ADRENERGIC DRUGS AND THEIR ANTAGONISTS IN ANAESTHESIA

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Adrenergic drugs and their antagonists have a broad range of actions. The following is orientated to a consideration of these drugs as they affect the anaesthetist in the operating theatre and in the pre- and postoperative management of patients.

THE PHYSIOLOGY AND PHARMACOLOGY OF SYMPATHETIC TRANSMITTERS

Adrenergic substances figure in both the sympathetic division of the autonomic nervous system and the endocrine system. In the former they act as the transmitter at the neuro-effector junction, and in the latter as the secretion of the adrenal medulla.

A teleological approach to the integrated activity of these two systems is appealingly simple. The "aim" of the sympathetic system initially appears to be twofold; firstly to adapt the organism quickly from basal to maximal activity in the face of danger, and secondly, if injury is sustained, to improve the chances of recovery and survival. The weakness of such an approach is immediately apparent. Identical mechanisms cannot be invoked to achieve disparate aims. For example, maximal muscle blood flow is a prerequisite for successful "flight or fight", but is unnecessary after injury. Thus, teleological reasoning has adversely influenced the understanding and treatment of "shock" for many years. It would seem more logical to assert that the mechanism is geared to the successful adaptation of the organism to a threatening situation. The response to trauma is less appropriate, particularly when injury is severe. Again, in terms of another well-worn cliché the concept of "the survival of the fittest" is not compatible with the concept of a mechanism aimed at the survival of the severely damaged.

If, then, one views the adrenergic system as a means of transforming the organism quickly from the basal state to maximal activity, the actions of these drugs can be viewed logically. They divide into a mechanism for improving cardiac output, a means of distributing it in the most appropriate way, and a mechanism for facilitating metabolic energy transformation both in terms of the whole organism and at a cellular level. In the present state of evolution of anaesthesia the greatest interest has centred on the effects on cardiac output and its distribution, and this will figure largely in the following discussion. In the author’s opinion, however, the metabolic aspects, particularly at the cellular or sub-cellular level will repay considerable interest in the future.

The process of cardiovascular adaptation is achieved by the varying interplay of two naturally occurring adrenergic substances acting on two types of receptors. The location and density of these receptors and the proportions of the two adrenergic stimulators to which they are exposed explain the range of physiological response of the system. Ahlquist (1948) first postulated that there existed two types of receptors, which he named alpha and beta. All tissues contain both receptors, but in every tissue one is predominant and biases the effect of adrenergic stimulation in that tissue. In blood vessels stimulation of alpha-receptors causes vasoconstriction, while beta-receptor stimulation causes vasodilatation. The distribution density of the receptors in any tissue can be deduced from our working concept of their purpose. Alpha-receptors predominate in tissues which in the short-term view can exist with a reduction in blood supply, such as skin, kidney and the splanchic bed. Beta-receptors predominate in muscle, ensuring a blood supply for maximal activity. In heart muscle also, beta-receptors predominate and in this situation stimulation by a suitable adrenergic substance results in an increase in the rate and force of the heart.

The receptors may be stimulated by adrenaline or noradrenaline, or both. Noradrenaline is the physiological adrenergic transmitter at most nerve
### Table I

Structure-activity relationships of some adrenergic stimulators.

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<th>Pharmacological consequence</th>
<th>Individual drugs</th>
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<td>Number of —OH groups in ring</td>
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<td>Meta-OH group present</td>
<td>Decrease in number of OH groups increases transmitter releasing action</td>
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endings, and has considerably greater stimulating activity at alpha-receptors than beta-receptors; vasoconstriction is therefore its dominant action. Alpha-receptors also predominate in the capacitance vessels of the cardiovascular system. Thus in the non-emergency situation the sympathetic nervous pathways, by influencing the overall arteriolar resistance and the capacity of the venous system, control cardiac output and blood pressure and enable changes in posture and moderate activity to be accommodated. Baroreceptors sense and regulate this mechanism in such a way as to ensure the adequacy of the arterial blood supply to the brain.

