The Clinical Pharmacology of Beta Adrenergic Blocking Drugs

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Although beta adrenergic blocking drugs are widely used in the treatment of a variety of diseases, the pharmacology of these drugs is often not appreciated by the physicians who prescribe them. The situation is accentuated in the British Isles, where at present (May, 1976) eight of these drugs are available for prescription (Table 1), with claims from different drug companies of the superior qualities of their drugs, which are often not supported by the small number of clinical reports in published form. In addition, several of these drugs are marketed under more than one proprietary name, a formula both for confusion and potential disaster (*Lancet*, 1975).

Table 1. Beta adrenergic blocking drugs

Propranolol	INDERAL
Practolol	ERALDIN
Oxprenolol	TRASICOR
Sotalol	BETA-CARDONE, SOTACOR
Alprenolol	APTIN
Pindolol	VISKEN
Timolol	BLOCARDREN
Acebutolol	SECTRAL
Metoprolol	LOPRESSOR, BETALOC

Several comprehensive reviews on the actions of beta adrenergic blocking drugs have appeared, but these have often detailed information about some aspects of the drugs without giving a general review of their properties. This article briefly describes the properties that appear to be relevant to the practising physician at the present time.

In 1948, Ahlquist classified adrenergic receptors into two groups which he designated alpha and beta. He based his hypotheses on the potency ratio of a series of six sympathomimetic amines on a variety of tissues. He concluded that one group of responses was due to the stimulation of one type of receptor, and that the other resulted from stimulation of a second type of receptor (Table 2). These receptors have not been identified but their characterisation has enabled the development of rational ideas on the actions of a variety of drugs that affect the receptors. His observations were largely ignored until the 1960s when drugs that specifically blocked beta receptors became available.

Table 2. Distribution of adrenergic receptors

Organ	Response	Receptor
Heart	Increase in heart rate	Beta
	Increase in cardiac contractility	Beta
	Accelerate A-V conduction	Beta
Bronchi	Dilatation	Beta
Blood vessels	Dilatation	Beta
	Constriction	Alpha
Eye	Dilatation of pupil	Alpha
Gastrointestinal tract	Reduction in mobility	Alpha and Beta

The first of these drugs was dichloroisoprenaline (Powell and Slater, 1958); its blocking properties were discovered by accident when these workers were examining analogues of isoprenaline for a bronchodilator action. As its name implies, the drug is a derivative of isoprenaline with the two hydroxyl groups replaced by two chlorine atoms. Subsequent observations showed that dichloroisoprenaline inhibited the increase in heart rate and fall in blood pressure produced by isoprenaline (Moran and Perkins, 1958, 1961). Reference to Ahlquist's classification of adrenergic receptors indicated that dichloroisoprenaline blocked only those responses elicited by stimulation of the beta group of receptors. The therapeutic potential of dichloroisoprenaline was not examined in man as it also produced cardiac stimulation (see below) but limited studies in man showed that it blocked the peripheral vasodilator action of isoprenaline (Glover *et al.*, 1962).

At this time, Black was looking for a drug that would selectively block beta adrenergic receptors, for it had occurred to him that there might be a chain of events – stress, increased sympathetic drive to the heart, noradrenaline release, and increased cardiac work – leading to angina if the blood supply to the myocardium was insufficient for the increased demand (Laurence, 1975). He

argued that a drug that would block the effects of noradrenaline on the heart, which are mediated through the beta receptors, would be of value in treating angina of effort.

Black and his colleagues at Imperial Chemical Industries investigated the properties of dichloroisoprenaline and compounds related to it for their ability to block beta adrenergic receptors. In 1962, Black and Stevenson described the properties of pronethalol, which inhibited the responses produced by stimulation of beta adrenergic receptors but differed from dichloroisoprenaline in that it produced no cardiac stimulation. Further studies confirmed that it had beta adrenergic properties in man, and, in patients, pronethalol was shown to be of value in the treatment of angina, cardiac arrhythmias and hypertension, thus confirming Black's hypothesis.

Clinical studies with pronethalol were restricted when it was shown to have a carcinogenic action in mice. Fortunately, the properties of propranolol had been discovered by this time and clinical evaluation of the effect of blockade of beta receptors was able to proceed (Black *et al.*, 1965).

