SOCIAL ASPECTS OF PHARMACEUTICAL INNOVATION:

HEART DISEASE

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Submitted for the degree of Doctor of Philosophy

THE UNIVERSITY OF ASTON IN BIRMINGHAM

APRIL 1981

SUMMARY

This study examines the invention, innovation, introduction and use of a new drug therapy for coronary heart disease and hypertension; beta-blockade. The relationships between drug introductions and changes in medical perceptions of disease are analysed, and the development and effects of our perception of heart disease through drug treatments and diagnostic technology is described.

The first section looks at the evolution of hypertension from its origin as a kidney disorder, Bright's disease, to the introduction and use of effective drugs for its treatment. It is shown that this has been greatly influenced by the introduction of new medical technologies. A medical controversy over its nature is shown both to be strongly influenced by the use of new drugs, and to influence their subsequent use.

The second section reviews the literature analysing drug innovation, and examines the innovation of the beta-blocking drugs, making extensive use of participant accounts. The way in which the develcpment of receptor theory, the theoretical basis of the innovation, was influenced by the innovation and use of drugs is discussed, then the innovation at ICI, the introduction into clinical use, and the production of similar drugs by other manufacturers are described. A study of the effects of these drugs is then undertaken, concentrating on therapeutic costs and benefits, and changes in medical perceptions of disease.

The third section analyses the effects of other drugs on heart disease, looking at changes in mortality statistics and in medical opinions.

The study concludes that linking work on drug innovation with that on drug effects is fruitful, that new drugs and diagnostic technology have greatly influenced medical perceptions of the nature and extent of heart disease, and that in hypertension, the improvement in drug treatment will soon result in much of the population being defined as in need of it life-long.

Drug Innovation
Therapeutic impact
Beta-blockers
Hypertension

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Social aspects of pharmaceutical innovation: heart disease

Acknowledgements

I would like to acknowledge financial support from the Science Research Council for three years, and from the Department of Health and Social Security for one year.

My grateful appreciation to those people who have given freely of their time and experience, particularly Trevor Twose and Desmond Fitzgerald at ICI who kindly gave me access to the information I needed, and Michael Barrett, Robin Shanks, and James Black who gave me great encouragement as well as many ideas.

Thanks to: Fred Steward, my long-suffering supervisor for his good advice and offer of his house to stay in when I was in great need. George Wibberley, who brought insights by asking many awkward questions. Lynda Page for transforming an illegible morass into impeccable typescript so cheerfully. My colleagues and friends at the Technology Policy Unit for their encouragement and support through difficult times.

And to all the people who have been close to me and helped in one way or another these four years - particularly Cindy Harris for love and moves in the right direction, and the Birmingham co-counselling community, particularly Marian Titley for confidently expecting the best:

Thank You.

J Woodbridge April 1 1981

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"The epidemic increase in coronary heart disease has fortunately coincided with the advent of a 'natural' pharmacological solution in the shape of the beta-adrenoceptor antagonists - a coincidence which is perhaps not entirely fortuitous."

S. H. Taylor[1]

"The prospect of mass drug prophylaxis raises new kinds of medical questions, of ethics and economics, of biology and psychology, of strategy and logistics, each of which will fill volumes. But meantime it presents a nice ethereal problem in day to day clinical practice: is the putative benefit of reducing the known increase in risk associated with raised blood pressure, greater than to a large extent unknowable disadvantages associated with life-long dependence on potent drugs? Now there's a poser for the long summer evenings."

C. Tudge[2]

"In all of today's discussion about the treatment of hypertension with beta-blockers, no-one has suggested (and I am sure no-one would suggest) that hypertension is basically a beta-blocker deficiency disease in aetiology, but is there any new knowledge from clinical pharmacology?"

D. R. Labarthe[3]

"After about fifteen years of data collecting, we believe that the alleged usefulness of antihypertensive drugs rests on conclusions drawn from notoriously uncertain statistical compilations, compounded by equally uncertain estimates of morbidity and mortality in the natural history of a disease of highly unpredictable course."

W. Gouldring, H. Chasis[4]

CONTENTS

Introduction

This thesis examines the relations of drug technology and heart disease in a variety of situations and with a variety of perspectives. In recent years much has been made of the "epidemic" of coronary heart disease (CHD), and cardiovascular disease.[1]*

> "If we could completely eradicate cardiovascular disease (CVD) in Europe, the life expectancy for men would be prolonged by eight years and for women by nine years. It is three to four times more than if we eradicated cancer."[2]

> "CHD evolves in the general population as a common, highly lethal disease which frequently attacks without warning, can be silent in its most dangerous form and which often presents with sudden death as the first symptom".[3]

The high mortality due to CHD seen as heart attacks, stroke, and sudden death, and morbidity due to angina and convalescence from attacks has been statistically associated with risk factors, the occurrence of which are predictors of forthcoming disease.

> "The 10-year mortality rate in men without any of the 3 major coronary risk factors; hypertension, hypercholesterolaemia or cigarette smoking is 30/000. When hypertension is present as a sole risk factor, mortality rate is about doubled (53/000). When one additional factor, either hypercholesterolaemia or cigarette smoking is also present the death rate is tripled (93/000). The proportion dying within 10 years jumps to 136/000 for men who had all 3 of these major risk factors."[4]

In this work I have concentrated on hypertension as the prime target for drug intervention in CHD.

> "Simply put, hypertension is mankind's most common disease, affecting 15 - 20% of all adults. In 1960, hypertension was responsible for 82 m. days of restricted activity, 26 m. days of disability in bed and 7.3 m. days of work loss (in U.S.). These figures are almost certainly underestimates."[5]

*CHD being the progressive reduction in oxygen supply to the heart, a subdivision of CVD which includes other conditions such as hypertension.

Faced with this proliferation of disease, it is no surprise that there is a proliferation of treatment, increasing use and increasing innovation. This represents a substantial change in the role of drug treatment as its target increasingly becomes degenerative, rather than infectious disease which is declining in importance due to public health measures, better nutrition and anti-infective drugs.

But are drugs the most appropriate tools for treating heart disease? What are the effects of the innovation and widespread use of new types of drug, invariably taken life-long, often in the absence of symptoms of illness?

Many recent general critiques of medicine have criticised the excessive reliance of modern medicine on drugs; for example Illich's "Medical Nemesis",[6] Dixon's "Beyond the Magic Bullet"[7] and the work of John Powles.[8] Although these have provided invaluable general insights, they have not worked at the level of specific innovations, so that the balance of social benefit of new introductions is not examined.

Likewise, proponents of drug therapy usually take the benefits of "successful" drugs as being self-evident and, giving drug therapy the credit for our low mortality from infectious disease and longer life-spans, imply that degenerative disease, too, will be overcome by the same means.[9]

This thesis was undertaken at the Technology Policy Unit, University of Aston, a unit concerned with the interdisciplinary study of technological innovation, its social impacts, and policies for its direction and control. I have therefore looked at drug

innovation from a variety of disciplinary perspectives; from the effect of the drugs on the patient (clinical), to that on the doctor (medical-sociological), on medical thought (techno-sociological), and on society at large (epidemiological, political).

Mostly I have neglected the economic style of analysis in favour of that of the sociology of knowledge for two reasons: because economic perspectives are already extensively represented in the literature on the study of drug effects[10] (at the expense of exploring other modes of analysis, it seems to me), and because I think the conceptual effects of reliance on drug treatments to be extremely important and worthy of more detailed research than they have so far received. The term "heart disease" defines both a condition and a viewpoint, that is, the observable, measurable, treatable process which develops within individuals is defined by the way in which one sees it, that is through the technologies of observation, measurement, and treatment. The exploration of this network of relations is the main concern of this thesis.

The work falls into three parts. Considering the dearth of case-studies on specific drug innovations which also consider their effects, I have concentrated on the innovation and social impacts of one set of "successful" new drugs, the beta blockers, which case-study forms the central part of this work. It is set in the context of an analysis of the evolution of hypertension, concentrating on the role of drug, diagnostic and surgical technologies in this process which is contained in the first section, and a study of the broader impacts of cardiovascular drug innovations in the third.

The material in the first section is included because hypertension seems in many ways to be a good case-study of a

degenerative disease for which drug treatment has recently become effective, and it seemed necessary to have some perspective on the way in which earlier drugs had been used in this condition, and the changes that their use had produced in order to fully appreciate the impact of the beta-blockers. In this section I have also looked at a conflict in medical opinion about the nature of hypertension and have shown how it was influenced by the increasing use of drugs at the time, and in turn how its outcome influenced subsequent drug introduction and use.

The case-study on the innovation of beta-blockade begins with a historical analysis of its scientific basis, that is the concept of drug receptors, and its use in the study of adrenaline and its functions. The role of drugs in the formation and evolution of this central concept in medical science is discussed.

From the sources of the project to its effects. I wanted to do a fairly thorough consideration of the development of beta-blockade, to describe the process of clinical feedback changing the aims of drug research, and also to consider its effects from a variety of perspectives.

At the therapeutic level I have assessed the clinical literature in each of the main indications, to picture how much and what kind of advance beta-blockade is compared with drugs which were previously used. At the level of medical and scientific literature and ideas, I have assessed the wider impacts of beta-blockade on the way in which the conditions in which it is used are conceived.

From the consideration of the way in which hypertension has evolved and the influences of diagnostic and drug technology, and the way in which beta-blockade has evolved and its influences on

hypertension and angina, in the third section I have essayed a broader analysis of the conceptual changes connected with the use of the increasing variety of drug treatments for the various kinds of CVD. Both changes in the extent of disease and changes in our understanding of the disease are related to the introduction of new drug and diagnostic technologies.

Finally the conclusions of the work are set out.

I see the main contributions of this work being the connection of drug innovation study with study of its effects, and a step towards greater knowledge of the conceptual effects of drugs, the changes in world-view which their use provokes and sustains.

Section 1. The Evolution of Hypertension

1.0 Introduction

While considering the use of drugs in heart disease, and the effects that this has on what is usually seen as the extent of our knowledge of disease, but is more correctly described as the way in which we perceive disease, I became interested in the condition of high blood pressure.

This seemed to be a medical area in which the definition of the disease was dependent on the means available to diagnose and treat it. Firstly, it came into existence as a consequence of the use of the sphygmomanometer, and then was ignored because it could not be effectively treated; then, when drugs were introduced, they produced a dramatic increase in the number of people treated and the number of books and papers on the subject. The interplay between the development of drugs and diagnostic technology and disease definitions displayed so openly became an area impossible to ignore. The fact that beta-blockers have achieved their greatest success in this condition made the history of its drug-definition necessary to investigate.

The section is in three parts in chronological sequence. The first follows the creation of 'hypertension' from its original status as kidney disease recognised by Bright in the 1820s until its definition in a form similar to that of the present day in 1915.

The second looks at the impact of emerging scientific disciplines on the evolution of 'hypertension' from 1915 until 1945. The use of surgical and dietetic remedies is also considered as setting the terms within which drug theory was first used. The evolution of drug treatments is covered in the last section, which

also looks at a medical controversy over whether hypertension was a disease entity or just the upper end of a range of blood pressures existing in the population, the effects of drugs on the terms of this argument, and the implications for drug treatment of its outcome.

1.1 Bright's disease 1820-1915

> "Human anatomy has not changed over the centuries but pharmacopoeias and methods of medical treatment have, wiping out the past in their progress. Hence the history of therapeutics is an intrinsically more difficult subject than the history of anatomy, calling for special skills which must be developed by trial and error methods. It is a subject also which calls for the exercise of great care and judgement since it can be reconstructed only theoretically and imaginatively." M. Boas Hall[1]

The first recognitions of the syndrome we now call hypertension, and of the importance of the level of blood pressure occurred in connection with the evolution of a condition known as Bright's disease in the 19th century. The history of this evolution illustrates the impact both of scientific diagnostic technology and of scientific philosophy (the latter carried by the former) on the profession of medicine, which had hitherto emphasised its craft aspects.

The recognition of a specific disease entity centred on the correlation of observable post-mortem changes in the structure of the kidney, a condition of dropsy (an accumulation of fluid in the tissues) before death, and concomitant changes in the urine (becoming coagulable by heat). This was made by several doctors before Richard Bright*, a clinician at Guy's Hospital, but it was Bright who captured the disease in clinical descriptions and began its classification in the first volume of his 'Reports of Medical Cases selected with a view of illustrating the symptoms and cure of disease by a reference to morbid anatomy', published in 1827.

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*The chemical analysis of urine began with the determination of its specific gravity by Boerhaave (1668-1738). A colleague of his, Frederik Dekkers (1648-1720) demonstrated the presence of albumen by first boiling the urine, then adding a drop or two of acetic acid (1694).[2]

Saundby in his 'Lectures on Bright's disease' (1889) comments:

> "Although Van Helmont regarded the kidneys as the seat of dropsy, and the discovery of Cotunnius that the urine of dropsy was coagulable by heat was published as early as 1770, there can be no doubt that the whole honour of establishing the true relations of dropsy and albuminuria to disease of the kidneys belongs to the great physician and pathologist of Guy's Hospital, RICHARD BRIGHT. Blackall of Exeter would perhaps have forestalled him but Blackall shows himself to be entirely ignorant of the local causes of dropsy, assigning to it a constitutional origin, and inclining to the opinion that albuminuria was due to 'the elimination of the dropsical fluid by the urinary passages'. Bright's 'Reports of Medical Cases' presents a striking contrast in the definite solidism of his pathology to this vague humoralism. He distinctly ascribes albuminuria and dropsy to the altered anatomical condition of the kidneys, and he figures accurately the changes in the kidneys just as they are recognised by us today."[3]

He described three main groups of kidney disease. In the first type "degeneration was noted, apparently connected with a cachectic state of the body". The second form he described was "one in which the whole cortical part of the kidney is converted into a granulated texture and where there appears to be a copious morbid interstitial deposit of an opake white substance". Kidneys of the third type were "rough to the touch externally" and had "numerous projections, yellow, red, and purplish, not much exceeding in size a large pin's head".

He laid stress on the association of dropsy, albuminuria, and "hardened kidneys", and concluded as follows; "I have never yet examined the body of a patient dying with dropsy, attended by coagulable urine, in whom some obvious derangement was not discovered in the kidneys". He also noted "the hypertrophy of the heart seems in some degree to have kept pace with the advance of disease in the kidneys".[4]

Some elements of Bright's text do raise the possibility of a more general theory of causation, for example on the cardiac

hypertrophy he says that an "altered quality of the blood that so affects the minute and capillary circulation as to render greater action necessary to force blood through the distant subdivisions of the vascular system." This speculation awaited greater subtlety of chemical analysis than was then possible.

At this time, Bright's disease exemplified two tendencies in medicine which we should now regard as being in opposition: the classificatory method, owing much to the 17th century tradition of natural history, involving classification of the appearance of the body of the patient, and comparison of the uncertain perception of the disease in life with the certainty of the morbid anatomy, and the newer analytic techniques which were transmitted to clinical practice via doctors interested in physiological experimentation.

> "Chemistry made its first great impact on clinical medicine with the work of Richard Bright and his team of chemical experts, Bostock, Babington, and Rees, who between them in their investigations of Bright's disease detected albumen in the urine, reduced plasma albumen, a raised blood urea, and the presence of urea in the cerebrospinal fluid."[5]

Prout in 1821 produced a routine for the chemical testing of urine which included measurement of reaction to litmus, specific gravity, a boiling test for albumen, and a tasting test for sugar. Nevertheless, the chemical methods used during the next 30 years remained too cumbersome for clinical use. From 1850 onwards, progress was rapid. Tests for sugar, acetone and many other substances appeared, and volumetric methods replaced the cumbersome gravimetric methods. By 1860 a text produced specially for doctors instructed how to test for 17 normal and 17 abnormal constituents.

The thermometer was introduced into medicine by Ludwig Traube (who also pioneered the use of experimental animals in medical physiology) and Carl Wunderlich, who tested 25,000 patients with it, publishing results in 1868, thereby establishing thermometry as a valuable clinical tool.[6]

In fact, the correlation of the results of a chemical analysis with clinical symptoms to form a diagnosis was one of the first instances of the use of a basic science in clinical practice. But these tendencies, the classificatory and the analytic, were not as oppositional as a retrospective view of their developments might suggest. Some of the more low-technology methods of extending clinical examination were innovated and used to extend and refine the current classifications of disease - for example, Auenbrugger's percussion (tapping and listening to the chest) and Laennec's mediate auscultation, the forerunner of the stethoscope. However, the new devices; the microscope, sphygmomanometer, chemical analysis, all threatened in some way the old craft of clinical judgement by making available data beyond the range of the physician's senses, gathered by methods that were obscure and owed more and more to the progress of sciences whose rationale became increasingly foreign to the traditional medical humanism.*

Virchow described the eight years before 1855 as follows:

> "1847 were days of great scientific degeneration in medicine. The method of orderly investigation had been almost completely lost. The great upheavals that microscopy, chemistry, and pathological anatomy had brought about were at first accompanied by the most dismal consequences. People found themselves helpless in the ruins as the old system collapsed; filled with exaggerated expectations they seized on any fragment which a bold speculator might choose to cast out."[8]

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*Foucault connects the rejection of measurement with the sovereignity of the power of the visual.[7]

But this ferment left much of the traditional medicine intact - after 1839 when the inflammatory nature of Bright's disease was first noted, British and Continental specialists' major concern was the classification and reclassification of the inflammatory processes on the basis of different sets of clinical observations. The main method of understanding the disease process at the time was the connection of clinical signs and symptoms with post-mortem studies. But these methods emphasised structural abnormalities at the expense of the functional abnormalities that were deduced from them. For example, the connections between the degenerating kidney and the hypertrophied heart were debated endlessly, with many different classifications of degeneration and hypertrophy.[9]

However, there were those who looked farther than the anatomical changes in the kidney - George Johnson was one of these. In 1852 he proposed that impurities in the blood that should have been eliminated by the kidneys are retained in Bright's disease and cause constriction of the arterioles,and thereby a rise in blood pressure.[10] This view was attacked by Gull and Sutton (1872) who described a 'more general affection' of the small arteries and capillaries:

> "There is a diseased state characterised by hyaline-fibroid formation in the arteries and capillaries attended with atrophy of the adjacent tissues. It is probable that this morbid change commonly begins in the kidneys, but there is evidence of its also beginning primarily in other organs. The contraction and atrophy of the kidneys are part and parcel of the general morbid change. This morbid change in the arterioles and capillaries is the primary and essential condition of the morbid state called chronic Bright's disease."[11]

It was only with the advance of physiological methods that an understanding of the disease appropriate for therapy could be

constructed. It was at about this time that increasing attention was paid to the circulation, mostly because of the advances that had been made earlier in the century in the physical diagnosis of circulatory problems*, but also because of the desire to connect the signs observable by such methods with pathological lesions. This was particularly so in the influential Vienna school of Rokitansky (1804-1878) and Skoda (c.1840) who tried to put the techniques of Laennec and Auenbrugger on a more scientific basis, and studied the origins of the signs in different kinds of pathology.[13]

The circulation was an obvious target for the new experimental physiological research. The earliest sphygmomanometer, or device for measuring blood pressure was the apparatus of Herisson invented in 1834, which although designed to measure the amplitude of the pulse could also be used to measure arterial pressure. The first device specifically designed for this purpose was that of Vierordt (1854), in which weights were added to a scale pan until the pulse compressed by a button was obliterated. The instrument used by

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*Begun by Auenbrugger's technique of percussion of the chest, which began to make an impact after its French introduction by Corvisart (1808), Laennec's primitive stethoscope (1819), and the work done by later doctors on refining the techniques - Corrigan, Traube, Da Costa, Stokes, Flint, Duroziez and others.[14]

Although Claude Bernard's most influential work - the 'Introduction to the Study of Experimental Medicine', published in 1865, dealt with the circulation and other relevant topics in an experimental way, it does not seem to have materially affected the perspective of specialists until later: "the influence of the concepts Bernard introduced such as 'general physiology' and the 'milieu interieur' does not seem to have been widely felt until the turn of the century."[15]

Mahomed was a modification of this. The first apparatus using a hydraulic method was Von Basch's, this was improved by Riva-Rocci in 1896 who used a pneumatic cuff around the wrist to obliterate the pulse instead of finger pressure. The cuff was later widened (1901) to give more accurate readings. Korotkoff in 1905 used pressure variations in the sphygmomanometer to derive readings for both systolic and diastolic pressures. However during most of this period the commonest method of measurement was the clinician's judgement of the hardness of the pulse.

F. A. Mahomed, a clinician at Guy's Hospital, using the sphygmograph and a modified Vierordt sphygmomanometer, attempted to clarify the relationship between cardiac hypertrophy and Bright's disease in 1879. His conclusions were that the primary condition was a 'poisoned condition of the blood', that this produced an impeded circulation through the capillaries, and subsequently the cardiovascular changes.

> "The arguments upon which this hypothesis has been based are as follows:- First, that high arterial pressure is found to exist before any sign of failure of the kidneys to perform their function occurs. Second, that certain poisons are known to produce kidney disease, and that these poisons produce high pressure in the arteries, while no symptoms of kidney failure are discoverable ... Third, the condition of high pressure is found to occur in some young people, in all other respects perfectly healthy ...; such patients very often have a family history of gout or Bright's disease, and if they live long enough, will almost inevitably develop it themselves. Fourth, far from the kidney disease being the primary condition I find that patients with primary kidney disease, such as is seen in surgical kidneys or scrofulous kidneys, even of the most advanced nature, do <u>not</u> have high pressure in their arteries, while patients with acute Bright's disease, if the poison be acute and temporary, may lose all signs of high arterial pressure during their recovery, even at a time when the kidneys are manifestly crippled, the urine being albuminous and the solids deficient in amount."

In his paper in 1881 on "Chronic Bright's disease without albuminuria" he wrote:

> "From these considerations it follows that we have to deal with three stages of chronic Bright's disease: first, the functional stage, which is limited to the condition of high arterial pressure without organic changes in either the vascular system or the kidneys; second, the chronic Bright's disease without nephritis, the stage of organic changes in the vascular system and in the kidney; third, chronic Bright's disease with nephritis, the natural but by no means the invariable termination of the disease."[16]

Here, the close connection between raised blood pressure and deteriorating kidney function has been observed. However, there were a number of difficulties for this theory: most specialists were still reliant on post-mortem examinations for their understanding of disease; this meant it was difficult to follow changes in the disease's early stages in life, where the arterial changes were supposed to occur, and also that there was an emphasis on classifications of isolated anatomical structures, and not much attempt at relating these to their function.

The emphasis on structural abnormality must have been increased by the beginnings of the widespread use of the microscope in clinical examination,* which allowed a much more precise localisation of inflammation and other cellular changes. This was stimulated by the impact of Virchow's 'Cellular Pathology' (1858), which demonstrated the importance of the microscope, and also the effectiveness of a physiological approach to the

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*Beale was running courses on clinical microscopy in London in 1854 - he also produced a textbook 'The microscope in medicine' in the same year. William Osler followed his example with a lecture course on the microscope at McGill University in 1874.

circulation (through his work on thrombosis and embolism). Virchow stressed the importance of functional change as opposed to structural change, and linked this with a scientific experimental approach.

However, the accepted classifications of Bright's disease disregarded the question of blood pressure or of cardiac hypertrophy, and instead focused on the nature of the structural changes occurring in the kidney. Chronic parenchymatous nephritis was thought to result from inflammation of the epithelial structures of the kidney, whereas chronic interstitial nephritis was marked by a growth of the interstitial connective tissue, causing atrophy of the kidney tubules. These two types were distinguished by clinical symptoms, such as extent of albuminuria, specific gravity of urine, but neither blood pressure nor degree of cardiac hypertrophy were considered significant.

Although there was extensive criticism of this classification, both from those such as Weigert, who in 1879 showed that the two types of tissue change could occur in the same patient at different times, and thus were probably different stages in the same disease process, and from those such as Vierordt who found several cases of Bright's disease with high blood pressure (1855), it continued unchanged until 1905 when Mueller proposed a separation of an inflammatory type from a degenerative type. Blood pressure measurement became more widely used in Bright's disease with the diffusion of the first portable apparatus simple enough for clinical use, that of Riva-Rocci (1896), but a standard text on the pulse in 1890, which connects kidney disease with high blood pressure, does not mention the use of measuring apparatus, the estimation of pressure by the fingers was used.[17]

Treatment of the disease was largely similar to that used for most diseases: those advocated by Saundby (1889) are "rest and warmth aided by suitable diet and purgatives. The diet should be milk and farinaceous food".[18] The patient was given hot air baths to stimulate sweating.

Saundby makes an interesting point about the large apparent increase in Bright's disease in the last quarter of the nineteenth century. According to pathology registers at the General Hospital, Birmingham, from 1875 to 1884 "about 1 in 3 deaths were due to acute and chronic cases of Bright's disease. From 1875 to 1884 Registrar-General's returns show an increase in population of 20%, of nephritis 18%, and of Bright's disease 64%". He comments "this result is in all probability due to the fact that the profession is beginning to look for latent cases of chronic Bright's disease, and has learnt to recognise them better than was formerly the case".[19]

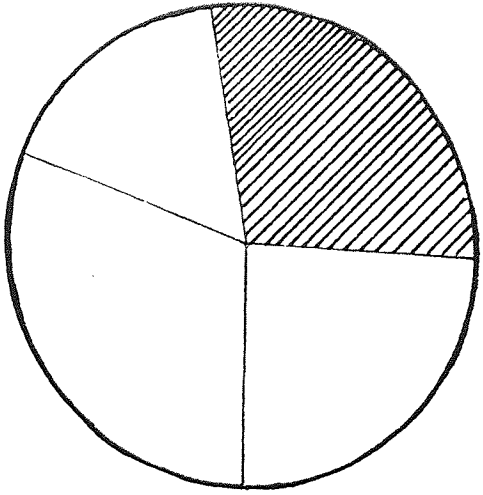
Pickering (1955) summarises the changes in definition of hypertension around the turn of the century as follows:

> "The recognition that there is a condition which may pursue a course quite different from Bright's disease of the kidneys we owe largely to Von Basch, Huchard and Allbutt. Von Basch (1893), who made very many estimations of blood pressure, was well acquainted with what we now call essential hypertension, which he called latent arteriosclerosis. In France, Huchard (1889), recognised clearly that hypertension might occur independently of nephritis. At the same time, Allbutt had observed the occurrence of raised arterial pressure in the absence of albuminuria. In 1915 he wrote 'Thus gradually I became convinced that cases, such as we are considering, must be divided, first, into Bright's disease ... secondly, into the class to which soon afterwards I gave the name Hyperpiesis, a malady in which at or towards middle life blood pressures rise excessively, a malady having a course of its own and deserving the name of a disease; and thirdly, into at least one other class of arterial degeneration, one not typically associated with rise of blood pressure, a class in which indeed the blood pressure does not

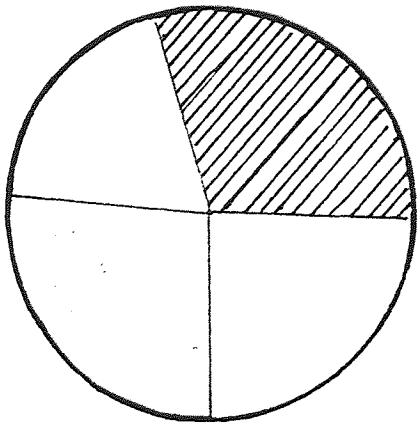
> exceed, or scarcely exceeds the rise common to all persons in later life; a series of which the course, symptoms, and issues are altogether different'."20

The modern classification was constructed in 1914 by Volhard and Fahr, which used three main groups: inflammatory, degenerative and arteriosclerotic. The last was subdivided into simple benign hypertension and malignant contracted kidney.

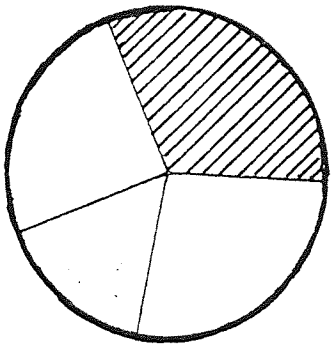
By 1915, then, Bright's disease and hypertension were distinguished from each other, the first being a malfunction of the kidney, the second a malfunction of the circulation. This separation was largely due to the development and widespread use of simple diagnostic technology - the chemical test for albumen in the urine, and the sphygmomanometer.



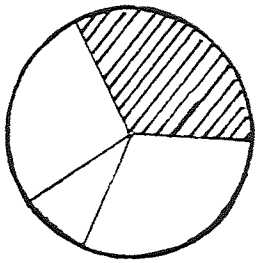
1900 Male



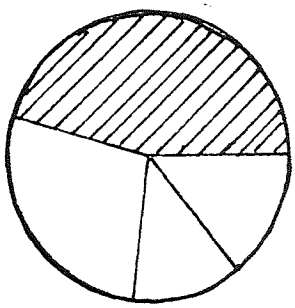
1900 Female



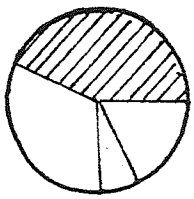
1930 Male



1930 Female



1960 Male



1960 Female

Fig. 1.1 Comparison of infectious and degenerative disease as causes of death 1900-1960 (From Robb-Smith, A. H. T.)[3] in those aged 45-74.

The radius of each circle is proportional to the total death rate.

Degenerative heart and vascular disease ...

Infectious diseases ...

1.2 Hypertension 1915-1945

At the beginning of the 20th century there were several tendencies in medicine which greatly influenced the evolution of the notion of hypertension.

The application of diagnostic technology which began with the thermometer[1] was crucial to the evolution of hypertension as a disease defined more and more by the single criterion of elevated sphygmomanometer readings. This process began with the wider routine use of the instrument in clinical practice, standardisation, and the accumulation of experience with the correlation of high pressures with deteriorating physical health.

Increasingly, physiological and biochemical ideas and information were becoming more influential in clinical practice. The success of these analytic methods in producing "objective" data to aid diagnosis ensured that doctors could no longer afford to ignore this new source of information.

The progressive reduction of mortality and morbidity from infectious disease evident since the 1850s made the degenerative diseases, hitherto masked, become more prominent problems[2] (see fig. 1.1). At first this did not result in more medical interest, as the diseases were not understood, and no effective treatments existed. However, physiological and biochemical experimentation began to provide the base upon which to build.

Treatment during this period (1915-25) was usually dietary restriction, Mahomed having recommended a low-protein diet in the 1880s, which was still widely used. In 1904 the low-salt diet was proposed (Ambard and Beaujard) on the grounds of decreasing water retention. Low-salt diets were also widely used until the advent of surgical interventions.[4]

These began in 1914 with Crile's use of the removal of an adrenal gland to relieve hypertension. The rationale behind this was the recent discovery that adrenaline raised blood pressure, and that patients with inoperative glands had low blood pressure. Crile, of Cleveland, USA, combined adrenalectomy with cervical sympathectomy (severing the sympathetic nerves in the neck) and ligation of the thyroid arteries. "This drastic type of surgery did not achieve the hoped-for results and was abandoned."[5]

More radical sympathectomy was advised by Rowntree and Adson at the prestigious Mayo clinic, and this was extended by Peet at the University of Michigan, and Smithwick of Boston "each of whom developed his own type of operation". Thus extremely radical surgical operations became widely used to treat hypertensives. These operations were derived from theories that hypertension was connected with the over-activity of sympathetic nerves, and also the observation that spinal anaesthesia produced a low blood pressure, hence it was thought that surgical excision might perpetuate this.

> "Surgeons have tended to attribute recurrences of hypertension after operation to over-activity of the remaining sympathetic nerves and, striving always for perfection, have successively extended the operation. Thus the early operations of Peet (1935-40) on the splanchnic nerves and lumbar ganglia above the diaphragm, and of Adson on the splanchnic nerves and lumbar ganglia below the diaphragm (1939-40) were combined by Smithwick (1940 onwards), while Grimson ablates the whole sympathetic chain from T2 to L3 on both sides.* It is not clear, however, that the results in terms of comfort or longevity are much better with the larger than the smaller operations."**[6]

---

*Smithwick's operation denervated the kidneys, adrenals and splanchnic beds, Grimson's the heart, lungs, abdomen and eye.

** Schroeder (1953) reckons on an increasing rate of normotensives the more extensive the operation. He quotes 11% for Peet's, 15-20% for Smithwick's, and 35% for Grimson's.[7]

Early studies using the sphygmomanometer divided people with hypertension into two groups: those with diseases of the kidneys, and those with "essential hypertension" - that is a permanent elevation in pressure without any obvious underlying cause. However, most patients with hypertension did end up with some form of kidney disease. Goldblatt, a pathologist at Western Reserve University, Cleveland, hypothesised that a reduction in blood flow through the kidneys might give rise to hypertension. He found in 1932 that narrowing the renal arteries in dogs with a clamp produced a raised blood pressure.

This stimulated several kidney removal operations (nephrectomies) in patients with one diseased kidney.* Nephrectomies became generally used for the relief of hypertension. However, most of these operations were unsuccessful.

The connections between the development of the physiological knowledge of disease and the use of this as a rationale for surgical interventions are clear in these cases. But biochemical knowledge did not have such a direct application, although considerable biochemical work was being done on the hormonal basis of hypertension. This began with Tigerstedt and Bergman's extraction in 1898 of a pressor (blood pressure increasing) substance from kidneys that they called renin. This was not confirmed until 1938 when Pickering and Prinzmetal discovered a similar phenomenon.

---

*Evans, a standard cardiology text of 1948 comments:

> "Since Goldblatt's work on renal ischaemia it was natural for clinicians to seek examples of unilateral renal disease amongst their patients with hypertension and to watch the effects of nephrectomy."[9]

Renin was isolated by Page in the late 1930s and then considerable work went into elaborating the interplay between renin, angiotensin, which is a hypertension-inducing substance liberated in the blood by renin, and aldosterone, which is a salt-retaining hormone produced by the adrenal cortex.

Despite all this basic biochemical research, drug treatments had been empirical and ineffective. Doctors were misled by the reduction in pressure brought about by greater familiarity with the doctor, and greater doctor interest, so that many drugs were recommended which controlled observations showed to be ineffective.

In 1937 a standard cardiological text comments on the drugs used to treat hypertension:

> "Perhaps the most striking reflection upon their value is the short period of popularity that each enjoys before it is displaced by a rival"...

and concluded "it is doubtful if the policy of attempting to lower blood pressure is sound".[8]

A text of 1948 makes a similar evaluation:

> "The drug treatment of simple hypertension has proved unsatisfactory. Of the many drugs recommended there is not any agreement on which is the best to employ, and none have gained any outstanding reputation. None of these drugs produce hypotensive effects: Iodine, Bromine, Luminal, Sodium nitrite, Glycerine trinitrate, Chloral hydrate, Papaverine, Bismuth subnitrate, Erythritol tetranitrate, Euphyllin, Doryl, Pacyl, Hypoton, Diuretin, Potassium thiocyanate, Atropine, Benzyl benzoate, Phyllosan, Padutin, Anabolin, Detenzyl."[9]

During most of this period there was general acceptance of the division between 'benign' and 'malignant' forms of hypertension.

> "Keith, Wagener and Kernohan (1928) later presented a classic description of the 'syndrome of malignant hypertension', based on the study of 81 cases. After this description it became customary to regard benign and malignant hypertension as clinically distinct entities with different rates of progression, and different incidence of renal involvement, clinical and pathologic manifestations and prognosis."[10]

But at what pressure levels treatment should begin has been a consistent problem since the 1930s. From a text of 1937:

> "the death rate is very decidedly higher in cases where the pressure ranges above, than cases where it ranges below 200 mm Hg."[11]

Thus in the early part of this century, the concentration on malignant hypertension with what we would now regard as very high pressures dovetailed with treatments which were extremely unpleasant, and thus of use only to those with a very poor prognosis.

In 1939 a new classification of hypertension was proposed by Keith, Wagener and Barker of the Mayo clinic and was widely accepted. This divided hypertension into four grades of severity, based on observations of the state of arteries in the eye. But although these were seen to some extent as grades of the same disease, they still drew a strong distinction between the relatively good prognoses of Groups I and II and the poor prognoses of III and IV.[12]

As physiological and biochemical work proceeded, and the interesting problems of hormonal interplays, nervous organisation and physiological control were increasingly understood, treatments were subject to closer scrutiny.

Controlled trials revealed the lack of effectiveness of drug treatments, follow-ups of those subject to sympathectomy revealed benefits in severe cases, not much change in those who had initially lower pressures. Studies of low-salt diets, mainly the rice - fruit diet of Kempner (1948) showed significant benefit if the monotonous diet was adhered to.*

---

*Falls in pressure averaged 47 mm/21 mm in 322 of the 500 patients in whom treatment was effective.

It was particularly in terms of sympathectomy that attempts were made to differentiate hypertension during the 1940s:

> "The chief difficulty, now universally admitted despite early enthusiasm is that there is no certain way of distinguishing between those in whom the operation will succeed and those in whom it will fail, even by employing batteries of sedation, cold pressor, Tetra-Ethyl Ammonium and other tests."[13]

With the advent of the first widely used treatment, then, came the first attempts to differentiate the disease in terms of the treatment; that is, to try and separate by some means those who would respond from those who would not. Previously, hypertension had been differentiated only in two ways; either in terms of the supposed aetiology or cause, or in terms of severity, graded either by the retinal classification or sphygmomanometer readings. From this time onwards, hypertension was increasingly to become defined in this new way, as amenable or otherwise to current treatment.

1.3 Drugs and a conflict in medical opinion 1945-1960

As we have seen, many drugs were tried during the 1930s and 1940s but few came into regular use owing to lack of consistent effectiveness. Two exceptions to this were the sedatives - used to damp down transient increases in pressure but having no prolonged hypotensive effect, and thiocyanate, which had a hypotensive effect but only close to its toxic dose, and hence was difficult to use. After blood cyanate measurements became possible it enjoyed limited use in severe cases.[1]

At the beginning of this period, the main therapeutic technique for severe hypertension was surgical sympathectomy.[2] With the successful use of antimalarial, antiemetic and anti-diarrhoeal drugs in World War II, the idea of looking for effective antihypertensive drugs became more feasible, especially as some of the drugs synthesised for these purposes did have hypotensive side effects.

The first systematic evaluation of new drugs in hypertension was undertaken by E. D. Freis as a direct outgrowth of investigative work on the value of sympathectomy in the later 1940s in America.[3] The director of the Squibb Institute for Medical Research asked the group that were conducting the investigations to work with the Institute to develop and evaluate drugs for hypertension treatment - that is, to substitute a reversible chemical sympathectomy for the surgical operation.

The first drug tried was pentaquine, an antimalarial which had produced hypotension in normal volunteers. The doses necessary to produce an appreciable hypotensive effect were too toxic for clinical use, although some patients did derive some benefit from

its use. The same was true of the next drug tried, veratrum. When it was combined with the currently popular low-sodium diet of Kempner, however, a greater hypotensive effect was seen.

Attention then turned to sympathetic blocking drugs, which had been extensively used as tools for understanding the workings of the nervous system. Phentolamine and piperoxan, two α-adrenergic blocking agents were tested in hypertension, but were found to produce a rapid heart rate and accompanying unpleasant sensations in most cases; only in cases of hypertension produced by tumours secreting catecholamines (phaeochromocytoma) were they of value.

It had long been known that sympathetic blocking drugs can act at different points in the sympathetic chain. Agents which acted further back in the nervous chain at the level of the ganglia - the connection in the sympathetic system between the spinal cord and the vasoconstrictor nerves - were tried. Tetra-ethylammonium (TEA), a powerful ganglion-blocker was found to have too short an effect to have any practical value.[4]

The first useful hypotensive drugs were the methonium salts pentamethonium and hexamethonium, longer-acting ganglion-blockers, reported by Paton and Zaimis in 1948 and first used clinically by Arnold and Rosenheim at University College Hospital, London, in 1949. These compounds had many disadvantages - they blocked parasympathetic as well as sympathetic nerves, so that patients' visual accommodation was worsened, digestive and urinary problems were common, and impotence in males also frequent. Also resistance to the effects of the drugs often developed, necessitating a periodic increase in dose. They had to be given intravenously

as oral absorption was irregular and unreliable. However, their use, particularly by Smirk in New Zealand provided the first examples of an increased life-expectancy in hypertensives brought about by drug treatment:

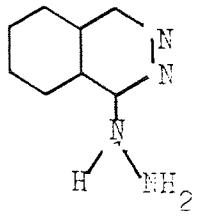
> "The reversals of malignant hypertension to a more benign phase of the disease were so dramatic that they revolutionised the methods of treating hypertension which, until that time, had been dominated by surgical sympathectomy and low salt diets."[5]

After this initial success more new drugs were screened for antihypertensive activity and many new antihypertensive drugs appeared. Out of a search for better antimalarials came a series of phthalazine compounds which were shown to lower blood pressure in animals. Hydralazine produced a more gradual and prolonged reduction in pressure than hexamethonium and appeared to act as a direct vasodilator rather than as a neuron blocker, but produced a faster heart rate which was unpleasant. Combined therapy with hydralazine and hexamethonium reduced side-effects and allowed a lower dosage of each component. This regime was first used by Schroeder in 1954 in America. Thus began the use of multiple-drug therapy in hypertension, which has persisted to the present day.

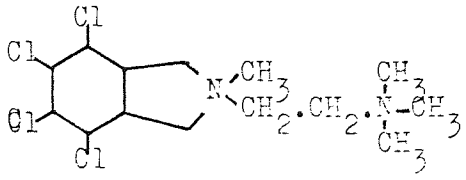
An Indian cardiologist, Vakil, found in 1949 that the powdered root of the plant Rauwolfia serpentina which had been used for a long time as a treatment for mentally disturbed patients had antihypertensive effects. From a sample sent to CIBA, the active alkaloid reserpine was extracted (1952). This has a general damping effect on the sympathetic nervous system, and apart from a tendency to provoke depression it has few side-effects.

As the success of first hexamethonium, and then the other compounds mentioned became known, many drug companies began

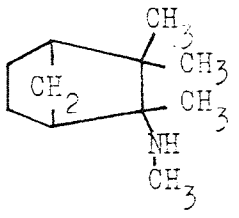
Hydrazino-phthalazine
(Hydralazine)
CIBA 1952

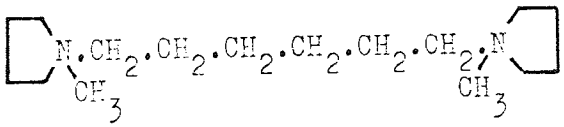


Chlorisondamine
CIBA 'Ecolid'



Mecamylamine





Pentolinium

Fig. 1.2 Structures of early antihypertensive drugs

molecular modification of the structures to produce more specific action, oral activity in the case of the ganglion-blockers, and fewer side-effects.* Orally-active ganglion-blockers were introduced in 1955 and 1957 (pentolinium, mecamylamine, pempidine and chlorisondamine) but although these were longer acting and less toxic, they were rapidly superseded, as drugs with fewer side-effects became available.

The sources of these new drugs were twofold. First, the burgeoning growth of the field of pharmacology during the 1930s and through the war produced a situation where the scientific knowledge base in the areas of nerve transmission and neuro-endocrine control of body functions had become definite enough to provide a significant input into the search for new drugs. This was largely due to the fact that much of this knowledge had been gained through the use of drugs (see section 2.1).

Second, an outgrowth of clinical usage of the large number of anti-infectives and other drugs produced during the war years were many instances of side-effects which could be therapeutically useful. These were used as chemical starting points for modification by chemists looking for approaches to new disease problems, such as hypertension.

The discovery of methyldopa is often cited as an example of rational drug discovery. After studies on reserpine showed that its effects were due to depletion of the noradrenaline stored in sympathetic nerve endings, attempts were made to produce this depletion through enzyme inhibition, that is to block the synthesis of noradrenaline. This was a well-known field of study and an effective inhibitor was produced quite rapidly (Sourkes, 1954).[5a]

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*Over 250 hydralazine-like compounds were reported, of which 6 went to clinical trial, 2 of which were marketed.[6]

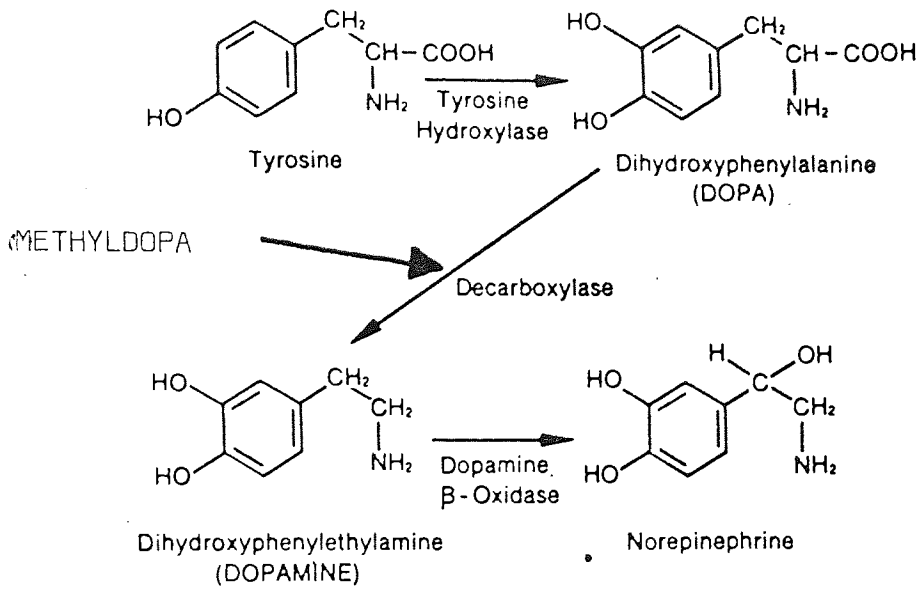


Fig. 1.3 Methyldopa as metabolic inhibitor.

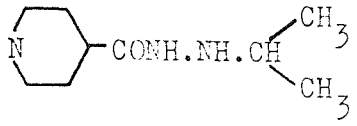
Source: Plummer, A., DeStevens, G.[7]

However, methyldopa did not lower blood pressure in animals, and its activity in humans was found indirectly in 1960 via studies on amino acid metabolism.[7] It has since become very widely used because of its potency, predictability and low level of side-effects.

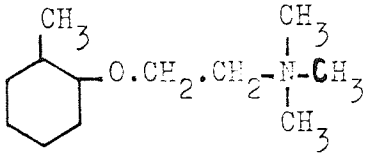
The introduction of more selective adrenergic blocking drugs, which was an obvious need in the early 1950s, hinged on the observation that an antitubercular drug, iproniazid, had antidepressant effects, and also when used for this purpose produced a hypotensive effect as well. Thus a single mechanism - the inhibition of the enzyme monoamine oxidase-had two clinically useful effects. Chemists began to study the MAO-inhibitors to try and develop a more specific action. At Wellcome Laboratories from one of these studies, a compound was developed which blocked the sympathetic nervous chain at another point: where the nerves liberate noradrenaline into the blood. This compound (xylocholine) was modified to give a more specific action, and was marketed as bretylium, the first of the class of adrenergic neuron blocking agents. These deplete the noradrenaline stores in the adrenergic neurons, and prevent its re-uptake. Blockade is more specific than ganglion-blockers as they act more directly on the hormonal link between sympathetic nerves and the heart and blood vessels, and do not affect higher centres.[8]

Bretylium, however, was not a successful drug as tolerance rapidly developed. The first successful adrenergic neuron blocking drug was guanethidine (1960) which replaced ganglion-blocking drugs for the treatment of severe hypertension. Other follow-on compounds in the series have a shorter duration of action and slightly fewer side-effects.[9]

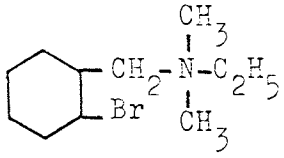
Iproniazid
(anti-tubercular
lead compound)



Xylocholine



Bretylium



Guanethidine

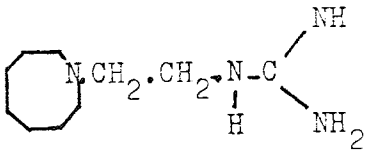


Fig. 1.4 Structures of adrenergic neuron blocking drugs.

The greatest contribution to antihypertensive treatment was made by the discovery of new diuretics. Compounds which increase urine production and thus reduce the fluid volume of the body have been known since 1919, when diuresis was observed after the injection of merbaphen, a mercurial anti-syphilitic agent. From this beginning, the class of mercurial diuretics arose which were mostly used in the treatment of congestive heart failure, to combat the fluid accumulation of this condition.[10]

The first connection with hypertension came with the introduction of the ganglion-blocking compounds. It was noticed that the tolerance which developed to the hypotensive effects of the drugs was correlated with fluid retention, and when a low-salt diet was instituted or a mercurial diuretic used, the blood-pressure dropped. There were problems of toxicity with the mercurial diuretics so that other chemical structures were investigated.

The observation that provided the lead was the small diuresis produced by sulphanilamide in congestive heart failure, noticed in 1949. This precipitated extensive research in many laboratories to find the mechanism involved, and discover more potent compounds. The diuresis was quickly linked with the inhibition by sulphanilamide of the enzyme carbonic anhydrase which is essential to provide hydrogen ions for kidney functioning. Out of much work on carbonic anhydrase inhibitors came not only diuretics which used this mechanism, but also the very successful thiazide diuretics. These were found to be effective antihypertensives in their own right with predictable action and few side-effects. They quickly became a mainstay of therapy.[11]

In a period of eight to ten years, then, hypertension treatment had been revolutionised by the introduction of new drugs. We have

seen that this was led up to by the increasing amount of basic scientific knowledge which could be applied, and by the observation of side-effects of the multitude of new drugs produced as a result of the war effort. What changes in disease perception was this rapid, radical introduction of new therapies associated with?

I shall attempt to distinguish two main kinds of change in "hypertension" during the period 1945-1960, effected mainly by improvements in treatment. The first is a commonplace effect of reducing the level of severity of the disease at which treatment would be instituted, the second a more radical change in what the term "hypertension" signified.

The first effect I have documented by reviewing recommended treatment levels by hypertension texts at different times. The biggest change in the diagnostic criterion is from the retinal classification of Keith, Wagener and Barker (1939) to the sphygmomanometer reading. This coincides with the simplification of treatment, it becoming solely concerned with lowering blood pressure, whereas earlier perspectives had seen this as not enough. This is connected with the dramatic successes of the early anti-hypertensive drugs, and will be discussed in greater detail later.

The other change is a steady reduction in the blood pressure level at which treatment was recommended (see Table 1.1). Up until the mid-1960s this can be linked with improvements in treatment, as the reduction in unpleasantness of treatment made treatment at lower levels of pressure, that is involving lower levels of benefit, possible (Tables 1.2-1.4).

In this period 3 main steps can be seen:

1925-1948 From sympathectomy to ganglion blocking drugs. Concept of treatment at definite manometric levels becomes established. Malignant (diastolic 130+) hypertension begins to be effectively treated.

1948-1957 Ganglion blockers to hydralazine, reserpine, ganglion-blockers.

Table 1.1 Blood pressure levels of symptomless people at which treatment should be initiated

Date	Authority	mmHg	treatment
Up to 1948	Symptomless people not treated - cardiac enlargement necessary[13]		sympathectomy
1955	G. W. Pickering	-/130+[14]	ganglion-blockers
1956	R. Platt	-/120+[15]	reserpine
1956	F. H. Smirk	250/120[16]	ganglion-blockers
1959	A. W. D. Leishman	-/130-149[17]	pentolinium + reserpine
1960	CIBA symposium	160-180/100[18]	Thiazide diuretic/ hydralazine/ guanethidine
1964	B. N. C. Prichard	200+/115+[19]	pronethalol
1974	American Heart Association	160/95[20]	

N.B. Pressures quoted as systolic/diastolic

Table 1.2 Percentage of total number of hypertensives who began treatment within 3 months of referral to outpatients (Chelmsford)

	1957/58	1959/60	1961/62	1963	1964
Total	123	116	135	110	111
No. treated	55	51	96	68	79
%	46	44	71	62	71

Source: Hamilton, M., 1966[24]

Table 1.3 Percentage of newly treated hypertensives who were put on thiazides

	1957/58	1959/60	1961/62	1963	1964
Total no. treated	55	51	96	68	79
On thiazides	14	15	53	36	47
%	25	29	55	53	59

Source: Hamilton, M., 1966[24]

Table 1.4 The reduction in unpleasantness of antihypertensive therapy 1950-1960

Drug	Effects
Hexamethonium	Postural hypotension Impotence Urinary retention Constipation Dry mouth Reduction of sweating Paralysis of visual accommodation
Rauwolfia/reserpine	Depression Drowsiness Nausea/diarrhoea Slow heart rate Excessive salivation
Guanethidine	Postural hypotension Diarrhoea Inhibition of ejaculation
Thiazides	Biochemical alterations: low potassium high uric acid Tendency to precipitate gout and diabetes

Source : American Heart Journal, 92, 114-118 (1976)

Table 1.5 The definition of treatment levels by clinical trials 1964-70

Study	Levels treated (mmHg)	Result
Hamilton (1964)	diastolic over 110 mean 136	Morbidity and mortality clearly reduced
Veteran's Administration (1967)	diastolic 115-129 mean 121	
Veteran's Administration (1970)	diastolic 90-114	75% 'morbid events'* prevented by treatment of diastolic 105-114. 35% prevented at 90-104

*'morbid events' - comprise stroke and heart attack.

Trials considered in more detail with references in Section 2.4.1.

1957-1961 Hydralazine, reserpine to thiazides, methyldopa,

hydralazine, reserpine, guanethidine, ganglion-blockers.

Initial treatment levels drop to 160/95 - 180/100.

During the 1960s treatment levels began to be defined by clinical trials of treatment. The first trials and the recommendations arising from them are shown in Table 1.5. As Hamilton states:

> "Prior to these trials it had been generally believed that treatment of hypertension should be reserved for the treatment of complications. Now, for the first time, it became clear that control of a raised arterial pressure could prevent the advent of complications ..."[12]

There were more significant effects of the rapid increase in effectiveness of treatment. These centred on a change in the perceived nature of hypertension, as medical attention was focused on it in particular ways by the success of treatment. In the early part of the period, doctors were faced with a condition they could do little or nothing about. Their responses were mixed:

> "We may choose to be disinterested in the therapeusis of a disease that is both rare and unyielding to all forms of treatment, this is hardly neglect. On the other hand (this) presents a challenge."[21]

They saw hypertension as a complex condition of which the increase in blood pressure was only one manifestation:

> "Despite the desirability of lowering the abnormal elevation in the blood pressure seen in hypertension, it is now generally recognised that this alone, assuming that it could be done, would not constitute an adequate or satisfactory therapy for the disorder."[22]

And their attitudes to lowering blood pressure as the main medical strategy were mixed:

> "For many years, and to some extent today, objections have been raised to hypotensive programs because of evidence that atherosclerosis can progress and kill despite lowered blood pressure, and belief that the

> process is neither ameliorated nor delayed by lowering the blood pressure. Moreover, it has been claimed that lowering blood pressure may deprive the tissues beyond constricted or organically narrowed arterioles of adequate nourishment. For example, coronary disease may progress following a sympathectomy; falls in blood pressure especially when sudden and severe and accompanied by shunting of large volumes of blood into venous areas may precipitate precordial pain and even myocardial infarction as well as cerebral thrombosis and ischaemia."[23]

The demonstration of increased life expectancy in the malignant phase simply by reduction of blood-pressure, led to a concentration on the quantitative measure of blood-pressure levels as an index of disease severity, rather than the old distinction into four groups. This process gave rise to an increasing tendency to define hypertension in quantitative, rather than qualitative terms. Thus, the impact of effective treatment produced a situation in which the traditional definition of the disease as a pathological process affecting a defined subset of the population, one of whose manifestations was a raised blood pressure, became increasingly disconnected from the nature of doctors' encounters with the disease during treatment. This dichotomy rapidly became polarised into a conflict of medical opinion which I will consider in the remainder of this section.

The individuals involved were George Pickering, a distinguished member of the Royal College of Physicians, who had trained in physiology at Cambridge and was Professor of Medicine at London, subsequently at Oxford; and Robert Platt, an experienced clinician and Professor of Medicine, who at Manchester had specialised in renal conditions and the heredity of hypertension.[27]

The controversy began in 1954 as a result of studies into the range of blood pressure in a population of people attending outpatient clinics. The authors, Hamilton, Pickering, Fraser-

Roberts and Sowry, all had backgrounds in medical genetics or hypertension, or both, and they were all eminent in their fields. What they found when the pressures were adjusted for the rise which they observed with age, were distributions which looked more like continuous variation in one population, than any segregation into hypertensive and normal populations, which all previous studies had reported ("unimodal" rather than "bimodal").

The paper's introduction tentatively begins the break with the classical concept of essential hypertension:

> "The essence of so-called essential hypertension is an abnormally high arterial pressure; in the early stages there are no other associated abnormalities ... it is not easy to define precisely what constitutes a high pressure.* But any definition which does not consider the distribution of pressures in the general population and their relation to age is at least based on incomplete data."[28]

What is asserted here is that the study of diseases must be based on the whole population, and not, as hitherto, clinician's impressions of their patients. They go on to point out how previous studies have manipulated data to fit clinical conceptions, by separating two groups at arbitrary levels, treating their data on these groups in different ways, and using the difference thus obtained to justify the separation.

By studying the pressures of the relatives of hypertensives, and of controls, they examine the inheritance of essential hypertension. This had previously been thought to be due to a single dominant gene, which produces a separation into two different groups.

What they found was a continuous variation (fig. 1.5) which they argued was due to the influence of many genes (multifactorial inheritance).

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*See Table 1.6

Table 1.6 Suggested dividing lines between 'normotension' and 'hypertension'

Division	Author
120/80	S. C. Robinson and M. Brucer (1939)
130/70	F. J. Browne until 1947
140/80	D. Ayman (1934)
140/90	G. A. Perera (1948)
150/90	C. B. Thomas (1952), Hines (1940), Herndon (1946)
160/100	P. Bechgaard (1946)
180/100	A. M. Burgess (1948)
180/110	W. Evans (1956)

Source: Pickering, G. W. (1955)[14]

Criteria used in 31 studies of blood pressure[25]

	120/80	1
	150/90	4
	150/95	2
	155/95	1
systolic only:	140	8
	143	1
	145	1
	150	6
	160	1
diastolic only:	90	3
	100	3

WHO defined: 160/95 1959[26]

So their epidemiological investigations brought them to a new concept of essential hypertension:

> "The data presented in this paper have led us to doubt whether there is any justification other than that of convenience for drawing a line dividing normal from abnormal pressure ... according to where we draw the line , so we can make essential hypertension as common or as rare as we wish. ... This conception of the nature of essential hypertension appears to be a novel one, though it is so obvious that it is difficult to understand why it has not been clearly stated before. It would imply that the causes of essential hypertension are to be found in the genetic and environmental factors which influence blood pressure in the general population."[29]

This concept was further developed by Pickering in his book "High Blood Pressure" published in 1955, which was reviewed in the British Medical Journal as being controversial but an invaluable compilation of modern data on hypertension.[30] "Knowledge of hypertension is on the move again", McMichael wrote. The book had considerable influence in the prevailing increase in interest in treating hypertension.

It was five years after the 1954 article that Platt challenged Pickering and his co-authors' interpretations of the data they had gathered in an article in the Lancet. Platt was well aware of the strength of the views he was opposing:

> "This new concept of essential hypertension, attractive as it is in its simplicity, has failed to convince a number of clinicians who feel that it does not fit in with their experience, and who still think that the majority of middle-aged patients can be divided into those who have high blood pressure and those who do not. This may be because clinicians are slow to adopt a new theory, because clinical impressions are notoriously inaccurate, or because the human mind likes to place things into categories and especially likes to go on doing so if this is the established custom. On the other hand, it may be that a bimodal curve is concealed in the skew deviation already mentioned ..."[31]

After this elegant admission of clinicians' selective perception, Platt went on to analyse the blood pressures of the children of

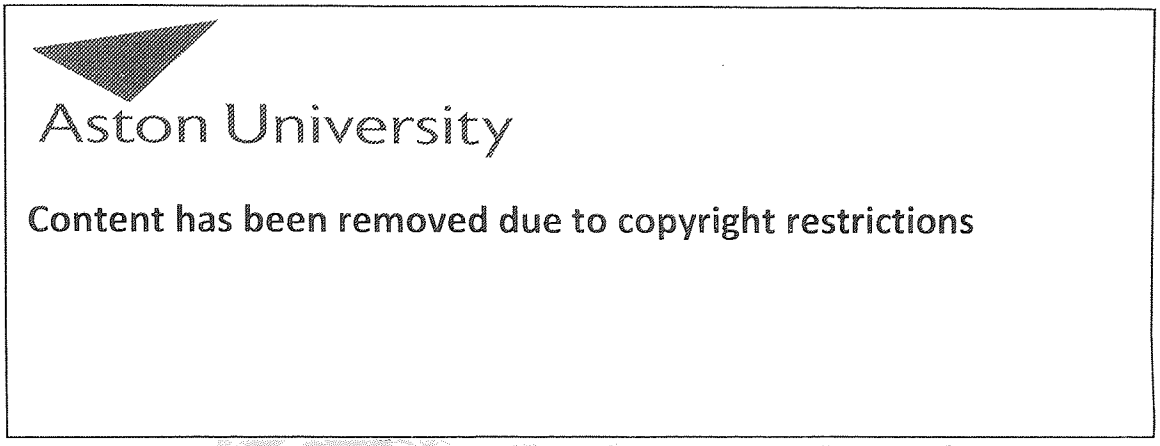
those who had high pressures, reasoning that if hypertension was due to a single gene, as he had previously argued (though not on very good evidence) then the pressures of the children should segregate into two groups, and the graphs should show two most common pressures, the "normotensive" group and the "hypertensive" group (bimodal). His previous work had involved family histories, which Platt admitted were not very reliable, but he had found that in nearly every case one or both parents of people with hypertension were also affected. He supposed that this was due to inheritance of a single dominant gene.

His graphs of the data presented in the 1954 paper reanalysed show convincing bimodality (fig. 1.6), and he commented:

> "it is interesting that the main dip in the curve occurs at about 150/90, which is exactly the figure most commonly chosen by clinicians as the line between normal and high blood pressure in middle-aged subjects."[32]

This was obviously strong confirmatory evidence for him.

His defence of the normotensive - hypertensive distinction was supported by another Lancet article later in the same year. Morrison and Morris used their data from the well-known survey of the heart disease experienced by London bus drivers and conductors to approach this problem.[33] Because they had no data on whether the parents of those surveyed were hypertensive or not they divided parents into two groups, those dying from age 40 to 64, who were assumed to contain considerably more hypertensives than the group that lived to older than 65, and analysed the blood pressures of the two corresponding groups of busworkers. The systolic curves of the drivers with one or both parents dead in middle age had a pronounced dip at around 160 mm (fig. 1.7). The diastolic pressure curves of both groups were unimodal.



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diastolic age - corrected score

Fig. 1.5 Diastolic pressures corrected for age, of general population and relatives of hypertensives, Hamilton et al. (1954).

cases

cases

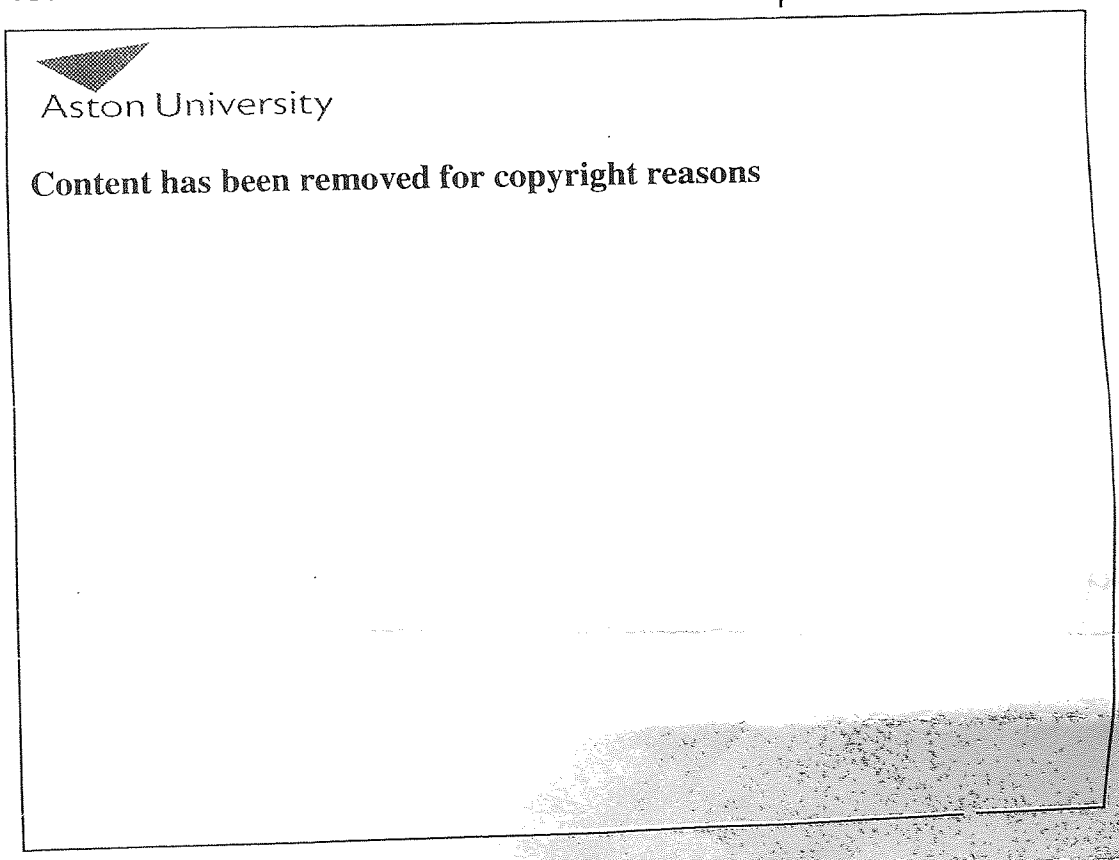


Fig. 1.6 Data of Hamilton et al. reinterpreted by Platt (1959) A and B from Hamilton, C Hamilton + study of Sobye

Fig. 1.7. Systolic pressures recorded in the London bus survey (1959)
A. Drivers with one or both parents dead in middle age
B. Drivers with both parents living to old age
C. All drivers

Fig. 1.8 Diastolic pressures of drivers with one or both parents prematurely dead.

Fig. 1.9 The separation of two groups from Fig. 1.8 on the basis of systolic pressure.

London bus survey (1959)

> "However if we accept the presumptive division between normotensives and hypertensives, this is at about 160 systolic - we can divide the diastolic pressures in fig. 1.8 into those of men whose systolic pressures are below 160 and those men with systolic pressures of 160+". (fig. 1.9)[34]

They also found blood-pressures rising with age in the prematurely dead-parent group but not showing this tendency as much in the other group. They discuss the significance of their findings as follows:

> "However it arises, high blood pressure is a 'disease' in any ordinary sense of the term since it lowers the expectation of life ... further study will be on a surer basis if the search is focussed on the cause or causes of a specific disease whose victims are qualitatively different from the rest of the population. Moreover the possibilities of prevention may be greater if hypertension is ascribable to some particular chemical, hormonal or enzymatic anomaly which may be corrected, rather than to the unfortunate end of a universal distribution involving multiple causes."[35]

These conclusions were echoed by the leader of the next issue of the Lancet:

> "The former group clearly showed a bimodal distribution while the latter did not. Thus, by using the inheritance factor it was possible to separate busmen into clearcut hypertensive and non-hypertensive groups".
>
> "We find this new evidence that essential hypertension is a specific disease both convincing and more in keeping with its clinical behaviour. For the clinician there is promise of a more meaningful diagnosis: definite distinction between normal and high blood pressure may at last be in sight ... For the investigator there is renewed assurance that the search for the cause of essential hypertension is still justifiable, and indeed, more necessary than ever since a bimodal distribution points to some specific cause."[36]

At the Prague conference convened by the World Health Organisation in 1960 to discuss "The pathogenesis of hypertension", Pickering's presentation and concept were criticised or ignored by all the other participants in the session. Controversy focused on Pickering's invocation of biometric practice in the treatment of his results:

> "to work in terms of essential hypertension and normal pressure is really about as helpful as it would have been to Francis Galton if he worked in terms of tall subjects over 5'8" and short subjects. You cannot approach a biometrical problem in this way."[37]

He had to use a system of scoring to allow for pressure differences with age and sex.

> "This method of assessing the extent of the deviation from the norm is unfamiliar to most physicians and has therefore been much criticised. However its principle is acceptable under standard practice in biometry..."[38]

His conclusion on inheritance studies was that "it looked as though what was inherited was not hypertension, but the degree of hypertension".

Morris criticised the system of scoring as assuming the things it was used to prove.

> "A preliminary word on the use of 'scores' instead of pressures. I find no justification for this. In the present state of knowledge of the natural history of essential hypertension and of the relation of sex and age to high blood pressure without evident cause, it does not help me at all to give the same score + 70, and thus equate single casual systolic pressures of 150 mm in a man of 22, 200 mm in a woman of 47 and 230 mm in a man of 67. The system of scoring takes for granted many things that it is very necessary to prove."[39]

The Russian doctor, V. V. Parin, criticised Pickering's viewpoint for its abstractness and lack of relation to real experience of the disease:

> "Professor Miasnikov ... showed that the hypertension process involves a change from a series of quantitative changes to a sudden qualitative change ... I believe that Pickering ignores the existence of such critical turning points because he has observed only one parameter which has been artificially removed from the dynamic total complex that is this disease - without correlation with other important factors. The argument that blood pressure distribution curves are very similar to height distribution curves says nothing of the biological basis involved."[40]

and delivered what amounts to a moral reproof:

> "Medicine is not a pure abstract science, it is part and parcel of the problems of human beings and their diseases, and particularly at a symposium organised by the WHO we have the duty to try and understand what is clearly a disease process in order to help ill people. This 'quantitative' approach of Sir George serves merely to disarm medicine."[41]

Pickering responds briefly by re-emphasising the difference between biological and clinical conceptions, and the partiality of the latter view:

> "Dr. Brod made the point that our results might be due to the fact that we had included abnormal people in our population. Now my difficulty is that I don't know what the word 'normal' means ... I have talked to biometrical friends and I don't think that 'normal' has a very exact connotation in a biological science. Of course, if you define something as abnormal, you exclude it. Then of course you find just exactly what you looked for. And as we were not interested in finding what we looked for, but interested in finding the whole thing , we didn't exclude anybody."[42]

Throughout these criticisms of Pickering's view was the theme of its being basically 'unmedical' and therefore an inadequate approach to disease. Stung by this and similar rejections, Pickering began writing a book to support his views on the nature of hypertension. He and his colleagues replied to the Platt and Morris papers in the Lancet in 1960.[43]

The main theme of their presentation was the artefactual nature of the dips in pressure curves seen by these authors as significant. They point out that the dips at 90 diastolic stay at this point at all ages, despite the general rise in pressure with age (fig. 1.10). They correlate a greater possibility for unconscious observer preference for not including readings at the dividing line (digit preference) in one study, with more pronounced dips in the data derived from it. They point out that Platt's separation between the pressures of the relatives of

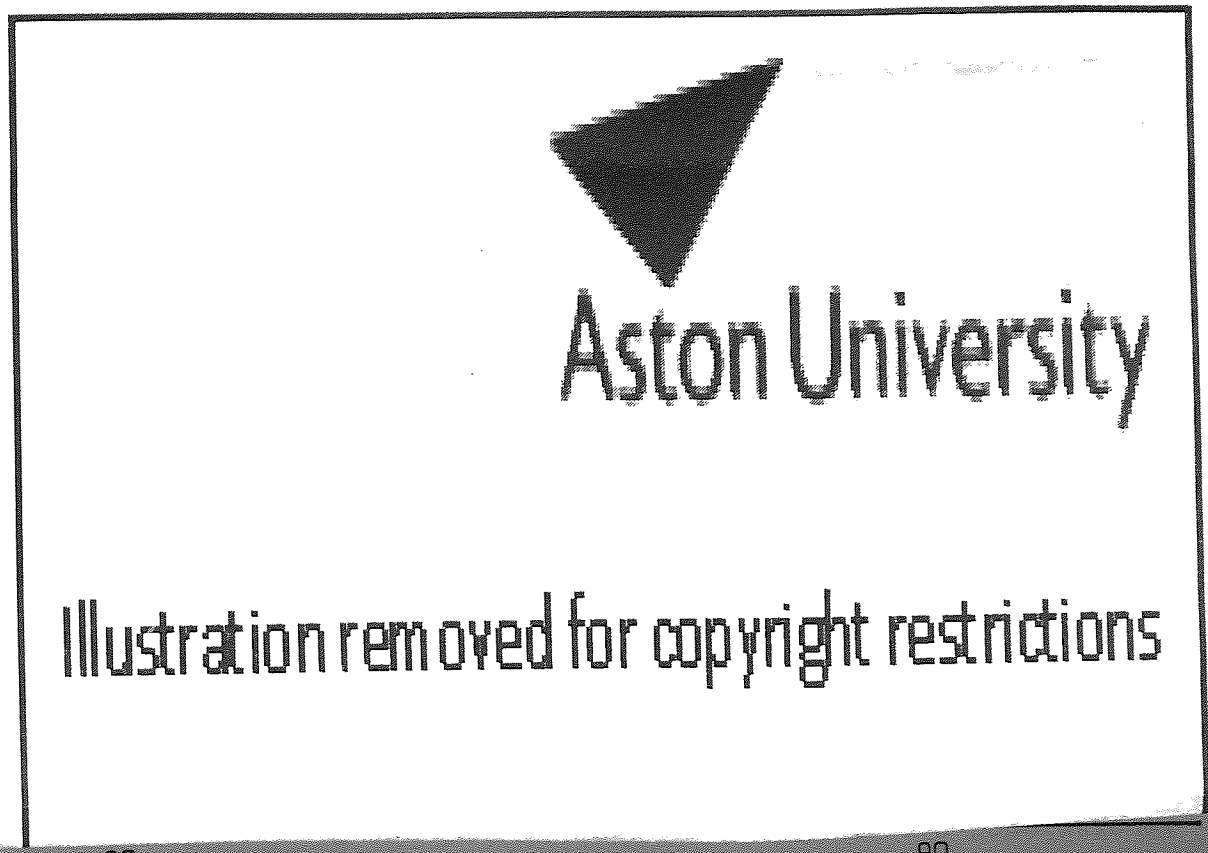


Fig. 1.10 Diastolic pressure graphs of different age groups showing consistent dip at 90 mm, from Pickering (1960).

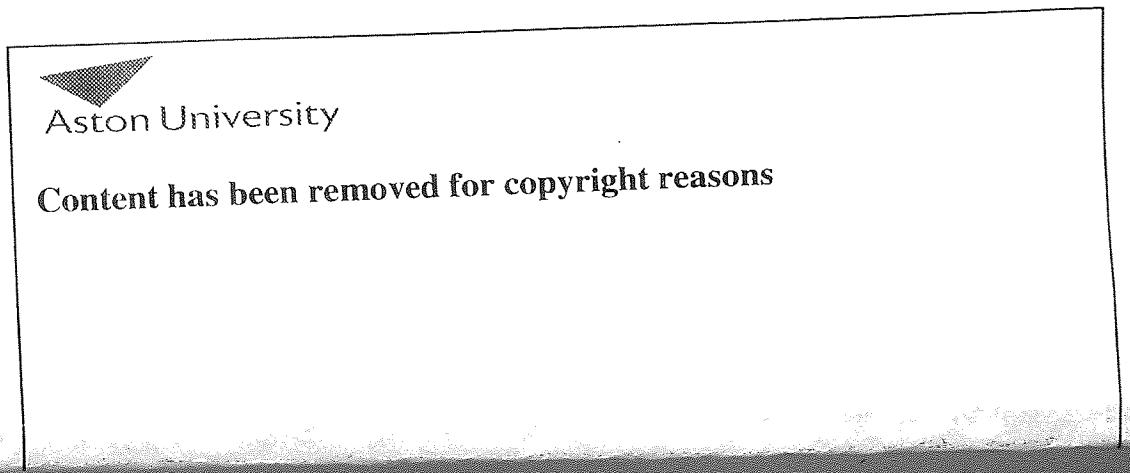


Fig. 1.11 Two separate populations combined (A) may be indistinguishable from a continuous distribution (B) C shows a systolic curve from Hamilton for comparison, Platt (1960).

normotensive and hypertensive people is only significant in one age group and in one study.