Under conditions of greater stress when sympathetic nervous activity is intense, the mechanism is reinforced by the release from the adrenal medulla of additional noradrenaline, and even more adrenaline, roughly in the proportions 20:80 in man (von Euler, 1954). The dominant secretion here, adrenaline, differs from noradrenaline in having greater beta-receptor stimulating activity. In consequence, reinforcement of cardiac output occurs by increase in rate and force of contraction; voluntary muscle blood vessels are also dilated. Adrenaline is also a powerful alpha-receptor stimulator, and in tissues in which this is the predominant receptor, vasoconstriction still occurs. Specific blockade of alpha-receptors enables beta-receptor stimulation to be unmasked—this is the basis for the “adrenaline-reversal” phenomenon of ergot. Thus these two adrenergic substances mediate the whole range of responses by stimulating the two types of receptors at different intensities.

Although no other adrenergic compounds exert any physiological action, it is convenient to review them generally at this point. Their more detailed pharmacology is presented by Foster (1966), and by Rand and Trinker (1966) elsewhere in this issue.

We have seen that two closely related chemical compounds stimulate two kinds of receptors with differing intensity. Small modifications of these molecules result in many compounds having related effects. Thus some synthetic compounds have marked activity at alpha-receptors, some stimulate beta-receptors predominantly and others influence both receptors in varying proportions. However, many synthetic adrenergic drugs also act indirectly to cause a release of noradrenaline from sympathetic nerve endings. Since this is predominantly an alpha-receptor effect, such compounds have marked alpha-activity irrespective of their own direct actions on receptors. Agents which affect the storage and release of noradrenaline must be expected to modify the response to such indirectly acting drugs (Dingle, 1965).
Structure-activity relationships.

The proportion of direct to indirect action at alpha-receptors is related to the number of hydroxyl groups both on the ring and in the beta-carbon position of the chain (see table I). Adrenaline and noradrenaline have hydroxyl groups in the meta- and para-positions of the ring, and on the beta-carbon of the chain. The presence of a hydroxyl group on the beta-carbon in the chain confers an overriding direct action as in methoxamine, whereas reduction to one or no hydroxyl group on the ring enhances the indirect noradrenaline-releasing action. Phenylephrine and metaraminol have the beta-carbon hydroxyl, and one hydroxyl on the ring, and therefore are still dominantly direct acting. Methamphetamine and mephentermine have no hydroxyl groups either in the beta-position of the chain or on the ring and therefore act indirectly. The size of the substitution group on the amine radical determines the relative effects on alpha- and beta-receptors. In general, the smaller the group the greater is the stimulation of alpha-receptors. Beta-activity is associated with large substitutions at this site. Substitution on the alpha-carbon atom of the chain interferes with oxidation of the amine and prolongs its action, if no meta-OH group is present.

Other molecular modifications result in compounds which have an affinity for one or other receptor site without stimulating it, and produce a relatively long-acting competitive blockade of the receptors against the various stimulators. Anaesthetists are familiar with this concept in the action of tubocurarine in blocking the neuromuscular site against the action of the normal transmitter, without stimulating the receptor. The refinement in the situation under discussion is that the blocking drugs are specific for one or other receptor types, and in the presence of blockade of one, transmitters effective at both will continue to exert an action at the other site. It must be emphasized that the blocking compounds are remarkably specific whereas most stimulating drugs are non-specific, exerting actions at both alpha and beta receptors.

Adrenergic stimulators in anaesthesia

The literature on adrenergic drugs is so vast that it is possible to quote references in favour of almost any drug in any situation. Exhaustive reviews rarely clarify and in the following the practical aspects of the clinical situation will be foremost within the theoretical framework already outlined.

The presence of certain volatile anaesthetics create a special and common problem when adrenergic stimulators are given for any purpose. This is discussed by Katz and Katz (1966) and Price (1965) in this issue.

Regional alpha-receptor stimulation.

In situations in which local areas of vasoconstriction are required, a drug with maximal alpha-receptor activity is indicated. Furthermore, it should act directly on the receptors rather than by release of noradrenaline. Adrenaline is commonly incorporated in injections of local anaesthetics, often in amounts that are unrelated to the nature or concentration of the drug (Aström, 1965). Phenylephrine being an almost pure alpha-stimulator is also a good choice in this application and is widely incorporated in nasal decongestants.

Adrenergic drugs in hypotension.

The indications for systemic adrenergic drugs have been often debated. Several types of situation can be delineated in which their use can be considered as rational even though there may be disagreement concerning necessity.

Efferent sympathetic block.

