this concept has important implications for neuroglial function and the blood-brain barrier. It follows that substances essential to neuronal maintenance and activity must pass from the blood-stream outwards by way of the neuroglial cytoplasm. The sucker-feet of astrocytes deployed along the vessel walls thus acquire a new significance: formerly regarded as simply providing tensile strength, they are now seen to play a dual role. Similarly the oligodendrocytes, which so often cling as satellites not only to the bodies of neurones but also to the walls of vessels, must have metabolic functions aside from those of the interfascicular oligodendrocytes which have long been supposed to help in the upkeep of the myelin sheaths.

Œdema of the Brain

The electron-microscopists have furthermore directed their studies to the condition of œdema of the brain. The conventional light-microscopist would have little hesitation in deciding that in œdema the tissue elements appear to be forced apart by extracellular fluid. The electron-microscopists, however, assert that this is wrong: the swelling is due to expansion of the cells and their cytoplasmic processes, and there is no increase in extracellular space. We should not, I think, immediately jettison the older view for the new. For on inquiry I understand that the observations made by electron-microscopy are confined to the grey matter; apparently there are certain technical obstacles that have so far precluded any trustworthy investigations of the white matter. This being so, we are back where we started from; for it is common knowledge that œdema of the brain, as a clinical and pathological manifestation, is essentially a disorder of the white matter; the cortex is seemingly little affected. Therefore until the electron-microscopists have resolved their technical difficulties, and are in a position to pronounce upon the state of the white matter in œdema we should do well to reserve judgment. Meanwhile I am given to understand that a slightly less dogmatic attitude towards the changes in œdema is being adopted.

The possibility that the outcome may prove something of a compromise is suggested by the recent investigations at Bethesda by my colleague L. J. Rubinstein, with Klatzo and Miquel (1962). Using a standardised lesion, produced by the application of cold to the exposed cortex in the cat, they studied successive changes in the œdematous white matter below the superficial area of necrosis. Their preparations clearly show a marked expansion of the fibrillary astrocytes within a few hours of the injury, accompanied by thickening of the neuroglial fibrils and, as shown by special histochemical methods for enzymes, a heightening of metabolic activity. Surprisingly, the oligodendroglia displays no obvious morphological changes, and the acute swelling of these cells, so characteristic of the œdematous human brain, was rarely seen. But at the same time the cell elements appeared to be more widely spaced so that the concept of seepage of fluid into extracellular spaces remains a possibility.

A further interesting point in this work is the observation that increased enzyme activity persists in the regional astrocytes over a period of months after the injury, when glial scar-formation is established. The significance of this is obscure, but it will be of interest to discover whether all foci of gliosis, however produced, are metabolically hyperactive, and for how long this persists.

Enough has perhaps been said to show that we have now entered a fresh phase in our ideas about the functions of the neuroglia. But before leaving the subject of œdema there is a further point that might profitably be considered. As we all know, œdema results from a variety of causes. These need not be recapitulated, but our minds should be prepared for the possibility that the morphological and histochemical changes that doubtless will ultimately be demonstrated may vary considerably with the causative agent responsible for the change. For the neurological surgeon this might well mean that different sorts of therapeutic approach would be needed to combat this important, and frequently disastrous, condition.

The "Blood-brain Barrier"

The problem of œdema, however caused, is naturally linked with that of the so-called blood-brain barrier. Amongst the current lines of investigation into the workings of this barrier I find none more intriguing than the method by which the various substances to be tested are labelled with radioactive isotopes and introduced into the blood-stream, after which autoradiograms are prepared from whole-brain slices at various intervals of time. In their fascinating paper on Drugs in the Brain, Roth and Barlow (1961) review the experiences of their group of workers. They have demonstrated surprising variations in the penetrability of different areas of the brain by different drugs. Thus with phenobarbitone the grey matter was more rapidly penetrated than the white. Though we might suppose this to be due to the greater vascularity of the grey matter, the authors discount this factor; for they found that the highly vascular colliculi and geniculate bodies contained less of the drug than would be expected on this basis. On the other hand thiopentone ('Pentothal') followed a pattern of distribution, at 1 and 5 minutes after injection, that conformed to the degree of vascularity of different parts of the brain. Acetozolamide ('Diamox'), used in the treatment of epilepsy, appeared first in the cerebrospinal fluid, and thence penetrated the ventricular walls. At later stages, when diffusion had ceased, a concentration of the drug was found in three distinct areas—the hypothalamus, the caudate nucleus, and the hippocampus. Yet the equally accessible optic thalamus was exempt. As Roth and Barlow suggest, such selectivity seems to indicate some kind of localised and active biochemical binding. Neuropharmacology thus enters a new era, in which the different aspects of regional penetrability demonstrated by autoradiography, will need to be linked to the metabolic peculiarities of the regions concerned.