During the past ten years the effects of propranolol in laboratory animals and man, have been extensively studied. Recently, other drugs that block beta receptors have been described and they may also possess other properties, including membrane stabilising activity, intrinsic sympathomimetic activity, and cardio-selectivity. As these properties, and their significance in the clinical use of these drugs is often confusing to physicians, they will be described here.

BLOCKADE OF BETA ADRENERGIC RECEPTORS

Beta blocking drugs are all competitive inhibitors of agonist drugs such as isoprenaline at beta adrenergic receptor sites (Barrett, 1973). Thus, to obtain a standardised response from a sensitive tissue will require a higher concentration of agonist in the presence of a beta blocking drug than without it. Because the inhibition is competitive, the effect of any beta blocking drug can be overcome by increasing the concentration of the agonist, and, therefore, it is inappropriate to speak of 'total' or 'complete' beta blockade (Gibson, 1974).

The stimulation of beta adrenergic receptors produced by the administration of isoprenaline has been used extensively to demonstrate the activity of drugs that block these receptors in animals. The increases in heart rate and cardiac force and the dilatation of the peripheral blood vessels produced by isoprenaline are reduced by beta blocking drugs (Shanks, 1966). By measuring the effects of different drugs on increasing doses of isoprenaline in animals, comparisons have been made between the relative potencies of the different beta blocking agents (Table 3). In man, blockade of an isoprenaline tachycardia has also been used to demonstrate the activity of beta adrenergic blocking drugs. Unfortunately, there has not been a strict application of pharmacological principles and reliance has been placed on the reduction or inhibition produced by a single dose of isoprenaline (Brick *et al.*,

Table 3. Comparative beta blocking activity
Based on inhibition of an isoprenaline tachycardia in animals

Propranolol	1.0
Practolol	0.3
Oxprenolol	1.0
Sotalol	0.3
Alprenolol	1.0
Pindolol	4.0
Timolol	Not available
Acebutolol	0.3
Metoprolol	0.3

1968). Recently, more controlled observations have been made by obtaining dose-response curves to a series of doses of isoprenaline given by rapid intravenous injection in man (Cleaveland *et al.*, 1972; George *et al.*, 1972). However, comparative data are not available for many of the drugs and it is impossible to obtain potency ratios in man.

As the sympathetic stimulation of intravenous isoprenaline is not physiological, tests have been devised to estimate the effects of beta adrenergic blocking drugs on endogenous sympathetic stimulation. These include submaximal exercise, and the reflex tachycardias induced by standing, tilting or the administration of glyceryl trinitrate. Of these, the most reliable is probably submaximal exercise, but the heart rate is under both sympathetic and parasympathetic control, and only at the highest levels of exercise (sufficient to increase heart rate to 160 beats/minute or greater) does the vagal component become insignificant (Robinson *et al.*, 1953; Robinson *et al.*, 1966). Less severe exercise may be used in patients, but the lower the heart rate response, the less dependable are the results. In addition, comparisons between different beta blocking drugs can only be made if the exercise test is standardised, and this largely means carrying it out in the same laboratory. Using such a test, the reduction of an exercise tachycardia in healthy men produced by propranolol and sotalol has been shown to be dose related (Shanks *et al.*, 1975), but the reduction after practolol did not increase significantly with doses larger than 100 mg (Carruthers *et al.*, 1974). This was thought to be a manifestation of intrinsic sympathomimetic activity (see below).

CARDIO-SELECTIVITY

Lands and his colleagues (1967) suggested that beta adrenergic receptors could be divided into two main groups, which they designated beta 1 and beta 2. The cardiac responses were attributed to beta 1 receptors and dilatation of the bronchi and blood vessels to beta 2 receptors. This subdivision was supported by the development of practolol which, in animals, inhibited the effect of isoprenaline on

the heart but had little effect on vasodilatation and bronchodilatation (Dunlop and Shanks, 1968). Subsequent claims have been made for the cardio-selectivity of other beta blocking drugs on the basis of animal studies, including acebutalol (Basil *et al.*, 1973), ICI 66082 (Barrett *et al.*, 1973), tolamolol (Adam *et al.*, 1974) and metoprolol (Ablad *et al.*, 1975).