This may accompany extensive spinal and epidural anaesthesia, or the administration of systemic ganglion block. An inadequate efferent sympathetic response may also play some part in postural hypotension.

Spinal or epidural analgesia blocks sympathetic impulses to an extent that depends on the number of segments of the thoraco-lumbar chain that are anaesthetized. There is an accompanying bradycardia which has been attributed to the blocking of the sympathetic cardiac nerves which will follow an autonomic block up to the level of T.4. This is not uncommon because the sympathetic level can be expected to be at least two segments greater than the sensory level. It may be that the temporary denervation of the adrenals, which is followed by a fall in circulating adrenaline (Marley and Paton, 1961) is also important. Systemic ganglion blocking agents, on the other hand, block parasympathetic ganglia also, and when vagal tone predominates tachycardia follows.
Even after complete sympathetic blockade the blood pressure does not necessarily fall to unrecordable levels, and opinions differ as to the desirability of raising it. Macintosh (1957) stated that apart from the special situation of a delay in starting a Caesarian section, he had never given a vasopressor for the hypotension of spinal analgesia. Not all would accept this point of view. Ultimately, the decision to attempt to raise the blood pressure will be taken by the individual anaesthetist according to his views as to what is safe for any particular patient in the relevant circumstances. A majority view would probably be that in a previously normotensive patient the systolic pressure should not fall below 60 mm Hg, although it is difficult to adduce evidence that this figure is more correct than another (Larson, 1964). The fundamental necessity is adequate coronary and cerebral perfusion, which may be as dependent on the rate of fall of blood pressure as much as the absolute level reached.

Although the hypotension is related to diminished sympathetic activity, sympathetic stimulation is not the only, or necessarily the best way of reversing it. The absolute level of pressure for any degree of blockade is the resultant of the vascular capacity and the intravascular volume. In some situations, for example, when a considerable degree of hypotension is desired, increasing the intravascular volume may be a more controllable way of making marginal adjustments albeit relatively slowly. Changes in posture, too, may be all that is necessary (Shepperd and Grace, 1961).

If a rapid change is required the choice of drugs is influenced by practical considerations. A predominant alpha-activity is required, but in the normal patient whether this is achieved directly or by release of normal transmitter is immaterial. However, those acting directly appear to be less likely to cause trouble to a myocardium already sensitized by halogenated hydrocarbon anaesthetic. Pure alpha-stimulation has been condemned on the grounds that it raises the cardiac work load but does not directly help cardiac output (Eckstein and Abbound, 1962). Stimulation of alpha-receptors in capacitance vessels with consequent increase in venous return will increase cardiac output reflexly, however, and in practice methoxamine is found very satisfactory by many anaesthetists. Dosage of this and other adrenergic drugs should err on the cautious side, however, because the vessels soon acquire an undue sensitivity in the presence of sympathetic blockade. This has been demonstrated in the laboratory and may have clinical relevance (Bromage, 1953). There is a limited tendency for the pressure to overshoot with methoxamine overdose, which may be associated with a vagally-mediated bradycardia. Drugs, with a significant beta-stimulating action would tend to negate this mechanism. Methoxamine appears to be free from danger with a sensitized myocardium, and has even been used as an anti-arrhythmic agent. Indeed it has been stated to possess beta-blocking activity (Rand and Trinker, 1966).

There is no reason to suppose that flow is improved through the constricted vascular beds. A drug which acted on the capacitance vessels of the circulation without affecting the resistance vessels would be a great advance. Until then one must feel that more often than not in this situation vasopressors are a placebo for the anaesthetist rather than of benefit to the patient.

Unexplained hypotension during general anaesthesia.

Vasopressors may be used in other acute hypotensive crises, but this should be regarded as symptomatic treatment pending diagnosis. In such situations a degree of beta-stimulation is usually desirable, since in many instances of relative overdose of anaesthetic drugs myocardial depression is an important contributory factor. Acute hypotension after thiopentone induction, particularly if there is no tachycardia, should be viewed as partly a central problem and a pure alpha-stimulator would be inappropriate. A combined alpha- and beta-stimulator such as methamphetamine would seem a better choice.

Anaphylaxis.