Thus the blood-brain barrier promises to be far too complex to be defined in general terms applicable to the brain as a whole until the regional basis of diffusion is thoroughly dissected and understood. The furthering of this knowledge must be ardently desired by the neurological surgeon, since various forms of therapy, including the possible future treatment of inoperable tumours by cytotoxic substances, are inseparable from it. Hazy as we so often are about what obtains in the normal brain, it is obvious that far more precision is necessary before the clinician can attack a glioblastoma with some sort of cytotoxic agent without risk of damaging other parts of the brain. The manifestly abnormal structure of the blood-vessels in these tumours suggests that their permeability might well follow unique lines, but it cannot of course be assumed that these would be favourable to the treatment proposed. But this problem is perhaps beyond the scope of modern research, since malignant gliomas can be established in the laboratory animal. If the therapeutic agent to be tested could be labelled with a radioactive isotope, then autoradiography might det-

whether the tumour was selectively penetrated or not. But, lacking technical experience in these matters, it would be unbecoming for me to suggest this line of approach other than tentatively.

The handling of a malignant tumour in a young infant would also present a special problem; for, as Roth and Barlow's studies have demonstrated, the pattern of brain-penetrability in the infant differs from that of the adult. Thus the unmyelinated white matter is shown by auto-radiography to contain a significant excess of the various labelled substances tested. But, as myelination proceeds and the brain matures, this penetration correspondingly decreases. Roth and Barlow consider that myelin itself constitutes a barrier; but whether this is so, or whether the change hinges on some other aspect of maturation, is a question that must remain open for the present.

Tissue Culture

Finally I cannot forbear some reference to the method of tissue culture as a tool of research. As yet this has not been fully exploited in spite of the great technical improvements that have been introduced in the past decade. Much could be learnt from observing the effects of specific agents upon the living cell—e.g., the enhancement by serotonin of the contraction of oligodendroglial cells (Benitez et al. 1955). Cinematography is of course implicated here as an auxiliary technique. More recently Margaret Murray's team has done illuminating work bearing on experimental allergic encephalomyelitis. Treating cultures of newborn-rat cerebellum with the sera of rabbits which had been sensitised by the method of Waksman et al. with emulsions of brain and adjuvants, they demonstrated that those sera had a rapid dissolving effect upon the myelin sheaths in their cultures, but the neurones and axis cylinders were relatively spared. In control experiments the sera of untreated animals produced no effect (Bornstein and Appel 1961).

At Leeds Prof. C. E. Lumsden (1960) has demonstrated the phagocytosis of human lepra bacilli by Schwann cells in culture. A fertile source of these cells was found in biopsy material from acoustic tumours. Apart from the light thrown by this work on the probable method of propagation of the disease in man, these observations have the additional merit of supplementing our knowledge of Schwann-cell activities. These might well be regarded as first-class examples of the way in which the tissue-culture technique can be harnessed to current problems.

Further Research

Many other lines of research might be touched upon, but my review to be longer. Those I have mentioned have been chosen because they seem to offer the greatest promise. In particular electron-microscopy, histochemistry and autoradiography have the great merit of breaking entirely new ground, and the harvest should be rich. To reap this harvest a stern effort is necessary. It is to estimate that new methods of research are so often needed. The spare parts of a bicycle-pump will no longer suffice in the laboratory. On the contrary elaborate apparatus is needed. After a few years this is apt to become out of date in favour of something even more expensive. The initial outlay for all this should be squarely faced and, provided that the right man produces the right sort of work, no time should be lost in setting him to work. Heed the counsel of perfection: in this country procedure committees inevitably delays decision. Moreover the Treasury departments, and other bodies that hold the moneybags, do not always appreciate the urgency of research that is not of an obvious ad-hoc character.

Whilst I was writing these lines *The Lancet* (1961, ii, 1137) reached me with a report of the Second International Congress of Neurological Surgery held in Washington. I find my sentiments echoed in the concluding paragraph of this report:

> " It is healthy for us to consider where British neurosurgery stands in the world forum provided by this congress. In applied (clinical) neurology and in accepted surgical techniques it equals the best found anywhere. . . . But where we fall behind is in the area of basic research. . . . The imagination of our neurosurgeons will readily provide the ideas, but the imagination of the hospital and Ministry administrators must be fired so that they see the need and provide the means."

I conclude with the sincere hope that suitable incendiary rockets may be devised to promote this desirable effect. The alternative is too dreary to be contemplated.