Assessment of cardio-selectivity in man is not easy. Ideally, such a claim must be based on demonstrating that the drug blocks the effect of an agonist, e.g. isoprenaline, on the heart while having minimal effects on the bronchodilator and vasodilator responses. Measurement of effects of beta blocking drugs on resting respiratory function either in normal or asthmatic subjects does not fulfil these criteria and cannot be accepted as evidence of cardio-selectivity. It is akin to measuring the cardiovascular effects of these drugs by changes in resting heart rate, the fallacious results of which have recently been demonstrated in patients with thyrotoxicosis (Carruthers *et al.*, 1974a). Recently, Kumana *et al.* (1974) have shown that peak flow rate (PFR) in normal subjects increases with severe exercise and they have used this as a basis for assessing the beta 2 effect of drugs. Similarly, cardiovascular and respiratory responses to isoprenaline can be measured before and after the administration of a beta blocking drug.

Using their technique, Kumana *et al.* (1974) found that practolol did not alter exercise PFR significantly at a time when significant reduction of exercise tachycardia was occurring. However, although propranolol had more effect than practolol on exercise PFR, comparison of the two active drugs only showed significant differences at six hours. In another study, in asthmatic subjects, practolol was found to inhibit the increase in heart rate but not the increase in FEV_1 produced by isoprenaline (Powles *et al.*, 1969). Recent studies with ICI 66082 (Marlin *et al.*, 1975) and acebutalol (Kumana *et al.*, 1975) have indicated that these drugs have an effect on exercise PFR that is greater than that of practolol but less than that of propranolol. In addition, acebutalol does block the peripheral vasodilator effect of isoprenaline (Briant *et al.*, 1971) in asthmatic patients and has been shown to reduce significantly the increase in FEV_1 produced by isoprenaline (Skinner *et al.*, 1975); unfortunately many of the studies in asthmatic patients are less convincing. In some no agonist was used, and in others the effect of the agonist on the cardiovascular system was not measured or no attempt was made to ensure that the degree of cardiac beta blocking activity by different drugs was similar before comparison to their pulmonary effects was deduced. In recent studies the effects of metoprolol have been compared with those of propranolol, practolol and placebo on resting heart rate and airways resistance, and on dose response curves to isoprenaline in asthmatic patients. Metoprolol was shown to be similar to practolol, as both drugs inhibited isoprenaline-induced changes in heart rate without affecting changes in airways resistance (Johnsson *et al.*, 1975a; Thiringer and Svedmyr, 1976).

Practolol and metoprolol are the only drugs that have been shown con-

vincingly to be cardio-selective in man. However, the specificity is more relative than absolute and some patients with chronic obstructive airways disease will show deterioration of respiratory function after practolol and metoprolol as well as other beta blocking drugs.

INTRINSIC SYMPATHOMIMETIC ACTIVITY

Dichloroisoprenaline, although blocking beta adrenergic receptors, also produced marked cardiac stimulation (Moran and Perkins, 1958) which has been attributed to stimulation of beta receptors and has been termed 'intrinsic sympathomimetic activity' (Dresel, 1960). Tachycardia and palpitations occurring during the administration of dichloroisoprenaline to man (Glover *et al.*, 1962) made the drug unsuitable for clinical evaluation. In contrast, pronethalol was thought initially to be devoid of intrinsic sympathomimetic activity (Black and Stevenson, 1962), but with the development of propranolol comparison between the effects of the two drugs in anaesthetised animals showed a difference in their effects on resting heart rate (Black *et al.*, 1965). Although pronethalol had no effect on heart rate, propranolol produced brachycardia. In animals pre-treated with syrosingopine, to deplete the stores of noradrenaline in the heart and thus abolish sympathetic drive, pronethalol increased heart rate, whereas propranolol produced no change (Black *et al.*, 1965). These observations were explained by suggesting that pronethalol had a slight intrinsic sympathomimetic activity in addition to its activity in blocking beta adrenergic receptors. Several of the more recently described drugs, including oxprenolol, alprenolol, practolol, pindolol and acebutalol, possess intrinsic sympathomimetic activity (*see* Table 1).

