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ADRENERGIC BLOCKADE AS A RESEARCH TOOL IN CLINICAL MEDICINE

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MR. PRESIDENT, ladies and gentlemen, it is with much pleasure that I have come to Dublin to give the Tenth Graves Lecture. I was very honoured to be chosen by the Royal Academy of Medicine in Ireland and the Medical Research Council of Ireland to give this lecture for which I have chosen the subject "Adrenergic blockade as a research tool in clinical medicine".

My interest in adrenergic blocking drugs was kindled almost exactly 10 years ago when I was working in the Department of Physiology in the Medical College of Georgia in Augusta with W. F. Hamilton who developed the dye dilution method for the measurement of cardiac output. In the Medical College the Departments of Physiology and Pharmacology shared the same offices and laboratories. At an inter-departmental meeting, the Professor of Pharmacology, Raymond Ahlquist, described his research work. He had recently obtained a drug, dichloroisoprenaline or DCI, from Eli Lilly and Company and showed that it blocked the tachycardia and peripheral vasodilatation produced by isoprenaline. These responses resulted from stimulation of the adrenergic receptors which he had classified as beta. DCI had no effect on the alpha receptors. Shortly afterwards I returned to the Department of Physiology in the Queen's University, Belfast, where we showed in man that dichloroisoprenaline blocked adrenergic beta receptors in the peripheral blood vessels. This was the first demonstration of the activity of a beta receptor blocking agent in man. Ahlquist or ourselves could not have predicted that 10 years later derivatives of dichloroisoprenaline would be so widely used not only in the treatment of disease but also as tools for investigation of the mechanisms contributing to disease processes.

In this lecture I would like to describe some of the investigative studies which have been made with drugs which block adrenergic receptors.

Although a remarkably complete and accurate description of "adrenergic blockade" was given by Sir Henry Dale in his paper entitled "On some physiological actions of ergot", which was published in 1906, interest in this subject has increased more in the past 15 years than in the preceding 55 years from Dale's original observation. There are many reasons for this increase in interest in adrenergic blockade.

Of prime importance has been the development of a much clearer understanding of adrenergic mechanisms resulting largely from the development of sensitive biochemical methods for the demonstration and determination of adrenaline, noradrenaline and their metabolites in tissues.

Secondly, the development of drugs which effect the sympathetic nervous system.

Thirdly is the realisation that a knowledge of adrenergic mechanisms is essential to our understanding of various disease processes.

Dale showed that ergot blocked some of the actions of adrenaline in 1906 but he did not introduce the term "adrenergic" to describe chemical transmission at sympathetic endings until 1934 (Dale, 1934). The term 'adrenergic blockade' has been clearly defined by pharmacologists but in clinical studies the term has often been interpreted more widely. It is important that in the context of this lecture a clear definition of the term should be used.

The pre-ganglionic sympathetic fibres arise in the cells of the lateral horn of the spinal cord and pass by way of the anterior nerve roots and the white rami communicantes to the sympathetic ganglia. These form two chains lying on either side of the vertebral column. The post-ganglionic fibres arise in the ganglia and pass by way of the grey rami communicantes and the spinal nerves for distribution to the organs and tissues which they supply. Impulses which pass along these nerve fibres exert their action on the cells by the liberation of noradrenaline from the store of noradrenaline at the nerve ending. The noradrenaline activates a specialised part of the cell which has been termed a receptor—in this case an adrenergic receptor. These receptors are acted on by noradrenaline released from the stores at the nerve endings, by noradrenaline and adrenaline which may be released from the adrenal medulla and also by catecholamines administered to the body, for example, by intravenous injection. Very little is known about the way in which noradrenaline and other catecholamines stimulate adrenergic receptors. It must be realised that we do not know what a receptor is either histologically or biochemically. It has been defined by de Jongh (1964) as 'To most of the modern pharmacologicts the receptor is like a beautiful but remote lady. He has written her many a letter and quite often she has answered the letters. From these answers the pharmacologist has built himself an image of this fair lady. He cannot, however, truly claim ever to have seen her, although one day he may do so'.

The action of the sympathetic nervous system can be blocked at various sites. In the ganglia by hexamethonium, mecamylamine and related drugs. The transmission of nerve impulses along the post-ganglionic fibre is blocked by guanethidine and bethanidine. The release of the transmitter substance is altered by reserpine and guanethidine. Although these drugs reduce activity of the sympathetic nervous system, they do not produce adrenergic blockade. This term is confined to describe the effects of drugs which block the action of the neurotransmitter, noradrenaline, or other endogenous or exogenous catecholamines on the receptor. The mechanism of action of these antagonists is not clearly understood.

Adrenergic receptors are now divided into two main groups following Ahlquist's observations in 1948. On the basis of the activity of a series of closely related sympathomimetic amines on a variety of tissues Ahlquist concluded that there were two distinct types of adrenergic receptor. These he designated alpha and beta. A modification of the findings on which his

classification was based is outlined in Table 1. Phenylephrine stimulated the receptors in the peripheral blood vessels but in none of the other sites. Isoprenaline increased heart rate and force, dilated the arterioles in skeletal muscle and dilated the bronchi; it did not produce a vasoconstriction. The receptors stimulated by phenylephrine have been designated alpha and those stimulated by isoprenaline have been designated beta.

TABLE 1

Comparison of isoprenaline and phenylephrine.

Drug	Heart		Bronchi	Blood vessels	
	Rate	Force	Dilatation	Constriction in skin	Dilatation in muscle
Isoprenaline	+	+	+	—	+
Phenylephrine	—	—	—	+	—

\+ denotes a response

— denotes no response

The distribution of these receptors in different organs is given in Table 2. Alpha adrenergic receptors are present in the smooth muscle of blood vessels of skin and kidney and in the dilator pupillae muscle. Beta receptors are present in the heart, the bronchi and blood vessels in skeletal muscle.

This classification of adrenergic receptors has been vindicated by the development of drugs which specifically block either alpha or beta receptors. This was first shown by Dale in 1906 when he reported that ergot extracts blocked the vasoconstrictor but not the vasodilator action of adrenaline. In current terminology we would say that ergot blocked alpha receptors and not beta receptors.

