"double-blind" study in which some patients were treated with cortisone tablets, 25 mg. b.d., while the remainder received inert tablets.

Cortisone, in the dose used, proved to have no effect on the liability to relapse of the disease during the year of observation.

The other important finding during this period was that patients treated in the acute attack with corticotrophin were more liable to relapse than patients who had been treated with cortisone. The superiority of corticotrophin in bringing about clinical remission in the acute attack is therefore partly offset by the greater chance of subsequent relapse.

In the third part of the trial a number of the patients who relapsed during the year of maintenance were treated openly with cortisone. The results were similar to those obtained with cortisone in the original attack. In other words, patients who have previously responded well to corticosteroid therapy are neither specially likely to respond well when a subsequent attack of the disease occurs nor likely to be unduly refractory to corticosteroids.

The essential conclusions are: (1) There is little to choose between corticotrophin and cortisone in the treatment of a first attack of ulcerative colitis. (2) In a frank relapse of established ulcerative colitis corticotrophin is superior to cortisone in bringing about a fairly speedy clinical remission, but at the price of a greater risk of complications and of a higher risk of subsequent relapse. Consequently it may normally be best to begin with cortisone and to hold corticotrophin in reserve for use in patients who do not respond well. (3) Maintenance treatment with cortisone in a dosage of 25 mg. b.d. is totally ineffective in reducing the liability to relapse.

The findings are discussed in relation to new corticosteroids which have been developed since this study began and to other forms of treatment which have been used to induce remission of an attack. The need for organized therapeutic trials to compare the efficacy of these various agents is stressed.

We are indebted to the Medical Research Council for the provision of corticotrophin and cortisone, facilities for meetings, and clerical assistance; and in particular wish to thank Dr. Margaret Gorrill, of the Council's staff. We have also received invaluable help from the pharmacists of all the hospitals concerned.

REFERENCES

- Bargen, J. A. (1955). *Sth. med. J. (Bgham, Ala.)*, **48**, 192.
 Fierst, S. M., Robinson, E., Langsam, A., Werner, A., and Ingegno, A. P. (1957). *J. Amer. med. Ass.*, **163**, 1444.
 Kirsner, J. B., and Palmer, W. L. (1954). *Ann. intern. Med.*, **41**, 232.
 — Bicks, R. O., and Palmer, W. L. (1957a). *A.M.A. Arch. intern. Med.*, **99**, 642.
 — Sklar, M., and Palmer, W. L. (1957b). *Amer. J. Med.*, **22**, 264.
 Maltby, E. J., Dickson, R. C., and O'Sullivan, P. M. (1956). *Canad. med. Ass. J.*, **74**, 4.
 Morrison, L. M. (1952). *Gastroenterology*, **21**, 133.
 — (1953). *J. Amer. med. Ass.*, **151**, 366.
 Sklar, M., Kirsner, J. B., and Palmer, W. L. (1957). *Ann. intern. Med.*, **46**, 1.
 Svartz, N. (1942). *Acta med. scand.*, **110**, 577.
 — (1948). *Ibid.*, Suppl. 206, p. 465.
 — (1954). *Gastroenterology*, **26**, 26.
 — (1956). *Gastroenterologia (Basel)*, **86**, 683.
 Truelove, S. C. (1958). *Brit. med. J.*, **2**, 1072.
 — and Witts, L. J. (1954). *Ibid.*, **2**, 375.
 — (1955). *Ibid.*, **2**, 1041.
 Watkinson, G. (1958). *Ibid.*, **2**, 1077.

FALL OF BLOOD PRESSURE AFTER A NORADRENALINE INFUSION AND ITS TREATMENT BY PRESSOR AGENTS

BY

J. H. BURN, M.D., F.R.S.

AND

M. J. RAND, Ph.D.

From the Department of Pharmacology, University of Oxford

In circumstances in which the blood pressure has fallen low, noradrenaline is often given by intravenous drip in order to restore it; for this purpose noradrenaline is preferred to adrenaline because it is a more effective pressor agent and because under its influence the heart rate does not rise. The observation has often been made, however, that when the drip of noradrenaline is stopped the blood pressure falls to a low level and that the drip has to be started again to maintain the pressure at a reasonable height. Anaesthetists and others accustomed to using a noradrenaline drip know that the drip should not be stopped suddenly but should be reduced gradually, and some speak of "weaning" the patient from the drip.

Recent observations which we have made have enabled us to offer an explanation of the fall in blood pressure which occurs on stopping a noradrenaline drip, and to suggest measures for dealing with it.