Morris' thesis is undermined by quoting mortality statistics. Morris assumed that premature death was linked with hypertension; Pickering and colleagues quote: 28% of deaths at ages 40-64 are due to associations with hypertension, whereas 48% of those 65+ are, thus neatly overturning his thesis.

Showing some curves of height of children presented in a similar way to the data on hypertension they state:

> "No student of the genetics of nature has yet attached significance to these dips".

They show the basis of these irregularities being in small sample size.

Platt's reply[44] centred on the way in which he felt the methods of Pickering could conceal the existence of two populations. In a series of graphs he drew two separate populations, combined them where they overlapped, and compared the result with an irregular curve which the Pickering group held to reveal continuous distribution (fig. 1.11).

> "Morrison and Morris are accused of confusing irregularity with bimodality. The graphs above show how easily true bimodality can be confused with irregularity..."

He went on to comment more generally:

> "the methods of the Pickering group seem to me just those which could best conceal the existence of two populations if in fact they do exist ... The 'new' concept of essential hypertension far from 'stimulating inquiry' stifles it at birth."[45]

Here the controversy lapsed for over a year apart from sporadic outbursts from Pickering. It was re-opened by a review of Pickering's book 'The Nature of Essential Hypertension" in the Lancet, which was generally critical, and supportive of the clinical

viewpoint. Two of its statements are quoted to show attitudes which were about to undergo radical change:

> "in any case it is certain that the treatment at present available is not influenced by views on underlying mechanisms ... it is often clear that the height of the blood pressure is not itself the most important factor."[46]

Pickering's next statement moved away from arguing over data interpretation, and instead pointed out the different concepts of disease that were at issue:

> "is it not possible that the habit of mind enforced by our instructional discipline has blinded us to the existence of another kind of disease which the physiological type of essential hypertension is an example? The fact that few of those who reviewed my book refer to this idea, its only important contribution, suggests that this is so."[47]

Platt's response was prompt, and the letters were now headed "logic and hypertension" instead of "the nature of essential hypertension" as formerly. This marked a change in approach:

> "Not only does he commit a super-snarkism but also an ignoratio elenchi ...'I have said it thrice; what I tell you three times is true' has now been outdone by Sir George who on the same evidence must have said it at least six times, although the fallacies in his arguments have been repeatedly pointed out ... if the Pickering methods were transferred to the study of mental deficiency, they would deny the existence of phenylketonuria ... The ignoratio elenchi is an ancient device defined in my dictionary as argument that appears to refute while actually disproving something not advanced by him ... the range of figures for blood pressure in the general population ... shows clearly that studies of normal populations may have little relevance to what doctors know as essential hypertension."[48]

Pickering replied promptly with an equally acrimonious contribution:

> "I recognise that I hold a heterodox, almost a revolutionary view ... and I intend to express it until valid evidence is produced that my view is wrong and the alternative view is right ...

> Platt's more recent evidence is not acceptable. In the Eugenics Review he considers a series 2 6 3 4 10 4 3 3 0 1 as evidence of bimodality. More recently a series 6 11 8 9 13 11 10 6 5 1 5 1 is interpreted as 'it does look rather more as if there are three real peaks'. Could Sir Robert get a mathematician's opinion on the meaning of these figures?
>
> I understand that phenylketonuria was not detected from the shape of the frequency-distribution curve, but by testing the urine with ferric chloride. Those who still cling to the single-gene hypotheses of essential hypertension can best prove their point by finding that biochemical fault of which it would be the manifestation."[49]

The focus of the argument seems to be changing from the differential interpretation of data, to dispute over the usefulness of different conceptions of disease. This theme was continued by John McMichael later in the same year, who compared hypertension with anaemia which he said would also have a continuous distribution, but that it was work on the mechanisms involved which had led to clinical success:

> "Many of us have tried in private, on the rostrum, and in print to convince Sir George Pickering that the search for definable influences and separable clinical groupings in hypertension is a continuing challenge."[50]

A short rhyme was published immediately after this which indicates an appreciation by readers, and probably journal editors also, that the arguments of the participants were in many ways not making contact with each other :

> "Schoolmen contending, ego on high
> Words without ending, truth's never nigh
> Facts may be lacking, argument's free
> Keep on attacking P versus P
> ... Readers are tiring, editors bored
> Spare us more firing, spare us O Lord
> Peace be to Pickering, silence on Platt
> Truce to their bickering, leave it at that."[51]

Subsequently, it has generally been felt that Pickering's view has prevailed - most discussions of the nature of hypertension

have deferentially cited his views as authoritative statements,[52,53] and the level at which to treat has been defined by the outcome of clinical trials, rather than a distinction between diseased and non-diseased states.[54]

This controversy has been recorded in detail because of its significance for the drug treatment of hypertension. Powles outlines this as follows:

> "The extent to which human population biology ... has failed to influence medical theory is quite remarkable. The resulting inability to deal theoretically (as distinct from statistically) with biological phenomena at levels of organisation above a single organism has left medical theory seriously deficient. Medicine has deprived itself of the only possible theoretical basis on which criteria for biological normality in man could rest. The serious issue of whether a bodily change that is induced by our way of life and predisposes to overt disease should be regarded as pathological has been reduced to the trivial one of whether the distribution of blood pressures in the population is unimodal or bimodal ... It hardly needs to be added that the debate gains its significance not from a felt need to prevent the development of the abnormal but from the felt imperative to knock it into line with drugs."[55]

I would like to take this analysis further and discuss why clinical and biological views of hypertension were so opposed, what the significance of the increasing availability of effective drugs was for the development of the argument, and how the outcome affected the subsequent evolution of hypertension.

It is obvious that the clinician's objectives are very different from those of an epidemiologist or biologist, and in relation to this his thinking is also different. Freidson characterises the clinical viewpoint as follows:

> "By and large I think it can be said that the practitioner has a different view of his work than the theoretician or investigator. In fact he has a different way of looking at the world. First, the aim of the practitioner is not knowledge but action.

> ... the practitioner is a fairly crude pragmatist. He is prone to rely on apparent 'results' rather than on theory ... the clinician is prone in time to trust his own accumulation of personal first-hand experience in preference to abstract principles or 'book knowledge' ... one whose work requires practical application to concrete cases simply cannot maintain the same frame of mind as the scholar or scientist ... the practitioner comes essentially to rely on the authority of his own senses, independently of the general authority of tradition or science."[56]

In the case of hypertension, clinicians relied particularly on the two-population model, because it makes treatment much easier. Some distinction between those needing attention and those not is necessary, or at least the notion that there is such a distinction, which can be reached by further research, otherwise the practice of medicine becomes much more problematic. The notion of a continuous distribution in the population is not so convincing when what one is confronted with are individuals with high pressures.

Pickering's approach was that of an experimental scientist who kept his scientific approach when confronted with disease. When dealing with populations, a statistical model was appropriate rather than the clinical model.

These different approaches could only conflict on an issue broad enough for each of them to appropriate certain data bearing on the problem. Thus Platt used family histories to relate the clinical model to a scientific framework, whereas Pickering used population surveys to relate the statistical behaviour of a biological variable with a medical conception - the nature of hypertension - that had until then only had a clinical definition.

The controversy was obviously rooted in the increasing interest in hypertension treatment already noted and the changes

in conceptions that this brought about. Particularly important must have been the progressive lowering of the stage at which it was recommended to begin treatment, from 250/120-130 in 1955 using ganglion-blockers to 160-180/100 in 1960 using thiazides, hydralazine and guanethidine. This marked a change from treating obviously diseased patients with pathological changes in retinal arteries, heart size, kidney function, etc. to treating symptomless people, as these symptoms usually begin about midway in this range, and a concentration on the height of the blood pressure as the main guide to action. This involved a change from qualitative to quantitative criteria for treatment. It was in this context that the controversy over the nature of the disease had its significance. Obviously the changing level at which treatment was started, and the strong connection of this with the presence of disease lent indirect support to Pickering's conception. The impact of controlled clinical trials of drug therapy, beginning with anginal remedies and the anticoagulants, was bringing into therapeutics an awareness of the greater value of statistical significance than clinical experience as practical guide to action.

The outcome of the controversy; the apparent victory of Pickering, has had an important influence in shaping hypertension and its treatment in the 1960s and 1970s. What it has meant is that doctors have to a considerable extent moved on to using other criteria to decide when to treat than the presence or absence of the disease of hypertension. The only criterion available is a judgement of the balance of costs and benefits associated with treatment. Increasing emphasis on this has resulted in a series of large controlled trials, which have been extensively publicised and on the results of which recommendations for treatment are based.

The benefits of treatment are becoming better known as experience accumulates, and benefit seems to accrue even at small elevations from average pressures. This is a very potent stimulus for workers in the pharmaceutical industry to reduce the costs and risks of antihypertensive drugs.

The continued innovation of drugs with milder side-effects has enabled the treatment of those with lower and lower pressures. This situation has come about as a result of the disappearance of a defined disease, so that part of the treatment criteria are now defined by the characteristics of the treatment. As drugs improve, less and less benefit is theoretically required for treatment to be instigated. It is true that most doctors do not see their medical role as involving the treatment of an additional 15-20% of the population, most of whom are apparently normal and have no symptoms, yet this is what the revision of the nature of hypertension has produced - a situation where the number of people defined as needing treatment depends on the characteristics of the drugs available, and the better the drugs, the more people will be treated.

What I have argued is that the outcome of the controversy between Platt and Pickering, or between clinical and biological perspectives on hypertension, has been to substitute a cost/benefit criterion for a simple diseased/normal distinction. This criterion currently limits the application of drug treatment to around 40% of the population only by two drug-defined factors, the psychological cost of being defined as in need of permanent treatment, and the unpleasantness of the usual side-effects and the slight risk of severe side-effects from the drug. The partial replacement of a traditional clinical model of disease by a new viewpoint has

contributed to the application of a rational criterion for therapy which has resulted in the medicalisation of a substantial and ever-increasing fraction of the population.

2.0.1 Approaches to the study of drug innovation

> "Perhaps science is not the father of technology, but an anonymous well-wisher that sends it gifts through the post..."
>
> F. R. Jevons

The aim of this section is to review the literature on drug innovation which looks at similar or related problems to those that the present study addresses. What it aims to do is to point out both the useful ideas and the gaps that exist in the literature; in the combinations of methods used, in perspectives, and in the kind of questions that are asked, and situate the types of analysis used in this study within a broader tradition.

Studies are grouped in terms of the area they survey, from studies on single drugs, which comprise the bulk of the literature, through studies on drug classes, to more generalised perspectives on the drug innovation process. This brings out interesting differences in the types of question that have been asked and answered at each level of analysis. The studies are analysed according to:

1) The methods used and the questions asked.

2) The type of innovation model used and whether it is implicit or explicit.

3) The factors seen as influencing the innovative process and the relative importance assigned to them.

4) If the innovation is evaluated, and if so, how.

The type of innovation model has been classified according to the scheme proposed in Langrish *et al*. (1972).

> "Most writers on innovation have either clearly stated or implicitly assumed that the innovative process consists of a linear sequence of events. These linear models of innovation can be divided into two types: those in which the start of the process is a discovery,

and those in which the start of the process is some form of need ... these two types of model can each be further divided into two subdivisions producing four models of the innovative process as follows:

Discovery push	a. Science discovers, technology applies.
	b. Technological discovery.
Need pull	a. Customer need.
	b. Management by objective."[1]

However, they go on to say:

> "When the Queen's Award innovations are examined, very few of them fit any one of the above models in a clear and unambiguous way. The reason for this is quite simple. It is extremely difficult to describe the majority of the cases in terms of a linear sequence with a clearly defined starting point ... Innovation is a complex process involving the interaction of many factors."[2]

The first section examines some studies of individual drug innovations written from a variety of perspectives. The second looks at two articles written on the molecular modification, or follow-on process, that is the production of new drugs by the systematic modification of those in existence, and essays a brief critique of the views put forward. The third contains general perspectives on the drug innovation process from a variety of sources. The fourth summarises and integrates material from the preceding sections.

> "As to inventions, we are still in the antediluvian geologic age, holding a cataclysmic rather than an evolutionary theory of the origin of things."
>
> S. C. Gilfillan

> "The inadequate conception of invention as an intermittent and discontinuous phenomenon is shared by the historian and the economist."
>
> N. Rosenberg

There are many of these, so only a small proportion have been selected for comment, as most of them are short factual historical accounts of particular innovations, usually concentrating on the invention stage with little consideration either of the factors influencing this stage, or of the importance of the events leading up to this stage, apart from a selective chain of scientific discoveries.

Most of these accounts follow the classical format of medical histories, which might be characterised as concentrating on the personality of 'the great man', and showing that the success of the innovation was due to the originality and correctness of his ideas and his persistence in pursuing them, usually against the disbelief of his colleagues. This tendency is exemplified by some of the books written on the discovery of penicillin.[3]

Obviously some factors brought out by this kind of account do materially affect the innovation process. The roles played by important individuals in the process in modern organizations have been analysed and classified as 'gatekeepers'[4] and 'product champions'.[5] The latter has much in common with the 'great man', and is characterised by Schon as follows:

> "It is characteristic of champions of new developments that they identify with the idea as their own and with its promotion as a cause to a degree that goes far beyond the requirements of their job."[6]

This process is important in the case-study, and is discussed further there.

However, the classical mythology of the heroes of medicine is not very fruitful when one is trying to see innovation in its social context, so while these studies sometimes provide excellent source material their perspective limits their usefulness. Not all single-drug studies fall into this category. Some are excellent histories which convey a flavour of immediacy and a genuine quality, some look at the factors immediately affecting the innovation process, while some have a longer historical perspective, and look for the scientific roots of particular discoveries.

One can trace some interesting links between studies in this area. An important early attempt to examine case-studies of innovation was the classical and oft-cited work of Jewkes, Sawers and Stillerman.[7] They took 50 case-studies on a large range of modern inventions of which 3 were on medicinals - insulin, penicillin and streptomycin. Although still quoted by general articles on drug innovation its cases on drugs are by today's standards inadequate on several counts. The cases are very short, about a page in length, and much of this is taken from secondary sources, especially in the piece on penicillin. Consequently inaccuracy is combined with brevity and a lack of orienting methodology. Where the book succeeded was to show by means of the case-study approach that it was possible to examine innovations more closely and systematically than had hitherto been done by individual accounts.

The Wealth from Knowledge study, written by Langrish and a group at Manchester[8] is a direct descendant of this approach, which

shares some of its failings, but contributes significantly to a more sophisticated analysis of the factors influencing innovation. The logical extension of this approach is exemplified by the "Interactions of science and technology in the innovative process" study[9] where a set of 21 factors thought to be influential , gathered from the literature, are each rated in influencing importance for each decisive event in the innovation process.

Another common concern of many of these studies is the desire to emphasise the role played by basic science in the innovations studied. Both the 'interactions of science and technology' study and Judith Swazey's account of chlorpromazine[10] rely on historiographs to show significant lines of development leading up to the innovation. But these almost exclusively concern intrascientific events - the factors influencing these go unmentioned in 'Interactions' and unanalysed in 'Chlorpromazine and Psychiatry'. A scientific bias is difficult to avoid when studying the technical roots of an innovation as other social and technical information is not as well preserved as are the major areas of scientific development.

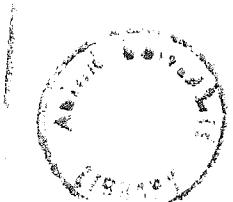
Penicillin in perspective[11] is a naturalistic account for the general reader of the discovery and development of penicillin, so an explicit analysis of influencing factors is not attempted. Wilson has taken older accounts and retained the "drama of discovery" and added considerable background material which makes the significance of many of the events in the process described much fuller. In particular, the information on the development of the concept of chemotherapy, and the concurrent rise of the drug industry give a much-needed historical context to the successes of Prontosil and the beginnings of industrial production of

penicillin by the large-scale growth of mould. The integration of background material with participant accounts as seen in this book is a very powerful recounting technique and one which is taken up in the present study.

By contrast, the collection of case-studies written by a group of academics at Manchester, published under the title of Wealth from Knowledge[12] is a more specialist study. It looks at some innovations which won the Queen's Award to Industry, and through a combination of background reading and participant interviews, "aimed in particular to relate the technological to the organisational and other aspects".

> "Investigation of the technological background of each innovation was carried out in order to assess the type and magnitude of the technical breakthrough and to give indications of the types of institutions involved and the stage of development reached before the product or process was taken up by the innovating firm. Information on the industrial or social needs requiring the innovation was also gathered. The innovations were then studied within the organisational context of the firms in order to find out as much as possible about how they were taken up, developed, and marketed ... much of our discussion is centred around the question of the sources from which innovation arises ... the conditions in which the inventive steps were taken must themselves be considered as essential ingredients of any proper understanding of the innovative process. As Gilfillan pointed out, not only do inventions cause changes in the milieu but also, vice versa, changes in the milieu call forth inventions. With this in mind we have concentrated a good deal of attention on the needs - the commercial, institutional, social and suchlike pressures - which form part of the environment in which inventions are made. Here it is necessary to consider factors arising inside the innovating firms as well as external ones."[13]

With this perspective they looked at 84 inventions in chemical, electrical, mechanical, engineering and craft-based industries. Only one of these was the production of a new drug - the invention by the Beecham group of the semi-synthetic penicillins.



These are novel penicillins produced by the attachment of synthetic side-chains to a basic penicillin nucleus. These side-chains can confer resistance to enzyme inactivation and different spectra of antibiotic activity.

Their account of the innovation singles out three themes as worthy of comment: - the role of basic science in the innovation, which they conclude is mostly of 'distant origin', the chemical techniques having been discovered in the late 19th century, but that the recent work on penicillins which was built on in this innovation was due mostly to the Second World War effort.

- the organisation of scientists in the pharmaceutical industry. They conclude that the interdisciplinary organisation of project teams is an important source of creative interactions.
- the management of research. They conclude that success was also due to the initial impetus which came from the chairman of the group to go into antibiotic research, and his policy of paying for the best possible scientific advice.

Their attempts to assess the effects of this innovation are token, limited to citing the number of countries of sale and some estimate of the increase in profits made by the pharmaceutical group of Beechams, as by the design of the study the innovations had all been selected as "successful" because of their inclusion in the Queen's Award Scheme.

This short study is interesting as one of the attempts to study pharmaceutical innovation within a wider context. However, it explicitly restricts its analysis to factors initiating activity by the innovating firm, rather than considering underlying factors outside the firm. Its use of participant interviews allows it to convey many of the important details surrounding the innovation, from the meetings that took place and the suggestions that were then made by individuals to licensing and investment decisions made as a result of the research. The overall aim of the study to generalise about the innovation process from a large number of case-studies does impose limitations on the significance of one isolated study. The restricted length of the piece means that the factors seen as most important are not substantiated, and there is only a very sketchy attempt to look at the significance of the effects.

The final report of a project funded by the American National Science Foundation was published in 1973 with the title Interactions of Science and Technology in the Innovative Process.[14] Its explicit objectives were to:

> *investigate, document, and record the history of several innovations of high social impact, especially the role and interactions of science and technology in the innovations; and to identify and characterise the significant events of each innovation.
> *identify the decisive events in the history of each innovation; and to assess the importance of various social, institutional, and cultural factors in their effect on the decisive events of each case studied.
> *identify certain general or qualitative "characteristics" that apply to the innovations as a whole.[15]

However, it was seen by many as the response of the American scientific community to Project HINDSIGHT. HINDSIGHT was a project commissioned by the American Department of Defense to determine how significant the basic research funded by the

Department of Defense had been in selected important military innovations. This study originated the "events" methodology, and used it with a 20 year retrospective time horizon to produce results which alarmed the American science community - that 9% of the essential events in the case-studies were scientific, 91% were technological - and of this 9%, 97% was Mission-oriented research.

The case-study of particular interest here, out of the 12 included in the report, is that on the contraceptive pill. The methods of the study involved the demarcation of 'significant events', defined as

> "an occurrence judged by the investigator to encapsulate an important activity in the history of an innovation or its further improvement, ... Generally these events follow one another in historical sequence, along channels of development of knowledge."

and decisive events:

> "Selected from among the significant events, a decisive event is an occurrence that provides a major and essential impetus to the innovation ... one should be convinced that, without it, the innovation would not have occurred, or would have been seriously delayed."

The report also is explicit about its technical perspective:

> "since science and technology lie at the focus of the investigation, the great majority of significant events are technical in nature. However, a few events that did not involve science and technology were important enough to be included..."[16]

Technical events were further classified as resulting from Mission-oriented or Non-Mission-oriented research, or as being Development - that is part of a process which "starts with the design of a feasible prototype and ends with the first commercial application and use". 21 factors which were thought to be probably important in influencing the innovation process were derived from the literature and from the experience of the researchers.

Table 2.1

Factors influencing the decisive events

Recognition of Scientific Opportunity

Recognition of Technical Opportunity

Recognition of the Need

Management Venture Decision (Formation of R & D Team)

Availability of Funding

Internal R & D Management

Formal Market Analysis

Prior Demonstration of Technical Feasibility

Technological Gatekeeper

Technical Entrepreneur

Patent/License Considerations

Technology Interest Group (Invisible College)

In-House Colleagues (R & D Team)

External Direction to R & D Personnel

Competitive Pressures

Serendipity

Technology Confluence

General Economic Factors

Social Factors

Political Factors

Health and Environmental Factors

Source: Interactions of Science and Technology in the innovative process Battelle 1973

Each of these factors was given a rating for its influence on each decisive event from 0-3 (no-high importance). The study then ended up with quantitative measures of importance for the 21 factors on the events they had identified as decisive. 'Overall recognition of technical opportunity' and 'Recognition of the need' were most important and Political and Social factors were least.

Using this methodology to look at the origins of the contraceptive pill, they trace several lines of development in basic science which were essential for the innovation. The specialities involved were: steroid chemistry, physiology of reproduction, and hormone research. Of the 15 decisive events identified, 5 are scientific discoveries which had important later implications, 2 are the actual innovative proposals, and the remainder are divided between technical events in the developing firms and more economically based decisions on starting a new firm (Syntex), and on marketing the pill.

Their analysis of the innovation rests mainly on a list of the decisive events that they isolated and a table of the relative importance of the 21 factors on these with a short explication. There is also a pictorial representation of the events in chronological order following each other along "the channels of development of knowledge" - the "historiograph". This is a very immediate representation of the historical developments, but also a partial and misleading interpretation. Events outside these "channels" are not shown, to make the diagram clearer, but the omission of the more diffuse social and political factors is crucial from the perspective adopted in the present work. Some of the individual characteristics of the innovation of the pill are lost in this classification in an early stage in the analysis.

The major drawback of this study is the way in which the methodological attempts to derive a quantitative index as a basis for comparing different innovations which begin as clarifying real events end up recasting reality in their own terms. The segregation of decisive events as being the main elements for analysis is arguable, but the ensuing exercise in spurious quantification, where the fact that, for example, the "Recognition of Technical Opportunity was more important than Recognition of Scientific Opportunity in 6 events, less important in 4 events, and equally important in 5 events" is seen as a significant statement, seems indefensible. The overwhelming need for numbers to give an air of exactitude leads to arbitrary distinctions becoming unquestioned.

This move is more explicit in HINDSIGHT, the work from which this methodology is borrowed:

> "The validity of Project HINDSIGHT's methodology is equal to that of the statistics of large numbers".[17]

and has been well criticised by Kreilkamp:

> "Much of the intellectual damage done by HINDSIGHT's choice of the events model can be summed up in a single term - reductionism. The events model distorts the historical movements of technology by oversimplifying them ... its epistemological preference for quantitative knowledge over qualitative regardless of costs in accuracy or nuance ... amounts to a preference for numbers over realities."[18]

If the classifications of the study are analysed from this perspective, it appears that their interpretation of social and political factors, defined as "group customs, beliefs and attitudes, and elections or war" respectively, is very limited. For example, in their account of the research they state that reports that German aviators could fly higher because of cortisone injections led to large government support for cortisone research. Three of

the scientific decisive events were apparently directly connected with research into cortisone yet they are all rated 0 for political and social factors. The historiograph also omits the cortisone story and the events are placed in the "channels" of steroid chemistry and hormone research.

It seems then that the classificatory emphasis of this study, in its attempt to bring out common elements of different innovations, omits even important influences apparent in the account, let alone material which is not in the account.

But for all its faults the study was an ambitious attempt to push the analysis of influencing factors one stage further, and to get some measure of comparability between case-studies. These real problems demand new approaches like those used; the matrices of relative importance of factors, and the historiograph - but their limitations need to be more clearly defined.

The book-length study, Chlorpromazine and Psychiatry , written by a historian, Judith Swazey, was sponsored by the American National Institute of Mental Health. It looks at

> "The general processes involved in scientific discovery and its practical application, in the hope that this would help not only to clarify what took place, but also indicate how one or another type of intervention might have affected the chain of events. Recognizing that the ultimate goal of basic scientific research is social benefit, the committee decided to begin this project with those discoveries that have had the greatest practical value in the treatment of mental and nervous disorder and then to examine the history of how these came about."[19]

The Committee on Brain Sciences chose chlorpromazine (Largactil, Thorazine) as "the outstanding practical contribution to psychiatry over the last 20 years".[20] What Judith Swazey has done is to look at the sources, the innovation process and its effects at similar length to the present study. Her examination mostly concerns intrascientific material, as the study refers explicitly to the National Science Foundation sponsored works TRACES and Science and Technology in the Innovative Process in its conclusion, and is much concerned with the contribution made by basic research, and whether this could be organised more effectively.

Swazey focuses her attention on two areas; the scientific sources of chlorpromazine, and the way in which it entered and transformed psychiatry. Many of the strengths and weaknesses of her book come from the fact that she is not a member of either drug producer or drug user groups, in contrast to the authors of most drug studies. The strengths are her competence as a historian which gives rise to an approach which is tentative and academically sound, and her distance from the events being considered which permits the use of new perspectives.

She is acutely aware of the selective nature of historical analysis in the consideration of sources:

> "But how far back in time should one move in tracing the antecedents of a given scientific event? Distortions can result both from a (temporally) too brief retrospective analysis, and from a too nearly 'infinite' historical regression."[21]

and the present study has been greatly influenced by her perspective on the events after the introduction of chlorpromazine (CPZ):

> "In Part II the emphasis shifts toward explaining several other, more sociologic dimensions of the discovery-innovation process ... This shift is based on a realization that the development, introduction, and uses of any new treatment are determined not only by internal scientific and medical considerations, but by a number of concomitant social factors. The spread of knowledge about an innovative drug and the willingness of physicians to explore its use, for example, are shaped in part by the development and marketing activities of the pharmaceutical manufacturer, by informal lines of personal contact and influence among physicians ... and by the individual physician's initial response to the claims made for the new agent, in terms of his perception of the major problems and needs of his patients and the adequacy or inadequacy of the variable treatment or management options."[22]

However, these social factors are overshadowed by a concentration on details of the initial scientific papers. It is obviously difficult to illustrate such widespread impacts as CPZ had more thoroughly than just listing some expert opinions. But the effects of CPZ are left to the experts to evaluate and the overall impression is that the analysis has been overwhelmed by the scale of the effects with which it attempts to grapple. The usual problems of evaluating drug impacts are added to in the case of CPZ by other factors:

- that previous therapies that it replaced were largely incomparable like shock, sleep therapy etc.
- that as the first-of-a-kind, evaluative procedures such

as double-blind trials, and consideration of the effects of increased attention by doctors during such trials were only evolved during its use.

- that the conditions in which it came to be used are notorious for their lack of objective definition.

This unwillingness or feeling of inability to critically evaluate impacts seems to me to be the principal weakness of her "outsider" approach.

This part of the study contrasts greatly with the fascinatingly detailed picture that she was able to build up of the events and personal interactions within and between the pharmaceutical companies involved in developing and marketing CPZ. Most of this information is highly inaccessible, and its opening up is one of the major benefits of such an official study.

The case-study approach, then, is used here to examine the relations between the evolution of scientific and medical disciplines and drug innovation. Swazey does not have an explicit model of the innovation process - in fact that is not where her major interest lies. The main factors seen as influential on the process, which are considered in some detail, are developments in basic science and deviant strands of medical thought. For example, the unconventional ideas of a French surgeon, Laborit, on shock, Swazey sees as important. She comments:

> "Not infrequently, what are viewed today as valid and important theoretical, experimental or practical advances were generated by theories that have been judged 'unorthodox' or 'nonsensical' both contemporaneously and historically, or by experimental hypotheses, data and conclusions that seem to be instances of 'poor' 'invalid' or 'wrong' science ... someone 'outside the system' - a person whose theories, or laboratory or clinical work are noticeably unconventional can often 'make connections', see new facts or implications not perceived by persons working within a more orthodox framework."[23]

An aspect of the subject of the present case-study has already been the subject of another smaller study - a thesis on The contribution of basic science to medicine by David Malkin at Manchester.[24] He used the innovation of practolol as one of nine case-studies of novel, successful, pharmaceutical innovations. He derived most of the detailed information needed from participant interviews and carried out only limited literature surveys.

The main theme of the study is the exhaustive analysis of "bits" of information that are isolated from the participant accounts. The information from all the case-studies is considered en bloc and the analysis proceeds to a categorization of its type, role, and rate of transmission. Malkin finds that the most important source of extra-company information is clinical trials, and the second most important is the scientific literature.

The aim of this study is therefore very different from that of the present study - the case-studies' detail is not recorded for its own sake, but as a prelude to an eventually quantitative analysis, and the results are expressed quantitatively. As the concept and techniques of this study are so different from the present work it is included here as an example of a radically different approach which although based on, in some respects, very similar subject matter, has few connections with the present enterprise. The approach adopted is much closer to 'Science and Technology in the Innovative Process' in the way in which the participant accounts are analysed. Malkin uses an implicit linear model of innovation to structure his analysis and enable the quantitative expression of results. This misses out

much of the uncertainty characteristic of the innovation process, and replaces it with a manageable set of processes, amenable to quantitative analysis and to change by management direction. The extent to which this ideal world can yield useful guides for practical action must be open to debate.

Another thesis from Manchester looks at the innovation of the contraceptive pill and examines the relationship between academic and industrial work from the 1930s when the hormones were first isolated until the pill became commercially available in 1960.[25]

Vivien Seal describes the work of five companies in detail, mostly by reference to the chemical literature and analysed according to the sources of each technique or reaction. However, despite the great technical detail, other things are considered. There is an extensive discussion of the influence of non-technical factors in the innovation process which includes not only quotes from participants describing the influence of these factors, but information on legislation and the roles played by the organisations of the medical profession. A bibliographical section covers the most important journals for steroid publications, and analyses changes in numbers of papers from academic and industrial sources from 1935 to 1965. References in 2 key texts were analysed for academic or industrial sources. Participant interviews and communications were also used, but were frequently found difficult to obtain.

Seal explicitly disclaims any linear innovation model, holding basically to the position that innovation is a complex interaction between science and technology, but at least in the

case she analyses, the academic research contributed rather more to the technical basis of the innovation than the industrial did.

Seal presents considerable evidence to show the non-technical factors, such as public and medical prejudice and hostile legislation being the major delaying factor on the innovation. The effect of the Second World War is considered, and the developments of useful research in related fields not subject to public hostility. These are seen by Seal as being also of major importance - the discovery of cortisone's anti-arthritic properties, and the use of progestogens as fertility enhancing agents.

The effects of the innovation are not evaluated beyond a brief mention of the numbers of women using the pill and the thromboembolic complications, which result from its use.

The major contribution of this work seems to me to be the integration of new methodologies such as the bibliographical techniques and the tracing of "idea strands" in the synthetic development of the compounds with the detailed analysis of the synthetic routes used, of the synthetic techniques used, and the naturalistic description of the non-technical factors.

It is evident from this study that the integration of such diverse methodologies leads to a more complete picture of the innovative process and the many factors which affect it.

The evolution of chemical classes

When one considers all the new chemical entities innovated in any year, it is apparent that most of these are not radically new chemical structures, they are modifications of drugs that have previously been successful. This type of innovation is termed "molecular modification"[26] or, more pointedly, "me-too".[27, 28] This process produces therapeutic classes and sub-classes of compounds; members of a class serve similar therapeutic functions, members of a sub-class are chemically similar. Thus, chemical class is equivalent to therapeutic sub-class. For example, "diuretics" are a therapeutic class within which are the main sub-class of the thiazides (16 marketed compounds), carbonic anhydrase inhibitors (3), potassium-conserving compounds (2), fast-acting compounds (2), and other less prescribed groups.

Many interesting questions are raised by this innovatory pattern. I look at two American studies of the process by which therapeutic subclasses emerge - the first describes the "follow-on development process" in diuretics, and the second the evolution of the sulpha drugs.

An early attempt to consider the factors influencing the so-called "me-too" process - that is, the proliferation of drugs with very similar chemical and therapeutic characteristics, was a study by Bernard Kemp on the thiazide diuretics.[29] The main concern of this paper is to establish that the existence of chemical patents means that firms wishing to enter a profitable therapeutic market must produce compounds sufficiently different to avoid the existing patent coverage, yet retaining, and preferably improving upon, the activity of the original "breakthrough"

compound. He takes an economic perspective which views the potential profits in a therapeutic area as determining whether "follow-on" compounds will be marketed, and if so, how many. He substantiates this with reference to the different sub-classes of diuretic of varying profitability by comparing the number of follow-ons in each sub-class and their market shares. He concludes that although follow-ons reduce the market share of the breakthrough compound, in the case of the diuretics the market as a whole has expanded tremendously,* so that these compounds are still profitable. This results in a competitive market which keeps prices low and offers a choice of therapy.

> "The (follow-on) process was successful for diuretics as a therapeutic class ... the preliminary measures of success are the large number of analogs that have been developed, the number of follow-ons, and the speed with which they came on the market."
>
> "In diuretics, however, the follow-on development process must be considered somewhat less successful if its performance is judged by the erosion that the follow-ons caused in the market position of the breakthrough firm. The evaluation of its success in influencing market performance is more speculative and mixed..."[30]

Kemp then goes on to cite his measures of "success". They are: sales of each sub-class, drug prices, maintenance of profit margins, and the development of new, differentiated therapeutic and price options. He continues:

> "Suspending the question of whether the follow-on development process is desirable from a socioeconomic viewpoint, there is no doubt that it is working in two senses: resources are directed into the development of follow-ons and meaningful therapeutic options within the same sub-class of therapeutic agents have been developed, marketed, and sustained by physicians' prescriptions and patients' purchases."[31]

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*The average annual rate of increase in sales 1953-1969 ranged from 146% for the potassium-conserving compounds to 2,150% for the thiazides.

He thus arrives at the conclusion that since the industry continues to produce follow-ons, the benefits to them "probably" exceed the costs.

> "Moreover, in diuretics the unexpected, sizable, and probably unrecognised spill-over effects led to larger benefits than could reasonably be expected ... This dose not necessarily prove that ... the follow-on development process leads to net social benefits. All that can be said analytically at this juncture is that the value of the resources committed to the practice involves a social cost, the magnitude of which is presently unknown ..."[32]

The only clue I can discover to the nature of these effects which spill over is an earlier aside to the effect that:

> "The socioeconomically desirable function of the discovery of new uses, more widespread information, and more rapid expansion of appropriate existing uses may not be independent of the rivalry of multiple firms attempting to get a market niche."[33]

This is a simple consideration of the virtues of an entrepreneurial capitalist market, which in the pharmaceutical sector must be balanced against the social costs of such a system - adverse drug reactions, over-reliance on drugs, unnecessary duplication of products etc. Kemp does not consider these.

For the purposes of this study, Kemp's paper is of great interest for the questions it raises, but the limited perspectives of the paper itself limit its usefulness. He does not state whether the much greater number of follow-ons in the thiazide sub-class compared with the other sub-classes could be related to the greater profitability of the former, despite the obvious relevance that such a connection would have for his thesis. He mentions questions of benefit only to exclude a critical question about follow-on compounds - what is their therapeutic value? Their economic value is obviously relevant, but surely not of

exclusive importance. He even implicitly attempts to use economic data - sales figures - to answer this question, presumably following the dubious logic that if a follow-on compound takes some of the market share held by the breakthrough compound, this demonstrates the existence of "meaningful therapeutic options" within that sub-class. The continued sale of many drugs known to have little or no clinical value is well-known - for example, the long-acting coronary vasodilators which are widely prescribed in angina.[34] The reasons for this so-called "irrational prescribing" are dealt with elsewhere. For example:

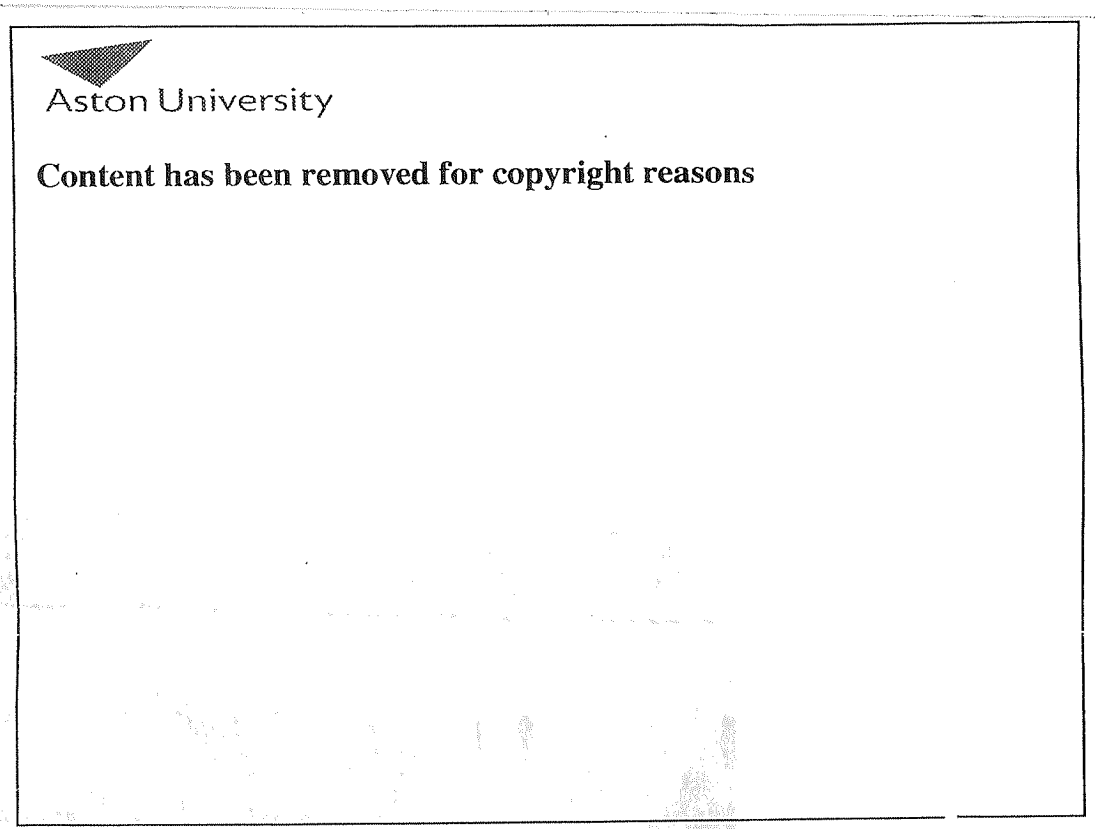
> "Within each sub-class the follow-ons present the physician and patient with differentiated therapeutic options. In some cases they are slightly differentiated; in others, the differentiation is more pronounced. For example, hydrochlorothiazide is produced by three companies under three brand names, presumably by the same process of production resulting in equivalent potency, absorption, and attained blood levels."[35]

The meaningfulness of this particular option must lie in the price difference between the brands, however this is not of great practical significance, since as Kemp later indicates:

> "The market share data indicate that, in practice, physicians have not typically taken advantage of the lower-priced options."[36]

This is not completely fair; many follow-ons do incorporate some advantages over the parent compounds, since part of the process of producing a successful follow-on is to ensure that it is differentiated from the other compounds in the sub-class in ways which are usually minor, but which can be presented as important, for example, potency or duration of action. However, Kemp does not discuss the practical significance of these differences.

The importance of Kemp's paper lies in directing attention towards the most frequent type of innovative pattern in



Source: Kemp, B. A. The follow-on development process and the market for diuretics, in Drug Development and Marketing, ed. Helms, R. B., (American Enterprise Institute 1975).

Source: DeStevens, G., Diuretics, Academic Press, 1963.

pharmaceutics, the small modification, away from the breakthrough discovery with which most individual, descriptive accounts are concerned. He also provides extensive data on drug introductions to support his case, which is a useful source for further work.

Another look at the thiazides illustrates some of the other aspects of the follow-on process (see Table 2.2, Fig. 2.1).

The follow-on compounds differ only in their potency; which is a measure of the amount of chemical needed to produce equivalent effects, and in their duration of action. Although "with the introduction of each of these drugs the major advantage stressed other than an increase in potency has been the more favourable ratio of sodium/potassium that they produce in the urine", apparently this is only true for short-term administration - in long-term use there are no significant differences.[37,38] It seems that a major goal of molecular modification was to alter the electrolyte imbalances brought about by the use of the early thiazides. This does not seem to have been achieved. The advantages of the increase in potency achieved are debatable:

> "Do we need molecular manipulations that allow us to have multiple entries into the same area so that now we give 0.5 mg/dose instead of 50 mg? What benefit is there to increase the per milligram potency when the side-effects are as increased per milligram as the therapeutic benefits?"[39]

> "Apart from other possible advantages of these more potent thiazides, one reason for their acceptance surely is the reluctance of physicians to expose their patients to any larger amount of medicine than necessary."[40]

The duration of action is a much more important marketing consideration, especially in their usage as antihypertensives, which was a major indication from the beginning of the

1960s.* What seems to be important is the ability to promote the compound as "once-a-day therapy". As elaborated on elsewhere, because of the largely asymptomatic nature of treated hypertension, the convenience or otherwise of therapy becomes a major factor in patient compliance. This goal, as can be seen, was quickly reached. As can be seen from Table 2.2, later follow-on compounds show increasing potency and increasing duration of action over earlier ones.

Otherwise, there is no clinical difference between these compounds. The minor differences noted are emphasised by the need of marketers to maintain product images. Their prices have remained stable,** although the follow-ons have been marketed at lower prices than the established compounds. More recently, the production of hydrochlorothiazide by small companies has reduced prices still further.***

Another look at the benefits of the follow-on process is provided by G. H. Schneller of Wyeth Laboratories.[41] His subject is the group of sulpha drugs whose prototype, Prontosil, discovered by Gerhard Domagk in 1935, was the first successful antibacterial drug. He portrays a succession of side-effect problems with these drugs which are solved by successively marketed molecular modifications (=the follow-ons of Kemp). The nausea and vomiting experienced by 25-40% of patients taking sulphanilamide (1938)

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*For example, hydrochlorothiazide, marketed as a diuretic in 1959, was offered: with reserpine by MSD; with apresoline by CIBA; with deserpidine by Abbott — in 1961, as antihypertensive combinations.

**For 19 of 25 diuretic compounds list prices did not change from the time of introduction to 1969.[42]

***Average thiazide price per hundred $5.72 in 1969, $3.94 in 1974.[43]

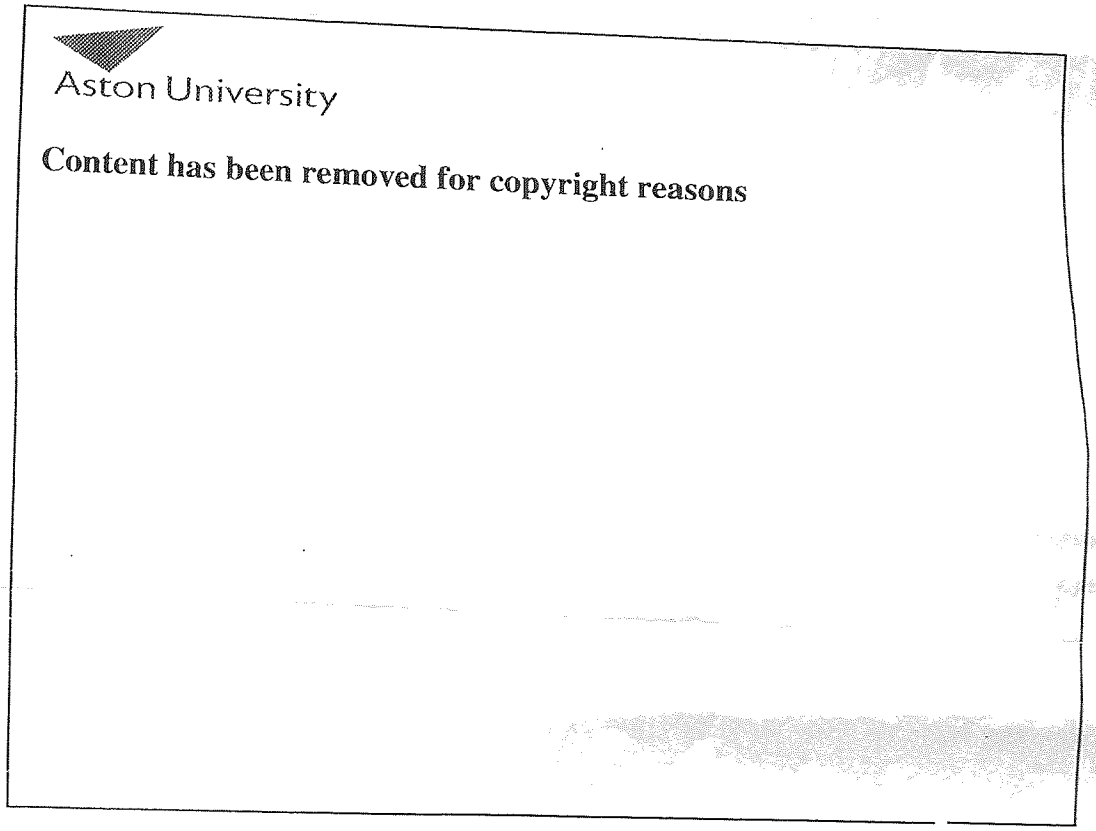

Fig. 2.2 Evolution of a drug class - sulphonamides according to G. S. Schneller

was only experienced by 10% of those taking sulphathiazole (1942), which also showed a wider antibacterial spectrum of activity. The sulphapyrimidines (1946) had still fewer side-effects, and by combined use avoided the occasional tendency for crystals of the drug to precipitate out from the urine causing severe kidney damage (see Figure 2.2).

Schneller then confirms that the drugs superseded one another by examining their appearance in and deletion from the United States Pharmacopoeia and National Formulary (lists of accepted drugs). He points out that varieties of sulphonamide suited to intestinal, urinary, and ocular infections were developed. He also notes that three important new drug classes have evolved out of the sulphonamides - the carbonic anhydrase inhibitors, and the thiazides - these being two new diuretic sub-classes, and the oral antidiabetic agents. He again uses the acceptance of drugs in these classes by the official pharmacopoeias as indices of worth.

From all this he concludes:

> "The history of the evolution of the sulfonamides teaches us that:
> 1) Molecular modification of known drugs is a rational avenue of drug research whose practice has been most beneficial to public health.
> 2) A multiplicity of good drugs in a therapeutic class is indispensable to the optimum therapy of the individual patient."[44]

This is initially a very persuasive argument - a commonly held view in drug industry publications backed up with some convincing data. The accumulation of small modifications together with the feedback of significant clinical observations led to the production of new classes of drugs. But to support such

sweeping concluding generalisations, Schneller would have to show that most of the marketed follow-on drugs are significant advances. He attempts this by stressing the need for a choice of drugs in a class to cater for patients who do not tolerate or respond to the drug of choice, but then undermines his own case by continuing:

> "that (the reason that some patients may not tolerate or respond to the drug of choice) is also why the National Formulary lists 8 sulfonamide (thiazide) diuretics in addition to the 4 listed in the United States Pharmacopoeia."[45]

However, in the literature I have read on the sulfonamides or the thiazides[46, 47] I have not found any suggestions that another drug in the same class should be tried if the patient does not tolerate or respond to the first drug used. Such a possibility would certainly be widely advertised if there was any evidence to support it.[48]

Schneller's use of official pharmacopoeia to show the acceptance of molecular modifications also directs attention away from the vast numbers of sulpha drugs that have been marketed with little or no evidence that they are any better than compounds already available. He quotes 15 sulfonamide modifications as clinical advances - he omits to mention the rest, 30 at least on a brief count (Table 2.3) that have been marketed and the relative therapeutic contribution made by them. A similar situation exists as described in the thiazide subclass, but not to the same extent in the anti-diabetics or the carbonic anhydrase inhibitors. So here Schneller is making out a case for the benefits of molecular modification without considering the costs which are associated with it.

Other accounts, such as those by Struller[49] and Zbinden[50] consider the clinical value of molecular modification more closely.

Zbinden's analysis proceeds as follows:

> "From the chemical point of view, this small crop of closely related compounds derived from over 10,000 new agents does not look too exciting. The question then arises whether conservative variations of the sulfanilamide substituents have provoked significant changes of the biological properties."[51]

A prescription analysis shows the older sulphonamides to be rarely used, and this is used to demonstrate that newer compounds offer advantages:

> "(Taking into account) that experience with salicylates, phenothiazines, barbiturates, and many other agents has shown that small but significant differences between drugs of similar structure and activity may be recognised by the practising physicians who are constantly exploring and comparing the clinical usefulness of older and newer drugs. It is therefore probable that this definite trend away from the older agents indicates that the newer sulphas offer some real advantages in clinical practice."[52]

However, the number of doctors informed and experienced enough to make rational choices between such an array of compounds showing small variations in effects must be small, consisting of specialists, who are unlikely to be numerous enough to affect total prescribing statistics. Other reasons for the adoption of new compounds are also plausible: extensive promotion, effects of use by eminent specialists or simple faith in new remedies.[53, 54]

The newer long-acting drugs have the advantages of lowering the dose, thereby lessening the risk of crystallisation in the kidney, but their toxic effects are more difficult to deal with, and their use is only recommended under special conditions - in chronic infections and for prophylaxis.[55]

From this brief analysis it would seem that the ratio is not as convincingly positive as Schneller would have us believe. It would be interesting to extend the analysis to assess the costs

Table 2.3 Marketed sulphonamides listed in the Merck Index*

Compound	Patent date	Firm
Sulphabenzamide	1941	Monsanto
Sulphabromomethazine	1946	Merck
Sulphachloropyridazine	1957	American Cyanamid
Sulphacytine	1967	Parke Davis
Sulphadiazine	1946	Merck, Sharp and Dohme
Sulphadicramide	1947	private patent
Sulphadimethoxine	1961	ICI
Sulphadimidine	1942	American Cyanamid
Sulphadoxine	1962	Hoffmann-La Roche
Sulphaethidole	1951	Schering
Sulphaethoxypyridazine	1955	American Cyanamid
Sulphisomidine	1945	-
Sulphalene	1963	Farmitalia
Sulphamerazine	1946	Merck, Sharp and Dohme
Sulphameter	1961	Schering
Sulphamethazine	1946	M.S.D.
Sulphamethoyl	1944	-
Sulphamethizole	1948	Lundbeck
Sulphamethomidine	1955	Nordmark
Sulphomethoxine	1967	-
Sulphamoxole	1960	-
Sulphamethoxazole	1959	Shionogi
Sulphamethoxydiazine	1959	-
Sulphamethoxypyridazine	1955	American Cyanamid
Sulphamethoxypyrazine	1963	-
Sulphamoxole	1957	Nordmark
Sulphanilylurea	1946	Geigy
Sulphanitran	1941	-
Sulphaperine	1946	M.S.D.
Sulphaphenazole	1958	CIBA
Sulphaproxyline	1950	Geigy
Sulphapyrazine	1947	-
Sulphapyridine	1938	May & Baker
Sulphaquinoxaline	1946	Merck
Sulpharside	1953	Rhone-Poulenc
Sulphasomizole	1960	May & Baker
Sulphathiazole	1941	-
Sulphathiourea	1945	-
Sulphatolamide	1954	Schenley Industries
Sulphazamet	1960	CIBA
Sulphapyrazone	1961	-
Sulfirane	1950	Sharples Chemicals
Sulfisomidine	1944	Geigy
Sulfisoxazole	1947	Hoffmann-La Roche
Sulfurazole	1947	-

*Those with patents given to firms, plus those seen by Zbinden as "important".

and benefits of the prototypes and follow-ons of the antidiabetics, carbonic anhydrase inhibitors and thiazide diuretics, and in general the costs and benefits of the emphasis on diversity in medicines.

As a step in this direction, information has been compiled from the literature reviewed, and from my own researches. In Table 2.4 are listed some general characteristics of innovation by molecular modification, and in fig. 2.3 a longer-term perspective is put forward based on experience with the sulphonamides.

Table 2.4

Characteristics of innovation by molecular modification

*Resultant compounds are only marginally different in structure from those already available. Typically, the new compounds possess higher potency and longer duration of action - only in very few cases are they genuine therapeutic alternatives if the patient does not respond to, or cannot tolerate the drug of choice.

*Increased promotion generates increased use of sub-class, attention focused on properties which differ between available compounds, not those which are shared.

*Confusion among users thus results not only from the existence of a diversity of compounds, but the emphasis on the diversity of properties.

*Much clinical experimentation is then undertaken to test these compounds comparatively. This generates more data on differences.

*If the evolution of the class is prolonged - that is, if sales are high enough, sequential steps and emphasis on diversity will lead to accentuation of ancillary properties other than those employed in common therapeutic use. If these are recognised as useful, they will be developed and new drug classes will result.

Fig. 2.3 Process of innovation by molecular modification

Sources: Kemp, B. A.[29]

Sprague, F. & Zbinden, G. in Molecular modification in drug design[50]

Perspectives on the general drug innovation process

The NEDO report[56] published in 1973 for the National Economic Development Office was mainly directed at comparing the innovative activity of the British drug industry with that in other countries. It is consequently primarily concerned with economic measures of input and output:

> "On the output of pharmaceutical R & D the study concluded that numbers of new pharmaceutical chemical entities marketed and their total market performance provide the most meaningful measures of innovative success. In addition to total market performance, the report suggests that (a) market share within the product's own therapeutic group, (b) an assessment of therapeutic significance and (c) an assessment of degree of chemical novelty, would be useful subsidiary measures of the value of individual new chemical entities."[57]

In attempting to define appropriate measures of output the report rejected number of patents filed, numbers of compounds screened, and numbers of screening tests performed, as these vary considerably according to the research strategy of the firm.

The methodology of the study is relevant to the present work mostly for its pioneering attempts to assess the significance of new drugs by asking clinical experts to rate them on a five point scale:

Category 1: A fundamental new medicine of major clinical significance.

Category 2: An important new medicine offering substantial advantages for a majority of patients.

Category 3: A useful new medicine offering advantages for a minority of patients.

Category 4: A new medicine offering marginal advantages over previously available therapies.

Category 5: A new medicine offering little or no advantage over previously available therapies.

Pairs of experts assessing the same drugs showed a high degree of agreement, but it was noted that the higher than average ratings given to UK compounds were probably partly due to the fact that the experts participating were all British. A scale of chemical novelty was also mentioned in the study, but this was described only in outline.

From the interviews with Research Directors, the following general characteristics of drug innovation were noted. Four types of research strategy were distinguished:

1. Compounds synthesised because of chemical interest are screened for biological activity.
2. Compounds similar to those which are known to have activity are synthesised and screened for similar or related activities (follow-on).
3. Compounds expected on theoretical grounds to be active are synthesised.
4. Compounds similar to those present in the human body are synthesised and tested, the activity shown is not known in advance.

On the question of "rational", that is, theoretically based versus "empirical" (more or less random screening) research, the report comments:

> "In practice, companies' research programmes strike some balance between these alternative approaches which are in many ways complementary to each other. Thus there is no clear-cut differentiation between companies simply synthesising or screening large numbers of compounds and others pursuing a purely rational approach; ... (a) more prevalent point of view (was that) the purely rational approach to pharmaceutical research was simply too risky because of the present inadequate state of knowledge of biochemistry and pharmacology in most of the remaining problem areas of medicine. Thus any company following a rational approach to a particular problem was prudent to back this by some purely empirical work also." [58]

The report analysed the different types of innovation as follows:

> "There is a very wide variation in the degree of significance of new medicines marketed. At one extreme, there are the new brands which are virtually identical to existing formulations; at the other there are entirely new chemical or biological entities providing fundamentally new therapeutic or preventive approaches. There are, in fact, relatively few examples at either extremity of this spectrum ... Numerically, the majority of new medicines put on the market fall in one of two categories: first, substantially new and different formulations or preparations of existing compounds; or second, medicines based on new chemical or biological entities representing useful improvements in therapy rather than a breakthrough."[59]

The NEDO report, then, defined a key problem area in the study of drug innovation, that is how the significance of new products can be assessed. For the purposes of the report, economic criteria such as sales volume were adequate. For studies attempting a broader analysis where purely economic criteria are less significant, however, the areas outlined by the report are among the most problematic.

Another perspective on the drug innovation process is provided by Schwartzman in his book Innovation in the Pharmaceutical Industry.[60] This looks at the process primarily in an econometric manner, but also has some useful insights into influencing factors.

Schwartzman emphasizes the limited amount of basic knowledge available, and hence the importance of a working hypothesis modified by experiment and observation. This hypothesis is only partly substantiated if compounds can be found which have the desired effects in animal tests, as humans often react differently to the drug. Thus there is much trial-and-error involved. This necessitates good communications between workers in different disciplines:

> "Drug discovery is essentially a feedback process between applied research in therapeutics and fundamental biological knowledge ... the history of drug discovery is replete with instances where a finding of applied research has been the touchstone for significant advance in the understanding of biological mechanisms."[61]

Schwartzman goes on to state that this is the primary source for new drugs, and the most useful area for investment and study by the pharmaceutical industry. He adopts a linear innovation model starting from the development of a hypothesis, that is, discovery-push in Langrish's classification, although in other parts of the book he emphasises the extent to which innovation can be managed by firms seeking to enter profitable therapeutic fields.[62] Both, however, stress the importance of the technological input into the innovation process.

The effects of innovation are analysed by Schwartzman in mainly economic terms, that is sales, rate of return on innovation expenditure, rather than estimates of their therapeutic effectiveness.

Summary

What can be drawn from this review of the most relevant literature? It is apparent that for the most part single-drug studies and studies of drug classes employ different perspectives.

Single-drug studies can convey the atmosphere of research directly, using participant interviews, and are able to analyse this and other detailed material to bring out the influencing factors, and the technological and scientific roots of the studied innovation. However, because they concentrate on "successful" innovations, the context in which the therapy was successful and in what ways it was so are often not adequately dealt with.

Because original drugs are studied, the scientific basis is more significant than it would be for a representative sample of all drugs. For this reason and because scientific information is more readily preserved and accessible, this aspect tends to be over-emphasised.

Studies of more "normal" patterns of innovation, that is, those involving some element of modification of currently available drugs emphasise different factors. Feedback from clinical use is obviously more important, thus the scientific basis is not considered in such detail. The effects of such follow-on compounds are difficult to estimate in anything other than simple economic terms.

The separation of these two different types of study is unfortunate as much is to be gained by the possibility of comparing the innovation of a single successful prototype drug with the follow-on innovations that subsequently take place. It is in this area that the present case-study is situated.

2.0.2 Analysing the innovation process - a social perspective

> "The most important thing is to squeeze out through ingenious manipulations and sensitivity analyses some new form of understanding that enables us to look at all dimensions of the problem."
>
> G. Strasser

What are the aims of this study of drug innovation? The production of new drugs is an activity which has many very important effects on society. The far-reaching nature of these effects are alluded to in many of the articles or papers written about the pharmaceutical industry. They have only been considered and evaluated seriously and systematically, it seems to me, in studies that look at the industry and the drugs it produces as a whole. This is obviously because it is easier to get and analyse data on total drug sales, total drug use, and total drug introductions and the social impacts of these, than it is to do the same for a therapeutic group, chemical class or individual drug.

As we have seen, studies of single-drug innovation do not usually consider the effects of the innovations they study in any detail.

However, case-studies on the innovation of these small groups can produce important information which is beyond the reach of a larger-scale study. Only at this level can we find specific examples to substantiate or undermine more general theories, or suggest new ideas. Only at this level can we analyse the motivations of researchers, the influences of economic pressures, and the nature of company decision-making, which any serious study of drug innovation must consider.

Mowery and Rosenberg make the same point about economic studies of innovation:

> "Until quite recently economists devoted little attention to the factors which influence the rate and direction of innovation. Much of the formal economic theory on technological change is really concerned with the description of the consequences of technological innovation at a very high level of aggregation or abstraction. Little consideration has been paid to the study at a less aggregated level of the specific innovative outputs of industries and firms, and the forces explaining differences ... Serious empirical work on biases and inducements in the innovative process at an industry or firm level of analysis is even more conspicuously lacking."[1]

Thus, single-drug studies have often viewed drug innovation as though it were wholly concerned with the production of original, successful compounds. Many of them are still set in an intra-scientific viewpoint, which looks at the achievements of 'great men', and pays relatively little attention to the social context in which these great men worked, and none to the social factors that influenced their work.

How are the results of these small-scale studies to be integrated with the more condensed data from the larger? If the former are cast within an individualistic format, with no consideration of wider effects, then this is not really possible. But there is an obvious need for such an integration; we find it very difficult to make the connections between particular activities and the wider effects of these 'in the world', especially when the time lag involved is many years, but these connections are important from the point of view of directing innovation in a socially useful fashion.

If these connections were made, the influence of those explicit directing factors that already exist, such as company R & D investment decisions, and state regulatory requirements could be analysed, the role of implicit factors such as the definition of disease by drug-related criteria might become clearer, and

possible new directions in the relationship between science and medicine and their implications might be spelled out.

Some small-scale studies do attempt some kind of consideration of the effects of the innovations they look at, but at most, these take the form of a brief review of the clinical literature on the drug and a couple of expert opinions, rather than an assessment that, for example, takes account of the difference between clinical trials and everyday use. Going further than these assessments is problematic. How widely does one try to follow the effects? What criteria can one use to evaluate these effects?

This case-study attempts to situate the innovation of the beta-blocking group of drugs within the context of the evolution of the major sources which made the project probable, and the ramifications of the many effects which it had. Its central concerns are the social inputs and impacts that situate the innovation process.

The most immediate social inputs are the social relations within the innovating company, initially between the workers within the project team, subsequently between the project team and clinical and commercial departments. The technical events which occur in the innovation process have little meaning unless the social relations between the participants are understood to some extent. These events are viewed differently by each of the participants, and it is in the course of interaction between them that the full significance of technical successes and failures is brought out, and then acted upon.

The most immediate social impacts are the effects of the therapeutic use of the new drug. Ideally, one would want to consider wider social networks, such as those in which the use of previous

drugs creates a concept of what characteristics new drugs might have, and those in which the new knowledge arising from the use of the new drug alters our conceptions of the diseases they are used to treat.

It may be that analyses of the drug innovation process which are primarily oriented towards the consideration of its social aspects might provide a unifying focus for study in an area which has been characterised by the use of a variety of incompatible approaches, as Nelson and Winter (1973) point out:

> "There is a rapidly increasing literature on the nature of the research and development process, the links between science and invention, the sources of invention (large firms, small firms, private inventors), the kinds of organizational and other factors associated with successful choice and carrying out of a project, etc. Other studies have probed learning phenomena and, more generally, the way technologies (or a particular technology) evolve over time. A significant literature exists on organizational factors influencing the decision to adopt an innovation. Diffusion of innovation has been a fertile research field in several disciplines ... unfortunately these studies add much less than we would hope to our understanding ... the basic problem was stated briefly earlier - by and large, these studies have proceeded within disjoint theoretical frameworks. There are virtually no conceptual bridges between Project SAPPHO which probes at conditions for successful innovation, the Jewkes, Sawers and Stillerman study of the sources of invention, and studies by economists such as Mansfield and Griliches on diffusion ... our knowledge is balkanised. We cannot, in general, bring together several different bodies of analysis to focus on any one question, or tie together the various pieces to achieve an integrated broader perspective."[2]

Any study which would attempt to do this must necessarily adopt an interdisciplinary approach:

> "(the analysis of technological change) is a phenomenon having dimensions which do not fall conveniently within the boundaries of any single academic discipline. Research upon the subject must, necessarily, be inter-disciplinary in nature. The exhortation to undertake interdisciplinary research, we all know, is a familiar one - just as we also know how infrequently it has

> been undertaken successfully. The crossing of disciplinary boundaries is likely to be a hazardous operation ..."[3]

This account has drawn primarily from two disciplines, the sociology of science, and technology assessment.

Much of the material that has influenced the study comes from the area of the sociology of knowledge, more particularly the perspectives on science found in the journal Social Studies of Science (previously Science Studies), since these are particularly involved in dealing with disjoint frameworks, and the study has come to focus on the interactions of a diverse body of evolving scientific expertise in the study of adrenergic mechanisms with the conflicting requirements of the pharmaceutical industry and the craft of medicine which has evolved with it.

Although most contributions look at intra-scientific factors such as growth of disciplines, histories of controversies, and the nature of scientific elites, there are a number of relevant areas. Work on scientific innovations includes studies of their reception by other scientists, their diffusion into public consciousness, and the methodology of their study.

Technology assessment has been defined as

> "the process including primary cost-benefit analysis of short-term market-place economics, but particularly going beyond these to identify affected parties and unanticipated impacts in as broad and long-range fashion as is possible."[4]

The way in which the analysis of the effects of beta-blockade has been conducted is derived from this tradition, as is also the source-innovation-effect structure of the case-study. It is characteristic of this interdisciplinary discipline to try out new techniques of analysis, some of which have been used in this study.

The beta-blocker innovation at ICI was selected for study for the following reasons.

1) The beta-blockers are generally agreed to be the most important advance in drug therapy in the field of heart disease for the last 10-15 years.[5] An assessment of their therapeutic impact would therefore be an important contribution.

2) The increasing use of these drugs for long-term therapy is an example of a more general trend in drug therapy from short to long-term interventions. Taken with the occurrence of severe adverse effects, and subsequent withdrawal of the beta-blocker practolol (Eraldin), this makes the problem of risk/benefit evaluation especially critical.

2) After the success of the first marketed compound, many others have been marketed, which have been said to show only marginal differences in clinical use. This process is similar to the development of other successful drug groups such as the diuretics and sulphonamides. It was hoped to analyse the factors involved in this follow-on process and its effects.

4) Because the innovation was made at ICI, it was thought that detailed information, such as that gained by interviews, would be more easily obtained than would be the case if a foreign company had been responsible.

The approach adopted was to obtain participant accounts from all the workers who played a major role in the innovation process, and to orient other information around this basic data. In order for the accounts to accurately reflect participants' views, much background literature was assimilated before the interviews. At the interviews my aims were stated as follows:

"The aim of the project is to get behind the rather polished and linear view of the process expressed in most retrospective accounts and to get a more detailed picture of the interaction of the variety of scientific and non-scientific influences involved.

Some of the specific points that we are interested in include:

the relationship of decisions on therapeutic need and market potential in the general cardiovascular area to the initiation and development of the beta-blocker project;

the similarities and differences of approach of the different scientific specialisms bearing on the research;

the significance of inputs from scientific and medical work external to the firm (academic, other industrial work);

the effects of organisational approaches to research (e.g. relative emphasis on autonomy or accountability of groups or individuals) on the progress of the work;

implications of changes in the competitive environment following the marketing of propranolol - the decisions to develop and market practolol and atenolol;

the process of identification of therapeutic characteristics, such as cardioselectivity as research goals;

approaches to ensuring the acceptability of a novel therapy to the medical profession."

In interviews I assumed the role of "informed outsider", attempting before anything else to gain what Mulkay has described as "rapport" by showing appreciation of and interest in the technical problems, before asking about social factors or individual viewpoints.[6] I used a check-list of points to be covered before each interview, based on published material and other interviews. Most of the interviews were taped and transcribed to produce verbatim quotes. Most difficulty was experienced with interviews with hospital doctors, who were not willing to share any awareness of problems with beta-blocker's clinical use, nor to discuss the evolution of its use. Thus participant information on clinical use has been lacking.

The sequence of events in the innovation process was derived

from the interview data and from two other sources: six-monthly research reports written by project leaders to which I was kindly given access by ICI, and patenting information on the compounds discovered and tested. When accounts of key events in the project differed, which they often did, this is recorded, rather than attempting to find a consensus view. This procedure is similar to that described by Woolgar.[7]

From this basis of an account of the social and technical events in the innovation process, study was extended to the sources of this process, and the effects which it had.

The account given of the sources is largely concerned with the theoretical basis of the project, receptor theory. It was considered important to analyse the consensus history, and examine the influence of drug usage on the evolution of receptor theory, as there was reason to believe that this influence was significant but had not previously been described.

Original articles were studied in the context of contemporary material on the innovation and use of relevant drugs, and other technological advances, and connections were the object of further study. This method is similar to that adopted by Swazey[8] but with more emphasis on extra-scientific material. Review articles were found to be an important source of links and perspectives.

Information about clinical use was readily available from the clinical literature, but for the purposes of examining clinical development had to be supplemented by information gained by personal inquiry of participants. Prescription data provided by the DHSS was used to follow the use of different follow-on compounds. Describing the follow-on process necessitated study of the chemical

and patent literature for description and dating of the synthetic work undertaken by companies. Study of the way in which the novel therapy of beta-blockade was introduced, and what factors were involved in its slow acceptance, involved detailed analysis of early clinical papers and reviews, coupled with comparison of participant accounts.

The way in which the effects of beta-blocker use were analysed is described in section 2.4.

Perspectives on Section 2.1

"If we were to awaken a man from sleep by shouting in his ear 'Medicine depends on basic scientific thought' he might unthinkingly say 'Amen!'"

Owsei Temkin[1]

"The study of scientist s' every-day research activity, then, involves the understanding of development in the sciences in two ways. First, it is impossible to make sense of it without comprehending the particular 'official history' that is currently accepted. Second, the way that history is used and integrated with the outcome of the research affects future conceptions of development in that field".

A. Bitz, A. McAlpine, R. D. Whitley[2]

"It is interesting to examine some of the expressions used in describing or defining the receptor a half-century or more after Ehrlich. In a conceptual sense there has been surprisingly little change. Furthermore, we have made relatively modest advances in understanding events at the molecular level of receptors considering the large number and variety of new drugs and other biologically active compounds discovered in this period."

C. J. Cavallito[3]

"Thus far, the biochemistry of adrenergic receptors has constituted a field in which our ignorance is matched only by the lack of sound and tested methods of approach."

B. Belleau[4]

Section 2.1 Drug innovation and receptor theory

The first published comment on the theoretical history of the concept of beta-blockade was in an editorial of the British Medical Journal concerning the clinical trials of pronethalol, in November 1963:

> "The physiological basis for the use of this drug lies in the alpha and beta adrenergic receptors. As so often, Sir Henry Dale was first in the field here. He used the concept of a special receptor site for adrenaline when he recognised that ergot blocked only the 'excitatory' actions of adrenaline and had no effect on the 'inhibitory' actions. R. P. Ahlquist, in studies on sympathomimetic amines, introduced the term alpha and beta receptor..."[1]

This claim for an intellectual pedigree stretching back through Ahlquist to Dale is very close to the simple and seductive idea that what has occurred is a progressive refinement of scientific theory on this subject. The implicit theory of 'progressive refinement' is a frequent prelude to many general reviews of beta-blocking drugs, for example:

> "Langley in 1905, first suggested that adrenergic receptors contained inhibitory and excitatory receptor substances. This concept was supported by Dale's observations a year later that while the excitatory actions of adrenaline were blocked by ergot, the inhibitory ones were not, suggesting the existence of two types of adrenergic receptors. Ahlquist extended this concept when he studied the effect of six sympathomimetic amines on a variety of adrenergic responses."[2]

This kind of historical background concentrates on the contributions made by individual scientists to the development of the receptor concept, and retrospectively reinterprets their work in the light of later developments (for example, implying that Dale supported the concept of receptors; he did not[3, 4]). It is also selective in the individuals to whom it refers, passing directly from Dale in 1906 to Ahlquist in 1948.

This lineage can be traced to its origin in Ahlquist's key paper of 1948[5], and the importance given to this by Black[6]. Some reasons for the tendency to present scientific history in this way were given by Gilbert[7], who connects the style of scientific papers with the philosophy which underlies them:

> Truth is determined by the constitution of nature; anyone who knows the proper procedures can learn the truth. Since the subjectivity of the researcher should have no influence on the truth, his identity should not affect his report....the report he relays must therefore be indistinguishable from those provided by other scientists who have learnt to see the truth correctly. Consequently, the scientist can demonstrate the veracity of his reporting by showing that he has followed the correct procedure for uncovering the truth..."

He goes on to state that cited papers contain adopted or approved theories and procedures, which thereby justify the citing paper's claims.

The present case does seem to illustrate some of these features. The reference to early experiments by Dale, who later became a key figure in physiology as an authorative precursor, though as Black later admits, 'he never gave receptor theory the benefit of his huge scientific support'[8]. The way in which Ahlquist's work is presented as following naturally from Dale's work gives little consideration to the intervening 40 years of scientific development. But other elements are also important in this case. Firstly, the reliance in these accounts on unconventional scientific theories in order to support the new technology with which they are involved may result in a special need to root the new views and methods in the 'established wisdom'. Secondly, this partial approach to scientific history is not found in the papers introducing the new technology, but in the editorials and 'popularising' writings of others.

Interestingly enough, Black himself totally repaints the theoretical lineage in an unconventional paper entitled "Ahlquist and the development of beta-adrenoceptor antagonists", written for a conference on propranolol in 1976[9] ;

> Summary
> "The power and fecundity of Ahlquist's original concept of alpha- and beta-receptors can now be seen in dramatic contrast to the obfuscation and sterility of the then contemporary theory of two "sympathins". But when his famous paper appeared in 1948, pharmacologists apparently were not ready for the new idea. Receptor theory was perhaps too esoteric (Dale, one of the great pharmacologists of his time, studiously ignored it)....The relationship of the new idea to Ehrlich's older ones, with consequent utilitarian implications, was overlooked."

The historical analysis in this paper contrasts greatly with a generalised account of scientist's histories given by Mulkay (1974)[10]:

> "when one examines participant's historical writings, on the whole they tend to miss out the slow, groping development which often occurs. Instead, they tend to take on a fairly stereotyped form; they note the major discoveries which occurred early on, and then they skip quickly through to the current framework of knowledge - as if all that happened in between was part of an inevitable progression."

Or does it? True, there is some suggestion that changes in the perceptual framework through which physiologists and pharmacologists view their work (analogous to the 'paradigm changes' of Kuhn), affected the acceptance or rejection of Ahlquist's key paper on adrenergic receptors. But the old views are still considered 'wrong', and so unworthy of serious mention, as will become clear later. It seems that even the imaginative participant scientist's viewpoint is limited by the fact that his belief in the rightness of the current framework of science seems a necessary part of his practice.

To summarise, then, the history of the events leading up to the acceptance and use of receptor theory in the production of new

drugs, as found in the scientific literature is sketchy, and fails to tackle the question critical for this account:* what are the connections between the introductions of experimental and therapeutic drugs in the adrenergic area and the evolution of receptor theory? But if the usefulness of the histories prefixed to scientific papers is flawed by their symbolic rather than realistic content, the restricted perspective of academic histories of medicine is not much more helpful. Most of these are more concerned with analysing the evolution of the ideas of 'great men' than the spread of those ideas.

For example, Parascandola and Jasensky's study of the 'Origins of the Receptor theory of drug action'[11] contains no discussion of the scientific debate at the time when the theory was first constructed, nor any consideration of the social influences on the developing scientific programme. All the material used is from the writings of the two 'great men', Ehrlich and Langley, so the reader gets no perspective at all on their work.