Several drugs are now available which selectively block adrenergic alpha receptors and not beta. These are termed adrenergic alpha blocking agents. These drugs include phenyoxybenzamine, phentolamine and thymoxamine. These drugs will block the vasoconstrictor action of all catecholamines but will not affect their action on the heart or bronchi.

It is only during the past 12 years that drugs which block adrenergic beta receptors have become available. The first was dichloroisoprenaline (Powell & Slater, 1958). Although it blocked these receptors it also produced an initial stimulation which resulted in an increase in heart rate (Moran Perkins, 1958; Shanks, 1966), so that it was unsuitable for clinical studies. In 1962 pronethalol was described as a beta receptor blocking agent and was shown to be of value in clinical medicine as a research tool and in the treatment of various disease processes (Black & Stevenson, 1962;

Stock & Dale, 1963). Studies with pronethalol were limited as it was shown to produce tumours of the thymus gland in mice (Alcock & Bond, 1964). Shortly afterwards propranolol was shown to be a potent beta receptor blocking agent relatively free from undesired side-effects (Black, Duncan Shanks, 1965). Propranolol has been shown to be effective in the treatment of conditions such as angina of effort, various cardiac arrhythmias and hypertension. During the past 5 years several more drugs which block adrenergic beta receptors have been described. There are small differences in the additional properties that these compounds possess, but their most important property is that of beta receptor blockade (Fitzgerald, 1969; Shanks, 1969).

I do not intend to discuss the additional properties of these drugs but to confine my remarks to the beta adrenergic blocking properties of the drugs. Propranolol has been used much more extensively than any of these other drugs, and although I will confine my remarks almost exclusively to it, this does not mean that the finding which will be reported are exclusive to it.

It is not generally realised that both alpha and beta receptor blocking drugs have been of great value in investigating the role of the adrenergic nervous system in different physiological and clinical situations.

As my early years were spent in the Department of Physiology in Belfast with Professor A. D. M. Greenfield who was an ardent supporter of medical research in Ireland, it is appropriate that I should begin by discussing the role that propranolol has played in advancing our understanding of the factors which contribute to the increase in heart rate which occurs on exercise.

Several observations were made during the early part of this century into

TABLE 2

Distribution and function of adrenergic receptors.

Organ	Response to sympathetic stimulation	Recepor
Heart	Increase in heart rate	Beta
	Increase in cardiac contractility	Beta
Blood vessels	Constriction in skin and kidney	Alpha
	Dilatation in skeletal muscle	Beta
Eye	Dilatation of pupil	Alpha
Bronchi	Dilatation	Beta
Gastro-intestinal tract	Reduction in motility	Alpha and beta

the role of the autonomic nervous system in an exercise induced tachycardia. Until recently observations were confined to animals, and involved studies on the effect of vagotomy to interrupt parasympathetic activity and of stellate ganglionectomy to interrupt sympathetic activity (Gasser & Meek, 1914). After both procedures heart rate increased on exercise. More recently Shepherd and his colleagues at the Mayo Clinic reported that after total cardiac denervation, dogs exhibited a large but subnormal increase in heart rate during exercise (Donald & Samueloff, 1966).

Studies of a similar nature have not been possible until recently in man. One of the positive results of cardiac transplantation in man has been the demonstration that the transplanted heart will beat more quickly on exercise; comparative studies involving either the two hearts in the recipient or the one heart in donor and recipient have not been possible in these circumstances.

Elucidation of the function of the autonomic nervous system in controlling the heart rate during exercise in man has had to depend on the development of drugs which would specifically block the effects of the parasympathetic and sympathetic nervous systems on the heart.

Although atropine has been available for many years, its effect on changes in heart rate on exercise have not been widely studied. Robinson and his colleagues in 1953 showed that atropine had little effect on the maximum heart rate during exercise (Robinson, Pearcy, Brueckman, Nicholas & Miller, 1953).

Cannon and Bacq first suggested in 1931 that the tachycardia which occurred in cats during exertion was due to the action on the heart of an "adreninlike" substance released into the blood stream. Vendsalu in 1960 confirmed that the levels of noradrenaline and adrenaline in the blood in man during exercise were increased.

The sympathetic nervous system can affect the heart in two ways during exercise. Firstly, by an increase in activity of the sympathetic nerves to the heart, and secondly, by the action of adrenaline and noradrenaline released from the adrenal medulla and entering the circulation. These two mechanisms increase heart rate by stimulating adrenergic beta receptors in the heart. The advent of drugs which block these receptors has provided a very useful tool for investigating the role of the sympathetic nervous system in the cardiac response to exercise in man. For the first time both nervous and humoral components could be blocked and, in addition, alpha receptors and the parasympathetic system were not antagonised.

The effect of the intravenous administration of propranolol on the increase in heart rate produced by severe exercise is shown in Figure 1. These results are the mean observations in 5 healthy male subjects. Heart rate was recorded with the subjects standing before and at the end of a three-minute period of severe exercise. The first period of exercise produced a marked increase in heart rate. After a period of rest of 20 minutes duration, heart rate was recorded before and 5 minutes after the intravenous injection of saline. The heart rate at the end of the period of exercise was unchanged from the value during the preceding period of exercise. Similar observations were made before and after the intravenous injection of 4, 8 and 16

mg. of propranolol. After 4 mg. propranolol resting heart rate and the heart rate at the end of exercise were significantly reduced. The two larger doses of propranolol produced further falls in resting and exercising heart rates.

The maximum heart rate during the control period of exercise was 155 beats per minute and after 16 mg. propranolol was 108 beats per minute. Thus propranolol reduced the exercise tachycardia by 47 beats per minute. Similar results have been obtained with other drugs which block adrenergic beta receptors (Brick, Hutchison, McDevitt, Roddie & Shanks, 1968). Thus it can be concluded that this part of an exercise tachycardia is due to increased activity of the sympathetic nervous system. After the largest dose of propranolol heart rate still increased by 36 beats per minute on exercise. This could be due to:—

1. Incomplete beta receptor blockade although this is unlikely as a total dose of 28 mg. propranolol had been given in 50 minutes.
2. Reduced activity of the parasympathetic nervous system.
3. Other unknown factors.