Methods

The observations have been made in spinal cats prepared by Dale's method. The cat was anaesthetized with ether and the cord was exposed and cut at the level of the second cervical vertebra. The brain was then destroyed by a probe passed through the foramen magnum, after which artificial respiration was given and ether was discontinued. Noradrenaline was infused at a constant rate by using a motor-driven syringe (C. F. Palmer (London) Ltd.). Cats were given reserpine dissolved in 20% ascorbic acid by intraperitoneal injections of 3 mg./kg. on two successive days. The cats were then used for experiment on the third day. In some experiments the volume of the spleen was recorded by drawing it outside the body wall and enclosing it in a plethysmograph.

Results

Noradrenaline is ordinarily thought of as the substance released at the terminations of the post-ganglionic sympathetic fibres, and also released, together with adrenaline, from the adrenal medulla. This view is, however, incomplete. Noradrenaline is present in all organs innervated by sympathetic nerves, and can be extracted from them. This was shown by Schmiterlw (1948) for the large vessels of the ox, the horse, the dog, and the pig; and also by Euler and Purkhold (1951) for the spleen, the kidney, the liver, and the salivary glands; and by Goodall (1951) for the heart. Furthermore, Adams-Ray and Nordenstam (1956) have shown that chromaffin cells, which are known to contain adrenaline and noradrenaline, are present in human skin, and our colleague, Mr. E. H. Leach, has also found them adjoining the vessels in the skin of the rabbit ear. We were able to extract

noradrenaline from the skin of the rabbit ear (Burn and Rand, 1958a).

Evidence has recently been obtained that the noradrenaline present in these organs exerts an action of its own and modifies the response of the organ to noradrenaline reaching the organ in the blood stream. This evidence has been obtained by making use of the observation that when animals are injected with reserpine the store of noradrenaline disappears. Bertler, Carlsson, and Rosengren (1956) first observed this disappearance in the heart, and we observed the disappearance in the blood vessels (Burn and Rand, 1957). The chromaffin cells in the skin of the rabbit ear also disappear after treatment with reserpine. It has thus been possible to compare the vascular response to various pressor agents in normal animals containing noradrenaline in the vessel walls with the response in reserpine-treated animals, the vessels of which no longer contain noradrenaline, and in the skin of which chromaffin cells can no longer be found.

Noradrenaline Infusion

When noradrenaline is infused at a constant rate into a spinal cat the blood pressure rises steeply at first, but it does not remain steady at a high level. Instead the blood pressure falls in spite of the fact that the rate of infusion remains unchanged. This fall is particularly striking in cats which have been treated with reserpine and which have no noradrenaline in the vessel walls. Fig. 1 shows the effect of an infusion of noradrenaline at a rate of 65 $\mu\text{g./min.}$ for 30 minutes. The blood pressure rose to 227 mm. when the infusion began, but it fell to 68 mm. after 16 minutes and remained at about this level.

FIG. 1.—Blood pressure of spinal cat treated previously with reserpine. Intravenous infusion of noradrenaline at 65 $\mu\text{g./min.}$ as shown by the straight line. The pressure rose when the infusion began, but soon fell although the rate of infusion was maintained.

Such an infusion caused a change in the effect of noradrenaline which is illustrated in Fig. 2, taken from another experiment in a cat treated with reserpine. In Fig. 2a the injection of 3 $\mu\text{g.}$ of noradrenaline caused a rise of pressure of 78 mm.; when this rise had subsided an infusion of noradrenaline was begun, and, as in Fig. 1, the pressure fell while the infusion continued. When the infusion was stopped and the pressure had

returned to the previous level, the injection of 3 $\mu\text{g.}$ of noradrenaline then had no pressor action (Fig. 2c). Two minutes later 3.5 mg. of ephedrine hydrochloride was injected, this being equivalent to 1 mg./kg. and to the injection of 65 mg. (1 gr.) in a man. This caused a large rise of pressure. We have previously shown (Burn and Rand, 1958b) that when ephedrine is injected into a cat treated with reserpine it is without appreciable

FIG. 2.—Blood pressure of spinal cat treated previously with reserpine. (a) Rise of pressure caused by 3 $\mu\text{g.}$ noradrenaline. Beginning of intravenous infusion of noradrenaline. (b) Pressure during continuation of infusion. (c) Injection of 3 $\mu\text{g.}$ noradrenaline after infusion was stopped; injection of 1 mg. ephedrine per kg.

pressor action. Thus Fig. 2 shows that the noradrenaline infusion, which so greatly reduced the action of noradrenaline itself, greatly increased that of ephedrine.