For the purposes of this thesis, it is not intended to do more than sketch the outlines of what an adequate history of the development of science in this area might be like from the point of view of the influence of drugs, given that most of the general accounts available approach the area from a different perspective. It would attempt to make the connection between the use of blocking compounds as tools for theoretical development in physiology, and the drug-oriented content of these theories. It would consider the effect of the feedback from the sporadic therapeutic use of

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*but for the significance of scientific histories to an understanding of current scientific activity see Bitz et. al.[12]

these compounds. It would consider correspondences between successful profitable therapeutic areas and concentrations of talent and effort on related areas in pharmacology and physiology. The information needed to make these connections and analyse their implications is scattered very widely in the literature on the subject. Background material on what the accepted views of workers in different scientific specialities were at different times is particularly important and elusive.

The concept of beta-blockade rests fundamentally on two areas of scientific investigation; the sympathetic nervous system and the interactions between drug or hormone and cell. These areas, however, are not distinct. The drug-receptor concept was applied to the sympathetic nervous system (S.N.S.) very early on (by Dale) and it was through a later interaction that beta-blockade came into being.

The outline will start with the work of Ehrlich and Langley, as both the scientific and academic histories do. The conclusion of the paper on 'The origin of Receptor theory' is that:

> "The concept of drug receptors was first clearly stated by J. N. Langley in 1905, and Paul Ehrlich in 1907. Langley's concept developed out of his investigations on the actions of nicotine and adrenaline on the body, which were occasioned by his interest in the sympathetic nervous system. Ehrlich's theory developed out of his studies on drug resistance, which were a result of his interest in the chemotherapy of trypanosomes. While their ideas were developed separately, and from different sources, their thoughts did interact. Langley recognised the similarity of his concept of receptive side-chains of protoplasm to Ehrlich's side-chain theory of immunity, Ehrlich admitted to being influenced by Langley's work in his decision to apply the side-chain or receptor concept to drugs. For Ehrlich the theory formed the theoretical basis for his work in chemotherapy."[13]

So from this account it appears that receptor theory arose from the first work which had to account for the selectivity shown by some compounds; the selective blocking of nerve impulses to muscles by nicotine studied by Langley, and the selective staining of protoplasm by dyes studied by Ehrlich. However, this use of toxic compounds in physiology can be traced back further, to the work of Claude Bernard. In his work on curare he emphasized its ability to discriminate between sensory and motor nerves,

> "Curare performs a physiological analysis which is not limited to dissociating the properties of the muscular system. It distinguishes between the properties of motor and sensory nerves, since we find that it maintains the properties of the sensory nerves, and destroys those of the motor nerves."

and refers to toxic substances as

> "Kinds of physiological instruments more sensitive than our mechanical means, and well suited to act, so to say, in dissecting one by one the properties of the anatomical elements of the living organism".[14]

The effects of adrenaline on the body were first discovered in 1894 by Oliver and Schafer. The extract of adrenal gland which they used had a marked ability to raise blood pressure. Adrenal extract was investigated by the first academic pharmacologist in the USA, J. J. Abel (appointed Professor of Pharmacology at the University of Michigan in 1890), who began work around 1892. In 1897 he succeeded in separating out the benzoyl derivative of adrenaline, and showing its great pressor activity. J. Takamine, a Japanese chemist also working in the field derived the pure hormone, which he named adrenaline. This was the first hormone to be isolated. Takamine was working as a consultant for Parke-Davis and later became scientific director. He patented the product and the processes of extracting it from the adrenal glands of animals,

and beginning in 1900, Parke-Davis marketed it under the trade-name of Adrenalin*. Adrenaline was used in shock, as a nasal decongestant, bronchodilator in asthma, containing agent for local anaesthetics (it delays them from leaving the injection site by constricting the blood vessels, and also decreases the risk of haemorrhage) and as uterine relaxant in obstetrics. This wide usage necessitated a better production process. The first chemical synthesis of a natural hormone was achieved in 1904, by F. Stolz at the Hoechst Dye Works. Hoechst then began marketing adrenaline under the name of Suprarenin.[15-17]

In the early 1900's there was much interest in the developing discipline of pharmacology in the similarity between the effects of sympathetic nerve stimulation and those of injected adrenaline (the parasympathetic transmitter, acetylcholine, was described by Hunt and Taveau (1906) and characterised by Dale (1914)). The identity of these sympathetic responses was suggested by Elliott in 1903, and shown by him in 1905.[18]

Meanwhile, both Ehrlich and Langley were elaborating their receptor concepts. In 1905 Langley published work that he had done on the effects of adrenaline on intact and denervated muscle. From various experiments he concluded that the compounds did not act on the contractile substance of the muscle, but on an intermediary:

> "I take it that in general an increase or decrease of function in a cell brought about by chemical or nerve stimulation depends on the presence in the cell of different receptive bodies ... so we may suppose that in all cells two constituents at least are to be distinguished; a chief substance which is concerned with the chief function of the cell as contraction or

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*The patents were challenged by a rival company on the grounds that since the hormone existed in nature, it could not be patented, but the challenge was quashed.[19]

> secretion, and receptive substances which are acted upon by chemical bodies and in certain cases by nervous stimuli. The receptive substance affects, or is capable of affecting the metabolism of the chief substance."[20]

Here Langley makes an explicit distinction between the receptor and the rest of the cell. Ehrlich was making this distinction at this time with his initial work on chemotherapy; attempting to produce a dye which would have a selective toxic attraction for the 'side-chains' as Ehrlich called them, of trypanosomes.

These receptor concepts could have been useful in clarifying important experimental results recorded by Dale in 1906, but they were then, and were to remain for many years a minority paradigm, a speculation of uncertain value. Dale was working with ergot extracts, looking at their effects on muscle reactions to adrenaline. He found widely differing responses in different tissues. He found that "the cardioaccelerator effect of adrenaline ... is not blocked by such doses of ergot as suffice to reverse the effect on the blood pressure". In his interpretation of the results he stated:

> "Ergot contains a principle which has a paralytic action on the motor elements of that myotrophic structure or substance which is excited by adrenaline and by impulses in fibres of the true sympathetic system; the inhibitor elements of the same being relatively or absolutely unaffected."[21]

In other words, ergot has a selective action, it blocks excitatory effects without blocking inhibitory, and in some tissues Dale observed that a weak inhibitory response usually concealed by a strong excitatory response was "revealed by the discriminating paralysis caused by ergot."

The differential actions of the drug extract were difficult to explain in terms of the current pharmacological theory. The alternative to supposing that different tissues were somehow constitutionally more or less responsive, i.e. some sort of receptor

theory, was to suppose that chemicals exerting selective effects somehow found it easier to reach those tissues they affected, and were barred from those tissues that were unresponsive. This was generally preferred as an explanation as it did not involve postulating the existence of invisible 'receptors' which could discriminate between chemicals. Although the chemical basis for this specificity was known:

> "even in the last century it was seen that the reaction of a receptor with a drug resembled the reactions of enzymes with their substrates, coenzymes and antagonists. The great specificity of structure required for a drug to show activity had well-known parallels in enzyme work ... By 1910 it was known that many enzymes could be blocked by substances whose molecular structure resembled those of their substrates."[22]

the simple theory did not provide a useful explanation of the facts.

Dale's influential later paper with Barger on the structure-activity relationships of sympathomimetic amines discusses the problem of receptors:

> "it by no means follows that the peculiar distribution of the action of nicotine or the sympathomimetic amines depends on the existence of specific chemical receptors in the cells peculiarly sensitive to them, as supposed by Langley. Stimulation may be a chemical process: but the fact that certain cells are preferentially stimulated by a certain group of substances ... may mean that in those cells those substances easily reach the site of action ... (this was the rival "potential" theory, championed by Straub)[23]
> Our results provide no decisive evidence in one direction or another. The theory of receptive side-chains is, indeed, very difficult to apply to our results with such precision as ought to be possible in the case of simple substances of known constitution."[24]

In general Dale felt that the many irregularities in the data could best be accounted for by several influencing variables. The idea that the physical properties of a stimulant, for example, its lipid solubility might affect the distribution of its effects,

rather than its chemical properties, seemed a better explanation, given that not much was known about mechanisms of drug distribution and action.

This choice was undoubtedly affected by the impact of the 'Overton-Meyer rule', which was influential in the early 1900's (proposed in 1899 and 1901). This stated that chemically inert substances of widely different molecular structure have depressant properties on protoplasm, and the higher the partition coefficient of the drug between lipid and water (a measure of its relative solubilities), the greater the depressant action. This was an important factor in emphasising the influence of physical variables on drug effects, and minimising that of chemical variables, especially as the only example of structure-activity correlation had been described thirty years earlier, in 1869 (Crum Brown and Fraser).[25]

Many later workers, however, took Dale's "elements" or "myoneural junctions" as prototypic receptors, so that his work became cited in support of a concept that he never endorsed; for example,

> "We see here the assumption that a given myoneural junction has a fixed function, which may be motor or may be inhibitor but does not vary, and we see also how the assumption facilitates the explanation of the curious phenomena produced by the injection of ergot. Despite the passage of many years since the work was done, there never has been any clear evidence of the distribution of the 2 kinds of myoneural junction. The term myoneural junction indeed was no longer used, but the conception remained that the action of a substance at one particular site was always the same. ... These quotations serve to indicate the view still held that the structure of the receptor, which is regarded as constant at any one place, though varying from place to place, governs the effect of the active substance on the underlying muscle."[26]

The major impact of Dale's 1906 and 1910 papers was to provide a framework for the further investigation of the adrenergic system

using two techniques involving drugs: selective blockade by antagonists, and comparing the relative potencies of a series of agonists.[27] These quickly became dominant methods in pharmacology, and brought to prominence the explanatory use of terms such as "elements".

In this period, there were several factors that were beginning to give receptor theory more prominence, if not respectability. First, there was the success of Ehrlich's work on chemotherapy, the production of chemicals that were selectively toxic to disease-causing organisms, but not to man. The production of Salvarsan, No. 606 in a series of arsenobenzenes, and its clinical success against syphilis in 1910 was an important event for receptor theory. Now it could be seen that these ideas did have practical value. The success of Salvarsan led other institutions to begin work on similar dye or heavy-metal compounds, so now receptor theory had a practical base. But few new remedies were found, and by the end of the 1920's chemotherapy was beginning to be considered as a dead-end.

Many of the remedies produced by Ehrlich and his colleagues although active in animals were not active in many, for example 'Optochin', a derivative of quinine, cured pneumonia in the mouse, but was ineffective in man, 'Trypaflavin' cured trypanosomiasis in mice, but not in man (1911-1912). Two antibacterials produced by a pupil of Ehrlich's were used extensively in the First World War, acriflavine and proflavine, but:

> "The First World War passed without any notable advance in chemotherapy. The control of bacterial infection in the blood-stream was still an unrealized dream, and the feeling was widespread that chemotherapy had promised more than it had given or was likely to give."[28]

However, chemotherapy did seem more successful with protozoal diseases. Two drugs were discovered in 1920 which became the basis of a successful treatment of sleeping sickness (tryparsamide and suramin), and the first synthetic anti-malarials appeared in 1932 and 1933 (pamaquine and mepacrine). Until Domagk's discovery of the antibacterial sulphonamides, though, it was thought with some justification that chemotherapy applied principally to tropical diseases, and so was only of limited interest.

Second, there was the work done in the 1920's by Clark, Gaddum, Schild and others on the mathematization of receptor theory.

> "Classical studies by A. R. Clark in the 1920's had an important impact on the receptor theory, since his quantitative studies showed that binding to receptors obeyed the law of mass action, that the interactions involved were reversible (and therefore non-covalent) and that specificity of action was manifested at very low dilutions."[29]

This work gained a certain acceptability for receptor theory, but also rendered it esoteric, so it still remained a minority paradigm.

It was most likely the high degree of abstraction used by these receptor theorists that lessened the impact of their work. It was felt by many that receptors were purely hypothetical, since no direct evidence of them existed,[30]* and the algebraic equations presented as evidence were simply not convincing.

The production of the first of the sulphonamides in 1932 was the beginning of the golden age of chemotherapy as new drugs were discovered which were effective against a wider variety of infectious

---

*"Adrenaline and related substances were discussed in the 1924 edition of Heffter's Handbook, by P. Trendelenburg. On 164 pages he describes what was then known ... of adrenaline and its closest relatives. The receptor concept was not mentioned in 1924. Five years later, to Dale's analysis of the actions of ergotoxin he writes of receptors: "ist eine unbewiesene (unproven) hypothese."" [31]

diseases. But these were by no means all the compounds that were being produced by the rapidly-expanding dye-drug industry. Aspirin and other anti-fever drugs had high sales, and in the mid-twenties the second adrenaline-like compound first began to be used in medicine. It was ephedrine, which initially was extracted from Chinese plants. It had a greater duration of action than adrenaline, could be given orally in asthma, whereas adrenaline had to be injected, and did not vasoconstrict to the point of ischaemia in the nose, which adrenaline could do.* A synthetic ephedrine was soon produced, and by 1930, 23 companies in 7 countries were marketing the compound. Because tolerance developed both to adrenaline and to ephedrine, there was a considerable incentive to produce new synthetic derivatives.**

But meanwhile, research into the adrenergic system was not proceeding particularly rapidly, as Nickerson points out in commenting on Dale's paper:

> "This field of investigation attracted the attention of many pharmacologists in succeeding years, but it is noteworthy that during the next forty years very few important observations regarding the basic characteristics of this type of pharmacology were made which were not defined with reasonable clarity in this early publication."[32]

Research interest and advances had moved to other fields; the acetylcholine system, the chemical transmission of nerve impulses. But a reconceptualisation of the adrenergic system was made by W. B. Cannon in the early 1930's.

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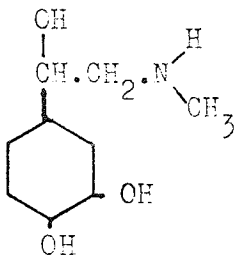
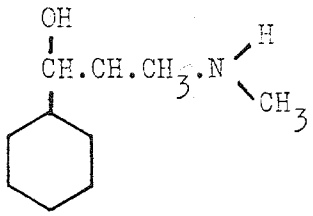
*for a general review of sympathomimetic compounds and therapy see ref.[33]

**By 1939 over 200 compounds having the same basic carbon skeleton as adrenaline had been synthesized and investigated.[34]



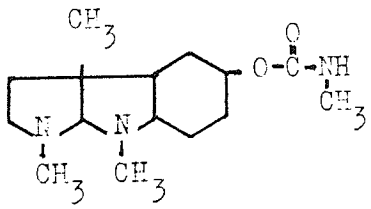
Adrenaline

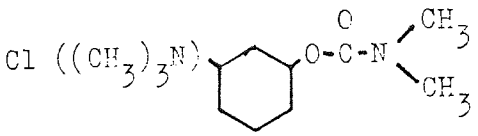


Ephedrine

Fig. 2.4 Structures of adrenaline and ephedrine

Physostigmine





Neostigmine

Fig. 2.5 Structures of physostigmine and neostigmine

He used the adrenergic system as an example of the functional adaptation of the organism to survival, not only in the well-known "fright, fight, and flight" response, in which the body's reaction to adrenaline prepares it for muscular activity, but also in the regulation of the internal environment, for example, blood sugar:

> "The observations ... have revealed a mechanism, or set of mechanisms having the function of maintaining the physiological percentage of blood sugar when there is danger of deficiency. If that percentage falls below a critical point ... neurones of the sympathetic system are set in action, as indicated by increased adrenal secretion. ... Both the nerve impulses and the secreted adrenin have the effect of liberating sugar from the liver into the circulation, and thus tending to restore the disturbed equilibrium."[35]

So a powerful vision is created of the physiological mechanisms of the body reacting to maintain the delicate equilibria which characterise animal life. Cannon also did some important work on the adrenal system. With Rosenblueth in 1933 he did some experiments on the effects of substances released into the blood by sympathetic nerve stimulation, and found excitatory and inhibitory effects in different tissues.[36] They hypothesised that this was due to the 'sympathin' released being converted into two different species, excitatory sympathin in tissues which responded by excitation, and inhibitory sympathin in tissues which responded with inhibition. This theory elaborated on the original discovery of Loewi on frog heart and Cannon and Uridil on mammals that chemical transmission of nerve impulses occurred. This was thought to be adrenaline. Then Cannon's later experiments showed that the 'sympathin' released by the hepatic nerves did not have identical effects to adrenaline. Later work on organ extracts seemed to show the presence of adrenaline, which appeared to support the theory. This theory, although more of an attempt to make the transmitters rather than receptors selective

did explicitly connect with Langley's work: Langley's "receptive substances" would correspond to the substances E and I here postulated."[37]

Cannon's sympathin theory seems to have been regarded as more of a working hypothesis than an accurate description of reality, as evidence against it began to accumulate quite quickly. A number of workers showed in 1937 that the distant effects of stimulating hepatic nerves were better reproduced by noradrenaline than by adrenaline.[38] But the alternative was a big step; to suppose the possibility of selective receptors in cells. A precondition of this was the accumulation of data from the use of more selective blocking agents that were beginning to be used (see fig. 2.6), and an interpretation of this data by studying the relationships between structure and activity. This was done to a greater extent in the cholinergic system than in the adrenergic, for example Stedman's work on physostigmine (also known as eserine) which blocks the enzyme which deactivates acetylcholine.[39]

He concluded that it was the methylurethane group of physostigmine that was responsible for its action, and he prepared derivatives of phenol which included this. A charged group was necessary and was provided by the addition of an ammonia-like group. This resulted in Neostigmine which had fewer side effects.

The competitive action of other acetylcholine blockers was related to their structure by Ing in 1936. In 1940 Woods showed that p-aminobenzoic acid when added to culture media would antagonise the antibacterial action of sulphanilamide, and attributed this to the structural similarity of the compounds. (sulphanilamide is incorporated into the bacterium instead of P-ABA and is non-functional). So it became clear that at least certain sorts of blockade were related to small changes in chemical

structure.[40] The pharmacological technique of relating structure to activity became a major tool in the developing drug industry.

So the further development of receptor theory was dependent on the development of more sophisticated analytical techniques involving drugs; a process aided by the development of the drug industry.

In his potted history of beta-blockade, Black castigates Cannon's theory as 'baroque' and consisting of 'obfuscation and sterility'. He also points out an anti-therapeutic element in Cannon's homeostatic concepts:

> "apparently imprinted the minds of generations of biologists with images of a system beautifully adapted to survival. ... There was not much room in these theories for the idea that the activity of the sympathetic nervous system would not necessarily or always (in cardiac disease, for example) have survival value." [41]

The implication of these criticisms is that Cannon's sympathin theory was stultifyingly complex merely to explain the results of one experiment, and that a holistic theory is necessarily an anti-therapeutic theory.* But what the sympathin theory attempted was to provide a generalised, flexible framework for further work on the adrenergic system, and it would seem that it was in that spirit that it was taken. It is perhaps unfortunate that such ideas can outlive their usefulness simply because being flexible, they are

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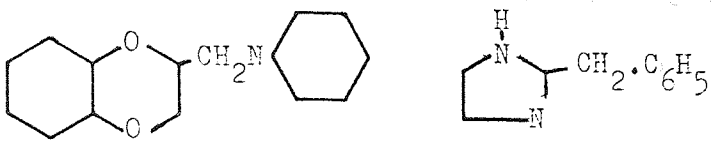
*Ahlquist himself was capable of "ignoring" occasional experimental disproofs when his theory was at stake as is shown by the following quote commenting on a proposed addition of gamma and delta-receptor classes:

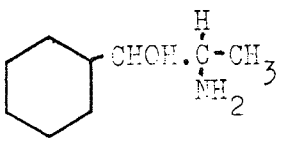
> "However, since experimental design, deliberate or unconscious, can produce results that will support almost any theory, it is obvious that we will favor our previous ideas" (i.e. α & β). [42]



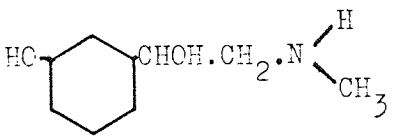
A. Piperoxan

B. Tolazoline

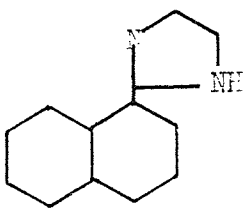
Fig. 2.6 Structures of benzodioxan and imidazoline blocking compounds



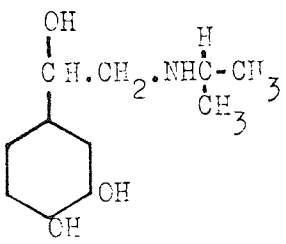
Phenylpropanolamine
synthesised 1909



Phenylephrine
synthesised 1928



Naphazoline
synthesised 1939



Isoprenaline
synthesised 1939

Fig. 2.7 Structures of adrenergic stimulant drugs

difficult to disprove, but this seems inevitable. The 1933 paper also contains the following passage, which runs counter to the criticism of Cannon's theories as anti-therapeutic:

> "Thus adrenin E, if made, could be used to stimulate the heart, contract blood vessels, etc., without inhibiting the digestive process. And adrenin I could be employed to relax spasm of the bronchioles, or alimentary canal, for example, without raising arterial pressure or increasing blood sugar. Such possibilities render important the attempt to make modified forms of adrenin."[43]

Cannon is obviously well aware of the therapeutic implications of more selective drugs; a holistic theory seems rather to be anti-interventionist than anti-therapeutic, that is it discourages thinking about or therapy of a disease as a manifestation of a single cause, but does not discourage more integrated forms of therapy.

The atmosphere in the late 1930's is summed up by Ahlquist:

> "the following terms were regarded as almost synonymous: sympathetic, adrenergic, vasoconstriction, pressor, and decongestant. Chemists made new compounds structurally related to adrenaline, and pharmacologists tested them for blood-vessel constricting effects. If the drug raised the blood pressure (pressor response) it was marketed as a decongestant for stuffy noses."[44]

So, although new varieties of adrenergic blockers had been found, the benzodioxanes and the imidazolines, their relative unselectivity did not greatly advance the cause of receptor theory, since there were not many perceived anomalies in the current explanatory framework. In 1940, however, Konzett's work on isoprenaline complicated the picture. This sympathetic amine did not produce a pressor response or vasoconstriction. It did the reverse. "This anomalous behavoour was most difficult to explain to medical students".[45] With the gradual breakdown of the sympathin theory, there was much confusion.

Two factors clarified this confusion. The first, in 1945, was the description of a new series of specific, effective and long-acting adrenergic blockers, the beta-haloalkylamines. They were quickly taken up as useful tools:

> "Since the beta-haloalkylamines produced essentially complete blockade of contractions of smooth muscle in response to adrenergic stimuli (adrenergic agonists or sympathetic nervous stimulation) without blocking the increase in rate and force of heart contractions in response to the same stimuli, they clearly differentiated between the adrenoceptors mediating excitatory responses in smooth muscle, and those mediating excitatory responses in the heart."[46]

The second, was the characterisation of the transmitter released from sympathetic nerves as noradrenaline in 1946 by von Euler. So the confusion over which of the large number of sympathomimetic amines were natural transmitters began to abate.

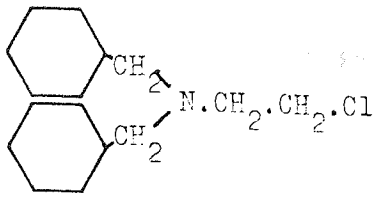
With the new blocking agents it became possible to investigate the sensitivity of tissues to adrenergic stimuli much more precisely than had previously been the case. A general consensus emerged that

> "the chronotropic and inotropic ... responses of the mammalian heart are not effectively blocked by the classical adrenergic blocking agents."[47]

The characterisation of noradrenaline as the sympathetic transmitter had finally demolished the factual basis of the sympathin theory; what remained was the heuristic framework that the theory provided, a way of seeing that was shortly to be challenged.

The research project involved was an investigation into the ability of sympathomimetic compounds to reduce the tone of uterine muscle, and thereby alleviate period pains. Ephedrine had already been used for this purpose because of its long duration of action. R. P. Ahlquist, working at the University of Augusta, Georgia,

A



B

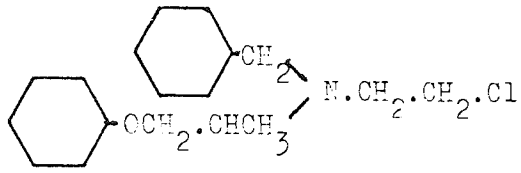


Fig. 2.8 Structures of the beta-haloalkylamines
A. Dibenamine
B. Dibenzyline, phenoxybenzamine.

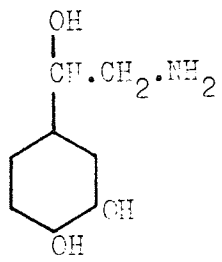


Fig. 2.9 Structure of noradrenaline

had developed a test model, but found some unexpected results:

> "In a search for a substance that would effectively prevent the spasmogenic action of vasopressin on the myometrium, we studied several compounds related to adrenaline. Although none were found suitable, some were noted to have effects that seemed contradictory to our naive ideas of the general relationship between chemical structure and adrenergic action."[48]

When he compared the potency of a number of sympathomimetic amines on different tissues, Ahlquist found that two distinct series of effectiveness emerged. One concerned mostly excitatory responses, such as vasoconstriction, and dilation of the pupil. For these functions adrenaline was most effective, followed by noradrenaline, then isoprenaline. The other series concerned mostly inhibitory responses, such as vasodilatation, but also included myocardial stimulation. For these functions the order was isoprenaline, adrenaline and noradrenaline.

In his paper published in the American Journal of Physiology in 1948[49] Ahlquist proposed that these two sequences were the result of the existence of two different adrenergic receptors, alpha and beta. He saw this theory as totally antagonistic to the sympathin theory, the evidence for which he attempted to reinterpret.

> "This concept of two fundamental types of receptors is directly opposed to the concept of two mediator substances (sympathin E and sympathin I) as propounded by Cannon and Rosenblueth, and now widely quoted as a "law" of physiology."[50]

Ahlquist contrasts this situation in the adrenergic system with that in the cholinergic:

> "Fortunately in the case of the cholinergic nerves, there has never been any suggestion that there might be two mediators although both excitatory and inhibitory effects are produced. The diverse effects of the cholinergic mediator, acetylcholine, have always been ascribed to differences in the receptors upon which it acts."

The differences between the effects of sympathin and injected adrenaline seen by them, Ahlquist explained on the basis of the greater vasoconstriction produced by the sympathin (released by prolonged nerve stimulation) tending to restrict its flow round the body. Ahlquist maintained on the basis of his results that adrenaline was the only adrenergic transmitter, mainly because adrenaline was a good stimulant of both receptors - hence Ahlquist thought it most likely to be the natural transmitter. He comments on the paper's initial lack of impact in a reminiscence published in 1973:

> "The original paper was rejected by the Journal of Pharmacology and Experimental Therapeutics, was a loser in the Abel Award competition, and finally was published in the American Journal of Physiology due to my personal friendship with a great physiologist, W. F. Hamilton. Bursting into print in 1948, it was ignored for more than five years except when someone referred to the methods used, or the results obtained, but never to the concept."[51]

Black, in his paper on the role of Ahlquist in the development of beta-blockers asks, "How could such a fecund idea fail to be accepted straightaway?" Ahlquist himself says the paper "did not fit with ideas developed since the 1890's on the actions of adrenaline". Black talks about the anti-receptor theorising of Dale and Cannon:

> "Looking back, his paper can be seen to have been hidden in the long shadows cast by two giants - H. H. Dale in England and W. B. Cannon in the USA."

About Dale he comments:

> "he never gave receptor theory the benefit of his huge scientific support. Dale's attitude seems to have had a powerful effect in delaying the introduction of the idea of receptors into pharmacological teaching, and his impact was still dominant when Ahlquist's paper appeared in 1948."[52]

Black's criticisms of Cannon's theory have already been touched on:

> "this baroque theory was still accepted doctrine in 1948, and Ahlquist's paper had to grapple with it. However, the contemporary combined forces of a theory of multiple transmitters and a low regard for receptor theory as a basis for classifying drug actions were too much for the new hypothesis to overcome on the first round."[53]

What does not seem to be mentioned is another way in which the paper 'did not fit'. Being written at around the same time as U. S. von Euler was working on the characterisation of the biological sympathetic transmitter, Ahlquist seems to have been led by his wholesale rejection of the multiple-transmitter theory to identify the most active agonist as the only natural transmitter, and attempts to explain away some real differences between transmitters observed by Cannon and Rosenblueth, and subsequently repeated by other workers, along with the considerable amount of speculation that went with them:

> "The evidence presented strongly supports the concept that adrenaline is the only sympathetic adrenergic mediator ... Adrenaline ... is the most active substance on the alpha receptor and almost the most active on the beta receptor. It is, therefore, the one amine which is both the best excitatory agonist and the best inhibitory agonist on the effector cells thus far tested. It is fundamentally the most logical substance to be the sympathetic neuro-hormone since all histological and embryological evidence points to the similarity of the adrenal medulla and the adrenergic post-ganglionic nerves."[54]

To most workers in the field this paper must have seemed as much like an attempt to establish adrenaline as the biological sympathetic transmitter as an attempt to look at the problem of the effects of sympathomimetic amines from a new perspective. For example, his approach is strongly criticised in Euler's 1951 review 'on the nature of the adrenergic mediator' where Euler's comment is:

> "Inferences as to the adrenergic mediators drawn from the relative activity of certain possible candidates for such transmitters may be misleading."[55]

Thus interpreted, it is not surprising that his paper rapidly became 'obsolete' as Euler's use of biochemical techniques to study the occurrence of the various transmitters in different tissues confirmed noradrenaline as the usual sympathetic transmitter, with adrenaline only functional in the adrenal glands.

This was a surprising observation for 'classical' pharmacologists who worked with simple organ extracts and biological tests. Euler's work was representative of a growing trend to the use of more sophisticated forms of chemical analysis in the study of biological systems, which was an expanding discipline in its own right - biochemistry. Organ extracts were treated with different adsorptive agents, paper and column chromatography were used to separate constituents, and fluorescence methods allowed the visualisation of minute quantities of material. With this increasing technical sophistication, many old experimental results were reinterpreted as having been due to impurities.[56]

This biochemical sophistication also opened up other paths of investigation; the study of chemical reactions within the organism, for example. The pathway by which catecholamines are biologically synthesised was first proposed in 1939 (Blaschko). From this base the metabolic connections between noradrenaline and adrenaline became further evidence for noradrenaline's role as sympathetic transmitter.[57]

So Ahlquist's paper was not only outside the dominant tradition of multiple-transmitter theories, but also had one of its major assumptions disproved almost immediately. This is possibly a more important reason why it was ignored.

In the late 1940 s and early 1950 s the various influences favouring a general conceptualisation of the reactions of drugs

with tissues in terms of receptors were becoming more significant. Medicinal chemistry had a strong institutional base in universities and drug companies after the increase in research in the area after the war. The theoretical basis of chemistry had developed to a point at which structure-activity correlations became more logical, and so conceptualisation in terms of receptors had more meaning.

> "The period of the 2nd World War was a turning point in the study of structure-action relationships ... less often were groups assumed to be the direct source of some pharmacological effect, and more attention was given to the physical properties which these groups introduced and maintained. The chief physical properties studies were a) electron distribution, which could facilitate or forbid the combination of a drug with its receptor and b) steric properties which governed access to the correct receptor and a good fit upon arrival there."[58]

Receptor theory itself was becoming more sophisticated, Ariens and Stephenson in the 1940's carrying on the work of Gaddum and Clark in the 1930's.

Classical receptor theory, deriving from A. J. Clark (1937) assumes that the effect of a drug is proportional to the fraction of receptors occupied by drug molecules, and that a maximal effect is obtainable only when all receptors are occupied by the drug. This formulation is, however, inadequate to explain the actions of agonists, though it accounts for the behaviour of inhibitors. Two parameters were introduced to deal with this, affinity, which is a measure of the attraction between the stimulant and receptor, and intrinsic activity, which is a measure of the ability of the drug receptor complex to evoke a physiological response (Ariens, 1954).[59]

Stephenson, a British theorist, modified the theory on the basis of new experimental data which suggested that a maximal response could be produced by a drug without occupying all the

receptors. His concept of efficacy was a measure of the number of receptors which a drug had to occupy to get a maximal response (1956). He also introduced the concept of the partial agonist, which has high affinity with low efficacy. The percolation of these concepts was slow, and in the adrenergic area at least was heavily dependent on the introduction of drugs whose properties could only be satisfactorily explained by these theories.[60]

This was a very academic tradition, it had little in common with the chemist's use of receptors, and it was regarded with some suspicion by orthodox pharmacologists.

In a paper written by Stephenson in 1956 which makes an important distinction between the affinity of a drug for a receptor and its potency once attached, which later became an important concept for the development of beta-blockade, the following comment appears at the end of the discussion:

> "The approach to the study of the action of drugs used in this paper is not universally popular among pharmacologists; some, indeed, despise discussion in terms of receptors..."[61]

He goes on to justify making clearer assumptions about the way in which drugs interact with cells, but the implication is that this is an unorthodox line of approach which has to be defended.

Most of the receptor theorists worked on the acetylcholine system which gave more reproducible results than the adrenergic system, and also did not have such a wide variety of effector compounds, thus making the idea of 'a receptor' more probable.[62] To pharmacologists involved with the adrenergic system, the wide variety of chemical structure of the adrenergic blockers meant that it was difficult to see how a single receptor could account for such an unspecific selectivity.

> "Present data indicate that alterations in the destruction or transformation of the mediator *in vivo*, and alterations in cell permeability are not important factors in adrenergic blockade. However, the question why certain chemical structures and not others produce effective blockade remains unanswered."[63]

With the increasing explanatory power and prestige of structure-activity correlation, Ahlquist's theory began to be taken more seriously. A. M. Lands, an old and experienced worker in the academic study of adrenergic mechanisms, commented in the first volume of *Pharmacological Reviews* (1949):

> "the concept of the sympathins E and I as mediators of adrenergic nerve impulses seems to have outlived its period of usefulness."[64]

He mentions the dual receptor classification, but appears unable to accept that a compound which is a potent vasodilator can also be a potent cardioaccelerator. He therefore suggests a third receptor for cardiac stimulation and comments:

> "with this increase in knowledge, it is not too much to hope that there will be a correlative development of synthetic agents of great therapeutic importance."[65]

All authorities agree, though, that the major turning-point for Ahlquist's theory was the discovery of a compound whose actions could best be described in terms of his theory, that is, Dichloroisoprenaline. DCI is a close analogue of isoprenaline, with chlorine atoms replacing the hydroxyl groups.[66-68]

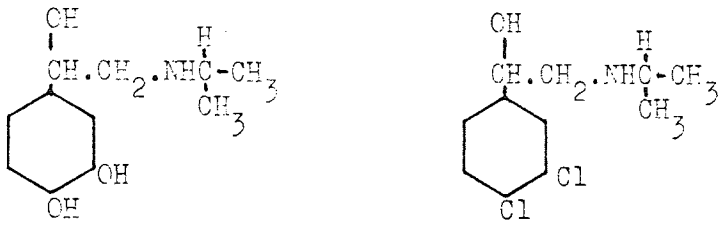


Fig. 2.10 Structures of isoprenaline and dichloroisoprenaline (DCI).

> "The proposal of Ahlquist was not, however, generally accepted until the accidental discovery of a chemical agent which produced a selective antagonism at beta-adrenoceptors. Regrettably, the manner of presentation of modern scientific papers does not encourage publication of background information to new discoveries and we are all the poorer for it. From the available literature it is evident that the Lilly Research Laboratories were engaged in a search for long-acting, specific bronchodilator substances and were examining chlorinated phenyl analogs of isopropylaminoethanol."[69]

It had an ability to interfere specifically with the action of isoprenaline without having any excitatory action of its own. This was interpreted by the pharmacologists Powell and Slater in terms of elaboration of receptor theory as the first example of a compound whose affinity for the receptor was much greater than its activity once bound. However, they did not connect DCI with Ahlquist's theory.

> "It is evident that Powell and Slater did not appreciate the full significance of their discovery since no mention was made of Ahlquist's receptor hypothesis. ... Yet of the intellectual processes leading to the conversion of this presumably 'failed' bronchodilator into the first of a new series of autonomic drugs nothing is recorded."[70]

In an article on the role of drugs as tools in physiological analysis, Shideman comments on DCI and the third receptor proposal of Lands: "Again a drug arrives on the scene to clarify this point".[71] From what has been said above, it is evident that there were cogent reasons why such a drug was synthesised and why it was interpreted in terms of receptor theory. The impact of significant drugs on the development of physiological theory is not as fortuitous as it is sometimes described.

Six months after the initial description in the Journal of Pharmacology and Experimental Therapeutics,[72] another paper appeared in the same journal which explicitly connected the properties of DCI with Ahlquist's theory.[73]

Neil Moran and Marjorie Perkins were working in the same department as Ahlquist - at the University of Augusta, Georgia. They had a different perspective on DCI; they were interested in it as a major piece of evidence for Ahlquist's theory. Their paper begins:

> "Although the cellular receptor mechanisms with which drugs react are poorly understood on the basis of their physico-chemical and morphological properties, the operational classification of receptors is of potential heuristic value."[74]

They go on to point out the problem with the classification of adrenergic receptors: that adrenergic blocking drugs then current did not block either the excitatory reactions of the heart or the inhibitory reactions of smooth muscle.

> "Since the classification of drug receptors depends to a large extent on the use of selective blocking drugs to differentiate one receptor from another, the status of adrenergic cardiac receptors has remained in doubt."[75]

In an exhaustive sequence of experiments, they showed that DCI exerts a specific blocking action on the increased rate and contractile force of the heart produced as a response to adrenergic stimuli. They also noted:

> "The initial increase in heart rate and force produced by DCI, followed by prolonged blockade of the cardiac responses to adrenergic stimuli is indicative of a reaction between drug and receptors which results in a primary stimulation of the heart, succeeded by blockade, perhaps due to a persistent complex between drug and receptors."[76]

There are two significant points about the paper from the point of view of the history of beta-blockade. It connected the unusual properties of DCI with Ahlquist's dual receptor theory; (the evidences) "support the postulate of Ahlquist (1948) ... the concept of alpha and beta receptors represents, therefore, a useful classification of adrenergic receptors", and hence gave the

latter a great deal of credibility that it had not previously had, for example,

> "(The) elegant use in 1958 of Ahlquist's hypothesis to classify the pharmacological properties of DCI provided the turning point and the rapid acceptance of the idea of a dual receptor mechanism."[77]

In addition, the paper provides the first clear description of Intrinsic Sympathomimetic Activity (ISA) which was later to become an important and controversial property.

As will be seen later, Ahlquist's theory provided the theoretical basis for Black's work. The papers of Powell and Slater and Moran and Perkins gave him the lead that he needed - a compound that had many of the pharmacological actions that he was looking for.

Discussion

Tracing the development of receptor theory back to the writing of Claude Bernard clearly reveals the dependence of much modern therapeutics on the offspring of 19th century reductionist physiological techniques. Bernard derives a particular kind of knowledge from the use of curare, a 'pharmacological dissection' of the animal into physiological elements. The fact that such dissection techniques are the easiest, and maybe the only way to get some understanding of the elements of which animal bodies are made has meant that this stage of understanding has been prolonged, as opposed to a holistic study of the relationships between these elements which has, in general, been considered of secondary importance. In this case, the development of a theory of'elements', and its evolution into the concept of receptors, can be correlated quite well with the introduction and use of new pharmacological dissectors (blocking compounds).

The interaction between these two has been two-way, but the innovation of new blockers appears more directive than the production of new theory:

Table 2.5

Instances citable as Drugs-produce-theory

Curare	- Bernard separates sensory and motor nerves (c.1856). Introduces idea of pharmacological dissection.
Nicotine	- Langley investigates myoneural junctions, conceives of 'receptive substances' (1897-1904).
Dyes	- Ehrlich discovers selective effect, conceives of 'side-chain' theory of receptors, chemotherapy (1902-1910).
Ergotoxin	- Dale finds a separation of motor and inhibitor functions of adrenaline, comes close to idea of receptors (1906).
Beta-haloalkylamines	- Goodman and Nickerson find that heart adrenoreceptors are unblockable by classical blockers (1945).
Various adrenergic stimulants	- Ahlquist finds a separation of α- and β-receptors.

The ganglion-blockers, methyldopa, and adrenergic neuron blockers such as guanethidine also exerted strong influences on medical theory (see S.1.3).

Table 2.6

Instances citable as Theory-produces-drugs

Fourneau's ideas on the medical and research utility of blocking compounds (1933) lead to the production of piperoxan, the first of a new class of adrenergic blockers.

Black's ideas on the medical usefulness of β-receptor blockade produce the clinical β-blocking drugs.

However, these are partial and myopic interpretations of the interactions between drugs and theory. Two more interesting types of interaction are when drugs take on a new significance through the reinterpretation of a theory, and when theory is revalued because of the introduction of new drugs. An example of the former occurs when the failed bronchodilator DCI is then taken up widely as a research tool because of its redefinition as beta-blocking compound by Ahlquist and Moran and Perkins. The same drug can also be seen as an example of the latter, since it played a major role in the eventual acceptance of Ahlquist's theory.

These more complex classifications give a truer picture of the interaction which concerns us, since the evolution of receptor theory, as we have seen, has involved a continuous interaction of theory and observations of drug action.

Beginning with the 'elements' of Dale when there was little scientific basis for the receptor concept, so that although it fitted the observations at a crude level, it had little explanatory force, it became increasingly useful as basic pharmacological research expanded. In this account I have emphasized the influence of new drug innovations on the elaboration of receptor theory, but other factors were also significant.

The idea of receptors was taken up as a direction in medical research by Ehrlich and in mathematical pharmacology by Gaddum and Clark, as a useful abstract concept while the lack of supporting evidence for the existence of receptors made their acceptance by orthodox pharmacologists unlikely.

With the increasing sophistication of chemical technology, receptor theory found wider acceptance. Factors in this were the increasing success of structure-activity correlation, from Barger

and Dale's work in 1910 to the work of Ahlquist in 1948, the work on enzyme structure and activity and the study of the properties of their inhibitors, and a more general reshaping of perspectives in pharmacology.

This change was evident in the 1930's but proponents of the new philosophy, the study of the chemical and physical basis of pharmacological action, were cautious:

> "This subject is of basic importance in pharmacology and in chemotherapy and is becoming of increasing importance in physiology and in enzyme chemistry. Hence, any quantitative information that can be obtained is of great value. These reasons justify the attempt to apply methods of physical chemistry to living cells, even though the latter are very unsuitable material for such work. It must, however, be remembered that such an attempt implies using methods for purposes for which they were not intended and this is always a dangerous practice."[78]

It was not until World War II and after that receptor theory was accepted within pharmacology, as a result of the development of technology and the increased significance of drug research. It can be seen, then, that the receptor concept is a product of the application of chemistry to biology:

> "In the nineteenth century the molecule became much more than the backbone of large parts of physics, it became also the central concept in chemistry, converting chemistry into the science which studies reactions between molecules. The extensive application of chemistry to the science of life quite naturally promoted the molecule to a more fundamental functional unit than even the cell."[79]

As such, its acceptance marks the success of chemical knowledge in understanding the structure of living matter. The use of drugs both in research and in therapy has contributed extensively to this acceptance.

Section 2.2 Innovation

2.2.1 Discovery and development of pronethalol and propranolol

In 1957, at ICI, pharmaceutical researchers in the cardiovascular area were completing work on an orally-active ganglion-blocker known as Tenormal.* At this point it was clear that there was not much future in the production of further ganglion-blocking compounds, as other antihypertensives with fewer side-effects, such as reserpine, guanethidine, and methyldopa, were coming into wider use. In the words of one of the technicians who had been in the cardiovascular research section at ICI since the mid-1950s.

> "ICI in fact at that time was ripe for an idea to change the direction of cardiovascular work."[1]

This was provided by a doctor whose primary interest was in physiology - James Black. He had conceived the idea that some of the effects of adrenaline on the heart were not always functional, especially in disease states such as angina, where the heart needs more oxygen than can be delivered to it by narrowed coronary arteries. If the effects of adrenaline on the heart could be pharmacologically distinguished from its effects on the rest of the body, then there was a possibility that a drug might be developed which would block the actions of adrenaline on the heart, thus reducing its demand for oxygen, and thereby reducing the frequency and severity of attacks of anginal pain felt by sufferers from the disease on exercise.

It is worth looking at Black's history at this point, firstly to see how he arrived at these ideas which were, to say the least,

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*This compound, pempidine, was independently researched by May and Baker, and marketed by them in 1958 as 'Perolysen' (Spinks and Young, Nature 181 1397 (ICI), Lee et al. ibid, 1717 (M & B) 1958).

highly controversial, and secondly to look at what elements in his background made it possible for him to bring those ideas to a practical success.

Black took up his interest in physiology soon after he graduated in medicine in 1947. In the late nineteen forties, as a postgraduate student at the University of Dundee, he was confronted with the first of a series of problems in measuring physiological variables which required extensive improvisation of equipment:

> "My first experiment (was) finding a way - at that time there wasn't a way - of recording rat blood pressure. To do this I had to make a special little manometer of very low capacity ... I started doing pressure-flow studies on gut circulation mainly ... there were technical difficulties in doing this. I spent I suppose three years struggling with technical problems, I had to make my own photokymograph, optical manometers. It was all very primitive in those days, everything one had to make oneself ..."[2]

He then became interested in fluid exchange in relation to blood flow, and this involved developing methods for controlling and studying the circulation. A move to the Veterinary School at Glasgow gave him the opportunity of building up a physiology lab from scratch:

> "... what fascinated me was the salivary gland (of sheep) which pours out saliva continuously - this seemed to offer me a possibility (of looking at) the relationship of blood flow as a limiting factor on secretion. So this got me involved again in controlled circulation in relation to blood flow. I am now building up a place where I have recording equipment, the hardware; the manometers, the flowmeters, I'm building a cardiovascular lab."[3]

His knowledge of circulatory physiology, then, was based on extensive experience with work at the boundaries of what was technically possible. That is, Black was used to improvising and converting equipment to measure parameters that standard equipment could not.

But Black was not only a technically proficient physiologist, he was also receptive to new ways of thinking, and because of his medical background had a clinical orientation that a pure scientist would not have had:

> "There are big Infirmaries in Glasgow with people like George Smith (a heart surgeon) who are hungry for a place to work, and by a series of accidents they find that this was a place where you could work. And so I learned from George Smith how to do coronary circulation which I already knew vaguely, having had an interest in coronary physiology. But I was learning by direct tradition something which I was familiar with ... so here was a man who was trained in the best school in the States, and I had this direct plug-in - up to this time I'd had no training at all, I'd been doing it all myself. So I learned from him how to open-chest dogs, how to open up the pericardium, cannulate, catheter. That was how I got interested in coronary circulation."[4]

Here Black is changing his area of interest from physiological experimentation per se to using the experiments as an extension of clinical research:

> "His problem was that he had worked on trying to increase the blood flow to the heart through collateral circulation (the circulation through connections between coronary arteries) - this was Beck's work.[5] What he wanted to do was to see whether he could achieve the same thing by increasing the supply of oxygen, so he did the hyperbaric chamber (a chamber which could be filled with oxygen under pressure which produced more dissolved oxygen in the blood). So now then it seems to me at that point from the kind of background that I had and the kind of reading and thinking I'd been doing about the coronary circulation - I know how little one had to increase retrograde flow - if you take a coronary artery, 100 mls/minute going through, you measure the retrograde flow that can come in from collaterals, it's about 2 mls/minute, so you go from 100 to 2. And Gregg had shown that if you could merely double that backflow, go from 2 to 4 the heart wouldn't die. This kind of background - I realized that the amount that George could increase in delivery was small as it was mainly dissolved oxygen, and the amount the heart needed was small, so really its a terrible tragedy, dying of a heart attack because the margin between life and death is so small. Right then, if a small increase in supply is so hellish effective, why not a small decrease in demand?"

JW: "A very radical step."

JWB: "I don't think so - an awful lot is made of this, I think it's overstated - people have been doing this kind of thing in simply the everyday business of investigators, and that is to stand a problem on its head".[6]

What can be simply said about this is that the importance of Black's contribution lay not so much in his arrival at unconventional theories on this aspect of physiology, but more in his attempts and eventual success in translating them into a practical therapy.

In fact Black was not the only person looking at adrenergic systems and heart disease who arrived at similar ideas about the damaging effects of released adrenaline increasing the heart's demand for oxygen beyond the supply, even though such a viewpoint ran counter to the accepted ideas of the time.

> "In the fifties we're talking about ideas still dominated by Cannon*, and the idea that sympathetic nerves were beautifully adapted to behaviour, it was almost heresy to suggest that the sympathetics could be anything other than adaptive."[7]

> "Then the influence of W. B. Cannon, with the sheer success of his work in the twenties in formulating his doctrine of homeostasis and the emergency theory of the function of the sympathetic nervous system - the mediation of the fight, fright, and flight reaction - apparently imprinted the minds of generations of biologists with images of a system beautifully adapted to survival with its activity ebbing and flowing in a unitary pattern, harmoniously reciprocating with the parasympathetic system. There was not much room in these theories for the idea that the activity of the sympathetic nervous system would not necessarily or always (in cardiac disease for example) have survival value".[8]

However, there was some evidence to back up doubts about the beneficial role of adrenaline.

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*Cannon's theories are considered in more detail in section 2.1.

> "It was known that in some patients anginal pain could be initiated not only by exercise, but also by cold, eating, excitement, anxiety, or anger. Enhanced levels of sympathetic action were usually assumed to be features of these episodes."[9]

Adrenaline injections were in fact used for a short time as a tool for the diagnosis of angina pectoris - the characteristic pain of angina was induced by the injection - but the procedure was discontinued as being too dangerous.[10]

> "There were heretics around - there was a man called Raab - they were more essays in hot gospelling than medical science, because there was a minimum amount of measurement and a maximum amount of speculation - he implied that adrenaline was pure poison because it increased the heart's demand for oxygen. So not much evidence but a lot of talk."[11]

So if adrenaline did have adverse effects on the heart in disease states what could be done about it?

> "An operation which was quite fashionable was to denervate the coronary arteries, and the theory was that you were cutting the pain fibres, but in fact they were also cutting the sympathetics because they come down the coronary arteries ... so perhaps what it was doing was effectively sympathectomising the heart."[12]

This was realised by Dr. D. A. Chamberlain, who showed that anginal patients had a lower exercise heart rate when sympathectomised.[13] He also connected this surgical sympathectomy with the possibility of a reversible but analogous chemical sympathectomy when the chemical Dichloroisoprenaline (DCI), an analogue of the stimulant isoprenaline, was first described. However, as he was working in the hospital service, he did not have much opportunity to test his theory, and in fact had great difficulty in getting any DCI from Eli Lilly to test.[14]

Black did not in fact make this particular connection, probably because of his lack of medical practice, but instead he had the idea that the action of adrenaline on the heart could somehow be interfered with.

"Pharmacology to me was a closed book ... the question is selectivity, 'how can you block the effect of adrenaline on the heart?' was a simple sort of question - so you reach for the nearest textbook of pharmacology and that's where Ahlquist's paper was ... but for that accident..... He was an expert on adrenergic systems, but he also gave himself a big spread on his dual receptor hypothesis. At that time I didn't know much physiology, but I didn't know any pharmacology at all, so it was all very naive. It just seemed that here was an action of adrenaline which apparently you couldn't block, and apparently it was a different receptor, that's what Ahlquist said, so why don't we get something which blocks it - it seemed a rather obvious thing to do."[15]

In a paper on the subject Black comments:

"I had great faith in Ahlquist's receptors. Luckily, with a background and interest in physiology and medicine I had never been exposed to the prevailing prejudices against the concept of hormone receptors. Dale, of course, had never seen the need to alter his early negative attitude to the idea of receptors, and his massive influence was still dominant in the pharmacological thinking of the fifties. Seeing only the power and beauty of elementary receptor theory, I was determined to try and find a selective beta-receptor antagonist."[16]

Here the factors which made Black's breakthrough possible become a bit clearer. His unorthodox background, the mind of a doctor interested mainly in physiology, in daily contact with the research problems of practising surgeons must have been a fertile breeding ground for making connections between disparate scientific specialities. He had confidence in his own ideas even when they went beyond the sphere of his detailed knowledge, a rare characteristic in scientists. These two factors were obviously related to his impressive personality, which as we shall see was instrumental in his acceptance by ICI, and highly influential of the style in which the project developed in the first few years.

His confidence in theoretical generalisations outside the area of his detailed knowledge probably partly relates to his professional and personal self-confidence, but is also connected to the reason

he gives for his devotion to receptor theory: its "power and beauty". The same concept is often expressed by scientists who have an idealistic attitude to their practice of science - and these are often held to be the most innovative. Black knew that Ahlquist's theory was simple and coherent, so therefore he strongly believed that it ought to be true.

> "I had some more luck at this point. I had applied to the new Pharmaceutical Division of Imperial Chemical Industries, Ltd. for a research grant. A site visit was arranged and one of the investigators who came to Glasgow in 1957 was Dr. D. G. Davey, a parasitologist who was about to take charge of Biological Research at ICI. He invited me to come to ICI to work on my beta-blocker project and, once there in 1958, he gave the early work much-needed protection and support. I think it would be hard to overestimate the part which Davey played from then on in promoting the development of this work."[17]

Why did ICI decide to support Black's work, which was, to say the least, controversial? One of the clinical pharmacologists later involved in the project commented on this question,

> "If you think about Jim Black's thinking around the late fifties, the idea that you block half the nerve supply to the heart, most normal people are going to say the man's mad, you see, it's crazy."[18]

It would seem that much of the decision rested on an intuitive level. Davey evidently responded to the unconventionality of Black's ideas and his effervescent style. He says,

> "My contribution to beta-blockade, put very simply is that I wholeheartedly backed Black's views. You might say I was in tune with him (a lot of people were not) and we were mutually receptive. Otherwise, I suppose, I could have damned the project."[19]

Black himself comments:

> "You must understand that this started off in an atmosphere of great scepticism, so as Donald Davey says, he was the permissive factor, he allowed it to go on - so I would say that Davey was enthusiastic, whether he was enthusiastic for me to be given my head, or whether he was enthusiastic for the project, I'm not entirely sure, but certainly he supported it. But generally speaking there was a lot of hostility to the work in the early days."[20]

However, this intuition rested on a firm technical base,

> "Anyway, Black is one of the best pharmacologists and the best cardiovascular pharmacologist I have known."[21]

This is very close to what was said by the clinical pharmacologist quoted above, who is now Research Manager.

> "I think the best drugs come out despite the research directives if I'm quite blunt, and my view is quite simply that you've got to back them, and if you've got a first-class man who's got a good hypothesis then you change direction and you follow it."[22]

ICI were at this time without any significant new projects in the cardiovascular area. Black's project was unorthodox and novel, and hence risky. But it was also cheap and the objectives were pharmacologically rather than clinically defined. This made the production of a drug which was pharmacologically effective more likely, but meant taking a bigger gamble on whether this pharmacological effect would be clinically useful. However, with his physiological and experimental medical experience Black could have made that gamble look quite attractive.

Another point made by the present Research Manager also seems to the point:

> "If he (a scientist) convinced me of something I would certainly divert funds to follow some of his ideas, because I think he's got a first-class mind, and he understands the applied research area very well which you know quite a lot of academic scientists don't."[23]

Black's medical background must have been largely responsible for the clinical derivation of the theoretical basis of the project. However, Black was cautious:

> "When I started at ICI in the middle of 1958 I had defined the project in explicit pharmacological terms but chose to be vague about its therapeutic potential."[24]

Although Black took over responsibility for the antihypertensive work of the section as well as his own project, as he recalls it it seems very informal:

"My recollection is that I went to ICI without any contract and without any obligation that I had to do something like write a report before I started. I went there knowing what I wanted to do in a kind of way and set about it, and my recollection is that would be around about July-August 1958."[25]

Black's "official account" paints a rational picture of the beginning of the project.

"I had defined a suitable screening test, namely to see if any substances could be found which would annul the actions of adrenaline on the Langendorff isolated guinea-pig heart preparation. John Stevenson was assigned to make the new compounds. All we needed was a chemical starting point and we were off! After some floundering we decided to follow up the idea of trying to make a 'doubled-up' version of noradrenaline. With this aim in mind we set out to make and test a variety of dibenzylethylamines and dibenzylethanolamines."[26]

In fact, however, the starting point was more problematic than this, partly due to Black's lack of knowledge of pharmacology, and partly due to the lack of pharmacological theory about receptors and antagonists.

"Where we were showing our ignorance was where to start, and I remember a lot of talk we had, especially with John Stevenson, and we fossicked about in the literature and we came across a paper in Comptes Rendus - about half a page or something claiming that you could make antagonists "par doublement la molecule" - so this was what we set out to do."[27]

So the project began with one chemist synthesising compounds which were then tested by Black, the pharmacologist. The first report on the project, dated 22 January 1959 details briefly the unsatisfactory research into better coronary vasodilators for angina, gives the background evidence for the harmful nature of adrenaline in anginal states, then goes on to state:

"It seems clear that the search for compounds which will block cardiac sympathetic responses constitutes a clear-cut pharmacological problem, and screening tests are being developed. In addition, experiments are planned which will attempt to elucidate further the possible value of such compounds in coronary artery disease."

Simple Screening Tests

1. Rat blood pressure - a quantitative test involving adrenaline (alpha-receptor) and isoprenaline (beta-receptor) will probably be used as the first test.
2. Isolated rat papillary muscle - the isometric contraction induced by isoprenaline and modified by blocking compounds will be measured by an electronic transducer.
3. Perfused isolated rabbit ear.
4. Pitressin - this is a coronary vasoconstrictor, the use of which produces characteristic electrocardiographic changes. The ability of blocking compounds to delay or prevent these changes will be assessed."[28]

These tests show Black's use of his experience in physiological experimentation, and also his interest in using new methods of measurement - the transducer was probably built at ICI, the accepted method up till then being the smoked drum. The rabbit ear test was a comparison of the state of blood vessel tone after adrenaline and blocking compounds.

The experiments on the 'doubled-up' antagonists were temporarily halted by the appearance of a paper in the Journal of Pharmacology and Experimental Therapeutics.[29] This came from two researchers at the Eli Lilly Co., C. E. Powell and I. H. Slater, and concerned the properties of a dichloro substituted analogue of isoprenaline. This was

> "Among many analogues made attempting to separate the bronchodilatory (anti-asthmatic) action of adrenaline from the cardiostimulant action by Eli Lilly who were after a bronchodilator."[30]

Because of this, the tests they used were related to the activity of DiChloroIsoprenaline (DCI) on smooth muscle rather

than cardiac muscle. They did test heart muscle, but not mammalian - they used frog heart and found a blocking action only at high concentrations, which they put down to an unspecific depressor effect. The interesting point about DCI was that it appeared to interfere specifically with the action of adrenaline but did not seem to have excitatory properties of its own. This was interpreted by them in terms of receptor theory as meaning that the affinity of DCI for the adrenergic receptor was not related to the effects of the compound when it had bound to this receptor, which was unusual:

> "The blockade seen with 20522 represents a special case only insofar as this amine is relatively devoid of either inhibitory or excitatory action in the doses used. Thus it can be postulated that combination of 20522 with 'adrenergic inhibitory sites' fails to trigger the series of reactions that lead to typical inhibitory effects. Yet the evidence strongly suggests that 20522 does combine with the receptor site and that the drug-receptor complex is fairly stable ... for these reasons it can be expected that 20522 will cause a fairly stable blockade and should prove useful as a tool in the study of pharmacological problems related to adrenergic mechanisms."[31]

They later published a short piece on the support given to Ahlquist's hypothesis by DCI - after Moran and Perkins.[32] Thus they saw DCI as an interesting tool rather than a possible therapeutic compound.

> "I think ... the most telling thing is the fact that Eli Lilly had the first beta-blocker, DCI - they took it into man. Their Medical Department could only see that this drug would be for use in people with a tumour that produces excess catecholamines - phaeochromocytoma. What they couldn't perceive was that there are situations where there is an <u>inappropriate</u> activation of the sympathetico-adrenal system."[33]

Eli Lilly did not follow up this compound, although it was

apparently tried in a few cases of phaeochromocytoma.* This condition is fairly rare, and so without an idea of the wider possibilities of adrenergic blockade on the heart, marketing such a compound would not have been commercially justifiable.

> "I think Lilly had pronethalol sitting in their drawer. Moran will tell you he went up and talked to the chemist and the chemist was a bit upset because he had all these things down and nobody wanted to go on any more with them."[34]

DCI anyway has a considerable amount of stimulant action, so that blockade would be only partial. However, Black was quick to see the significance of this compound in the light of his own preoccupations:

> "And so we were looking for the doubled-up version, and then the DCI paper was published late '58, but we didn't get it till early '59 - I remember reading it, and thinking 'My God, this is it!"[35]

It seems though, for one reason or another, that Black did not attempt to investigate the properties of DCI for himself until a second paper on it had appeared, six months later, in the same journal. This was Moran and Perkin's paper which connected the actions of DCI with Ahlquist's theory, and described DCI as a beta receptor blocker.[36]

> "And then Neil published his paper and I read it and it looked good to me, and yet I was suspicious. I was suspicious because I'd never used strain-gauge arches, and his work was based on strain-gauge arches. And he'd recently published a paper about two years before claiming that phenoxybenzamine would block the actions of adrenalin on the heart (it doesn't) so I was suspicious that maybe there was a technique thing here."[37]

---

*The potential use of β-blocking activity with DCI was never fully realized. A limited number of publications appeared which reported its successful use in the management of certain cardiac dysrhythmias and in the protection of the heart during the surgical removal of a phaeochromocytoma.[38]

The grounds for Black's suspicions were seemingly that Moran had used a technique with which Black was unfamiliar; he was therefore doubtful of the results.

"Anyway, we very quickly made our own DCI."

(Chamberlain was only able to get DCI after he spent a year writing and cajoling Eli Lilly to give him some).

> "Our first experiments with DCI on the isolated, spontaneously-beating heart showed it to be nearly as potent as isoprenaline itself as an agonist, and we promptly lost interest."[39]

Black's initial doubts about Neil Moran's techniques probably contributed considerably to the completeness of his loss of interest in DCI. Had Black been more familiar with the work of Stephenson (1956) and others on the properties of partial agonists which was mentioned by Powell and Slater, he might not have been as disillusioned by these results.

A major problem at this stage was to decide what type of test was best at detecting useful blocking activity.

> "So originally, there we were, really running two things together - we were running a bit of anti-hypertensive drug stuff, finishing off the work on Tenormal, and at the same time trying to build up models to record heart changes - we went through things like tortoise heart, isolated frog heart, stuck electrodes through rabbit chest walls..."[40]

Through 1959, Black and Dunlop, a technician with a lot of experience in the cardiovascular area were testing compounds and attempting to refine the tests they were using. The Research report of June 1959 illustrates the slow progress with this, commenting on the isolated papillary muscle test which Black had originally described in the report six months before.

> "This preparation is only moderately sensitive to catecholamines, but its high degree of stability for long periods makes it the preparation of choice. A suitable method of recording the response has still to be found."[41]

So there were problems with the experimental equipment. A lot of it had to be specially made, and the 'one-off' prototypes were not very sophisticated.

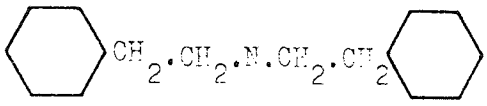
> "It seems really incredible now, but one of the first ways we measured the force of contraction (of the heart) was to have a dog on a suspended plate and going back to the law that for every section there's an equal and opposite reaction, we measured the movement of the plate."[42]

However, there was some in-house expertise to draw on. Brian Horsfall, a technician who, like Dunlop, had been at ICI for over 20 years, was interested in electronics, and began to convert and improvise transducers such as were needed for accurately measuring muscular contraction. With Black's encouragement ("I've always been interested in engineering, instrumentation")[43] he set up an instrumentation section in a utility room in Black's laboratories. Dunlop recalls,

> "In fact you couldn't record the parameters we wanted to examine under conventional laboratory systems - the only thing available to pharmacologists was the old smoked drum. Brian Horsfall was making heart rate meters very early on before conventional meters were available. He made our strain gauges, it was very much a team job."[44]

So during 1959 Black and Dunlop were continuing to test the 'doubled-up' compounds that they hoped would be effective antagonists.

> "John was working up compounds like (B) hoping to get to (A) someday"[45]



B

Fig. 2.11 Doubled-up catecholamine structure used as first chemical lead.

In late 1959 the problems with the new test had been ironed out and Black was standardizing it with some compounds that had been through the old test.

> "We didn't twig until I got the papillary muscle preparation, and you usually recheck things, put back in the DCI and I can remember my jaw dropping, there it was, what I was looking for!"[46]

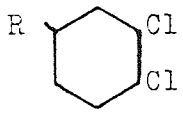
DCI was an effective blocker on the new test, but not on the old. What did this signify? Research report January 1960:

> "Isolated heart muscle 112 compounds tested, of which 10 are active, none as much as DCI. This is a disturbing result, because it was reported that 32,278 (DCI) did not block the action of adrenaline on guinea-pig heart, and that compound itself was a potent cardiac stimulant."[47]

The problem was now up to John Stevenson, the synthetic chemist, to modify the structure of DCI so as to remove the stimulant activity, but keep the blocking activity. But how was it to be done?

> "Knowing little about the molecular biology of such hormones at the time, I assumed it likely that the side-chain was quite specific, since relatively small changes had quite large quantitative effects whilst not affecting the general type of activity. A change in the shape of the ring and its substituents seemed the right route to take ... now if we look at the shape of the aromatic ring and its substituents A in adrenaline and B in DCI we see that another aromatic system with similar shape and one in which the electron density is, as it were, more spread out is C. Not a very logical process but the one I went through which resulted in 38,174 being the first compound which I made specifically for the project and which, surprisingly, considering its simplicity, turned out to be a new and patentable compound."[48]

Stephenson, reasoning that the 3,4-phenyl substitution was important for inhibitory activity, considered other ways of achieving this apart from simple dichloro substitution. It was possible that the presence of a second phenyl ring attached



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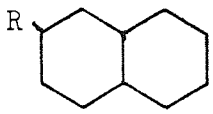


C

Fig. 2.12 Structural transition from dichloroisoprenaline to pronethalol.

$$R = CHOH.CH_2.NHCH(CH_3)_2$$

in the 3,4, position might provide a similar increase in electron density as two chlorine atoms. Barrett comments:

> "A short synthetic programme soon revealed the validity of the arguments in practice, if not in theory."[49]

All this was in fact an extremely rapid process.

> "As soon as we saw that DCI had what we were looking for as far as the rate-controlled preparation was concerned, within 24 hours in my memory, it may have been 48, but it just seemed to be an instantaneous thing, we went straight to pronethalol".[50]

Black talks of working with Stevenson as being very different from working with the more common, methodical, pedantic chemist.

JW: "What was the logic in the construction of pronethalol?"
JB: "John was always drawing things - maybe if we make this a bit bigger, these chlorines are big - maybe just a bit bigger ..."
JW: "Bert Crowther talked about the substitution as being 'a bit way out'."
JB: "It wasn't way out for John, it was as natural as breathing. He had an effervescent mind ... one of the real joys of that time was John coming down with his big notebook - it was always covered. He'd spend all night and come home covered with things and say 'look', and I'd sit and watch ... so quite a natural thing for him, probably unnatural for someone like Bert, because Bert would be systematic. He would say 'right halogens, we'd better try bromine, fluorine, then maybe we'll take this out and put a methyl, the methylethyl', and he would have set about it in a much more Teutonic way. John was the opposite of a Teuton, he was definitely Latin - just the conception - bang!"[51]

So pronethalol was produced by John Stevenson's inspiration in January 1960. One of the first tests was to see whether the new compound had the stimulant activity of DCI, or whether the chemical modification had removed it. The initial testing was very encouraging: 38,174 showed high levels of block, and apparently no stimulant activity. This was the beginning of a period of intense activity around the comparison of DCI with 38,174 on a battery of tests: suppressing the effects of adrenaline and isoprenaline on isolated preparations, on intact cats,

effects on the ECG changes caused by closing off a branch of the coronary artery. These being satisfactory, other necessary measurements were made; the oral absorption, and the lethal dose (for 50% of the test population) (LD_{50}). The report of June 1960 which gives the details of these tests has an optimistic note:

> "A new compound, 38,174, appears to possess most of the properties that may be necessary to protect the heart in coronary artery disease. It has not yet been shown that 38,174 is a candidate for clinical trial, and much work on toxicity and particularly on pharmacological side-effects including hypotensive action* will be necessary before its suitability for trial can be assessed.
>
> The new work will be given very high priority, as will the evaluation of new analogues, and this will probably involve a much reduced effort on potential hypotensive compounds."[52]

Black had taken on responsibility for the antihypertensive work as well as for his own project.

> "My feeling would be that I would have spent all of the second half of '58 on this. During '59 I suppose I must have still spent a lot - my feeling is that it must have been late '59-60 before I begin to get involved. I was doing a lot on the side, looking at other things, I looked at nitroglycerine, Mono-Amine Oxidase inhibitors - also I was trying to learn ..."[53]

Recently the work had involved evaluating the current compounds in use, synthesizing analogues, and attempting to develop more useful compounds. However, Black saw that most of the problems with the ganglion-blocking agents were inherent in their mode of action; the development of tolerance and the unpleasant side-effects could not be separated from the blood-pressure lowering action. These drugs act peripherally, that is not on

---

*they had picked up a hypotensive action on cats.

the brain itself, but on the nerves that radiate from it. Black therefore began looking for centrally-active antihypertensives. This work was quite connected with the beta-blockade project, since their accumulated expertise in tests involving catecholamines allowed them to simplify what could otherwise have been a very lengthy procedure. Starting with compounds with an antihypertensive action, it was necessary to find out at what level of the nervous system they were acting by a hierarchical system of several tests. They did in fact find what seemed to be a direct centrally-active compound, but there were problems at the toxicity stage, and with so much other activity the work was dropped.[54]

At this stage, work on the project was concentrated on two areas; chemists were synthesizing analogues of 38,174 in an attempt to define the range of structures which might show activity, and which compound might be most suitable for further testing, and Black and Dunlop were testing these compounds and also assessing the suitability of 38,174 for clinical trial.

> "In this field, as is so often the case, minor modification of structure often has little overall effect on the biological activity ... a rival company could make a simple chemical analogue, and market it with a fraction of the development costs ... the original investigator attempts therefore to gain patent protection for as many related compounds to the chosen example to prevent this happening. When pronethalol was launched, about 800 other agents, some as good, but most only slightly inferior were included in the patent applications.
>
> Patent law does not require that all the compounds be made and tested since examples are sufficient. A patent may not be granted if the modification is 'obvious', for example, substituting 3 methyl groups for 2 in an amine. This means that a tension situation almost inevitably arises between the chemists who want to make as few compounds as possible in a large number of chemical classes, and the pharmacologists who would like to see as many step-wise modifications in a single chemical class."[55]

The patent on pronethalol, which included derivatives and production routes was applied for in May 1960. At around the same time John Stevenson left ICI.

> "He went I suppose because he was manic-depressive, very bright, and very frustrated with the kind of atmosphere which they had in chemistry at that time. Bert Crowther who was the section head was of the old school.
>
> JW: He got fed up with the organisation?
>
> Well, yes, he was disillusioned, it was too unimaginative for his style. On their part, I think that chemists thought that he was too slapdash but I think that he was a Latin and they were Teutons."[56]

It would be too simplistic to see this simply as a conflict between an innovator who has a relatively rigid, idiosyncratic style of work and values his freedom to work in the way that suits him best, and the need of an organization to have a relatively homogeneous style of work, but there are obviously elements of this conflict here, and this is a recurrent feature of the project. Other chemists were brought in, perhaps no less innovative but more reconciled to the fairly routine work of development. Ralph Howe took up the chemical work:

> "The problem was then thrown at myself and Les Smith. 'Here is the patent application on this compound which we think might be important, will you complete the patent?' Les Smith and I set to and did what is called a patent-completion job; looking at structure-activity and trying to get a better compound than the original one, and in fact we came up with compounds which were slightly more potent, but not markedly so ... Les Smith and I contributed a lot to the process of development - sorting out the processes to make Alderlin and its analogues - that all entered the patent."[57]

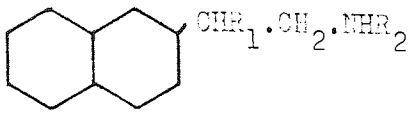
However, Black was somewhat distant from these concerns:

> "In effect the thing is more like the flow of the tide than anything else. It's a very common style to say having found something one must look around until one finds something better. As far as I was concerned I had found what I was looking for, that is I'd found something that met my criteria. That is they would behave as though they were antagonising beta-receptors,

pharmacological criteria. Isoprenaline-induced tachycardia, isoprenaline-induced fall in blood pressure. We were quickly able to show that the animals were not incapacitated. We'd dose all kinds of animals, it was obvious that, other than the dog which showed some peripheral vaso-dilation in the abdomen which will go bright red in very large doses, other than that in the ordinary way, the only thing you saw was that the pulse rate got slower, so we saw no evidence of gross toxicity. It did what I was looking for, it didn't do anything obvious that I wasn't looking for, so what was I looking for, I had it! So there are two things happening, the one you have first is the one you know most about, you're learning on it all the time. We were looking for others but I wasn't waiting for anything, because I saw no reason why I shouldn't take this one."[58]

Howe and Smith, however, were busy creating new compounds around the structure of 38,174, as well as finding better ways of producing it. A patent applied for in May covers another method of producing the derivatives claimed a year earlier (Brit. pat. 953,010). Howe had discovered that in compounds which showed optical activity (that is they rotate the plane of polarization of a beam of polarised light passed through a solution) the β-blocking activity was virtually confined to one isomer (the left handed) only, which was 40 times as potent as the other. Three of the patents cover this work, which was not taken up in production as the increased potency did not justify the increased production cost (B.p. 1,024,643; 1,018,113).

The latter patent exemplified another trend in the molecular modification of 38,174, that as well as increasingly complex alterations to the side-chain covered in three patents late in 1961 (B.p. 1,005,021/022/025) Howe and Smith were also trying alterations to the nucleus, using a single ring as in DCI. This is also the subject of another patent (990,061) which has the most comprehensive side-chain coverage to date. B.p. 984,291 covered the enlargement of the nucleus to give three-ringed



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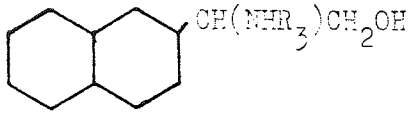

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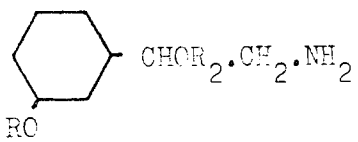

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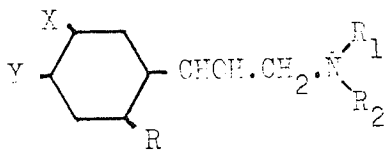

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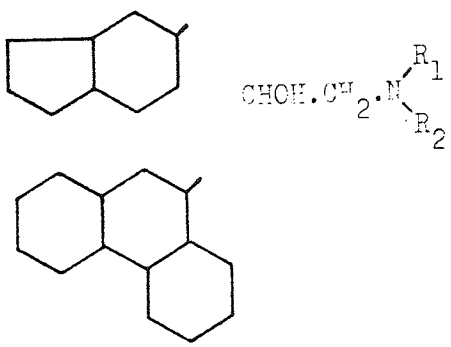

B.p. 984,291

Fig. 2.13 Structures patented by ICI in 1961
R, X, Y, indicate areas of variation

compounds. None of these compounds was significantly more active than 38,174, and compounds with larger nuclei and/or longer side-chains were substantially less active.[59]

By February 1961 the chronic toxicity tests on rats had been done and showed no lesions. The intestinal absorption in dogs was being measured so that toxicity studies in dogs could be carried out. 15 analogues of 38,174 had been synthesised and tested, none was more active than the parent compound.[60]

> "you just got excited at each stage. The first time you showed in a dog that you are able to distinguish cardiac from vascular phenomena, that's a very exciting time, the first time you showed that you're interfering with excercise-tachycardia in conscious animals ... I remember Brian Horsfall made me a little treadmill for rats, we could get the ECG's off these rats and we know we could exercise these rats and they could still exercise as much, but the pulse rate was a bit slower. So each time we learned something was a stage of excitement."[61]

This point was critical for the project - would pronethalol reduce the heart's ability to work under stress, by removing the catecholamine 'drive'? Studies on dog hearts blocked with pronethalol while their contractility and stroke volume were monitored indicated that the blocked hearts were able both to adjust stroke volume to increased venous return, and to maintain stroke volume when the arterial pressure load was increased. So reduction in cardiac 'competence' was not expected in man.