The contribution of changes in parasympathetic activity to this increase in heart rate have been investigated by Chamberlain and his colleagues

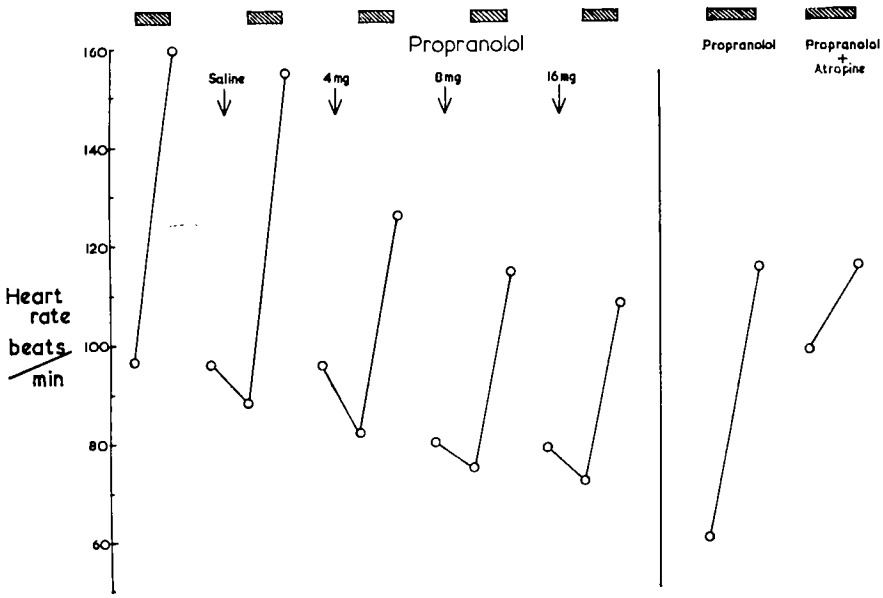

Fig. 1. Left hand panel—The effect of the intravenous injection of saline and increasing doses of propranolol on heart rate at rest and at the end of a 3-minute period of exercise (///). Each point is the mean of observation in 5 subjects.

Right hand panel—Observations were made on 10 subjects on two occasions when heart rate was recorded at rest and at end of exercise. On first occasion observations were made 1 hour after oral administration of propranolol, 80 mg., and on second occasion after the administration of propranolol and atropine (3.0 mg. by intravenous injection). Each point is mean of observations in 10 subjects (Results from Chamberlain *et al.*, 1967).

(Chamberlain, Turner & Sneddon, 1967). Although their experimental set-up was different to that described above, their observations are relevant to the present discussion. A summary of their results in 10 healthy subjects is shown in the right-hand portion of Figure 1. Heart rate was measured before and at the end of strenuous exercise performed one hour after the oral administration of 80 mg. propranolol. Resting and the post-exercise heart rate were similar to those obtained in the present study after 16 mg. of propranolol intravenously.

Chamberlain and his colleagues then administered atropine by intravenous injection, giving up to 3.0 mg., to their subjects. Heart rate was recorded before and after exercise (Figure 1). The resting heart rate was increased but the maximum heart rate on exercise was unaltered. These results show that a reduction in parasympathetic activity and an increase in sympathetic activity both contribute to the increase in heart rate which occurs during exercise. After blockade of both sympathetic and parasympathetic systems an increase in heart rate still occurs on exercise. The mechanism of this increase remains to be determined.

A diagramatic representation of the interplay between the sympathetic and parasympathetic nervous systems during the increase in heart rate on exercise is shown in Figure 2. During slight exercise heart rate increases by a reduction in vagal activity but the increase during moderate and severe exercise occurs mainly from an increase in sympathetic activity.

Several important conclusions can be drawn from these studies:—

1. They illustrate the way in which integrated action of the autonomic nervous system controls heart rate changes on exercise. The same occurs during the response to changes in posture.

2. Assessment of the activity of beta receptor blocking agents in man is often made by studying their effect on the tachycardia of exercise. These studies indicate that severe exercise must be used as the stimulus so that the increase in heart rate is due to increased sympathetic activity and not only to changes in parasympathetic activity. Assessment of beta adrenergic blockade in this way is of much greater clinical relevance than assessment through blockade of an isoprenaline tachycardia.

3. After propranolol the amount of cardiac work is reduced at the higher external work loads. This may be the basis on which the drug works in angina of effort. It reduces the amount of cardiac work for a given amount of external work. As anginal pain is determined by the amount of cardiac work, a reduction will increase the amount of external work that can be done before the onset of pain.

Drugs which block adrenergic alpha receptors have helped our understanding of only a limited number of situations, whereas drugs which block adrenergic beta receptors have been of much greater help as a research tool in medicine. This has probably resulted from a number of factors. Alpha receptors are situated in peripheral blood vessels and the dilator pupillae muscle. These structures are not often involved in disease processes whereas

the heart and bronchi which contain beta receptors are much more often involved. The interest in adrenergic receptors and the effect of drugs on them has grown rapidly during the past 6-7 years. This has coincided with the introduction of beta receptor blocking compounds. The two events are probably more than casually related. The development of clinical pharmacology has provided centres, albeit few as yet, at which the effects of drugs can be studied in detail. This has coincided with the appearance of beta receptor blocking drugs which were thus readily available for study. If alpha blocking agents had just appeared at this time then they might have been studied in the same detail.

Although the diagnosis of phaeochromocytoma is now relatively simple with the recent development of sensitive fluorometric methods for the accurate estimation of the concentrations in the blood of adrenaline and noradrenaline, many physicians have utilised adrenergic blockade as a tool in the diagnosis of this condition. The first complete description of the anatomical and pathological features of this rare tumour was in 1922 by Labé, Tinel and Doumer who suggested that the paroxysmal hypertension was due to the occasional release of hypertensive amines by the tumour. But it was not until 1950 that von Euler showed that increased amounts of adrenaline and noradrenaline were excreted in the urine in patients with this condition (Engel and von Euler, 1950).