Currie et al. (1966) reported a case of anaphylactic response to thiopentone and referred to three other possible examples. Currie et al. (1966) and Strunk (1962) both treated with an alpha-stimulator the extreme hypotension that occurred. When arterial pressure was again measurable a small pulse pressure was associated with tachycardia. The authors comment that some beta-stimulation in addition would have been more ap-
Appropriate, and with this one must agree. Adrenaline is the standard treatment for anaphylaxis and stimulates both types of receptor. An initial dose of 0.25-0.50 mg, followed by an infusion of 1 mg in 250 ml of isotonic diluent would be appropriate, adjusting the drip rate as indicated. The possibility of anaphylactic reactions to other drugs or transfused proteins should always be borne in mind in cases of catastrophic and unexplained hypotension. The anaphylactic response can occur during anaesthesia, although some of its manifestations in the skin may unfortunately be suppressed. If bronchospasm is prominent and resistant to aminophylline, a more pronounced beta-stimulation with an isoprenaline spray may be helpful. Because of its vigorous circulatory actions, isoprenaline by injection cannot be recommended for the treatment of bronchospasm.

Other indications for beta-receptor stimulation.

Isoprenaline is an alternative to electrical pacemaking in cases of heart block. The atrophicventricular conducting tissue may be traumatized during cardiac surgery, particularly in the repair of some ventricular septal defects. There may be only a short period of malfunction and during this time the ventricular rate can be maintained effectively with an isoprenaline infusion. For the same reason, it would be a useful drug to have to hand when anaesthetizing known cases of Stokes-Adams syndrome. For a single injection, 0.05-0.10 mg should be given.

Isoprenaline sprays can be of value in the treatment of bronchospasm from any cause. The chief difficulty lies in their effective administration in anaesthetic circuits.

ADRENERGIC STIMULATORS IN THE PRESENCE OF OTHER DRUGS

Reserpine.

After therapy with agents that deplete the stores of normal transmitter, indirectly acting stimulators are relatively ineffective, at least in theory, whereas the receptors themselves acquire a greater sensitivity to direct acting drugs. Probably reserpine does not constitute a serious hazard and need not be discontinued preoperatively (Katz, Weitraub and Papper, 1964). If a vasopressor is required a direct acting drug such as methoxamine or phenylephrine should be used in cautious doses.

Methyldopa (Aldomet).

This also depletes tissues of adrenaline and noradrenaline, but the receptors can still be stimulated by direct acting agents. It is possible that it acts as an alternative substrate in noradrenaline synthesis and is elaborated as a “false” transmitter, alpha-methyl noradrenaline, which itself has a weak adrenergic action (Day and Rand, 1964). In the author’s view it is not necessary to stop treatment with this drug prior to anaesthesia either though not everyone would accept this (Dingle, 1965). This “false transmitter” action may be applicable to other drugs. For example, chronic administration of metaraminol results in a subsequent hypotensive effect of the drug. It is suggested that this substance releases transmitter and then is itself taken up by the nerve endings. When released it is a less effective receptor stimulator (Crout et al., 1964). Failure of long-term vasoconstrictor therapy with indirect acting agents may be partly explicable in these terms.

Guanethidine, bretylium and bethanidine.

Although there are differences in the mechanism of action of these drugs, they all prevent the release of transmitter from the nerve terminal. Consequently in their presence direct acting vasoconstrictor agents should be used.

Vane (1962) suggests that there are other sites of uptake for catecholamines apart from the active receptor site, and that many hypotensive drugs combine with these non-specific sites, but not with the receptor sites. When the non-specific sites are blocked by these compounds, more noradrenaline is available for receptor-site action, which may explain the sensitivity to catecholamines which quickly develops.

Monoamine-oxidase inhibitors.