REFERENCES

Benitez, H. H., Murray, M. R., Woolley, D. W. (1955) Proceedings of 2nd International Congress of Neuropathology part ii, 423.
Bornstein, M. B., Appel, S. H. (1961) *J. Neuropath. exp. Neurol.* **20**, 141.
Isaacs, H., Medalie, M., Politzer, W. M. (1959) *Brit. med. J.* i, 401.
Lumsden, C. E. (1960) International Congress Clinical Pathology, Madrid.
Mason, G. A., Hart-Mercer, J., Millar, E. J., Strang, L. B., Wynne, N. A. (1957) *Lancet*, ii, 322.
Robertson, W. F. (1900) A Text-book of Pathology in relation to Mental Diseases. Edinburgh.
Roth, L. J., Barlow, C. F. (1961) *Science*, **134**, 22.
Rubinstein, L. J., Klatzo, I., Miquel, J. (1962) *J. Neuropath. exp. Neurol.* **21**, 116.
Scharrer, E., Scharrer, B. (1940) *Res. Publ. Ass. nerv. ment. Dis.* (1939) **20**, 170.
Sloper, J. C., Adams, C. W. M. (1956) *J. Path. Bact.* **72**, 587.

PHARMACOLOGY OF A NEW ADRENERGIC BETA-RECEPTOR-BLOCKING COMPOUND (NETHALIDE)

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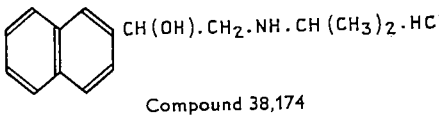
IT is well established that the classical adrenergic blocking drugs, such as phenoxybenzamine, do not effectively antagonise the myocardial responses to catecholamines (Nickerson 1959). An explanation of this was offered when Ahlquist (1948) proposed a dual adrenergic receptor mechanism which included the myocardial responses in the beta-receptor group. After Powell and Slater (1958) had introduced dichloroisoprenaline (D.C.I.) as a specific adrenergic beta-receptor antagonist, Moran and Perkins (1958) showed that it effectively antagonised the myocardial rate and tension changes produced by catecholamines. However, later work (Furchgott 1959, Dresel 1960), and our own observations, showed that D.C.I. itself was also a potent sympathomimetic agent, both on isolated heart preparations and on the heart-rate of anæsthetised and conscious cats and dogs. Since 1958 we have been trying to find an effective beta-receptor blocker which would be free from intrinsic sympathomimetic activity so that its possible therapeutic use could be explored in certain cardiac disorders, such as angina and the tachycardias. Compound 38,174 (2-isopropylamino-1-[2-naphthyl]ethanol hydrochloride,* now referred to as nethalide, 'Alderlin' †) appears to satisfy these criteria.

* U.K. patent application no. 15716/60.
† 'Alderlin' is a trade mark which is the property of Imperial Chemical Industries, Ltd.



Compound 38,174

This paper summarises some of the pharmacology and toxicology of compound 38,174.

Results

Effects of Compound 38,174 on Isolated Tissues

The adrenergic blocking actions of compound 38,174 were investigated in a series of isolated tissue preparations by means of conventional in-vitro techniques. In these experiments replicated 3-point dose-response curves to adrenaline were obtained in the presence of at least two different concentrations of antagonist; the results are summarised in the table. Highly active blockade was only found on those tissues which have been classified as containing adrenergic beta receptors.

Unlike D.C.I., compound 38,174 showed little intrinsic sympathomimetic activity on these preparations. The antagonism to catecholamines seemed to be specific since the positive inotropic responses of papillary muscles to barium chloride and ouabain were not blocked. Depression of the papillary muscle contractions could be produced by drug concentrations which were ten times greater than the blocking concentration.

Effects of Compound 38,174 on Heart-rate

The effects of compound 38,174 on catecholamine-induced tachycardia were investigated in cats anæsthetised with choralose. Heart-rates were recorded on a kymograph using a cardiotachometer which was triggered by the cardiac QRS voltage. Repeated submaximal increments in heart-rate were produced by either right stellate ganglion stimulation (in animals with chest closed and spontaneously breathing) or by intravenous injections of isoprenaline. These responses were standardised during the control period. Estimates of inhibition of these heart-rate changes were made either 15 minutes after a single intravenous injection of the compound, or at the end of a 30-minute continuous intravenous infusion of the compound.

In 8 experiments, an average of 40% (S.E. ±2·4) increase in heart-rate, produced by isoprenaline injections, was reduced by an average of 57% (S.E. ±7·0) after a single intravenous injection of 2·5 mg. of compound 38,174 per kg. body-weight. In a similar series of 6 experiments, the 52% (S.E. ±10·1) increase in heart-rate, produced by right stellate ganglion stimulation, was reduced by 90% (S.E. ±2·0) after 5 mg. per kg. body-weight intravenously.