This condition was probably the first in which an adrenergic blocking agent was used for research and diagnostic purposes. Before the advent of the present methods for chemical estimation of catecholamines and their

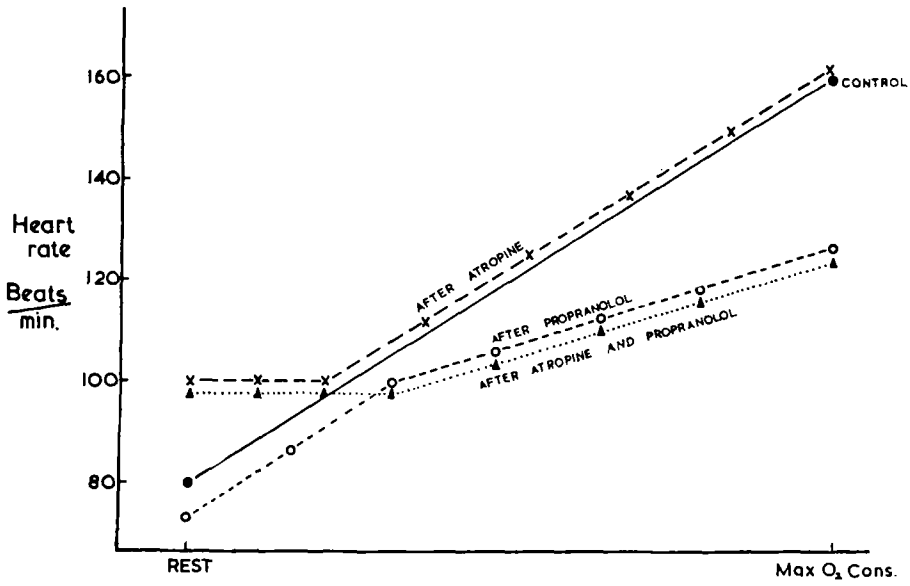

Fig. 2—Diagrammatic representation of the changes in heart rate during exercise of increasing severity in normal subjects (●——●), after treatment with atropine (x---x), after treatment with propranolol (o---o) and after atropine and propranolol (Δ . . . . Δ).

metabolites, the "Rogitine or phentolamine Test" was widely used for diagnosis of phaeochromocytoma. This test was first described by Grimson and Sougino in 1949 and replaced the dibenamine and benzodioxane tests introduced a few years earlier.

These tests were based on the ability of the drugs to block the action of the increased amounts of circulating adrenaline and noradrenaline on adrenergic alpha receptors. In patients with phaeochromocytoma and a raised arterial pressure, the administration of phenotolamine produces a prompt reduction in arterial pressure. The response is positive when the pressure falls by 20-30 mm Hg after 2-3 minutes and lasts 10 minutes.

Many tests of this nature have been carried out in patients with raised arterial pressure to exclude the presence of a phaeochromocytoma. Although the number of positives may have been small, they demonstrated a type of hypertension which could be cured.

It is well known that the administration of propranolol to patients with asthma increases their airways resistance to such an extent that they wheeze (McNeill, 1964; Macdonald, Ingram and McNeill, 1967). As a consequence, asthma is one of the main contradictions for the use of this drug. It is not generally realised that another benefit of these studies by McNeill and his colleagues was an increase in our knowledge of the function of the autonomic nervous system in controlling the calibre of the airways.

The calibre of the bronchi is controlled by both the sympathetic and parasympathetic nervous systems. Stimulation of adrenergic beta receptors produces a bronchodilatation—the basis for the use of drugs such as isoprenaline and adrenaline in asthma. Activity of the parasympathetic constricts the bronchi and increases airways resistance.

The results in Figure 2 are taken from a paper by McNeill and his colleagues and show the changes in airways resistance in a mild asthmatic subject (Macdonald, *et al.*, 1967). The intravenous injection of propranolol 5 mg. produced a marked increase in airways resistance. Observations on a separate occasion showed that the intravenous injection of atropine had little effect on airways resistance. The subsequent injection of propranolol after atropine was without effect on airways resistance.

Three important conclusions can be drawn from these results :—

1. The increase in airways resistance produced by propranolol is due to an unmasking of the bronchoconstrictor action of the parasympathetic nervous system as the increase in resistance does not occur after atropine treatment.
2. In a patient with asthma tonic activity of the sympathetic system appears to play an important role in maintaining the calibre of the bronchi as bronchospasm develops when it is removed.
3. Thirdly, these results indicate that when a patient treated with propranolol has an increase in airways resistance and becomes wheezy he should be treated by the intravenous administration of atropine. and not by the administration of a drug to stimulate beta receptors such as isoprenaline. This also applies to patients who develop a bradycardia after the administration of propranolol. This is most

easily corrected by the intravenous administration of atropine as the bradycardia is due to the unmasking of the slowing action of the vagus on the heart.

I think that it would be appropriate that the remainder of my lecture be concerned with studies in thyrotoxicosis, a condition first described in 1835 by Robert Graves, after whom this lecture is named. Two of the cardinal features of the condition described by Graves were tachycardia and palpitations. In the following years other features including finger tremor, hyperkinetic movement, peripheral vasodilatation, sweating and various eye signs were described.

It was not until later in the nineteenth century that the effects of the sympathetic nervous system on various functions were elucidated. A great impetus to these studies was given by the isolation and synthesis of adrenaline at the beginning of this century. The availability of adrenaline enabled one to reproduce the effects of activation of the sympathetic nervous system without anaesthetizing the animal for electrical stimulation of sympathetic nerves. The administration of adrenaline increased heart rate, produced palpitations, nervousness (excitement), finger tremor and sweating, effects which are similar to some of the symptoms of Grave's disease. McCarrison appears to have been the first to recognise the similar-

