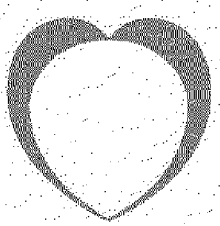
Research Annual Report 1978



Baker Institute
Alfred Hospital

Annual Report 1978 Baker Medical Research Institute

Affiliated with Monash University

This report provides audited accounts and details of scientific activity in the calendar year 1978. It reports on new people joining the Institute and planning during the first half of 1979.

Fifty-second Annual Report of

THE THOMAS BAKER, ALICE BAKER and ELEANOR SHAW MEDICAL RESEARCH INSTITUTE

Thirtieth Annual Report of

THE ALFRED HOSPITAL CLINICAL RESEARCH UNIT

Twenty-second Annual Report of

THE EWEN DOWNIE METABOLIC UNIT

Report of

C. J. OFFICER BROWN CARDIOTHORACIC SURGICAL UNIT

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CONTENTS

Professor P. I. Korner

DIRECTOR'S REPORT

During 1978 several new laboratories were established and these have greatly increased the breadth of our approach and enhanced our technical capabilities. The Baker Institute is now Australia's largest cardiovascular research institute. Its main work is in the field of blood pressure control and hypertension and disturbances of fat metabolism and atherosclerosis. In 1978 it employed a staff of 73 people and its expenditure was $1,227,375. Because of the increase in complexity of the scientific and business affairs of the Institute the Trustees considered it desirable to establish a Business and Management Committee to provide a wide range of counsel and advice. This committee, consisting of the Trustees of the Institute and Mr. W. D. McPherson, Mr. John Moir (who became a Trustee in February 1979), Mr. L. M. Muir and Sir John Reid, met for the first time in February 1978, and has met at two-monthly intervals since. Amongst the questions they have been studying is that of incorporating the Institute under its own Act of Parliament and it is hoped that this will lead to enlargement of the board of management and facilitate its work.

The new laboratories established since the last report include (in chronological order) a Morphology and Cell Biology laboratory, an Experimental Cardiac Surgery laboratory, and a Nutrition laboratory and laboratories in Clinical and Basic Cardiovascular Pharmacology. All of them have been staffed by outstanding young Australian scientists returning to Australia after a period of study abroad. The Morphology and Cell Biology laboratory was established by Drs. Gordon and Julie Campbell who returned to Australia in January 1978 after holding respectively National Heart Foundation and Life Insurance Medical Research Fund Overseas Fellowships. Their expertise is in the fields of electronmicroscopy and tissue culture and an important aspect of their own research deals with the changes in vessel structure in hypertension and with the cellular factors important in the development of the atherosclerotic plaque. The laboratory also fulfils an important service function and has greatly heightened the awareness of all other groups of the importance of studying structural changes in relation to a considerable range of problems.

In March 1978 Dr. Kerin O'Dea joined Dr. Nestel's Cardiovascular Metabolism and Nutrition Research Unit. Dr. O'Dea is a nutritional biochemist interested in the role of diet in insulin secretion and the development of diabetes and in the binding of insulin to cell membranes. There is no doubt that much needs to be done to explore the role of nutritional factors in the development of atherosclerosis and the role of diet in its prevention. Much research is still needed in this area and an extension of our activities in the field of nutrition is therefore timely.

An Experimental Cardiac Surgery laboratory was established early in 1978 by Mr. Frank Rosenfeldt who joined the Baker Institute and C.J. Officer Brown Cardiothoracic Surgical Unit as Edward Wilson Research Fellow. The Experimental Cardiac Surgery laboratory is the first established in Australia. One of the big problems of open-heart surgery today has been the relatively high incidence of damage to the heart muscle that occurs either during or immediately after the end of the operation. One of Mr. Rosenfeldt's particular interests is to explore new methods which will minimize the degree of damage which the heart, that has already been damaged by the disease processes, can ill afford to sustain. Apart from making operations safer, such research should lead to better long-term function and even survival after coronary artery by-pass surgery.

The creation of an experimental heart surgery laboratory has reactivated a long-standing association between the Baker Institute and Alfred Hospital. In the 1950's the laboratory work in open-heart surgery at the Baker Institute helped the introduction of open-heart surgery at Alfred Hospital. The Hospital was the first to introduce this dramatic and exciting new form of treatment in Australia. With the greatly increased numbers of open-heart operations in recent years, largely due to the demands for coronary artery surgery, the establishment of an experimental laboratory devoted specifically to the analysis and solution of pathophysiological problems associated with the surgery has become most important. Its siting in the Baker Institute is advantageous since the know-how and technical resources of the Institute make it far easier to begin work in this area than if it were established on its own in a university department of surgery. There is a very great need to have this type of facility in Australia, and we are currently exploring new sources of funds for this work to continue it beyond the end of 1979 when the Edward Wilson Fellowship expires. This Fellowship has been granted through the Alfred Hospital Research Fund. The maximum period of award is for two years, and it has been invaluable in this instance to allow the introduction of an area of applied research at Alfred Hospital, which is likely to lead to substantial improvements in long-term results of open-heart surgery.

