dog it was possible to increase the rate of flow without increasing the volume in three out of four animals. This may be allied with the observation of delayed disappearance of the swelling in man (up to 24 hr), which suggests oedema in the gland. A combination of arterial dilatation with some degree of venous constriction raising the capillary pressure and thyroid volume is possibly the correct explanation. Söderberg (1958) produced only a decrease in blood flow through the rabbit's thyroid with intra-arterial or intravenous noradrenaline, but did not show the increase we have noted. It is possible that he did not use small enough doses.

It is a surprising finding that there is a small dose of intra-arterial noradrenaline which is vasodilator, when all doses of adrenaline are vasoconstrictor. There seems to be only one other site in the body in which this is true. There is evidence that noradrenaline is a vasodilator of the human coronary arteries, where adrenaline has a constrictor effect (Smith, Syverton & Coxe, 1951). Much previous work has been confused by observations on the intact heart and not on the isolated coronary arteries (Wégria, 1951) and in these experiments the effect of the substances on the activity of the heart must be taken into account. One might consider that these dilator effects of noradrenaline might have a purpose, but if this is in some way to control the activity of the gland we were unable to show any effect on iodine uptake of the gland in two subjects. In the one dog studied the output of radioactive PBI in the thyroid vein seemed to be inversely proportional to the blood flow, so that the output per minute was steady.

As the doses (20 μc) in man had of necessity to be small, it is not possible to say that either adrenaline or noradrenaline had no effect on the release of PBI into the circulation. The increase of activity in the peripheral blood which would be achieved by release from the gland is probably too small for satisfactory measurement. More detailed study of iodinated compounds coming out of the gland would be needed for certainty.

Since noradrenaline is released at most sympathetic nerve endings, it was expected that cervical sympathetic stimulation would affect thyroid blood flow; but there was no change in four dogs. A minimum of dissection was performed in two of these to avoid damage to the nerves. This suggests that the sympathetic innervation of the dog's thyroid is very slight and ineffective. Söderberg (1958) has shown that stimulation of the cervical sympathetic in the rabbit produced a decrease in blood flow and PBI output from the gland.

SUMMARY

1. Observations have been made on the increase in size of the thyroid with intravenous administration of noradrenaline. It is related closely, but not directly, to the increase in blood flow noted both in man and dogs.

2. In the dog small intra-arterial infusions of noradrenaline (about 0·01 μg/min) were vasodilator, but all larger doses and all doses of adrenaline were vasoconstrictor.

3. No change in ^{131}I uptake in two subjects or in protein-bound iodine blood levels in two further subjects was noted with intravenous infusions of noradrenaline or adrenaline. In one dog no change in the output per minute of radioactive protein-bound iodine in the thyroid vein was observed with similar infusions.

REFERENCES

Barnett, A. J., Blacket, R. B., Depoorter, A. E., Sanderson, P. H. & Wilson, G. M. (1950). Action of noradrenaline in man and its relation to phaeochromocytoma and hypertension. *Clin. Sci.* **9**, 151–179.

Davis, P., Peart, W. S. & van't Hoff, W. (1955). Malignant phaeochromocytoma with functioning metastases. *Lancet*, **269**, 274–275.

Labbé, M., Tinel, J. & Doumer, E. (1922). Crises solaires et hypertension paroxystique en rapport avec une tumeur surrénale. *Bull. Soc. méd. Hôp. Paris*, **46**, 982–990.

Mowbray, J. F. (1959). Measurement of tissue blood flow using small heated thermocouple needles. *J. appl. Physiol.* **14**, 647–648.

Mowbray, J. F. & Peart, W. S. (1958). Some effects of noradrenaline and adrenaline on the thyroid. *J. Physiol.* **143**, 12*P*.

Smith, D. J., Syverton, J. T. & Coxe, J. W. (1951). In vitro studies of the coronary arteries of man and swine as demonstrated by a new technic, angioplethysmokymography. *Circulation*, **4**, 890–898.

Söderberg, U. (1958). Short term reactions in the thyroid gland revealed by continuous measurement of blood flow, rate of uptake of radio-active iodine and rate of release of labelled hormones. *Acta physiol. scand.* **42**, Suppl. 147, 1–113.

Strombeck, J. P. & Hedberg, T. P. (1939). Tumor of suprarenal medulla associated with paroxysmal hypertension. Report of case preoperatively diagnosed and cured by extirpation after capsular incision. *Acta chir. scand.* **82**, 177–189.

von Euler, U.S. (1951). Increased urinary excretion of noradrenaline and adrenaline in cases of phaeochromocytoma. *Ann. Surg.* **134**, 929–933.

Wégria, R. (1951). Pharmacology of the coronary circulation. *Pharmacol. Rev.* **3**, 197–246.