The fact that in an animal treated with reserpine (in which noradrenaline is absent from the artery walls) ephedrine and other sympathomimetic amines have little or no pressor effect, and that they recover their pressor action after an infusion of noradrenaline, has led us to suggest that during an infusion noradrenaline is taken up and held in a store from which amines like ephedrine can release it. For convenience we shall speak of the noradrenaline which is taken up during an infusion as the store in the wall, though we do not know whether it is actually in the wall or in chromaffin cells.

The store in the wall, then, increases during an infusion of noradrenaline, and it seems to be because of this increase that the effect of noradrenaline in Fig 2c is much smaller than its effect in Fig. 2a. When an intravenous drip of noradrenaline is given to a patient we may conclude that noradrenaline is being taken up, and the vessel walls thereby become insensitive to noradrenaline. They are, however, most responsive to those sympathomimetic amines which act like ephedrine.

Sympathomimetic Amines

Sympathomimetic amines may be divided into three classes. The first class contains those substances which are derivatives of catechol and are therefore called catecholamines; these are noradrenaline, adrenaline, and dopamine. "Neophryn" (known abroad as "neosynephrine") behaves as a member of this class. A single injection produces an intense but brief response, and the pressor action of all of them is diminished after an infusion of noradrenaline. In contrast to these are members of the third class,

which includes derivatives of phenylethylamine like tyramine, and some of phenylethanolamine like ephedrine. Their pressor action is distinguished by being of longer duration, by being small in the reserpine-treated animal, and by being increased after an infusion of noradrenaline. We may consider that the members of the first class act directly on the vessel walls, while the vessels of the third class act by liberating noradrenaline from the store. The second class, which contains other derivatives of phenylethanolamine, is intermediate between the first and the third class. Its members have a good pressor action in the reserpine-treated animal; this action is reduced after an infusion of noradrenaline, but it is not reduced very much. We have examined six substances sold as pressor amines by pharmaceutical houses, three of them belonging to the third class of sympathomimetic amines and three belonging to the second.

Derivatives of Phenylethylamine

The three derivatives of phenylethylamine which we have examined were "methedrine," "mephine," and "vonedrine." Methedrine has the same formula as ephedrine but lacks the $-OH$ on the β carbon atom; mephine is *N*-methylphenyl tertiary butylamine; and vonedrine is phenylpropylmethylamine. We determined the rise of blood pressure caused by the injection of approximately 2 mg. (base) into a spinal cat—first in a normal cat, second in a cat previously treated with reserpine, and third in a normal cat at the end of an intravenous infusion of noradrenaline. The rate of infusion was always $65 \mu\text{g./min.}$, and it was continued in each experiment until a total of 2 mg. of noradrenaline was infused. Each injection of each substance was made into a cat which had not received a previous injection of any substance other than noradrenaline.

A comparison of the action of methedrine in a normal cat with its action in a cat treated with reserpine is given in Fig. 3, in which the spleen volume is also recorded. The injection of 2 mg. into a normal cat caused a rise of blood pressure and diminution of the volume of the spleen (Fig. 3.a). The same injection into a cat treated with reserpine had very little pressor action and caused no diminution of spleen volume (Fig. 3.b). The injection of 2 mg. of methedrine into a normal cat after an infusion of noradrenaline caused a greater pressor effect than that in Fig. 3.a in one experiment, and an equal effect in a second (see Table).

FIG. 3.—Blood pressure and spleen volume. Injection of 2 mg. methedrine hydrochloride into (a) normal spinal cat, (b) spinal cat previously treated with reserpine.

Rise of Blood Pressure (mm. Hg) Following the Injection of Different Pressor Substances Into Spinal Cats

Substance	Dose (Base) mg.	Normal Cat	Cat Treated with Reserpine	Normal Cat After Infusion of Noradrenaline
Methedrine ..	1.6	120	30	145
" ..	1.6			120
Mephine ..	2.0	38	34	136
" ..	2.0	12		
Vonedrine ..	1.6	110	30	94
" ..	1.6	90		
Aramine ..	2.0	176	164	112
Vasoxine ..	1.7	122	90	80
Propadrine ..	1.6	52	80	74

The action of mephine was surprisingly small in each of two normal cats, the rise in one being shown in Fig. 4.a; however, when mephine was given to a cat after an infusion of noradrenaline the rise of pressure was much

FIG. 4.—(a) Injection of 2 mg. mephine in normal spinal cat. (b) The same injection in a normal cat at the end of an intravenous infusion of noradrenaline.

greater, as shown in Fig. 4.b. Vonedrine behaved like methedrine, having only a feeble pressor action in a cat treated with reserpine, but a good pressor action after a noradrenaline infusion. Thus these three derivatives of phenylethylamine were found to have the greatest pressor effect of which they were capable at the end of a noradrenaline infusion.