There has been no unequivocal demonstration of intrinsic sympathomimetic activity in man. It has been shown that the reduction in heart rate produced by the intravenous administration of drugs such as oxprenolol, alprenolol and practolol may be less than that produced by propranolol with high doses (Prichard *et al.*, 1970), but comparison of doses used in clinical practice has not shown a clear difference in their effects on resting heart rate (Gibson, 1974). A comparison of the effects of propranolol and practolol on an exercise tachycardia (Brick *et al.*, 1968) has shown that, whereas increasing doses of propranolol produce a progressive reduction in an exercise tachycardia, the effect of practolol reaches a plateau where increasing doses do not produce a further reduction and the reduction is significantly less than that which occurs with propranolol. This difference in the effects of these two drugs probably results from the presence of intrinsic sympathomimetic activity in practolol. A similar plateau has been seen with the effects of oral practolol (Carruthers *et al.*, 1974) and oxprenolol (Harry *et al.*, 1975) on exercise tachycardia.

There has been considerable controversy about the role of intrinsic sympathomimetic activity in the therapeutic use of beta blocking drugs. The presence of this activity does not seem to influence the beneficial effect of these drugs in the

treatment of disease. It has been suggested that this activity may be of value in preventing two of the adverse effects that may occur after beta blocking drugs – bronchospasm and cardiac failure (Ablad *et al.*, 1967). There is no evidence to support such claims. Although drugs with intrinsic sympathomimetic activity (oxprenolol, alprenolol, pindolol) on average produce in asthmatic patients a smaller reduction in FEV_1 than propranolol, in some individual patients the effects of propranolol and alprenolol are similar (Connolly and Batten, 1970). Marked increases in airways resistance may occur after the administration of oxprenolol (Clarke and MacDonald, 1970). Thus, all these drugs must be given with great care to patients with a history of airways obstruction.

The development of cardiac failure after the administration of beta adrenergic blocking drugs is a rare but serious adverse effect. The presence of intrinsic sympathomimetic activity does not seem to prevent the development of cardiac failure (Fitzgerald, 1969).

Drugs with intrinsic sympathomimetic activity were said to be ineffective and potentially hazardous in thyrotoxicosis (Turner, 1974). Recent studies with practolol have suggested that it is only inferior to propranolol in its effects on heart rate in controlling the peripheral manifestations of thyrotoxicosis (Nelson and McDevitt, 1975).

MEMBRANE STABILISING ACTIVITY

Shortly after Stock and Dale (1963) showed that pronethalol was effective in the treatment of various cardiac arrhythmias, Morales-Aguilera and Vaughan Williams (1965) demonstrated, in animals, that it had a quinidine-like effect on the heart and that it was a potent local anaesthetic. The result is to reduce the rate of rise of the intracardiac action potential without altering the duration of the spike or the resting potential. In anaesthetised guinea-pigs, pronethalol reduced the toxicity on the heart of ouabain (Sekiya and Vaughan Williams, 1963) and subsequently Lucchesi (1965) showed that its dextro-isomer, which has little beta blocking activity but comparable membrane stabilising activity, was equally effective in abolishing ouabain-induced arrhythmias in dogs. The term 'membrane stabilising activity' has been coined to include quinidine-like effect and local anaesthetic activity. Several beta blocking drugs possess this property (*see* Table 1). There has been much controversy over the contribution that membrane stabilising activity makes to the effect of these drugs in angina pectoris and in cardiac arrhythmias in man. However, the membrane stabilising effect of propranolol has been demonstrated *in vitro* with human muscle only at a minumum concentration of propranolol of 10 ng/litre (Coltart and Meldrum, 1970) which is about 100 times greater than the level associated with near maximum inhibition of exercise tachycardia (Coltart and Shand, 1970) or suppression of ectopic beats (Coltart *et al.*, 1971). In addition, the dextro-isomer of propranolol, which is membrane active but almost devoid of beta blocking activity, is not effective in angina

(Wilson *et al.*, 1969) even in doses up to 80 ng intravenously (Boakes and Prichard, 1973), whereas drugs without membrane stabilising activity, such as practolol and sotalol, have been shown to be effective (Wilson *et al.*, 1969; George *et al.*, 1970; Berman and Gooding, 1975). Membrane action is not thought to be of importance in the use of beta blocking drugs as anti-arrhythmics (Singh and Jewitt, 1974), hence it would seem that this is not an important property of beta adrenergic blocking drugs in the doses used in clinical practice.

