tissues in which adrenaline produced an excitatory effect from those in which its effects were inhibitory. The observation was re-examined many years later by Cannon and Rosenblueth (1937), who were particularly concerned with the nature of the transmitter substance released by sympathetic nerves in tissues activated by sympathetic impulses compared with those which were inhibited. They hypothesised that a single transmitter substance (thought at that time to be probably adrenaline) was released by all sympathetic nerves and that this then combined with another substance in or near the effector cell to produce either an excitatory or an inhibitory transmitter. These modified transmitters, Cannon and Rosenblueth called Sympathin E (excitor effects) and Sympathin I (inhibitory effects). The major point discussed in the hypothesis was that the transmitter taken from a tissue showing excitatory effects (Sympathin E) did not excite tissues in which sympathetic impulses were normally inhibitory but in fact was without effect or even inhibited them. This observation was much more in accord with Langley's earlier suggestion of differing receptors rather than differing transmitter substances.

The modern view is based upon the classification of adrenoceptors suggested by Ahlquist (1948). He studied the effects produced by adrenaline, noradrenaline and isoprenaline on a range of tissues taken from mammalian species. It was found that the various responses fell into either of two major classes. In the first class, adrenaline was the most powerful agonist and isoprenaline the least, and in the second class, isoprenaline was the most potent and noradrenaline the least. Ahlquist suggested that the two sets of responses reflected actions mediated by different sets of adrenoceptors which he designated alpha for the first type and beta for the second, stimulation of which gives two distinct patterns of activity. In general, alpha-adrenoceptors mediate excitatory effects such as vasoconstriction, contraction of the smooth muscle of the uterus and vas deferens, whilst beta-adrenoceptors subserve inhibitory effects such as vasodilatation and relaxation of the smooth muscle of the respiratory tract and detrusor muscle of the bladder.

There are two major exceptions to this simple classification of alpha-excitatory and beta-inhibitory adrenoceptors; the alpha-adrenoceptors in the gastro-

intestinal tract subserve inhibition of tone and motility of the smooth muscle and in the cardiac muscle the adrenoceptors which mediate increases in cardiac force and rate are of the beta-type.

It follows from Ahlquist's work that adrenoceptors agonists may stimulate one or other type of adrenoceptor preferentially or, like adrenaline, stimulate both types. Thus in general, noradrenaline has mainly alpha-adrenoceptor stimulant activity whilst isoprenaline is practically specific for beta-adrenoceptors.

In the 1960, Sarnoff and his group, as well as Gault and his associates (1966) re-examined the role of the sympathetic system and defined clearly the effect of sympathetic activity on the intrinsic myocardial contractility and oxygen consumption. The introduction of drugs with beta-blocking activity was started by Powell and Slater (1958) who described a compound dichloroisoproterenol (DCI) 1-(3',4'-dihydroxyphenyl)-2-isopropylaminoethanol) which specifically blocked beta-adrenergic receptor sites. At that time, the full therapeutic implications of these advances in knowledge were not immediately realized.

However, since the discovery of DCI, there has been an intensive research programme in Europe and America aiming at the development of an agent that would specifically block cardiac beta-receptors.

By specific antagonism is meant blockade of stimulation through a particular receptor site. So specific beta-receptor blockade means inhibition of responses due to beta-receptor stimulation without an effect on other tissue responses. For example, the inotropic response of the heart to nerve stimulation or sympathomimetic amines would be blocked, but the response to other inotropic agents such as calcium, theophylline or digoxine would be unaffected. In contrast, agents such as barbiturates which depress tissue function would inhibit the response to all these inotropic agents equally and are not specific beta-blockers. So the correct definition of specific beta-blockade is important and in this respect some unsubstantiated claims have been made. A competitive antagonism or blockade implies that the agonist and antagonist compete for the receptors in a reversible fashion, so that if the concentration of the agonist is sufficiently increased the block can be overcome. So a competitive antagonist may be defined as

one which moves the dose-response curve to the right when considering the interaction between a given stimulant and receptor site, DCI meets this criterion. Possession of specific competitive blocking properties is often accompanied by close structural similarity to the compounds producing stimulation. This is the case with dichloroisoproterenol (DCI).