> "We made very few studies on myocardial excitability in animals before trying pronethalol in man. The prevention of the arrhythmias produced by the catecholamines was the limit of our knowledge. This, with some observations on the effect of pronethalol on baroreceptor reflexes, intestinal motility, respiration, and a few simple observations on the Central Nervous System,* was the extent of our pre-clinical information."[62]

---

*A. C. Dornhorst predicted some CNS disturbance on the basis that 5 - 10 x the effective blocking dose in cats and dogs caused coarse tremors and convulsions.

After the toxicity studies on dogs had been completed, this would be late in 1961, the next step was human administration. This was before the thalidomide tragedy had stimulated a tightening up of the regulations concerning the amount of testing that a new drug had to undergo before it could be given to human volunteers, so the process was much less formal, and there is less recorded about it.

> "So then you take it into volunteers, and the whole step - we weren't burdened by what we would be burdened with today, and so the whole thing didn't have the amount of premeditation that it would have to have today."[63]

At this point the Medical Department enters the picture. Ken Green from the Department, responsible for pronethalol, explains:

> "The Medical Department takes a candidate drug, that is, one that has been shown to have a therapeutic action and on which toxicity studies have been done. One of the doctors is then allocated to the project, he learns the pharmacology and takes the drugs to clinics - to top people who might be interested judging from published work.
>
> I and Jimmy Black took tablets of the stuff and checked the effect on ourselves in a casual sort of way, we didn't measure blood levels or anything like that. We knew at any rate that people weren't going to drop dead by the time we asked clinicians to try it."[64]

The clinical investigations on Alderlin were done by four groups:

Professor A. C. Dornhorst's team at St. George's Hospital, London.

Professor M. L. Rosenheim's team at University College Hospital, London.

Dr. R. M. Fulton and Dr. K. G. Green, Stockport Hospitals Group.

Dr. J. P. P. Stock, N. Staffordshire Hospitals Group.

Dr. Fulton worked with Green of the Medical Department at his clinic at Stepping Hill. Stock was an expert cardiologist: "the greatest arrhythmia chap in the country, we thought".

Dornhorst and Rosenheim were both senior specialists, the former in chest and cardiac medicine, the latter in hypertension and its treatment. Black had been impressed by Dornhorst when he had visited the project:

> "The first time I remember, we got Dornhorst who was recommended to us by Desmond Lawrence, and Dornhorst came up to the Lab, spent two days and we showed him everything, all our experiments, our dogs. I had described how the dogs seemed to get a kind of CNS-lesion of some kind, they developed a funny gait, they seemed to go up on their hind legs and were sort of stiff, a paresis of some kind, we didn't quite understand, so I gave some dogs a dose that I knew would produce this, and he looked at this. Then we were down in the doghouse and he said you know, what happens to their body temperatures, and I thought God I don't know, I've never tried it, so I said right let's measure it. We looked around, couldn't find a thermometer, and he said you know they just look cold to me. He says let's heat them up. So there we were in the doghouse, chasing these dogs up and down the centre aisle and we convinced ourselves that after about five minutes' exercise when we were exhausted, that this began to disappear. I think that he probably was right, they did get a bit bothered by the temperature, and I think they just were cold. But what was interesting about Dornhorst's visit was the shrewdness of his clinical judgement, of that type, he went straight to the heart of the problem, and thought about the problem in ways which we hadn't been thinking about it, very direct way."[65]

Dr. Green explains how he minimised the nausea frequently produced by pronethalol:

> "Pronethalol was rather funny in that we started on I think 100 mg doses but it made a lot of people feel a bit sick. At St. George's and University College, they reported after a few months that volunteers couldn't take this, it made them sick. But we at Stepping Hill had had the same effect with other drugs, and we said 'all right, obviously start with a smaller dose and build up', and we found that patients who were started on a quarter tablet and built up to one tablet over a three day period were all right."[66]

Who decided what tests were to be used in the clinical trials?

> "Dornhorst and Brian Robinson, who was the young clinical investigator we had at the time, they decided that we were going to go for intra-arterial injection, this was

> something he know all about, he know all about strain-gauge arches on limbs for measuring muscle blood-flow. So he simply did what he was comfortable with."
>
> "Having found that volunteers could take it we started treating patients very cautiously. We started with angina and also arrhythmias. Within a couple of months it was clear that the drug was working for both conditions. In those days before Dunlop, it wasn't necessary to collect a thousand patients, if you were sure, I was sure that we'd got something that worked then we could market it. One or two other investigators were brought in to do the clinical trials but I don't suppose we had information on more than a hundred or two cases treated for more than about six months, for angina alone about six months."[67]

Ralph Howe talks about the reaction among the chemists in the company to the clinical trial of the compound they had produced:

> "The day we threw our collective hats in the air was when the compound was given to a woman who had to operate a bicycle ergometer in a hospital, measuring effort. She had what I think is called predictable angina, in that she could pedal away for let's say one minute before she had to give up with angina. The crucial test was, she was given a placebo and the angina came on when it was expected, she was given a similar tablet containing Alderlin, and she was able to pedal for the full three minutes of the test. Then she was given the placebo and she had to pack in again (these were suitably spaced of course). That was the first indication that came back to the chemists, that what our pharmacologists had been finding in the cat was translatable into man."[68]

So it seemed that the therapeutic potential of pronethalol and the receptor concept had been demonstrated. But what about side-effects, both those of the individual drug and the physiological reactions to beta-blockade - was beta-blockade tolerable? One of the reactions that had been observed in animal experiments was a lowering of blood pressure. This would be an important effect, both as a potentially dangerous side-effect, and as a potentially important new therapeutic action.

> "The hypotensive actions of Alderlin are puzzling. From our work on cats and dogs*, it was expected that Professor Dornhorst would have seen some hypotension when the medical students were dosed intravenously. Apparently he found no hypotension."[69]

'Muzziness' had been reported by many of the people who took 38,174, and anti-emetics were used to control the symptoms.[70] It was obviously important to determine whether these symptoms were related to the physiological effects of beta-blockade, or just a peculiarity of the one compound. Although excited about pronethalol Black was also aware of its shortcomings which were becoming apparent. The Research report of January 1962 states that:

> "136 near analogues and related compounds have been tested. While these tests have been mainly concerned with patent completion, we are still looking for a compound which will; be longer acting, have greater resistance to catecholamine 'breakthrough', show less penetration of the central nervous system. So far, no compound superior to 38,174 has been found."[71]

So in the absence of any better compound, pronethalol was prepared for marketing. This involved elaborate toxicological experiments; estimation of levels of the drug in the blood and tissues, and their change over time, isolating metabolites of the drug, that is the modifications produced by the body's chemistry, and administering the drug daily for weeks and months (long-term toxicity test). Also, the interactions between pronethalol and digitalis, and pronethalol and vasodilation by nitrites was studied in animals, and no significant interactions were found. However, interactions with barbiturates, anaesthetics, and morphine were

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*Work reported in the Lancet paper of August 1962 gives a lowering of blood pressure of 11% in anaesthetised cats at a dose of 2.5 mg/kg body weight and 19% at 5. The hypotension after slow administration was associated with peripheral vasodilation - widening of the peripheral blood vessels.[72]

not studied, but the significant decrease in LD_{50} produced may have been a cause of a number of severe adverse reactions associated with pronethalol.[73]

The initial work on pronethalol was published in the Lancet of August 18th 1962. This comprised a three-page piece by Black and Stephenson[74] summarising the isolated-tissue and whole-animal pharmacology, absorption and metabolism, and preliminary toxicology; two pages by Dornhorst and Robinson[75] on the effects on normal subjects and anginal patients, at rest and on exercise; and a page on the effects on glucose and fatty-acid mobilisation in man from St. George's Hospital.[76] Black and Stephenson's paper introduces the now classic pedigree of beta-blockade.

> "It is well established that the classical adrenergic blocking drugs, such as phenoxybenzamine do not effectively antagonise the myocardial responses to catecholamines (Nickerson 1959). An explanation of this was offered when Ahlquist (1948) proposed a dual adrenergic receptor mechanism which included the myocardial responses in the beta group. After Powell and Slater (1958) had introduced dichloroisoprenaline as a specific β-adrenergic antagonist, Moran and Perkins (1958) showed that it effectively antagonised the myocardial rate and tension changes produced by catecholamines ..."[77]

It goes on to detail experiments on isolated tissue of different receptor type - only those tissues with beta-receptors had their responses to adrenaline blocked. Most of the ECG changes produced by adrenaline were blocked. Effects on heart contractions and blood pressure were also reported. The preliminary toxicology reported acute doses for mice and rats, and rats dosed twice daily at a quarter of this level for four weeks produced no post-mortem changes attributable to the drug. Dogs dosed at 160 mg/kg for six months showed no abnormalities.

> "A chronic toxicity test in rats is still in progress, and will be terminated at one year ... The toxicity

tests have established that there is a wide margin between active and toxic doses. Muscular tremor, the first sign of toxicity in dogs first appeared at doses estimated to be about 7 - 10 times the effective blocking doses."[78]

It seemed from the experiments in the Lancet paper on the effects of pronethalol, glucose and free fatty acids, that pronethalol did not possess any of the Partial Agonist Action that had characterised DCI. But Barrett who was doing related work at ICI at this time did not confirm this:

"Just prior to the departure of Dr. Black to the World Congress of Cardiology in Mexico City in 1962, he asked the author to check that ... pronethalol also inhibited adrenaline induced mobilization of Free Fatty Acids. We chose to use an anaesthetised dog and to our surprise found no blockade, but a marked increase in FFA levels following pronethalol injection. Thus it became evident that although PAA was greatly reduced by comparison with DCI, it had not been eliminated."[79]

The reported clinical work involved measurements of blood flow, blood pressure, cardiac output at rest and while using an exercise bicycle. The effect of intravenous infusion at 1.5 mg/kg was to abolish the cardiac effects of injected isoprenaline but also produced feelings of unsteadiness and nausea. Oral administration also produced unsteadiness, nausea and vomiting in some subjects, but the symptoms tended to subside with continued administration, and there was much variation with individual susceptibility. Other symptoms sometimes noted included sleeplessness and diarrhoea. Heart rate fell after oral dosing at 2 - 300 mg, an average of 9%.

"The athletically trained tended to show little or no reduction, whilst in the nervous and those unaccustomed to exercise, slowing was more distinct. An average 13% fall was seen on exercise. In the anginal patients the average resting rate fell 14%, exercise rate 18%. Out of 14 patients, 9 achieved a further 20 watt increment in the rate of work before pain developed, in 5 the ECG showed less abnormality than it had at comparable rates of work in the control run."

Placebo runs were used as baselines for the anginal tests.

"Reduction of adrenergic cardiac stimulation clearly produces no disability in normal subjects. There is, however, reason to think that in circulatory failure the maintenance of cardiac output may critically

> depend on neurogenic drive, and in such circumstances great caution will be needed in the use of this and similar drugs."[80]

These, then, were the preliminary communications on the work done on pronethalol. It might be thought that the problems with side-effects had been minimised, and although this seems in retrospect to be true, one must remember that cardiovascular drugs were then less sophisticated, and so a generally higher level of side-effects was acceptable. However, at ICI, the shortcomings of Alderlin were stimulating further work:

> "Black always said that Alderlin was a prototype, I don't think he ever thought it was going to make it - it was going to test the theory in man, but I think he felt that it lacked potency ..."[81]

A. Crowther, head of the Chemistry Section, also said of the compound that it was a poor drug but they might not be able to find a better one, so that more chemical effort was needed.[82] From early 1962, another chemist, B. J. McLoughlin, began work on analogues of Alderlin, and ICI advertised for another cardiovascular pharmacologist/physiologist to work with Black.

The man who filled this post had already had experience with beta-blockers. R. G. Shanks, after taking a B.Sc. in physiology at Belfast and then a medical degree at the same university, worked at the medical college of the University of Georgia with Ahlquist for a year. Here he met Neil Moran and learnt of his work with DCI. When he returned to Belfast as a junior lecturer he got some DCI from Eli Lilly and studied its physiological effects in man.[83]

> "At a meeting of the Physiological Society in February 1962, Dornhorst approached me to say that he had been to ICI, they had this compound like DCI, and he wanted to know what he could do with it to show that it had beta-blocking properties in man and Dornhorst and I discussed the work I'd done with DCI and what we might do with pronethalol."[84]

"In response to this advertisement I went for an interview, and met this chap Black, not really intending to go to work there, but was so taken by their facilities and by James Black that I left Belfast ... I went then in September 1962 and joined Black, and Black and myself and Dunlop and Horsfall were then the team working on beta-blocking drugs." [85]

The October 1962 Research report summarises the work done on Alderlin analogues in the preceding six months:

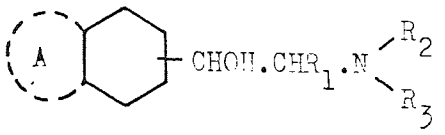
"Almost all compounds tested have been naphthalene, phenyl, or heterocyclic analogues of Alderlin.

Series	Active	Weakly active	Inactive	Total
Naphthalene	35	54	48	137
Phenyl	11	18	10	39
Heterocyclic	12	23	29	64

These results emphasize that in these series we are dealing with a bandspread of activity which will make it easy for competitors but difficult for us ... to find the peak, the crème de la crème of desirable properties." [86]

The structures patented in 1962 were the result of a number of different strategies to increase potency. Alterations to the nucleus involved various heterocyclic compounds (rings containing more than one kind of atom) made in the first six to eight months of 1962, and phenyl compounds with an extended side-chain, made towards the end of 1962. These latter compounds, and the naphthalene analogues were considerably more potent than compounds with the original side-chain.

Black goes on to talk about the most promising of the naphthalene analogues. This compound, code-numbered 45,520, although Black does not seem to recognise it as such, was a different type of compound from those that had been synthesised up to this point. It was also much more potent than Alderlin - anything from 10 to 40 times as potent, depending on the test used. The side-chain of pronethalol was lengthened by the addition of an $-OCH_2-$ group. [87]



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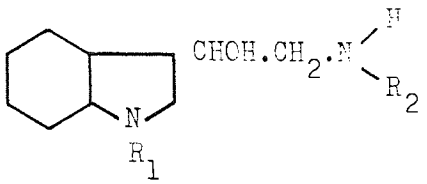

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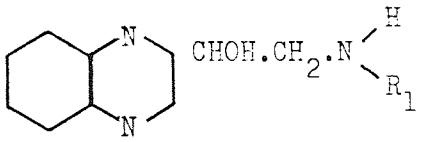

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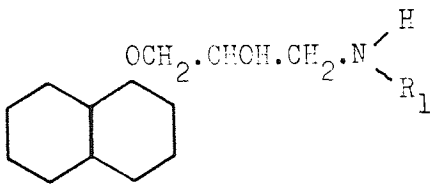

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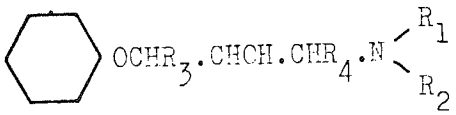


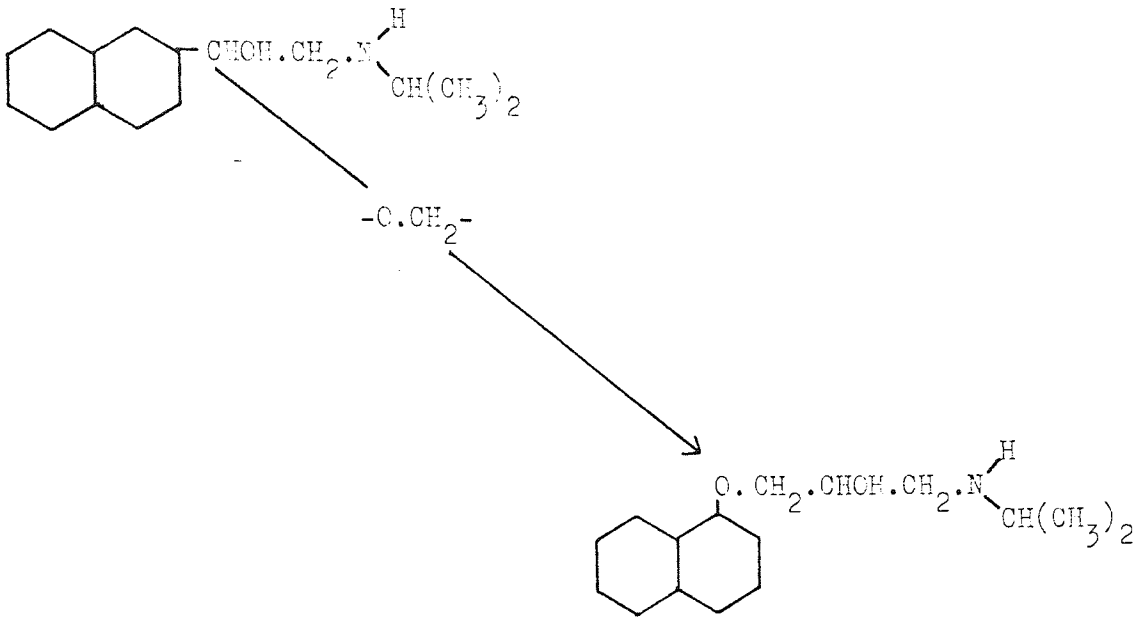
1,069,341

Fig. 2.14 Structures patented by ICI in 1962

A is heterocyclic ring

Fig. 2.15

Structural change from pronethalol to propranolol



How it came to be made is described in different ways by those in different positions within the project. One of the chemists:

> "What we were concerned with were compounds around the structure of Alderlin. You don't go from Alderlin to 45,520 on a patent completion, you're making a step jump ... to my view this was a completely novel break, in terms of the type of chemical that was being made, and this break was made by Bert Crowther and Leslie Smith ... from my experience I've an idea how they got there. The point is that phenylethylamines have what is known as sympathomimetic activity and a medicinal chemist will know that phenoxyethylamines have a similar sort of activity. So if you're working with a phenylethylamine you should really look at the phenoxyethylamine as well. Now if you try to make that switch in the structure of Alderlin you arrive at a compound that would be unstable ... so what you do in that situation, you try to stabilize it by putting an extra CH_2 in, and that's in fact what Crowther and Smith did. They came up with 45,520."[88]

One of the pharmacologist's views on the same process:

"They were putting extra things on this. One of the things they did was to put an OCH_2 on - that wasn't very good, then they just moved all of that round there - no real reason - that was 45,520."[89]

Black's views:

"Gradually the hostility died down and the enthusiasm building up, so you get the Chemistry group growing and a great deal of systematic chemistry now carried out round these compounds. Out of this came propranolol. Les Smith actually made the compound. It was embarrassing because he was a technician, we called them experimental officers, but he was definitely of the lower orders."[90]

Malkin's interview with Smith cites an earlier paper[91] as source:

"Smith was assigned side-chain alterations. He tried lengthening the chain with extra - CH_2- groups but activity was low. Smith read Petrov's paper - he was working on local anaesthetics for British Drug Houses. Normally β-naphthol would be used, but Smith used α-naphthol as it was on the shelf at the time. (The β-naphthol compound is much less active.)"[92]

This apparently small molecular modification in the structure of Alderlin, owing apparently more to common sense than to anything out of the ordinary (since the analogy between the chemistry of adrenergic stimulant and adrenergic blocking compounds was known from very early on), in fact put the possibilities of beta-blockade in a new perspective:

"Certainly it was a much more potent compound, and brought us from a compound which may not have been potent enough to something which could definitely be ... I used to get the results back from the pharmacologist, Dr. Black ... it was immediately apparent to me when these results came back (that) here was a very good compound. And in fact the files will show I wrote on it in pencil in the corner, 'this is it'."[93]

What had caused the excitement was that although much more potent than Alderlin, the dose required to produce a toxic reaction was about the same. This implied that the new compound would have a much increased therapeutic ratio $(\frac{\text{therapeutic dose}}{\text{toxic dose}})$.

There are two other very significant items in this October '62 report which foreshadow important directions in which beta-blockade was to develop in later years. One concerns Ahlquist's classification of receptors. They had found compounds that blocked the fall in blood pressure produced by isoprenaline, but not the cardiac excitation:

> "I think these results mean that one must be cautious about turning Ahlquist's dual receptor theory of adrenergic mechanisms into a sacred cow. His criteria were based on the potency ratios of catecholamines and the selective action of the then (1945) known adrenergic blocking drugs. Other criteria are becoming available, not only these new blocking compounds, but also the time course or pattern of the different tissue responses."[94]

Here we find the first reappraisal of Ahlquist's theory in the light of new experimental evidence. This opened up new possibilities for beta-blockade; if the beta-receptors themselves were divisible into distinct populations responsible for different effects, there was the possibility of the production of even more selective blocking compounds.* The other point concerns the question of a hypotensive effect produced by Alderlin.

> "During the trial at University College Hospital, it was found that Alderlin in maximum tolerated doses produced small but significant reductions in arterial blood pressure. The interesting thing is that this hypotension was not related to posture."[95]

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*A similar phenomenon was seen by workers on the beta-blocking project at A. B. Haessle, Sweden, in 1964, on a compound known as 35/25. It served as a lead to the production of a selective compound, metoprolol. The differentiation of adrenergic beta-receptors (into B_1 and B_2) was not officially proposed until 1967 (Lands). This possibility apparently had to be rediscovered by those working at ICI (see later).

This is a clear statement of a possibility which later became very significant for the project, that as antihypertensive compounds, beta-blockers might not show the variation of blood pressure with posture seen with all other types of antihypertensive. This would be an important advantage, as patients often find the giddiness produced by this effect a limiting factor in their tolerance of antihypertensive drugs,[96] but obviously would have to wait for the advent of more potent compounds.

At this time there was considerable friction building up between Black and the 'establishment' at ICI. Problems arose on many fronts:

> "Black wasn't an easy chap to deal with, because he always wanted to do things differently, he wanted to test the compounds and write the cards properly, he wanted ICI to change the way in which they paid expenses to him, he wanted ICI to change the way in which they patented drugs, he wanted the meetings changed ... he just wasn't the man to fit into an organization."[97]

A key area of disagreement was the research strategy. A large part of the research effort, as we have seen, went into the molecular variation of known blocking compounds, and the systematic patenting of these.

> "It was obvious that we had so many compounds which had the property (of beta-blockade) that we wouldn't be able to get an exclusive situation, that was plain to me. ICI tried hard to get it, and I tried to persuade them that they couldn't have it and therefore the best thing to do was to be first and pick the best. I don't know that we did that, but I think perhaps tactically they were wrong in what they tried to do. I think that we should have gone on to define the properties we were interested in rather more thoroughly."[98]

It is difficult to argue with this perspective in retrospect, given that ICI's strategy has not in fact worked:

> "Every drug company that wanted to make a beta-blocking drug, it has been possible for them to make a drug that was outside everyone else's patents".[99]

However, as many of the properties of the drugs were only beginning to be characterised, and the real significance of them would only be found by clinical testing, it is not certain that a more deliberate pharmacological approach would have been of immediate benefit. In fact, the 'old chemical attitude' of ICI did produce a number of unsuspected leads later on.

This disagreement over patenting strategy was symptomatic of Black's increasing disenchantment with ICI:

> "I was restless in many ways, restless because the problem at ICI as I then saw it was that it didn't make use of its talents. It had so many talents and somehow they seemed to me to be squandered."[100]

So Black was withdrawing from the project, partly because of a growing fascination with another area which we shall consider later.

Meanwhile, the clinical experience with Alderlin was rapidly increasing. It was being studied at the centres that were continuing the clinical trial; in angina at University College Hospital,[101] St. George's Hospital, and the clinics of Drs. Fulton and Green; for cardiac arrhythmias at the Staffordshire Hospitals Group under J. P. P. Stock,[102] but also, as a consequence of the publication of the August '62 papers, it was increasingly being used by other investigators, initially mostly as a pharmacological tool, but some clinical work was also being done. Excluding the British clinical trials, 3 papers on Alderlin appeared in 1963, and 13 in 1964.

The drug was taken up quickly as an extremely useful experimental

tool on an international basis.* It was the second adrenergic blocker which supported Ahlquist's dual receptor classification, it did not have the residual stimulating action that DCI had, and was also of clinical relevance.

But doctors were not so ready to use the drug clinically as K. G. Green of the Medical Department explains:

> "I predicted that the introduction was going to be slow, because people weren't used to patients wandering around with heart rates below 60 - they found this a bit frightening, and we'd also learnt very soon that if you gave it intravenously, whereas a healthy volunteer could take 10 - 20 mg of pronethalol, if you gave 5 mg in a hurry to a patient who'd recently had an infarction his blood pressure dropped, and if there was any interference with his conduction mechanisms he'd get a slow heart rate and even cardiac arrest.
>
> So people were frightened in those days - and of course we weren't so commercially oriented as we are now - if the same situation came up now we'd say right - we won't market an intravenous preparation - whistle for it - but of course the people who knew how to use it were screaming for it."[103]

At ICI it was obvious that Alderlin was no longer the best compound they had. The October 1962 report notes that the action of Alderlin in producing CNS toxicity at relatively low doses was probably not an effect specific to its blocking action since its stereoisomer which had lower blocking potency had a similar CNS effectiveness.[104] In the early part of 1963 an event occurred which put an even higher priority on the development of 45,520; tumours were found in the mice in the long-term toxicity

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*1964 The 13 papers break down as : 1 general announcement
8 pharmacological investigations
4 clinical investigations

of these 3 were Scandinavian, 3 British, 3 Italian, 2 American, 2 Australian, 2 Swiss, and 1 French.

1965 The 38 papers break down as : 26 pharmacological investigations
12 clinical investigations

Of these, 14 were American, 12 British, 6 Italian, 3 German, 2 Swedish, and 1 Canadian.[105]

tests. In four different experiments, thymic tumours were found before 120 days. This had not been seen in rats, and also not in the studies that had been done on dogs, although these were not as extensive.[106]

> "The interesting thing is that the carcinogenic effect on mice was only discovered by accident. They were doing carcinogenic testing on rats, but the rats one or two months after dosing started to die. The rats died wheezing - some of them recovered, and some died. Because the animals were dying they had to do something so they went to mice.
>
> It was discovered that the rats died because they were dosed with a little syringe and a plastic cannula which was made up when they were small. As the rats grew, the cannula was no longer long enough to go into their oesophagous' and into their stomachs, so what was happening was that they were inhaling the solution and drowning in it."[107]

So as a result of this one mistake, the compound came under a shadow. Because of the extensive clinical interest, ICI decided to market the drug but to restrict its use to life-threatening conditions. This was conveyed by a letter written to the British Medical Journal, which appeared in the same issue as the reports of the clinical trials, coinciding with marketing, by Dr. G. E. Paget, who was responsible for the toxicological work on Alderlin.

> "Despite the evident clinical interest in the material it is not intended to promote sales of the drug for the large variety of conditions in which it might be beneficial, but to confine its use as far as possible to life-threatening conditions. This is because investigations of its toxicity have revealed that in certain circumstances it is a moderately potent carcinogen.
>
> Administration of the substance at high doses (up to 200 mg/kg) to rats for periods of up to two years, and to dogs for periods up to one year gave rise to no tissue changes of significance. When similar experiments were performed in mice, the experimental animals developed malignant tumours ... It therefore appears that pronethalol is a potent carcinogen to the mouse, but not to the rat, and possibly not to the dog. Nevertheless, the demonstration of potent carcinogenic action in a mammalian species is regarded as sufficient

> to contraindicate the use of the compound except for the treatment of conditions which themselves threaten life immediately or cause such morbidity that only short survival may be expected."[108]

Black, interestingly enough, has a very different perspective on this:

> "I would not have withdrawn from pronethalol. The evidence that it's a carcinogen, it's all stated in books as though it were a self-evident truth, a lot of people have tried to confirm it but the evidence is very thin. I would have proceeded cautiously, surely ... the decisions that were made were taken in the light of the knowledge that we had propranolol, and I wouldn't bank on what anybody tells you on what we might have said or done if we hadn't had propranolol - it's simply got to be a vital factor."[109]

Two points of interest in this account: Black had a loyalty to the compound which naturally arose from the fact that the compound was an embodiment of his theories, and he had put a lot of work into its development. The fact that the researchers felt they had a better compound was a key factor in 'giving up' Alderlin. What was being considered, then, was not the qualities, toxic and beneficial, of the compound in isolation, but in the context of its possible uses, which were mostly short-term, and possible replacements. One of the chemists substantiates this:

> "What came out in longer term testing was that the compound caused thymic tumours in certain species. The big question was, the sort of person who's going to be taking this doesn't have a thymus anyway, it will have involuted by the time they're thirty or forty, a question mark. But there was another compound coming along which resolved these doubts about whether we should go on with Alderlin - we felt we had something better, so we decided to give up Alderlin."[110]

The evidence may have been thin, but ICI were still marketing a drug with a known carcinogenic action. It had already undergone most of its preparation for marketing by the time this action was found, and this was probably a major reason for going ahead, although ICI cannot have hoped to recoup much of its investment

in the drug through limited sales to hospitals. But the compound seemed new and useful, particularly in acute situations, when the significance of its toxic side-effects would be minimised. The clinical trials published in the British Medical Journal in the same issue as the warning letter illustrate this:

> "The immediate suppression of digitalis-induced arrhythmias by pronethalol might clearly have considerable therapeutic value."[111]

> "Any treatment which can benefit patients suffering from angina pectoris or a cardiac arrhythmia must be looked at with specially keen interest, for no really new therapy has emerged for decades."[112]

The results of the trials were in many ways equivocal, however. As the editorial points out, there are many difficulties in the design of trials which rely on subjective assessments of benefit:

> "While clinical trials of any drug are often difficult to control and to assess satisfactorily, none is so difficult as that in which symptomatic relief is an end-point ... the placebo effect in this situation is considerable when the side-effects of a drug are conspicuous and the patient is aware of its administration even in a double-blind trial."[113]

These criticisms would put into question the results of at least one of the trials reported, in which the only criteria used were the patient's assessments of benefit.* The anginal trials involved only a small number of patients (12). This was described in the following way:

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*This was the trial at St. George's[114] in which the results were:

	Benefit	No Benefit
Drug	14	6
Dummy	3	17

Since the patients may well have been able to tell the active preparation, they may have preferred it on that basis rather than on the benefit or otherwise that it conferred.

> "The problem of assessing the numerous new drugs offered to clinicians is continuously increasing. It is not always possible, even if desirable, to mount a substantial and definitive therapeutic trial for each new drug in a single department. In these circumstances close observation of a few patients in several centres may provide data adequate to justify more general distribution of a new drug, with minimal diversion of workers from their other tasks."[115]

In one of the other trials the maximum tolerated dose of pronethalol was used, an average of 800 mg/day, which produced significant reductions in the number of attacks of pain felt by patients given the drug instead of the placebo, but also produced enough side-effects to nullify this benefit, as subjectively they did not feel better.** As a result of the Stockport trial, Fulton and Green concluded:

> "We consider that pronethalol may be useful in the management of about half the patients with severe angina pectoris."[116]

Three of the eighteen patients in the Stockport trial died in its one month duration; they were cases who had been referred because the standard drug therapy of nitroglycerin and long-acting vasodilators was not controlling their pain; this is some measure of the term severe.

The side-effects problem was evident in the trials and was admitted at two points:

> "The margin between the dose that is useful and that causing side-effects is often small."[117]

> "Figures for the incidence of most side-effects would be misleadingly high owing to the different ways in which the drug was used. Figures are therefore not given."***

**Trial at U.C.H. in which 11 out of 12 patients reported fewer attacks of pain.

***This refers to the U.C.H. trial which used maximum tolerated dose, and therefore provoked a high incidence of side-effects. But figures for the other trials could have been separated out.

The overall implication of the trials was then (with hindsight) that beta-blockade was therapeutically useful, if it could be made tolerable.

Alderlin was marketed on the 4th of November 1963. It was only shortly after this that Black left ICI and took up a post at Smith Kline and French. Why did he leave?

> "These things become independent of you after a time. The centre of gravity shifts from you to the clinical, and you have less impact on what was happening. It wasn't that I was miserable about anything specific, no-one had the knife in me or anything, I wasn't being inhibited - oh, I'd failed to get them interested in histamine, that's true, but apart from that. I was already obsessed with the histamine business because there seemed such a clear parallel and I was wanting to do this."[118]

Black had become fascinated by the application of the receptor concept to the histamine system, but he could not interest ICI in the idea of looking for blocking compounds in an analogous way to the adrenergic blockers.

JB: "How hard I tried I don't know, I certainly couldn't raise any interest."

JW: "Even after the success of the other? Or was that pharmacological rather than clinical success?"

JB: "I wouldn't credit them with too much thought on this. This business about you've done it once, so this somehow puts you in a different position, I don't think it does, that seems to have more impact outside than it does in. Really the question is, was it a good story? And the fact is that histamine was dead around the early 60 s - we had the work with gastrin bombing along, histamine was nowhere.

I think I did things at Smith Kline that I couldn't have done at ICI, I think I would have become completely bogged down in the beta-blocking thing. I'd have become more tied up with the frustration, I'd have been padding round the world going to bloody conferences, I'd have become invalided by it. So maybe I intuited that, maybe I realised that I had to escape."[119]

So Black left, basically because he did not like development work, which was what remained to be done at ICI. He cashed in on

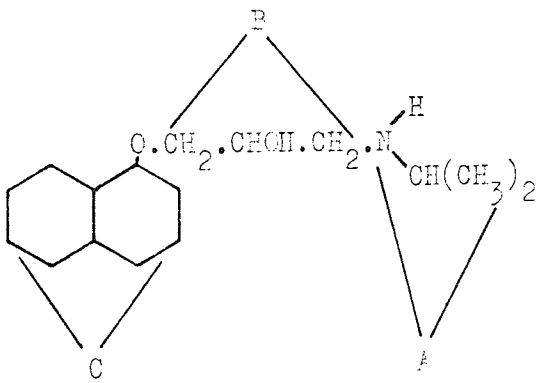
his success to give him an opportunity to pursue his ideas in another field. Although he abided by the letter of the 'gentleman's agreement' that senior research staff do not continue in the same area when they move from one company to another, obviously many of the same techniques would apply, and the move was not liked by ICI.[120]

So Shanks took over responsibility for the beta-blocking programme. He had already done much of the testing of the structural variations on the lead provided by 45,520.

Three types of variation in the compound were tried - on the terminal amino group (A), on the central group (B) and substitutions in the nucleus (C).[121]

Fig. 2.16

Areas of structural modification in the propranolol molecule



Of 38 type A variations, 10 type B, and 5 type C made between the end of 1962 and mid-'63 nearly all were active. Three examples of different types of compound were examined in detailed pharmacology and toxicology studies:

The naphthoxy analogue - 45,520

a phenoxy analogue - 45,763

a benzodioxan analogue - 45,847

The chemists were concentrating their activities on the more active phenoxy and particularly the benzodioxan series, and away from the less active heterocyclic compounds.[122]

During 1963, 8 patents were applied for, half the number of the previous year. These all concerned the benzodioxan compounds mentioned above, among which were the most potent blockers so far discovered - five to ten times the strength of propranolol. Various production processes were also patented. It would seem that the fact that 45,520 shared many of the production processes in which experience had been gained with 38,174 was a major advantage for the development of this compound which the increased potency of the benzodioxans did not offset.

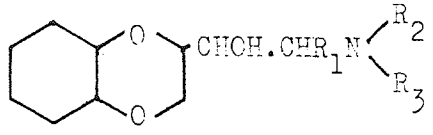
In Shanks' words:

> "The problem was that ICI had a whole selection of these compounds - what were they to do, what differences were there between them?"[123]

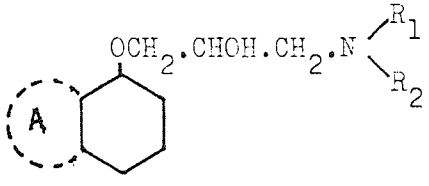
One of the characteristics of this period was the differentiating of other properties of these compounds besides their beta-blocking activity. At this time in the lab the most critical parameter seemed to be the degree of adrenergic stimulant activity possessed by the compounds. At the time this was termed Partial Agonist Activity (PAA), later it became known as Intrinsic Sympathomimetic Activity (ISA).

It was confirmed that pronethalol was not completely devoid of PAA in a comparison with the new agent 45,520 and other compounds which had been synthesized had varying degrees of this activity. Was this activity going to be of any clinical benefit?

> "We had another compound, 45,763, which had this PAA and I remember attending a number of meetings on 45,763 trying to decide what to do with it - would it be of any value clinically? And the Medical Department didn't think so - and not only did they not think so,

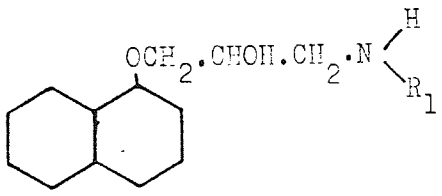


B.p. 1,038,333

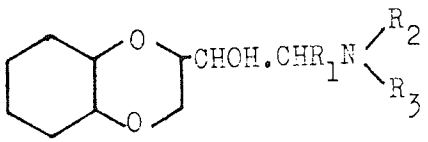


B.P. 1,058,822

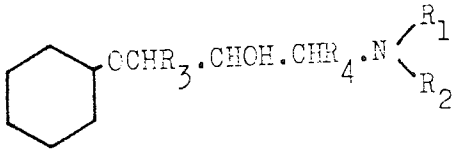
Fig. 2.17 Structures patented by ICI in 1963.
A is 5, 6, 7, or 8-membered heterocyclic ring



Naphthoxy



Benzodioxan



Phenoxy

Fig. 2.18 Three types of compound which underwent more detailed testing at ICI, 1962-1963.

but they didn't carry out any clinical investigations with it at all."[124]

Barrett suggests that a choice was made over pronethalol's successor between 45,520 and 45,763.

"The former was chosen on the grounds that the latter possessed some degree of PAA which was the reason given for dropping DCI."[125]

From the Research Reports, it seems more likely that 45,763, being discovered after 45,520, and having the disadvantage of PAA never competed seriously with 45,520, though it was later the subject of a letter to Nature.[126]

At this stage in the development work, then, there were many opportunities for friction to occur between the chemists, the pharmacologists, and those responsible for clinical development. A considerable amount of work had gone into the pharmacological and preliminary toxicological work on the phenoxy analogues which was taken no further, not to mention the initial chemical work; T. M. Wood had synthesized 48 compounds of this type in the first 6 months of 1963.[127] Pharmacological attention reverted to the routine testing of analogues, and further work on 45,520 which was undergoing extensive toxicity and tissue distribution studies up to the beginning of 1964. This was about the time when the new drug advisory body, the Committee on Safety of Drugs, was being formed (later the Committee on Safety of Medicines (CSM)).

"We could have marketed Inderal (45,520) without a CSM submission, but we decided as an exercise that we'd put one in"[128]

The submission was approved, apparently without need for more testing.

The project was now building up its level of activity. Shanks was in charge:

"I really controlled the whole pharmacology development programme for both propranolol and practolol. So that first paper by Black, Duncan, and Shanks, I did all the work for it. Then there are a couple of related papers: effects on cardiac function, effects on peripheral blood flow, effects on cardiac arrhythmias I did all that work, at the same time testing all the new compounds that were being made - but I had about 6 assistants - Long, Carter, and various other junior girls who did a lot of the work ... I was the only graduate working on beta-blockade at that point ... Dunlop was my assistant - he and I got on very well."[129]

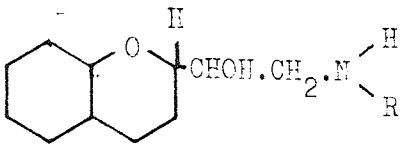
Dunlop had moved out of beta-blocking research after Shanks had joined the project and had moved to set up the testing needed by the newly-formed CSD, after Black left Davey asked him to move back. A definite hierarchy emerged as the team enlarged. Dunlop comments on what people would know about the strategy of the project:

"It depends what position you are in the hierarchy - Davey would know a lot more than Jim Black or Robin Shanks and they knew a lot more than me and I knew a lot more than the lab assistants."[130]

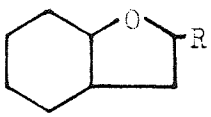
The chemistry section was run by Crowther:

"Being the section head in charge of the project, he assigned various chemists to do various bits; he drafted in chemical help from other sections, so at the height of our interest in developing this compound and finding out just how wide its activity might be, there were 18 pairs of hands working on it, of that about 5 were prime movers, and the rest were assistants."[131]

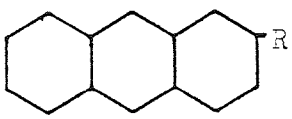
The chemists were now making a variety of substituted ring compounds after their discovery of the highly active benzodioxan series. The structures illustrated in fig. 2.19 were synthesised around during the first half of 1964.[132] Howe began work trying to locate the part of the pronethalol molecule responsible for its carcinogenic action.[133] This was important if 45,520 which had a very similar structure was to be cleared of carcinogenic risk, especially important for U.S. marketing.



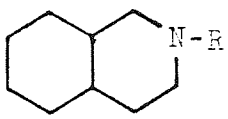
Chromans



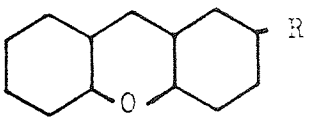
Benzofurans



Anthracenes



Isoquinolines



Xanthenes

Fig. 2.19 Structures synthesised by ICI in 1964.
R = side-chain as for chromans

At this point the pharmacologists were occupied with testing the large numbers of new structures being synthesised, rather than looking at the compounds in more detail. As Shanks says, he and Crowther "met once a week, and he told me what he had been making, and we just continued to test them".[134]

Although the marketing of Alderlin had been greatly restricted, clinical studies continued to be done. Work done by Vaughan-Williams at Oxford on isolated hearts had shown that pronethalol was likely to be useful clinically in preventing the arrhythmias which are caused by digitalis overdose.[135] In studies in humans under anaesthesia, Payne and Senfield found that pronethalol was useful in treating similar arrhythmias caused by the anaesthetic.[136] Gill and Vaughan-Williams showed that pronethalol itself was a local anaesthetic twice as powerful as procaine.[137]

The most important study, from the point of view of the development of beta-blockade was the first use of a beta-blocker as an antihypertensive, by one of the clinicians who had participated in the earlier trials in angina.[138]

Brian Prichard had noticed a small fall in the blood pressure of the anginal patients in this trial which lasted 8 weeks, using the maximum tolerated dose of the drug. He decided to test this effect on normotensive and hypertensive patients over a longer period. As before, he used very high doses - the maximum daily dose was given as 800 mg in the British Medical Journal,[139] but Prichard was using 400 - 1600 mg/day. His 15 patients, 4 normotensive with angina, the rest hypertensive, took pronethalol for 3 months. Whereas in the angina trial, falls of 8/5 mm when supine and 6/5 when standing had been found, he produced falls of 33/23 and 27/16. He comments:

"In all of 11 hypertensive patients on pronethalol there has been a considerable fall in blood-pressure with the absence of postural hypotension. Side-effects, chiefly tiredness were avoided by carefully adjusting the dose. The slight hypotensive action seen in the double-blind trial in angina ... may be due to the fact that longer administration is needed to produce the maximum effect."[140]

Prichard describes the particular advantage that beta-blockers might have as antihypertensive therapy:

"It is well-known that hypertensive patients may overact to many cardiovascular stimuli. Interference with the cardiac component of such responses might exert a useful effect in preventing the transient rises in blood pressure that so readily occur in hypertensives, and so be valuable in therapy."[141]

This paper caused very little reaction at the time, but later came to be seen as having great significance in the clinical development of beta-blockade.[142] Prichard concluded:

"When a non-carcinogenic beta-receptor blocking drug is produced, it would be well-worth trying in the treatment of hypertension."

By mid-1964, 45,520, now named propranolol was being prepared for marketing.

2.2.2 Research at A. B. Haessle and Mead Johnson

A. B. Haessle

Ths Swedish company, A. B. Haessle also became interested in the possibilities of adrenaline-blocking compounds at about the same time as ICI, though from a rather different perspective. The research director of A. B. Haessle comments:

> "In 1959 we identified a medical need for new drugs in the cardiovascular field, especially new antiarrhythmic drugs. During a meeting in February in 1960 we decided to start a project aiming at a new type of antiarrhythmic drug. Synthesis and screening of compounds started in 1960."

The two companies were after the same pharmacological action, with slightly different medical applications in mind. It seems to have been the impact of recent advances in academic work on adrenergic amines that determined the choice of starting point.

> "Within the monoaminergic sympathico-adrenal field of research major Swedish contributions have been made. Noradrenaline was identified in 1946 as the transmitter at sympathetic adrenergic nerve endings by Professor Ulf S. von Euler, University of Stockholm.
>
> The late Professor N-A. Hillary and coworkers developed the fluorescence histochemistry method for visualization of biogenic amines.
>
> These two fundamental discoveries became the starting point for a rapid and most important development within the field of central and peripheral monoadrenergic mechanisms - of greatest importance also for the understanding of cardiovascular control.
>
> Another important factor was that scientists of the Department of Pharmacy, University of Goteborg had a great interest in catecholamine-research. These university scientists suggested that we concentrated our antiarrhythmic research-programme on compounds protecting the heart from over-stimulation by adrenaline and noradrenaline due to physical or emotional stress situations. This was the definition of our research-project aiming at beta-blocking compounds."

The structure of DCI was taken as the chemical lead for further syntheses.

The controversial concepts in which Black was trying to interest ICI in 1957-58 were apparently more respectable in Sweden in 1959-60, as there is no suggestion of anyone occupying a "product champion" role as Black did. There were two main differences between the independent, yet closely similar research projects. Haessle were after an antiarrhythmic rather than antianginal drug, and they did not want a pure blocking action, as Black did:

> "we from the beginning were aiming at compounds with a certain intrinsic activity to compensate for the basic adrenergic stimulation at rest which (it) might not be desirable to block."[1]

The contrasting attitude of the ICI project is illustrated by their research director, Fitzgerald:

> "You make up your mind whether you want to block the beta-receptor or not - if you want to block it, you block it."[2]

Extensive chemical syntheses and testing were done, part of which was published in 1963.[3] Relating their work to DCI and pronethalol, they describe compounds of the general formula illustrated in fig. 2.20, and come to very similar conclusions as were reached by the ICI chemists in Parts I and V of their published work on the effects of changes in R_1, R_2 and R_4 on beta-blocking activity and ISA, which were the properties with which their tests were mainly concerned, though they did additionally test the antiarrhythmic potency of their compounds. Their best compounds at this stage were B and C in fig. 2.20.

In the course of testing variations on these lead compounds, they found that adding a methyl group to the first carbon of the ethanolamine side-chain of these compounds produced some unusual effects. The compounds were sent for testing to Neil Moran, who had previously worked on DCI. He found that these compounds

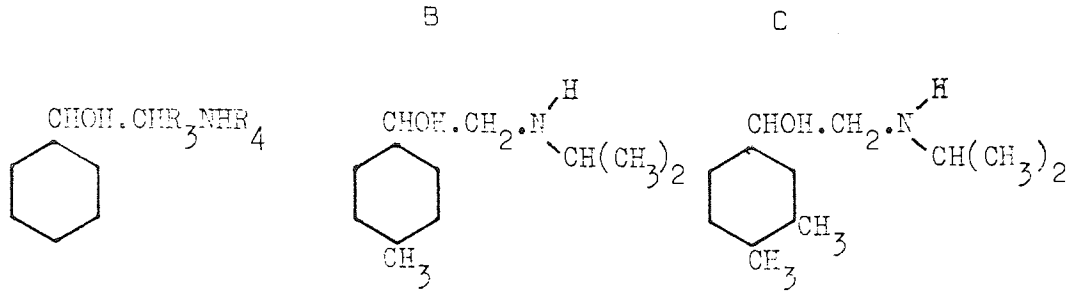


Fig. 2.20 Early chemical work by A. B. Haessle; areas of molecular variation and preferred compounds.

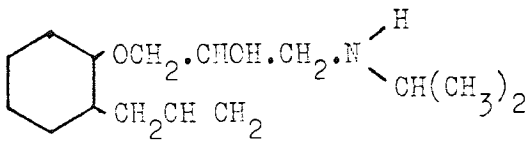
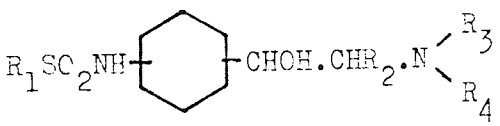


Fig. 2.21 Structure of H56/28 - alprenolol.



R_1	R_2	R_3	R_4
CH_3	H	H	$CH(CH_3)_2$
CH_3	H	H	$C(CH_3)_3$
CH_3	CH_3	H	CH_3

Fig. 2.22 Molecular variations tried by Mead Johnson

(coded H35/25 and H13/59, respectively) had no effect on beta-receptors in the heart, but both produced a fall in blood pressure. This was interpreted as showing that the peripheral beta-receptors affecting blood pressure were in some way different from those in the heart.[4]

So in 1963 the Haessle workers had found that compounds could be produced which distinguished two types of beta-receptor. What significance this might have was not known.

Two other important events for the project occurred in 1963. H29/50 was first tested in man in that year, which gave the same kind of encouragement to the Haessle project as the testing of 38,174 had (in late 1961-early 1962) to the ICI workers. A new cardiovascular pharmacologist, Bengt Åblad joined the team in that year. The Research Director, Ivan Östholm says of him:

> "According to my personal opinion, the most important turning point was the employment in 1963 of doctor Bengt Åblad. It was thanks to him that our biological test-methods were more oriented towards the therapeutic effect which we were aiming at. Due to the fact that his thesis had been studying pharmacological mechanisms both in animal and in man, he had a much deeper understanding of biological concepts and the clinical relevance of animal test methods than we had before. Dr. Åblad introduced new test methods, e.g. in cat where the endogenous sympathetic activity was eliminated."[5]

The important step from the ethanolamine to the propanolamine side-chain (similar to the change from pronethalol to propranolol) is described by the chemist, P. Berntsson as follows:

> "Already in 1961 the synthesis of compounds with the ethanolamine side-chain [$-\underset{\underset{OH}{|}}{C}HCH_2NHCH(CH_3)$] started. However, all compounds with this side chain were found to have too high an intrinsic activity. Thus it became necessary to change the chemical structure to make the compounds a little more different from the isoprenaline structure. It is quite obvious to try to change the side chain. The simplest change for an organic chemist is actually to make compounds with the oxypropanolamine side chain. They are made in a very simple two step synthesis from a phenol; epichlorohydrine and isopropylamine."[6]

It is difficult to assess whether this change was due to Haessle chemists learning of the structure and exceptional activity of propranolol or whether, as they suggest, it was arrived at independently.* Berntsson goes on to say:

> "The fact that several companies filed patent applications for this type of compound at about the same time indicates that the step from ethanolamines to oxypropranolamines is an obvious one from the chemical point of view. All other possible changes of the side chain are much more complicated from the chemical point of view and are all (as far as I know) synthesized later."

One compound out of "almost 100"[8] made with this oxypropranolamine side-chain was synthesized in 1964 which seemed to fulfill the aims of the project. It was coded H 56/28 and became known as alprenolol. The rationale behind the selection of alprenolol with its weak stimulating action is described by Haessle pharmacologists:

> "The experience from the use of propranolol in patients with cardiac disease indicates that the most important undesirable effect of this drug is cardiac depression due to the elimination of cardiac sympathetic drive. Such a complication should be expected to occur less frequently in the clinical use of H 56/28 because its beta-receptor blocking action is combined with a weak heart stimulating action."[9]

It was tested in man in early 1965 and the pharmacology first reported in 1966.[10] While H 56/28 was being prepared for marketing it was tested as an antihypertensive, based on the good results that Prichard in England and Werko in Sweden were getting with propranolol.[11]

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*Interestingly enough, the paper describing the chemical synthesis of these compounds (Brandstrom 1966) derives the oxypropranolamine side-chain from Fourneau's work on benzodioxan adrenergic blockers in 1936.[7]

The results showed promise but indicated that a different profile of activity would be best for this indication. This led to the development of metoprolol (see later).

Alprenolol could not be marketed in the U.K. because ICI's patents antedated those of A. B. Haessle.

Mead Johnson

This American company also noted the lead of DCI, and became involved in molecular modification of adrenaline and noradrenaline. However, they seemed to be mainly interested in the resultant chemicals in their traditional role as decongestants. This is implicit in the concluding remarks of their article in which their approach was outlined, published in 1966. Of a series of 26 compounds produced by the substitution of a sulphonamide group for the phenolic hydroxyl, the only one specifically mentioned as therapeutically useful is an alpha-stimulant, compound 6, which

> "has been shown to be an effective non-irritating long-acting nasal decongestant MJ-1996, Dricol, Fentrinol."[12]

Three compounds of the series which were shown to be beta-receptor blocking agents "are undergoing clinical examination." These compounds are illustrated in fig. 2.22.

Their strategy, as presented in the 1966 paper is rational, concluding that since the chemical character of the methylsulphonamide group (CH_3SO_2NH) was closer to that of the hydroxyl which it was replacing than previous substitutions which had been tried (into the structure of adrenaline), it would be more likely to be biologically active. Their clinical examinations of the beta-blockers were obviously not very promising even though the compounds showed very low toxicity as Mead Johnson did not market a beta-blocking drug until 1974.

2.3 Introduction, imitation and use

2.3.1 Propranolol's progress

Propranolol was marketed in the U.K. under the name of "Inderal" in August 1965 in the form of 10 mg and 40 mg tablets and 5 ml ampoules for intravenous use. The indications for which it was to be prescribed were"selected cardiac arrhythmias" and "angina pectoris". Shortly afterwards, in October, pronethalol was withdrawn. Before marketing about 2,000 patients had been treated (1,500 orally, the remainder by intravenous injection) by about 130 investigators in Great Britain, and about another 3,000 abroad.[1]

Two clinical trials in angina pectoris had been published in the British Medical Journal before general release, one open exercise trial by Hamer, Sowton and others in London,[2] and one double blind by Srivastava, Oewar and Newell at Newcastle.[3] Using 80 - 100 mg of propranolol/day the open study found that about half of the 20 patients did about half as much work again after propranolol as they had done before. The double-blind study using a lower doage of 60 mg/day found no significant difference in frequency of attacks between propranolol and placebo periods, though of the patients that preferred one or other of the regimes, the majority preferred propranolol.

Thus the initial clinical evaluation was in many ways equivocal. The open trial was criticised for lack of controls,[4] but the inconclusive results were mainly due to the unsophisticated nature of the trial protocols then in use, and the novelty of the effects observed.

Better results were produced by the use of 90 mg/day and 4-week assessment periods (twice that of Srivastava *et al.*) by

Keelan in a double-blind trial in the British Medical Journal early in 1965.[5] He found that 13 of 19 patients had fewer anginal attacks on propranolol. But the important push to Inderal's clinical development in angina was given by two trials by Gillam and Prichard in 1965[6] and 1966.[7]

Both used much larger dosages than other investigators; in fact using the maximum tolerated dose in a similar protocol to that which had been used earlier by them for pronethalol, with an arbitrary maximum of 400 mg/day. On an average of 292 mg/day all 14 patients who completed the 1965 trial showed a reduction in glycerine trinitrate (GTN) consumption. This well designed trial had a 3 month "run in period" to adjust dosage and stabilise the effect of increased medical interest. The trial published in 1966 was in fact reported at the Buxton conference on propranolol in November 1965. It used a variable dose schedule similar to the first trial, but as well as this regime and placebo, half-strength doses were used. 16 of the 17 patients in the trial had fewer attacks of pain, and took less GTN on both full and half strength than on placebo, and of this 16, 13 had greater benefit from the full-strength rather than half-strength. However at the conference Prichard's use of high doses and his claims about propranolol's long-term effects on blood pressure were met with considerable scepticism.*

The Buxton symposium on propranolol[8] also contained other significant observations. The use of propranolol and pronethalol

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*See for example, Braunwald's comments in his introduction and Werko and Taylor's comments on Prichard's "baroceptor reset" theory in the discussion of his paper.[8] Rrichard's paper reports no long-term effect on blood pressure.

in patients with impaired hearts was discussed and the dangers of intravenous use brought out:

> "I would like to suggest that there is a sharp cleavage between the oral and the intravenous use of these drugs and that the ampoule is a very dangerous weapon indeed ... I would again emphasize the importance of giving 0.5 - 1.0 mg and then waiting."[9]

In fact pressure was put on ICI to change the size of ampoule used for injection:

> "I would like to suggest that the ampoule size be reduced. It is 5 mg at the present and junior hospital staff are rather apt to assume that one ampoule is a safe dose."[10]

> "I would like to emphasize again the need for a smaller ampoule and I would quite agree with Professor Dornhorst that if one puts 5 mg in an ampoule, it is an invitation to give 5 mg."[11]

Stephen's paper on side-effects[12] which tabulated information on the pre-marketing clinical use implicates propranolol in 11 of the 26 deaths during propranolol therapy of 5,000 patients. Most if not all of these got 5 mg intravenously for a cardiac arrhythmia, which precipitated fatal heart failure. This was an important factor in delaying the wider acceptance of beta-blockers.[13] ICI, however, did not introduce the 1 mg size until 1976.

Vaughan-Williams' piece on the "quinidine-like" action of propranolol in reducing the rate of rise of electrical excitation in isolated hearts[14] suggested that it was this property of propranolol rather than its blockade of beta-receptors that made it an effective antiarrhythmic drug. There were also suggestions linking this property of propranolol with the fact that such high doses seemed to be needed for effective relief of anginal pain. Stephens comments:

> "In our lab we have shown that 30 mg propranolol will block exercise tachycardia for several hours. What we are concerned about is why the very much larger doses are necessary for the treatment of angina, and it seems clear to us that there must be some other mechanism involved in the reduction of angina apart from beta-blockade."[15]

There were even suggestions that propranolol might be acting merely as an anaesthetic on anginal patients. The bronchoconstricting effect of propranolol on asthmatic and bronchitic patients was becoming clear as another important contraindication to the use of beta-blockade.

The paper which drew most attention at the time was on the use of propranolol as a prophylactic antiarrhythmic in patients who had just had a heart attack, by Snow, which was also published in the Lancet.[16] Using 20 mg four times a day, treating alternately admitted patients, he reported a 13% mortality in the treated group compared with 29% in the untreated. Professor Dornhorst, the Section Chairman, who had been involved with the ICI team since the first clinical use of pronethalol said of Snow's results:

> "I think we must all agree that they do represent the most exciting development that has been talked about in this conference. I would just like to remind you that it was the prospect of this sort of effect which led Dr. J. W. Black to decide to work on beta-blocking drugs, and it looks as though there is a good chance that his vision will be vindicated."[17]

However, later multicentre trials with larger numbers of patients set up to confirm these results failed to show any effect.[18]

> "Accordingly the initial enthusiasm for propranolol, triggered by Dr. Snow's very impressive publication tended to wane."[19]

So the controversies surrounding propranolol's mode of action and its efficacy in the conditions for which it was indicated, angina and arrhythmias, did not encourage doctors to use it, neither

did the other uncertainties which Shanks summarises:

> "Propranolol took off very slowly - tremendous resistance to the drug for a variety of reasons ... doctors were scared of it because
> 1) it slowed heart rate
> 2) it produced cardiac failure
> 3) it might produce bronchospasm
> - so the sales of the drug went very slowly initially ... Propranolol really was too early a drug - it was too potent a drug for doctors to use because they didn't understand it."[20]

K. G. Green of the Medical Department was aware of this problem early on:

> "I predicted it would take 2 to 3 years before Inderal took off. People would have to learn the concept of beta-blockade and we would have to teach them. We had to make sure that the reps knew what the score was, Jim Black and Robin Shanks did a lot of lecturing."[21]

The growth in sales of propranolol can be seen in fig. 2.23 with the 10 mg and 40 mg tablets shown separately, and in fig. 2.24 combined, compared with the sales of nitrate preparations, the most widely used anti-anginal drugs, and all anti-anginal preparations. The slow growth 1965-70 is evident, but this increases markedly towards the end of this period.

The higher doses used by Prichard and Gillam (up to 400 mg/day) led to use of 160-320 mg/day becoming the norm, better results being obtained from trials,* and the use of propranolol being considered in less severe cases of angina.

Propranolol was approved for U.S. marketing in 1968 but only for the treatment of phaeochromocytoma and specified types of cardiac arrhythmia, not for angina. Thus, doctors using it for angina were open to malpractice suits, and the manufacturer (Ayerst) could not provide package information relating to its use in angina.

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*The increase in use of individualised dosages and run-in periods also contributed to this - see Prichard.[22, 23]

Thousand prescriptions

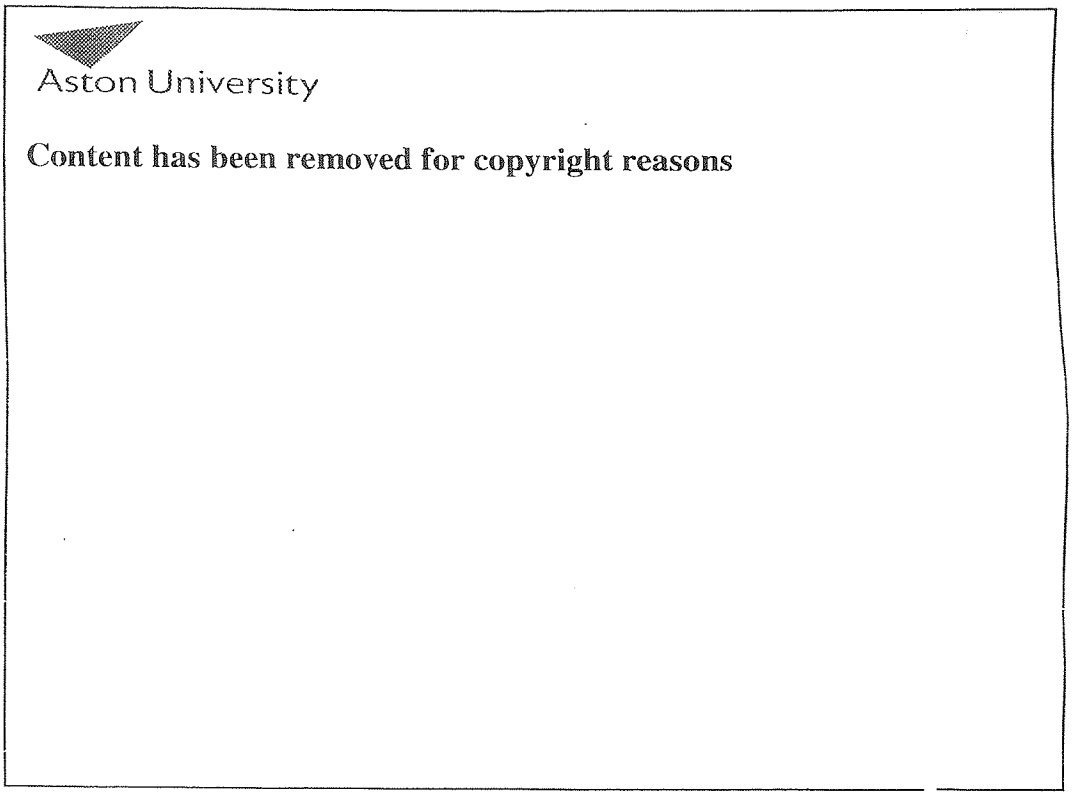

Fig. 2.23 Sales of Inderal (propranolol), Great Britain 1965-1970.
Source: Department of Health and Social Security

Fig. 2.24 Sales of preparations used in angina, Great Britain, 1964-1971

Source: New perspectives in beta-blockade CIBA Symposium 1973 p. 206.

The use of propranolol in hypertension was confined to a small number of investigators in the early years of propranolol's use, as apart from Prichard's initial report in the British Medical Journal in 1964,[24] and subsequent report at Buxton,[25] there were no very positive reports on its use as an antihypertensive and one negative.[26] There were several factors that contributed to this lack of acceptance of the possible usefulness of propranolol as an antihypertensive. The most important of these was the necessity to use large doses. This provoked two reactions - first the fear of precipitating heart failure which propranolol was knowr to do sometimes even at low doses, second, because it was known that quite a small dose of propranolol would block the tachycardia produced by a dose of isoprenaline that would produce a marked tachycardia when unopposed, and therefore apparently produce significant beta-blockade

> "it was felt that any larger dose of propranolol was unsafe and any effect would be unrelated to beta-adrenergic blockade."[27]

The lack of controlled trials was another important influence. Prichard was only doing open-type trials which do not compensate for the placebo effect, so that his results were not persuasive. ICI could not get trials set up to test his results, though:

> "I remember we couldn't get trials set up with propranolol in hypertension - it's unbelievable now - we couldn't get trials set up in this country - people felt it's cardiac depressant and doing nasties ... and of course its effect wasn't immediate."[28]

Prichard, worried about the dangers of precipitating heart failure, had been starting at very low doses - 10 mg three times daily, and then building up slowly. With this regime the full antihypertensive effect was not seen for 6-8 weeks. As Prichard and Gillam comment:

> "Patience was often required to get blood pressure control, and this may have been one of the factors which delayed the acceptance of propranolol as a practical treatment for hypertension."[29]

In fact, it seems now that this delayed effect is probably largely due to the slow building up of the dose. In cases where patients have been put on large starting doses this delay is much reduced.

ICI found it difficult to back Prichard up on the hypertension issue:

> "In animals you couldn't show a lowering of blood pressure - we didn't have an animal model to bang on the table and there was a lot of internal debate here, and I was puzzled ... Prichard was saying it would take a week for propranolol to lower blood pressure and of course in clinical practice guys don't want to wait a week - there's no real reason."[30]

In this early period the only other workers that produced similar results were Zacharias and his group at Clatterbridge Hospital, Wirral.

Gradually, however, more trials were done with propranolol at higher dosages and the majority of these showed a significant antihypertensive effect (Paterson and Dollery 1966, Richardson, Tewari and Grant, and Frohlich, 1968)[31-34] although some contrary results were still being published (Humphries and Delvin, 1968).[35] These were attributed to inadequate dosage. With this accumulation of positive evidence ICI were able to get clearance from the CSM for marketing propranolol in hypertension in January 1969. The most significant push for propranolol as an antihypertensive came later that year:

> "The major breakthrough for beta-blocking drugs in general, and propranolol in particular, as anti-hypertensive agents resulted from the findings published by Prichard and Gillam in the British Medical Journal in 1969."[36]

This for the first time put propranolol on a par with other major antihypertensive drugs such as methyldopa, guanethidine and bethanidine, in terms of its antihypertensive effects, and showed that most patients preferred it to the other drugs. This led to a rapid increase in interest in beta-blockers in general, and propranolol in particular, as antihypertensive agents.[37]

2.3.2 Beta-blocker research, and marketing of follow-on compounds (1965-70)

CIBA

The data available in CIBA's involvement in beta-blocking research is very limited.* The first article mentioning an interest in beta-blockade is dated December 1964. Published in 1965 it involves tests of pronethalol's ability to inhibit other antihypertensive drugs.[1] This theme is continued in a paper in the British Journal of Pharmacology in 1967 where the compound oxprenolol first appears.[2]

In these papers Brunner concentrates on the influence of beta-blockers on hydralazine which was marketed by CIBA. Oxprenolol, 39,089 Ba, is compared with propranolol in the 1967 paper where oxprenolol's ISA is first mentioned as a clinical advantage.

Oxprenolol was patented in Switzerland in September 1964, and in Britain very shortly afterwards. It was therefore discovered before the patents on either Haessle's alprenolol or ICI's propranolol were published (January 1969 and June 1965 respectively). Presumably, therefore, CIBA workers must have discovered the switch in the side-chain from ethanolamine to oxypropanolamine independently. This would suggest that it was indeed a reasonably obvious step.

Shanks characterises CIBA's work as follows:

> "They apparently made compounds which were not covered by ICI patents but do not have any back research commitment. Thus there was no leader to their reseach programme."[3]

---

*Two enquiries to CIBA about their beta-blocking research through its Marketing Services department led on one occasion to a response after some months that my request for information would have to have approval from Swiss headquarters, and then nothing. The other enquiry - a request for the names of those scientists responsible, and some idea of the contributions which they had made - brought copies of CIBA symposia on oxprenolol, which were exclusively clinical papers.

Fig. 2.25 shows the structure of oxprenolol.

ICI

In mid-1964, with propranolol well on the way to being marketed, what directions were the chemists and pharmacologists at ICI pursuing? The two obvious defects of propranolol were the local anaesthetic activity discovered by Vaughan-Williams and the precipitation of bronchospasm in asthmatics, due to the blockade of beta-receptors in the lung tubes, the bronchi.[4]

The first seemed to question the mode of action of beta-blockers in angina - might the reduction of anginal pain caused by propranolol not be due to a direct anaesthetic effect rather than its supposed reduction of cardiac work? This was a disturbing possibility, especially when as eminent an expert in antiarrhythmic drugs as Vaughan Williams then claimed that propranolol's effect on cardiac arrhythmias was due to other attributes of this anaesthetic activity - the so-called "quinidine-like effect."[5, 6]

The second restricted the use of propranolol - a compound with greater specificity might overcome both of these problems. It is difficult to know how conscious these directions were at the time of practolol's synthesis, but certainly early in its development they were widely seen as important.

In 1964, A. Crowther, who was in charge of the chemists working on propranolol modifications went to a conference of medicinal chemists in the USA.* He heard that Mead Johnson had been researching into beta-blockade, and their compounds using a sulphonamido

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*Malkin records this as a "Gordon Research Conference" in New Hampshire. I have also found that the sotalol material was presented at the medicinal chemistry section of the American Chemistry Society meeting in April 1964 in Philadelphia (published in Federation Proceedings in 1964).

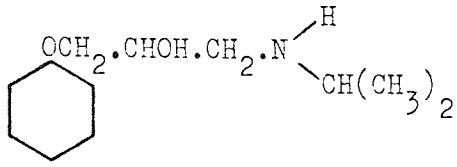
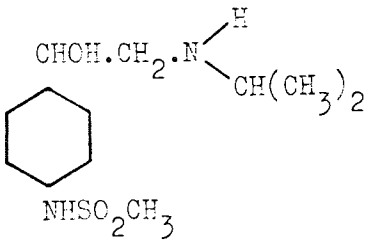
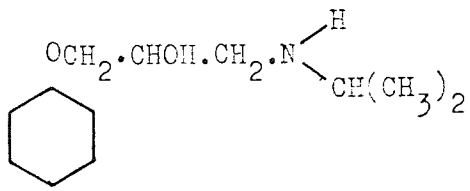


Fig. 2.25 Structure of oxprenolol.



sotalol



propranolol

practolol

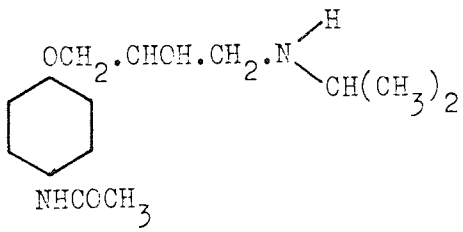


Fig. 2.26 Derivation of practolol.

substitution (see Sec. 2.2.2) had low toxicity. This was because they were water-soluble rather than fat-soluble like propranolol and hence did not readily enter the brain (which fat-soluble compounds do), and so did not produce any of the nervous system side effects of ICI's fat-soluble compounds. They also had none of propranolol's "quinidine-like" activity. He communicated this directly to the chemists at ICI. Howe, one of the chemists, recalls:

> "At the time I was as it were looking after the shop. I got the group of chemists together and said 'what shall we do about this?' It was fairly obvious that we ought to put this methylsulphonylamino group that Mead Johnson had found interesting in their series into the propranolol series."[7]

In fact, an acetamido substitution was used rather than sulphonamido as it was easier (Fig. 2.26 illustrates). The resultant compounds were not very active and so were not pursued.

The participants in the innovation differ on the question of how one of these compounds, 50,172, later known as practolol, came to be developed for marketing. Shanks' version is that it was a chance discovery during routine activity:

> "The results were written up on these cards ... and I had to go through all these cards and check the results every week, and I noticed this one compound blocking the heart rate but not blocking the peripheral vasodilator effect. And then I immediately did experiments in dogs and confirmed this."[8]

Barrett's version is that Shanks wanted to assess the importance of the local anaesthetic activity of propranolol by comparing propranolol with an equivalent compound without this activity - this was achieved by using one of the optical isomers which did not have this activity, but did have the local anaesthetic action, and a compound which had beta-blocking, but not local anaesthetic activity. 50,172 was chosen for this:

> "At the same time because of the concomitant blockade by propranolol of beta-receptors in the bronchi, and the risk of inducing bronchospasm, pressure was exerted by Dr. D. G. Davey (then Biology Manager at ICI) to re-examine past screening results to see if any evidence of cardiospecificity could be found ... A search revealed that by a curious coincidence this same 4-acetamido analog did in fact display a separation of beta-blocking activity in the desired direction."[9]

This version is also similar to the accepted oral history within ICI, as it was told to J. D. Fitzgerald in 1966-7 when he joined the beta-blocking team.[10] Also Dunlop recalls "looking at records" and that:

> "we were looking for a compound similar to MJ 1999 (sotalol) which had a bit of ISA."

He makes it clear that at this point ICI were slightly worried that a different activity profile from that which they had been looking for, and which propranolol embodied, might be more therapeutically successful (the fact that CIBA patented oxprenolol which was known to have ISA in August 1964, may be relevant here). He does not mention any special pressure to check out the possibilities of a more selective compound, and in fact comments

> "in spite of what anyone may tell you we weren't looking for a selective beta-blocker ."[11]

Whether the discovery of the possibility of blocking beta-receptors in the heart preferentially to those in the rest of the body was by design or accident is in some ways not a very significant question. It is apparent that at this time there were considerable pressures to direct research towards the production of compounds showing increased specificity. There were around five compounds in the acetamido-substituted series that showed this specificity for cardiac beta-receptors, and 50,172 had

clearance from the newly-constituted committee on the Safety of Drugs for use in man for the comparative experiment mentioned above. It was, therefore, an obvious choice for further development, though its beta-blocking potency was considerably less than that of propranolol.

Shanks' view on this differs slightly:

> "One of these (cardioselective) compounds was sotalol with the propranolol side chain and then there was the other one which was the side-chain turned round and attached to the other end - that was practolol. And ICI decided to look at this because it wasn't obviously just a copy of Mead Johnson's compound."[12]

He continues:

> "I discussed this with Dunlop and Barrett and said 'here's a compound that's different' - and we discussed the typology and I coined the term cardio-selectivity ... We then had to describe this at a management meeting and they had to decide what were the possible beneficial effects, and one was in cases of asthma and the second was a discussion on whether the coronary arteries had β-1 or β-2 receptors - if they had β-2 receptors then you wouldn't block them with practolol whereas you would block them with propranolol. This might mean that in patients with angina you would not block the vasodilator action, say of adrenaline."[13]

However, as propranolol had not yet been marketed, and the sales potential of beta-blockers did not seem very great, ICI were not very enthusiastic about developing another compound, even if it had new properties. Under pressure from the pharmacologists, Barrett, Shanks, and Davey, they agreed to start the preliminary toxicity tests.

> "But at that stage ICI didn't appreciate the advantages of a drug like practolol and Davey, my manager - he and I went to talk to a cardiologist called Stock and a physician called Kennedy to see would there be any future for a drug like practolol, and they said 'no future at all' - so the development of it was quite slow."[14]

New tests were needed to assess these new properties.

> "We measured hand blood flow and heart rate and showed that propranolol blocked both peripheral vasodilator and cardiostimulant actions of isoprenaline, but practolol only blocked the central effects. We then went to the chap next door - Ted Davies - he had a test running for bronchoconstriction, and showed that propranolol had bronchoconstrictor activity in guinea-pigs whereas practolol did not."[15]

But it was difficult at the time to see the potential of another beta-blocker - were its properties distinct enough to make it worth marketing? It seems that in this case it was the pressure from the pharmacologists that induced ICI to take the second compound through to clinical studies before the beta-blocking market opened up.

Shanks left ICI in mid-1966 for reasons discussed elsewhere, and the development and marketing of practolol came under the control of A. M. Barrett, previously an endocrinologist in pharmacology, and J. D. Fitzgerald on the clinical side. Both were ambitious, and as Barrett says:

> "A new drug which does well and makes money doesn't exactly hinder one's progress in the company."[16]

In 1967 came the news that CIBA was conducting clinical trials with oxprenolol and were going to market it. Practolol was seen as a counter-move by ICI.