HAEMODYNAMIC EFFECTS OF BETA BLOCKING DRUGS

Heart Rate

As already indicated, heart rate is determined by the simultaneous activity of both the sympathetic and parasympathetic nervous systems, with parasympathetic tone predominating at rest and sympathetic tone during extreme exercise (Robinson *et al.*, 1953; Robinson *et al.*, 1966). The effects of beta blocking drugs on heart rate are determined, therefore, by the circumstances under which the observations are made.

Generally, the intravenous administration of propranolol, and also drugs with intrinsic sympathomimetic activity such as oxprenolol, alprenolol and practolol, in low doses results in similar reductions in resting heart rate (Gibson, 1974). With higher doses subsequently producing approximately equal effects on an exercise tachycardia, propranolol and sotalol lowered resting heart rate more than oxprenolol and practolol (Prichard *et al.*, 1970).

Of more importance is the effect of beta adrenergic blocking drugs in the presence of increased adrenergic activity. The results may depend on the type of adrenergic activity used. Isoprenaline-induced tachycardia is one of the tests employed, and this can be shown to be competitively inhibited by propranolol (Cleaveland *et al.*, 1972). However, practolol is much less effective than might be expected in blocking an isoprenaline tachycardia (Brick *et al.*, 1968). This may be due to the fact that the tachycardia induced by isoprenaline is in part due to its direct chronotropic effect on the heart, but it is also contributed to by reflex vagal withdrawal induced by peripheral vasodilatation and subsequent hypotension (Dunlop and Shanks, 1968). Thus, practolol, which produces predominantly cardio-selective blockade, may not prevent the secondary vagal withdrawal. Other beta blocking drugs that exhibit this phenomenon are ICI 66082 (Graham *et al.*, 1973) tolamolol (Adam *et al.*, 1973) and metoprolol (Johnsson *et al.*, 1975b), and this may be presumptive evidence of cardio-selectivity.

Beta adrenergic blocking drugs also inhibit exercise tachycardia, and drugs such as practolol seem to be relatively more potent with this type of stimulus (Brick *et al.*, 1968). With most drugs the effect is dose-dependent, but drugs with intrinsic sympathomimetic activity reach a plateau where further increase in the dose does not significantly increase the effect (Carruthers *et al.*, 1974b; Harry *et al.*, 1975).

Cardiac Output

The reduction in heart rate associated with administration of beta adrenergic blocking drugs is usually accompanied by a reduction in cardiac output. These two are not causally related for, with the heart rate held constant by atrial or ventricular pacing, beta blockade still causes a reduction in cardiac output at rest and on exercise (Bloomfield and Sowton, 1967; Donoso *et al.*, 1967; Sowton and Hamer, 1966). However, it would still seem that the greater the drop in heart rate, the greater the reduction in cardiac output (Gibson, 1974). This is true both for propranolol, drugs with intrinsic sympathomimetic activity such as alprenolol and oxprenolol, and sotalol. The only exception is practolol, where a number of studies have demonstrated a smaller reduction in cardiac output per unit change in heart rate than for non-selective drugs (Gibson, 1974).

The reduction in cardiac output following the administration of beta blocking drugs is unlikely to be due to, or contributed to by, membrane stabilising activity, as the dextro-isomers of propranolol and alprenolol, which have this property but little beta blocking effect, do not reduce cardiac output (Bennett *et al.*, 1970; Ekelund *et al.*, 1971) and sotalol, without membrane activity, affects cardiac output similarly to propranolol. It would seem that the dominant effect is blockade of sympathetic activity and circulating catecholamines (Gibson, 1974). There is no evidence that drugs possessing intrinsic sympathomimetic activity reduce cardiac output less than drugs without this property, as was suggested by Ablad *et al.* (1967). The reason for the distinctive effect of practolol on cardiac output is not clear; one possible explanation is that the reduction in peripheral flow (or cardiac output) following administration of beta blocking drugs is due to an effect on the peripheral vasculature rather than directly on the heart (Gibson, 1974). Thus, practolol, which affects the heart but not the peripheral receptors, would act differently from the other drugs.