Besides antagonising these induced tachycardias, compound 38,174 usually produced a significant reduction in the resting heart-rate. This bradycardia was also seen in atropinised or vagotomised animals. In 7 experiments, 200 µg. of compound 38,174 per kg. body-weight per minute for 30 minutes reduced the heart-rate by 16% (S.E. ±3·0). When the heart-rate had returned to control levels, bilateral stellate ganglionectomy reduced the heart-rate by 11% (S.E. ±2·2). A second infusion of compound 38,174 now reduced the heart-rate by only 6% (S.E. ±1·1). Hence, it is possible that the bradycardia is due to blockade of the endogenous cardiac sympathetic drive.

Effects of Compound 38,174 on Electrocardiograms

In dogs anæsthetised with pentobarbitone, intravenous doses of compound 38,174 of up to 20 mg. per kg. body-weight produced very little change in the electrocardiogram. In 21 experiments the most consistent change was an increase in the Q-T interval which was proportional to the reduction in heart-rate.

In these experiments compound 38,174 was found to be effective in preventing most of the E.C.G. changes produced by catecholamines. Shortening of the P-R and Q-T intervals, produced by catecholamines and cardioaccelerator nerve stimulation, were regularly blocked. The compound prevented the T-wave changes normally produced by sympathetic-nerve stimulation (fig. 1) and isoprenaline. However, some T-wave changes were still produced when noradrenaline or adrenaline were given after the drug. These changes in terminal repolarisation are possibly related to the pressure-loading of the heart from unblocked peripheral vasoconstriction and are similar to those produced by a " pure " vasoconstrictor such as methoxamine.

Effects of Compound 38,174 on Heart Contractions

The effects of compound 38,174 on heart contractions were investigated in 5 cats using a Cushny myocardiograph, in 8 dogs using a direct-body acceleration ballistocardiograph, and in 5 dogs using a strain-gauge arch attached to the left ventricle. In the cat experiments, sympathetic inotropic responses were produced by left stellate ganglion stimulation and 5 mg. per kg. body-weight intravenously of the compound produced 86% (S.E. ±4·2) inhibition of the responses. In dogs, 2·5 mg. per kg. intravenously produced 78% (S.E. ±5·9) inhibition of the increase in peak-to-peak amplitude of the initial systolic excursions of the acceleration ballistocardiogram. Besides reducing the amplitude of inotropic increases to catecholamines, compound 38,174 antagonised the effects of catecholamines in shortening the delay between ventricular activation and systolic ejection and in shortening the duration of systole.

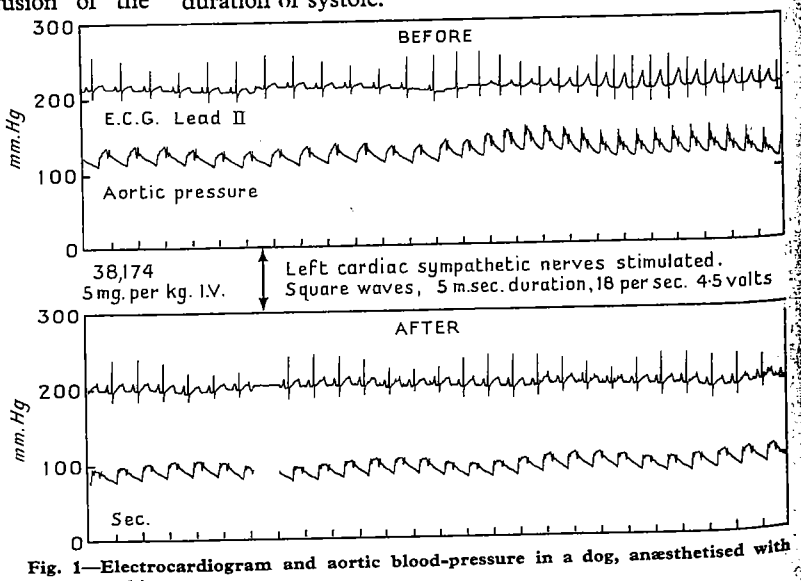


Fig. 1—Electrocardiogram and aortic blood-pressure in a dog, anæsthetised with pentobarbitone.

The animal was open-chested and maintained on a respiratory pump. Both cardio-accelerator nerves were cut. Stimulation of the left cardiac sympathetic nerve drove the heart into nodal rhythm and increased the pulse-pressure. After giving compound 38,174, these E.C.G. and pulse-pressure changes were completely blocked.