The situation with regard to these compounds is confused. Although both adrenaline and noradrenaline can be broken down by amine-oxidation, amine oxidase inhibitors do not greatly potentiate the effects of injected adrenaline and noradrenaline. Axelrod (1960) showed that nearly 70 per cent of a dose of injected adrenaline was inactivated by methylation of the ortho-hydroxyl group by the enzyme catechol-O-methyl transferase. Deamination by amine oxidase was then a secondary metabolic step.
One could deduce from this that adrenergic drugs which lack a hydroxyl group in the meta position would be more dependent on amine oxidase for their breakdown, and would have an enhanced action in the presence of amine oxidase inhibitors. On the other hand, drugs with a meta-hydroxyl group should be relatively safe. This would place methoxamine, methamphetamine, mephentermine, ephedrine and tyramine in the dangerous class, and adrenaline, noradrenaline, metaraminol and isoprenaline in the safe group. There is supporting evidence for the danger of methamphetamine (Mason, 1962), mephentermine (Stark, 1962), tyramine (Horwitz et al., 1964) and possibly ephedrine (Low-Beer and Tidmarsh, 1963). The dramatic response may be due to simultaneous alpha- and beta-stimulation. By contrast the “safe” group have not been shown to be entirely without danger. However, the response, particularly to those which release noradrenaline, is a potentiation of the normal response, and thus mainly involves excessive alpha activity.

If an exaggerated response to a vasopressor occurs, the logical treatment is an adrenergic blocker. If the response involves a reflex bradycardia beta blockers will be undesirable and alpha blockade is indicated. Phenolamine may be more controllable than phenoxybenzamine, being shorter acting. If, however, the vasopressor seems to be causing beta-stimulation as well, propranolol should be added. Subsequent precautions and management are outlined in the section on the use of adrenergic blockers. Whether such therapy would counteract the c.n.s. effects of the vasopressor is not known.

SHOCK

Both adrenergic stimulation and blockade have been advocated for hypotension associated with sympathetic overactivity as it appears in “shock”. A full review is outside the scope of this contribution; relevant aspects were discussed by Bloch et al. (1966) and by MacLean (1966) in the most recent educational number of this Journal.

Pre-operative resuscitation of “shock”.

It has been suggested in the opening section that sympathetic activity in response to hypotension, though an essential mechanism in the short term, leads eventually to changes which perpetuate and worsen the situation. If this view is correct, the use of drugs which intensify this inappropriate response cannot be as logical as the teleological suggestion of “aiding nature” would imply. The sympathetic vasoconstrictor mechanism is immensely powerful and needs no assistance in the normal individual. There is no evidence that converting a degree of vasoconstriction and a systolic pressure of 60 mg Hg into a greater degree of vasoconstriction and a systolic pressure of 80 mm Hg is in any way beneficial; indeed, rather the reverse. Many workers have advocated, therefore, that to improve tissue perfusion the inappropriate response should be blocked as part of the therapy. A full statement of this point of view has been published recently (Bloch, Pierce and Lillehei, 1966).

If it is accepted that “shock”, from whatever cause, progresses from a treatable condition to an untreatable one with time, and that the progression is the inevitable result of failing to treat successfully, then it is logical to attempt definitive treatment as soon as possible. The great majority of such cases will recover if treated early by conventional means. It is only the failure of conventional treatment that is likely to stimulate the application of relatively unconventional methods, and by then the crucial period during which the situation was reversible may well have passed. It would be of the greatest practical value to be able to identify at an early stage those cases in which conventional treatment is failing. One may suggest that the failure to raise the arterial pressure and to improve cutaneous blood flow in the presence of a central venous pressure of over 10 cm H₂O is a bad prognostic sign. From this point on there appear to be two valid lines of attack. MacLean (1966) reports that an intravenous infusion of isoprenaline 1 mg in 500 ml of isotonic diluent improves cardiac output and arterial pressure in this situation. This seems logical. Progressive cardiac failure is a feature of the shock syndrome, and specific beta-stimulation will not only improve the rate and force of the heart, but will lower the total peripheral resistance by dilating muscle blood vessels.

The other approach is to attempt to lower the peripheral resistance through the cutaneous and splanchnic beds, and thus revive tissue perfusion. This is secured by administering a powerful
alpha-receptor blocking agent, most commonly phenoxybenzamine, given slowly by infusion, 1 mg/kg body weight, during the course of an hour. Eckenhoff and Cooperman (1965) noted that this lowered the central venous pressure. However, the mortality in the cases of shock in which it was tried was nearly 100 per cent. No doubt it can be argued that without such treatment it would have been exactly 100 per cent. As the authors put it, "Our experience suggests that phenoxybenzamine may have a place in the therapy of shock, but if so we have not proved it". Even if improvement and survival are reported in the clinical shock syndrome, it will not be possible to say that such cases would not have recovered with conventional treatment. At present the therapy rests on extensive, and intellectually persuasive, experimental work.