Beta blockade is associated with a proportionately smaller decrease in oxygen uptake than the drop in cardiac output both at rest and on exercise, so there is a consistent increase in arteriovenous oxygen difference (Gibson, 1974).

Arterial Pressure

Numerous studies have shown little change in blood pressure after acute administration of beta adrenergic blocking agents. Recently, it has been suggested that doses causing a marked reduction in heart rate are consistently associated with a clear cut drop in arterial pressure (Gibson, 1974). This is presumably due to a drop in cardiac output which, at lower doses, may be offset by the pressor effect of blockade of peripheral beta receptors. Immediately after beta blockade there is a reduction in the rate of rise of blood pressure on exercise (Shinebourne *et al.*, 1967) and in the overshoot after Valsalva's manoeuvre (Prichard and Gillam, 1966). Chronic administration of all beta blocking drugs, irrespective of

their distinctive properties, is associated with an antihypertensive effect (Simpson, 1974).

PHARMACOKINETICS

All beta blocking drugs are well absorbed from the alimentary tract after oral administration; the absorption is fairly rapid and peak concentrations in the blood are seen after 1 to 3 hours.

Several of the drugs undergo extensive presystemic hepatic ('first-pass') elimination. This means that a drug in the portal vein after oral administration is extensively cleared by the liver before it can enter the systemic circulation. Such drugs have low bioavailability even though their absorption is good. The availability of small doses is very low but, as the dose is increased, progressively more reaches the system circulation (Shand and Rangno, 1972; Ablad *et al.*, 1972) due to saturation of tissue binding in the liver (Shand *et al.*, 1972). Drugs demonstrating this phenomenon include propranolol and alprenolol and, possibly also, oxprenolol (Riess *et al.*, 1970) and metoprolol (Johnsson *et al.*, 1975c).

Both propranolol (Fitzgerald and O'Donnell, 1971) and alprenolol (Ablad *et al.*, 1974) form active 4-hydroxy metabolites. With propranolol, the metabolite seems to form after oral administration only and to have a shorter half-life than the parent compound (Paterson *et al.*, 1970). It seemed to be active at two hours after an oral dose but not after six hours or after chronic administration (Cleaveland and Shand, 1972). Conversely, 2-hydroxalprenolol is found after both oral and intravenous administration of alprenolol: the plasma half-lives of the parent compound and metabolite after both routes of administration were similar (Ablad *et al.*, 1974).

Propranolol, alprenolol and oxprenolol are eliminated almost entirely by metabolism (Paterson *et al.*, 1970; Johnsson *et al.*, 1971). Eighty-five per cent of metoprolol is excreted in a metabolised form in the urine (Borg *et al.*, 1975). Pindolol is eliminated by both routes, 40 per cent of a dose being excreted unchanged in the urine (Ohnhaus, 1973). Seventy-five per cent of sotalol is eliminated unchanged in the urine (Shanks *et al.*, 1975) and practolol appears to be completely eliminated by the kidneys, 90 to 100 per cent being recovered unchanged in the urine (Bodem and Chidsey, 1973; Carruthers *et al.*, 1974b).

Half-lives of the various beta adrenergic drugs are also extremely variable. Propranolol, alprenolol, oxprenolol and pindolol have half-lives of the order of 2 to 4 hours (Shand, 1974). During chronic oral administration, however, the clearance of propranolol is reduced and the half-life prolonged to 4 to 6 hours (Evans and Shand, 1973). Metoprolol has a half-life of the same order (Johnsson *et al.*, 1975c), but practolol has a half-life of about 11 hours (Carruthers *et al.*, 1974b) and sotalol of about 13 hours (Shanks *et al.*, 1975). With practolol, biliary excretion and enterohepatic recirculation may be an important factor in this prolonged half-life (Carruthers *et al.*, 1975).