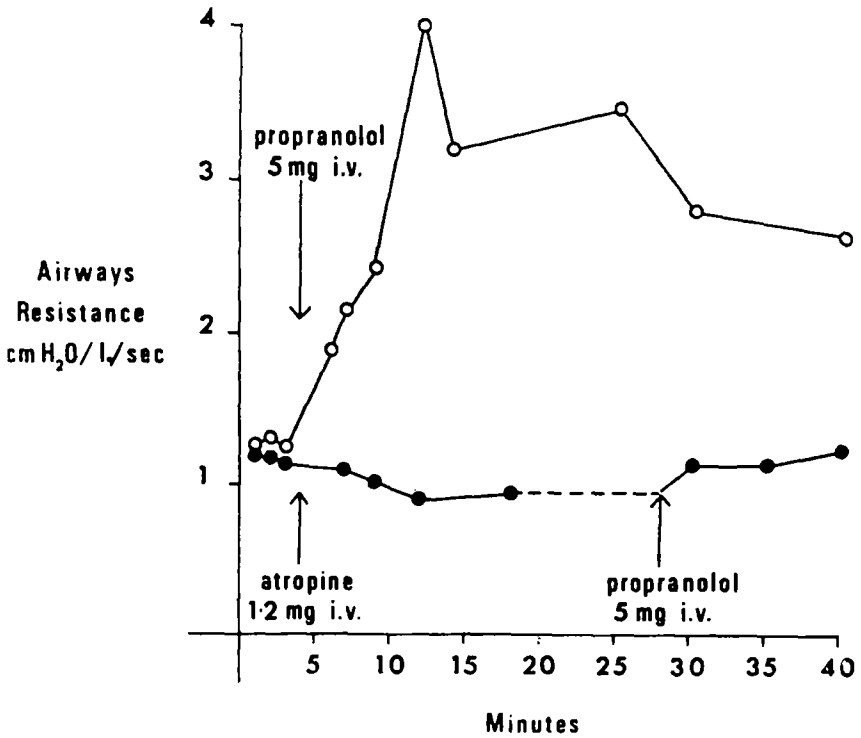

Fig. 3—The airways resistance (AWR) response of a mild asthmatic subject to propranolol, with and without prior atropine. The upper line (open circles) shows the rise in AWR after the administration of propranolol. The lower line (black circles) shows the fall in AWR after atropine and the reduced response to propranolol in the atropinized state (Macdonald *et al.*, 1967).

ity between the effects of excessive sympathetic nervous activity and of the features of hyperthyroidism. In his monograph "The Thyroid Gland" published in 1917, McCarrison states : "This agency, i.e., the underlying casual agency which is accentuated by various predisposing causes, is one which gives rise to continuous excitation of the sympathetic nervous system". And later, "Grave's Disease is above all things a condition of heightened excitability of the vegatative nerves accompanied by disordered metabolism and abnormal action of all organs innervated by them".

These observations prompted numerous investigations of the influence of changes in the thyroid state on the responses to adrenaline. These observations were often confined to measurements of blood pressure and did not include heart rate. Many of these investigators claimed that in man with naturally occurring thyrotoxicosis and in man and animals fed thyroid extracts, the cardiovascular effects of adrenaline were potentiated. As a consequence it has been taught for the past 50 years that the thyroid hormone potentiates the actions of the catecholamines and in particular adrenaline (Harrison, 1964). Many of these papers contain little or no statistical treatment of the data, no clear distinction is made between effects on arterial pressure and heart rate and there are relatively few observations in patients with hyperthyroidism, so that it is not possible to know if the effects of adrenaline are potentiated.

Observations have been made with drugs which block the sympathetic nervous system in patients with thyrotoxicosis. It has been shown that reserpine, guanethidine and propranolol reduce the heart rate in these patients and in normal subjects in whom a state of hypermetabolism has been produced by the administration of liothyronine (Canary, Schaff, Duffy and Kyle, 1957; de Groot, Leonard, Paley, Johnson and Warren, 1961; Lee, Bronsky and Waldstein, 1962; Goldstein and Killip, 1965; Howitt and Rowlands, 1966). All these drugs reduced the tachycardia but as no observations were made with the subjects in a euthyroid state, it was impossible to conclude if the tachycardia resulted from increased activity of the sympathetic nervous system.

It has now been conclusively demonstrated in carefully controlled studies that the administration of thyroxine or liothyroine to animals and to normal subjects does not augment the cardiovascular actions of catecholamines (Margolius and Gaffney, 1965; van der Schoot and Moran, 1965; Aoki, Wilson, Thielen, Sukensureyer and Leaverton, 1967). However, as differences may exist between naturally occurring thyrotoxicosis and induced states of hypermetabolism, we have utilised the adrenergic blocking properties of propranolol to study this problem as it is important to know if the thyroid hormones poteniate the action of the sympathetic nervous system in thyrotoxicosis.

Propranolol is superior to reserpine and guanethidine for such a study as it produces specific blockade of adrenergic beta receptors without interfering with the mechanisms controlling arterial pressure. Howitt and Rowlands showed in 1966 that the intravenous administration of propranolol to patients with thyrotoxicosis reduced their heart rate. As observations were not made in 'control' subjects they were unable to show if this reduction was different from that which propranolol produces in normal people.

In conjunction with my colleagues, Doctors Montgomery, Hadden, Weaver, Lowe and McDevitt, we have studied the effects of propranolol on resting heart rate in patients with thyrotoxicosis. The problem of obtaining matched control subjects was overcome by making observations in patients with hypothyroidism. In these patients heart rate is characteristically slow; this has been attributed to reduced activity of the sympathetic nervous system or to a reduced sensitivity of the peripheral tissues, in this case the heart, to adrenaline (McDevitt, Shanks, Hadden, Montgomery and Weaver, 1968).

The results of our studies are shown in the Figure 4. Observations were made in 10 patients with hyperthyroidism and in 5 with hypothyroidism. All patients were in hospital and observations were made with the patients in the supine position and after an overnight fast. Before the administration of propranolol, heart rate was 92 beats per minute in patients with thyrotoxicosis and 59 in those with hypothyroidism. All patients were given propranolol, 0.2 mg. per Kg. bodyweight by intravenous injection. This produced a prompt and significant reduction in the heart rate in patients with thyrotoxicosis and to our surprise an equally prompt and significant reduction in the patients with hypothyroidism. The absolute decrease in beats per minute was greater in thyrotoxicosis, 17.5, as opposed to 11.4 in hypothyroidism, but the percentage reduction was the same in both conditions.

Two important conclusions can be drawn from these results.