If, however, one embarks on this line of treatment, there are some practical points to be borne in mind. The blockade, once induced, is long-lasting and intense and there is no antidote to it. Postural hypotension may be severe. The blocking action is due to a metabolite of phenoxybenzamine (Belleau and Triggle, 1962) and develops slowly, not reaching a maximum for an hour. It would seem essential to measure central venous pressure, and to transfuse so as to keep this pressure at least to 5–8 cm H₂O. This condition calls for many additional and simultaneous lines of management if treatment is to be successful. These will include measuring and treating acid-base disturbances, rheological changes, and electrolyte disorders.

In summary, conventional therapy should be pushed energetically and its failure assessed in relation to central venous pressure. Cardiac augmentation with isoprenaline would seem to be the next logical step. Persistent failure to establish an adequate circulation with a maintained central venous pressure may then suggest that therapy with phenoxybenzamine should be tried.

**Shock during anaesthesia.**

Although the induction of anaesthesia is associated with a lessening of sympathetic nervous activity, in a crisis the vasoconstrictor mechanism still functions vigorously. Such a crisis arising during an operation may be a massive haemorrhage, and one must consider whether there are any circumstances in which adrenergic drugs will aid the resuscitation of acute haemorrhage. If the previous discussion has been valid these would arise only when physiological adrenergic mechanisms fail to maintain an arterial pressure adequate for cerebral perfusion. Thus, if systolic pressure falls to unrecordable levels, alpha-receptor stimulation may give a temporary respite while other more appropriate action is taken. Attention to the management of massive transfusion should be the first priority in such a situation. Failure of replacement transfusion to restore normal function may lead to a consideration of lines of treatment outlined above.

**ADRENERGIC RECEPTOR BLOCKADE**

Several drugs are available which selectively block one or other type of adrenergic receptor. The clinical picture that results partly depends on the level of activity of the sympato-adrenal system and the consequent degree of stimulation of the unblocked receptors.

Several drugs are available for alpha-receptor blockade, but only phenoxybenzamine and phen tolamine are at present being used at all commonly in clinical practice. Phentolamine is considerably shorter acting.

Pronethanol was the first specific beta-blocking drug to be introduced into clinical practice (Dornhorst and Robinson, 1962), but this has been withdrawn because of chronic toxic effects in mice. Propranolol, which is equally specific but ten times as potent, is without this drawback (Black et al., 1964).

Some of the published observations concerning pronethanol have not been repeated with propranolol, but in view of their similar specificity the author has considered it permissible to quote work with pronethanol allowing for the relative potency in recommending doses of propranolol.

**ALPHA-RECEPTOR BLOCKADE**

Apart from vasoconstricted states, of which shock, already discussed, is an example, alpha-receptor blockade has been advocated for the treatment of acute pulmonary congestion and oedema. The basis of therapy is to cause a greater reduction in systemic than in pulmonary vascular tone, with a shift of blood to the systemic vascular bed (Halmagyi et al., 1953).
**Phaeochromocytoma.**

This is dealt with elsewhere in this issue (De Blasi, 1966) and is mentioned only briefly here. The pre-operative use of alpha-blockers is designed to correct the circulatory abnormalities that result from excessive stimulation with adrenaline, which causes a diminished circulating volume and red cell mass which are then determinants of the postoperative shock syndrome that follows removal of the tumour (Brunjes, Johns and Crane, 1960; Johns and Brunjes, 1962). The rationale of beta-blockade before and during operation is to prevent the tachycardia and arrhythmias that may occur during surgical manipulation of the tumour (Dornhorst and Laurence, 1963). However, the additional use of a beta-blocker may result in a cardiovascular system that is unable to respond to haemorrhage. Postoperative difficulty in this respect has led to the abandonment of beta-blockade as a routine by some workers (Kaufman, 1966, personal communication).