The year saw the establishment of two cardiovascular pharmacology laboratories. In June 1978 Dr. Allan McLean returned from the United States where he held a National Health and Medical Research Council Fellowship in Clinical Pharmacology in San Antonio, Texas, and at the State University of New York at Buffalo. He had previously worked at the Alfred Hospital as registrar in the Clinical Research Unit and helped in the establishment of a diagnostic toxicological service. His main interest is in the alterations in drug kinetics and metabolism in cardiovascular disease and in renal and liver disorders. There is great need for better understanding of pharmacological principles by clinicians and the arrival of Dr. McLean at the Baker Institute and the Clinical Research Unit will undoubtedly help to lead to a more rational use of drugs in the Hospital. A laboratory in basic cardiovascular pharmacology was established in January 1979 when Dr. James A. Angus returned from a period of two years research as C. J. Martin Overseas Research Fellow of the National Health and Medical Research Council in Dr. James Black's laboratory in Britain. His main interest is in mechanisms of action of drugs that alter peripheral and central nervous autonomic function. Dr. Angus previously worked at the Baker Institute in 1975/76 and did some outstanding studies on the cardiovascular effect of histamine and on hypertension. The establishment of a basic pharmacology laboratory is of great importance in the development and analysis of the properties of new drugs. Basic and clinical pharmacology subserve a complementary function and it is important that both should be established at the Baker Institute.

At the beginning of 1978 Mr. Michael Downes assumed his duties as Financial Director of the Institute. Mr. Downes has streamlined and improved the business practices and has relieved me of a great deal of administrative work. Through his efforts our scientific work has become better known to the public. This is a matter of the utmost importance since the support of scientific research in the end depends on the scientist's capacity to convince the public that increased knowledge gained is beneficial not only for its own sake but in providing answers to some of the great health problems in the community. The need to explain what we do is now more important than ever before, since the present time has seen much activity by vocal minority groups clamouring for rejection of scientific thought and identifying it often as something impersonal and destructive. Such clamours have also occurred in relation to scientific medicine and it is in the national interest that scientists should learn to explain the aims and results of their work to laymen as well as to their fellow scientists. Mr. Downes' previous experience in the public relations field has greatly strengthened our dormant capacities to do this in simple jargon-free terms. He has introduced monthly tours of the Institute by community and business leaders, with excellent displays which demonstrate aspects of the basic and applied research going on in the Institute.

Our income from various grant sources has increased during the year. It is particularly pleasing that the State Government of Victoria has been sympathetic to our needs and has made grants totalling $130,000 during the 1978 financial year. An event of great importance has been the award by the National Health and Medical Research Council of a Programme Grant on 'Autonomic and Renal Control of Blood Pressure'. The award is for five years at $250,000 per annum. It covers aspects of the work undertaken by the Hypertension and Circulatory Control

Research Unit, including some collaborative research with Professor Colin Johnston's group from Monash University. As a result of this grant the funding of the salaries of some of our key research workers supported by N.H. & M.R.C. has become more secure which is a very great advantage. However, the grant still only meets about 60% of the actual cost of running the Hypertension and Circulatory Control Research Unit and makes no provision for even a modest increase in activity over the next five years. Such an increase is almost inevitable in a successfully operating research unit and it is hoped that N.H. & M.R.C. may modify some of their existing policies concerning Programme Grants. Work of the Cardiovascular Metabolism and Nutrition Research Units and of Dr. Campbell's laboratory has also received good support through three year N.H. & M.R.C. project grants, and it is hoped that long-term funds will also become available. At present the National Health and Medical Research Council seems reluctant to increase the number of Institute Grants such as those offered to the Walter & Eliza Hall Institute and the Howard Florey Institute. The new type of Programme Grant could be a real alternative to these, but they need to be substantially larger to provide really effective support for the type of multidisciplinary research performed in an institution such as the Baker Institute.

We continue to receive support for specific projects from the National Heart Foundation and Life Insurance Medical Research Fund. It is particular pleasure to record our thanks to the many organisations and individuals that have made grants to the Baker Institute. These are listed elsewhere in the Report. I want to mention specially the support of the Ian Potter Foundation which has allowed us to install two computer terminals linking the Baker Institute with the Computer Centres at Melbourne and Monash Universities, and the support of the Utah Foundation which made possible the purchase of a Fluorescence Microscope.