Firstly, they show that the heart in hypothyroidism is being stimulated

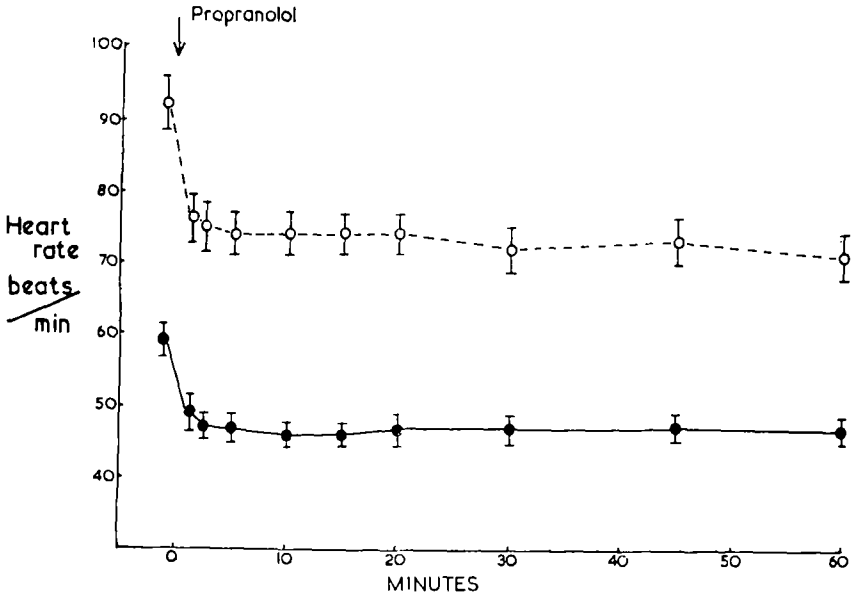

Fig. 4—Effect on heart rate of the intravenous injection of propranolol (0.2 mg. per Kg. body weight) in 10 patients with hyperthyroidism (o) and in 5 patients with hypothroidism (●). Each point represents the mean of observation for each group of patients.

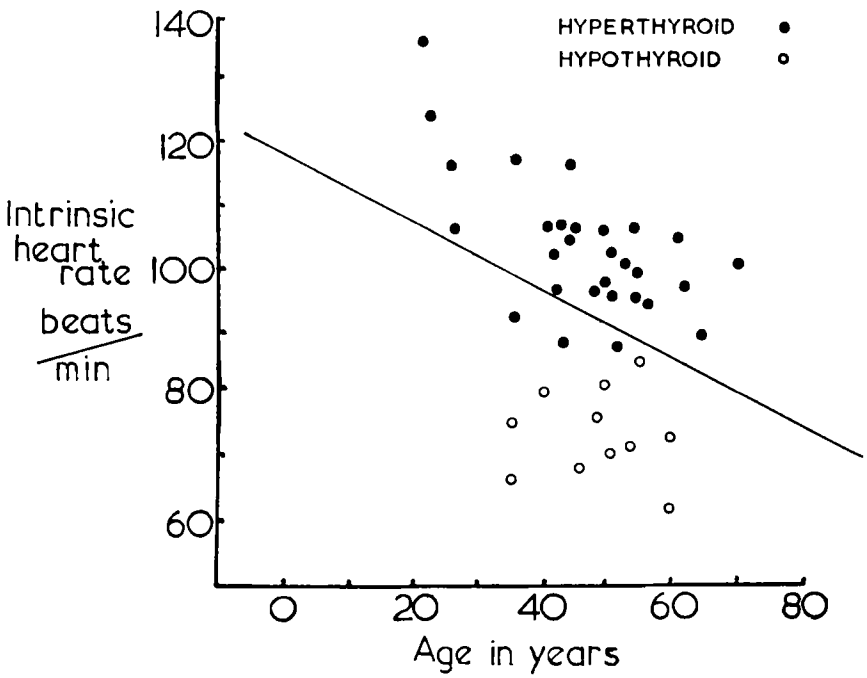

Fig. 5—Intrinsic heart rate in 29 patients with hyperthyroidism (o) and in 10 patients with hypohyroidism. The regresson line obtained from the results of Jose (1966) is included.

by the sympathetic nervous system. *Secondly*, these results indicate that overactivity of the sympathetic cannot account for the tachycardia of thyrotoxicosis as there is a highly significant difference in the resting heart rate in the 2 groups of patients after blockade of the effect of the sympathetic on the heart. In thyrotoxicosis after the administration of propranolol the heart rate was 74 beats per minute and in patients with hypothyroidism 47 beats per minute, a difference of 27 beats per minute which is highly significant. Some factor or factors other than the sympathetic nervous system must be acting on the heart in thyrotoxicosis to elevate the heart rate; absence of these factors results in the lower rate in hypothyroidism.

The difference in heart rate after propranolol in these two conditions could result from changes in activity of the parasympathetic nervous system. Increased activity would reduce heart rate and could account for the bradycardia of hypothyroidism. This was investigated by making observations in patients in whom the adrenergic receptors were blocked with propranolol and the parasympathetic receptors with atropine. The combined use of these two drugs in this way pharmacologically denervates the heart so that it is no longer under the control of the autonomic nervous system. This is the intrinsic heart rate which has been described by Jose (1966).

The results from 29 patients with thyrotoxicosis and 10 with hypothyroidism are given in Figure 5. As intrinsic heart rate is related to age, the regression line obtained from the results of Jose is included in Figure 5. In 26 out of 29 patients with hyperthyroidism the value for intrinsic heart

rate was greater than that which would have been expected for their age. In all patients with hypothyroidism the value was lower than predicted. There is a significant difference between the values for the two groups of patients.

The higher intrinsic heart rate in hyperthyroidism is probably due to the action on the sino-atrial node of increased amounts of circulating thyroid hormones. Studies in animals and man have shown that the administration of thyroid or thyroid hormones increases heart rate due to a direct action on the sino-atrial node (Aoki, *et al.*, 1967; Cairoli and Crout, 1967).

These studies with adrenergic blocking drugs have shown in man that the actions of the sympathetic nervous system on heart rate are not potentiated in thyrotoxicosis and suggest that the tachycardia in this condition is due to the actions of increased amounts of thyroid hormone supplementing the normal activity of the sympathetic nervous system (McDevitt, *et al.*, 1968).

These observations do not mean that care should not be exercised in the administration of catecholamines to patients with thyrotoxicosis. They already have a high heart rate and a further increase could be very unpleasant and even dangerous.