EFFECTS OF 38,174 ON RESPONSES OF ISOLATED TISSUES TO ADRENALINE

Tissue	Species	Response to adrenaline	Type of receptor	No. of experiments	Approx. conc. 38,174 giving 50% inhibition of adrenaline responses (g. per ml.)
Papillary muscle (rate controlled)	Guineapig	Increased tension	Beta	17	$10^{-7.7}$
Papillary muscle (rate controlled)	Cat	Increased tension	Beta	14	$10^{-7.3}$
Perfused heart (Langendorff)	Guineapig	Increased rate	Beta	5	$10^{-8.7}$
Tracheal chain	Guineapig	Relaxation	Beta	1	$10^{-7.7}$
Cæcum	Fowl	Relaxation	Beta	6	$10^{-8.0}$
Duodenum	Rabbit	Relaxation	Beta	3	$10^{-5.7}$
Uterus	Rabbit	Contraction	Alpha/beta	2	No block at 10^{-5}
Perfused ear vessels	Rabbit	Constriction	Alpha	4	No block at 10^{-6}

While rapid intravenous injections of compound 38,174 usually depress contractions, slow intravenous infusions produce very small changes. In the strain-gauge experiments, there was an average of 6% decrease in contractions after 2·5 mg. per kg. body-weight had been given over a period of 25 minutes. Part of one of these experiments is shown in fig. 2. In 4 of these experiments, aortic blood-flow was measured by applying an electro-magnetic (Medicon) flowmeter to the root of the aorta. In only 1 experiment was aortic blood-flow reduced even although there was a slight reduction in heart-force and heart-rate. These changes reflect the hypotension and peripheral vasodilatation produced by the compound.

Effects of Compound 38,174 on Blood-pressure

In anæsthetised animals arterial blood-pressure usually falls after administration of compound 38,174. In 13 experiments in cats, the blood-pressure was lowered by 11% (S.E. ±2·2) 15 minutes after 2·5 mg. per kg. intravenously, and by 19% (S.E. ±3·4) after 5 mg. per kg. intravenously. Rapid intravenous injections of the compound, which can produce myocardial depression, usually lead to a sharp fall in blood-pressure; reduced cardiac output may be involved. However, the hypotension which follows slow administration of the compound is associated with peripheral vasodilatation. The nature of this vasodilatation is still being investigated, but it seems to be more distinct in anæsthetised than in conscious animals.

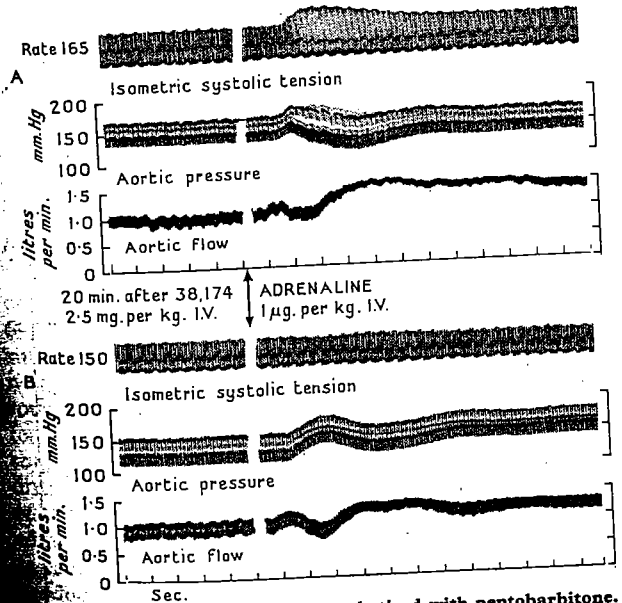


Fig. 2—Records from a dog anæsthetised with pentobarbitone. A strain-gauge arch was sutured to the wall of the left ventricle to record systolic isometric tension; the probe of a Medicon electromagnetic flowmeter was applied to the root of the aorta to record mean aortic blood-flow; and a steel probe was passed down the left common carotid artery into the aorta to record aortic blood-pressure on an electromanometer. The injection of adrenaline increased myocardial tension changes, aortic pulse-pressure, and aortic blood-flow. Compound 38,174 blocked the changes in myocardial tension and aortic pulse-pressure and reduced the increase in aortic blood-

Absorption, Distribution, Metabolism, and Duration of Action of Compound 38,174 (in collaboration with Dr. W. A. M. Duncan)

The compound was rapidly absorbed from the intestine of anæsthetised dogs. In 3 experiments, 50 mg. of compound was introduced into a 15 cm. loop of jejunum. 50% of the dose was absorbed in approximately 12 minutes, and 90% of the dose in 30 minutes. In conscious dogs peak blood-levels were reached about an hour after oral dosing.