The demands for new laboratory space this year have effectively disposed of all available space in the Baker Institute. However, some additional space will become available after November 1980. It was possible to complete the so-called 'Future Area' on the lower ground floor of the Institute and the space (130 sq. m.) will be rented to the Antarctic Division of the Commonwealth Department of Science until the above-mentioned date. In co-operation with the Alfred Hospital plans were completed during 1978 for extending the Hospital's Biology Research Unit for housing animals. This was necessary because our current facilities are no longer adequate to cope with the continuously increasing demand resulting from the establishment of new laboratories. A tender for the extensions has been let and the building will start in May/June 1979. The project has been made possible because the Trustees of the Institute supplied $200,000 towards the project and the Victorian Government has generously made available a grant up to $240,000 to cover the balance of the amount.

In conclusion, 1978/79 has seen considerable diversification of our research activities. What is of the greatest importance is that the work done at the Institute is highly regarded internationally. This is evident from the increasing number of our staff members invited to participate in important meetings and to contribute to 'state of the art' publications. Another indicator is the increasing number of scientists from overseas coming to the Baker Institute for collaborative research.

People

Sir John Reid
Business Management Advisory Committee

Sir John Reid, C.M.G.

Sir John was educated at The King's School, Parramatta, N.S.W. and Edinburgh Academy in Scotland. He commenced in a junior position at James Hardie & Co., Sydney in 1923 and became Chairman of the Board in 1946 until 1973. He has held directorships of many companies, has chaired the Finance Committee, University of Melbourne, Conservatorium and was Vice Chairman of the Australian Broadcasting Commission 1967-71.

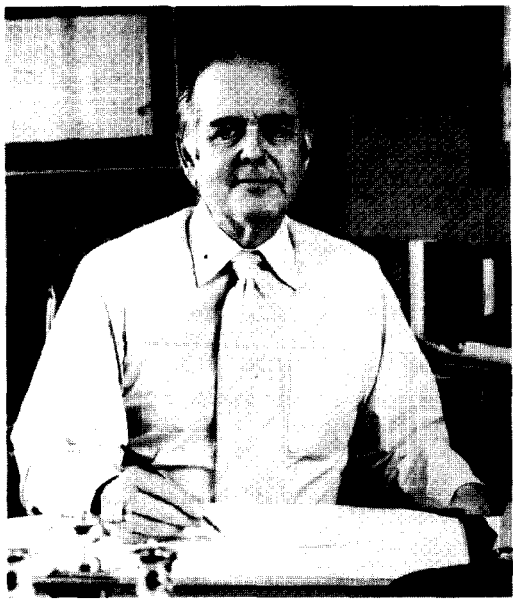
In the community service, Sir John is President of St. George's Hospital and has served on the Board since 1957. He is involved with the Y.M.C.A. (1946-76) and The Victorian College of the Arts since 1973.

Sir John was awarded the Companion of the Order of St. Michael and St. George in 1971, Knight Bachelor for Service to the Community and to the Arts 1974, holds honorary degrees Doctorate of Laws, Melbourne University, Doctorate of the Arts and Sciences, Victorian Institute of Colleges. He was the recipient of the Rotary Vocational Service Award 1978.

Sir John's distinguished service in industry, the arts, education, charitable activities and international commercial affairs for over half a lifetime has undoubtedly contributed greatly to the development of scientific and cultural activities in the community.

We are indeed proud to have Sir John Reid join the Baker Institute as a member of the Business Management Advisory Committee.

People



Professor R. R. Andrew, A.O.
Trustee

Professor R. R. Andrew A.O. — Trustee

Emeritus Professor Rod Andrew became a Trustee of the Baker Institute in 1960. His interest in the Baker Institute also involved participation in research projects part-time over many years, and holding a Sol Green Fellowship here during 1951-55.

He was Honorary Physician Alfred Hospital 1947-60, Dean of Medicine, Monash University 1960-76, Director Australian-American Educational Foundation 1964-76 (Chairman 1970-76), member Board of Management, Queen Victoria Medical Centre 1961-78. He served in the A.I.F. 1939-46 as Lt. Col. R.A.A.M.C.

Professor Andrew is presently the Director of Medical Education at St. Francis Xavier Cabrini Hospital.

His long standing interest in medical science and his work as a Trustee has contributed over a long period to the recognition and success of the Baker Institute.