Few years following the introduction of DCI, Black and Stephenson in 1962 introduced a second beta-adrenergic antagonist which was pronethalol, which was structurally related to both isoprenaline and dichloroisoproterenol. From the experiments conducted in animals and man, pronethalol had much weaker initial pharmacological intrinsic sympathomimetic activity. However, studies of its actions in man were curtailed because it produced tumours of the thymus gland of mice (Black and Stephenson, 1962).

However, Black and his colleagues had by this time prepared a non-carcinogenic beta-adrenoceptor blocker more potent than pronethalol and virtually devoid of intrinsic sympathomimetic activity. This substance was called propranolol, 1-isopropylamino-3-(1-naphthyloxy)-

2-propanol, and was first described by Black et al. (1965).

Inherent dangers in the clinical use of beta-adrenoceptor antagonists such as propranolol are the potential precipitation of bronchoconstriction in patients suffering from asthma or obstructive airways disorders secondary to blockade of beta-adrenergic receptors found in the smooth muscles of the bronchi. So, recent studies suggest that the division of adrenergic receptors solely into α and B types may be too simplistic. Evidence has accumulated pointing to the existence of subclasses of both α and B receptors. Support for such a hypothesis is fairly substantial in regard to B-receptor subtypes, while the evidence for α-receptor subclassification is just beginning to emerge.

A hypothesis introduced by Lands et al. (1967), that there were two types of beta-adrenoceptors, $beta_1$ particularly responsive to noradrenaline subserving lipolysis and cardiac stimulation and $beta_2$ with greater affinity to adrenaline subserving bronchodilatation and vasodilatation seemed to offer a great help. According to this classification, it could be assumed that if a

drug proved more potent in blocking cardiac receptors than the receptors in the bronchi and the blood vessels, then it would therefore, be safe to use in patients with obstructive lung disease.

The applicability of the $beta_1$ and the $beta_2$ adrenoceptors hypothesis to man was supported by Collier and Dornhorst (1969).

Attempts were made to introduce cardio-selective beta adrenoceptor blockers, blocking $beta_1$ adrenoceptors in the heart with no or minimal effects on the $beta_2$ adrenoceptors of the bronchial muscle or blood vessels. Thus, such blockers may be prescribed in patients suffering from obstructive pulmonary diseases.

The first cardioselective compound to be extensively used in man was practolol which was introduced by Dunlop and Shanks in 1968. Practolol differs from propranolol in a number of respects; the most important difference from propranolol is that it has a more marked blocking action on the $beta_1$-adrenoceptors of the heart than on the $beta_2$-adrenoceptors of the respiratory tract. Vaughan Williams et al. (1973) showed in dogs that

practolol was eight times more active in blocking cardiac ($beta_1$) than peripheral vascular ($beta_2$) adrenoceptors. This drug was, however, withdrawn from general clinical use in 1975 because of toxic effects apparently unrelated to beta-adrenoceptor blockade. The most common reactions being a psoriasis-like skin rash, drug red eye syndrome and occasionally blindness. Less common, but more serious fatal sclerosing peritonitis had been reported. Practolol remains, however, the prototype drug of cardioselective agents and has been replaced by less toxic cardioselective agents such as atenolol, metoprolol and acebutolol.

Metoprolol tartrate (Lopresor) was reported to be quite potent in blocking cardiac $beta_1$-adrenoceptors and much less active in blocking the $beta_2$-adrenoceptors of the respiratory tract. Selective B_1-adrenergic blocking agents that have either been introduced into therapy or are under investigation include metoprolol, atenolol, acebutolol, and tolamolol. It is important to remember that the selectivity of the B_1 blocker is not absolute; larger doses of these compounds will inhibit all beta-adrenergic receptors (Prichard, 1978).