It was marketed in 1970, mainly on the basis of its cardio-selectivity making its use easier because of the reduced danger of bronchoconstriction. Its use in congestive heart failure was also taken up as evidence of its safety.

2.3.3 Clinical use of beta-blockade, 1970-75

In August 1970 propranolol was joined by two new blockers, practolol from ICI, and oxprenolol from CIBA. At this stage the market for beta-blockade was expanding considerably, because of the publication of its successful use in hypertension which made it seem a much safer drug therapy than had hitherto been thought. Sales of all three blockers greatly increased during this period.

The way in which the new compounds were marketed were in many respects complementary. CIBA chose a 'scientific' approach with an electrocardiogram image showing that "Trasicor actually reverses ischaemic ECG changes both during exercise and at rest". Promoting oxprenolol as "a new and better beta-blocker with important advantages in angina pectoris", the main advantage stressed was the "beneficial mild ISA on myocardium". Later on in 1971 this was expanded to "improved safety - greater protection against induced heart failure, less likely to increase airways resistance".

Practolol was promoted in a more restrained manner - a picture of a middle-aged man climbing the steps of an airliner was captioned "Before Eraldin he'd have thought twice about going". The drug was heralded as "the latest, most advanced, long-term protection against angina", but the new property of cardioselectivity was not prominent, and was mainly stressed in terms of safety.

Propranolol in angina was promoted as a 'strong protector' - against an image of an old person on a park bench at sunset the caption read "Angina pectoris - there's no need to give up, Inderal helps make life worth living again".

In 1967, ICI had registered propranolol for the treatment of angina with the US Federal Drugs Administration (FDA), however it had not been approved:

"In April 1970 an ad hoc advisory committee unanimously agreed with the FDA's medical staff that propranolol should not be approved for treating angina because the existing studies were inadequate to demonstrate efficacy and there were unresolved safety questions. As a result of the committee's recommendation against approval, the drug's sponsor initiated controlled clinical trials that are still in progress ..." (1975)[1]

The FDA has very strict requirements for proof of safety and efficacy before any drug is marketed there. So propranolol, which in 1970 in Britain was an accepted drug for the treatment of angina was sent back for further studies.

Practolol sold very well in the early 1970s, taking off much quicker than propranolol, as there was a prepared market, but also substantially more rapidly than oxprenolol.

"The great advantage of practolol was not only that it was cardioselective for the patient with chest disease, but studies on cardiac function showed it didn't reduce heart rate and it didn't reduce cardiac output, therefore it did not produce cardiac failure. So doctors began to use this drug because it wouldn't affect the bronchi, secondly it didn't depress cardiac function, thirdly it was less active - only a fifth of the activity of propranolol."[2]

The biggest factor in the rapid take-off of practolol seems to have been its "safety" in comparison with propranolol which we have seen had an image as quite a dangerous drug.

"The really critical study was one that we didn't set up at all - Edgar Sowton and Derek Gibson published a paper in the BMJ unknown to me even though I was supposed to have some control over the situation, where they treated 19 patients in heart failure with practolol and brought them out of failure ... here for the first time was a beta-blocker that could be used in heart failure which took all the worry out of the decision-taking for a doctor - and its use expanded dramatically - so it tended to be used in situations in which one would be a little bit more cautious in using propranolol ... Derek Gibson used to call it the cosmetic beta-blocker ... patients with a high heart rate after operation - give them a little practolol and the heart rate would come down, they could go home and think that everything was better ..."[3]

So, despite the fact that it was considerably more expensive than propranolol (Table 2.7), practolol's advantage of easier use was quickly recognised.

Table 2.7 Comparative NHS cost of three beta-blockers, 1971.

100 tablets.

		Cost	Potency ratio	Actual cost for equivalent dose
Propranolol	40 mg	36/-	1	36/-
Practolol	100 mg	71/-	$^2/_5$	177/6
Oxprenolol	40 mg	52/-	$^2/_3$	78/-

E. B. Raftery says of practolol usage at Northwick Park Hospital in 1972:

> "The most expensive item on the last league table, both in terms of total cost and individual items, was practolol, and I was called very strongly to task on this and it was pointed out that other effective beta-blockers were much cheaper and that one should use them."[4]

From figures 2.27, 2.28, and 2.29 it can be seen from 1971-74 that practolol shows the fastest increase in prescriptions dispensed followed closely by oxprenolol, with propranolol showing a much slower rise with a much larger proprotion of generic prescriptions (using chemical name rather than brand name) which is characteristic of a more established drug. This shows that both of these new blockers must have been seen to offer something new, oxprenolol ISA with its claimed advantages of fewer side-effects and less risk of heart failure, and practolol cardio-selectivity with a similar array of advantages.

In 1972, Zacharias published his influential favourable review of six years experience with propranolol in hypertension (summarised in sec. 2.4.1). After this time publications were in

Fig. 2.27 Sales of propranolol, Great Britain 1970-1975
Generic prescriptions above line in columns
Source: DHSS

Thousand

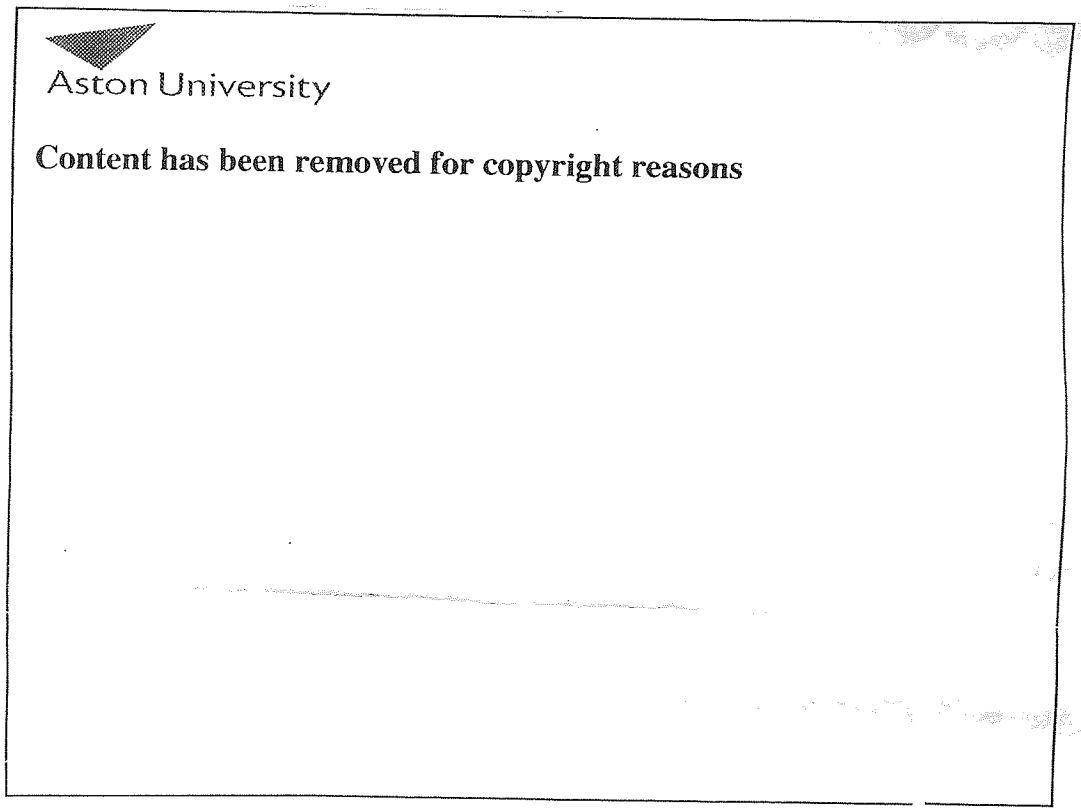


Fig. 2.28 Sales of oxprenolol, Great Britain 1970-1975
Source: DHSS

Fig. 2.28 Sales of oxprenolol, Great Britain 1970-1975.
Source: DHSS

Fig. 2.29 Sales of practolol, Great Britain 1970-1975
Source: DHSS

general more favourable to the use of beta-blockers in hypertension and more particularly to propranolol than had formerly been the case. In the same year, Zacharias also noted a high frequency of skin reactions among those patients on practolol which seemed to be related to the drug:

> "I have had an incidence of 3 out of 156 acute and 16 out of 156 of very slowly developing chronic skin reactions, which I think are almost certainly related to practolol, because these reactions get steadily worse if you don't do anything about it and get better immediately if you stop practolol. They take a long time to come on, 6-9 months perhaps, sometimes longer than a year, and they seem to be eczematous in nature."[5]

These reactions to practolol had also been noted earlier (1971),[6] but with a much lower frequency (7 out of 2,100), possibly due to shorter periods of administration. Rashes are not an uncommon side-effect of drug use, but the psoriasis-like form mostly seen with practolol was later to be described as "an easily recognisable diagnostic feature."[7]

In 1973 propranolol was approved for the treatment of angina in the U.S. by the FDA. However, it was a very qualified approval. The FDA's cardiovascular advisory committee was reconvened in April before the completion of ICI's American connection Ayerst's studies, and a majority of the committee voted to include on the package insert "a statement mentioning in a highly qualified way, the use of propranolol in angina".

> "The verbatim transcript of the meeting shows this action was taken both to soften physician criticism of the FDA, and to provide official information including precautions and warnings on the anti-anginal use of propranolol, since it was being used anyway."[8]

Many American doctors were using the drug in angina without FDA approval thus laying themselves open to malpractice suits,

but the FDA did not feel that the studies which were submitted to it were particularly convincing.

> "Prior to the meeting the sponsor selected and sent to each committee member 33 published reports from the world literature reporting studies that it thought were adequate and well-controlled for the purpose of establishing the efficacy of propranolol in angina. The efficacy standard set by Congress, and further defined by FDA regulations is a rigorous one. To demonstrate effectiveness there must be 'substantial evidence' consisting of 'adequate and well-controlled investigations' conducted by qualified experts in accordance with specified scientific principles ... At the April 1973 advisory committee meeting a majority of the five members present indicated they did not find a single study that met the statutory test."

FDA records state:

> "Although every study submitted did not in each instance meet all criteria, as a group they do provide evidence of a well-controlled quality to support safety and efficacy".

However, FDA records do not show that the agency or any of its staff accepted even one of the 33 published studies as adequate and well-controlled, although at least two such studies are required for approval.

The Director of the FDA's Bureau of Drugs, Dr. J. Richard Crout, testified that he disagreed with this:

> "I agree with you that the committee did not identify adequate and well-controlled clinical trials and said they couldn't. And I disagree with that advice because I believe there are 13 perfectly adequate and well-controlled clinical trials that meet all of the requirements ... and that there are 9 others in which there are minor deviations that are inconsequential." [9]

He identified these studies in March 1974, about 7 months after approval.

There was obviously no agreement even within the regulatory body on exactly what constituted "adequate and well-controlled

trials". This is, as has been discussed, a particular problem with such a variable condition as angina. The main conflict in the approval of propranolol was between legitimising widespread existing prescribing practice, or insisting on agreed standards of scientific evidence. In this case it seems that the pressure of accepted practice was enough to carry the day. Whatever the benefits and costs of this decision, the US was not touched by the adverse reactions to practolol which began to attract attention in 1974, as clinical trials were still in progress four years after UK marketing when the reports began.

Two consultant dermatologists reported in the British Medical Journal[10] in May 1974 an increasing frequency of distinctive psoriasis-like rashes in patients on practolol referred to them. They noted that the mean period of practolol use before the appearance of the rash was ten months, but as little as three weeks and as much as two years had been seen. In June an ophthalmologist, Wright, noted an association of shrinkage of the conjunctiva of the eye with the skin symptoms.[11] In July ICI's medical director, Dr. C. C. Downie, sent a letter to all doctors in the UK describing the skin rash and eye symptoms and suggesting practolol withdrawal in these conditions.

Throughout the second half of 1974 the correspondence columns of the British Medical Journal and the Lancet carried many letters on eye and skin conditions. In November, Felix, Ive, and Dahl published their studies on these reactions in a paper in the British Medical Journal.[12] ICI sent another warning circular in October detailing 164 cases of reactions and two new symptoms, drug-induced deafness and sclerosing peritonitis (thickening of abdominal membranes).

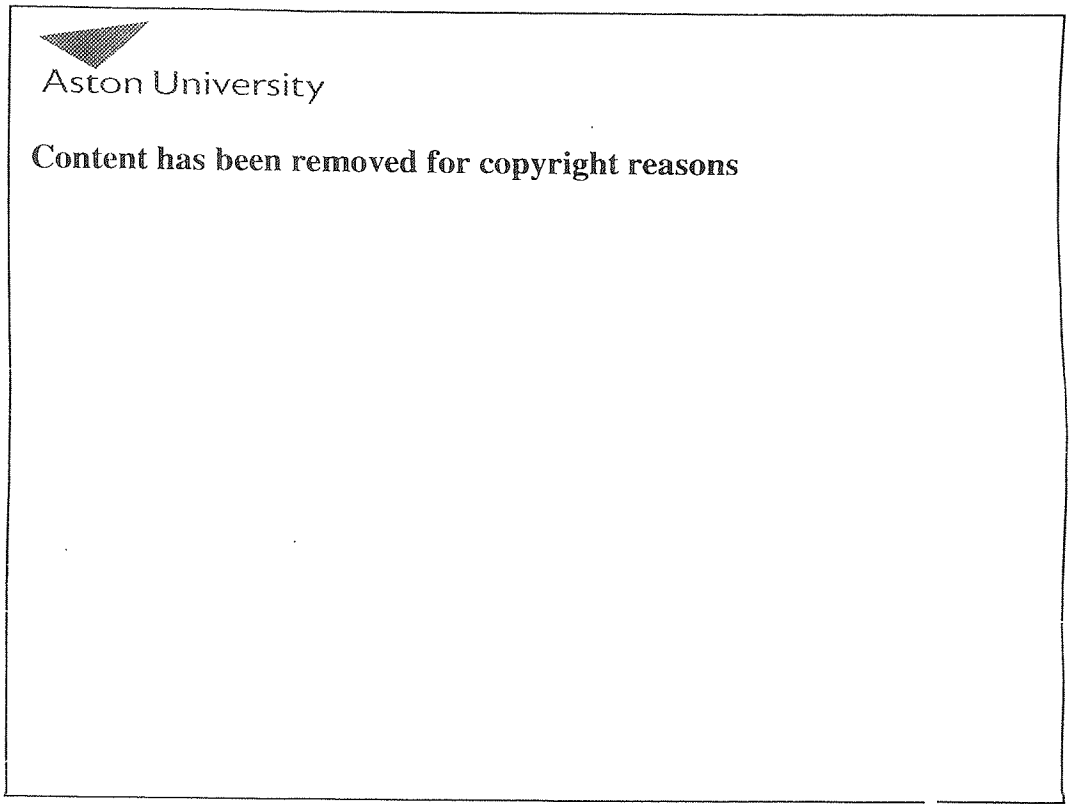


Fig. 2.30 Practolol prescriptions dispensed September 1974 - July 1975.
From Melville, A. in Mapes, R. (ed.) Prescribing practice and drug usage (Croom Helm, London, 1980).

In January 1975 the Government drug regulatory body, the Committee on Safety of Medicines (CSM) circulated its own warning to doctors and pharmacists:

> "By the end of 1974, 187 reports had been received of adverse effects on the eye occurring in patients who have been treated with practolol (Eraldin). Two-thirds of these reports described diminished tear secretion and conjunctivitis, and the remainder, corneal damage leading on occasion to impairment or loss of vision. These effects on the eye have been noted in patients who have received practolol for periods ranging from a few weeks to several years.
>
> There are also several hundred reports of psoriasiform or hyperkeratotic skin reactions, and 25 patients have complained of deafness. Fourteen patients have developed a syndrome resembling systemic lupus erythematosus and eight have developed an unusual form of sclerosing peritonitis. Half the patients with eye changes had a rash, and in others these adverse reactions were multiple. The mild eye changes and the majority of skin reactions usually recover when practolol has been withdrawn, but the outcome with corneal involvement is less certain and the damage may be irreversible.
>
> On the basis of reports to the Committee over 10 years, it seems unlikely that similar changes occur even after prolonged treatment with propranolol, but it is too early to comment on the more recently marketed beta-blocking agents.
>
> In view of the serious and unusual nature of these reactions, patients who need to continue to receive long-term treatment with practolol should be carefully observed with a view to the early detection of adverse reactions."[13]

In April, ICI advised in another circular that treatment should be reserved for asthmatics:

> "The reactions affecting the eyes and more particularly the peritoneum have proved to have such an incidence and severity for us now to recommend that "Eraldin" should be reserved for the treatment of patients where it has specific benefit compared with alternative forms of treatment."[14]

In July, ICI restricted the use of practolol to hospitals, with effect from October. The pattern of prescribing in this period is shown in fig. 2.30, from which it seems clear that the

single CSM warning had more effect than any of the ICI letters. Even after four warnings prescribing was still considerable, and it has been shown that by this late stage, between 50 and 70% of prescriptions were in the form of repeat prescriptions written by one of the staff of the prescribing doctor,[15] even though all warnings had stressed the necessity of continued monitoring.

The repercussions of this affair were extensive, and only those most relevant are discussed here (see Table 2.8).

The full extent of the reactions has never been documented by those with access to essential information. All that exists are estimates of exposure to practolol, these vary; 100,000,[16] more than 200,000,[17] and 1 million[18] patient-years of exposure have all been mentioned; of those suffering reactions, these vary from 18 dead, 20 blind and 1,000 with skin reactions to 2,800 who have symptoms that they suspect are due to practolol.[19]

Although legally they were not deemed negligent as they had exercised 'all reasonable care', ICI introduced a compensation scheme in 1975, under which patients could claim if they could get their GP's and a consultant's opinion that their disabilities were caused by practolol. However, many GP's were unwilling to indict themselves and some apparently genuine cases have received nothing. Most patients on practolol were old - their average age was around 62, and getting compensation involved hiring solicitors, going to see consultants who were mostly unused to diagnosing drug-induced disease, and in general being very persistent in the face of much medical opinion that their problems could not be due to the drug. Thus, the scheme, though described as a 'splendid gesture' was in some ways not particularly helpful.[20]

Table 2.8. Effects of extensive adverse reactions to practolol, 1974, onwards

* Extensive suffering.
* Legal controversy over liability and negligence.
* Questioning of doctor's competence.
* Other recently introduced beta-blockers under scrutiny and suspicion.
* Significance of multicentre study on the prevention of second and subsequent heart attacks by practolol rendered questionable.
* Increasing demands for better adverse drug reaction (ADR) reporting system.
* Increased level of general attacks on pharmaceutical industry.
* Greater opportunities for subsequently innovated blockers to gain market share.

Since the scheme was introduced about 2,600 people have applied. Half of these claims have been settled, 1,100 have been turned down and the rest are still outstanding. Though these claims outnumber thalidomide cases by about five to one, ICI have paid out much less than the £9 million the scheme was originally estimated to cost.

> "There have been no court cases so far. And one of the results of the scheme is that Eraldin has become the forgotten drug disaster."[21]

Given that many patients suffering from adverse reactions were not discovered by doctors until after widespread publicity, and in some cases only after the patients themselves had realised, this must call into question to what extent practolol was being properly prescribed before these reactions occurred. Melville and Mapes have correlated practolol prescribing practices of a sample of GP s with scores on a job satisfaction scale and arrived at the following conclusions:

> "It seems that we have three groups of doctors. The first group ceased to prescribe practolol after the first warnings; these were high on job satisfaction. The second group was also high on job satisfaction, its members continued to prescribe practolol, but never without seeing the patient and presumably watching for the appearance of side effects. The third group continued to prescribe the drug without necessarily seeing the patient. This last group showed low job satisfaction."[22]

The extent of the continued prescribing therefore, does seem to substantiate criticism of prescribing practice.

One important trial, the practolol multicentre trial which involved over 3,000 patients had to be terminated prematurely, but still produced significant results.[23] The use of practolol after an acute myocardial infarction produced a significant reduction in overall mortality and in sudden deaths, and this reduction was virtually confined to those patients whose infarct

was in the anterior (forward-facing) section of the heart. To what extent these results apply to other blockers is still not known.

The outcry after the practolol affair has led to new attempts to improve regulatory systems for picking up side effects occurring at low frequencies, so that fewer people suffer. The current 'yellow card' system whereby the doctor who notices any untoward reaction is supposed to notify the CSM is seriously underused. It is estimated that fewer than 1% of adverse reactions are reported and the system favours the reporting of known reactions rather than unknown. For example, in July 1974 the CSM had no evidence apart from that published in journals to send to doctors. However, after the ICI warning letter 202 reports were received.

In the wake of the Eraldin affair several new schemes for more effective drug monitoring have been put forward,[24, 25] and extensive discussion of the costs and merits of such systems has ensued.[26] These schemes all involve monitoring the initial use of the drug, either by the prescriber and patient completing questionnaires on untoward effects, or by the pharmacist collating prescriptions. The controversy revolves around how much information is wanted; the more sensitive the system, the more information needs to be gathered, and hence the more expense incurred. There is some evidence that the practolol side effects could have been detected with very simple systems:

> "The practolol syndrome could have been detected much earlier by a very simple cohort approach - and for that matter by a carefully designed clinical trial. The ad hoc study to which I referred briefly in my

paper disclosed a significant excess of eye troubles in fewer than one hundred patients receiving practolol."[27]

Concerning the costs and benefits of practolol, Wardell has claimed that its use in the US would have been beneficial,[28] saving 10,000 lives per year with a trivial cost in side-effects.[29]

"The proper use of practolol in postinfarction patients could now be saving 10,000 lives each year in the United States at a cost, in terms of side-effects that can now be made trivial by comparison. A similar argument - without the toxicity problems - applies to alprenolol."

Three points can be made about this type of extrapolation from clinical trials. Firstly, the 40% reduction in mortality in the first two years was observed when the drug was administered according to the trial protocol. There are many differences between the use of drugs in such trials and routine use in general practice, so it is by no means certain that this reduction in mortality could be duplicated on such a large scale. Secondly, that these lives saved are probably saved for at most a few years, as the mortality of patients who have already had one infarction is high. Thirdly, that side-effects could be made trivial only by frequent monitoring of patients. This, if possible to achieve, would result in greatly increased workload by doctors, seeing each patient every few months and examining them carefully. It is very unlikely that this would be universally practised.

It would seem, then, that the practolol adverse reactions have shown the potential dangers of the present system of drug testing and use, and the need for more reliable methods of monitoring drug reactions. The possibility of such reactions has to be weighed against the known benefits of their use, and should for this reason be more adequately documented.

2.3.4 Beta-blocker research and marketing of follow-on compounds (1974-76)

Six new beta-blockers were introduced between 1974 and 1976:

1974 Sotalol in June 1974 by Mead Johnson

Timolol in June 1974 by Merck, Sharp, and Dohme

Pindolol in October 1974 by Sandoz

1975 Acebutolol in April 1975 by May and Baker

Metoprolol in July 1975 by Geigy (research by Haessle)

1976 Atenolol in July 1976 by ICI

Their structures and pharmacological characteristics are shown in Table 2.9 and Fig. 2.31.

The proliferation of these "follow-on" compounds indicates a widespread perception of the profitability of such compounds. The pharmaceutical industry journal Scrip commented:

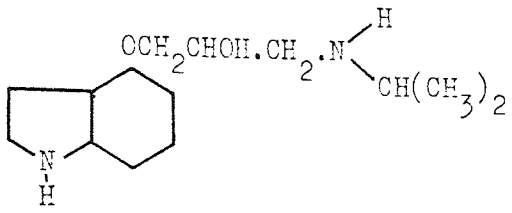
> "It looks as if a new jockeying for position can be expected in the UK's fast-growing and highly competitive hypertension market ... Undoubtedly, this is a crowded field. But cardiovascular disease therapy is a major growth area, at present worth approximately £30 million in the UK, and is a market which over the last year showed an increase of almost 25 percent. So it will be interesting to see just how this market is shared out. A further point - the UK is certainly an important indicator of what can be expected in the future for the US."[1]

Sotalol had been discovered over 10 years earlier (see Sec. 2.2.2) but had not previously been marketed. Haessle and ICI had both marketed non-selective compounds to which their newer selective compounds were obvious extensions. The other three companies were new entrants to the market, and their compounds though chemically different were clinically indistinguishable from earlier successful prototype blockers. The launch advertising for these compounds had to compete with that of the recently introduced larger dosage forms of propranolol and oxprenolol which

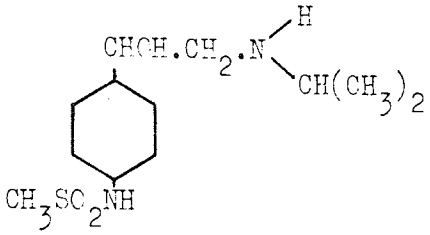
Table 2.9 Pharmacological characteristics of beta-blockers introduced 1974-1976

	M.S.A.	I.S.A.	Cardioselectivity
Sotalol	-	-	-
Timolol	±	-	-
Pindolol	+	+	-
Acebutolol	+	±	-
Metoprolol	±	-	+
Atenolol	-	-	+

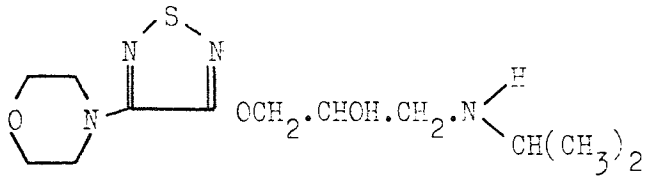
Pindolol



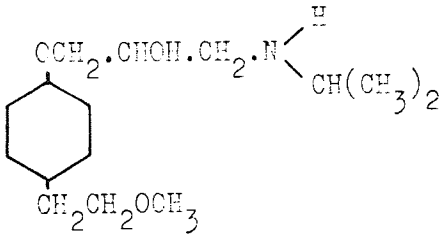
Sotalol



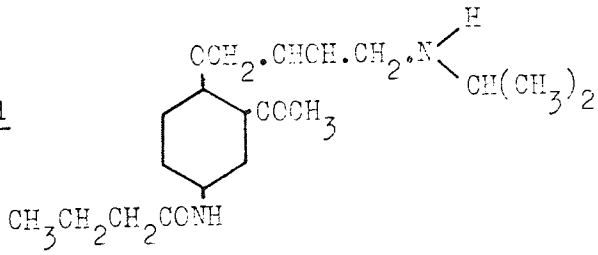
Timolol



Metoprolol



Acebutolol



Atenolol

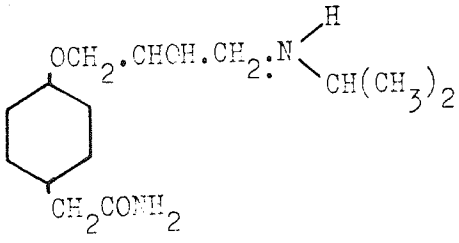


Fig. 2.31 Structures of the new beta-blockers introduced 1974-1976.

had recently been brought out (Inderal and Trasicor 80 mg 1972, Trasicor 160 mg 1974).

Much of the advertising built on images of beta-blockade which had previously been built up by ICI and CIBA. Trasicor "makes today worth living and promises a better tomorrow". For hypertension several drugs promised "round-the-clock control", simple dosage, no postural hypotension and minimal side-effects - usually against an image of a worried executive.

Blocadren (timolol) was claimed to be "a significant product of original research", but otherwise made only modest claims:

> "one major product for two major problems - effective in angina, effective in hypertension - one strength tablet, same average daily dose for angina, for hypertension."

This attempted to capitalise on the difficulties of the dose-finding procedure advocated by Prichard for propranolol in hypertension.

Visken (pindolol) was

> "the better way to manage hypertension - simple dosage, pharmacological profile indicates little risk of cardiac failure or bronchospasm, 24 hour control."

"An entirely new beta-blocker from Duncan Flockhart - beta-blockade pure and simple" was how Beta-cardone (sotalol) was introduced. Of all the adverts, this concentrated on pharmacological differences the most; "no cardiac stimulation, no direct myocardial depression". Bristol's Sotacor (also sotalol) was described as "the new leader of the leaders in hypertension"

> "beta-blockers are effective, but their potency and in some cases cardiac depressant properties have highlighted the need for a beta-blocking agent specifically designed for the management of hypertension - Sotacor - a purpose-structured molecule for predictable reduction of blood pressure."

The claims of the new compounds, then, were based as one would expect on the defects of established drugs, but most manufacturers, in the absence of real differences, were claiming specious advantages such as simple dosage and 24-hour control, when the dose-finding process and duration of effect of their compounds were not clinically significantly different from the established compounds.

The market shares in Great Britain achieved by these compounds up to 1976 is shown in fig. 2.32 in comparison with the established compounds. The compounds are discussed chronologically with the exception of sotalol which has already been covered.

Timolol ('Blocadren')

Produced by Merck, Sharp, and Dohme

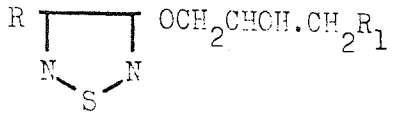
Introduced June 1974

This compound was first announced in 1970. From the published chemical work[2] it appears that timolol was synthesized at the Merck Frosst Laboratories in Montreal, Canada. Twenty-nine compounds are reported of the basic structure shown in fig. 2.33(a).

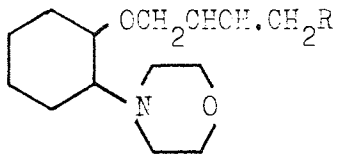
> "These compounds provide the first examples of beta-adrenergic blocking substances in which the conventional side-chain is attached to a single heterocyclic ring."

Their requirements were: high potency and specificity, minimal or no sympathomimetic action, rapid onset, and reasonable duration of action. A parallel study on compounds shown in fig. 2.33(b) showed high activity, so that the substituent ring was tried with the basic structure of the other series to give timolol .

Fig. 2.32 Sales of new blockers, Great Britain 1974-1976.
Source: DHSS



A



B

Fig. 2.33 Structures synthesised by Merck, Sharp & Dohme.

It was first tested in humans in 1971, and full-scale clinical trials in angina and hypertension were done in 1973-74.[3] Merck did not give much information when I enquired about the direction of the research, who was responsible for it, and what they felt its major contributions to the development of beta-blockade had been, stating only that scientists Hucker on the pharmacology side, and Tocco on the chemical side were responsible for the compound's development.

Pindolol ('Visken')

Produced by Sandoz

Introduced October 1974

Pindolol was patented in 1969 by F. Troxler for Sandoz in Switzerland.[4] It is very similar structurally to compounds made by ICI in 1965 (B.P. 1089769), the only difference being an -NH- group instead of an -S-. It has high intrinsic activity, which is claimed as an advantage, but restricts the use of large doses. It has sold well in Germany, France and Australia.

Acebutolol ('Sectral')

Produced by May and Baker

Introduced April 1975

Work seems to have begun at May and Baker sometime between 1966 and 1968, as a paper on chemical synthesis[5] in 1969 contains the following:

> "During a programme directed at the synthesis of compounds containing elements of the side-chain of adrenergically active drugs such as propranolol, incorporated into cyclic systems ..."

This early paper concerned attempts to produce compounds such as those illustrated in fig. 2.34(a), which turned out to

have only weak anti-adrenergic activity. The lead for preparing this type of compound was obviously the patenting of benzodioxan compounds including the pronethalol and propranolol side-chains by ICI (fig. 2.34(b)).

The next paper, published in the Journal of Medicinal Chemistry in 1970[6] described the programme's strategy in more detail.

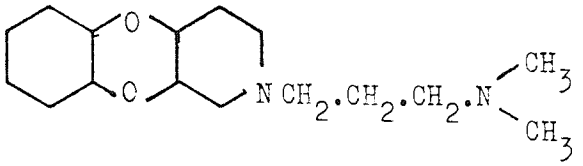
> "These compounds (previous beta-blockers) possess a number of pharmacological properties, e.g. beta-blocking, quinidine-like, local anaesthetic, and possibly hypotensive properties, and we considered the possibility of synthesizing structures in which the mobility of the side-chain was restricted in the hope of achieving some specificity of pharmacological action. One approach entailed linking the side-chain with the aromatic nucleus to form benzoxazocines such as I (fig. 2.35)"

This was found to possess significant beta-blocking activity.

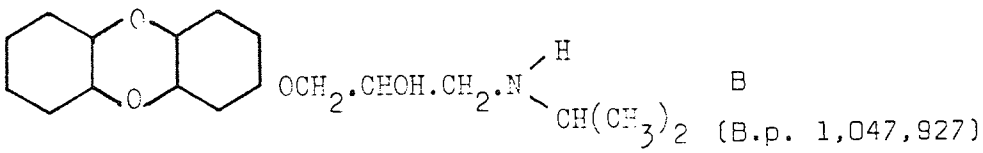
I have mentioned elsewhere the pressure towards specificity of action produced by the extensive pharmacological testing of these compounds in 1965-67. Obviously, researchers in rival labs saw this as a good opportunity to produce a new drug with some improvements over the prototype compounds of the class. However, ICI had very extensive patent coverage of heterocyclic blockers in general, and benzodioxan compounds in particular, because of their high activity. Hence there were unlikely to be many good possibilities left in this area.

In 1972, a paper in Experientia[7] announced a new cardioselective blocker whose testing in humans had been reported in 1971,[8] M & B 17803A. It can be seen how this structure could be derived from the benzoxazocines they had previously been studying (fig. 2.36).

This structure is also close to that of ICI's selective blocker, practolol, marketed in 1970* (see fig. 2.37).



A



B (B.p. 1,047,927)

Fig. 2.34 Structures synthesised by May and Baker (A) compared with compounds made earlier by ICI

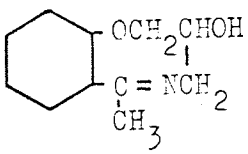


Fig. 2.35 Benzoxazocine lead compound produced by May and Baker.

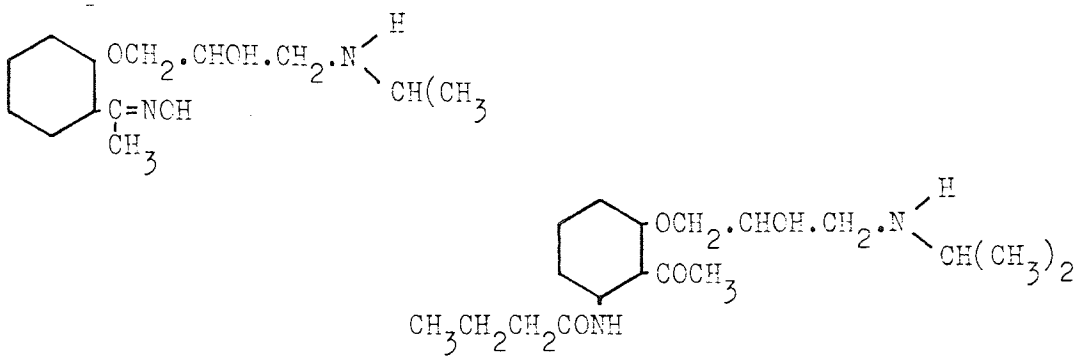


Fig. 2.36 Derivation of acebutolol from benzoxazocine compounds

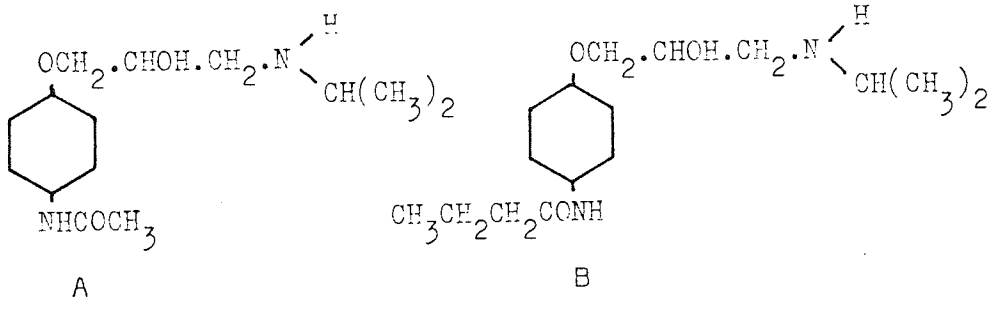


Fig. 2.37 Comparison of practolol (A) and acebutolol (B).

In the text of a later paper,[9] Wooldridge et al. discuss the programme's strategy further:

> "Practolol, however, is reported to inhibit the beta$_1$ response (heart) at lower doses than those required to inhibit the beta$_2$ response (vascular). We became interested in the possibility of modifying known beta-blocking compounds in order to enhance the selective blockade of the beta$_1$ or beta$_2$ responses. We first examined the possibility of achieving selectivity by partially immobilizing the side-chain of conventional beta-blockers by incorporating it into heterocyclic systems."

Practolol is here definitely seen as a lead compound, and the exercise is to produce a more selective compound which would be outside ICI's patents and hence marketable. Also,

> "For possible clinical use, a balance of beta-blocking potency, cardioselectivity and antiarrhythmic properties is required."

The research seems to have made extensive use of mathematical analysis - the "multiparameter extrathermodynamic approach developed by Hansch and others",[10] to select suitable compounds for synthesis. Wooldridge, the research manager says of this:

> "The quantitative structure-activity relationships established in the acebutolol series indicate that different relationships exist between physico-chemical parameters and the three measured properties of cardiac beta-receptor potency, selectivity, and anti-arrhythmic potency. The identification of these quantitative relationships assisted in the subsequent work and selection of compounds in this series."[11]

Wooldridge also lists two other contributions made by his group:

> "We discovered quite independently of ICI that β_1 and β_2 activity could be separated in a chemical series.

---

*And in fact is only just outside ICI's B.p. 1069341 which protects compounds similar to practolol.

> The structure-activity studies leading to acebutolol were not based on the practolol structure but were arrived at by a process of incorporating the propranolol side-chain into cyclic structures and then re-opening. This gave us the acetyl substituent which fortuitously appears to prevent the occurrence of practolol-like side-effects. We attribute this to the electron-withdrawing effect of the acetyl substituent thus rendering acebutolol less prone to metabolic hydroxylation compared to practolol."[12]

So the extent to which acebutolol was derived from practolol is controversial.

Marketing and clinical work

Clinical pharmacology in healthy volunteers was done 1970-74. Later work was done largely in France - as May and Baker is now a subsidiary of Rhone-Poulenc, the French drug firm.

Until May 1976, out of 65 clinical studies partly or wholly involving acebutolol, 26 were on hypertension (19 of these French), 15 angina, 18 cardiac arrhythmias, and 6 on treatment of asthmatics.[13]

The major marketing thrust with Sectral has been its claim to be cardioselective.* This has involved trials with hypertensive asthmatics and many comparisons with practolol. Also its MSA and weak ISA have been held to be advantages in the treatment of arrhythmias although this view has been much criticised.[14]

A 400 mg preparation ("once daily") has been brought out in a calendar pack to help patient compliance, which has been the major promotional campaign in 1978.

---

*Though Shanks of ICI says:

> "Acebutolol is widely advertised and promoted as being cardioselective and I've had a long battle with May and Baker and eventually won and they've had to withdraw their claims that it's cardio-selective."[15]

Metoprolol

'Lopresor' produced by Geigy, introduced in July 1975.

'Betaloc' produced by Astra, introduced in July 1975.

The research which culminated in the marketing of metoprolol began in 1967, at A. B. Haessle, Sweden, where feedback from clinical experience with alprenolol suggested that a compound with a different profile of activity was necessary for the treatment of hypertension. Doctors in Sweden began using beta-blockers in hypertension earlier than in Britain and the extent of usage in this condition increased more rapidly, so there was a greater incentive for the production of a more suitable blocker. I. Östholm, the research manager comments,

> "Aptin was, however, not effective enough in reducing blood pressure. We decided to develop a more potent beta-blocker for hypertension, a drug without intrinsic activity. We realised, however, that such a drug could produce adverse effects such as bronchoconstriction. We started a new project in 1967. New formulation of aim was to develop cardioselective ($beta_1$) beta-blocker which would be expected to give less risk of bronchial constriction and which would have no direct effect on peripheral circulation."[16]

Their expectation of being able to produce a selectively acting blocker was based on the finding of two such compounds, peripheral ($beta_2$)-selective, coded H35/25 discovered in 1963, and cardioselective, an analogue of alprenolol, para-alprenolol, discovered in 1966.

> "The substance H 64/52, which is the para analogue to alprenolol was synthesised in 1966 (fig. 2.38). This substance blocked the beta-receptors in the heart to a greater extent than those in the bronchi and peripheral vessels."[17]

Although the selectivity was not considered sufficient for chemical use, the compound served as a chemical lead for further syntheses.

> "Following a large number of syntheses around the structure of H 64/52 and pharmacological evaluation of these substances, the $beta_1$-selective compound H 93/26 was selected for trials in man."[18]

One interesting published outcome of this work was an evaluation of the effect of moving the substituent on the nucleus.[19] They found that with the substituent group in the para-position the compound showed cardioselectivity, but with it in the other two positions it did not (see fig. 2.39). They add further circumstantial evidence that oxprenolol is ortho - and is unselective, and practolol para- and selective. This study was important as an early attempt to specify the chemical basis of selectivity but its attractive conclusions have been later thought to be over-simplified.[20] So, after good evidence was available from relatively early on that a selective blocker was a possibility, and a clinical need for such a drug expressed, Haessle workers produced two $beta_1$-selective compounds which were examined in humans in 1969-70, H 87/07 and H 93/26. The latter was taken to full clinical studies, single dose anginal trials published in 1974, double-blind studies in 1975-77, though most of these employed a fixed dose, low numbers of patients, some do not have 'run-in' periods, and all were of fairly short duration (1 month average). Studies in hypertension were begun in 1976. Even considering the cardioselectivity of metoprolol, which is less than that of practolol, it is not advised in the treatment of hypertensive asthmatics, who need to take $beta_2$-stimulants to avoid asthmatic reactions.

Permission was sought from the FDA to market metoprolol in the US in November 1976. The data submitted included 18-month carcenogenicity studies, and seventeen "proper double-blind studies in reputable centres". The case was heard in October 1977 and its

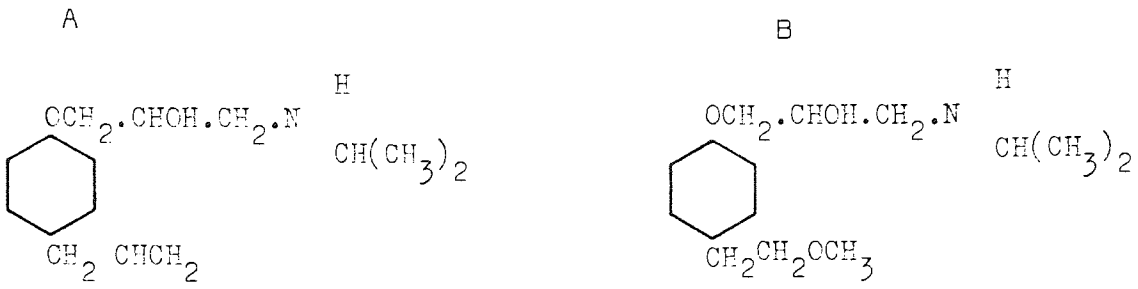


Fig. 2.38 Selective blockers - para-alprenolol (A) and metoprolol (B).

Fig. 2.39 Selectivity related to position of chemical groups by Ablad et al. (1970).

R_1 and R_2 as in Fig. 2.38 A

result was approval for metoprolol, but arguments over animal data and uncertainties over whether newer blockers were a significant advance over older produced two resolutions: that documented production of benign or malignant tumours should bar approval of a beta-blocker with no significant advantage over available drugs, and that ambiguous long-term animal findings be repeated and the drug involved should not be marketed unless there is evidence of advantage over available drugs.[21] It looks, therefore, as though metoprolol will do well in the US as it is extremely unlikely that any other selective blocker could claim to have significant advantages.

Atenolol ("Tenormin")

Produced by ICI

Marketed July 1976

Atenolol was produced at ICI by the same people who were responsible for the marketing of practolol, J. D. Fitzgerald and A. M. Barrett. After practolol had undergone toxicity tests and begun clinical trials what were their new research goals? They were being clarified by debates about the significance and desirability of the "ancillary properties" of beta-blockers.

The Membrane Stabilising Action (MSA) of propranolol was generally seen to be a disadvantage, as it led to weakening the force of contraction of the heart, which, although not significant in the majority of clinical situations, had especially with intravenous use been associated with causing heart failure. Although this was not subsequently confirmed, MSA was still an "emotional blocking point" for doctors as Barrett puts it and so was not desirable.

> "We wanted to have a drug which was a 'clean beta-blocker' - there's a lot of confusion in the States about MSA - so that was a key feature."[22]

Intrinsic Sympathomimetic Activity (ISA) - the ability of the blocking compound also to partially stimulate was a controversial property. Haessle's pharmacologists had claimed that this might reduce the incidence of heart failure, but this was hotly disputed by ICI's pharmacologists, who pointed out that there was no clinical evidence to support this view. ICI's strategy, begun by Black, was to go for the more difficult to find, pure blocking compounds, from the standpoint that compounds with some stimulant activity would not be so clinically effective. Cardioselectivity was wanted because of the reduced danger of bronchoconstriction. Practolol's water-solubility, as opposed to propranolol's lipid-solubility was also wanted to reduce central nervous system penetration, and therefore side-effects such as nightmares and hallucinations. A compound more potent than practolol was also required.[23]

This consideration of the importance of ancillary properties was motivated by uncertainties and doubts about practolol's clinical effects.

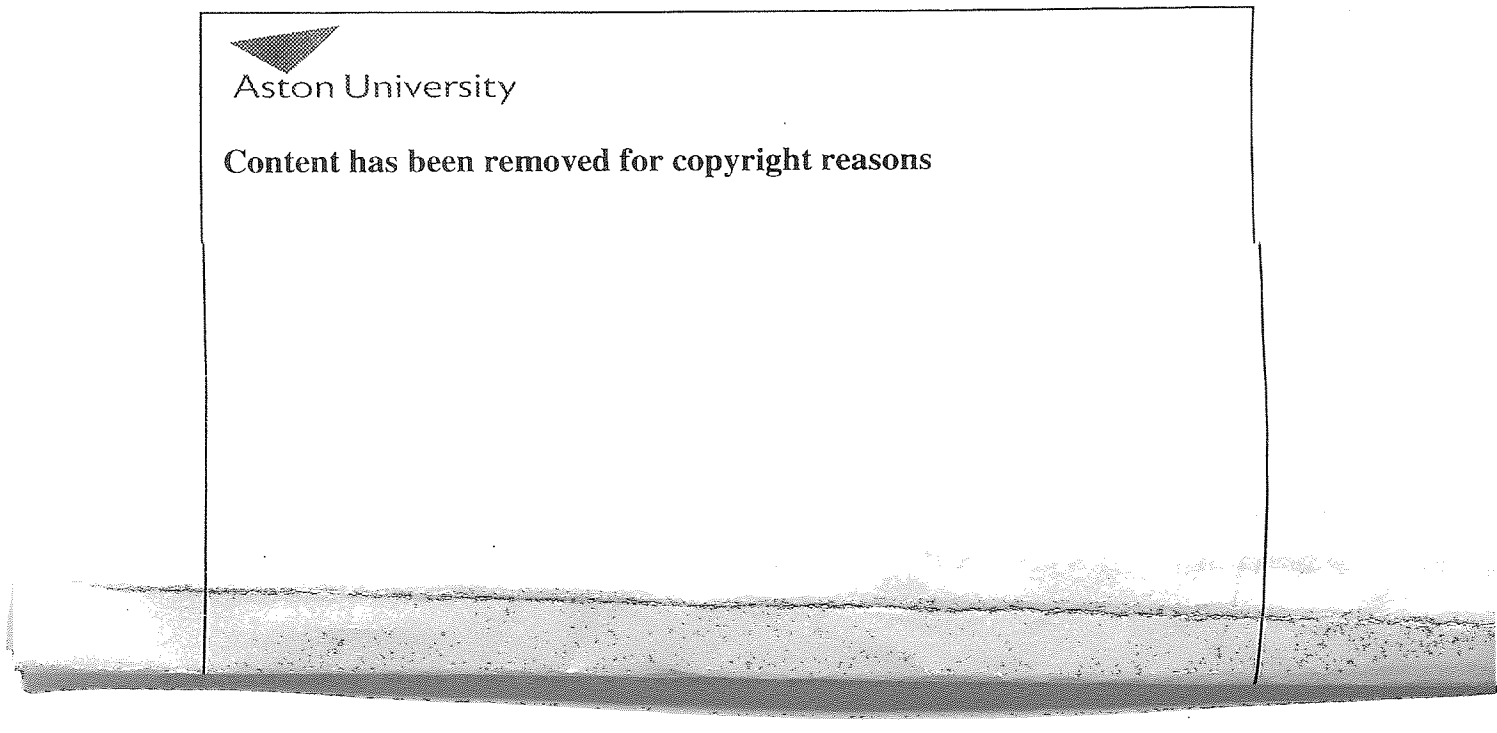
> "At that time we were faced with uncertainties concerning the efficacy of practolol relative to propranolol. From the point of view of safety we believed that practolol was a therapeutic advance because firstly its cardio-selectivity would reduce the incidence of bronchospasm in susceptible subjects, and secondly, cardiac function was much less reduced by practolol than by propranolol. The suspected but unproven lesser anti-anginal activity of practolol was attributed to these lesser haemodynamic effects."[24]

Little, then was known of the relative contributions made by differing ancillary properties of propranolol and practolol (see Table 2.10) to their physiological and clinical effects.

Table 2.10. Ancillary properties of propranolol, practolol and atenolol

	MSA	ISA	Cardioselectivity	Solubility
Propranolol	+	-	-	lipid
Practolol	-	+	+	water
Atenolol	-	-	+	water

Table 2.11. Three ICI blockers put forward for comparative evaluation



Source: Fitzgerald, J. D.[24]

Barrett and Fitzgerald saw this obstacle to further development quite clearly:

> "After Shanks left he (Barrett) took over beta-blocking research, and I think made a very significant impact in reorganising and clarifying it, and we had long arguments and debates about the whole thing ... At the time of the discovery of atenolol we were convinced of the need for several different beta-antagonists which possesssed the various permutations of pharmacological properties in addition to beta-antagonism."[25]

What they needed to do was to take a selection of compounds with different combinations of ancillary properties, and then test out their pharmacological and clinical effects.

> "We had four beta-blockers, we had a very tight, academic analysis, and we wanted to take all of them into man, evaluate them in all the clinical indications and find out what was the optimal spectrum, and we've never done that."[26]

Three of the compounds they wanted to evaluate are listed in Table 2.11.

60,847 had an identical profile to practolol except being 20 times as potent. This compound was to test the possibility that practolol's lesser efficacy in angina, suggested in 1968, was due to lack of potency. 61,081 was a more or less "clean" blocker, otherwise similar to practolol. 65,674 was to test the speculations that MSA was a valuable property, apart from its MSA it was otherwise similar to practolol except in its potency.[27]

The first two are obvious derivations from the lead compound of practolol, the last, synthesized about a year later, is different.

Because of the great interest that was building up in the significance of cardioselectivity, chemists at ICI were trying to work out its structural basis.

"At that time Dr. Hull (section leader) was convinced that the active hydrogen on the NH group in the para position of practolol contributed significantly to the selective action of beta-antagonists. He suggested to Dr. Le Count that if negatively charged substituents were placed in juxtaposition to this NH grouping, they might act as electron attracting groups to oppose similar action on the benzene ring."[28] (see fig. 2.40)

"One option was the malonyl analogue (fig. 2.41) in which the acidic proton (hydrogen) would be attached to a carbon atom. Responsibility for the synthesis of such derivatives was assumed by Dr. D. Le Count who included mono-carbonyl analogues in his programme."[29]

However, the theoretical model could not be completely tested in practice, so a compromise was reached:

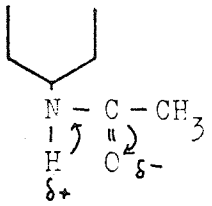
"the original substitutions proposed were rather difficult to synthesise, so Dr. Le Count made a series with a $CH_2.CONH_2$ function in the para position."[30]

One of these was atenolol. Basically, the active grouping in atenolol is the same as that in practolol, only reversed (see fig. 2.42).

"In December 1968, ICI 66082 (atenolol) was submitted for test and within 2 months it was known that it was as potent as propranolol and had neither partial agonist (ISA) nor membrane stabilising properties. Furthermore, it was shown to be cardioselective."[31]

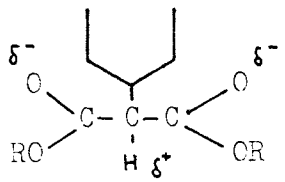
So this compound had the properties that they had wanted. The other three blockers were never evaluated in humans, because the recent restrictions surrounding human use (Medicines Act 1968) made more animal tests necessary before this could be done, and the process was thought to be too expensive to be justified. This led to some resentment by the pharmacologists:

"These decisions are made by the Medical Department in combination with the commercial departments - they've got their own goals, and in the end, of course, theirs is the final decision ... they wanted to do it in one particular way and not do anything else. They made some decisions to confine the studies to one particular condition and in one particular way, which are subsequently going to be shown to be quite counter-productive."[32]



Negative charges on the C=O group attracts the loosely bound positively charged hydrogen

Fig. 2.40 Electron forces in practolol thought by ICI pharmacologists to be significant for cardioselectivity.



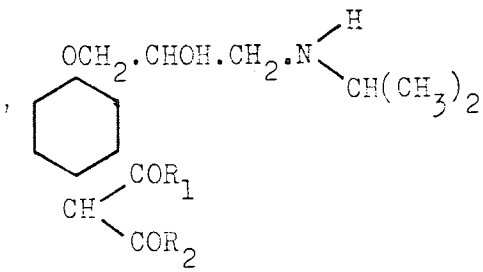
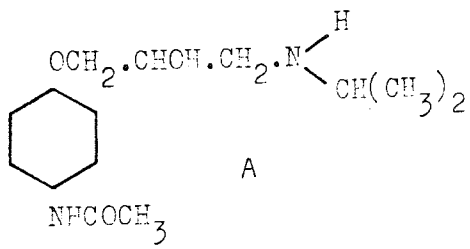
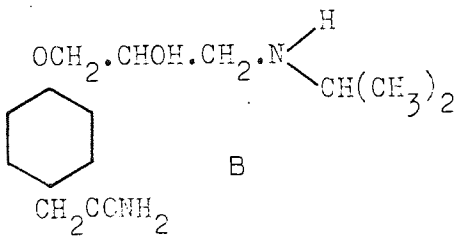


Fig. 2.41 Malonyl analogue thought to be cardioselective by ICI pharmacologists.



A



B

Fig. 2.42 Structures of practolol (A) and atenolol (B) compared.

Also there were toxicity problems:

> "We had two other compounds with high ISA and they hit the fence in toxicology so we lost out."[33]

So only atenolol was taken into humans and evaluated. In the event, one of its properties which became its strongest marketing claim was only discovered at this stage.

> "Atenolol has a half-life in man of 6-7 hours, yet a single daily dose is sufficient to lower elevated blood pressure."[34]

Despite the theoretical analysis that had been based on the extensive experience which ICI had had with beta-blockers, one of atenolol's key features was not predicted. "One tablet, once a day, simplicity in hypertension" was the leading claim made for atenolol in its marketing.

> "We certainly didn't expect it to be as effective as it is on a single daily dose - that was quite unanticipated, and it still doesn't add up actually."[35]

The uncertainties in pharmacological theory in this area are clear. Whether atenolol would have been marketed if practolol had not had to be withdrawn is an interesting, if difficult, question. Certainly it would not have been marketed so soon. However, there would have been little point in taking it to clinical studies if eventual marketing was not planned.

2.3.5 The evolution of beta-blockade

When one looks at the origin of beta-blockade - at James Black in 1957 and A. B. Haessle in 1959, it seems that two important factors were involved. The first and most important was the amount of research and interest in the field of catecholamines after the Second World War. The second was the evolution of ideas of medical needs which could be met by development of this research. This link had already been made in the field of hypertension by the clinical use of blocking compounds that had previously been research tools, and was made much more likely by the discovery and pharmacological evaluation of a drug which validated Ahlquist's drug-based theoretical classification of alpha and beta receptors, DCI.

Black's connection of the medical desirability of reducing the oxygen consumption of the heart with its pharmacological feasibility via Ahlquist's alpha - beta separation was a very significant connection when we consider the increase in importance of the cardiovascular area in therapeutics at this time, and the increase in pharmacological sophistication that had occurred since the war. But this connection would have taken much longer to bear fruit if DCI had not been pharmacologically evaluated in 1958.

It is difficult to assess the significance of Black's personal qualities for the timing of the innovation of beta-blockade as a therapy. Neither of the two extreme positions, either that Black's genius was entirely responsible, or conversely that introduction would have very shortly been made by someone else , i.e. that the discovery was 'timely', seem to me to be justifiable.

The first proposition falls on Haessle's independent decision to begin a project aimed at an antiarrhythmic compound that would block the actions of adrenaline, based too on the DCI structure, in February 1960. So the connections of the two above-mentioned factors was not necessarily only perceptible by genius. The second does not seem to take into account the influence of Black's enthusiasm on the team that worked with him, particularly his interactions with the chemist, Stephenson. His effect is aptly caught by Schon's description of the "product champion":

> "No ordinary involvement with a new idea provides the energy required to cope with the indifference and resistance that major change provokes ... Technological innovation requires leaps that cannot be justified before the fact by those charged with the task. So, there comes into being a man who takes the burden of risk on his shoulders without formal justification ... It is characteristic of champions of new developments that they identify with the idea as their own, and with its promotion as a cause to a degree that goes far beyond the requirements of their job."[1]

These characteristics were, I believe, a major reason why ICI had marketed their first blocker in 1963, whereas Haessle did not market until 1967. It is interesting to contrast the two research projects. Both relied on recent catecholamine research, but Haessle aiming for an anti-arrhythmic rather than anti-anginal compound were advised by university scientists to go for an adrenaline-blocking compound, probably on a very similar theoretical basis to Black's. The connection of DCI with Ahlquist's theory was quickly made by others, though probably not until after Black.

The other major difference in direction was over how much stimulant activity (ISA) was wanted. Black's position was that it was necessary to have no ISA to minimise adrenaline-induced myocardial oxygen consumption. Haessle took the position that

some ISA was necessary to substitute for the basal level of adrenergic drive. This difference later led to bad feeling and became the focus of much research when the ISA of oxprenolol was promoted as a clinical advantage.

The introduction of beta-blockade as a practical therapy presented special problems because of its novel mechanism of action which required some pharmacological understanding to use. This was tackled by extensive lecturing by the project personnel and many clinical papers repeating the basic pharmacology. Later, and particularly with the marketing of oxprenolol, conferences were found to be an effective method of widening use.[2]

Considerable scientific conflict was generated by debates on the significance of the 'ancillary properties' of beta-blockers almost as soon as they were introduced into clinical use. Initially the local anaesthetic activity of propranolol was the focus of controversy, later this shifted to the clinical significance of ISA. This argument began with the assertions of Haessle pharmacologists that alprenolol, due to its ISA, was less likely to provoke heart failure than propranolol.[3] This was vigorously contested by ICI workers who also opposed the extension of such claims made by CIBA, the marketers of oxprenolol. They claimed that the ISA of oxprenolol produced fewer side-effects such as bronchoconstriction, and cold extremities, as well as less risk of heart failure. In turn, CIBA's workers also denied that cardioselectivity had much clinical significance.[4]

This partisan pharmacology directed much of the work done on beta-blockade, thus it became devoted to looking for differences between compounds which in clinical use were frequently

admitted to be indistinguishable.[5] This process has become more complex with the introduction of more blockers, thus making it less possible to emphasize a unique profile of action for each, which is what is wanted for effective marketing.[6]

The new blockers are mostly molecular modifications of the propranolol side-chain with a variety of nuclei. Barrett, in his review on the design of beta-blocking drugs comments:

> "The extraordinarily broad patent coverage secured by Crowther and his colleagues has had a considerable influence on the freedom of action of competitors to market compounds of their choice. The pharmacologist who collects different available beta-blockers for comparative analysis is therefore comparing the results of the successful finding of patent loopholes rather than a series of compounds each one showing a potential improvement over the last ....
> ... it is perhaps cynical, but nevertheless partly true that this array reflects a greater tribute to chemical ingenuity rather than to logical drug design."[7]

Two factors can be seen in the "jostling of the major pharmaceutical houses to add such a drug to their range".[8] The first is the chemical interest of the compounds, the variety of structures showing activity and the uncertainty surrounding the clinical significance of their many actions. Chemists and pharmacologists in other firms were quick to spot and exploit the early leads partly because it was an interesting area in which to work. But this had been true since the synthesis of DCI in 1958. Barrett comments that Slater knew of many of the structures later patented by ICI in 1956.[9] Fitzgerald supports this:

> "I think Lilly had pronethalol sitting in their drawer. Moran will tell you, he went up and talked to the chemist, and the chemist was a bit upset because he had all these things down and nobody wanted to go on any more with them ..."[10]

The other factor that was involved was an appreciation of the size of the market for beta-blocking drugs. In the early years of

propranolol this was still small, but obviously had enough indications of growth for CIBA to decide it was worth marketing a competitor. Mead Johnson had long-acting blockers in 1962 but did not market one, sotalol, until 1974. With a lead-time of between five and seven years between patenting and marketing and one or two years of research prior to patenting,[11] the majority of companies must have initiated programmes 1965-1967, shortly after the marketing of propranolol.

In the same pattern as the thiazides, later beta-blockers have been more potent, milligramme for milligramme, and have a longer half-life than earlier compounds.[12] Apart from an increase in the number of cardioselective compounds available, though, there has been no trend in the other ancillary properties, which could be caused either by uncertainty about their value or by lack of choice in unpatented structures. The main research goals have been long half-life - achieved either with compounds that are slowly metabolised or by slow-release formulations of standard compounds, and cardioselectivity - the only ancillary property with generally agreed clinical benefit. As with the thiazides, the new blockers have not shown any clinically significant improvements over older compounds, although much pharmacological work has been devoted to attempting to show otherwise.[13, 14]

The need of the marketers to differentiate their product from the other drugs with which it competes leads to a concentration on differences which has obscured the similarity in the clinical effects of all these compounds.

For example, many papers have been devoted to comparative study of beta-blockers with respect to their MSA and ISA, the former of which has been strongly argued to be clinically irrelevant,

and the latter of which is clinically insignificant.[15] The factors involved in this were pharmacological interest and commercial advantage. The papers on ISA, particularly, were used to support the marketing of agents with this property as having significant advantages over agents without, to which question considerable scientific effort was devoted.[16]

The outcome of this is that clinical use of these drugs is complicated by an extensive consideration of scientific work, which is from the viewpoint of the majority of use, i.e. general practice, not relevant.

What of the future of beta-blockade? New blockers continue to be reported and marketed.[18] After the slow-formulations and the diuretic combinations, other combinations, for example, with vasodilators will be marketed. Research on new compounds will be aiming either at increased selectivity or a combination of beta-blocking and other properties, such as the alpha- and beta-blockers labetalol and RMI-81968, or the number of compounds with beta-blocking and vasodilating properties that have been discovered.[19] It is possible that study of the mechanism of action of beta-blockade may provide new leads for new drugs, maybe with activity profiles tailored to suit particular conditions.

The last words on the beta-blockers are fittingly those of James Black:

> "What I think we've learnt from the beta-blockers is that they really only achieve the same thing that you can achieve by being physically fit, and that is an economy of sympathetic drive. I don't think they can achieve anything else. There's nothing magic about these drugs, they're really doing something quite simple, something that's probably achievable in other ways, but this is an easy way. You should be taking the individual as a person and ... trying with the aim of learning to train their sympathetic activity,

> that's all that propranolol does. You can use propranolol to begin with to give them confidence ... doctors should be finding ways of using this so that the drug is never in fact given as something on which the patient has to rely wholly - it should be a sort of 3-legged stool, you need every leg. Diet and exercise should be just as important as the drug and the patient from Day One should think about them all as necessary."[20]

To what extent these drugs are used in this way is discussed in section 2.4.

2.3.6 Participants' viewpoints on the innovation process

In the preceding descriptions of the innovation of the beta-blockers at ICI it is clear that the social relations of the various workers affected the innovation process quite markedly. This is clearly seen during the time Black was working there. During the course of the interviews with key personnel which were done, much information about the social relations later, when the project expanded, was gained which has not been included elsewhere.

Three occupational groups are concerned with the innovation process. These and their subdivisions are illustrated in fig. 2.43. Each of these groups has a corresponding outlook, the interactions of which are examined in this section. Most of the material is from those in the scientific sector, as the information relating to social relations was obtained during the course of discussions mostly concerning technical matters, in which context I was viewed to some extent as an "insider".*

I shall discuss first their attitudes to the drugs which are the products of their labour, then their attitudes towards the other two occupational areas with which they interact. It is essential to realise that these interactions are not static - during the period of the beta-blocking project the influence that the commercial sector exerts on the scientists they feel has increased greatly. They are now much less free to take on new

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*This was much less true of interviews with those in the other two groups with whom, correspondingly, I did not have such open discussions.

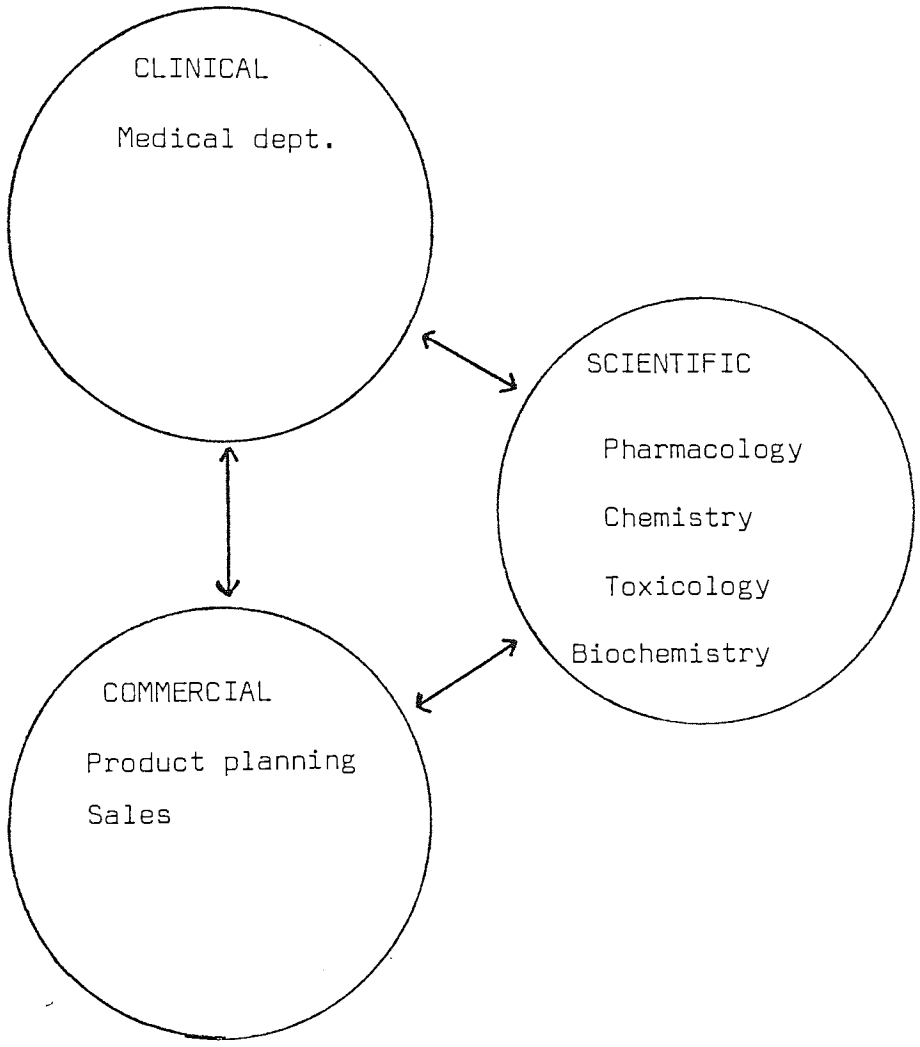


Fig. 2.43 Occupational groups involved in drug innovation within the company.

staff, or buy expensive equipment, and their candidate drugs are scrutinised much more carefully in terms of market potential.

Pharmacologists' attitudes towards the drugs they study is different from those held by doctors in a number of ways. Drugs in the same pharmacological class to them are more differentiated:

> "I think the important thing to realise is that to say that something is a beta-blocker isn't in fact to say that this class is an entity. The truth is that all these compounds are different - quite different collections of properties."[1]

They are often seen as primarily research tools rather than therapeutic agents:

> "it was a great boon to clinical scientists because it illuminated a whole new area of mechanisms in cardio-vascular disease, and this is what I think is the fun in drug discovery - if you can find something with a new pharmacological action, you have to take it into man and explore it."[2]

and drug discovery is seen as an intellectual game. Doctors are seen as ultimately responsible for the proliferation of drugs:

> "Now whether at the moment we need so many beta-blockers is arguable, but this is a problem so far as I can see for which the medical profession is entirely responsible. They have it in their hands to eliminate all useless products. The problem is an educational one ..."[3]

The pharmacologist's occupational outlook conflicts in some ways with the chemist's as the former values insight over the slower systematic reasoning which is essential to the medicinal chemist's slow stepwise progress. Conflicts therefore emerge in situations where a choice has to be made between following up one class of compound or widening the area of structures to be synthesised and tested. This is particularly true in situations where broad patent coverage is sought after.

Conflicts also exist during the development of candidate drugs when the scientists have to accept decisions made about

their drugs by clinical and commercial departments. If the researchers feel discounted by these groups, they may leave as the only way of expressing their resentment:

> "(The introduction of the drug) was taken out of our hands completely. That was run by the Medical Department and by the Development Department and by Sales Department and they didn't want to meet the people who discovered the drugs at all. They had marketed Savlon, Fluothane, Mycelin, and therefore they knew how to handle this drug ... teacher's little boy attitude."[4]

> "There were some very very unpleasant events ... some of the decisions that were made over the drug markedly influenced my decision to accept the job in Canada for a while, not out of pique, but I sensed that things were changing in terms of what I considered to be the optimum role of the research department in the industry. They wanted to do it in just one way and not do anything else ... these decisions are made by the Medical Department in combination with the Commercial Departments, they've got their own goals, and in the end of course, theirs is the final decision."[5]

Awareness of the extent to which competitive influences are felt to affect research varies among the researchers; a reason for this may be contained in the comment of one pharmacologist, that competition affects research, but that you only see it after you've left. Only highly motivated individuals whose motivation coincides with the company's interests are taken on. However, in the past the atmosphere of research seems to have been more relaxed. In the sixties the scientific heads of ICI's beta-blocking project were not concerned with justifying their allocation of finance:

> "At university I have to draw up proposals for each year with regard to the money I want, changes in staff - I never had to do that at ICI. There was no budget planning that I was involved in - now (my section head) might have had - but I as head of the beta-blocking programme didn't have to justify what I was spending at all. No overall plans from management at all."[6]

Wherever the allocation of resources was done, those in the

research labs felt that through most of the project decision-making was conducted at laboratory level:

> "Once a week (we met) with the chemists, and then once a month or once every two months meetings called project team when the biochemists, and the chemists, and the pharmacologists were able to talk all together. This would discuss the work that was being done and decisions would be taken about what was to be done over the next, say 3 months. But the next time Davey who would be the chairman or Spinks - they never said well at the last meeting we decided that A B C D should be done, what are the results - nobody bothered."[7]

This feeling of local decision making is now less strongly felt as the research organisation has expanded and become more commercially orientated.

There is a strong belief among the pharmacologists that I interviewed that the productivity of research depends on a few gifted individuals:

> "(The firm) was much smaller then, and with financial success they put a lot of money back into the research and they've expanded it. I'm not sure - in the end it's only one or two people who count, I think, in the pharmaceutical industry ... you can nominate quite clearly the people responsible for the industrial success of this division without any problem."[8]

Along with this goes a disbelief in planned research and a focusing on the talents of individuals:

> "I think probably the best drugs come out despite the research directives if I'm quite blunt, and my view is quite simply that you've got to back them, and if you've got a first-class man who's got a good hypothesis then you change direction and you follow it ..."[9]

These are often seen to be in conflict with the needs of the organization:

> "The problem at the firm as I then saw it was that it didn't make use of its talents. It had so many talents and somehow they seemed to me to be squandered."[10]

With successful research, promotion is looked for by those responsible, but there are often problems if the company maintains

two different promotion ladders, the scientific and the administrative, as good scientists are not always best suited to being good administrators.

> "... in order to get promotion you have to go into administration and one of the reasons I left was that Davey told me mid-1966 that they'd decided that I wouldn't make an administrator and that I would have to stay in the research laboratories ... and I knew that restricted my advancement very severely - Barrett was treated in exactly the same way, and we both left."[11]

Both these men are now in high positions in university pharmacology departments - which combine for them administrative, scientific activity and status. Others have moved up within the hierarchy of the firm, the most "successful" have moved to research directorships in other companies.

2.4.1 Approaches to the study of the effects of drug treatment

The effects of drugs cover a wide spectrum, from those which are only pharmacologically detectable through effects on disease and side-effects to long-term effects on the individual and wider effects on society.

The majority of the studies of the effects of drug treatment are done on a small scale, that is on a few tens of individuals over periods of weeks or months. These clinical trials, tests of the effectiveness of drugs in controlled conditions, are at present our only source of reliable detailed information on the therapeutic and unwanted effects of drugs.

The clinical trial uses a variety of techniques to ensure that the results of the trial are not affected by the doctor's or patient's perceptions of their treatment.[1, 2] However, the elaborate arrangements that are made to achieve this make the clinical trial situation very different from that of ordinary usage as Lasagna points out:

> The modern double-blind controlled clinical trial is often conducted by expert investigators on relatively homogenous patient populations, avoiding in so far as possible the concomitant administration of other drugs, invoking informed consent and signed release forms, often employing placebos, usually with neither doctor nor patient being aware of the drug taken by any given subject, and often adhering to a rigid protocol detailing what observations, including what lab tests are to be done at what intervals ... Such trials, while of clear utility in establishing efficacy, are nevertheless remarkably artificial in the sense of not resembling the real-life application of drugs to treatment of the ill ... it seems inevitable that the prediction of 'naturalistic' performance from controlled clinical trials will be faulty."[3]

Certainly the clinical trial has done more to upgrade the quality of drug treatment than any other single recent innovation,

but their format makes generalisation to less controlled situations a less straightforward process than it might at first seem.

Information about the larger-scale effects of drugs is achieved clinically either by the accumulation of clinical records over a long period, or by the aggregation of clinical trial results. The first method is now less common, but is still useful as a form of pilot study which may suggest directions for further clinical trials. Examples of this are the experience of doctors specializing in the treatment of hypertension in the late 1950s and early 1960s on the survival rates of patients treated with antihypertensives,[4] and comparisons of treated with untreated cases.[5] These paved the way for the controlled trials which, published in the middle and late 1960s,[6] greatly expanded the use of antihypertensive drugs.

The second method is now seen by many as a final stage in drug evaluation:

> "If the preliminary results obtained from Stage 1 and Stage 2 trials are satisfactory, the drug should enter the final assessment of the Stage 3 trial. During this phase it will be given to a large number of patients over a prolonged period of perhaps 1 - 2 years. Particular attention will be paid to the correct dosage for the individual patient, to the development of side-effects, and to comparison with other drugs having a similar action. ... The aim of such Stage 3 trials are
> 1) to evaluate the clinical value of the new product in relation to those already in use.
> 2) to attempt to determine how many patients will benefit from it.
> 3) if it is (most) suitable for any particular type of patient."[7]

However this ideal state is rarely achieved, since with older drugs such reliable information on large patient populations is not available, and with newer drugs less monitored studies such as those existing studies of general practice use, known as 'Post-Marketing Surveillance'[8], are the full extent of our knowledge. These do

not use controls and are orientated towards the detection of side-effects rather than the estimation of benefit/risk, hence they are not as reliable an indicator of the characteristics of a drug as a clinical trial, but may be a useful guide to its performance in practice.[9]

It can be seen that the only reliable direct information on drug effects is derived from small studies, so that any study which aims to consider drug effects on a larger scale must make use of assumptions, either generalising from a body of selected trials, or using less direct information. The first option involves assessing how the trial protocol might produce different results from those obtained in everyday use, the second assessing the accuracy of the other information used, and the extent to which other factors are likely to influence it.