During these studies we found, to our surprise, that after the intravenous administration of propranolol, patients with thyrotoxicosis spontaneously remarked that they felt much better. We expected them to notice a reduction in the tachycardia and of palpitations but they also commented on a reduction in sweating, feeling less warm and less nervous. In some patients the effect was dramatic. We then wondered if propranolol could be of further use in our study of hyperthyroidism, and in particular, in the treatment of the condition.

In the Metabolic Unit in the Royal Victoria Hospital, Belfast, we have utilised propranolol to control the features of hyperthyroidism and as it does not affect thyroid function, we have been able to study the effects of definite anti-thyroid treatment on thyroid function (Hadden, Bell, McDevitt, Shanks, Montgomery and Weaver, 1969).

Initial uncontrolled studies indicated that the oral administration of propranolol, 40 mg., four times daily, controlled many of the features of the disease without interfering with the function of the thyroid gland as the indices of thyroid function were not altered. Later a double blind controlled of propranolol against a placebo was carried out (Shanks, Hadden, Lowe, McDevitt and Montgomery, 1969). I would just like to mention it briefly in passing to show those facets of the disease which propranolol controlled. Observations were made on 16 patients who were assessed, using selected criteria, before entering the trial and at the end of the first week and at the end of the second week. Treatment lasted for two weeks during which time propranolol, 40 mg., four times daily, was given for one week and an identical placebo for the other week. The results were analysed using a sequential analysis and showed a significant preference for propranolol. The incidence of the signs and symptoms of thyrotoxicosis in the 16 patients before and after treatment are shown in Table 3. More patients felt better on propranolol. Propranolol reduced palpitations, excessive sweating, nervousness and the finger tremor. It had little effect on the eye signs. All the patients

TABLE 3

Incidence of symptoms and signs in 16 patients with thyrotoxicosis.

Subjective Assessment	At Onset	Number Improved After Propranolol	Number Improved After Placebo
How do you feel?	—	12	4
Palpitations	14	10	5
Preference for cold	9	3	0
Excessive sweating	14	10	3
Nervousness	16	11	2
Objective Assessment			
Lid Lag	8	0	1
Lid retraction	6	3	2
Fine tremor	14	10	1
Hyperkinetic movement	2	1	1
Warm hands and fine skin	14	7	2
Moist hands	11	4	1

were improved and many looked clinically euthyroid and were free of symptoms.

On completion of this study we were in a position to use propranolol to control the features of hyperthyroidism. This enabled us to use changes in serum protein bound iodine to study the effects of therapeutic doses of radio active iodine on thyroid function as propranolol does not alter protein bound iodine values (Hadden, *et al.*, 1969).

The introduction in 1942 by Hamilton and Lawrence and by Hertz and Roberts of radio active iodine for the treatment of thyrotoxicosis enabled a large dose of radiation to be delivered selectively to the secretory cells. Although it has ben widely used during the past two decades, several problems still exist about its use. Why do some patients respond and not others? Why do some become hypothyroid? How do you determine the dose for an individual patient? Problems with which everyone is familar. As radio active iodine does not affect thyroid function for at least 3 to 4 weeks, patients are often treated in addition with an antithyroid drug such as carbimazole to control their symptoms during this time. This, however, masks the effects of radio active iodine on thyroid function.

We have overcome this difficulty by treating patients with thyrotoxicosis with a combination of propranolol and radio active iodine. When the

diagnosis of thyrotoxicosis is established and it is decided to use radio active iodine for treatment, the required dose is administered and the patients started on propranolol, 40 mg., four times daily. Propranolol is continued until the patient becomes biochemically euthyroid. The patients have been seen at monthly intervals after the start of treatment.

Fifty-eight consecutive patients were given 3.0 to 5.0 mc. of radio active iodine; the mean dose was 4.1±0.08. Examination of the values for protein bound iodine indicated that 8 weeks after the administration of radio active iodine some patients showed a significant fall in serum protein bound iodine. These patients have been termed "responders". The remaining patients showed no change in protein bound iodine and have been termed "non-responders". The results from the 58 patients are shown in Figure 6

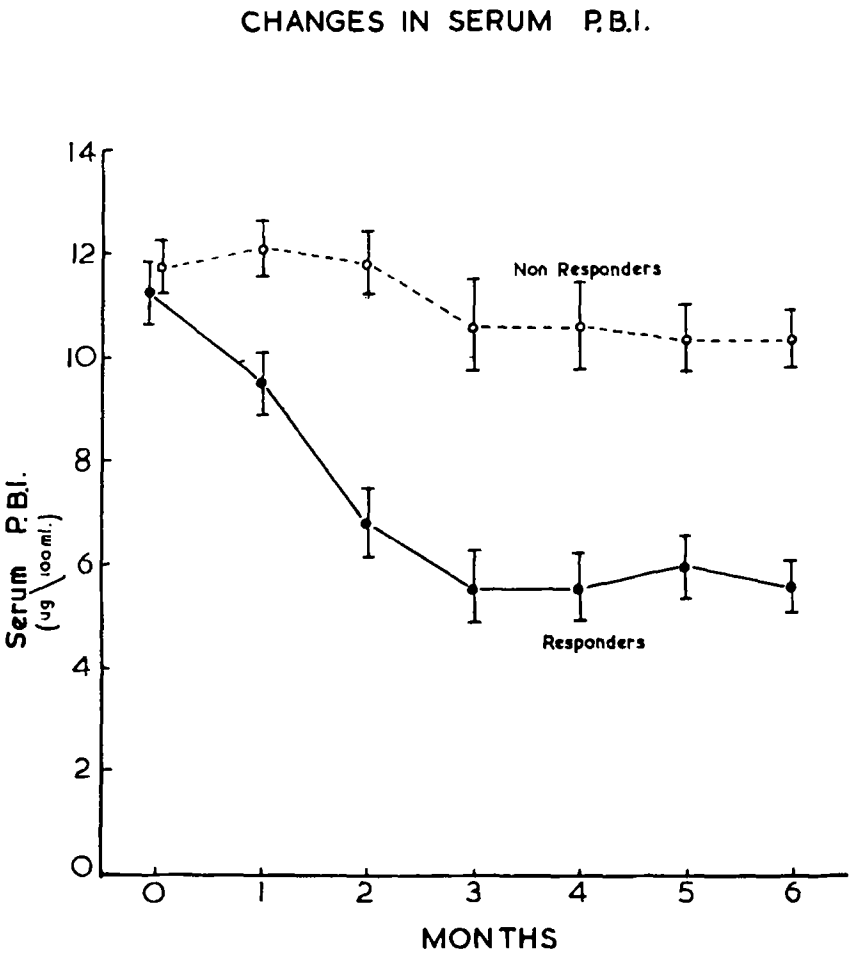

Fig. 6—Changes in serum protein bound iodine in 58 patients with hyperthyroidism treated with propranolol and radioactive iodine. Thirty-four patients were classified as responders and 24 as non-responders. Each point is the mean, with the standard error of the mean, for the stated number in each group.