After absorption, the drug appeared to be rapidly localised in the tissues from which it then disappeared at about the same rate as it did from the blood. The highest average tissue concentrations were found in the spleen, followed by kidney, brain, heart, and uterus; no drug was found in the liver or adipose tissue. The concentration of compound 38,174 in the brain was approximately 100 times, and the concentration in the heart about 30 times, the blood concentration. From an analysis of blood samples, no evidence has been obtained for tissue accumulation of the compound in dogs receiving up to 160 mg. per kg. body-weight per day.

In dogs, less than 1% of an administered dose is excreted unchanged in the urine, but so far no metabolic products have been identified. Using in-vitro techniques, it appears that the liver is the only organ which can rapidly metabolise the compound.

While compound 38,174 is essentially short-acting, the duration of effective blockade is determined by the dose and route of administration. 4 dogs still showed some blockade 4–6 hours after oral doses of 10 mg. per kg. body-weight.

Toxicology of Compound 38,174 (in collaboration with Dr. G. E. Paget)

Estimates of acute lethal toxicity were made in mice and rats. The L.D.$_{50}$ was 45–50 mg. per kg. body-weight when the drug was given intravenously, and around 900 mg. per kg. when the drug was given orally. Death occurred from pulmonary œdema and convulsions. Maximum oral doses of 300 mg. per kg. have been given to cats and 250 mg. per kg. to dogs. The cats developed coarse tremors and, on two occasions, went into convulsions. The dogs developed coarse tremors and sometimes were unable to stand; they seemed dissociated and withdrawn from their environment. These " central " manifestations appeared about 1 hour after dosing and had always completely disappeared by 6 hours.

When rats were given 250 mg. per kg. twice daily for 4 weeks, the weight gain was the same as in the control group. Other than dilated pulmonary lymphatics, no organ was found to contain histological lesions which could be attributed to the drug. Postmortem histological

examination of tissues from dogs which had received 150 mg. per kg. per day for 4 weeks showed no changes attributable to the drug. No significant hæmatological or biochemical changes were found. No abnormalities were found during life in blood biochemistry or electrocardiograms, and no postmortem abnormalities were found in another group of dogs which had been given 160 mg. per kg. per day for 6 months. A chronic toxicity test in rats is still in progress and will be terminated at 1 year.

Discussion

From the evidence presented here it appears that compound 38,174 effectively blocks the myocardial adrenergic receptors. This type of blockade seems to have few adverse physiological consequences. Doses of compound 38,174, which have been shown to produce effective β-receptor blockade, have been given to unrestrained mice, rats, rabbits, cats, dogs, and monkeys without producing any visible changes in visceral or behavioural activity. In these animals the only consistent change which has been established is that the animals develop some degree of bradycardia. This has been attributed to cardiac sympathetic blockade. The cardiovascular actions of compounds 38,174 did not limit the conscious animal's capacity for exercise in our screening and toxicity experiments.

The toxicity tests have established that there is a wide margin between active and toxic doses. Muscular tremor —the first sign of toxicity in dogs—first appeared at doses estimated to be about 7–10 times the effective blocking doses. In rats, signs of left ventricular failure appeared at doses about 20 times greater than the effective blocking dose. No other types of toxic manifestation were seen, and there was no microscopic or biochemical evidence of a chronic toxic effect on any internal organs.

We are hoping that this compound will be sufficiently active to examine some pharmacological and clinical problems. For example, will conditions such as atrial fibrillation, and atrial and ventricular tachycardia, be helped by reducing the cardiac sympathomimetic responses to anxiety, emotion, and exercise? Again, will myocardial adrenergic blockade reduce the myocardial demand for oxygen, and, if so, will this be helpful to patients with angina? These are some of the problems we are currently investigating with compound 38,174.

Summary

Evidence is presented in brief that 2-isopropylamino-1-(2-naphthyl) ethanol hydrochloride (nethalide, compound 38,174, ' Alderlin ') is an effective antagonist of adrenergic beta receptors.

This compound blocks the cardiac rate of tension changes produced by catecholamines, but differs from dichloroisoprenaline (D.C.I.) in being free from intrinsic sympathomimetic activity.

In conscious animals, bradycardia is the most obvious sign of activity of the compound; it is suggested that this is due to myocardial adrenergic blockade.

We have received help from so many colleagues that we cannot mention them all individually; but the outstanding contributions of our technicians, Mr. B. Horsfall, Mr. D. Dunlop, Mrs. J. Maund, Miss J. Witty, and Mr. R. Mellor, have earned our special thanks.