**BETA-RECEPTOR Blockade**

There do not appear to be any therapeutic indications for attempting to influence muscle blood flow under the basal conditions of anaesthesia, and systemic beta-blockade is used exclusively for its effect on the heart. It is of interest, however, that the chief therapeutic employment of beta-blockade has been in the control of arrhythmias, and there is evidence that this is a specific effect of these drugs on the conducting tissue, unrelated to their beta-blocking action (Sekiya and Williams, 1963; Morales-Aquilera and Williams, 1965; Lucchesi, 1965). The anti-arrhythmic effects can be obtained with smaller doses than are needed for full beta-receptor blockade, and these compounds are more effective than procaine or quinidine (Murray, McKnight and Davis, 1963; Rowlands, Howitt and Markman, 1965). Within the province of the anaesthetist, ventricular arrhythmias can be considered under two headings: those "due" to catecholamines, both endogenous and exogenous, and those associated with cardiac malfunction, either during heart surgery and angiography, or after cardiac arrest.

**Endogenous catecholamines.**

Arrhythmias commonly occur during otherwise satisfactory general anaesthesia.

In patients undergoing dental extractions under otherwise satisfactory endotracheal halothane or trichloroethylene anaesthesia ventricular arrhythmias have occurred in the course of dental manipulations. These have also been observed in outpatient dental extractions under halothane anaesthesia (Kaufman, 1966). These arrhythmias can be abolished by 2–3 mg of propranolol intravenously. The population at risk for these observations was admittedly unusual in containing a high proportion of patients with heart disease. Ventricular extrasystoles during insertion of the needle for regional analgesia, and in unpremedicated patients awaiting extraction, have cast doubt on the belief that local techniques are necessarily safer for patients with heart disease (Kaufman, 1966).

Payne and Senfield (1964) related twenty-two instances of ventricular arrhythmias to a raised arterial carbon dioxide tension often under deep anaesthesia. The average $P_{CO_2}$ level at which arrhythmias occurred varied with the anaesthetic agent used. All the arrhythmias were reversed with one or two doses of pronethalol. The frequency with which these arrhythmias occur may also depend on the speed with which the changes in $P_{CO_2}$ are induced. For example, Rowlands, Howitt and Markman (1965), who raised the arterial $P_{CO_2}$ by rebreathing in order to elicit arrhythmias in conscious patients, noticed these disturbances to be maximal just after disconnecting the rebreathing bag, when the level was changing fastest, but falling.

Thus it would seem that ventricular arrhythmias occur both when anaesthesia is too light and when ventilation is depressed in the presence of some anaesthetic agents. Treatment should therefore be primarily directed to these causes. However, because in some circumstances ventricular tachycardia or multiple extrasystoles may be the precursors of ventricular fibrillation, there is a natural desire to abolish them as soon as possible, particularly in patients with known cardiac disease. This must be balanced against any possible risk involved in doing so. Except in very deep anaesthesia it seems that doses of beta-blocking agents sufficient to abolish arrhythmias are not followed by a fall in arterial pressure or other evidence of cardiovascular depression, and...
propranolol 2–3 mg may be safely given if there are no other contraindications (see below).

**Exogenous catecholamines.**

Many of the foregoing remarks apply. The occurrence of ventricular arrhythmias following infiltration with solutions containing certain vaso-pressors, notably adrenaline, may in some circumstances call for prompt treatment. This seems to be particularly the case with infiltration for pelvic floor repairs, when large volumes are injected into a vascular site. Fatalities have been reported in these circumstances when halothane was being given (Rosen and Roe, 1963). One is tempted to ask whether it is permissible to take prophylactic action when such a possibility is envisaged. In guinea-pigs the threshold for digitalis-induced arrhythmias can be raised by premedication with a beta-blocker (Williams and Sekiya, 1963) and the threshold for catecholamine-induced arrhythmias during anaesthesia can be raised in dogs (Murray, McKnight and Davis, 1963). This not unnaturally lacks confirmation in man. But it would not seem unreasonable to give propranolol 2 mg intravenously, some 30–60 seconds before infiltration began, if one found oneself already inadvertently giving an unfavourable inhalation agent at the time such infiltration was needed.

**Arrhythmias due to direct stimulation.**

Very little can be stated positively concerning the use of beta-blockers in the control of directly stimulated arrhythmias, but similar considerations must apply. However, the caution concerning the use of this drug in cases of heart failure (see below) must be well to the fore. After an episode of cardiac arrest there are additional hazards in the presence of a metabolic acidosis which is often associated. Beta-blockade is effective in other kinds of arrhythmias, including digitalis overdose; Stock and Dale (1964) provide a convenient recent summary.