TABLE 4

Response to radioactive iodine

	No. of patients	Mean dose of ^{131}I (millicuries)	Responders No.	%	Non Responders No.	%	Hypothyroid No.	%
1 dose	58	4.1 (3.0—5.0)	34	59	24	41	5	8.6
1 year	56	4.1	44	79	12	21	7	12.5

and Table 4. After one dose, *34* out of the *58* patients had responded, i.e., 59 per cent. The remaining 41 per cent who had not responded were given a second dose of radio active iodine. At the end of 12 months 79 per cent of the patients had responded. At the end of one year 7 patients had became clinically and biochemically hypothyroid, an incidence of 12.5 per cent. All but one of these patients was hypothyroid 3 months after the onset of treatment. These results indicate a wide variation in the sensitivity of apparently similar patients to the same dose of radio active iodine irrespective of severity of the condition.

Further observations have been made during the past 15 months in which all patients have been given 2.5 mc. of radio active iodine. Forty-six patients out of a total of 72 have now been followed for a total of six months. The results from these patients are summarised in Table 5 which also includes the results from 19 patients who have been followed for 1 year. The response rate of 59 per cent to one dose and 79 per cent at the end of one year, is identical to the results obtained in the first group of patients who were given the larger dose of radio active iodine. The incidence of hypothyroidism was greater in the patients who received 2.5 mc.

TABLE 5

Response to radioactive iodine.

Response	Patients	Iodine^{131} treatment dose (millicuries)	Responders	Non Responders	Hypothyroid
1 dose	46	2.5	27 (59%)	19 (41%)	6 (13%)
1 year	19	2.5	15 (79%)	4 (21%)	4 (21%)

Before commencing these studies, we had thought that 2.5 mc. of radio active iodine would have had little effect on thyroid function, but it would appear that the response rate was not altered and in addition, the incidence of hypothyroidism was not reduced by using the smaller dose of radioactive iodine. It must be emphasised, however, that longer term follow-up of these patients may indicate differences in the incidence of hypothyroidism.

One of the main questions which these results has raised is in relation to the factors which may determine which patient will respond to a given, and in our case, a small dose of radio active iodine. The two factors which we have considered are the effects of age and of a past history of thyroid disease.

The response rate of the 58 patients who were given 3.0-5.0 mc. radioactive iodine has been determined in three age groups and the results are given in Table 6. The response rate is greater in the younger than in the older patients. In addition, the incidence of hypothyroidism is greater in the younger subjects. Does this mean that the thyroid gland in younger patients is more sensitive to localised radiation? It is impossible to answer this problem at present.

TABLE 6

Relationship of age to response after a single ^{131}I treatment dose of 3.0-5.0 mc.

Age (years)	Patients	Responders		Hypothyroid	
		No.	%	No.	%
40 - 49	21	14	67	3	14.3
50 - 59	22	15	68	2	9.1
60+	15	5	33	0	0
TOTAL	58	34	59	5	8.6

The second factor which we have considered is the effect of a past history of thyroid disease on the response to radioactive iodine. We have summated the results from all patients who have been treated with 2.5 and 3.0 to 5.0 mc. radioactive iodine and followed for 6 months. The results, analysed to show the effects of a single dose of radioactive iodine, are given in Table 7 which shows the percentage of patients who responded. In the three age groups the response rate was much greater in the patients who had no past history of thyroid disease. Of the seven patients over 60 years who had a past history, none responded to the first treatment dose of radioactive iodine. These results indicate that if a patient has a past history of thyroid

TABLE 7

Response to a single treatment dose of ^{131}I.

Past History	40-49 years		50-59 years		60+ years		Total	
	No.	%	No.	%	No.	%	No.	%
Present	18	38.9	11	45.5	7	0	36	33.3
Absent	27	81.5	23	73.9	18	61.1	68	73.5

disease, small doses of radioactive iodine may not be the treatment of choice if the patient is over 60 years of age.

Although propranolol was not developed for the treatment of thyrotoxisosis and has not been widely used for this purpose, I hope these studies have shown that it has been most valuable as a research tool enabling us to further our knowledge of thyrotoxicosis and of its management. We still have a considerable way to go as we would like to be able to identify before treatment those patients with thyrotoxicosis who will respond to radioactive iodine and, in addition, to be able to predict the dose of radioactive iodine which will be effective without producing hypothyroidism.

In this lecture I have tried to show the way in which studies with drugs which block adrenergic receptors have been of value in increasing our knowledge of the function of the adrenergic nervous system in health and disease.

There is still much which we do not know about the activity of the sympathetic and parasympathetic nervous systems in man. This has arisen to some extent as it lies outside the realms of the pharmacologist and physiologist on one hand and the physician on the other. I think it should be regarded as a challenge to clinical pharmacologists to increase our knowledge of this subject. This can only occur if it is appreciated that clinical pharmacology can make a large contribution to medicine and to do so requires sufficient numbers of trained staff with adequate facilities. Without both progress will be slow.

Figure 2 (right hand panel) and 4 are reproduced by permission of the Lancet Ltd., and Figure 3 by permission of Sherratts Ltd.

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ROYAL COLLEGE OF PHYSICIANS OF IRELAND

DR. JAVIER LENTINI OF BARCELONA

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on

"MEDICINE AND THE FINE ARTS"

and a lecture restricted to a medical audience

on THURSDAY, JUNE 25th, 1970 at 8.15 p.m.

on

"PROCTOLOGY AND THE FINE ARTS"

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