REFERENCES

Ahlquist, R. P. (1948) *Amer. J. Physiol.* **153**, 586.
Dresel, P. E. (1960) *Canad. J. Biochem.* **38**, 375.
Furchgott, R. F. (1959) *Pharmacol. Rev.* **11**, 429.
Moran, N. C., Perkins, M. E. (1958) *J. Pharmacol. exp. Therap.* **124**, 223.
Nickerson, M. (1959) *Pharmacol. Rev.* **11**, 443.
Powell, C. E., Slater, I. H. (1958) *J. Pharmacol. exp. Therap.* **122**, 480.

CLINICAL PHARMACOLOGY OF A BETA-ADRENERGIC-BLOCKING AGENT (NETHALIDE)

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FOLLOWING the demonstration by Black and Stephenson (1962) that 2-isopropylamino-1-(2-naphthyl) ethanol hydrochloride (compound 38,174, now referred to as nethalide), antagonises beta-adrenergic activities without the stimulatory effect of dichloroisoprenaline, it was decided to carry out experiments in man to see if comparable blocking action could be achieved without serious side-effects. We describe here the effect of the drug on the circulatory and respiratory response to adrenergic stimulation. Pilkington et al. (1962) deal with the effect on adrenergic metabolic actions.

Methods

Forearm blood-flow was measured by mercury strain-gauge plethysmography. Blood-pressure was recorded by means of a brachial arterial needle and Statham strain-gauge. Respiration was recorded by mercury in rubber strain-gauges around the chest and upper abdomen.

Exercise tests were performed in the sitting position on a bicycle ergometer. Normal subjects usually exercised for 3 to 5 minutes at each of two rates of work. Patients with ischæmic heart-disease exercised at a low rate initially (usually 20 watts), and the rate was increased in steps of 20 watts (corresponding to an increase in oxygen consumption of 200–300 ml. per

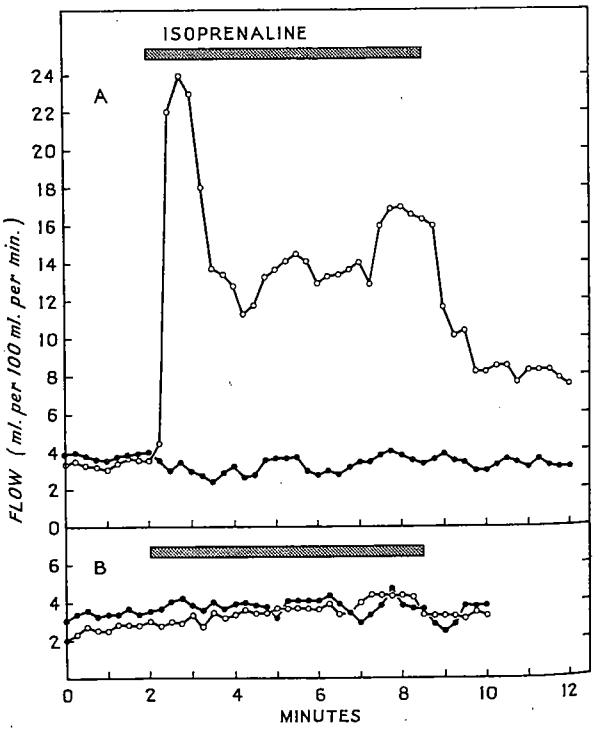

Fig. 1—Effect of compound 38,174 on response to intra-arterial isoprenaline (open circles denote experimental arm and closed circles control arm): A, effect on forearm blood-flow of intra-arterial isoprenaline, 0·1 μg. per min; B, same experiment following intra-arterial infusion of 20 mg. of compound 38,174, showing complete block of response.

minute) every 3 minutes until cardiac pain developed or the patient felt too tired to continue; the electrocardiogram was recorded every minute during the test.

Cardiac output was estimated by the dye-dilution technique using Coomassie-blue with the Cambridge earpiece and mark-2 recorder.

Results

Effects of Intra-arterial Infusion

Infusion of compound 38,174 into the brachial artery at a rate of 5 mg. per minute caused an immediate rise of forearm blood-flow to between 2 and 5 times the resting level, and a skin flush was usually seen. A steady state was reached after a minute or so, and thereafter the raised flow remained constant until the infusion was stopped, when it rapidly returned to the resting level.

After the infusion, the dilator response to intra-arterial isoprenaline (0·1 μg. per minute) was inhibited (fig. 1). Increasing the dose to 1 μg. per minute resulted in a partial breakthrough.

The initial response to intra-arterial adrenaline was reversed, the usual sharp increase in flow being replaced by a fall, giving a purely constrictor response. The response to intra-arterial noradrenaline was not significantly changed.