The first option is exemplified by studies such as those of Cretin (1977) on the cost-benefit analysis of treatment and prevention of myocardial infarction, and Weinstein and Stason (1976) on the cost-effectiveness of different treatments of hypertension.[10, 11]

Cretin addresses the question of which strategy; prevention by screening and dietary alteration of most susceptible individuals, the provision of mobile coronary care units, or the provision of coronary care units would be most cost-effective from the point of view of prolonging survival. He uses data on direct costs from the literature and estimates indirect costs, such as the medical care and added hospitalisation during subsequent infarctions likely when the first has been survived. He models benefits from published data on mortality rates from hospital wards and coronary care units, the effects of dietary intervention on serum

cholesterol, and the results of this reduction. The problems with this otherwise impressive technique are two-fold: the rate of discounting adopted, and the criteria of benefit.

There is little agreement on what rate of discounting, that is the amount by which a benefit conferred in the future is less valuable than a benefit in the present, should be adopted in these studies. However, the cost-benefit ratio of the different strategies varies widely with variance in this assumption. The criterion of benefit too, can be criticised for not taking into account factors such as the unpleasantness of a life-long diet low in cholesterol or of life-long adherence to drug treatment.

These objections are met to some extent by Weinstein and Stason's study '<u>Hypertension - the Policy Process</u>', a detailed examination of the cost-effectiveness of antihypertensive treatment. This makes very clear the areas in which the lack of knowledge makes rational decision-making difficult, for example, whether the reduction of blood pressure to normal levels after a period of high pressure increases the life expectancy of a hypertensive to that of a normotensive of the same age, or by some lesser amount? To cover these areas, Weinstein and Stason make a range of explicit assumptions, in this case using different 'fractions-of-benefit' and also a factor which takes into account that this benefit probably varies with the period of hypertension, and the age of the patient.

The study is committed to valuing health effects in health terms, so that the measures of benefit are life-years rather than dollars. These are adjusted for changes in quality of life due to cardiovascular morbidity and drug side-effects on the economic trade-off principle, of determining how much time the individual

would choose to lose if he could trade this off against not having the disability for the rest of the time.

Drug side-effects are accounted for by assessing their probability, the objective costs of hospitalization and medical treatment necessary, and the subjective loss in quality of life. In this assessment, a estimated loss of 1% in quality of life is much more significant than the objective costs.

The combination in this study of clinical data on the effects of hypertension, and of antihypertensive treatment, and cost-effectiveness and decision analysis modelling strategies produces a clear and flexible method of analysis, which points directly at areas where more information is needed. The economic basis of the study again raises the problem of discounting, however, which the authors settle by adopting the figure of 5% as this "approximates the real after tax rate of return acceptable to private investors".[12] The transition from discounting money to discounting life-years is described as "present years of life being valued more highly in present dollars than future years".[13]

Thus, the study's claim to value health effects in health terms is undermined slightly by the need to discount future benefits at some agreed rate for which the only guide is financial practice.

Studies employing the second option, that is using indirect information, often take the form of attempting some correlation between mortality statistics and drug consumption. This connection is difficult to make for the following reasons:

1) Many other factors besides changes in drug use affect the numbers of people ill or dying with stroke or hypertensive disease. Economic factors, social change, dietary changes, all exert unknown but significant effects.

2) Mortality statistics are not fixed unvarying categories, but reflect medical perceptions of disease which are subject to change, often influenced by changes in drug use. This is analysed further in a later section.

3) Changes in the volume of drugs used for a particular condition do not necessarily reflect a proportional amelioration of that condition - the appropriateness with which the drugs are used must be considered.

4) International comparisons which would compare the impacts of the differing drug use run into problems of differing mortality coding practices in different countries, and the influences of varying diets and styles of living. Without extensive data on these differences, and a knowledge of their possible effects, it would be impossible to realistically ascribe any of the mortality differences to the effects of drugs.

However, attempts of varying sophistication have been made. The most rudimentary of these is the superimposition of marketing dates of various drugs used to treat a condition on the mortality curve of that condition. This device is frequently found in texts attempting to show empirical evidence for the benefits of drug innovation (fig. 2.44).

The criticisms of this simple presentation are obvious - that neither the volume of use of the drugs nor other factors possibly involved in the changes in mortality are taken into account. Because of this, it is a misleading representation of the effects of drugs on disease because so much is missed out. For example, two different views of the decline of tuberculosis in this country (figs. 2.45, 2.46) support two very different arguments. Reekie and Weber (1979) comment on their presentation,

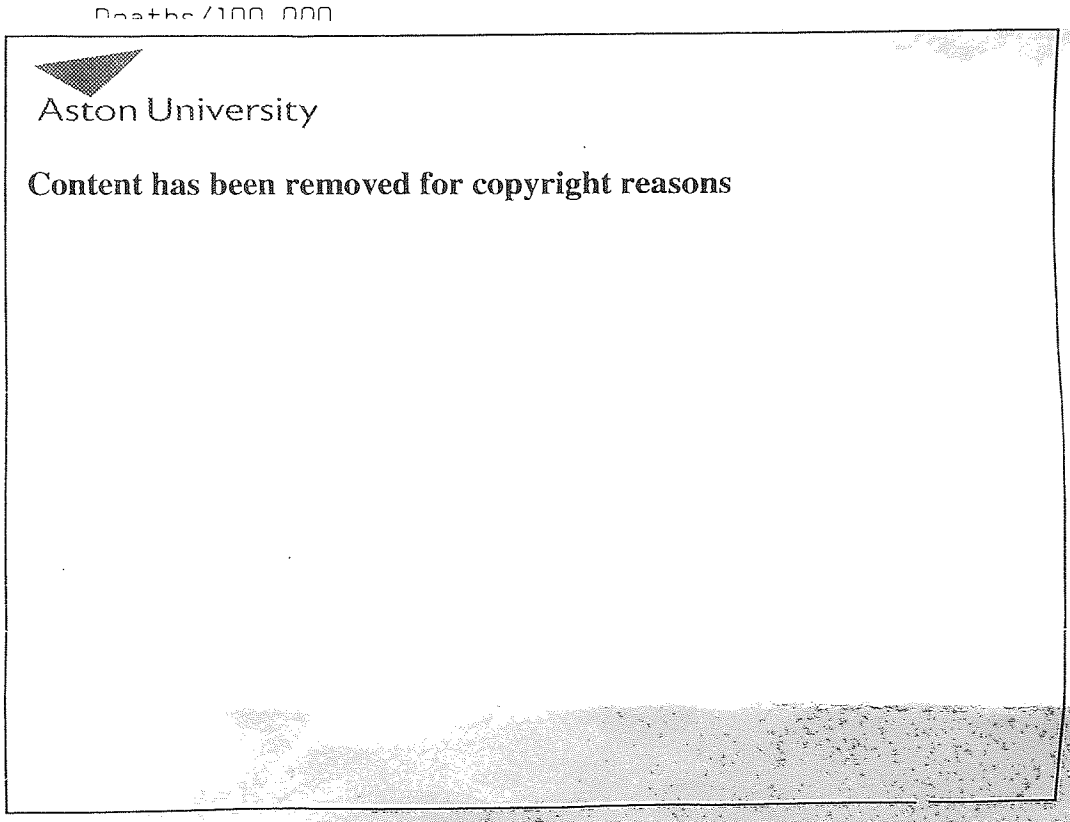


Fig. 2.44 Impact of antihypertensive drugs on deaths from hypertensive heart disease according to Silverman and Lee (1974).

Source: Silverman, M., P. R. Lee Pills, Profits and Politics (University of California Press, Berkeley, 1974)

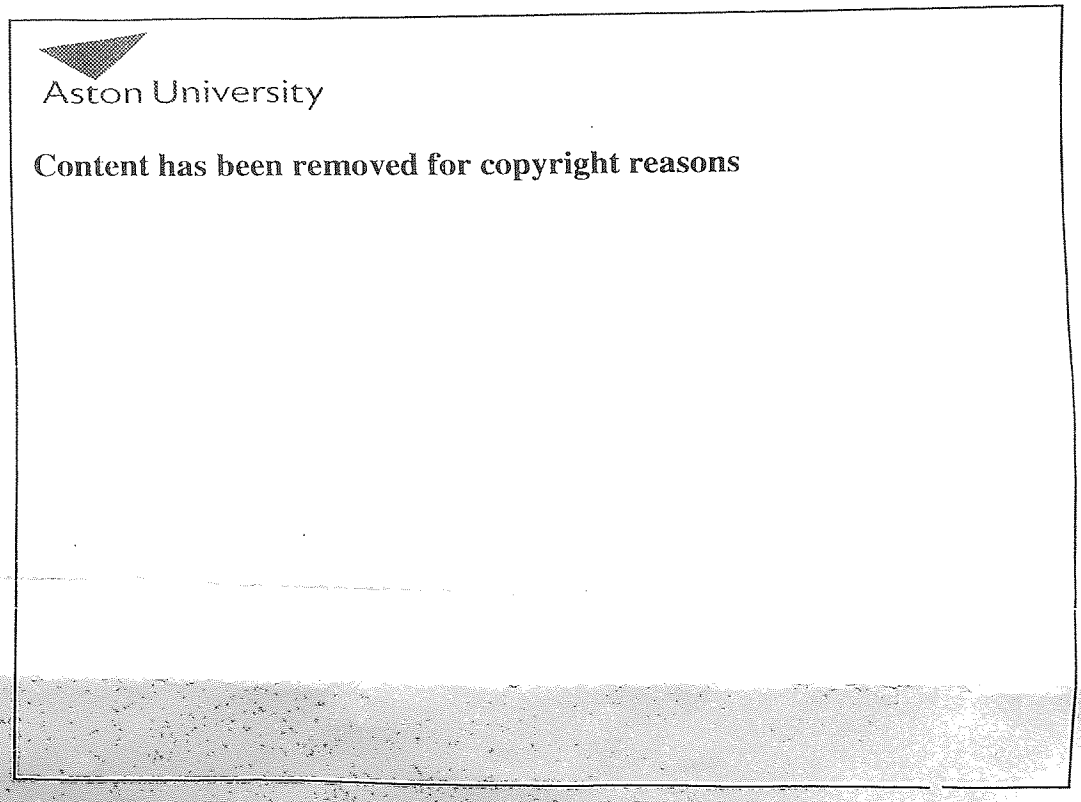


Fig. 2.45 Decline in tuberculosis mortality according to Reekie and Weber (1979).

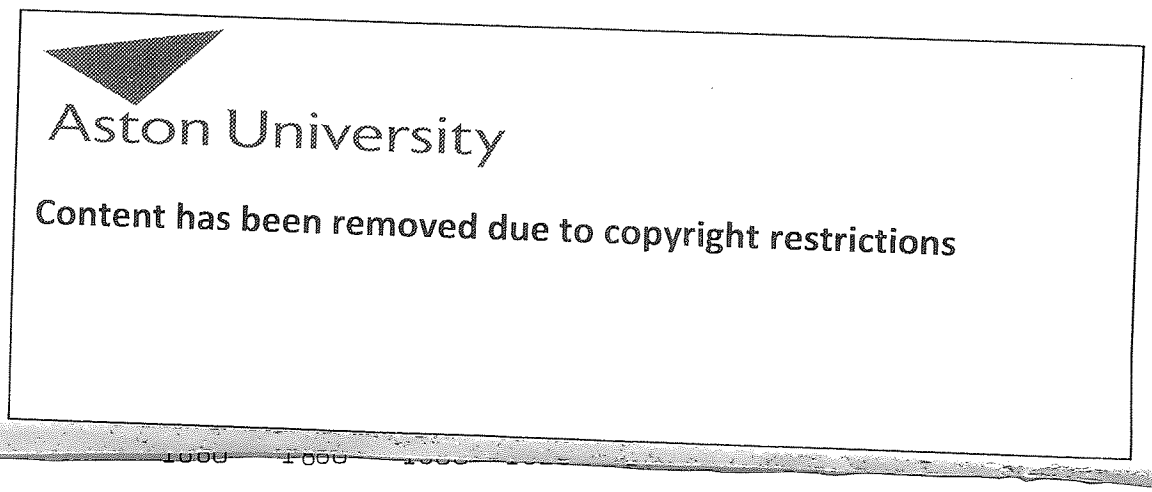


Fig. 2.46 Decline in tuberculosis mortality according to McKeown (1976).

"The decline in mortality from tuberculosis since the introduction of streptomycin, para-aminosalicylic acid and isoniazid has been one of the most dramatic medical advances of the century ... the pharmaceutical industry discovered, tested, developed, mass-produced and marketed antituberculosis drugs which swept the whole problem away ... this outstanding social advance was produced ... by the largely unaided efforts of the pharmaceutical industry."[14]

McKeown draws soberer conclusions from a longer time-scale:

"Effective treatment began in 1947 ... and 1954. By these dates mortality from tuberculosis had fallen to a small fraction of its level in 1848-54 ... Nevertheless, there is no doubt about the contribution of chemotherapy ..."[15]

Similar discrepancies occur in interpretations of the reduction in infectious disease mortality in the same period, some accounts linking coincidental events such as these reductions in mortality and introductions of new drugs as causal,[16] others maintaining that there was little connection.[17]

It is clear that a more detailed analysis is necessary to arrive at any definite conclusions. This involves measurement of drug usage for the condition studied, and knowledge of the efficacy of the treatment. Prineas and Lovell attempted such a study of the influence of antihypertensive drugs on the mortality due to stroke in Australia from 1950-1967.[18] When the increase in volume of prescriptions for antihypertensives (100%) was compared with the fall in stroke mortality (25%) over this period they found no definite correlation for two reasons. Firstly, mortality fell before the effective drugs were widely used, and secondly, the mortality fell even in older age groups where drugs were rarely used.

Reid and Grimley-Evans have looked at the impact of new drugs on non-infectious disease using more sophisticated mortality data. They comment:

> "in diseases where the case-fatality rate is not too low, mortality statistics with all their well-known defects may be the only available index of the impact of therapy on disease in the total community. Mortality studies are thus no substitute for a controlled trial, but they may provide a useful supplement to it."[19]

However, they go on to emphasise the various causes of change in death rates summarised above, and in their analyses of four degenerative conditions they are able to cite only one or two declines in mortality among specific age-groups which they feel can reasonably be attributed to drug treatment. Changes in death certification practices and concomitant social change seem to be the major factors which hinder the analysis. They include no prescribing data, so that their estimates of drug usage and effects appear wholly intuitive.

Reader looks again at mortality from coronary heart disease in Australia,[20] and concludes that from 1967-73 there has been a decline in mortality which he shows by simple calculation could be due to the effects of the current rate of antihypertensive prescribing. Basing his calculations on three recent population studies his estimates are illustrated in Table 2.12.

Estimating the numbers of hypertensives treated, Reader was able to derive the number of those treated effectively - about a third. Using the Veterans' Administration trial data on comparative mortality of treated and untreated hypertensive populations, he calculates the number of expected deaths per year if these were treated, or not treated. The difference between these figures (1,745) compares well with that derived from the fall in stroke and ischaemic heart disease mortality in this period (1,872). Thus he concludes that it is possible to detect the effects of anti-hypertensive treatment using mortality statistics.

Table 2.12 Estimation of the effect of treatment on mortality from stroke and ischaemic heart disease (ICD 330-334; 410-414) Australia 1973

Source: Reader, R.[20]

This attractive conclusion is worthy of further study; in particular, do age-specific death rates show the decline to be in all age-groups or is it correlated with the age-groups having the highest consumption of antihypertensive drugs? It was this lack of correlation that Prineas and Lovell found which casts some doubt on the significance of Reader's results. However, his model's combination of statistical and clinical trial information is potentially a most useful technique.

In summary, it can be said that the two approaches illustrated, modelling and the correlation of statistics have different orientations. The modelling technique is flexible and can give answers useful to decision-makers. It is thus primarily a future-oriented technique. The main drawback with this type of study is that clinical trial data is often used without an assessment of the effects of generalising to a less controlled setting. The correlation of statistics is a generally less sophisticated attempt to describe the effects of past interventions, and suffers primarily from the difficulty of separating out the influences of several different factors with a fairly crude information base.

2.4.2 Study of the effects of beta-blockade

In order to begin the study with as complete a picture of the effects of these drugs as possible, a method of analysis derived from Technology Assessment has been used. This involves the classification of different levels of effects in orders:

> "Technology Assessment can be viewed as an examination of the functional relationship of technology with respect to various aspects of society. These relationships can be interpreted as social responses to a given technological development. In their turn these responses are interconnected in space and time so that it appears possible to distinguish several categories of effects which seem to unfold in a concentrical way as first-order, second-order, and higher-order impacts or consequences."[1]

This ordering of the spectrum of effects applied to beta-blockade is shown in figure 2.47. In this model the most obvious benefits and costs at each level at which drug effects can be examined are included. The classification of orders is based on ease of analysis so each order has a defined literature and set of data associated with it. Thus, first-order effects are those directly attributable to the patient's reactions to the administration of beta-blockers, and the wider social effects of these reactions are not considered, second-order are the economic effects of the medical situation, third-order are the more extensive clinical and scientific impacts of the increased use of the drugs, and fourth-order are the longer-term impacts on the whole society. These effects are considered within the context of the effects of previous therapies supplemented or supplanted by beta-blockade.

Two points should be noted: first that the list is necessarily open-ended, second that it is essentially a one-way perspective - for example, it does not indicate the fact that feedback from clinical usage, just one of the societal responses considered, as

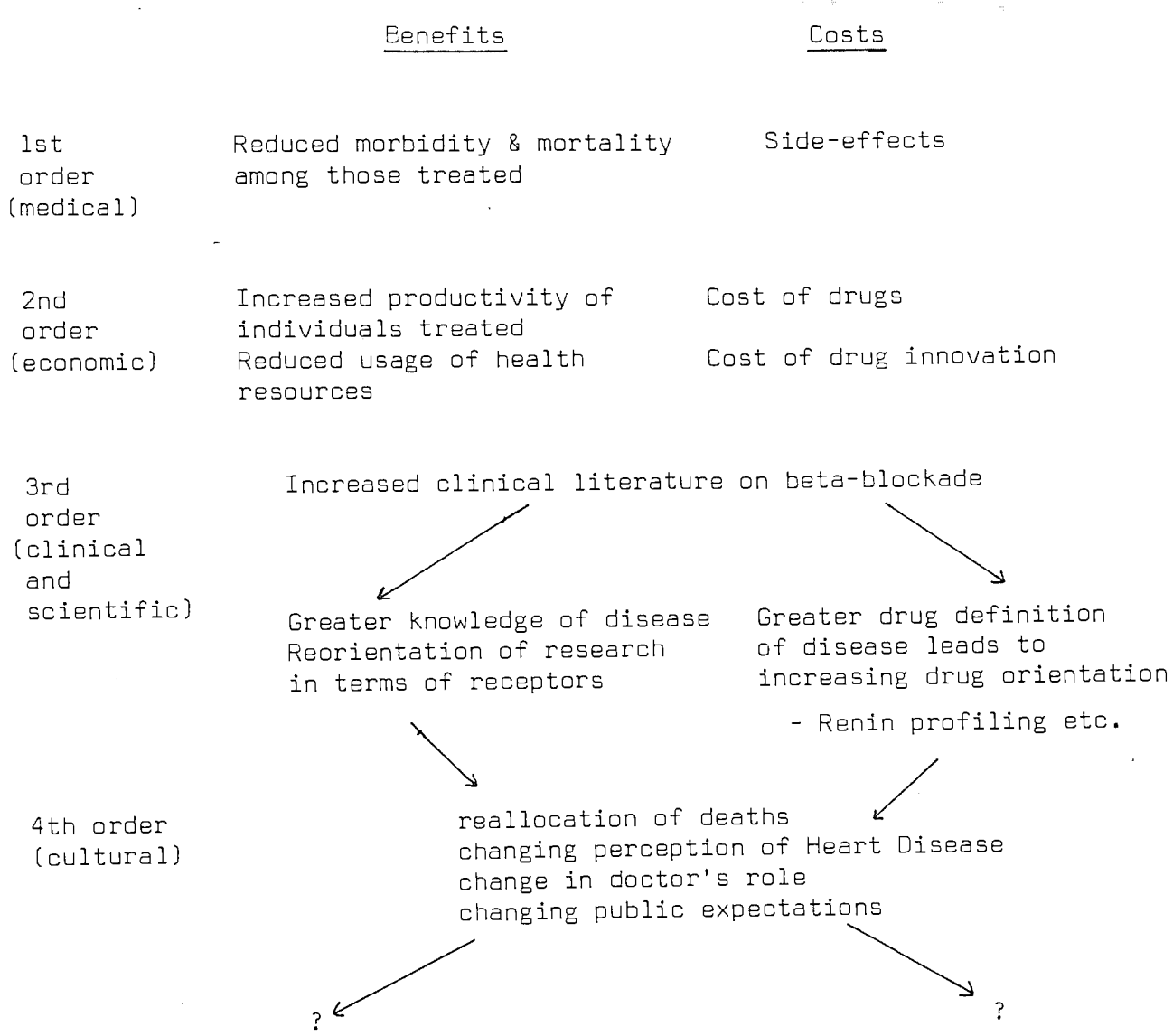


Fig. 2.47 Effects at different levels of the use of beta-blocking drugs.

demonstrated elsewhere, significantly alters subsequent research and development. Some examples of the feedback from societal response at different levels affecting the development of the technology are listed in Table 2.13.

It can be seen that a dialectical interaction is the most accurate conceptual form to adopt when considering the effects of pharmaceutical innovation. An example of the resultant 'cascade' is shown in Figure 2.48. It is obviously necessary, therefore, because of the quantity of information involved, to be selective regarding the areas of effects studied, and the detail in which they are analysed.

This study concentrates on the first and third levels of effects in this classification, that is the immediate therapeutic impact, and the related conceptual changes in medical science. These have been chosen for a variety of reasons.

The study of the clinical level was undertaken because of the importance of linking it with study of the innovation of the drugs involved which has already been stressed. There is much information available for analysis, and this represents a concentration of scientific and medical effort on the study of detailed drug effects which must be a prime focus of investigation.

The economic level of study was not pursued, primarily because of the frequency with which this approach has been used.[2] It was felt that unless the analysis was detailed, it would not provide many new insights, and since much of the necessary information was not available, this was not possible.

A study of the ways in which conceptual changes in medical perceptions of disease have been influenced by the introduction of new technology had already been undertaken in the area of

Table 2.13 Examples of the effects of social response at different levels on the development of beta-blockade

Clinical	*Efforts to reduce unwanted effects: altering dosage, instructions for use, contra-indications, produce new drugs. *Successful speculative usage in new indications can alter the direction of research, development, and marketing (e.g. Prichard and hypertension leads to work on once-a-day therapy.)
Economic	*Price considerations per equivalent dose obviously affect prescribing, hence marketing.
Wider medical and scientific	*New theories due to use of beta-blockade affecting the development of beta-blockade: *Vaughan-Williams' opinions on propranolol's mode of action, 1966, leads to production of new blockers without MSA. *Laragh's theories on the action of beta-blockers in lowering renin levels increases use in US in 1972. *Ablad's opinions on the importance of ISA leads to concentration on blockers with this property.
Cultural	*Beta-blockade widely used as an example of "successful" innovation by proponents of pharmaceutical industry's viewpoints.

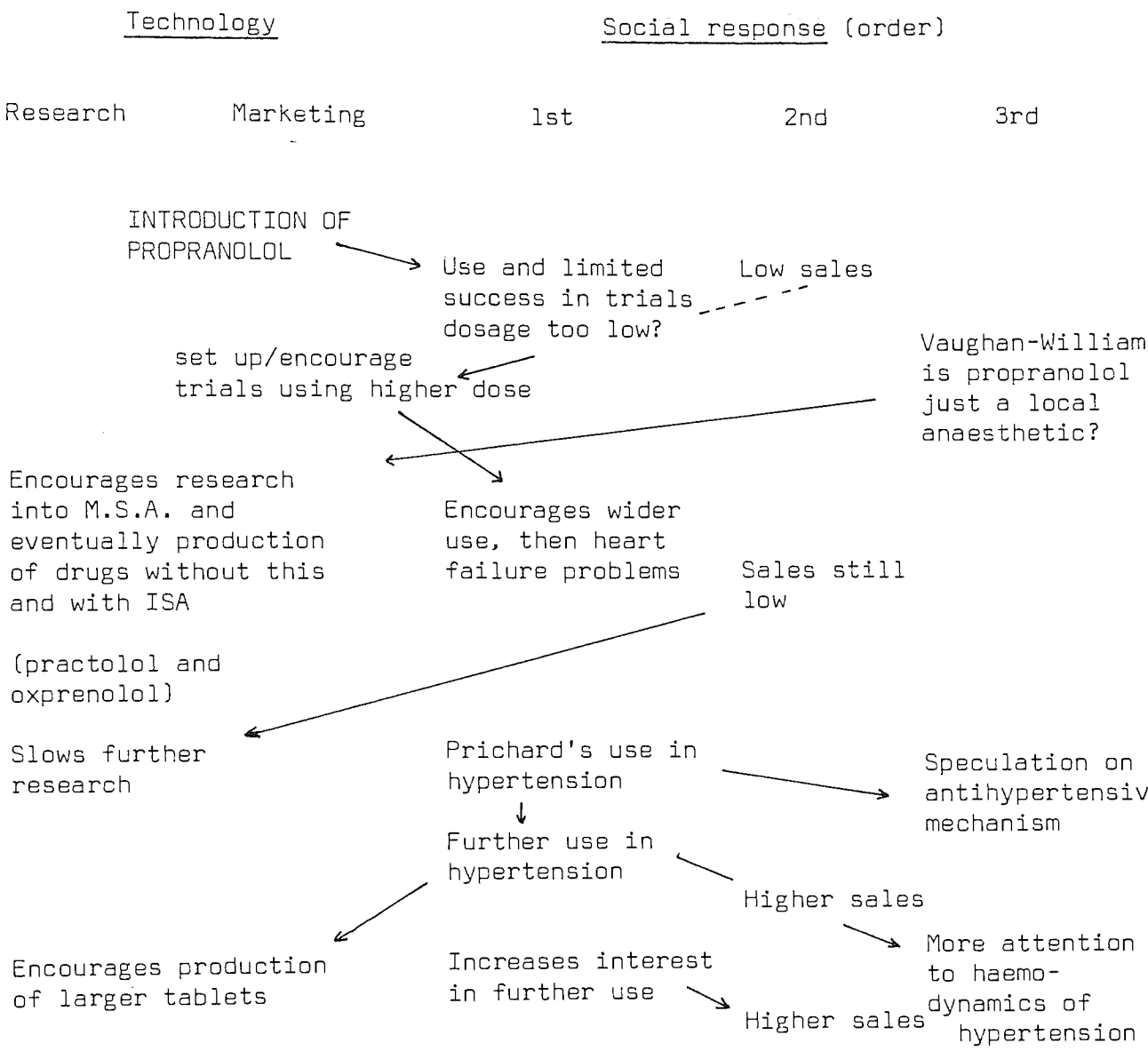


Fig. 2.48 The interactions between the effects of the use of beta-blocking drugs.

hypertension. It was interesting to see whether similar effects could be traced to the innovation of beta-blockade. This area seemed worth examining because of the potential significance for the evolution of medical theory and practice if such a connection were found, as this area has not been previously examined.

The cultural level was felt to be important, but both the information, and the necessary analytical techniques were lacking, so this area was not pursued further.

The estimation of therapeutic impact

> "There is little doubt that people are better off without high blood pressure than with it. On the other hand, treatment of hypertension ... can make a patient feel awful. It is not clear a priori that an iatrogenic disease is better than a natural one".
>
> Weinstein, M.B., Stason, W. B.

A detailed theoretical treatment of the problems of therapeutic impact assessment is found in Wardell and Lasagna's book 'Regulation and Drug Development':

> "To measure the total medical impact of a new therapeutic drug in a society, one would ideally need to perform an experiment. For example, the drug could be introduced into certain communities and withheld from other comparable ones in a randomized, controlled manner. Objective data could then be collected on the therapeutic outcome of relevant diseases in the control versus the test communities, and these could be weighed against the total drug toxicity recorded under the same conditions of use. Simultaneously, measurements could be made of the extent to which the new drug replaced older treatments. The therapeutic outcome - beneficial or toxic - could be assigned in each case to the treatment used. If all the relevant data were obtained, then the actual therapeutic impact of that drug could be defined ...
>
> Since such comprehensive data are not available, we need to examine other approaches to assessing the therapeutic impact of contemporary drugs.
>
> One logical approach is to construct a balance sheet of the currently measurable benefits and losses stemming from introduction of a drug. Benefit as a therapeutic concept involving a whole society's response to a drug has not yet been well defined or measured. This lack is illustrated by the literature

> involving therapeutic trials. That which deals with the controlled clinical trials ... describes the results obtained when drugs are administered under defined and controlled conditions to specific types of patients. The larger scale, often uncontrolled, postmarketing trials provide wider experience of treated disease, but in a manner whereby the therapeutic contribution of the drug under study may be unmeasurable. None of the current methods of drug evaluation are designed to measure the total impact of the drug under conditions of actual use - that is, when given in an unmonitored way to undefined patients. In short, therapeutic trials do not tell us how the drug actually performs in practice.
>
> At best then, therapeutic trials can measure only the potential benefit and harm available from a drug, not the benefit and harm actually realized in the community. Other kinds of data must be obtained to build a complete picture."[3]

Here we have a distinction between two classes of therapeutic impact - potential therapeutic impact, as measured by clinical trials, and actual therapeutic impact which is based on potential therapeutic impact but includes factors such as appropriateness of use and patient compliance.

Qualitative estimation of potential therapeutic impact

The first stage in this process is an assessment of the clinical literature on the drug. From a review of this it should be possible to arrive at an estimate of the potential benefits and costs resulting from the use of the new drug. Direct benefits are mainly reduced mortality and morbidity, both due to the disease and to the side-effects of older treatments, but also include possibilities of more convenient treatment. The direct costs are the incidence and severity of side-effects, and the increased expense of the new treatment.

This simplified analysis does not include all benefits and costs of the change in treatment. Other factors which are not accounted for are:

*costs of treating side-effects,

*costs of treating illness which occurs during years of life expectancy conferred by treatment, which therefore would not have occurred in its absence.

Obviously also the patients who were previously untreated will have a different cost-benefit ratio from those who were on the old treatments.

These benefits and costs are estimated separately for each condition in which the drug is used. In this study only the two major indications; hypertension and angina, have been considered in this manner, since information on the other indications is either more difficult to analyse or is not available. However, these benefits and costs are arrived at implicitly, if not explicitly, by comparison with the currently accepted medical therapies for the condition in question. Thus, the potential therapeutic impact of a new drug is related to the characteristics of the currently accepted treatment(s) of choice.

The potential therapeutic impact is not limited to those effects for which the drug is taken, however, as second-order and other more indirect effects must be considered. For example, the effect of treatment with the new drug may be so good, and the side-effects so slight, that many more people with less severe cases of the disease which the drug is used for may be treated. The effects of this kind of change may be far-reaching, as has been noted.

The review of the clinical literature should enable an assessment of the first-order impacts to be made, and also give some clues as to what second and higher-order impacts are also likely to be important. It should be possible, depending on the

amount of clinical work done, to determine which patients will benefit from the new drug, what proportion of the total number of patients with the disease they constitute, and how much they can be expected to benefit. The expected burden of side-effects should also be estimated, and to what extent it could be mitigated by the use of other medical techniques.

It would be a mistake, however, to see the clinical literature on a drug as a necessarily objective scientific record of its clinical usefulness. Various factors influence the extent to which the results of the trials may be generalised - these must be taken into consideration, but there are no straightforward ways of doing this.

Firstly the trial protocol may be defective. Two assessment schemes have been used, that of Gifford and Feinstein (1969)[4] who cite the features listed in Table 2.14 as the basis on which a clinical trial should be assessed, and that of Lionel and Herxheimer[5] whose check list covers all these points in a more detailed fashion.

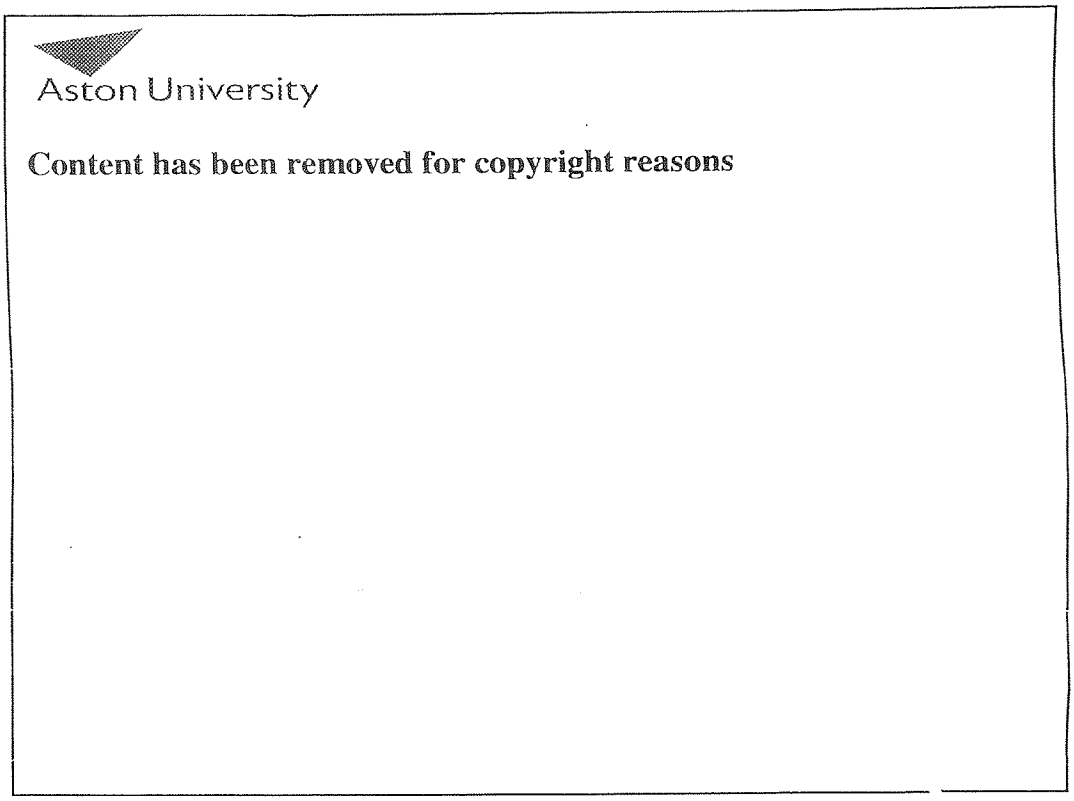
Many trials do not have all these features however. Lionel and Herxheimer, using a comprehensive check-list to assess the quality of trials published in British general medical journals found that only 51% were "acceptable". A further 16% were "probably acceptable" but had not included enough information, and the remaining 33% were considered unacceptable due to:

- the poor or inappropriate methods of assessment,
- the absent or inadequate controls,
- the lack of relevant statistical tests.

The clinical literature therefore cannot be uncritically accepted as is often the case.

Table 2.14 An assessment scheme for clinical trials

* It should be PROSPECTIVE



Source: Gifford, R. H., A. R. Feinstein[4]

Secondly, there are factors that favour a new drug when compared with an established drug. The side-effects of the old treatment are well-known and therefore readily recognised, whereas those of a new treatment are not and may easily be underestimated. The benefits of the new drug are often overemphasized by those doctors that undertake clinical trials with it because they easily become "product champions", identifying themselves with the new drug against the strong conservatism inherent in therapeutics. Trials may be sponsored by the company that produced the drug, in which case they may well be designed to present the drug in the most favourable light, emphasizing the benefits and minimising costs. These factors are to an outsider difficult to allow for, however they remain important considerations.

Quantitative estimation of therapeutic impact

In order to gauge the extent of the therapeutic impact of the beta-blockers, it is necessary to make some estimates of the number of people who use them, and what proportion of this use is substitution for previous therapy, and what proportion is for those previously untreated, as information on these matters is not available. There are several different sources of indirectly useful material, however, which can be used to make an estimate.

The numbers of prescriptions dispensed per year for each of the beta-blockers was obtained from the Department of Health and Social Security, which also publishes a yearly list of all drug prescriptions aggregated into therapeutic groups.[6] These figures have to be taken into conjunction with other estimates found in the literature to correlate prescription numbers with the number of patients taking the drugs, and to derive the proportions of the

prescriptions used in different conditions. These estimates are not usually accurate, so results critically depend on which estimates are taken as being most reliable.

The technique of correlating mortality statistics with drug usage has been mentioned, and a number of ways of doing this have been explored for hypertension, the best documented condition in which beta-blockers are used. However, for the reasons given above, and in section 3.1, no great reliance is placed on the results.

Estimates of potential costs and benefits derived from controlled trial situations must be modified to take into account at least the most obvious ways in which the use of drugs in medical practice differs from this ideal state. The two major factors involved are the appropriateness with which the drugs are prescribed, and the extent to which the patient takes the drugs as prescribed (adherence or compliance).

Appropriateness of prescribing

This question is of central importance to the estimation of therapeutic impact, yet there is very little information available concerning it. A direct survey of medical practitioners was not undertaken, as previous experience with these studies at Aston had shown a low response rate and a good deal of suspicion, even though the researcher was a qualified pharmacist.[7] It was felt that a similar study looking at more sensitive information, such as the appropriateness of drug prescribing, would not give information in proportion to the time such a study would take.

The sociological literature on prescribing concentrates mainly on the effects of various influences on prescribing such as

advertising, visits by representatives, colleague's opinions etc., rather than its appropriateness or otherwise.[8] This is probably because such a study would involve detailed knowledge of medical theory and practice in the area chosen, and hence be too extensive.

Appropriate prescribing is here defined as prescribing which takes into account the following criteria:

*is this the right drug for the patient's condition?

*do the contra-indications to the drug apply in this case?

*what are the right doses to prescribe?

*is the patient adequately monitored for side-effects and correct dosage?

Information on the extent to which these criteria are met by the use of beta-blockers in general practice is fragmented and scattered widely in the medical literature. Often inferences must be made from inadequate information, and various assumptions made. While optimal therapeutic use is largely well-defined by expert consensus, the extent to which this is followed in general practice warrants systematic study.

Patient compliance/adherence

A succinct description of this problem is given by Crooks and Parkin:

> "In any evaluation of drug therapy in terms of efficacy and toxicity it is clearly of great importance to be sure that the patients do in fact receive the drugs prescribed for them, and usually (though not invariably) appropriate measures are taken to ensure this in the design of clinical trials. The extrapolation of deduction from the results of clinical trials to general medical practice is thus only justified if the same degree of conformity with prescribing instructions exists, quite apart from other variables such as the type of population treated. It has become clear that this condition is frequently not fulfilled and major discrepancies between drugs prescribed by doctors and those taken by patients occur in various areas of general medical practice."[9]

More work has been done on this than on the problem of appropriateness of prescribing, probably because of the greater accessibility of patients as a low-status group to questionnaires. Most of it has however focussed on compliance as a general problem, rather than on specific areas, so that many of the most important questions raised by new drugs and the compliance problem remain unaddressed. Special problems exist in the case of hypertension because of the asymptomatic nature of the condition.

The basic question addressed - which is "how does uncertain patient compliance affect the extrapolation from clinical trial to general medical practice for beta-blocking drugs?" can be broken down into the following areas:

*Results of work on general patient compliance with drug therapy which is applicable for hypertension, which has a particularly severe compliance problem.

*Do reduced side-effects increase patient compliance?

*Do patient perceptions of increased effectiveness increase patient compliance?

*Does a less complicated regimen increase patient compliance?

Thus, if the appropriateness of prescribing, and the extent of patient adherence is estimated, the therapeutic impact of beta-blockers may be compared with that of substitute therapies.

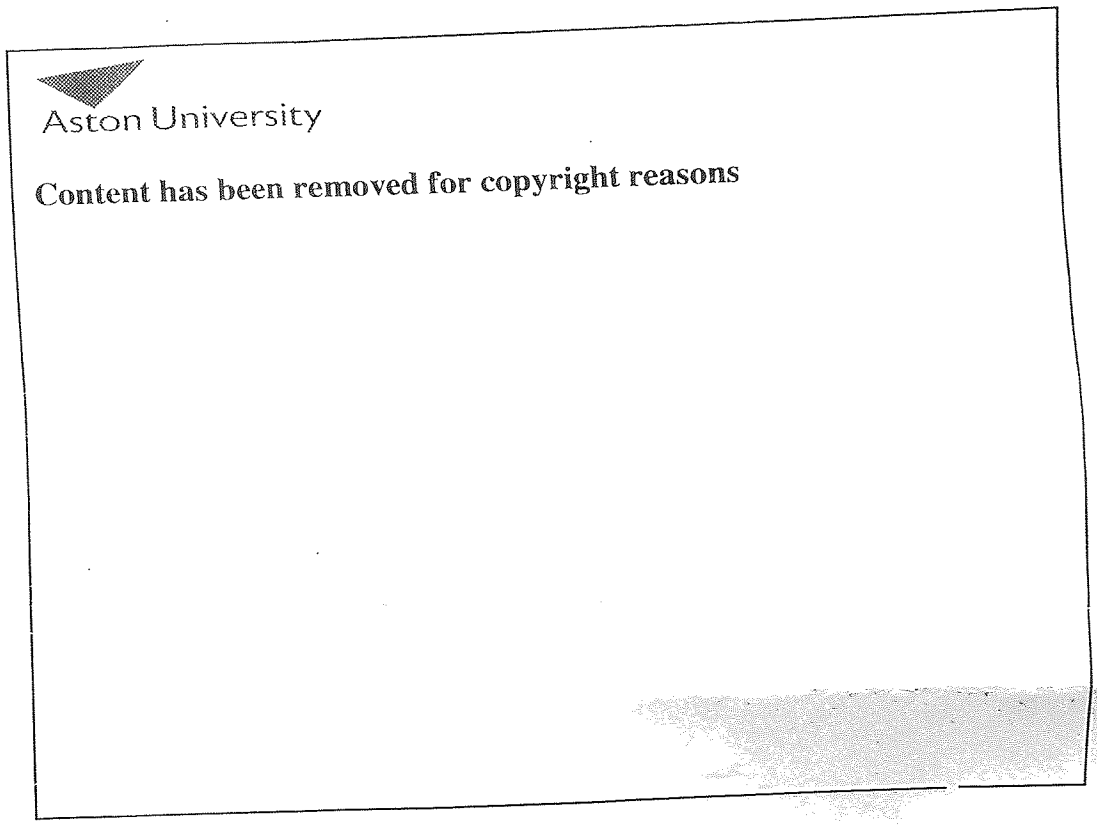
2.4.3 Beta-blockade and hypertension

The condition of hypertension, or high blood pressure, the evolution of which I have covered in the first section, is currently defined as having a diastolic pressure above an arbitrary cut-off point, usually 95-115 mmHg.[1] The elevation of pressure above 'normal' (taken as 120/80) is associated with an increased mortality, mostly through strokes and heart attacks (see Table 2.15).

It has been well-known since the nineteen-fifties that malignant hypertension, that is, maintained pressures above 200 mmHg systolic is usually fatal in a few years unless treated, but that antihypertensive treatment can prolong the life expectancy of these people dramatically.[2] However, it is only recently that treatment has been advocated for those with lower pressures. The first evidence that treatment can reduce the number of 'morbid events' (strokes and heart attacks) experienced by those who were symptomless, but nevertheless had diastolic pressures around 120-130 mm, came from the controlled trials of Hamilton in England[3] and the Veterans' Administration in the US [4] (Table 2.16).

Treatment (in Hamilton's study with a diuretic, a ganglion-blocker, and methyldopa ; in the Veterans' trial with a diuretic, reserpine and hydralazine) clearly reduced morbidity and mortality in men, but less clearly so in women. The failure of women in Hamilton's trial to benefit is thought to be due to difficulty in controlling their pressures.[5] The Veterans' trial was all-male, and this is one of the reasons behind its apparently more favourable outcome. All of the complications and strokes in Hamilton's treatment group were in females. Those women whose blood pressures were controlled did show benefit, however.

Table 2.15 Male mortality ratios for certain causes



from 'Hypertension - a suitable case for treatment? (Office of Health Economics, 1971)

Fig. 2.49 Expectation of life associated with various initial blood pressure levels in men and women aged 45.

Source: Hypertension - a suitable case for treatment? Office of Health Economics, 1971.

The usefulness of treating people with lower pressures, say from 90-115 mmHg is less clear-cut. The Veterans' Administration has conducted another trial with 380 men with diastolic pressures of between 90-114 mm.[6] There were half as many deaths and less than half the number of morbid events in the treatment as in the control group (Table 2.17).

However, the trial population is by no means typical of all hypertensives. All were men, all had voluntarily sought treatment, and they had a high prevalence of clinical symptoms at the beginning of the study. 'Unreliable' and 'uncooperative' patients were excluded at an early stage. Several trials are in progress at present to try and produce data more representative of the mildly hypertensive population,[7, 8] but it seems well established that antihypertensive treatment can produce significant benefits to those with blood pressures over 115 mmHg.

Are beta-blockers effective antihypertensives?

After some initial controversy, the publication of Prichard and Gillam's study[9] of the effects of propranolol on hypertension was the "major breakthrough for beta-blocking drugs in general and propranolol in particular as antihypertensive agents".[10] Before this, reports that beta-blockers had an antihypertensive effect were met with scepticism and disbelief, and in fact even as late as 1972, one paper on the effect of propranolol cited two references confirming the effect and 21 showing an insignificant effect.[11]

Prichard and Gillam's study followed 109 patients transferred to propranolol from other antihypertensive therapy over a period of between two to four years. Using a criterion of a diastolic pressure of 100 mm as good control, 84% of patients reached this

Table 2.17 Veterans' Administration trial on the effect of antihypertensive treatment in mild hypertension (1970)

middle-aged men diastolic 90-114

Source: Prichard, B. N. C. and P. M. S. Gillam, British Medical Journal 1, 7 (1979)

level, whereas on other drugs only 40-60% did so. It is difficult to assess the severity of the hypertension being treated as all were under treatment before the study began, but of the 80 patients previously treated with bethanidine, guanethidine, or methyldopa, only 46 had pressures of 100 mm or less, whereas on propranolol 70 did so, although 7 continued on their original drug as well at a lower dosage.

Another dramatic result was the lack of postural hypotension - a pronounced fall in blood pressure when standing up, found with most other antihypertensive agents (Table 2.18).

A questionnaire on patient's subjective feelings emphasised the relative lack of side-effects on propranolol therapy as compared with the three other drugs. Of 31 patients, when asked whether they felt better or worse on the new drug, 26 replied 'better' - and their reasons were usually lack of dizziness, diarrhoea, and tiredness that they had previously felt. However, it is well-known that patients tend to prefer the most recently administered drug,[12] so the questionnaire cannot be taken as a fair comparison of side-effects on different therapies.

A report of six years experience in the use of propranolol at a Hypertension Unit published in 1972 bears out many of these points.[13] Of 232 patients with an initial blood pressure of 205/118 mm, after 3 years on propranolol and diuretic their average blood pressure was 148/87 mm, on an average of 360 mg of propranolol per day. The blood pressure of over 90% of patients was well controlled, that is their diastolic pressure was less than 100 mm. The most serious side-effects seemed to be bronchospasm - an asthmatic reaction which caused 9 patients to withdraw, and

claudication - reduced peripheral circulation, which caused 6 to withdraw. In selecting patients for propranolol therapy, those who had any history of asthma or bad peripheral circulation, or heart block had already been excluded. The main adverse reactions, then, appeared to be contra-indications, that is, reactions experienced by groups of people identifiable by other signs and symptoms, rather than more generalised side-effects.

Early studies with other blockers demonstrated similar dose-finding difficulties, but after equivalent potency ratios were established, equivalence with propranolol was demonstrated.[14-18] Later studies have shown minor differences in types of side-effect and some evidence that drugs with ISA may not be as useful at high doses.[19-21] Many of the workers in this field now agree that it is predominantly the beta-receptor blocking potency of the drugs that determines how effective milligram for milligram they are as antihypertensives, rather than any of the ancillary properties they possess.[22, 23] Probably there are several other influencing factors, however.[24, 25]

A considerable number of clinical comparisons of the various beta-blockers have been done,[26-29] and the results of the majority of them show that there is no significant clinical difference between them except for the property of cardioselectivity - the ability of practolol, metoprolol and atenolol to selectively block beta-receptors in the heart rather than those in the lungs - and even the significance of this is disputed.[30] The many slight pharmacological differences between the compounds have been discussed far more than the fundamental similarity of the drug class. This is partly due to the initial investigation by expert

pharmacologists producing a highly differentiated view of the drugs' characteristics which does not have much relevance to normal clinical use, and partly due to the efforts of marketers to produce a definable image and particular set of advantages for their own compound - this is particularly the case with ISA.

Under less controlled conditions, general practice studies with propranolol and other blockers have shown similar but less striking effects. Lambert (1973)[31] reported a series of 30 patients whose average blood pressure dropped from 199/115 mmHg to 170/91 over an average 5 month period on an average of 303 mg/day. He noted that the most common presenting symptom, dizziness, was without exception relieved by propranolol, whereas other antihypertensives usually exacerbate this.

So it would seem that beta-blockers have a well-documented antihypertensive effect which is characterised by a low incidence of side-effects.

The most important unknown factor affecting the size of therapeutic effect to be expected from the use of beta-blockers is the controversial issue of cardio-protection - that is the possibility that beta-blockers may, unlike all other presently known antihypertensive agents, reduce the frequency and severity of heart attacks and sudden deaths associated with high blood pressure. It has long been hoped that effective drug treatment would eventually accomplish this ever since the Veterans' Administration trial in 1967 showed a reduction in stroke but no effect on the incidence of heart attacks.[32] Following the favourable results of the use of propranolol in angina pectoris, and subsequent suggestions that a decreased mortality resulted

from its use[33] studies to test the thesis that this would also be the case in hypertension were begun. Two of these have been completed, a group of 1000 male mild hypertensives in Gothenburg, Sweden picked up as part of a primary intervention trial, and a general practitioner study of 169 severe hypertensives undertaken by Stewart (1976).

The Gothenburg study[34] is the more often quoted, as it was the first large-scale study to demonstrate a reduction in coronary heart disease (CHD) in treated hypertensives. Beta-blockers were used as main therapy supplemented with diuretics and hydralazine where necessary.

However, the control groups used in this study were not strictly comparable, as they did not receive placebos or attend the hypertension clinic where the others were treated. The treatment group had higher blood pressure levels, and a higher predicted risk for CHD than the control group. Also, the group as a whole differed from the Veterans' Administration study group in being symptom-free men picked up from screening. A British Medical Journal editorial comments on the Veterans' Administration and the Gothenburg trials:

> "We urgently need to know whether the differences in outcome in these 2 studies reflect the different treatment regimens used or the types of patient treated. We shall not know the answer until the completion of prospective randomised studies to compare the outcome in patients being treated with either a diuretic or a beta-blocker. * In the meantime there seems no compelling reason to ignore the cheaper and well-tested thiazide diuretics in favour of the more costly beta-blockers ."[35]

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*One started in 1976 in Sweden by the same group as did the Gothenburg study,[37] another is the MRC trial of therapy in mild/moderate hypertension which is comparing bendrofluazide and propranolol.[38]

Table 2.19 Results of Gothenburg study on the cardioprotective effect of beta-blockers

Source: Stewart, I. McD. G. (1976)[36]

Stewart's study[36] took two groups of patients with similar cardiovascular risk factors. One group was treated with propranolol with the addition of diuretics and other drugs if necessary. The other group was treated with non-beta-blocking agents. The difference between the two groups was statistically significant. This trial was not double-blind, however, so one must take into account the possibility of observer bias and of differences in the medical care of the two groups.

These two trials taken together with the evidence of the effect of beta-blockade on mortality in angina pectoris, in the next section, is suggestive of the existence of a cardioprotective effect. This effect would probably be linked to mechanisms conferring benefit during myocardial infarction, hence it is relevant here to consider what benefit is conferred by the use of beta-blockade in infarction.

It was one of Black's ideas about the therapeutic usefulness of beta-blockade that the use of beta-blockers might prolong the lives of patients who either had, or were at risk of infarction.[39] The initial study by Snow, presented at the Buxton symposium in 1965[40] showed dramatic benefit, in that mortality after an infarction was reduced from 35% to 16% by 80 mg of propranolol a day. Later trials, however, failed to show any significant benefit from the use of propranolol immediately after an infarction.[41]

On the long-term use of beta-blockers after first infarction, there are two major sources of information other than the Gothenburg study already referred to. One is the Multicentre trial of practolol[42] which showed in over 3000 patients monitored from one to three years, a significant decrease in sudden death and in deaths plus non-fatal reinfarctions in the practolol treated group.

The benefit was confined to those with infarctions sited anteriorly.

Fitzgerald raises some of the questions arising from this trial now that practolol is no longer routinely used:

> "Are the beneficial effects due to practolol itself or are they due solely to antagonism of beta-receptors? If it is due to beta-antagonism, is the cardio-selective nature of practolol an important factor in the improved prognosis?"[43]

The other evidence comes from a study by Wilhelmsson[44] in which alprenolol treatment was compared with placebo in 230 patients who survived acute myocardial infarction. The reduction in sudden deaths with treatment (3 deaths as opposed to 11 with placebo) was significant, but not total deaths, nor number of reinfarctions.

Fitzgerald's conclusions from a painstaking review are that:

> "For the present, the practising physician should adopt a cautious attitude to the routine prophylactic administration of beta-antagonists in the everyday management of patients with coronary artery disease. The sobering story of the role of anticoagulant therapy in acute myocardial infarction is too recent to encourage an over-enthusiastic approach to the use of beta-antagonists to reduce mortality due to ischaemic heart disease, until all the available data are published."[45]

The use of beta-blockade in hypertension, then, may well carry extra benefits over and above those produced by conventional antihypertensives, but until the results of more large-scale controlled trials are known it is impossible to be definite about their magnitude.

Quantitative estimation of the extent of use of beta-blockade in hypertension

This section extrapolates from available information to arrive at an estimate of the number of people treated with beta-blockade for hypertension, and the proportions of these who have not previously been on drug treatment.

The problem with this procedure is that the data upon which it is based were never intended to be used in this way, so that major assumptions have to be made at each stage of the argument. This is well illustrated by the first step in the argument, which is to find the total volume of drugs used in treating hypertension over the study period of 1966-1975. Because prescription numbers are classified by therapeutic group, but hypertension is treated by two or three of these groups, a problem immediately arises of what proportion of these groups should be counted into the analysis. The relevant groups are coded as follows by the Department of Health and Social Security:[46]

04 Preparations acting on the heart

05 Diuretics

06 Antihypertensives

The prescription volumes for each of these categories, and that of all beta-blockers combined are shown in fig. 2.50. It can be seen that diuretic use is expanding rapidly - as a percentage of total drug use it increased from 2% in 1966 to 5% in 1976, antihypertensive use per se relatively slowly (36% increase), and that the increase in 04 is completely accounted for by the increase in beta-blockers. But this does not tell us much about drug usage in hypertension. To address this we must attempt to break down the categories by therapeutic use.

Fig. 2.50 Prescription volumes of therapeutic classes 04-06 and beta-blockers 1966-1975, Great Britain.
Source: DHSS

04, apart from beta-blockers contains only anti-arrhythmic and some anti-anginal drugs. It is therefore not included. 06 is included in its entirety, but 05 presents a problem. Diuretics are extensively used in antihypertensive treatment, but are also used in many other areas of medicine. This problem has been tackled by Reader (1976),[47] and Petursson et al. (1978)[48] in the course of similar analyses by assuming that 50% of diuretics are for antihypertensive use. This seems to me a reasonable assumption. Fig. 2.51 shows the resultant plot of 06 + half 05 for the years in question for Great Britain. This shows a steady increase in 1966-1967, a sharp increase in 1970 and thereafter a tendency for a faster rate of increase. This can be interpreted as evidence of the increase in medical interest in hypertension, particularly in 1970 and later, which is in considerable part due to the impact of beta-blockade.

How much of the total usage of beta-blockers shown in Fig. 2.50. can be attributed to their use as an antihypertensive? There is no published source of systematic data on this question, that is, involving a linkage between diagnosis and prescription. The only sources are market research firms, notably Intercontinental Medical Statistics, which do provide a commercial service involving this kind of information. The analysis has been based on the information obtainable which comprises three estimates relating to use in 1973, 1974, and 1980 (Table 2.21). Lewis' estimates are from the literature, Townshend's is by direct enquiry.

From these estimates the somewhat speculative graph, fig. 2.52, has been constructed from which I have derived proportions of beta-blocking prescriptions which can be attributed to antihypertensive use in the years 1972-1980. I have assumed that usage

Fig. 2.51 Estimated use of drugs for hypertensives 1966-1975, Great Britain.
Source: DHSS

Table 2.21 Estimates of proportions of prescriptions for beta-blockers used in different conditions

Year	Authority	Proportions
1973	Lewis (1974)[48]	50% angina and ischaemic heart disease 17% hypertension
1974	Lewis (1974)[48]	45% angina 33% hypertension
1979-1980	Townshend (1980)[49]	50% hypertension 33% angina/ischaemic heart disease 17% without clear diagnosis

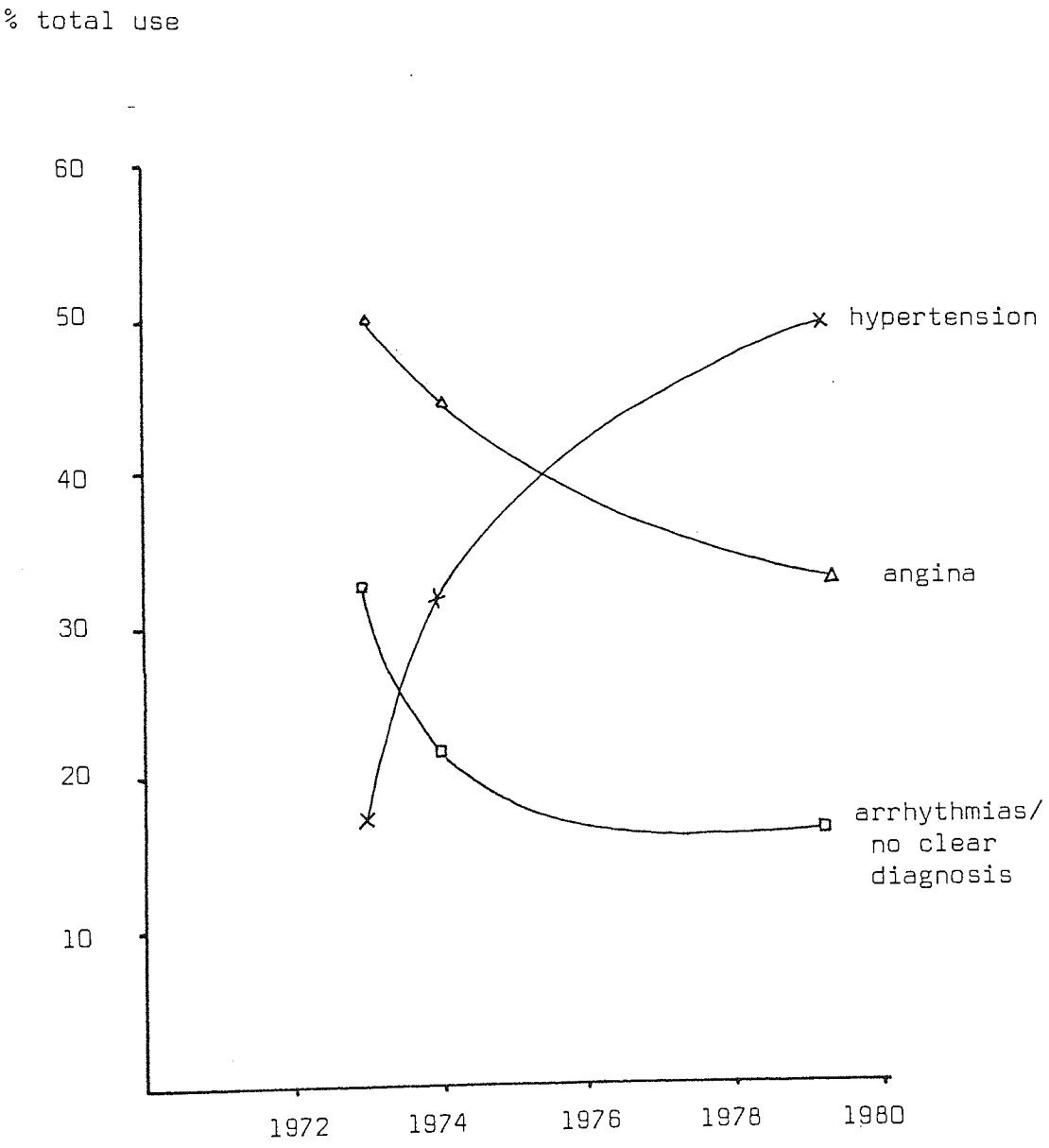


Fig. 2.52 Changes in relative importance of indications for beta-blockade

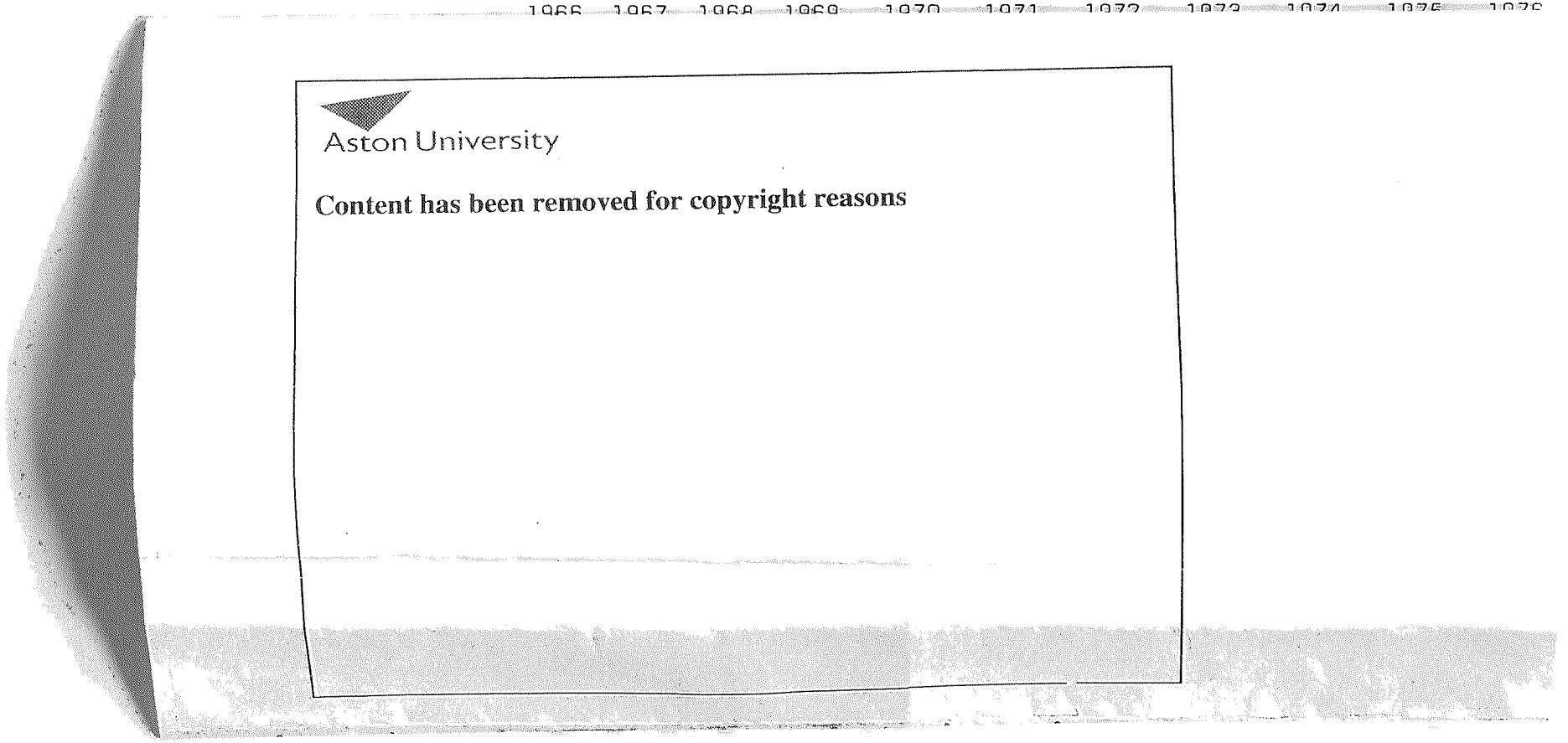
was negligible in this country before 1971. Table 2.22 shows the calculations resulting from this analysis.

Another problem remains, which is in many ways the most difficult, that is to estimate the proportions of beta-blocking usage in hypertension, that is to differentiate the output from Table 2.22 which is substitution for older drugs, and that which is use in previously untreated patients. Several methods of proceeding with this problem are theoretically possible, however only one appears to work in practice, due again to inadequacies in data. Straightforward approaches based on correlating changes in the numbers of hypertensives on treatment with changes in prescription volumes are impractical because of the absence of anything other than unreliable estimates of this number for the UK.

A more indirect method is based on the proposition that those patients who are well and comfortably controlled on a particular regime are left on it.[51] If this were true, from an assessment of clinical and open-trial data on the effects of drugs for which beta-blockers would be substituted, one can arrive at likely proportions of patients who would have reason for transfer. To what extent this theoretical transfer rate is duplicated in practice is obviously affected by other factors outside the scope of this analysis. Four categories of drugs for which beta-blockers might be substituted were considered (Table 2.23).

If prescribing practice for these drugs is similar to that found with beta-blockers, and assuming that this proportion of substitution (substitute use/total use in hypertension in 1976 = 583,000/2,066,000 = 28.2%) remained constant 1973-1976 but was negligible before this time, an estimate of the prescriptions for

Table 2.22 Estimates of beta-blocker usage in hypertension 1966-1976 (thousand prescriptions)



Source: Department of Health and Social Security

beta-blockers used as substitution for older therapies can be derived.

How is it possible to derive the number of people who used these prescriptions? Estimates of the number of people affected by practolol, the number of prescriptions for which are known, vary by a factor of two, as seen above. Methods such as extrapolating from estimates of the number of hypertnesives on treatment, or from better data applicable to Australia or the United States suffer from the necessity of making too many assumptions on too little background information to be useful.

In the course of a study on the practolol adverse reactions, Melville provides some useful data.[52] 290,000 prescriptions for practolol were dispensed in 1975, which amounts to nearly 28 million tablets.

> "The average prescription was for 96 tablets; this suggests a modal dosage of one tablet three times daily , with the patient returning for a new prescription each month."

Thus these 290,000 prescriptions may be said to be equivalent to 290,000 patient/months of treatment, or around 24,000 patients on continuous treatment in that year. If a similar pattern of monthly prescriptions is assumed to hold for other beta-blockers and there seems no reason to suppose otherwise, the number of people affected by beta-blockade as an antihypertensive may be estimated, if the proportion of short-term hospital use is estimated at 10% (from DHSS data and published estimates).

Table 2.23 Estimated substitution rates of older antihypertensives by beta-blockers

	% most likely to transfer on basis of side-effects or control	Reasoning
Methyldopa	10	Directly comparable to beta-blocker - see section for details
Diuretics	-	Low side-effects, first-line use, and undisputed supplementary use for beta-blockers and others makes transfer unlikely to be significant.
Adrenergic neuron blockers	15	Worse side-effects but good control.
Reserpine	5	Use small, unlikely to be affected as users probably conservative

A range of possibilities was considered:

	1976 total prescriptions (M)	% transfer	Prescription nos.
Methyldopa	4.06	5	202,900
		10	405,800
		15	608,700
Adrenergic neuron blockers	1.18	10	118,000
		15	177,000

Total substitution range (1976): Lowest 320,900

highest 785,700

Most likely: 582,800

Table 2.24 Estimated number of people directly affected by beta-blocker use in hypertension, 1976

All use (less 10% short-term)	155,000
On beta-blockers, previously untreated	111,250
Beta-blockers as substitute therapy	43,750
- for methyldopa (10% transfer)	32,000
- for adrenergic neuron blockers (12.5% transfer)	12,000

Patient adherence in hypertension with reference to beta-blockade

Non-adherence is a major problem in the treatment of hypertension.[53] If the use of beta-blockade increased adherence this would be a major advantage. The disease is asymptomatic, so that patients are much less adherent than they are when treatment is prescribed for a symptomatic condition,[54] treatment does produce definite unpleasant side-effects, and to be effective must be continued life-long.

The non-adherence problem can be subdivided into those who stop taking drugs completely ('drop-outs') and those who continue to take drugs but at reduced or irregular dosages, although both groups are referred to as non-adherers, or non-compliers. Table 2.25 shows drop-out rates experienced during various trials of anti-hypertensive therapy, some of which have used special methods designed to increase adherence. These range from teaching hypertensives how to record their own blood pressure to the use of calendar pack tablet dispensers or paramedical personnel to introduce a 'personal atmosphere' into the clinic.[59]

The data in Table 2.25 would suggest that a drop-out rate of around 50% can be expected unless special efforts are made to confront this problem. Even among those who return to follow-up visits adherence is still low (see Table 2.26).

The "health belief" model of Rosenstock,[63] modified by Becker and Maiman to deal with adherence behaviour[64] is useful when considering the causes of non-adherence. The model proposes that people are more likely to take preventive medical action and follow medical advice regarding an illness:

1) if they perceive the illness as being serious,

Table 2.25 Drop-out rates in antihypertensive treatment trials

Source: Sackett, D. L., Canadian Medical Association Journal 121 1979.

Table 2.26 Adherence to antihypertensive treatment

Source: as Table 2.25

2) if they feel personally susceptible to becoming ill if they fail to take appropriate action,

3) if they feel that the proposed program of medical treatment is likely to be effective,

4) if they encounter a tolerable number of difficulties in following the advice.

The only 'risk factors' for adherence likely to be altered by the substitution of beta-blockade for other antihypertensives are the following:

Side-effects

Studies mostly agree that these do not seem to significantly affect adherence, although some of these have been done on symptomatic conditions, rather than asymptomatic in which side-effects may be expected to be more significant.[65] Podell reported that side-effects were important contributors to poor blood pressure control in only 2 out of 53 patients.[66] Johnson et al. found that self-reported compliance was not related to self-reports of side-effects - 29% of patients with side-effects reported less than perfect adherence compared with 34% who had no side-effects.[67] However, the occurrence of unpleasant side-effects will usually result in the addition or substitution of other drugs which is likely to increase confusion and thus decrease adherence. There are therefore likely to be some gains from drugs with fewer side effects.

Less complex regime

Beta-blockade may simplify some hypertensive patients regimes. Many studies have shown that more complex regimes lead to increased error and increased non-adherence.[68] If substantial simplification of regime was facilitated by beta-blockade, this would be a major advantage.

Patient perceptions of effectiveness?

A national US health survey found that 65% of adults felt that hypertension referred to bad nerves, nervous conditions, too much tension and pressure, over-anxiety, over-activity, or over-excitement. In this situation* it is difficult to see how a drug could be seen as more effective than just "taking it easy".[73] In a health belief assessment project this attitude, which stressed the effectiveness of treatment, was not correlated significantly with increased adherence, although others were.[74]

*Though patients' attitudes will be changed to some extent by medical information given by their doctors, this will probably not significantly change these.

Appropriateness of prescribing of beta-blockers in hypertension

The main criteria for evaluating the appropriateness of use have been derived from the extensive clinical literature as the most problematic aspects of the use of beta-blockers in general practice. These were judged to be threefold; appropriate diagnosis, dose-finding, and adequate monitoring.

appropriate diagnosis

The extent to which the patients blood pressure is adequately checked before drug therapy is instituted is not known. While most authorities recommend checking three times to allow for stress-induced variability,[75] some general practitioners prescribe on a single measurement.[76] This would be more likely to be the case with beta-blockers, because of their acknowledged supplementary use as anti-anxiety agents.[77] Prescribing for anxiety thus grades into that for hypertension and presents all the well-known problems similar to those associated with tranquilliser prescribing.[78] This is likely to be a significant source of inappropriate prescribing, not shared by other antihypertensives that do not exert similar effects.

appropriate dose-finding

As is widely known, beta-blockers take some time to exert their antihypertensive effect. This means that their appropriate use in general practice would initially involve several visits to adjust the dose to that giving good control with minimal side-effects. This is a much more involved procedure than is the case with other comparable antihypertensives which have a more predictable action, and is a possible factor in inadequate blood pressure control.[79]

adequate monitoring

In a study on the adverse effects of practolol, Melville notes a frequency of around 20% of repeat prescriptions not signed by the doctor but by ancillary staff.[80] This repeat prescribing is common for long-term patients but often means that patient monitoring is inadequate, as ancillary staff are often busy and untrained in the detection of side-effects. Melville found this to be a major cause of the continuation of practolol use long after its severe side-effects were publicised. This is another possible source of inappropriate use.

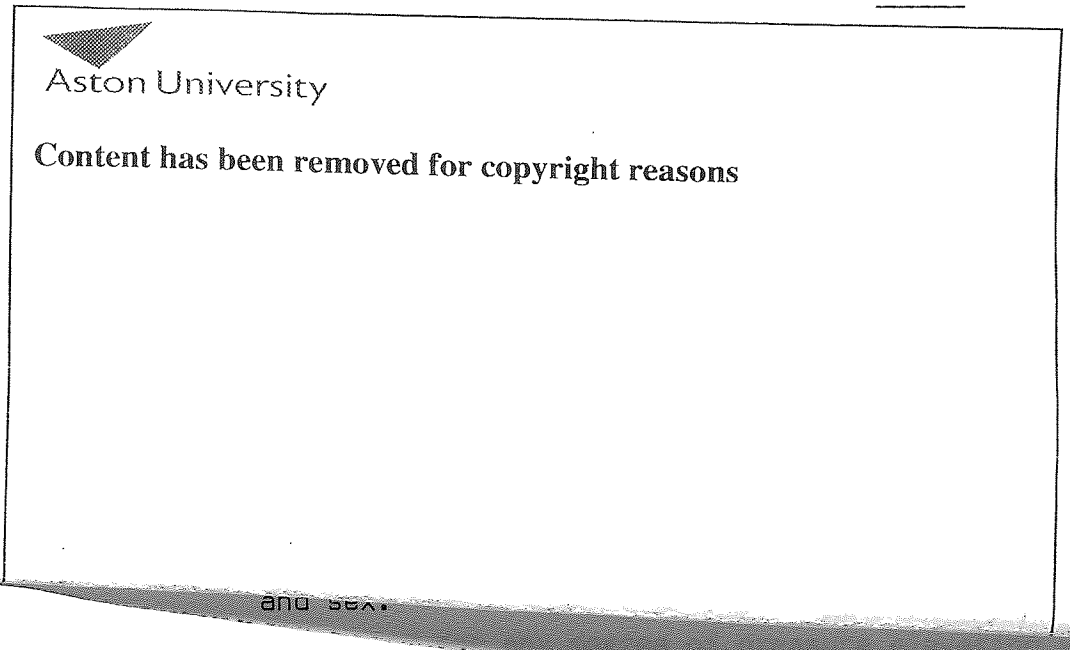
Beta-blockade or no treatment?

Around 100,000 people, by the estimates made, are currently on treatment with beta-blockers and have not been previously treated. The costs and benefits of their treatment depend on the degree of hypertension involved. For the majority of patients (60-70%)[81] who have mild/moderate hypertension, that is diastolic pressures of 95-115 mm mercury, the benefits of adequate treatment are an enhanced life-expectancy, shown in Table 2.27, and reduced likelihood of stroke and myocardial infarction (Table 2.28). The costs to the individual are the decreased quality of life resulting from the side-effects of beta-blockade, and from being defined as in need of life-long treatment, and hence in some sense permanently ill. Costs to society are the costs of the drugs, and also those of later hospitalization if life is prolonged. A detailed consideration of this problem can be found in Weinstein and Stason (1976).[82] Without more extensive study of subjective costs it is impossible to define the lower limit of blood pressure beyond which treatment does more harm than good.