Derivatives of Phenylethanolamine

Derivatives of phenylethanolamine differ from those already considered in having an $-OH$ group on the carbon atom in the side-chain which is next to the benzene ring. This $-OH$ group brings them nearer in structure to noradrenaline, and some of these substances form an intermediate group. Not all belong to this group, however, and ephedrine is one which acts like a derivative of phenylethylamine. The type of action depends on the steric configuration of the molecule, as we have discussed elsewhere (Burn and Rand, 1958b). The substances examined were "aramine," "vasoxine," and "propadrine." Propadrine has no groups in the ring, being in this respect similar to ephedrine. In the side-chain it has an $-OH$ group on the β carbon atom next the ring, and a $-CH_3$ group on the α carbon atom. The amine group is primary. Aramine has the same side chain

as propadrine and has an -OH in the meta position in the ring. Vasoxine also has the same side-chain as propadrine and has an -OCH₃ group in the 2 and 5 positions in the ring.

These substances seemed to act in part directly like noradrenaline, and in part indirectly by releasing noradrenaline. Their action in cats treated with reserpine was not very different from that in normal cats. That of aramine was slightly reduced (Fig. 5, a and b), that of vasoxine was rather more reduced (Fig. 6), while that of propadrine was increased (see Table). However, these three compounds stood in sharp contrast to the first three compounds because their pressor action after a noradrenaline infusion was less than their action in the cat previously treated with reserpine. We made no study of the duration of the rise of pressure or of the effect of repeating injections. We received the impression that aramine (Fig. 5) had the most prolonged action and that repeated injections of it were effective.

Discussion and Summary

The main conclusion from this investigation is that when an intravenous drip of noradrenaline has been given and the blood pressure falls to a low level on stopping it, the right procedure is to inject one of the pressor amines and not to resume the drip. Blacket, Pickering, and Wilson (1950) gave long intravenous infusions of noradrenaline to rabbits and found that the blood pressure fell to a very low point on stopping the infusion. During such an infusion the blood vessels

become increasingly insensitive to its pressor action. The low sensitivity to noradrenaline appears to be due to the vessels taking it up and holding it in some kind of store from which it is slowly discharged. This discharge leaves few receptors free on which noradrenaline present in the blood stream can act. The effect of the discharge on sympathetic impulses has not

FIG. 5.—Injection of 2 mg. aramine (a) into normal spinal cat; (b) into spinal cat treated with reserpine; (c) into spinal cat at the end of an intravenous infusion of noradrenaline. (a) and (b) should be compared with Fig. 3 (a) and (b).

FIG. 6.—Injection of 2 mg. vasoxine into (a) normal spinal cat, (b) spinal cat treated with reserpine. Upper record is volume of spleen.

been fully investigated, but sympathetic tone seems to be absent when a noradrenaline drip is stopped, perhaps because of ganglionic block (Bülbring and Burn, 1942).

However, when sympathetic tone is ineffective a rise of blood pressure follows the injection of a pressor amine like ephedrine or one of the six substances which we have examined. Three of these — methedrine, mephine, and vonedrine — appear to act only by liberating noradrenaline from the store, and are therefore most active at the termination of a noradrenaline infusion which has been filling the store. The other three compounds — aramine, vasoxine, and propadrine — differ in being more closely related to noradrenaline and having some direct action as well as some action in discharging the store. They do not therefore have so great a pressor action at the end of a noradrenaline infusion as they otherwise would, but their action is still large.

This work has been done during the tenure by one of us (M. J. R.) of a Fellowship given by the Australia and New Zealand Life Insurance Medical Research Fund.

REFERENCES

- Adams-Ray, J., and Nordenstam, H. (1956). *Lyon chir.*, **52**, 125.
- Bertler, A., Carlsson, A., and Rosengren, E. (1956). *Naturwissenschaften*, **43**, 521.
- Blacket, R. B., Pickering, G. W., and Wilson, G. M. (1950). *Clin. Sci.*, **9**, 247.
- Bülbring, E., and Burn, J. H. (1942). *J. Physiol. (Lond.)*, **101**, 289.
- Burn, J. H., and Rand, M. J. (1957). *Lancet*, **2**, 1097.
- (1958a). *Brit. med. J.*, **1**, 903.
- (1958b). *J. Physiol. (Lond.)*, **144**, 314.
- Euler, U. S. v., and Purkhöld, H. (1951). *Acta physiol. scand.*, **24**, 212.
- Goodall, McC. (1951). *Ibid.*, **24**, Suppl. 85.
- Schmitterlów, C. G. (1948). *Ibid.*, **16**, Suppl. 56.