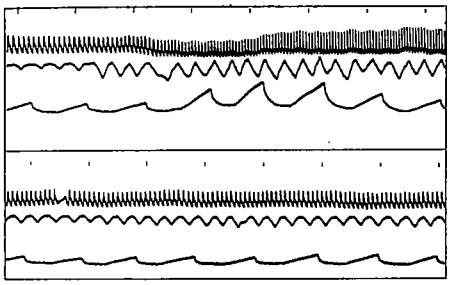

Fig. 2—Effect of compound 38,174 on response to intravenous isoprenaline.

Upper tracing shows effect of intravenous isoprenaline, 10 μg. per min., on (from above downwards) brachial arterial pressure, respiration, and forearm blood-flow (time intervals = 10 sec.).

Lower tracing shows effect of infusing isoprenaline at same rate after intravenous administration of 110 mg. of compound 38,174. The response is almost completely blocked.

Effects of Intravenous and Oral Administration

The drug was given intravenously to 6 subjects, a total of 1–1½ mg. per kg. body-weight being given over 6–10 minutes. Towards the end of the infusion, all the subjects developed a feeling of unsteadiness and some noted that objects appeared to move if the head was rotated suddenly while the gaze was fixed. These symptoms were never accompanied by nystagmus, but some subjects developed nausea and 1 had paræsthesiæ. The disturbance of balance resulted in an uncertain gait on a wide base, but Romberg's sign was negative. Oral administration, either as a single dose of 200–300 mg., or as repeated doses of 100–200 mg. three times a day, also produced unsteadiness, nausea, and vomiting in some subjects; but the symptoms tended to subside with continued administration, and there was much variation in individual susceptibility. Other symptoms sometimes noted included sleeplessness and diarrhœa.

When given intravenously, the drug had no consistent effect on the resting pulse-rate, blood-pressure, or respiration. The effect on the pulse-rate of oral administration in a larger series of subjects will be discussed later.

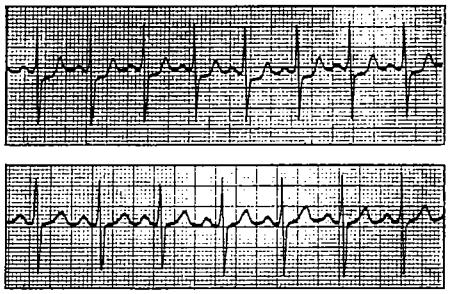

Fig. 3—Effect of compound 38,174 on the exercising electrocardiogram in angina.

Above, lead CR_2 during exercise at 40 watts. There is pathological ST depression, and the patient had cardiac pain.

Below. Same lead after same amount of exercise following oral administration of 250 mg. of compound 38,174. The rate is slower, there is no ST depression, and the patient did not have pain at this level of work.

Effect on Response to Intravenous Catecholamines

The cardiac effects of intravenous isoprenaline, 10 μg. per minute, were completely inhibited by prior administration of the drug, given intravenously (1–1½ mg. per kg. body-weight) in 3 cases, and orally (4 mg. per kg.) in 1 case (fig. 2). The effect on respiration and forearm blood-flow was also abolished. In 2 subjects, dose response curves of the circulatory response to isoprenaline (Dornhorst and Herxheimer 1958) were constructed before and after administration of the drug. These indicated that the potency of the isoprenaline was reduced to about one-eighth.

The response to intravenous adrenaline was strikingly altered when the drug had been given either intravenously or orally. Mean blood-pressure rose, bradycardia developed, and the effect on respiration was abolished. The unpleasant subjective sensations were much reduced.

The effect of intravenous noradrenaline was not greatly changed, but bradycardia was more pronounced and the respiratory effect was inhibited.

Effect on Cardiac Response to Exercise in Normal Subjects and in Patients with Ischæmic Heart-disease

The effect on the heart-rate at rest and during exercise was studied after giving the drug by mouth in single doses of 200–300 mg. In the 10 subjects with normal hearts, the resting rate was slowed by an average of 9%, the falls ranging from nil to 26%. The athletically trained tended to show little or no reduction, whilst, in the nervous and those unaccustomed to exercise, slowing was more distinct. In all 10 subjects the heart-rate during exercise was slowed by the drug, the falls ranging from 4 to 25%, with an average of 13%. Again the effect was most distinct in those unaccustomed to exertion.

In the 14 patients with angina, the heart-rate in the exercise test after the drug was compared with that in a test following a placebo, and not, as with the other subjects, with a simple control test. A reduction in the resting rate was found which varied from 3 to 31% with an average of 14%; the exercising rate fell by 10 to 31% with an average of 18%; 9 patients achieved one further 20 watt increment in the rate of work before pain developed. In 5, the electrocardiogram after taking the drug showed less abnormality than it had at comparable rates of work in the control run (fig. 3).

The effect of the drug on the cardiac output during exercise was studied in 2 normal subjects, and the results are shown in the accompanying table. The output was