With most beta blocking drugs plasma binding is low and therefore unlikely to influence kinetics. However, 90 to 96 per cent of propranolol is bound in the plasma of normal subjects (Evans *et al.*, 1973). Thus, small changes in plasma binding may result in substantial changes in the amount of free drug available at the receptor site. Recently, it has been shown that the beta blocking effect of propranolol can be more closely correlated with the amount of free propranolol in the blood than with the total propranolol concentration (Shand *et al.*, 1975). Thus, plasma binding of propranolol may be of some importance.

Generally, good correlation can be shown between the effects of beta blocking drugs and the logarithms of blood or plasma concentrations (Coltart and Shand, 1970; Ablad *et al.*, 1972; Carruthers *et al.*, 1974; Cuthbert and Collins, 1975; Shanks *et al.*, 1975; Johnsson *et al.*, 1975c). Despite this, large interindividual variations in circulating drug concentrations may be seen both with single doses and with steady state concentrations. These have been observed with propranolol (Shand *et al.*, 1970), alprenolol (Ablad *et al.*, 1972), oxprenolol (Riess *et al.*, 1970), and sotalol (Shanks *et al.*, 1975). Only small variations in interindividual blood concentrations are seen with practolol (Carruthers *et al.*, 1974). Such interindividual variations are thought to be contributed to by genetic and environmental differences in extraction ratio and, also, by presystemic elimination, particularly when this latter effect is substantial (Rowland, 1972).

Overall attention to pharmacokinetic detail may result in more efficient use of these drugs. In particular, the relationship between effectiveness and blood concentration, on the one hand, and large interindividual variations in blood levels, on the other, suggest that monitoring of blood or plasma levels may aid selection of dose in individual patients. However, with the wide therapeutic ratio for these drugs, it is probably most important to recognise undertreatment or lack of compliance. Drugs with prolonged half-lives of elimination such as sotalol or practolol have obvious advantages in the management of patients with diseases requiring long-term 24-hour beta blockade since this can be achieved with once or twice daily dosage (Carruthers *et al.*, 1974b). However, practolol cannot be recommended except in occasional special circumstances because of recent reports about its toxicity (Wright, 1975; Amos *et al.*, 1975).

CONCLUSION

While beta adrenergic blocking drugs have the associated properties of intrinsic sympathomimetic action, membrane stabilising action and cardio-selectivity, their pharmacological effects in man are due to their inhibitory action at the beta-adrenoceptor site. Thus, regardless of the presence or absence of membrane stabilising action or intrinsic sympathomimetic effect, these drugs exert similar effects.

It can be misleading to suggest that beta-adrenoceptor blocking drugs depress

the heart in man, i.e. by some direct action, and thus reduce the heart rate and cardiac output. This action is a function of reduction of beta-adrenoceptor stimulation. Cardio-selective drugs have the advantage of producing less airways obstruction in asthmatic subjects. It should be noted that as these drugs are cardio-selective, not cardio-specific, larger doses may therefore result in bronchial constriction in susceptible subjects.

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THE CENSORS SATISFIED

Today's Membership candidate, about to do battle with a computer, might think of his forebears taking the first examination in 1839. Then the successful man became a Licentiate; Membership was a later innovation. The College demanded that the candidate should produce satisfactory evidence of unimpeached moral character. Note the unimpeached, the character could be impeachable as long as no one found out. The candidate also had to be past his 26th birthday and to have diligently attended for three entire years the physician's practice in some general hospital of at least 100 beds with a regular establishment of physicians and surgeons. The College required that 'all those who received its Diploma should have had such a previous education as would imply a competent knowledge of Greek' but would dispense with this if other qualifications were satisfactory. 'It cannot, however, on any account, dispense with a familiar knowledge of the Latin language as constituting an essential part of a liberal education.' The College warned that, 'There will be ample security afforded to the public and the profession that none but those who have had a liberal and learned education can presume with the slightest hope of success to offer themselves for approval to the Censors' board'. What would those Censors have thought of multiple choice questions?