**Hypertrophic obstructive cardiomyopathy.**

This condition is considered in many instances to be an indication for termination of pregnancy. A feature is sudden cardiac arrest, believed to be due to stimulation of hypertrophic cardiac muscle by endogenous catecholamines. This muscle by its situation obstructs the outflow from the left ventricle. The circulatory insufficiency induces more intense sympathetic activity with rapid progression to a vicious circle. This may develop so quickly that treatment cannot become effective, and prevention with beta-blockade is recommended (Cherian et al., 1966). The patients may or may not be under specific treatment, but in any event propranolol 5 mg intramuscularly should be given with the premedication. Premedication should, of course, be adequate and followed by an excitement-free induction.

**Tachyphylaxis of ganglion blockade.**

During hypotensive anaesthesia with ganglion blockade, increasing doses may fail to control the arterial pressure, and tachycardia develops. This sequence is described as tachyphylaxis, and may be related to increases in circulating adrenaline. It has been noted that during ganglion blockade the vessels become more sensitive to catecholamines, and Coulter (1957) attempted to control this effect by giving an alpha-blocker. He noted that although the arterial pressure was lowered the tachycardia persisted. This suggests that beta-blockers might be appropriate. The author has been trying propranolol following trimetaphan as the hypotensive agent, with spontaneous ventilation. The response is complex but in line with expectations concerning the postulated pharmacology. There is a slight decrease in heart rate, and the arterial pressure declines progressively over several minutes. There is also a narrowing of the pulse and a rise in the diastolic pressure. This suggests that in addition to inhibition of the effects of circulating adrenaline on the heart, there is a block of vasodilator fibres in muscle blood vessels, and an overall rise in peripheral resistance. It seems that beta-blockade without alpha-blockade may not be a good way of controlling the situation, and double blockade, a distinctly hazardous way of dealing with a problem which can often be avoided with other techniques, can hardly be recommended. Potts (personal communication, 1966), however, found that propranolol, given first, allows good control of blood pressure with very small doses of trimetaphan. Final conclusions must await further evaluation.
HAZARDS OF ADRENERGIC BLOCKING AGENTS

Alpha-blockade.
In vasoconstrictive states, blockade of alpha-receptors will unmask circulating blood volume deficits. A further disastrous fall in arterial pressure will then result unless the circulating volume can be quickly increased. This therapy is most likely to be tried in patients with gross circulatory abnormalities, and they need intensive care. Central venous pressure should be measured. This is neither difficult nor expensive and can be done with easily available disposable equipment. Measurements of hematocrit, acid-base state, oxygen saturation, blood volume and electrolytes are likely to be crucial to successful management in some circumstances. Inevitably, in the present state of knowledge, some hopeless cases will be treated and only full documentation will enable better criteria to be developed.

Beta-blockade.
By contrast these drugs are often given to healthy people, on whom they have little effect under basal conditions. But in some circumstances they can initiate irreversible deterioration.

Heart failure. The failing myocardium comes to depend increasingly on an active sympathetic drive. Beta-blockade may induce a rapidly fatal failure in such patients. It should be used with great caution therefore even in patients who have had episodes of heart failure in the past.

Metabolic acidosis. In conditions of metabolic acidosis the circulation may also be dependent on sympathetic drive. This is particularly likely during the early stages of resuscitation after cardiac arrest. Attempts to control refractory ventricular arrhythmias with propranolol might be disastrous unless the metabolic derangement is treated first.

Bronchospasm. Beta-blockade will inhibit the bronchodilator receptors but will leave the bronchoconstrictor element unblocked. Patients already suffering from asthma or bronchospasm may be expected to be made worse.

Haemorrhage. Tachycardia, as a response to haemorrhage, will be blocked. If these agents are used in association with surgery the patients deserve close attention postoperatively with this in mind, for at least 4 hours.

It is necessary that the use of both adrenergic drugs and their antagonists should be based on a careful diagnosis, and knowledge of the relevant pharmacology if therapy is to be appropriate.

REFERENCES
Coulter, R. L. (1957). Controlled hypotension; the use of an adrenergic blocking agent to supplement hexamethonium. Anaesthesia, 12, 74.
A SYMPOSIUM ON ADVANCES IN ANAESTHESIA FOR EYE SURGERY

will be held at
ADDENBROOKE'S HOSPITAL, CAMBRIDGE,
on November 12, 1966.