Thus, most of those 100,000 people are trading some discomfort and psychological debility for 2-5 years of life. The economic costs are borne by society.

Table 2.27 Enhancement of life expectancy due to antihypertensive treatment

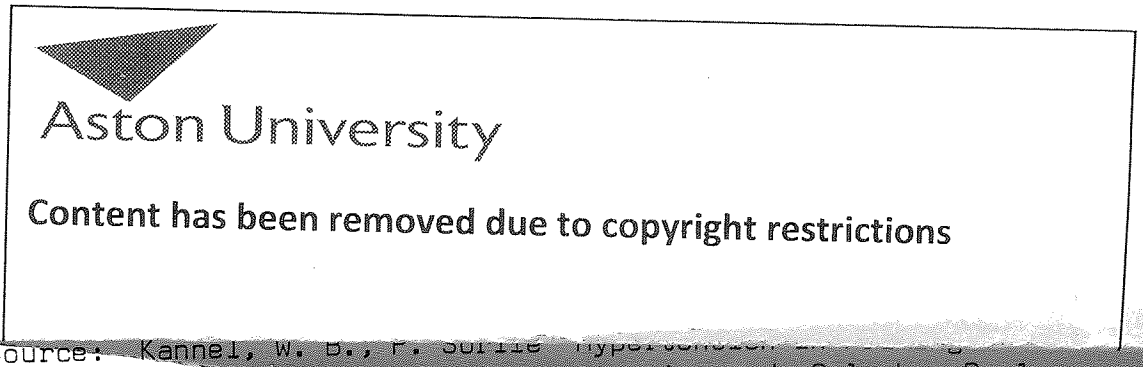
Men Women



and 65+.

Source: Weinstein, M. C. and W. B. Stason (1976)

Table 2.28 Reduction in likelihood of heart attack and stroke by antihypertensive treatment (Average annual incidence per 1,000 population with differing diastolic pressures)



Source: Kannel, W. B., P. Sorlie "Hypertension [illegible]
in Epidemiology and Control of Hypertension ed. Oglesby Paul
(Georg Thieme, Stuttgart, 1975) p. 553.

2.4.3.1. What advantages do beta-blockers have as antihypertensives? Comparison with thiazide diuretics

To assess the impact of beta-blockade on hypertension therapy involves its comparison with the treatments it is supplanting or seen to be competing with.

The effectiveness/side-effects profile of beta-blockade is closest to the thiazide diuretics and methyldopa, treatments for mild to moderate hypertension. It is in this area, rather than the earlier usage of very large doses, that the majority of British usage occurs.[83] When comparing beta-blockers with diuretics and methyldopa, however, one must bear in mind that the types of drugs favoured for any degree of pressure elevation vary greatly from one country to another, and that the two mentioned drugs are favourites in this area in Britain and the US, but not in other European countries. For example, methyldopa was prescribed in 6% of all hypertension cases in W. Germany compared with 50% in Britain. Reserpine and a diuretic were prescribed in 79% of cases in W. Germany and 56% in Italy, but only 7% in Britain.[84]

The drug therapy with which beta-blockers are most frequently compared are the thiazide diuretics. These produce similar reductions in blood pressure, have similar patient response rates, and the side-effects produced by both are mostly mild. Table 2.29 summarises the particular characteristics of each therapy.

From Table 2.29 it can be seen that, on the basis of these characteristics there is not a lot to choose between the two therapies as treatments for mild hypertension. This impression is borne out by most of the comparative trials and assessments that have been done. Early trials (1966-1972)[113, 114] were usually

Table 2.29 Comparison of beta-blockers and diuretics as antihypertensives

	Beta-blockers	Diuretics
Patient response rate: (as monotherapy)	85% Prichard and Gillam (1969)[85] 80% Zacharias (1972)[86] 60% Lorimer (1976)[87] 50-70% Clarkson (1976)[88] 40-65% Morgan (1974)[89]	less than 50% of mild/moderate hypertensives Wilson (1973)[95] 45% of mild have good response
Reductions in pressure: (mm mercury)	20/10 - 30/15 Brunner (1973)[90] 20/12 Conway (1975)[91]	13 in mean blood pressure[96] 8/4 - 19/11[97] 21/10 (average of collected studies on 453 patients) 14/8 as additional decrease to previous antihypertensive therapy in 650 patients[98]
Side-effects sufficient to cause drug withdrawal[92]	8%-26 of 325 treated patients, made up as: Stomach/gut disturbance 7 patients Sleep disturbance 6 patients Bronchospasm 2 patients Slow heart rate 1 patient Other 10 patients	14%-46 of 341, made up as: Serum potassium low 22 Serum uric acid high 7 Gout 3 Diabetes 4 Others 10
Other estimates of effects leading to withdrawal McMahon (1976)[93]	Zacharias (1972) 9.7% Laver (1974) 9.1% Tarazi (1972) 13.5% Hansson (1972) 8.9% Zacharias (1976) 9.7%	Other estimates[94] 1% cause withdrawal 25-50% patients have hypokalaemia

Table 2.29 continued

Side-effect frequency	Depression 1:25 Morgan (1972)[99] Hallucinations 1:80 Zacharias (1972)[100] Dreams 1:30 Tarazi and Dustan (1972)[101] (propranolol) 1:2 Morgan (1972)[102] (pindolol) oxprenolol, practolol much lower Prichard (1972)[103] Insomnia 1:50-100 Prichard and Gillam (1969)[104] Zacharias (1972)[105] Inducing heart failure 1:20 O'Brien and Mackinnon (1972)[106] 1:300 Zacharias (1972)[107] Peripheral circulation problems (Raynaud's phenomenon) 1:25 Tarazi and Dustan (1972)[108]	Serum potassium low in about 10% of patients[109] High serum uric acid is seen in about 30% of hypertensives. Thiazides more than double this incidence.[110]
Contraindications	Asthma and other chronic respiratory disease Imparied heart function (heart block, left ventricular failure) Bad peripheral circulation Depression - particularly with propranolol	Established diabetes or pre-diabetic condition Hyperuricaemia
Cost - 1 week's hospital course: (July 1978)	Atenolol once daily - £1.17p[111]	Bendrofluazide 5 mg once day - 1.7p[112]

more in favour of diuretics, later, more in favour of the beta-blocker.[115] This trend is partly due to the early use of fixed doses for trials which were inadequate for some individuals, and partly due to increasing experience with the effective use of beta-blockers in hypertension, for example, in increasing dose levels at beginning of treatment. The controversy which does exist over the relative merits of diuretics and beta-blockers centres on the more general and less easily measurable aspects of these therapies. These are summarised in Table 2.30 and are discussed in turn.

1) Those favourable to beta-blockers

The term cardioprotection refers to the possibility that beta-blockers can reduce the frequency of heart attacks and coronary complications secondary to hypertension, which are a major source of mortality left untouched by conventional anti-hypertensive treatment.[116] The evidence for this is as yet not well accepted, but if the few trials which have been done are confirmed this would be a major advantage (see earlier discussion). The well-publicised effects of beta-blockade on circulatory responses to stress are also often cited in this respect, and could become an important facotr in their wider use.[117]

The feeling that beta-blockers exert a more specific type of control of hypertension than has hitherto been possible, is widespread and appears to be a major factor in their usage by expert clinicians. The contrast with diuretics centres on four main areas.

It was suggested early on that beta-blockers might act by resetting the baroceptors - the feedback mechanisms that control

Table 2.30 Wider considerations in the comparison of beta-blockers and diuretics

Favourable to beta-blockers:	Cardioprotection
	More 'physiological' control
	Sense of well-being
Favourable to diuretics	Clinical experience
	Potentiates other antihypertensive therapy
	Possibility of serious side-effects with beta-blockers
	Once-daily dosage
	Average effective dose

blood pressure.[118] This would seem a very direct and satisfactory antihypertensive action. However, this explanation is now not so certain,[119] and is certainly not the whole story.[120]

In 1972, a major controversy over the significance of the levels of renin - a hormone secreted by the kidney in hypertension began.[121] Since that time there have been claims that a reduction in renin levels can be correlated with a fall in blood pressure,[122] and counter-claims that there is no such correlation.[123] Whatever the outcome, it is known that beta-blockers reduce renin levels whereas diuretics increase them, and the significance of these observations are a central topic of debate at clinical symposia. It is however, generally conceded that this gives some kind of advantage to the beta-blockers.

The main immediate cause of the increased blood pressure in hypertensives is an increase in the peripheral resistance against which the heart must pump.[124] With long-term beta-blocker therapy, those patients who respond show a significant reduction in peripheral resistance with little change in plasma volume.[125] This is in contrast to the diuretics which do not appear to affect peripheral resistance, but produce their antihypertensive effect by reducing the plasma volume, sometimes considerably.[126] This decrease in volume is accompanied by an increase in blood viscosity, and in the tendency of blood platelets to aggregate. Both of these effects are likely to increase the likelihood of thrombo-embolism and vascular damage.[127] There is therefore, considerable theoretical advantage for beta-blockers in their mode of action.

The side-effects of diuretics, while in the short-term being comparable in severity with those of the beta-blockers, in the long-term may be reducing the benefit resulting from the

lowered pressures they produce. Three effects are thought to contribute to this.

1. The tendency for serum levels of potassium to fall considerably. This makes heart arrhythmias more likely.

2. The increase in plasma levels of catecholamines, which are liable to increase the oxygen consumption of the heart, and exert other pathological effects,[128] (the reverse of the actions of beta-blockade).

3. It has recently been found that the increase in plasma cholesterol and fats caused by diuretics in many patients, especially those with lower pressures, by causing increased coronary risk is balancing out the benefit produced by the lowered pressure.[129] This is probably a factor in the failure of trials to produce a reduction of heart attack with antihypertensive treatment. Thiazides have also been shown to raise blood glucose levels[130] which is also a probable risk factor for coronary heart disease.[131]

The first and third of these factors necessitate periodic testing of patients on long-term diuretic therapy, and appear to be causing increasing concern, especially in Scandinavian countries being a major factor in the wider use of beta-blockers as first-line drugs.[132]

It has been reported in general practice studies with oxprenolol that between 20-30% of patients volunteered that they 'felt better' on the treatment than they had done untreated,[133] which is certainly a great contrast to the effects of most anti-hypertensive medication. I have not found this effect mentioned elsewhere, however it could be related to the known anti-anxiety action of beta-blockade.[134]

2. Those favourable to diuretics

Diuretics have been widely used in the treatment of hypertension both on their own and with other agents since the first clinical trials in the early 1960s. This has produced a history of some twenty years experience with these drugs as a mainstay of anti-hypertensive therapy. For example, in the US in 1976 diuretics accounted for 18.5 out of 29.1 million prescriptions for mild hypertension, and 12.9 out of 20 million for moderate and severe.[135] The side-effects of the diuretics are by now exceptionally well-recognised and widely-known, as also are the appropriate treatments. In a situation where treatment may continue for twenty or thirty years, the use of diuretics carrier fewer unknowns than any other form of drug therapy.

The pressure reduction brought about by most conventional agents is limited by the body's physiological response of fluid retention. Diuretics potentiate their action by counteracting this tendency.[136] Consequently, the stepped therapy pattern has emerged whereby the hypertensive patient will be initially treated with a diuretic, and to this other more potent drugs are added until the pressure is deemed to be adequately controlled.[137] This integration of diuretics into 'ideal' models of hypertensive therapy in a key role is a powerful factor in its continued wide-scale first-line use.

The discovery of irreversible tissue damage to a number of patients and the resultant death of some on practolol led to the withdrawal of that drug and widespread concern over the possibility that other beta-blockers might also produce these effects. Although these drugs can produce a rash very similar to that found with

practolol, it has invariably disappeared on stopping the drug. Propranolol has been in clinical use for long enough to be largely exempt from this concern, but the sales of the newer blockers have been severely affected, and the practolol episode has greatly slowed the spread of beta-blocker therapy.[138]

The diuretics underwent a development process, similar in many ways to that which the beta-blockers are now undergoing, and the main consequence of this was the production of compounds chemically very similar to the parent compound, but ten to one hundred times more potent and with a duration of action two to four times as long. This means that diuretic therapy in nearly all cases involves no more than one tablet per day. This is seen as a major advantage by most authorities because of the high drop-out rate associated with antihypertensive therapy, and the connections between the quantity of medication prescribed and amount of non-compliance with the regimen.[139] Although manufacturers of beta-blockers have brought out slow-release preparations, standard therapy is still usually twice or three times daily.[140]

With the beta-blockers there is a wide variation in the dose needed to control any particular elevation of blood pressure in different individuals. This is apparently related to a wide variation in the rate at which the drugs are metabolised.[141] This does present some problems, particularly in general practice where it may take some months to find the optimal dosage. An additional complication here is the frequent assertion that the antihypertensive action does not become evident for weeks after initial administration.[142] It now appears that this may be due more to the cautious small increases in dose used by Prichard than to a true delayed onset

of effects, and with some blockers the effect seems to occur more rapidly anyway.[143]

None of these complications occur with the diuretics. The hypotensive effect is predictable, is not greatly dependent on dosage over a wide range, and inter-individual variation is not a problem. Consequently, in this respect, diuretics are obviously more suited to the general practice situation in which the majority of hypertensives are treated.

Beta-blockade and diuretics

Four main areas seem most significant in the consideration of comparative costs and benefits:

*The balance of side-effects between the two therapies.

*The clinical significance of the cardioprotective and the anxiety and stress-reducing effects of beta-blockade.

*Differences in the appropriateness of prescribing.

*The comparative costs.

The balance of side-effects of the two therapies is marginally in favour of the beta-blockers, if the practolol reactions are not considered. This tendency to favour beta-blockers will probably increase as the biological effects of the long-term physiological changes caused by diuretics become better known.

The cardioprotective effect, if proven, will be a dramatic advantage for beta-blockers, however more evidence of this is needed. The anxiety and stress-reducing effects are an advantage in a proportion of patients.

Diuretics are likely to be more appropriately prescribed from the point of view of dosage, but less appropriately from the point of view of the necessity of adequate biochemical monitoring, so without further study the advantage cannot be said to lie clearly with either therapy.

The comparative cost estimates vary widely, from a British Medical Journal comparison in 1978 of a week's course costing £1.17 for the new beta-blocker and 1.7 p for the diuretic,[144] though other blockers are considerably cheaper, to a more recent statement that "there is probably little difference in the overall cost of treatment".[145] In this case the costs of periodic biochemical

analyses are also taken into account. There is, despite this last optimistic estimate, a substantial difference in the costs of treatment, principally as the diuretics are older drugs with an expanding market and a long history of price competition. As the beta-blockers age, their prices will become more comparable.

At the present time there is little rational incentive for the general practitioner to change from the use of diuretics to beta-blockade for general first-line use. Such a change would involve either a high evaluation of the cardioprotective and stress-reducing effects of beta-blockade, or a view of the long-term use of diuretics as carrying real dangers. Clinicians are more likely to take this perspective, but few of them recommend a change from diuretics as first-line drugs.

At present the main impact of beta-blockade on diuretic users is on the sub-group of hypertensives who would have especial benefit from a change, those with hypertension and angina, those particularly intolerant of the biochemical changes produced by diuretics, and those with a component of stress or anxiety, who form a small fraction of diuretic users. One important factor which could change this situation quickly is that differences in effectiveness might be found between diuretics and beta-blockers in one or more of the several trials now being made into the effect of treating mild hypertension. This could produce considerable changes in use, given the present uncertainty over the significance of key differences between the treatments.

So the beta-blockers can be seen to be comparable in many ways with the drugs that are the most widely-prescribed in hypertension. The extent to which these are prescribed in combination is also very extensive, for example at Sahlgrenska Hospital at

Goteborg in Sweden, one fifth of hypertensive patients are on diuretics, one-fifth on beta-blockers, and one-fifth on the two combined.[146] As an indicator of future treatment in other countries this illustrates the impact of beta-blockade in hypertension.

2.4.3.2 Comparison with methyldopa

Methyldopa is the most widely prescribed pure antihypertensive in the United Kingdom.[147] Since its launch in 1962 considerable clinical experience has accumulated, and in this country it is used in preference to drugs such as reserpine and hydralazine which are preferred in continental Europe. Its side-effects are therefore well-defined (Table 2.31).

The severity and rate of occurrence of side-effects with methyldopa can be seen to be significantly greater than with the diuretics, and in many ways place it between the diuretics and the adrenergic blocking drugs in patient preference. Its effects on blood pressure are also in this range, producing good control in about half of moderately hypertensive patients (170-250/115-160 mm).[154] Other estimates of its effects are an average reduction of 20/13 mm in mild hypertensives, and up to 38/22 mm in severe.[155] With added diuretics the upper range is more consistently reached, and there are less problems with the need to increase the dose over time due to expanded blood volume - a form of tolerance that often occurs with this drug. Where the beta-blockers fit into this picture is a matter of great and enduring controversy. A number of direct comparisons of beta-blockers and methyldopa have been done with varying conclusions.

Table 2.31 Side-effects of methyldopa

Symptoms	Estimated incidence
Tiredness	75% spontaneously reported-Prichard et al. (1968)[148] 41% Johnson et al. (1966)[149] 28% average of 19 reports-McMahon (1978)[150]
Depression	c. 10%-Prichard et al. (1968 Johnson (1966)
Positive Coombs test (index of developing anaemia)	11% of those on 1 gram or less 36% of those on 2 grammes or more Prichard et al. (1968)
Haemolytic anaemia	0.1 - 0.2 - 2%-McMahon (1978) Hamilton (1968)[151]
Fluid retention	usually a concomitant diuretic is prescribed
Unusual dreams	17% spontaneously reported-Prichard et al. (1968) 3.8% McMahon (1978)
Postural hypotension - giddiness when standing up	38% when questioned-Prichard et al. (1968) 15% McMahon (1978)
Reduced libido:	McMahon (1978) Bullpitt & Dollery (1973)[152]
difficulty of erection	1.3% 32% with diuretic: 37%
difficulty of ejaculation	0.5% 5% 24%
Dry mouth	8.7%
Headache	8.6%
Diarrhoea	4.6% McMahon (1978)
Patients for whom these effects were intolerable	8.5% average, range 4%-20% McMahon (1978) 7-21% Weinstein and Stason (1976)[153]

Discrepancies in the frequencies of side-effects reported by different authorities reflect the fact that studies specifically examining side-effect frequency, such as those of Prichard et al. and Bullpitt and Dollery, will record higher frequencies than those seen in clinical trial reports where side-effects are not looked for to the same extent, as in the review of McMahon.

The earliest such study, mentioned earlier (Prichard and Gillam, 1969)[156] found that propranolol and methyldopa were approximately equipotent with propranolol showing significantly fewer side-effects, the lack of giddiness when standing being particularly important. However, about half their patients were also using diuretics with both drugs so this was not a straight comparison between the drugs.

A later comparison (1973) did not get as good an effect with methyldopa as has generally been reported. This was a crossover study in 15 moderately hypertensive patients between 800 mg/day alprenolol and 1.5 g/day methyldopa.[157] The average reduction in blood pressure on the two drugs was 30/10 mm and 7/5 mm respectively.

More recently, comparisons of the newer blockers with methyldopa have been done using lower dosages of methyldopa which produce fewer side-effects.[158] It claims that both methyldopa in low dosage (750 mg/day) and the beta-blocker (atenolol) had side-effects indistinguishable from placebo, and produced more or less equivalent pressure reductions(28/14 and 27/17 respectively). Using 1.5 g/day of methyldopa produced more side-effects but no better reduction in pressure.

In a comparison of oxprenolol with methyldopa, Barritt[159] found no differences in side-effects and noted that postural hypotension caused no problems with methyldopa. Of the 29 patients in this double-blind study, 11 were well controlled (diastolic 100 or less) on either drug at low dosage (320 mg. oxprenolol , 1 g. or less methyldopa). It was largely the same patients who were controlled on either drug, however (9 out of 11).

The issue of overlap in responsiveness could be important in the wider use of beta-blockers in hypertension, as an important role is being made out for them as supplementary or replacement therapy for methyldopa in those patients whose pressure is not well-controlled by it or in whom side-effects are troublesome.

Two papers on oxprenolol cover its addition to methyldopa in these situations,[160] which reduces the pressure but does not much affect the side-effects, and its partial or complete substitution for methyldopa.[161] This, being a general practice study is open to criticism for lack of a control group - necessary because hypertensives' blood pressure frequently drops in response to increased medical interest[162] and stressing patients' preferences for the new drug - which is a well-known phenomenon, even if the new drug is actually no better than the old.[163]

However, it is accepted as an outcome of these studies that beta-blockers with a diuretic could effectively substitute for methyldopa in many patients who are troubled by its side-effects.

Beta-blockade and methyldopa

What changes can be expected by the patients, previously estimated to number 32,000, who have transferred from methyldopa to beta-blockers? A considerable increase in the quality of their lives, with less tiredness and giddiness from postural hypotension as the main gains. An increase in tablet-taking, from once-a-day to an average of twice-a-day. A possible decrease in heart attacks and sudden death compared with methyldopa.

The main factors opposing increased transfer are the doctors' familiarity with methyldopa, its predictability and its lower cost. In the future it is probable that with increasing familiarity with beta-blockade, and lower cost, there will be increasing substitution. If newer data on cardioprotection confirms this effect, transfer will increase considerably.

2.4.3.3 Beta-blockade and adrenergic neuron blockers

The comparison of propranolol with guanethidine and bethanidine by Prichard and Gillam (1969)[164] emphasised beta-blockades' lack of the unpleasant side-effects of the earlier adrenergic neuron blockers. With the advent of methyldopa only the most severe hypertensives were still on these drugs, but beta-blockade in combination with diuretics and recently, vasodilators, have made a considerable impact on these more severe cases.[165] The new regimes are often more complex than the old, but not invariably so, as diuretics are frequently already prescribed with guanethidine and bethanidine.

Thus beta-blockers have transformed the role of vasodilators in hypertension, as their most severe side-effects are counteracted by beta-blockers. Correspondingly, the use of adrenergic neuron blocking agents is decreasing considerably - prescriptions of the main agent, guanethidine, dropped from 635,000 in 1970 to 450,000 in 1976.[166]

The patients, estimated at 12,000, who have transferred can expect similar, but more pronounced benefits to those transferring from methyldopa. As with that drug, transfer will increase considerably on present expectations.

2.4.4 Beta-blockade and angina pectoris

It is much more difficult to assess the therapeutic impact of beta-blockers on angina than it is in the case of hypertension. This is because angina is a complex of symptoms, rather than a well-defined 'disease'. The characteristic symptom is a numbing pain in the chest on exercise, which gets better on resting. This is caused by exercise causing the heart to demand more oxygen than can be supplied by narrowed coronary vessels. However, descriptions of the pain vary widely, so that a firm diagnosis involves the taking of an electrocardiogram (ECG) at rest and on exercise. A study by Rose illustrates this variability.[1] Of 1100 men beginning the four-year study 43 were initially assessed by questionnaire as having angina. Each year thereafter only about 40% of these were still angina-positive, whilst other men previously free of symptoms, developed them. However, the persistence of symptoms, though rare, was strongly correlated with the presence of an abnormal electrocardiogram.

Because of these characteristics, it is difficult to estimate the incidence of angina, as patients recorded as new cases may have been previously recorded under other manifestations. Data from the Health Insurance Plan New York put incidence at around 1 per thousand males at age 45 - 0.2 per thousand for women, rising to 4 or 5 per thousand at age 65 - women about 3 per thousand.[2] The prognosis of stable angina has been assessed on the basis of the population survey at Framingham in the United States, and the risks of suffering a heart attack are shown in Figure 2.53. After about eight years in men this risk of around 50% is about double that for the general population.

Years after onset of angina pectoris

Fig. 2.53 Probability of heart attack in men and women age 25-62 with angina pectoris, from Framingham study data

effective Severe side eff

Fig. 2.54 Results of survey of British experts on drug usage in angina from Wardell and Lasagna (1975).

The extent of coronary artery disease is probably the most important determinant of prognosis in patients with stable angina. Coronary angiography which can display the extent of coronary artery disease has shown that the annual mortality rate is five times as great when all three arteries were significantly diseased compared with disease in one artery. Other determinants are co-existent hypertension, smoking, level of physical activity and diabetes.

Therapy in angina is mostly directed at the relief of pain. Classically this has been achieved by the use of tablets of glycerine trinitrate (GTN) allowed to dissolve beneath the tongue (W. Murrell, 1879). Trials of new drugs for this condition have been severely hampered by the fact that a placebo will produce benefit in 35-60% of patients.[3]

GTN treatment benefits around 75% of patients within 3 minutes and a further 15% within 15 minutes.[4] Side-effects of headaches and skin flushing generally become less severe as treatment continues, though therapeutic action is maintained. The action of GTN lasts for about 45 minutes - doses can be repeated as often as required. The correlation of the therapeutic action of GTN with its action as a coronary vasodilator suggested to many that other nitrate compounds also showing this activity could be used prophylactically, if their duration of action were more prolonged. Thus out of many searches for long-acting vasodilators have come a variety of compounds, but none of these are as effective as GTN. In fact, long-acting nitrates are generally thought to be no better than placebo, however, they are still frequently prescribed.[5] It now seems likely that a major component of the therapeutic action

of GTN is its action as a more general vasodilator, reducing load on the heart.

As had been hoped by Black, the beta-blockers have proved to be compounds of major usefulness in the treatment of angina. The main useful effects of beta-blockers are to reduce heart rate and systolic pressure, thus reducing the heart's oxygen consumption.

A review of early clinical experience with propranolol[6] of 22 series involving 466 patients showed an improvement rate of 75% - when double-blind studies only were considered the rate was 74% of 280 patients, though it is interesting to note that in one series reported,[7] 77% of propranolol 'failures' occurred in patients with no coronary angiographic changes, and thus no objective evidence of angina - only 14% of failures had these changes, thus there is evidence of an extent of misdiagnosis.

The criterion for improvement was increased capacity for exercise before an attack of pain. 37% of these patients had complete relief of pain on moderate exercise. Prichard (1974)[8] reports 13 anginal trials involving propranolol up to 1969, the response rate varying from 55-75% in fixed single-dose level trials to 80-100% in trials where doses were adjusted for maximum benefit. Other studies have shown fewer electrocardiographic abnormalities on exercise after propranolol than after placebo,[9] and many studies have shown fewer anginal attacks and less GTN consumption during propranolol therapy.[10] Fitzgerald (1972) lists 51 controlled trials of which 48 showed the beta-blocker superior to placebo.[11]

There do not seem to be significant differences between the different beta-blockers available. Propranolol, practolol and oxprenolol were compared by Thadani (1973),[12] and these drugs and

pindolol by Sowton (1975).[13] No clinical differences in effectiveness were found. The percentage of favourable results in clinical trials are also similar for these compounds: 74-90% in open studies and 69-75% in double-blind studies.[14] Prichard also compared practolol, sotalol, and propranolol and found no differences on an acute exercise test.[15] He also reviewed other comparisons.[16]

However, the results obtained from acute exercise tests cannot be uncritically generalised. A variable dose trial of each of the drugs to be compared is necessary to get the optimum dose for comparison.[17] Many anginal trials involving beta-blockers have failed to show benefit because of bad trial design: insufficient time for run-in to the trial proper,* drugs administered for too short a period to get full results, and insufficient dosage.

A straight line dose-response relationship was found by Prichard and Gillam (1971)[18] which showed no reduction of benefit even at 400 mg/day which is considered a high dosage.**

It is uncertain whether the use of beta-blockers in angina pectoris is associated with a lower mortality rate than the usual 3-4%/year. This figure is only an average; it varies from 10% in patients where two or three main coronary arteries are affected to 2% where only one main artery is involved.[19] If the ventricles of the heart are damaged the prognosis is worse and if hypertension co-exists, the mortality is raised to around 8%. The mortality is also affected by the duration of the angina, being reported to

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*Patients' angina improves with greater doctor interest and contact.[20] This run-in period is to stabilise this before drugs are administered.

**This was with propranolol; this would probably not apply to those compounds with ISA where large doses would be self-defeating. Benefit criteria were number of anginal attacks and GTN consumption.

be 4-6% where the disease has been present from 1-6 years and 10% where it has been present longer.[21]

The effect of this variability is to make studies involving large numbers of patients necessary to detect even a quite significant reduction in mortality produced by beta-blocker therapy. In small studies the selection of patients has a pronounced effect on the results obtained. For example in the study of Russek (1975)[22] the patients described as 'good risks' had a mortality of 1.25% per year, those seen as 'poor risks' 16%.

The results of studies on the effects of beta-blockade on the mortality due to angina are shown in Table 2.32.

Many of the studies that have been done have been defective in design - this factor added to the uncertainties already mentioned has resulted in a situation where the cumulative impact of these studies is described conservatively in terms like "certainly encouraging"[23] or "providing suggestive evidence".[24] In the reviews of this work there are references to similar work on the benefits of anticoagulant therapy in preventing further heart attacks in patients who had already had one. It seems that no-one is anxious to repeat the experience of great enthusiasm for a therapy, then the voicing of doubts and then total disrepute which occurred over anticoagulants, as well as many other innovations, especially in an area where repeatable evaluations are so notoriously difficult to achieve (see section 3.2).

The work done to date on the effects of beta-blockers on mortality is, at first sight suggestive of a reduction in mortality of the order of 25%, however the variability of the condition makes this conclusion unreliable. Until larger studies are done with better trial design and a greater standardisation of the

Table 2.32 The effects of beta-blockers on mortality in angina pectoris

Source: Rivier, J. L.[21]
Fitzgerald, J. D.[24]

degree of angina involved, no clearer estimate can be made. If the contribution of beta-blockers to reducing the mortality in angina cannot be clearly evaluated, what of their effects on morbidity?

In a survey of British doctors at teaching hospitals regarded as experts, in 1972, Wardell and Lasagna produced the following results to questions about drug therapy in angina regarding four drug groups - nitroglycerine, beta-blockers, long acting nitrates, and prenylamine (a new agent of unknown value).[25] Questions that were asked were; how frequently the drugs were used, how effective they were, and how often side-effects were a problem. The results of this study are displayed in fig. 2.54.

From this survey it seems that beta-blockers have become, with GTN, a mainstay of therapy in angina, being most useful in those patients that do not respond to GTN, but being effective as a prophylactic in their own right.

Other indicators of the importance of beta-blocker therapy were the doctors opinions of what would happen to their patients if the beta-blockers were withdrawn, and alternative therapy substituted:

*less than $^{1}/_{3}$ patients currently treated with beta-blockers would be unaffected,

*$^{2}/_{3}$ of them would have worse control of their angina,

*$^{1}/_{2}$ would find alternative therapy less convenient,

*$^{1}/_{4}$ would have more side-effects,

*$^{1}/_{4}$ would be less compliant with the new regimen,

$^{1}/_{5}$ would have a worse prognosis.

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*given that in 1972 there were very few indications of what changes in mortality might be expected from treatment with beta-blockers, this is a speculative estimate.

Opinions on the number of patients that might benefit from the use of beta-blockers varies. Prichard, who has had extensive experience with anti-anginal drugs writes:

> "The taking of an effective prophylactic for angina will reduce the pain on exercise, emotion, etc., anticipated or not. It seems reasonable to use an effective prophylactic such as a beta-blocking drug in any patients who are experiencing regular attacks of pain ... Although beta-blockade may not totally relieve pain, it does allow more pain-free exercise."[30]

Fitzgerald summarises the effects of beta-blockers as seen in clinical trials as follows:

> "There is much difference of opinion as to the validity of criteria such as exercise tolerance, exercise ECG changes, frequency of attacks of pain and trinitrin consumption used in the assessment of drugs in this condition. If one accepts these criteria, then the likely effect of beta-blockade is that exercise tolerance will be increased 20-60%, exercise ECG improved in over 50% of cases and frequency of anginal attacks reduced in about 70% of cases."[31]

A more conservative view is given by "Today's Drugs", 1971 (a collection of reprints from the British Medical Journal) which discusses the myocardial depressant action of propranolol, and then states:

> "Controlled clinical trials of propranolol and other sympathetic blockers have not been uniformly successful. However, these agents have a clear-cut and obvious effect on the circulation, and it seems certain that they are effective in relieving angina in some patients."[32]

However, by 1977 the consensus view had changed:

> "Propranolol and oxprenolol were a great advance in treating patients with severe angina ... Not all patients are helped by beta-blockade, a few are actually made worse. Nevertheless, most patients improve, and the results are often dramatic. In patients with associated hypertension, beta-blockade offers a chance of 'killing two birds with one stone'."

No mention is made of myocardial depression, and the tone is generally more confident:

> "Most patients with angina can live a more or less normal life with the help of GTN and beta-blocking drugs."[33]

In the United States a very cautious attitude to the use of propranolol has prevailed. It was not approved for use in angina until 1973, and even then only reluctantly (see section 2.3.3). Suggestions of 10% of patients developing heart failure were made, and doctors advised to reserve treatment for those with severe angina unresponsive to other treatment.[34] Recently the consensus view, represented by the American Medical Association has been more favourable:

> "Beta-adrenergic blocking agents have provided a significant advance in the long-term management of angina pectoris ... in the absence of contra-indications, propranolol should be considered for trial in all patients with frequent attacks of angina."[35]

Therapeutic impact of beta-blockers in angina

One can assume that most of those patients with angina are on treatment, given the severe pain characteristic of the condition. The numbers of prescriptions dispensed for beta-blockers and other anti-anginal preparations are shown in fig. 2.55. The proportion of total beta-blocker use consumed for angina is estimated from the same data base as that used for hypertension. It can be seen that in 1976 beta-blocker use in angina was approaching the combined total of all other drug use. If the same prescribing patterns are seen with other blockers as with practolol, it may be estimated that the 2 million prescriptions dispensed in 1976 were taken by around 170,000 people.

The benefits these people derive from beta-blockade are increased ability to exercise before pain (between 10 and 40% more work), and fewer attacks of pain.[36] Thus the quality of their lives may be greatly improved, offset by the side-effects of the drugs, generally less severe than in hypertension as the dosage used is generally lower. It is difficult to be more precise about the magnitude of benefit, as obviously there is a trade-off between the possibilities of more exercise, and having fewer attacks of pain.

Whether the beta-blockers confer any reduction in mortality is, as has been seen, a question as yet not adequately answered. All that can be said is that certainly the drugs do not increase mortality, but larger studies in which patients' angina is better characterised are necessary to prove a more positive conclusion.

Fig. 2.55 Prescriptions dispensed for anti-anginal compounds (A) and beta-blockers used in angina (B) 1966-1976 G.B.

(A, calculated as sum of individual anti-anginal drugs from DHSS statistics)

Glossary of arrhythmia terminology

Atrial fibrillation:	Independent spontaneous local twitching of atria, leading to irregularities in ventricular rhythm.
Atrial flutter:	Rapid irregular atrial impulses, and irregular atrial contractions, heart rate 60-180 beats per minute, grossly irregular.
Bradycardia:	Slower than normal heart rate.
Ectopic:	Heart beats not initiated by usual source, the pacemaker - hence producing inefficient pumping.
Paroxysmal:	Occurring in sudden and severe episodes.
Tachycardia:	Faster than normal heart rate.
Ventricular fibrillation:	As for atrial except much more serious - rapidly leading to unconsciousness and death if uncorrected.

Synonyms

Supraventricular ≡ Atrial

Diphenylhydantoin ≡ Phenytoin

Lignocaine ≡ Lidocaine

2.4.5 Beta-blockade and heart arrhythmias

The majority of arrhythmias or disorders of heart rhythm in which beta-blockers are used occur in two situations; after a heart attack or during a digitalis overdose. The therapy of arrhythmias is a complex and controversial subject, and the role of beta-blockade is one of the more controversial areas, so it is not possible to do more than compile tentative general agreements from the material available. Some comments by Fitzgerald (1975) are relevant here:

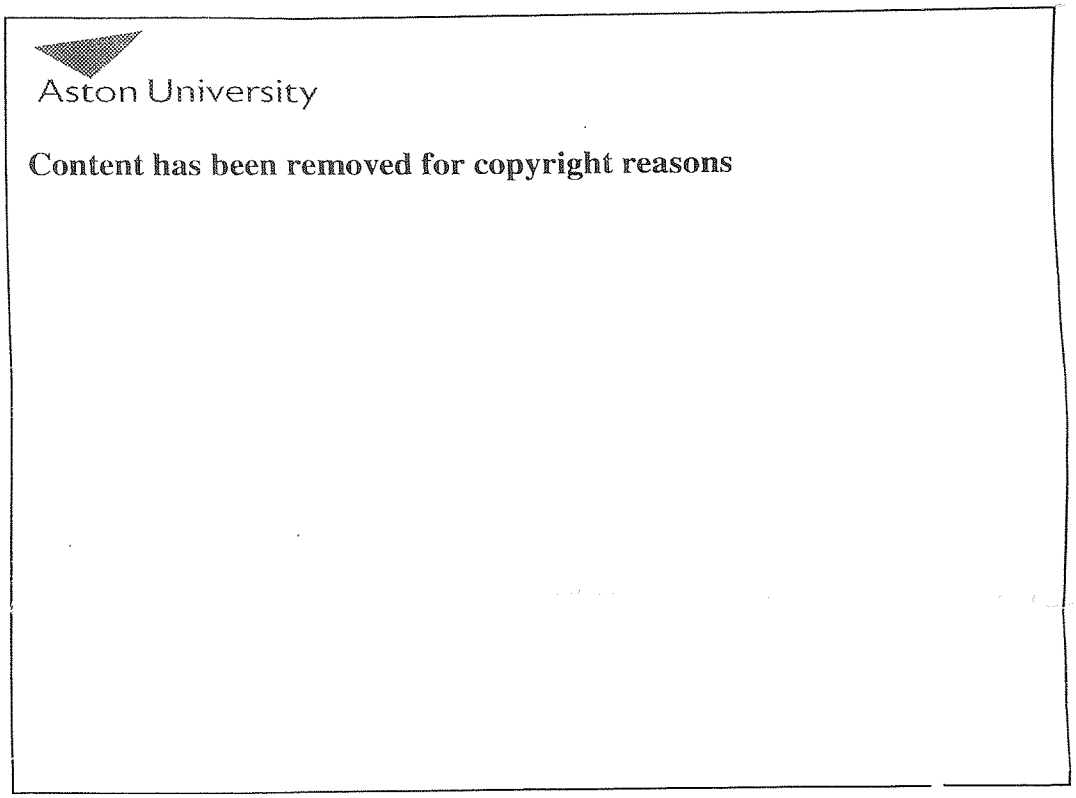
> "It is not possible at present to give an evaluation of the efficacy of propranolol in relation to other antiarrhythmic agents in these various arrhythmias since comparative antiarrhythmic studies have not been carried out. Therefore the views expressed represent mostly uncontrolled clinical experience. The possible fallacies associated with the largely uncontrolled evaluation of antiarrhythmic drugs must be borne in mind."[1]

The most dangerous arrhythmias are those concerning the ventricles (lower chambers) of the heart, since these do most of the work involved in pumping the blood round the body. These are of four types, as listed in Table 2.33.

Arrhythmias of the atria, the upper chambers of the heart, (also known as supraventricular) also affect ventricular performance, and hence can be dangerous. Types of arrhythmia and treatments of choice are shown in Table 2.34.

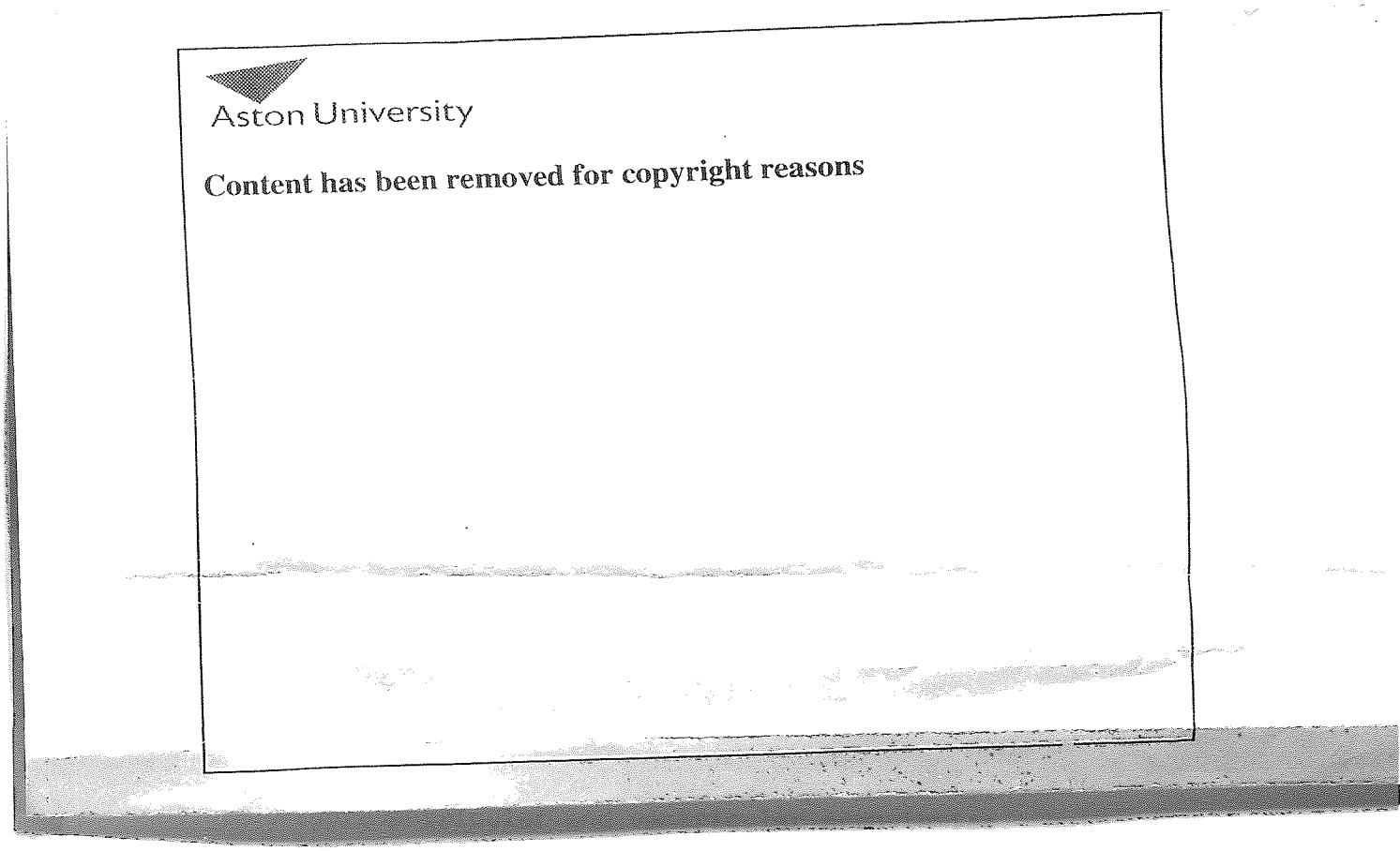
There is general agreement that beta-blockade is the drug treatment of choice for arrhythmias due to digitalis overdose, after potassium supplements and digitalis withdrawal have been tried, however Stock who originally found its greatest value in this indication has now decided that it is contraindicated.[4] It is also useful in controlling tachyarrhythmias during anaesthesia,

Table 2.33 Ventricular arrhythmias



Source: American Medical Association Drug Evaluations 1977.
Gibson, D., E. Sowton, 1969[3]

Table 2.34 Types of atrial arrhythmias



Sources: AMA Drug Evaluations 1977

Fitzgerald (1972)[2]

though there is a difference of opinion on how necessary drug treatment is in this condition.[5]

Assessment of such patchy evidence is difficult if it is not to be misleading - as Fitzgerald states:

> "Clearly there is an urgent need for painstaking evaluation of relative efficacy of anti-dysrythmic drugs in man ..."[6]

This is now becoming possible:

> "in most ... cases episodes of arrhythmia are unpredictable and relatively infrequent, and satisfactory methods of assessing the efficacy of anti-arrhythmic drugs have only recently become available. This situation has been transformed by the development of several new techniques, such as continuous ECG tape recording (Holter monitoring) and programmed intracardiac stimulation. It has also been aided by a better understanding of the use of randomised double-blind studies."[7]

Julian's assessment of the beta-blockers as anti-arrhythmics is that they

> "are effective in a minority of patients with supraventricular and ventricular arrhythmias, but they may well have a special role in the prevention of that type of ventricular fibrillation which occurs at the onset of myocardial infarction."[8]

Another earlier (1973) assessment from a symposium on beta-blockers:

> "Propranolol has been shown to be effective in terminating and preventing various tachyarrhythmias including those of the digitalis-induced and digitalis-resistant type, but it has seldom been employed as a drug of primary choice."[9]

So it would seem that the status of beta-blockade as an anti-arrhythmic therapy is that of a good second-line treatment, with a few circumstances where it could be the treatment-of-choice: such as arrhythmias induced by catecholamines, and certain types of Paroxysmal atrial tachycardia. Because usage is hospital-based and short-term it is not possible to be more precise about its therapeutic contribution in terms of costs and benefits.

2.4.6 Other indications for beta-blockade

As the beta-blockers show such a wide spectrum of effects on human physiology, soon after their introduction enterprising clinicians began to use the drugs in a more speculative way, concentrating on the therapeutic use of what were previously seen as 'side-effects'. These other indications are responsible for less than 5% of prescriptions, some are secondary treatments for refractory conditions while others are important therapeutic advances in rare conditions.

Two physiological imbalances which are surgically correctable, hyperthyroidism and phaeochromocytoma produce unpleasant symptoms which are relieved by beta-blockade.[10, 11] Patients waiting for surgery are thus considerably benefited by this use.

Tremor has been controlled by the use of beta-blockade.[12] Alternative treatments are tranquillisers or sedatives which sometimes become ineffective with chronic use, so beta-blockade is a useful alternative.

Migraine has been treated by beta-blockade,[13] this being first noted as a side-effect in an anti-anginal trial in 1966.[14] The first double-blind trials were done in 1974 which showed a significant reduction in attack rate on propranolol, and a preference for it among patients with whom conventional treatment had failed.[15] It therefore seems to be in this indication a useful supplementary treatment.

Propranolol has also found some use in anxiety states and schizophrenia. It blocks the sensations usually associated with anxiety, such as sweating and fast heart rate, and trials comparing it with conventional anti-anxiety treatments have found little difference.[16, 17] Beta-blockers have also been extensively studied

in stress situations such as examinations or public speaking, where their effects have been to dramatically reduce subjective levels of anxiety whilst not interfering with performance to the extent that tranquilliser therapy might do.[18] The possible extensions of their use in this area are obviously great.[19]

In schizophrenia, theories implicating excessive levels of catecholamines in the brain led to trials of propranolol in this condition.[20] Uncontrolled trials with small numbers of patients have reported an improvement on treatment of over 50%.[21] However the marked cardiovascular effects of the beta-blockers render their extensive use in this condition unlikely.[22]

2.4.7 Impacts on scientific literature, technology and medical thought

The previous section has been concerned with estimating the therapeutic impact of the beta-blockers. As has been discussed earlier, however, the consideration of effects beyond the immediate or long-term state of the patient is also important. The medical literature on the use of beta-blockade has been taken as source material for this, and has been analysed in order to examine the growth of the field of the study of beta-blockade, the increase in clinical interest in the drugs, and the influence of their use in changing medical and ultimately societal understanding of the diseases in which they are used.

This has been done in two ways. The quantitative aspects have been examined by counting references to key publications in the area - the technique of citation analysis, and the conceptual aspects by documenting changes in expert medical opinion and practice, and relating these to drug use.

The rationale for the use of citation analysis is given by Dieks and Chang (1976):

> "Most authors of scientific publications adopt the scholarly habit of acknowledging sources by quoting references. The use made of a paper and the influence exerted by it on later work is in some way reflected in the number of citations it receives. The more important a paper is for later development, the more citations it generally will obtain."[1]

There is much controversy concerning the supposed connections between a high citation count and the 'importance' or 'quality' of such a text, given that texts are cited for a variety of reasons, however a reasonable agreement exists between the results of citation analysis and those of other methods such as assessment by

a panel of experts, when these have been compared.[2]

The study of citations has gained popularity through the use of the Science Citation Index,[3] a publication which compiles the papers in any one year since 1965 which contain references to any scientific paper previously published in any of the wide range of journals surveyed by the Index. This renders raw citation data readily accessible.

The technique of citation analysis can be used in a number of ways:

> "Citations of scientific articles have been used in recent years as measurements of the scientific accomplishments of an individual, a group, an institution, or a country, as well as for following the temporal evolution of science in general, or a certain field of science in particular."[4]

In this work, it has been used to study the growth in interest in beta-blockade by examining citations of key papers. It was felt after preliminary study that simpler methods, such as a search of medical abstracts and indexes would not be comprehensive, as papers obviously stimulated by beta-blockade were categorised under a wide variety of headings, until the field became developed enough to warrant its own section.

The idea of following key papers arose out of a recognition that a high percentage of both clinical and pharmacological papers cited one or more of them in the paper's introduction. It was assumed that the citation patterns of these texts would thus parallel the increase in interest in the field of beta-blockade generally.

Three groups of papers were chosen for analysis, one containing the theoretical base and important early work, one being announcements of beta-blocking drugs by Black, and one being the

first announcements of the antihypertensive action of beta-blockers.

The first set of papers examined were thought to contain fundamental information for the new field. These were Ahlquist's separation of alpha- and beta-adrenergic receptors, American Journal of Physiology 153 586 (1948); Powell and Slater's announcement of the properties of DCI, Journal of Pharmacology and Experimental Therapeutics 122 480 (1958); and Moran and Perkins' connection of DCI with Ahlquist's theory, Journal of Pharmacology and Experimental Therapeutics 124 223 (1958).

The citation dynamics of these papers are shown in fig. 2.56. It can be seen that the three papers have very similar citation patterns, showing peak cites between 1965-1967, and then decay. This supports the hypothesis that the citations of these papers are linked. The theoretical paper of Ahlquist shows many more citations, has a later peak, and a slower decline. This can be interpreted to substantiate the impression gained from the literature that theoretical forerunners are more often cited than technological forerunners, and that they retain some usefulness as cited papers for a longer period.

The paper of Powell and Slater, and that of Moran and Perkins show consistently high cites 1965-1967, but a considerable decline thereafter, the latter paper declining more. It is probable that this indicates that both papers were superseded by others over this period, but that the connection of Ahlquist's theory with DCI was less enduring than the announcement of DCI.

The citation dynamics of the main papers authored by Black; Lancet 2 311 (1962) announcing pronethalol, Lancet 1 1080 (1964) announcing propranolol and British Journal of Pharmacology 25 577 (1965), comparing pronethalol and propranolol are illustrated in fig. 2.57.

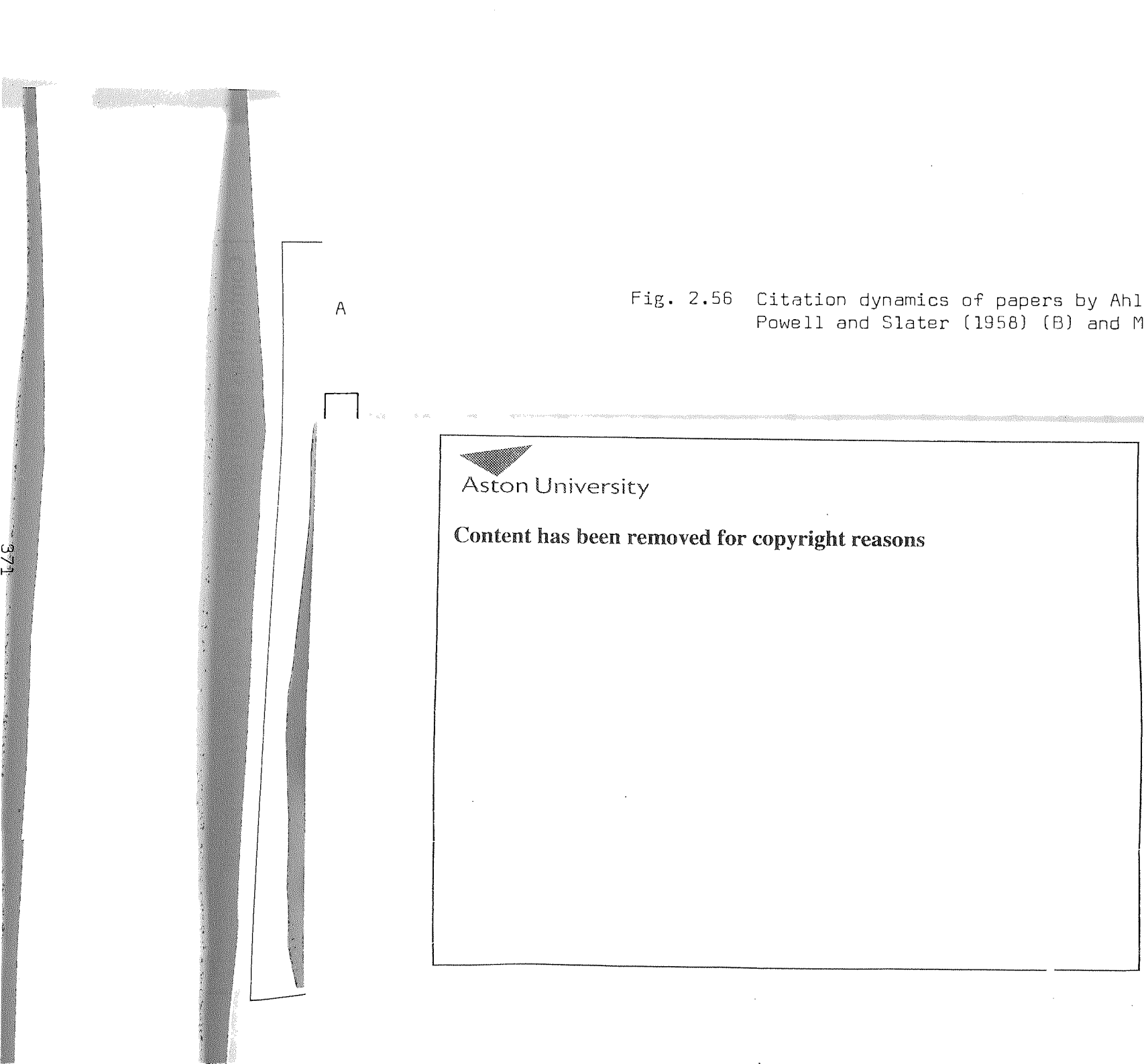


Fig. 2.56 Citation dynamics of papers by Ahlquist (1948) (A), Powell and Slater (1958) (B) and Moran and Perkins (1958) (C).

The first two papers are simply announcements of the pharmacological properties of the new compounds, whereas the third is a more detailed description of pharmacological test methods. This difference is reflected in the citation dynamics, the announcements both peaking in 1966 and showing a steep decline, the test methods showing a maximum impact sustained over three years and a moderate decline thereafter.

The citations of the announcement papers seem to reflect growth of interest in the field, as they have very similar patterns, though published two years apart. They illustrate the rate of take-up of beta-blockade, both as a clinical drug and also as an experimental tool, which can be seen for pronethalol to have taken around four years to peak, for propranolol around two years. As new publications on these drugs, and also announcements of other blockers appeared, their decline began.

The paper on test-methods shows much more sustained interest, as if the subject matter provoked less immediate interest, but proved of lasting value in the continuing pharmacological work on the characterisation of the properties of beta-blockers.

Fig. 2.58 illustrates the citations of two key papers by Prichard and Gillam in the use of beta-blockade in hypertension, British Medical Journal 2 725 (1964) describing the first use of propranolol, and British Medical Journal 1 7 (1969) comparing guanethidine and methyldopa with propranolol. The former paper can be seen not to follow the typical citation pattern of a rapid initial rise to peak and then a slower decay. Instead, it has a low initial peak in 1966, declines to 1971, and then rises to peak again, at almost double the original citation frequency in

Fig. 2.57 Citation dynamics of papers by Black (1962) (A), Black (1964) (B) and Black, Duncan and Shanks (1965) (C).

1976. The latter paper duplicates the pattern of the 1964 paper from 1970 to 1978.

The explanation of this pattern lies in the way in which the use of beta-blockers in hypertension developed, which has been discussed earlier. Initial interest was dispelled by negative reports, until the publication of the 1969 paper, and that of Zacharias in 1972 showed that impressive results could be achieved.[5] This provoked widespread interest and use producing the peak in the middle seventies.

Thus, the citation dynamics of these papers correlates very well with other information on the development of beta-blockade's use and provides evidence of the impact of its introduction on medical literature.

When considering the qualitative aspects of the impact of beta-blockade, that is the conceptual changes that it produced, it is helpful to separate out the different areas in which changes occurred. This is illustrated in fig. 2.59, showing the radiation of effects from direct to indirect impacts. Thus beta-blockade popularised the use of the receptor concept in drug research, it was a prime factor in the improvement of clinical trials, and it changed some conceptions of the conditions it was most effective in treating. These three areas are considered in turn.

Drug research

When Black moved to Smith, Kline and French in 1964, he applied receptor concepts to a new physiological area - histamine. The outcome of this research was cimetidine, a drug affecting gastric secretion, used in the treatment of gastric ulcer. This has been hailed as being another remarkable discovery

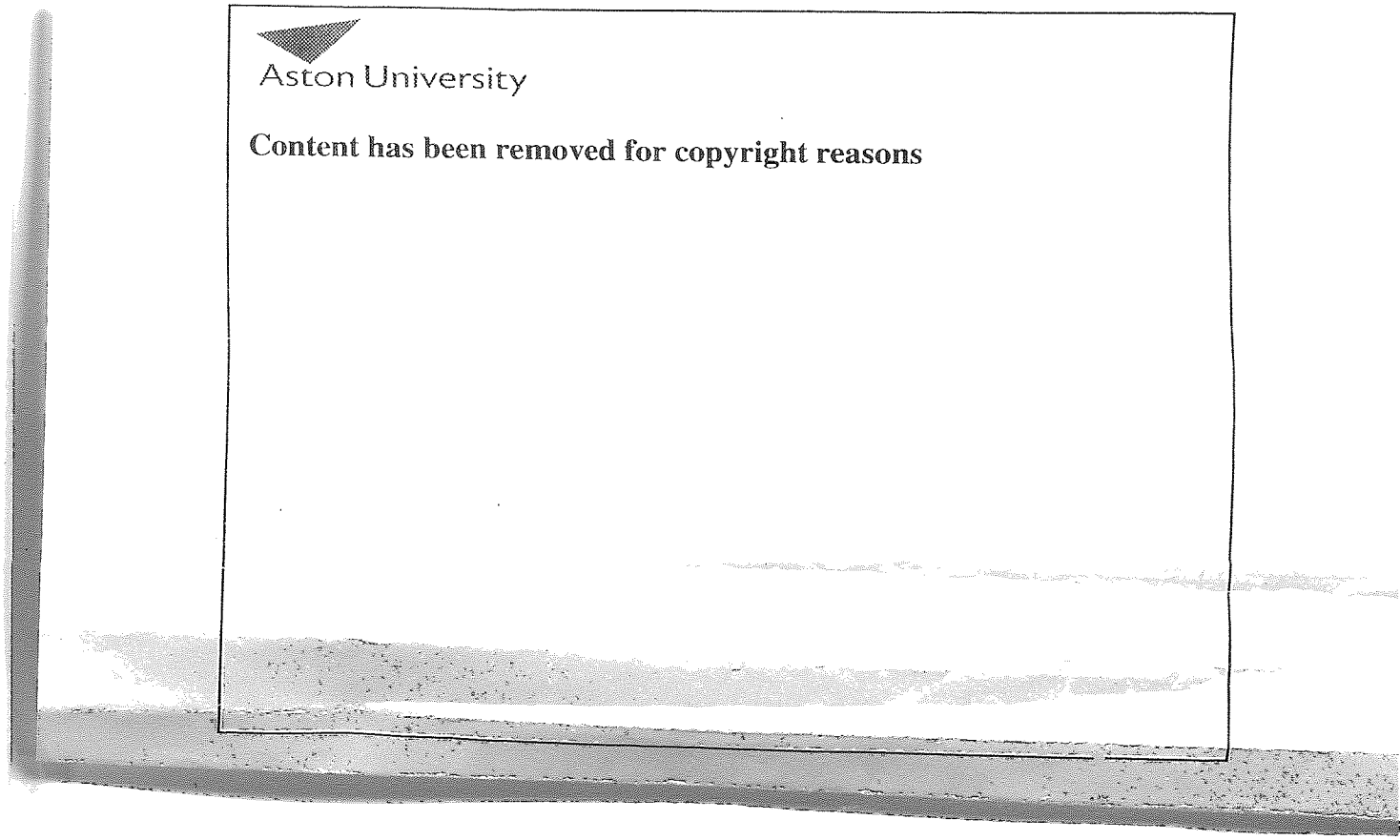


Fig. 2.58 Citation dynamics of papers by Prichard (1964) and Prichard and Gillam (1969).

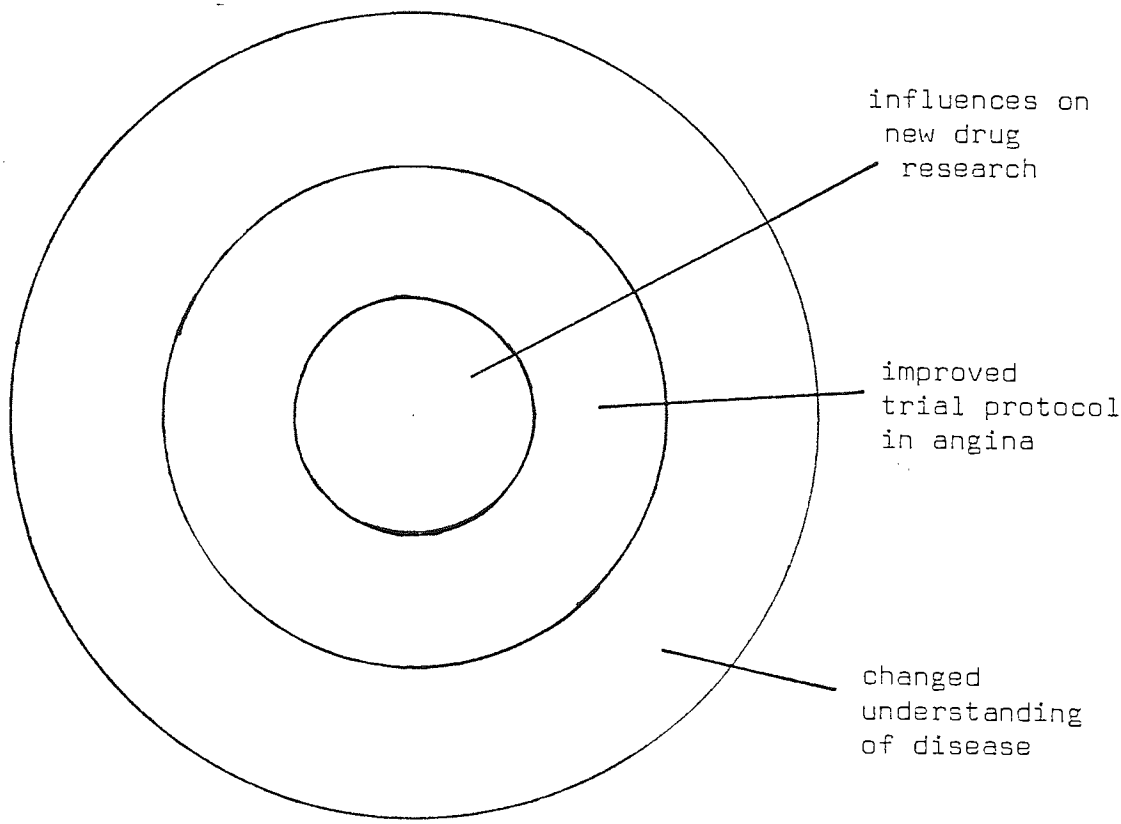


Fig. 2.59 Direct and indirect impacts of beta-blockade.

of fundamental importance.[6] The impact of these two successes of what Black has called the "pharmacological taxonomy" method of drug research[7] has been to make rational drug research, as opposed to empirical screening, appear more attractive. There is increasing interest in the study of drug receptors in pharmacology in general,[8] but the main impact of receptor theory has been in the adrenergic area in follow-ons to beta-blockers, and in more selective beta-stimulants.

There has been a tendency to try adding on other properties to those of the 'standard' beta-blocker. Two examples of this process are the alpha and beta-blocker, labetalol, introduced by Allen and Hanbury's in 1977, and combined beta-blockers and vasodilators presented by Merck, and Smith, Kline and French.[9]

Labetalol has not been very successful, as its alpha-blocking component introduces the giddiness characteristic of postural hypotension that beta-blockers do not show. It has, however, become known as a useful drug in hypotensive crisis.[10] Attempts to develop the receptor concept within the field of beta-blockade have not been successful, attempts at greater selectivity than the $beta_1$ and $beta_2$ subdivision producing no clinically useful results.[11]

In the field of beta-stimulants, that are extensively used in the treatment of acute asthma attacks as bronchodilators, the selective possibilities of the $beta_1$ and $beta_2$ separation have been exploited in a series of compounds that have supplanted the established unselective isoprenaline. These are salbutamol, introduced in 1969, terbutaline in 1971, and rimiterol in 1974.

The separation of cardiac from bronchial effects by the introduction of selective compounds has made their use safer -

as an increase in asthma mortality in the mid 1960s has been attributed to the cardiac effects of unselective bronchodilator aerosols.[12, 13] However, the production of salbutamol at least was motivated primarily by the desire for a longer-acting compound rather than one displaying selectivity. In this case, the Research Director, Jack, knew of Ahlquist's work, and was motivated by the production of a partially selective, but less potent compound, orciprenaline (1961) to try for an improved compound.[14]

Here then, the impact was due primarily to Ahlquist's work rather than that of Black. In general, the proponents of 'rational research' based on scientific knowledge make extensive use of the beta-blockers as a successful example of this process.[15] Thus they have a general legitimating function beyond concentration on receptor concepts to a wider focus on applying basic scientific research to drug innovation.

Improvement of clinical trials in angina

Until the late 1950s, clinical trials of new drugs in angina were the reports of clinicians trying out the drugs on small numbers of patients. These were invariably extremely favourable. However, later attempts to examine clinical benefit more closely often could not confirm these enthusiastic early reports. The importance of the placebo effect was gradually recognised, but the effect of increased medical interest, as in a trial, in improving patients' condition regardless of drug therapy was often not allowed for even in double-blind trials. Finally, patients used for trial did not always have comparable angina, stable angina, or sometimes even angina at all. Seventy-eight different conditions can stimulate the pain of angina closely

enough to confuse.[16] The case of dipyridamole is typical of the many coronary vasodilators that were produced during this period:

> "The first publications (1959-1961) relative to the anti-anginal effect of Persantin, were, as is usual, extremely favourable. Then several subsequent investigations (1961-1963) cast doubts on this beneficial effect. In 1964 the American Council on Drugs stated that additional clinical investigations were needed to determine whether or not Persantin is effective for sufferers from angina pectoris.[17] But later research did not clarify this problem. [18,19]

There were problems with the statistical interpretation of results:

> "it will be repeatedly seen in the case of different drugs that only ten or a dozen anginal patients which were drugged during one fortnight or one month took part in many clinical studies. Numbers were evidently too small to yield a statistically significant result. Under such conditions anybody can obtain any result ... a hundred patients under observation for a year would appear to represent minimum conditions."[20]

Indeed, the first anti-anginal evaluations of pronethalol were equivocal, using low numbers of patients over short periods.[21] Protocols improved dramatically over the succeeding few years as problems with trial design became clear: low, fixed doses meant that few patients responded, and the optimum dosage was not found, and lack of a 'run-in' period produced fluctuations in symptoms due to medical interest. Prichard and Gillam did much to improve this situation, using variable doses and run-in periods from 1965 onwards. The increased response rates they achieved stimulated other investigators to adopt similar techniques. The comparative sophistication of modern protocols is illustrated by Prichard's (1972) list of desirable trial criteria:

*Patients selected should have clear diagnosis (with characteristic ECG changes) and stable angina.

*Run in period (ideally 3 months) to stabilise effects of increased medical interest, and train patients in recording angina

attacks and nitroglycerine consumption.

*Length of individual double-blind periods should be carefully adjusted and order randomised.

*Observer who assesses patient should not have any information on previous visit and should take pulse rate last (low pulse-rate with beta-blockers may be detectable and may cause doctor or patient preference for active treatment).

*Comparisons between drugs should be done 'within-patient', that is comparing the effects of the drugs on the same patient, rather than using two groups which raises many comparability problems.[22]

The clinical trial in angina has hence become considerably more sophisticated in the 1960s than it was in the 1950s. This may be partially ascribed to better objective methods of anginal assessment,[23] but is is mostly due to the need to evaluate the various beta-blocking compounds.

Changes in our understanding of disease

Beta-blockade has changed medical ideas about the major conditions in which it is used. This is a similar, but more powerful effect than that produced by the use of drugs as experimental tools. Simply, it has focused attention on those physiological parameters of disease which it affects, so that these have come to be seen as more important indicators of severity or prognosis than they hitherto were.

In angina, beta-blockers embodied a therapeutic concept derived by Black, that concentrated on reducing the heart's demand for oxygen, rather than the hitherto accepted practice of attempting to increase supply, which was implicit in the innovation

and widescale use of vasodilators in the nineteen-fifties. Thus the adoption of beta-blockade as a major anti-anginal treatment paralleled a change in what were seen as the important parameters in the anginal condition:

> "(Black's prediction of anginal relief by beta-blockade) was based on the belief that episodes of angina were precipitated by an increase in the work and oxygen requirements of the left ventricle as a result of sympathetic stimulation, and the knowledge that these effects were mediated by beta-adrenoceptors. This view of the nature of the anginal episode is now generally accepted."[24]

> "The availability of propranolol permitted the assessment of the relative importance of heart rate, myocardial contractility and myocardial wall tension to myocardial oxygen consumption. The observation that propranolol causes no increase in the threshold of anginal pain when pain is induced by atrial pacing indicates how important the role of heart rate change is in this condition. Thus, beta-antagonists clarified the haemodynamic changes leading to the onset of anginal pain."[25]

The concentration on parameters affected by beta-blockade (myocardial oxygen consumption, heart rate change) is evident. Much work on angina becomes oriented around these parameters:

> "It must be acknowledged that, despite numerous studies, it has not yet proved possible to determine what is the most important factor accounting for the clinical improvement elicited by beta-blockers ... Hence it is in this direction that further research should, I feel, be undertaken."[26]

This concentration on the effects of drugs on disease parameters can be traced to the need for a rational basis for therapy, which may be subdivided into the need to know why and how the drug works (need for a mechanism), and the need to know when to use it (need for clinical guidelines). Thus the desire for security is expressed as the desire for scientific knowledge. I shall illustrate these tendencies in the case of hypertension.

The "need for a mechanism" is seen most strongly by the pharmacologists of pharmaceutical firms who know that this is a powerful way to interest specialist clinicians - the medical elite - in the use of the drugs:

> "in animals you couldn't show a lowering of blood pressure ... we didn't have an animal model to bang on the table, and there was a lot of internal debate, and I was puzzled ..."[27]

> "it's just going into man now, if it comes out all right the first thing the doctor will say is 'how does it work?' The evidence has to be very water-tight and perhaps the animal models are wrong....."[28]

> "How does propranolol lower arterial blood pressure? Nobody knows, but ICI haven't generated the work to look at it, they've been dependent on people outside ... but nobody tried to work it out. I feel that product development has been very poor."[29]

Most concern with mechanisms, however, is felt in connection with the need for doctors to feel that their treatment of hypertension is becoming more scientific and less a matter of unguided trial and error:

> "All therapy continues to remain, of necessity, largely empirical. However, we are slowly emerging from an era of 'blind empiricism' to one of enlightened empiricism."[30]

> "Propranolol has been used in the treatment of hypertension for more than ten years, yet its mode of action in lowering arterial pressure remains a matter of controversy."[31]

> "Different theories were proposed, each stressing one of the many actions of the drug - its chronic reduction of cardiac output, its suppression of renin release, or its interference with central noradrenergic neurons and presynaptic adrenergic receptors. Definition of these mechanisms is important not only theoretically for better understanding of hypertension, but also practically to establish the indications for propranolol therapy and its limitations."[32]

One of the most discussed parameters which has become significant through the use of beta-blockade, both as clinical guideline and

as a redefinition of hypertension, is the level of one of the blood pressure influencing hormones, renin. This is how it has been introduced by one of its protagonists:

> "Antihypertensive drug programmes are traditionally based on trial and error. Among patients with essential hypertension, impressive differences in the response to individual compounds can be observed. Thus a drug that normalises blood pressure in one individual may be relatively ineffective in another ... The reason for this lack of predictability is to be sought in specific abnormalities or causal mechanisms, which, in the large majority of hypertensive patients, have not yet been identified. Physiological characterisation of the renin-aldosterone system as it interacts with daily urinary sodium excretion in normal subjects has made it possible to classify patients with common essential hypertension into groups with high, normal and low plasma renin activity. Such a classification provides the possibility of matching drug response with a hormonal setting."[33]

Propranolol is seen by the renin workers as an anti-renin drug that reduces blood pressure in high and normal renin hypertensives, but not in low renin patients.

> "We feel that the studies cited above have important clinical implications that need not wait much longer for their implementation in medical practice. A properly obtained hormonal profile indexed against sodium excretion provides a sensitive physiological indicator of renin involvement in all forms of hypertension and a useful predictor of the therapeutic effect of propranolol ... the low renin patient is not a candidate for propranolol therapy but for most high renin patients, and for an important fraction of normal renin patients, propranolol offers good news ... it is a direct therapeutic answer to a specific biochemical lesion."[34]

This work had an extensive impact:

> "Hundreds of papers were published on the subject from that laboratory. A large number of investigations were launched to confirm or deny these landmark findings throughout the world. The news of these findings and scientific debate reached the layman via the local and national press."[35]

Thus, the advent of sensitive physiological testing dovetails with the wide-scale use of a drug whose mechanism of action is controversial to redefine the disease in terms of the drug's effects. Many disputes on the accuracy and significance of this work on renin have revealed little except the need for further research, with general practitioners strongly opposing the idea of biochemical tests being a useful aid in their choice of treatment.[36] It seems that a categorisation of hypertension based on response to drug treatment is an attractive concept, certainly for conference-going clinicians. A final quote illustrates some general points underlying this discussion:

> "When the beta-blockers first came out it seemed very possible from the very dramatic response that some patients got, and the failure of other patients to respond, that this might indeed offer a clue to the pathogenesis of hypertension. ... There is obviously no doubt that the use of pharmacological agents over the last twenty years has led to a substantial increase in the understanding of the pathogenic mechanisms of hypertension. Unfortunately, with the beta-blockers as with methyldopa and other drugs, the more one knows about these, the less one knows how they work."[37]

Another change in our understanding of hypertension, which has come about largely because of the use of beta-blockade, is the recent focusing of attention on the deleterious effects of stress:

> "Beta-blockers are playing an important part in gaining acceptance for theories implicating stress as one of the major factors in cardiovascular disease because they can be regarded as stress-blocking drugs."[38]

> "emotionally-induced increases in cardiac work are wasteful in the absence of physical exertion and may even prove harmful in patients with CHD ... the advent of clinically acceptable beta-receptor antagonists now allows the sympathetic origin of such cardiovascular responses to be tested and therapeutically modulated."[39]

Many studies have now been done on the beneficial effects of beta-blockade on electrocardiographic manifestations of stress,

and many of these have claimed a role for beta-blockade in the prevention of CHD on the basis of these effects. This has been extended to studies of the effects of beta-blockade in moderating the high heart rates associated with public speaking, car driving and other "stressful activities". One of these investigators has commented:

> "... We were not suggesting that all normal people should be 'treated' with beta-blockers. ... Consider a normal person addressing an audience or speaking at a board meeting who becomes aware of a tumult in his chest resulting from nervous tachycardia ... It is our contention that he would benefit from medication which, besides enabling him to speak more effectively by shielding him from the distraction of his palpitation, might at the same time be protecting him from a deleterious influence on his coronary arteries ..."[40]

So treatment with beta-blocking drugs is being extended from people with defined diseases to normal people in stressful situations as a somatic anti-anxiety treatment. This possibility has, of course, been quickly perceived by the manufacturers of these drugs:

> "'Beta-blockers may well become unique in being the first group of drugs which, though developed to benefit the abnormal heart, can also be used to treat the normal person'. The prophecy implied in this statement may at the moment sound futuristic; perhaps it even smacks of utopianism. But it does impart the feeling that in the realm of cardiovascular diseases we are now about to witness the dawn of an era of prophylactic therapy. This is a feeling which we in the pharmaceutical industry also share ..."[41]

There are then powerful tendencies towards widening the use of these drugs even beyond the 15-25% of the population for whom they are already indicated. It seems to me that the effects of this on medicine and society will be very great and are as yet unexamined. The wider implications of these effects are examined further in section 3.2.

3.0 Drugs and our perceptions of heart disease

The case-study on beta-blockers has shown that the use of these drugs has resulted in widespread changes in the way that doctors perceive angina and hypertension. These are mostly changes in the mechanism by which the disease is seen to act.

In section 1 it was shown that the disease entity, hypertension, has undergone great changes in the periods examined which have been shown to be largely due to the use of new drugs and diagnostic technology. These changes have not only involved mechanism of action, but also diagnostic criteria, and how the disease is defined, thus potentially including far more people.

Given the recent concern about the 'epidemic of coronary heart disease' it seemed important to make some more general assessment of the effects of drugs on heart disease. If the effects of beta-blockade on the conditions in which it is used are perceptible even with ten years usage, then the other classes of heart drugs used more widely over longer periods must have had considerable influence on our perceptions of heart disease.

This has been examined in two areas; changes in the extent of heart disease and changes in our understanding of heart disease. The first involved correlating the usage of drug treatments with changes in mortality statistics. This connection is important because of the attempts which have been made to link drug use with declines in mortality. The argument of this section is that drug use leads to changes in disease perception which results in a reclassification of statistics which can, therefore, be misleading taken at face value.

The second extends a similar analysis as that which has been done on the effects of beta-blockers to the other classes of drugs used in heart disease.

3.1 Drugs and the extent of heart disease

> "Disease is very old, and nothing about it has changed. It is we who change as we learn to recognise what was formerly imperceptible."
>
> W. Charcot

The way in which the extent of heart disease is measured in society is predominantly through the use of mortality statistics, that is records kept about the number of people dying from different causes. Other records of ill-health (morbidity) such as number of days off work sick, or general practitioner consultation rates are less used because they are affected by other social factors as well as the effects of disease.

However, mortality statistics are not the objective record of disease that they might at first appear. They are a record of the way in which a particular group within medicine - medical statisticians - have found it useful to categorise disease. These categories are not static. The changes in this classification reflect changes in the way doctors of all sorts diagnose disease, but mostly reflect the sophisticated conceptions of medical statisticians. These changes have been quite radical as cardio-vascular disease has moved from being a peripheral cause of death to being the single largest cause of death, displacing the declining infectious diseases.

The death certificate, which is the observational base for all subsequent data is filled in by the doctor who has attended the patient according to a set of terms and guideline "rules for classification" which, since around 1900 have been adapted and extended by decennial international conferences of medical statisticians. The way in which the classifications of heart

disease have changed is illustrative not only of actual changes in disease prevalence, or changing attitudes towards the disease, but also of changing ideas about the role of the International Classification of Diseases itself, in a situation where degenerative diseases are being classified according to categories originally derived from experience with infectious diseases.

The classification of diseases, or of anything else for that matter, depends on the use to be made of the information, as William Farr made clear in 1856:

> "Classification is a method of generalization. Several classifications may, therefore be used with advantage; and the physician, the pathologist, or the jurist, each from his own point of view, may legitimately classify the disease and the causes of death in the way that he thinks best adapted to facilitate his enquiries, and to yield general results ... The medical practitioner may found his main divisions of diseases on their treatment as medical or surgical; the pathologist on the nature of the morbid action or product, the anatomist or physiologist on the tissues or organs involved; the medical jurist on the suddenness or the slowness of the death; and all these points well deserve attention in a statistical classification."[1]

> "A specific disease entity should have a separate title in the classification only when its separation is warranted because of the frequency of its occurrence, or its importance as a morbid condition justifies its isolation as a separate category."[2]

Here Farr identifies the classification of disease as a record of ways of seeing causes of death, useful from the point of view of its users. This implies, then, that the current classification of causes of death will reflect the preoccupations of the medical world as perceived by those statisticians who adapt the classification at ten-year intervals. In this respect, therefore, there is great difficulty in comparing deaths recorded from cardiovascular disease in 1900 with those recorded in 1960,

since the only threads that link the two observational sets are two slowly evolving frameworks; that of the codification of the causes of death, and that of medical preoccupations, and the terminology and practices which dialectically relate them. The impact of developing technology, and drugs in particular, on this relationship will now be examined.

Cardiovascular disease has been subdivided in many ways since heart disease first became a recognised cause of death (as 'fatty heart' in the middle of the 19th century). The changes in the classification of heart disease in the Registrar-General's manual of the causes of death, 1900-1965, are shown in Table 3.1.

Two areas will be examined, degenerative and ischaemic heart disease, and nephritis and hypertension. The first category was represented in the 1850s mostly by the condition of 'fatty heart' in which accumulation of fat around the heart was recorded as the cause of death. It was given extensive treatment in standard texts of the time and was subdivided in different classifications.[3] However, with the increasing sophistication of pathological analysis with the widespread use of the microscope, fatty heart became less discussed.

> "By the end of the century, fibroid disease and chronic myocarditis had supplanted fatty heart as the fashionable diagnosis ... In spite of the recognition of cardiac infarction due to coronary occlusion by pathologists before the turn of the century, it was not until Herrick's second paper (1919) aroused the interest of American physicians that it gradually permeated the field of clinical medicine, and in no time the so-called modern epidemic of coronary disease erupted."[4]

So in this case it seems to have been the recognition of the importance of blood supply to the heart muscle that lead firstly to the change from a diagnosis of 'fatty heart' to one of 'fibroid disease' and then to one of 'ischaemic heart disease'. This

Table 3.1 Comparison of categories of causes of death in the Registrar-General's tables 1900 to 1965

Year Analysed Classification	1900 General Register Office List (1880-1900)	1910 General Register Office List (1901-1910)	1920 International List (1909 second revision)	1930 International List (1920 third revision)	1939 International List (19 fourth revision)
Term used in Tables DEGENERATIVE HEART OISEASE Ischaemic Heart Disease	Angina Pectoris	Angina Pectoris	80 Angina Pectoris	89 Angina Pectoris	94 Diseases of the coronary arteries angina pectoris
Myocardial Degeneration	Hypertrophy of Heart	(i) Hypertrophy of Heart (ii) Dilatation of Heart (iii) Fatty Degeneration of Heart	79B Fatty Degeneration of Heart C Other organic disease of Heart	90(5) Fatty Heart (6) Cardiac dilation cause unspecified (7) Other or unspecified Myocardial disease	93(b) Myocardial degeneration (1) Fatty Heart (2) Cardiovascular degeneration (3) Other diseases included under 93(c) Myocarditis not distinguished a acute or chroni
Other Heart Oisease	Syncope Other and undefined diseases of circulatory system	Syncope, Heart Disease (not specified)	v. supra (79C)	90(9) Heart Disease (undefined)	95 Other Diseases of the heart
General Arteriosclerosis	Senile Gangrene	(i) Senile Gangrene (ii) Other diseases of blood vessels	81B Arterial Sclerosis 142A Senile gangrene	91(b)2. Arteriosclerosis without record of cerebral vascular lesion 151 Gangrene (1) Senile gangrene (2) Other gangrene	97(3) Arteriosclerosi without record cerebral vascu lesion 98(a) Senile Gangren
Chronic Nephritis	Bright's disease albuminuria Uraemia	Chronic Bright's disease albuminuria	120 Bright's disease A Bright's disease B Nephritis (qualified) 10 years and over and uracmia	129 Chronic Nephritis (including unspecified over 10 years of age)	131 Chronic nephriti 132 Nephritis not st to be acute or chronic
Hypertension					102 Abnormalities of blood pressure

th in the

1910 ral Register Office (1901-1910)	1920 International List (1909 second revision)	1930 International List (1920 third revision)	1939 International List (1929 fourth revision)	1950, 1960 International Statistical Classification (1948 sixth revision. 1955 seventh revision)	1965 8th revision
na Pectoris	80 Angina Pectoris	89 Angina Pectoris	94 Diseases of the coronary arteries angina pectoris	420 Arteriosclerotic heart disease, including coronary disease .0 Arteriosclerotic heart disease so described .1 Heart disease specified as involving coronary arteries .2 Angina pectoris without mention of coronary disease	410-414 Ischaemic heart disease 410 myocardial infarction 413 angina pectoris
) Hypertrophy of Heart) Dilatation of Heart) Fatty Degeneration of Heart	79B Fatty Degeneration of Heart C Other organic disease of Heart	90(5) Fatty Heart (6) Cardiac dilation cause unspecified (7) Other or unspecified Myocardial disease	93(b) Myocardial degeneration (1) Fatty Heart (2) Cardiovascular degeneration (3) Other diseases included under 93(b) 93(c) Myocarditis not distinguished as acute or chronic	422 Other Myocardial degeneration .0 Fatty Degeneration .1 with arteriosclerosis .2 Other	428 Other myocardial insufficiency
cope, Heart Disease t specified)	v. supra (79C)	90(9) Heart Disease (undefined)	95 Other Diseases of the heart	434 Other and unspecified diseases of the heart	429 Ill-defined heart disease
) Senile Gangrene) Other diseases of blood vessels	81B Arterial Sclerosis 142A Senile gangrene	91(b)2. Arteriosclerosis without record of cerebral vascular lesion 151 Gangrene (1) Senile gangrene (2) Other gangrene	97(3) Arteriosclerosis without record of cerebral vascular lesion 98(a) Senile Gangrene	450 General Arterio-sclerosis .0 without mention of gangrene .1 with mention of gangrene as a consequence	440-448 Diseases of arteries, arterioles & capillaries 440 Arteriosclerosis
onic Bright's disease buminuria	120 Bright's disease A Bright's disease B Nephritis (qualified) 10 years and over and uracmia	129 Chronic Nephritis (including unspecified over 10 years of age)	131 Chronic nephritis 132 Nephritis not stated to be acute or chronic	592 Chronic Nephritis 593 Nephritis not specified as acute or chronic 594 Other renal sclerosis	
			102 Abnormalities of blood pressure	440/443 Hypertensive Heart disease 444/447 Other hypertensive disease	400-404 Hypertensive disease 400 Malignant hypertension 401 essential benign ht. 402 hypertensive H.D. 403 hypertensive renal disease 404 ht. heart & renal disease

recognition was due to a number of factors.

Increasing interest in the coronary circulation can be documented from 1768 when Heberden first described angina pectoris through the early 1800s when ossified coronary arteries began to be noted, and their significance disputed, to the microscopic examinations of heart muscle which led to the description of fibrosis. Lauder Brunton's use of amyl nitrite to relieve anginal pain in 1867 began the use of vasodilators for this condition, and thus reinforced ideas of it as a state of insufficient oxygen reaching the heart. William Murrell introduced the more practical glycerine trinitrate in 1875.

These ideas took some time to spread into general usage and from there to become incorporated in changes in death certification. Changes in death-rates due to different certified classes 1900-1960 are shown in fig. 3.1. Major changes in heart disease death rates are mainly caused by transfer of deaths from one group to another as the total death rate is similar at the end of the period to what it was in 1900. 1900-1930 shows the change from 'other heart disease' to 'myocardial degeneration', 'fatty heart' having transferred to this category, before this time presumably being included in 'other heart disease'. This change reflects also an increasing precision of diagnosis as the findings of diagnostic technology such as X-rays (1896) and the electrocardiograph (1903) permeated clinical medicine. One can see the classification of myocardial degeneration becoming more elaborate in parallel with its increasing usage up to 1939. From 1920 onwards arteriosclerosis became seen as an important factor in degenerative heart disease, so deaths from this cause were transferred, initially to 'myocardial degeneration', later to 'coronary heart disease'.

Fig. 3.1 Death rates for heart diseases, England and Wales, 1900-1960 from Robb-Smith (1967).

Source: Robb-Smith, A. H. T. The Enigma of Coronary Heart Disease (Lloyd-Luke, London, 1967).

> "It will be apparent that gradually over the years, the content of the ischaemic heart disease category has widened as terms such as cardiac rupture etc., have been transferred to it from the 'myocardial degeneration' categories ... Arteriosclerosis was first distinguished in the second revision of the International List (1909) ... Until 1928 the number of deaths attributed to this term steadily rose, partly due to the reassignment of deaths which would formerly have been classed as senility, partly owing to the operation of the selection rules for joint causes ... The new form of death certificate and changes in the assignment rules introduced at the fourth revision conference (1929) resulted in a steady fall in the age-specific death rate for arteriosclerosis."[5]

As clinical appreciation of the role of arteriosclerosis in myocardial degeneration increased, so deaths which would previously have been coded as myocardial degeneration became coded as coronary heart disease.

> "It was in the 1920s, as I myself recall quite clearly that the pathologists and clinicians began to work more closely together in the evolution of our knowledge of cardiovascular disease. Experts in biological chemistry, physiology and statistics lent their aid ... The next decade of the 1930s was a most exciting one of new diagnoses by improved techniques, not only roentgenologic and electrocardiographic but by better interpretation of symptoms and signs discovered on physical examination."[6]

It is clear, then, that the impact of emerging scientific disciplines and the new diagnostic technology was instrumental in the creation of coronary heart disease as we know it. These changes are now an integral part of modern medicine, as a recent article on trends in heart disease makes clear:

> "In 1950 'other myocardial degeneration' (ICD 422) comprised 42% of all deaths attributed to the circulatory system. By 1967, the last year in which this classification was used, it comprised 15% of all cardiovascular deaths. In 1973 'other myocardial insufficiency' (ICD 428) which appears to be the closest approximation to ICD 422 comprised only 4% of all cardiovascular deaths. It is almost incredible that this disease entity which made such a major contribution to cardio-vascular deaths at the beginning of the period cannot

> be found with any degree of specificity in clinical or pathological textbooks of the period. It is extremely doubtful whether the distinction between 'other myocardial degeneration' and 'arteriosclerotic heart disease' could have been made with any reliability and it is likely that many deaths ascribed to myocardial degeneration in 1950 would have been ascribed to arteriosclerotic heart disease by 1967."[7]

It can be seen that the impression of specificity of diagnosis given by precise disease categories reflects medical perceptions of the nature of heart disease more than it does the reality of disease. This is as true in the present with all its diagnostic aids as it was in the past, because the drugs and the diagnostic aids are not neutral aids to vision, they are material embodiments of theories about disease.[8] This is evident in the case of hypertension, whose redefinition through new methods of treatment has been discussed earlier.

The classification of deaths follows the introduction of drugs and diagnostic aids closely. In 1900 Bright's disease, or the presence of high levels of albumin, or urea in the urine are the three categories of nephritis (kidney disease). The diagnoses of albuminuria and uraemia depend on chemical tests which were developed by chemists working with Bright.

Blood pressure is not mentioned until 1929, up to which time deaths certified due to Bright's disease/nephritis remained approximately constant. The 1929 rubric 'abnormalities in blood pressure' is a clear consequence of the widespread use of the sphygmomanometer and the impact of experimental work on the effects of high blood pressure. Hypertension was not taken as a main axis for classification until the 1948 revision, by which time the mortality rate had increased dramatically (fig. 3.2).

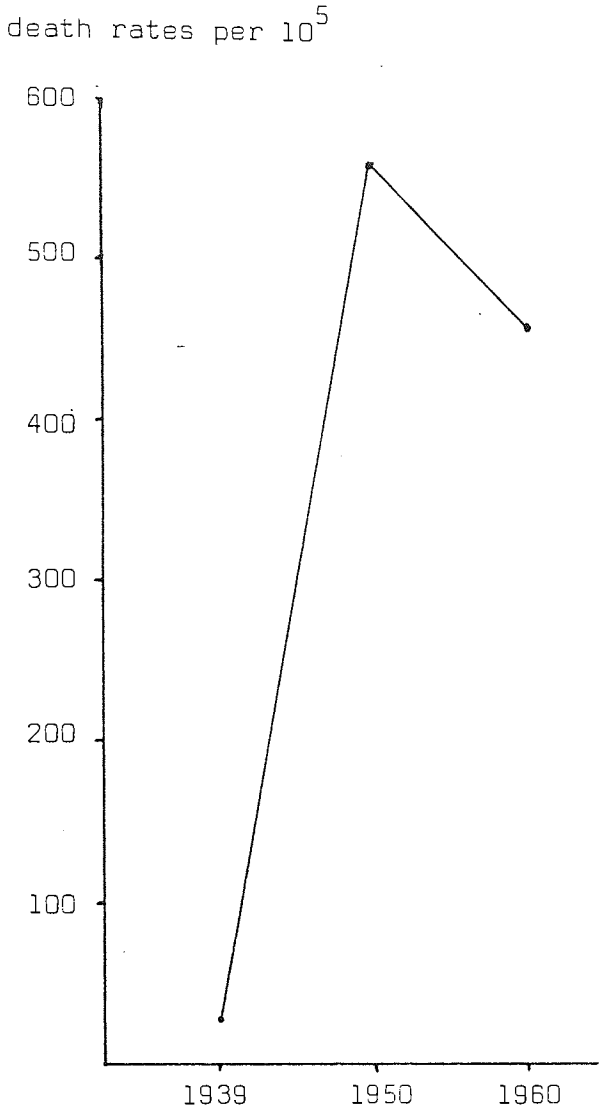


Fig. 3.2 Mortality rate from hypertension 1939-1960 in those aged 45 or over in England and Wales

Source: as in Fig. 3.1

This is generally thought to be due to a transference of deaths previously seen as 'nephritis', as mortality attributed to this has been in decline from around the time of the introduction of hypertension, but more rapidly recently. Reid and Evans (1970) conclude from an examination of this data that

> "Two conclusions seem to emerge. The first is that the increasing use of a new diagnostic tool such as the sphygmomanometer will inevitably lead to the substitution of more sophisticated diagnostic labels without necessarily implying a change in the frequency of the underlying cardiovascular disease. When changes are then made in the International List, the effect can be dramatic. The second is that current improvement in the death-rate from diseases in which hypertension is a cardinal feature should not be attributed uncritically to the new hypotensive agents."[9]

It is clearly misleading to examine the effects of drugs on death-rates without at the same time examining the effects of the drugs in altering the classification and diagnosis-frequency of disease. This is a major problem in using mortality statistics as an index of the success of treatment. There is also a suggestion that:

> "the last quarter of a century has brought a greater awareness of the role of hypertension as a major risk factor in ischaemic heart disease and this may have resulted in some transfer of diagnosis from hypertensive heart disease to ischaemic heart disease. It seems unlikely that treatment of hypertension has been responsible for this considerable decrease in hypertensive disease mortality."[10]

However, if the evidence collected on the effects of hypertension treatment is sound, this treatment has been largely responsible for this 'considerable decrease', but indirectly, through its focusing medical attention on the role of hypertension in ischaemic heart disease.

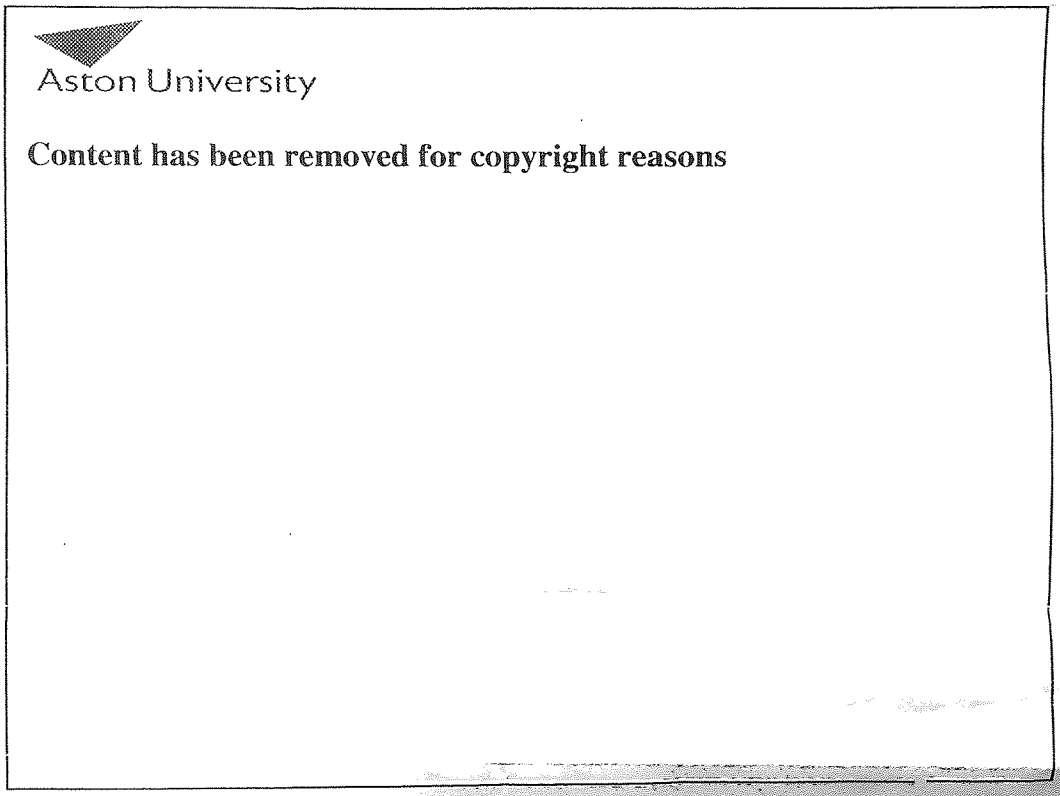
Looking at the changes in medical statistics of heart disease, then, it is possible to correlate many of these with the introductions

of new diagnostic and drug technologies, and thereby to suggest that these technologies have constituted a strong influence on medical perceptions of heart disease.

In view of the changes in categories which I have reviewed, it is difficult to be anything other than pessimistic about the chances of detecting the therapeutic effects of the use of anti-hypertensive drugs in National Mortality Statistics. Those studies which have claimed to detect this, Office of Health Economics (1971)[11] for the UK, and Reader (1976)[12] in Australia, either accept the decline in hypertensive deaths, or the reduction in stroke mortality as critical evidence. As we have seen, the former can be explained in other ways, and the latter is most obvious in older age-groups where antihypertensives are much less frequently used than in younger age-groups where reduction is less. The evidence can therefore be taken either way.

From a cursory study of anti-hypertensive drug prescribing statistics, it would seem that hypertension is becoming increasingly common (fig. 3.3). What has been happening is that the advent of drugs with fewer side-effects has meant that more people have been treated; that treatment has been started at ever lower levels of blood pressure.[13] This has been justified by the results of clinical trials, particularly by the Veterans' Administration. Their 1970 finding of benefit in those with mild hypertension (diastolic pressure 90-104) has increased the candidates for drug treatment by about eightfold, from 4% to 35% of the middle-aged population.[16] Thus as treatments become more palatable, more people are defined as ill.

Table 3.2 Prevalence changes in hypertension with variation in pressure at which it is defined



Source: Labarthe, D. R. (1978)[14]
Padfield, P. L. et al. (1975)[15]

3.2 Drugs and our understanding of heart disease

As I have already discussed in connection with the beta-blockers and the development of research into adrenergic mechanisms, the use of new drugs both in therapy and research focuses the attention of clinicians and investigators on those physiological parameters which they affect. Looking at the recent increase in cardiovascular innovations (fig. 3.4) and in prescribing (fig. 3.3) it seems because of the extent of drug use, that the area of cardiovascular disease should be a good test case for documenting this idea on a wider scale. Table 3.3 is a list of the categories of drugs used in cardiovascular disease and their date of origin.

The categories will be discussed in turn; the effect of drugs on the nature of hypertension has already been touched on, and will be discussed only briefly here. In the field of hypertension the first important drugs were those acting as blockers at some level in the sympathetic nervous system. In the 1950s these drugs initiated a mass of research into nervous control of blood pressure using the drugs in the classic Bernardian manner as dissecting instruments. Of reserpine, for example, Plummer and deStevens comment:

> "Reserpine has provided insights into the finer details of the biochemical processes responsible for the function of the (sympathetic nervous) system. Not since J. N. Langley in the last century first mapped the sympathetic ganglia through the use of nicotine has so much significant new information been obtained through the aid of a single chemical."[1]

Each new generation of blocking drugs have focused investigators' attention on their sites of action. The use of blockers of the sympathetic nervous system, itself provoked by clinician's suspicions of the nervous origin of hypertension, has reinforced this perspective with a mass of technical knowledge:

Million
prescriptions

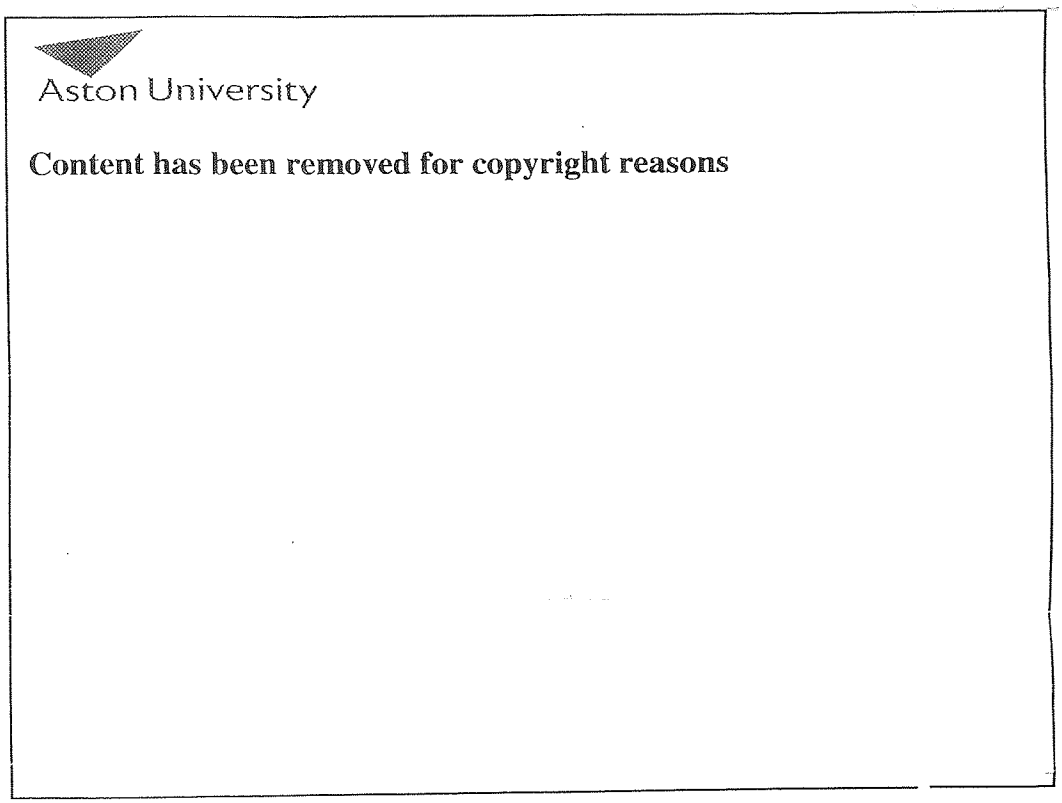
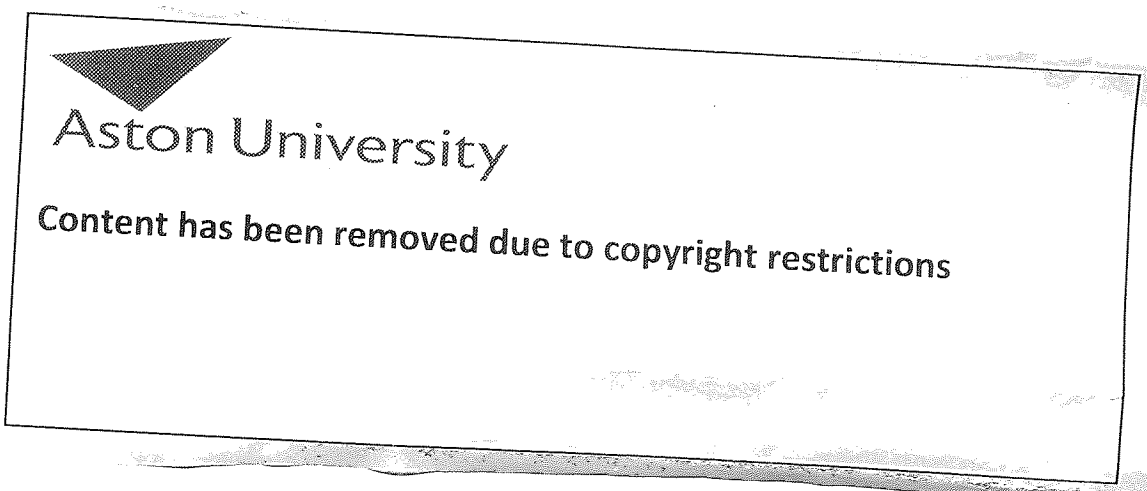


Fig. 3.3 Antihypertensive drug prescribing, Australia 1960-1967, United States 1970-1976.

Million



Source: A. Petursson, S. R. et al., National rates and patterns of consumption of antihypertensive drugs Annals of the New York Academy of Science 304 320 (1978)

B. Lovell, R., R. Prineas, Trends in prescribing of hypotensive drugs, Medical Journal of Australia 2 557 (1971)

Fig. 3.4 New drugs marketed in Great Britain classified by Disease Area, from Steward (1977).

From Steward, H. F. Public Policy and innovation in the Drug Industry in Providing for the Health Services, eds. Black, D. and G. P. Thomas (Croom Helm, London, 1977).

Table 3.3 Major drug classes used in cardiovascular diseases

		Year introduced
Antihypertensives		
Diuretics -	mercurial	1920-25
	thiazide	1957-
Sympathetic inhibitors -	alpha-blockers	1946-
	ganglion-blockers	1948-
	Noradrenaline depletors	1952-
	Competitive inhibitors	1954-
	beta-blockers	1963-
Vasodilators -	hydrallazine	1954-
Anti-anginals		
Coronary vasodilators -	short-acting: nitroglycerine	1875
	long-acting: erythritol tetranitrate	1955-
	beta-blockers	1963-
Drugs which alter properties of the blood		
Hypolipidaemics -	clofibrate	1963
	cholestyramine	1970
Anticoagulants -	heparin	1936
	coumarin derivatives	1944-

Note: Antiarrhythmic drugs not classifiable in this way.

"Patients with pheochromocytoma have hypertension of proven neural origin. They manifest autonomic excess with alternating or persistent features of flushing, pallor, and diaphoresis ... Because many patients with primary hypertension exhibit similar autonomic features there has been a popular clinical impression that the sympathetic nervous system is important in the genesis of primary hypertension. After Von Euler characterised noradrenaline as the sympathetic neurotransmitter, the search was launched for abnormalities of noradrenaline synthesis and metabolism in hypertension. A barrage of clinical studies have been leveled at human fluids in attempts to quantitate sympathetic nervous system activity."[2]

The complex feedback mechanisms controlling hypertension have been worked out largely with the help of drugs. Their importance derives mostly from the specific alterations produced by drug therapy, shown in fig. 3.5.

The massive use of diuretics in hypertension have led to a concentration on sodium and potassium levels in the blood, the latter of which must be monitored as the increased potassium excretion produced by diuretics can be deleterious, and on the measurement of variables such as blood volume and peripheral resistance (of the blood vessels).[3] The therapeutic use of vasodilators has led to consideration of parameters such as cardiac output as well as those influenced by the thiazides.[4]

In angina the supposed therapeutic action of nitroglycerine, that is dilation of the coronary arteries, which supply the heart, led to the definition of angina as a condition in which the heart did not get enough oxygen, that is enough blood, for its needs. This also provided the direction for research into better anti-anginal drugs:

"the concept of coronary vasodilation has dominated pharmacological research for over 30 years, during which period a veritable escalade towards the most powerful and longest-acting coronaro-dilator has taken place. This tendency is seen especially in the successive development of prenylamine (1960),

Fig. 3.5 Sites of action of antihypertensive drugs

Source: A guide to beta-blockade - hypertension
Geigy Pharmaceuticals Professional Services
Publication (May 1977).

THZ - Thiazide diuretics

Bb - Beta-blockers

VD - Vasodilators

ANB - Adrenergic Neuron Blocking drugs

MD - Methyldopa

benziodarone (1958), dipyridamole (1959), carbochroman (1963) and hexobendine (1964-66). Nevertheless the concept of exclusive coronary vasodilation seems nowadays to be largely outmoded."[5]

It has been found that coronary vasodilation is not necessarily correlated with clinical benefit, though the difficulty of adequately testing such drugs are acute. Many clinicians still believe in the value of these compounds, though their efficacy has been seriously questioned by better-designed trials.

"Vasodilators still have a huge market - Persantin for example, which no-one's ever shown that it has any clinical benefit still sells a bomb because it's based on a pharmacological idea which appeals to certain medical traditions, particularly in Japan and in the Latin countries - the idea of dilating the blood vessels and flooding the tissue with more blood is very attractive."[6]

"The efforts of pharmacologists were next concentrated on the type of drug which would be capable of reducing the work of the cardiac muscle so as to reduce its oxygen requirements. This aspect was dictated mainly by the results of clinical experimentation with the nitro-derivatives, especially nitroglycerin."[7]

This showed that these drugs acted by reducing cardiac work rather than increasing blood supply. This dovetailed with Raab's speculations about the bad effects of adrenaline on the heart, and, as we have seen, laid the ground for the medical acceptance of beta-blockade in angina.

The extensive investigations which were carried out on the mechanism of action of these drugs led to the description of important related parameters in angina; left ventricular end-diastolic pressure, left ventricular stroke-work index, tension-time index and rate of change of left ventricular pressure with respect to time:

"In 1970 Cross rightly pointed out that until recently little was known about the haemodynamic and physiological events which are associated with angina. In recent years, however, far-reaching pathophysiological investigations have been devoted to this important question."[8]

The increasing use of quantitative parameters has had a very significant impact in the definition of angina, which had hitherto been notoriously diffuse and not amenable to rational therapy.[9]

In the area of anti-arrhythmic drugs, it seems that the conceptual impact of these has been secondary to the impact of diagnostic techniques such as electrocardiography, ultrasound, cardiac catheterisation etc. Rather, these drugs have provided therapeutic potential which has been analysed by these techniques, but it is the techniques themselves rather than the drugs, which have moulded medical opinion.[10, 11]

The case of drugs altering blood characteristics is different, in that their usefulness is a matter of great and continuing dispute. There are two main categories: anticoagulants and hypolipidaemics (fat-lowering agents).

Anticoagulants are old drugs - heparin was introduced in 1931, but was expensive for many years because of the cost of its extraction and purification. The first synthetic anticoagulants were the coumarin derivatives of which dicoumarol was the prototype, introduced in 1941. There was extensive interest in its use in patients who had survived their first heart attack to prevent further attacks. Its use became a standard treatment:

> "Anticoagulant therapy has become an integral part of medical practice."[12]

However, doubts of its clinical effectiveness grew:

> "We have had long-term anticoagulant therapy for 20 years, still we do not know the most simple and basic answers - is it of value at all?"[13]

The difficulty of getting evidence about the clinical effectiveness of these drugs was due to several factors. Clinical

trial techniques were still rudimentary, few anticoagulant trials were double-blind because this led to difficulties with adjusting the dose, and many doctors felt it unethical to perform such trials anyway. In the absence of good clinical data, studies of the causation of infarction were adduced as evidence of the usefulness of anticoagulant therapy:

> "Although atherosclerosis is considered a disease of multifactorial aetiology, it is highly significant that each of the seemingly different factors thought to be implicated in its causation can also be shown to have the effect, in common of increasing the coagulability of the blood. In addition, a subtle state of hypercoagulability is claimed to be detectable in a high proportion of atherosclerotic subjects. Thus there is good reason to believe that thrombosis is the key to the riddle of atherosclerosis."[14]

but the clinical validity of these experiments was debatable. Astrup comments:

> "Many investigators have tried to correlate the occurrence of arterial disease and of coronary heart disease with so-called 'hypercoagulability' of the circulating blood."[15]

and continues by showing the doubtful nature of these attempts.

The therapeutic use of anticoagulant drugs led to an increase in the medical significance of thrombosis - the 'multifactorial' nature of atherosclerosis becomes less important as blood coagulability, the parameter affected by therapy, comes to be seen as influencing the others. Finally, the needs of therapy also pointed out directions for further research:

> "Anticoagulant therapy induces a hypocoagulable state, and we hope this means an antithrombotic state. Such therapy can therefore be expected to be of value only when the cause of infarction is thrombosis. We do not know how often this occurs."[16]

> "Knowledge about the mechanism of blood coagulation and about thrombosis and thrombolysis has increased considerably over recent years. Opinions have been

> changing and new concepts have been developed. It became more and more apparent that an oversimplification had occurred, and that disappointing clinical results often could be traced to lack of understanding of the fundamental processes involved."[17]

It can be seen that research into the aetiology of heart attacks was firmly linked to the current needs of drug therapy.

The study of the role of lipids in atherosclerosis is a well-established branch of pathophysiology. This has been an academic field for many years,[18] though increasing attention has recently been paid to the possible uses of lipid-lowering drugs:

> "Most people currently believe that an understanding of lipid pathophysiology will lead to an understanding of atherosclerosis, and this in turn will lead to the possibility of controlling the progress of atherosclerosis."[19]

However, the lipid-lowering drugs that have been marketed, such as clofibrate, have not been shown to be effective in reducing mortality, so that their use has not been widespread.[20] Thus the methods and typology of lipid studies have revolved around the use of diets and genetic study.[21] It seems that this field will, however, shortly be transformed as new drugs emerge which are more effective.[22]

In summary, then, it would appear that drugs have had a major impact on concepts of disease in the areas of hypertension, angina, and, to a lesser extent anticoagulation. In the field of cardiac arrhythmias they have been overshadowed by the impact of new diagnostic technology, and in hyperlipidaemia they have as yet only had a minor influence.

4.0 Conclusions

The three main areas of this thesis, that is, the study of the innovation and use of the beta-blockers and of their effects, the evolution of the theoretical basis of that innovation, and the interactions of heart drugs and heart disease, particularly hypertension, will be discussed in turn.

A survey of literature examining drug innovation has shown that existing analyses have been limited in their scope, and that these limitations have fragmented our understanding of this area. The study of drug innovation has been largely divorced from the study of its effects, and this has led to a tendency to ignore the importance of the feedback from clinical use into the drug innovation process. Single-drug studies tend to concentrate on original drugs with considerable novelty and impact where clinical usage and refinement are not often considered. Studies of drug classes look at large numbers of very similar drugs, cite economic factors, and yet do not evaluate the therapeutic impact of this situation.

Linkage of drug innovation study with drug effect study in the case of beta-blockade shows a composite picture - the evolution from a chemical lead to a prototype drug, and by imitation and attempted refinement, to a drug class. This seems to be quite a common pattern,[1] yet it can only be described and evaluated by studies that look both at innovation and at effects.

The use of participant accounts in the study of the beta-blocker innovation has shown the importance of the social interactions between the participants in the innovation process. This is evident in Black's descriptions of his relationships with his section head, Davey, and chemist, Stephenson.

The differing views expressed on some of the key events of the innovation process show that the significance of technical events, which studies sometimes portray as self-evident, is often only recognised some time afterwards, for example the discovery of cardioselectivity, and that this recognition involves debate between these differing views. Conflict between participants also occurs, principally over differences in strategy between occupational groups with different outlooks, which are frequently unresolvable, given the hierarchical power structure within the company. This leads to a high turnover in staff which has been blamed for a lack of research continuity in development.[2] However, a considerable degree of flexibility is seen in the early organization of the project which has been shown to be an important factor in its success.

The innovation of highly original drugs has been described in terms of one person's 'genius'. In this case what was involved was a person who used already available knowledge in new ways, and who was enthusiastic enough to convince others that his ideas could work. Black's new perspectives can be partly ascribed to his unusual technical background, partly to his trust in his own intuition.

The importance of refining test methods is also very evident, the chemical lead of DCI only being recognised by its use to standardise a new test.

However, these steps were also being taken independently by workers in another company. In this case, because more local academic research had been done in this area, the project was less dependent on one person's vision and had fewer obstacles to

overcome. Thus it can be said that the innovation was 'timely' - that both the basic knowledge, and the need for its application were present.

The follow-on process, whereby other manufacturers produce similar compounds, began with the announcement of the discovery of propranolol in 1964, before the size of the market for beta-blockers was known. This was caused by the chemical interest of these compounds. This interest shown by chemists and pharmacologists was sometimes stifled by low assessments of commercial viability, as in the case of Mead Johnson, but in other cases such as practolol, where more investment had already taken place, this interest was enough to take it to clinical studies.

Clinical experimentation and feedback played a very significant role in the development of the drug class. Because of the novelty of the therapeutic action, and the potency shown by the prototype drug, enlargement of clinical use was slow, and highly dependent on a few pioneering investigators. This was particularly true of use in hypertension, which took four to five years to become an accepted use. Feedback from clinical use on the effects of the ancillary properties which had been characterised pharmacologically, led to the production of compounds with different activity profiles more suited to use in hypertension.

Differences between compounds in the drug class have been shown in the laboratory, but these have been shown to have little clinical significance. However, these differences have been widely used in marketing to suggest clinical advantages for one or other of the compounds. Thus commercial pressures have caused pharmacological differences between the compounds to be stressed, leading to clinical confusion.

The wider use of beta-blockade has been shown to be dependent on doctors' perceptions of the compounds' safety and ease of use in a situation where the prototype drug was not widely used because of doubts about these features. Follow-on compounds stressed these, and consequently gained considerable market share.

Studies on the effects of drug use suffer from severe limitations due to lack of information. Translating the volume of drug use into short-term use, long-term use, and use in different conditions is impossible without connecting diagnosis with prescription, which only special surveys can do. Thus there is a need for more co-operation between researchers and the medical profession.

The problem is an urgent one, as it is important to know what effect the large and increasing spending on drugs is having. Data on side-effects is fragmentary, based on small samples and difficult to interpret, as the format of each study is different. The national reporting system is grossly under-used and so is not a reliable source of information. Data on benefit is also only derivable from small-scale studies, and the extent to which this can be generalised has been found to be questionable.

Within these limitations two types of therapeutic impact study have been conducted, a modelling approach, using selected clinical trial information with explicit assumptions made to cover lack of information, and a statistical approach, attempting to correlate drug prescribing with reductions in mortality. The former suffers from our present uncertainty as to how much the differences between drug use in clinical trials and that in every-day medical practice affects therapeutic impact, which is an area

deserving of more attention. The latter suffers from the multitude of factors apart from drug use which affect mortality. Possibly more sophisticated epidemiological approaches taking more of these factors into account might overcome these problems.

It has also been found necessary to define closely the areas of drug impact studied. The framework presented of 'orders' of effect can be used to limit the scope of the study whilst taking into account the complex ramifications of drug effects. Many areas of these have not yet been subject to systematic study. Direct therapeutic impact, and impacts on medical literature and opinion were chosen as the most rewarding areas for the present study.

The therapeutic impact of beta-blockade has been examined by the use of clinical trial information, expert estimates, and prescription statistics. It is shown that the number of people affected by the drugs in hypertension and angina can be found by this method, and with more detailed information a comparison of costs and benefits of the drug innovation may be made.

It is concluded on the information available, that beta-blockade constitutes a significant medical advance in the treatment of these two conditions. In hypertension it is estimated that up to 1976 around 150,000 people have been affected, of whom 110,000 were previously not treated. These people were found to be trading some discomfort and psychological debility due to life-long drug taking for an additional life expectancy of 2 to 5 years, and a reduced likelihood of disablement by stroke or heart attack. Of the other 40,000, 30,000 were estimated to have transferred from methyldopa therapy. These can expect less tiredness and giddiness with probably similar reduction in mortality and morbidity. The

10,000 transferring from adrenergic neuron blocking agents can expect less giddiness on standing, and fewer digestive upsets.

In angina it is estimated that of around 170,000 people on beta-blockers 30 to 50% have their tolerance for exercise increased, and around 50% have their frequency of attacks reduced. The costs are similar to those in hypertension, but less marked, as dosage is less, so that side-effects are somewhat reduced, and the vast majority of these people will have been already taking glycerine trinitrate whose usage they will be able to decrease.

In order to make more detailed conclusions, it would be necessary to build up a picture of the spectrum of normal use; that is, the types of patients, the dosage of drugs, the amount of monitoring, and the extent of adherence, and compare this with the situations of the various clinical trial protocols, and less controlled surveys which have been done. This would enable much more accurate extrapolation from trial data. It would also be desirable to analyse in a sample of patients the subjective effects of permanent drug taking, as these subjective costs appear to be most important in the cost/benefit equation, and yet are extremely ill defined.[3]

The impacts on medical literature and opinion were found to be considerable. A large body of information on clinical use has developed, which has been shown to have exerted influence on the way in which particularly hypertension, and to some extent angina have been defined. This is discussed further later. The introduction of the beta-blockers has also improved the quality of clinical trials in angina, and popularised use of the receptor concept in drug research.

Study of the sources of the concept of receptors, the scientific work on adrenergic systems, and the influence of drug introductions and use, points to a number of interesting conclusions. The historical surveys found in scientific papers are more concerned to establish a tradition of 'correct' work leading up to the accepted present view than to present an accurate picture of events, hence they are for the purposes of this study, a misleading source of information.

Receptor concepts were derived from physiological studies involving drugs, in order to explain results, but they were not generally accepted, as they had little meaning outside this small field. Increased usage of drugs and mathematical use of receptor theory helped to increase their acceptance, but the consensus 'sympathin' theory was only displaced by the discovery of the anomalous properties of the adrenergic stimulant isoprenaline, in 1940, and a combination of more effective blocking drugs and technical methods available after the war.

Ahlquist's application of receptor theory to the adrenergic system critically depended on the new blocking drugs, but also had one of its claims disproved almost immediately by von Euler's characterisation of noradrenaline as the natural chemical transmitter in nerves. Thus it was not until the properties of DCI were described and then connected with Ahlquist's theory that it became accepted.

Both DCI and isoprenaline, and many other drugs in this field were synthesised as therapeutic compounds by the developing drug industry, which thus has had considerable influence on the development of this academic field.

In the adrenergic area, then, it has been more often the case that drugs have been directive of the production of new theory, than that the reverse has occurred. What is striking is the interdependence of drug-oriented theories and drugs, which have mutually influenced each other in this area over sixty or seventy years.

The understanding of physiological mechanisms which has evolved in this process, aided by the development of other analytic tools, is a fruitful field for the innovation of new drugs, because knowledge is already structured in an intricate relationship with the properties of drug action, thus the quest for new knowledge is already in some way linked to ideas of what the properties of new drugs might be.

The same interpenetration of technology and ideas is also seen in the relation of diagnostic technology, drugs, and definitions of disease in the cardiovascular area.

In the early period of the evolution of hypertension (1820-1915), the adoption of the diagnostic technology of the sphygmomanometer and the chemical analysis of urine were responsible for the differentiation of Bright's disease from an entity whose characterisation was based on the morbid anatomy of the kidney, into two new classes of disease: Bright's disease or nephritis, which was seen as a kidney disorder, and hypertension, a circulatory disorder. However, the invention and adoption of the technology was the material expression of the acceptance of the new physiological approach to medicine which also itself exerted considerable independent influence. Thus medical technology and medical theory are interwoven, an idea or approach implies a technology, and refinements in the technology result in refinements of theory.

In this case the widespread adoption of the sphygmomanometer resulted in the discovery of a new enigmatic clinical entity, hypertension.

The correlation of high sphygmomanometric readings with cardiac and circulatory damage and low life expectancy increased medical interest in hypertension. The contemporaneous decline in infectious disease due to public health measures and improved nutrition assisted in this process, as degenerative diseases were seen to become more serious.

The outcome of this interest was a succession of attempts at therapeutic interventions. Beginning with restrictive diets at the turn of the century, attention turned to surgery as a result of the discovery of the effects of adrenaline on blood pressure, and its control by the sympathetic nervous system. These were the first attempts at therapy to be influenced by physiological research, and though their outcome was unclear, as statistical analysis of therapy was in its infancy, surgical intervention enjoyed considerable prestige in the years before and during the Second World War in America.

In this period it can be seen that the way in which hypertension was subdivided, into 'benign' and 'malignant' forms, related as much to the characteristics of the therapy as they did to those of the disease:- that because of its expense, risk, and unpleasantness, surgical sympathectomy was reserved for those with 'malignant' disease. Benign and malignant forms were distinguished primarily by examination of damage to the arteries in the eye rather than sphygmomanometric readings. This reflected a belief that the blood-pressure reading, although important in defining the disease, was not a reliable indicator of its severity.

As familiarity with severe hypertension developed through its treatment by sympathectomy, and follow-ups of those treated showed equivocal results, increasing attempts were made to differentiate those subsets of the disease which would benefit most from treatment. With the first effective treatment for hypertension, then, came the first attempts to differentiate the disease in terms of the treatment, rather than in terms of cause or severity as had previously been done, though these two factors were still of course important.

The rapid introduction of antihypertensive drugs after the Second World War, stemming from the hypotensive side-effects of the wartime anti-infectives produced many effects, the most important of which were: that the levels of hypertension at which treatment was recommended fell as the side-effects of the drugs became less severe, and that medical strategy came to be increasingly focused on lowering blood-pressure as the most important task. The latter result came about as statistical comparisons of treated and untreated hypertensives found that drug treatment prolonged life and reduced disability.

These changes in treatment are linked with changes in perception of disease, from a clinical model of diseased or normal, to an epidemiological conception of a continuum of blood pressures. The controversy between Platt and Pickering on this matter was, it has been argued, strongly influenced by the introduction of better drugs enabling those with lower pressures, and thus less obviously 'diseased' to be treated. The surprising outcome of the controversy, that is the acceptance of an epidemiological rather than clinical viewpoint by clinicians, is understandable on the

basis of a change in doctors' experience of hypertension due to the changes in treatment mentioned. This acceptance then prepared the ground for the treatment of people with ever-lower pressures, and the larger and larger clinical trials necessary to test the smaller benefits in question.

Correspondingly, in the general area of heart disease, it has been shown that the impact of medical technology and drugs has resulted in great changes in the way heart disease has been classified, particularly the rise of arteriosclerosis and hypertension as causes of death, and the subsequent rise of ischaemic heart disease, as the role of hypertension as a risk factor for the disease became known.

Drug technology has also resulted in changes in our understanding of the diseases it is used to treat. This has been shown to be the case in hypertension and angina, where the introduction of drugs with different mechanisms of action focused the attention of doctors on the aspects of the disease process illuminated at the time. In other categories of heart disease where drugs have been less useful, they have not in general seemed to bring about similar conceptual changes.

The history of drug therapies and heart disease which has been reviewed, has pointed out the conceptual impacts which these therapies have had on medicine. This is true also of the introduction of beta-blockade. Pharmacologists at the innovating firm were aware from the beginning of the need for a convincing mechanism of action in order to market the drugs effectively. As clinical use increased more and more, attempts were made to find methods for determining which patients would respond and which would not. These become increasingly divorced from the routine treatment of

hypertension, because of the sophistication of the biochemical test methods necessary to detect differences which some investigators presented as significant. The nature of hypertension became increasingly debated in terms of these differences. It seems urgent for these conceptual impacts of drug treatment on medicine to be more widely known.

The introduction of these increasingly palatable antihypertensive drugs raises other questions. The pharmacological treatment of around 20% of the population is indicated now. With the advent of larger clinical trials studying those with lower pressures, and the rapidly increasing scale of antihypertensive treatment, what is needed is an appraisal of what the subjective costs of this are on the treated individuals.

In the words of Sir George Pickering:

> "Liberty and the pursuit of happiness tend to be utterly ignored in the treatment of hypertension ... What I fear is that over-zealous and over-eager doctors may inflict a great deal of needless suffering on their fellow human beings."

Increasingly tolerable drugs may minimise this suffering for individuals, but as we have seen, their use extends this suffering through an ever-increasing fraction of the population. Their use demands further evaluation.

Appendix I Beta-blockers - pharmacological and commercial information

Table A.1. Pharmacological properties of beta-blockers in common use

Manufacturer	Approved name	Trade name	Date introduced	Original Dosage	MSA	ISA	C/S
ICI	Pronethalol	Alderlin[1]	Nov. 1963		?	+	-
ICI	Propranolol	Inderal	Jan. 1965	10, 40			
		Berkolol	Jan. 1980	10, 40, 80, 160	+	-	-
ICI	Practolol	Eraldin[2]	June 1970	100	-	+	+
CIBA	Oxprenolol	Trasicor	July 1970	20, 40	+	+	-
Mead Johnson	Sotalol	Beta-cardone	July 1974	40, 80	-	-	-
Bristol		Sotacor	July 1974				
MSD	Timolol	Blocadren	Sept. 1974	10	±	-	-
Leo		Betim	Aug. 1978				
Sandoz	Pindolol	Visken	Dec. 1974	5, 15	+	+	-
Astra	Alprenolol	Aptin[3]			+	+	-
May and Baker	Acebutolol	Sectral	July 1975	100	+	±	?
Astra	Metoprolol	Betaloc	July 1975	50, 100	±	-	+
Geigy		Lopresor	July 1975				
Stuart (ICI)[4]	Atenolol	Tenormin	July 1976	100	-	-	+
Squibb	Nadolol	Corgard	Mar. 1979	80	-	-	-

1. Withdrawn from use for toxicity reasons 1965
2. Withdrawn from general use for toxicity reasons 1975
3. Not marketed in the UK
4. Stuart Pharmaceuticals marketing an ICI-developed compound

± = weak

Table A.I. Pharmacological properties of beta-blockers in common use

Sources: Davies, J. C. Journal of the Royal College of General Practitioners 26 219 (1976)

ND - not documented

Other estimates of

Equivalent dosages (mg)

Waal-Manning[a]	160 propranolol 12.5 pindolol	200 oxprenolol	650 practolol
Kincaid-Smith[b]	289 propranolol	58 pindolol	
Bengtsson[c]	180 propranolol	450 alprenolol	

Introduction of larger tablets

Propranolol and oxprenolol were introduced in tablets of 10 and 40 and 20 and 40 mg respectively. Larger tablets were successively introduced as the average anginal dose increased, and high doses were found effective in hypertension.

	1965	1970	1972	1974	1979
Propranolol	10.40		80 (August)		160 (February)
Oxprenolol		20.40	80 (December)	160 (September)	

This has also occurred with acebutolol, introduced as 100 mg since when 200 mg appeared in September 1976 and a 400 has recently been introduced

a. Waal-Manning, H. J. 'Comparative studies on the hypotensive effects of beta-blockers' New Zealand Medical Journal 71 383 (1970) (abstract)

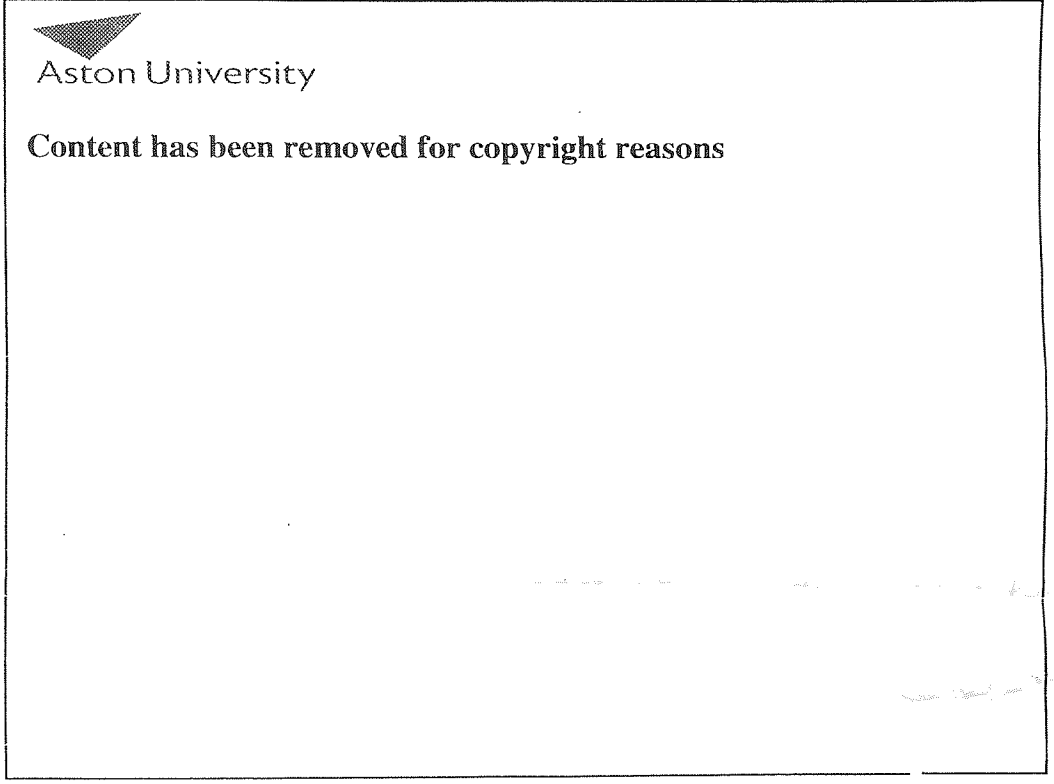
b. Kincaid-Smith, P. 'Management of severe hypertension' American Journal of Cardiology 32 575 (1973)

c. Bengtsson, C. 'Comparison between alprenolol and propranolol as antihypertensive agents' Acta Medica Scandinavica Suppl. 554 9 (1974)

Table A.II. The introduction of diuretic combinations and slow-release preparations

Trade Name	Manufacturer	Components (mg)	Date introduced
Slow-Trasicor	CIBA	Slow-release oxprenolol 160	Nov. 1976
Co-Betaloc	Astra	Metoprolol 100 Hydrochlorothiazide 12.5	Sept. 1978
Viskaldix	Sandoz	Pindolol 10 Clopamide 5	Nov. 1978
Trasidrex	CIBA	Oxprenolol 160 Cyclopenthiazide 0.25	Feb. 1979
Inderal LA	ICI	Slow-release propranolol 160	Feb. 1979
Tenoretic	Stuart (ICI)	Atenolol 100 Chlorthalidone 25	Sept. 1979
Betaloc SA	Astra	Slow-release metoprolol	Sept. 1979
Sotazide	Bristol	Sotalol 160 Hydrochlorothiazide 25	Apr. 1980
Inderetic	ICI	Propranolol 80 Bendrofluazide 2.5	June 1980
Lopresoretic	Geigy	Metaprolol 100 Chlorthalidone 12.5	Jan. 1981
Moducren	Morson	Timolol 10 Hydrochlorothiazide 10 Amiloride 2.5	Feb. 1981

Table A.III. Other beta-blockers not in common use



Source: Evans, D. B., R. Fox, F. P. Hanck, Beta-adrenergic receptor blockers as therapeutic agents, In Annual Reports in Medicinal Chemistry 14, Ed. Krapcho, L. (Academic Press 1979) p. 83.

Table A.III continued

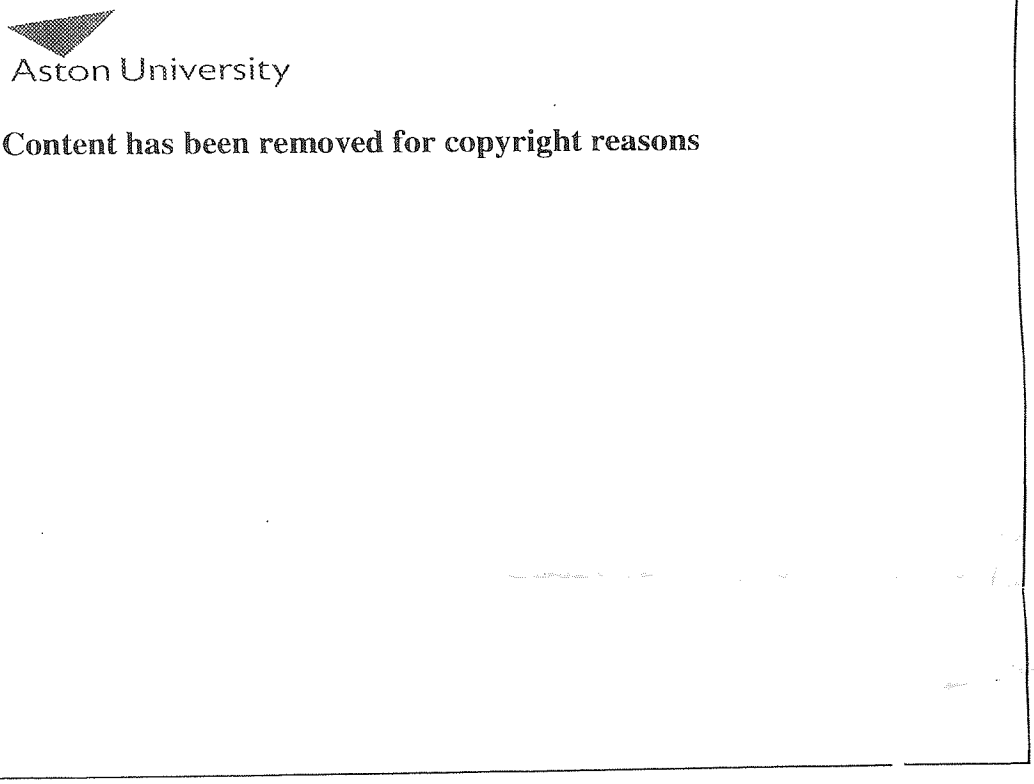
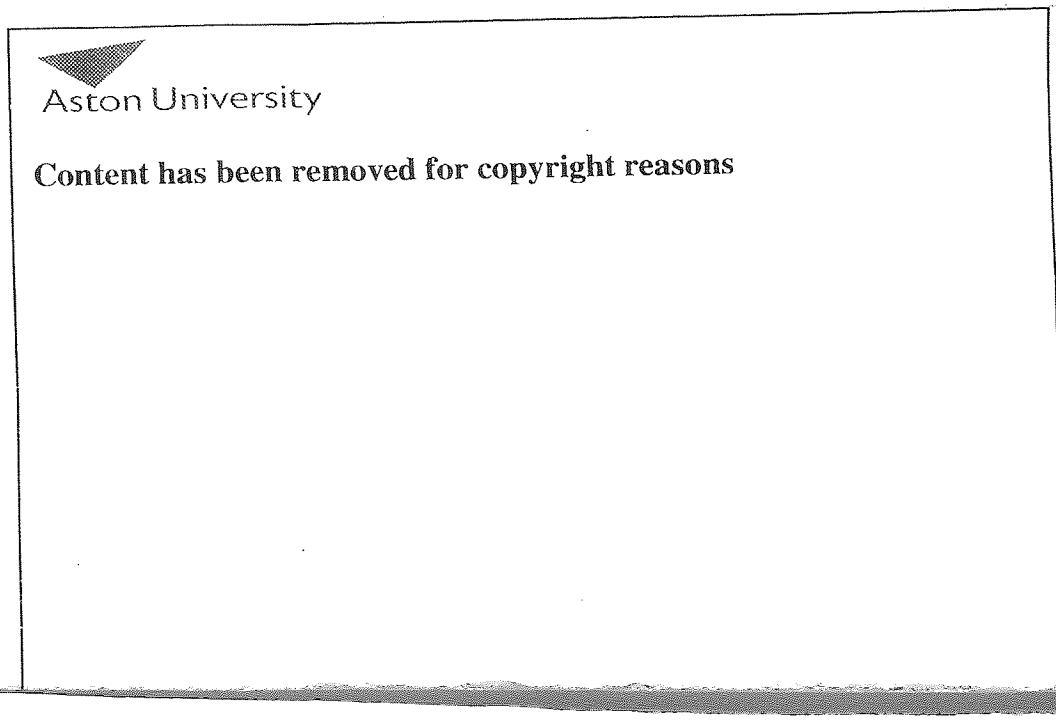


Table A.III continued

Generic Name (Inn.da)	Code	Structure	Status[a]	C/S	ISA	MSA

Table A.III continued

Table A.IV Marketed beta-blockers with low sales 1970-1975



Source: Scrip No. 168, 16 August 1975

Table AV. Beta-blocker prices, May 1980 (Monthly Index of Medical Specialties)

Beta-blockers

Name	Dose (mg)	Tablets / £
Acebutolol	100	100 / 5.82
	200	100 / 11.20
	400	28 / 6.30
Atenolol	100	28 / 6.46
Metoprolol	50	100 / 4.83
	100	100 / 8.97
Nadolol	40	100 / 10.20
	80	100 / 15.00
Oxprenolol	20	100 / 3.34
	40	100 / 5.50
	80	100 / 8.40
	160	100 / 15.12
Pindolol	5	100 / 8.32
Propranolol - Inderal	10	250 / 3.92
	40	250 / 9.21
	80	100 / 5.60
	160	50 / 5.60
- Berkolol	10	500 / 5.88
	40	1000 / 27.86
	80	500 / 21.06
	160	100 / 8.42
Sotalol	80	100 / 6.52
	160	56/ 5.87
	200	100 / 15.70
Timolol (MSD)	10	100 / 8.05
(Leo)	10	100 / 7.00

Slow-release preparations

Betaloc SA	200	30 / 7.60
Inderal LA	160	28 / 5.55
Slow Trasicor	160	28 / 6.66

Diuretic combinations

Co-Betaloc	100 / 13.32
Inderetic	100 / 9.81
Prestim	100 / 10.64
Sotazide	28 / 6.78
Tenoretic	28 / 7.26
Trasidrex	28 / 7.12
Viskaldix	28 / 6.98

Appendix II Published information on chemical work at ICI - papers and patents

This contains lists and summaries of papers in the Journal of Medicinal Chemistry written by the chemists at ICI, and patents covering their work, 1960-1966.

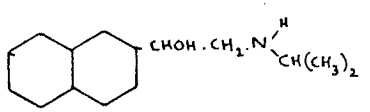
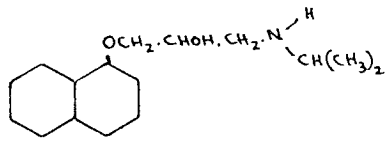
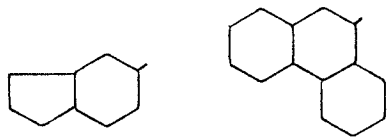
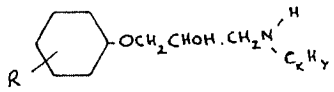
Key to abbreviations of authors' names

AFC	A. F. Crowther	AM	A. Mitchell
MSC	M. S. Chodnekar	BSR	B. S. Rao
DJG	D. J. Gilman	RPS	R. P. Slatcher
WH	W. Hepworth	LHS	L. H. Smith
AGM	A. G. MacGregor	MAS	M. A. Stevens
BJM	B. J. McLoughlin	RWT	R. W. Turner
KBM	K. B. Mallion	TMW	T. M. Wood

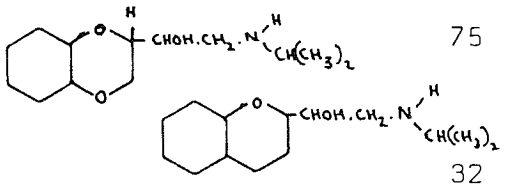
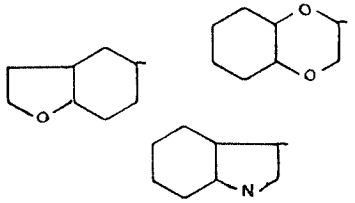
Glossary of chemical group names

Name	Structure
Acyl	$R\text{-}C(=O)$
Alkenyl	C_nH_{2n}
Alkoxy	$C_nH_{2n+2}\text{-}O$
Alkyl	C_nH_{2n+2}
Alkynyl	C_nH_{2n-2}
Allyl	$CH_2{=}CH\text{-}CH_2$
Amino	$\text{-}NH_2$
Aralkyl	 C_nH_{2n+2}
Aryl	
Cycloalkyl	Alkyl group in ring form
Haloalkyl	Alkyl group with one or more halogen atoms
Heterocyclic	Ring compound containing more than one kind of atom
Hydroxy	$\text{-}OH$
- oxy	Group with oxygen atom added
- oyl	Acyl radical formed from acid named x-oic becomes x-oyl

Table A.VI. Publication of chemical syntheses involved in the beta-blockade project in the Journal of Medicinal Chemistry

Part	Vol.	Page	Year	Authors	Subject	Typical structures	No. cpds.	Related pats.
I	11	1000	1968	AFC RH BSR LHS JSS	Pronethalol and related N-alkyl and N-aralkyl derivatives of 2-Amino-1 -(2-naphthyl)ethanol*		76	953,010 991,203 1,005,024/5
II	11	1009	1968	AFC LHS	Propranolol and related 3-Amino-1-Naphthoxy derivatives*		69	994,918
III	11	1118	1968	RH BSR	The optical isomers of pronethalol, propranolol, and several related compounds			
IV	12	452	1969	MSC RH BJM BSR LHS	Variation of the 2-naphthyl group of pronethalol*		64	984,291 998,524 1,005,026
V	12	638	1969	AFC DJG BJM LHS RWT TMW	1-Amino-3-(substituted phenoxy)-2-propanols		83	1,069,341/5 1,123,258 1,128,052
VI	12	642	1969	RH	Pronethalol and propranolol analogues with alkyl substitutions in the alkanol side-chain**		34	

Publication of chemical syntheses, continued

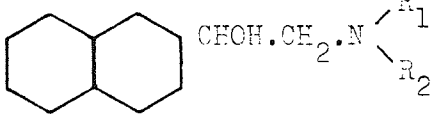
Part	Vol.	Page	Year	Authors	Subject	Typical structures	No. cpds.	Related pats.
VII	13	169	1970	RH, BSR, MSC	2(1,4 benzodioxanyl) and 2-Chromanyl analogues of pronethalol**		75	1,038,332-6 1,054,655
VIII	13	398	1970	RH	Reactions of beta-halo-alkylamines related to pronethalol and propranolol*		32	1,005,021
IX	14	326	1971	MD, LHS	Absolute configuration of propranolol and of a number of related aryloxypropanol-amines and arylethanolamines			
X	14	511	1971	AFC, RH, LHS	(3-Amino-2-hydroxypropoxy) anilides++			
XI	15	49	1972	MSC, AFC, WH, RH BJM, AM, BSR, RPS, LHS, MAS	Heterocyclic analogues of pronethalol**		32	1,013,224 1,019,225 1,135,340
XII	15	260	1972	AFC, RH, BJM, KBM, BSR, LHS, RWT	Heterocyclic compounds related to propranolol***		83	1,021,522 1,047,927 1,058,822 1,089,769 1,129,072

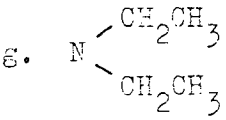
* Tested by Black and Dunlop
** Tested by Black, Shanks, Dunlop
*** Tested by Shanks, Duncan, Carter
++ Tested by A. M. Barrett, D. Dunlop, R. G. Shanks

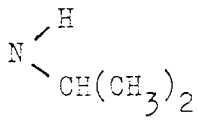
Outlines of structure-activity relations in Journal of Medicinal Chemistry

Part I

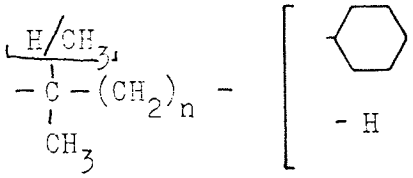
Initial chemical effort went into modifying the N-substitution. They found that disubstituted compounds (I) were only weakly active. In a series of 76 compounds they conclude that greatest activity was associated with a branched alkyl chain, where the α-carbon substituent was methyl (II) and that this activity was maintained if a phenyl group was added on the end of the chain. If there was no ring in the chain activity was maximal at C_{3-4}, if there was activity was found even at C_6.



I E.g. 

II 

In summary, activity similar to pronethalol was found in those compounds where R_2 =



where n = 1, 2, 3
- if phenyl 4 also

This is similar to the structure-activity relations of the β-stimulant analogues of isoprenaline.

Part II

Similar structure-activity relations already found for aryl-ethanolamines also hold for these compounds. N-disubstituted compounds were moderately active, aryl substitutions were inactive, aralkyl active.

Substitutions in the ring were not very active
52 compounds made exploring N-substitution.
16 compounds made exploring ring substitution.

Part III

Howe's work showed that the laevo-isomer (that which rotates plane of polarization of polarized light beam leftwards) was 40 times as active as the dextro-isomers.

The stimulus for the work was to see whether blocking activity was in one isomer, and with DCI whether the ISA was the same isomer as beta-blocking activity.

Part IV

Alterations in the nucleus of pronethalol, by substituting a 5-membered ring for one 6-membered, or by adding other rings did not increase activity, and if bulky groups were used, decreased it.

Part V

If the ring group in propranolol furthest from the side-chain was removed, and various substitutions in the resultant phenoxy-propanolamine molecule tried, many highly active compounds resulted

Compounds with 2 or 3-substituted halogens, methyls, alkyloxy, hydroxy, aryl and aryloxy all highly active, 2-substituted not as active. Disubstitution on 3,5 most active, even some trisubstitutions were quite active.

Part VI

Substitutions in the side-chain proved to be in general less active.

Part VII

"When it became clear that compounds of the propranolol type were considerably more potent as beta-adrenergic blocking agents than those of the pronethalol type, it became of interest to prepare 1-4, benzodioxan and chroman analogs which contain features of both types."

The benzodioxan series produced compounds with the highest potency so far seen - 5 to 10 times that of propranolol. The chroman compounds were approximately equivalent to propranolol.

Part VIII

This work was done by Howe in order to clear propranolol of the carcinogenic associations with pronethalol, especially for the FDA. The compounds were used as intermediates.

Part X

Following the substitution of the RCONH- group into the phenoxypropanolamine molecule, variations were tried producing a range of selective blockers. Movement of the 4-RCONH group to the 3 or 2 position resulted in a loss of selectivity.

Part XI

The naphthalene ring of pronethalol can be replaced by many heterocyclic ring systems to give compounds which have the same level of potency. All more potent compounds contained features of the potent benzodioxan and chroman analogs already described.

Part XII

The replacement of the naphthalene ring of propranolol by a variety of heterocyclic ring systems is also possible without loss of activity.

Table AVII

ICI patents covering beta-blocking compounds:-

chronological list by date of application

1960:	May	909,357
1961:	May	953,010
	Sept.	1,024,643
	Oct.	1,005,021
	Oct.	1,005,022
	Oct.	1,005,023[p]
	Nov.	1,005,024[p]
	Dec.	1,018,113
	Dec.	984,291
	Dec.	990,061
	Dec.	1,005,025
1962:	Jan.	998,524
	May	991,203[p]
	May	1,005,027[p]
	May	984,306[p]
	May	1,019,772
	May	991,140[p]
	June	1,013,224
	Aug.	1,005,026
	Aug.	1,028,812
	Aug.	1,028,813
	Sept.	1,024,914
	Oct.	1,019,225
	Nov.	994,918
	Nov.	995,800
	Dec.	1,069,341
	Dec.	1,069,345
1963:	Feb.	1,038,332
	Feb.	1,038,333
	July	1,058,822
	July	1,069,342
	Sept.	1,069,343
	Dec.	1,038,334[p]
	Dec.	1,038,335[p]
	Dec.	1,038,336[p]
1964:	Jan.	1,054,655
	Jan.	1,059,968
	Mar.	1,047,927
	Apr.	1,069,411
	Oct.	1,078,852
1965:	Feb.	1,079,584[p]
	Mar.	1,062,354[p]
	Mar.	1,066,613
	June	1,089,769
	June	1,128,052
	June	1,136,919
	Sept.	1,123,258
	Sept.	1,079,989
1966:	Feb.	1,129,072
	June	1,136,918
	Dec.	1,135,340

p indicates a patent covering prccess rather than pharmacologically active compounds.

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