Professor G. C. Schofield
Trustee

Professor G. C. Schofield — Trustee

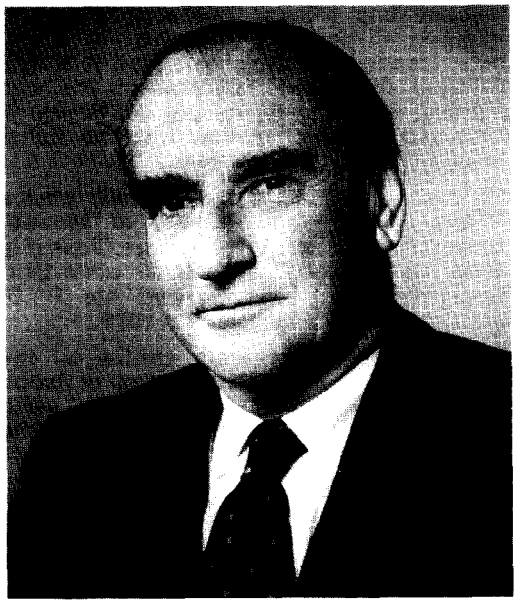
Graeme Schofield is Dean of Medicine at Monash University, an appointment he took on the retirement of Professor Andrew in 1976. He was formerly Foundation Professor of Anatomy at Monash University since February 1961.

He is a member of the Boards of Management of Alfred Hospital (as from 1978) and the Queen Victoria Medical Centre (as from 1977) and a member of Council of the Victorian Branch of the Australian Medical Association.

He is a member of the National Health and Medical Research Council (representing Universities with Medical Schools) and of the executive of the Medical Research Advisory Committee and is Chairman of the Project Grants Committee of the N.H. & M.R.C.

His research interests are in experimental cytology with particular reference to microspectrofluorometric analysis and analysis of cellular function. We are fortunate to have Professor Schofield as a trustee of the Baker Institute.

People



Dr. H. B. Kay, A.M.
Trustee

Dr. H. B. Kay, A.M. — Trustee

Dr. Kay has enjoyed a long and distinguished association with the Alfred Hospital and Baker Institute. He was appointed an Honorary Physician in the Hospital in 1946 and made an Honorary Fellow of the Clinical Research Unit in 1948.

In those early associations Dr. Kay worked at the Baker Institute part time on projects related to perfecting the techniques of Cardiac Catheterisation. He is now a widely respected cardiologist in Melbourne.

He served in the AIF 1940-46 as a Major in the R.A.A.M.C. He was elected to the Hospital Board of Management in 1972, made a consultant in 1975 and has been a Trustee of the Baker Institute since 1977.

He is President of the Australian Postgraduate Federation in Medicine, Vice President of the National Heart Foundation (Victorian Division) and a member of the Board of Directors of the NHF. Dr. Kay's contribution to the success of the Baker Institute is most appreciated.

Mr. L. M. Muir
Business Management Advisory Committee

L. M. Muir

Lawrence Macdonald Muir is one of this country's most highly regarded businessmen and we are delighted that he is a member of the Institute's Business Management Advisory Committee.

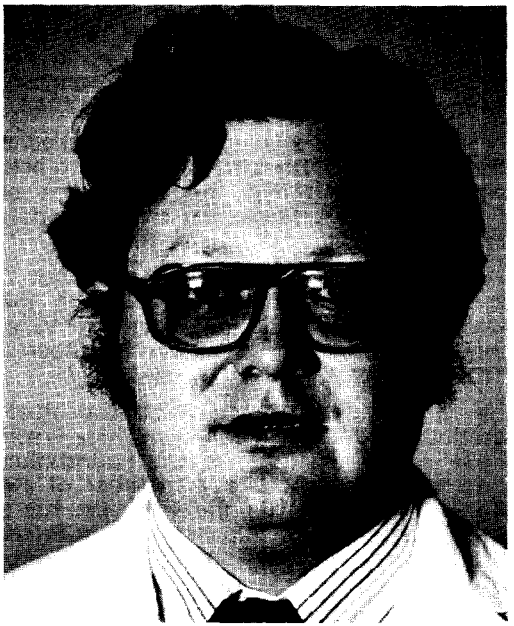
He was born of Scottish parents in Victoria, served in the Royal Australian Navy 1942-46, retiring as Lieutenant Commander.

He completed a Law Degree at the University of Melbourne 1949, and has been active in the sharebroking profession since 1950, specialising in corporate financing and underwriting activities. Member of The Stock Exchange of Melbourne Ltd. since 1960, Partner of Potter Partners since 1962 and Senior Partner since July 1976.

Mr Muir's work in community service includes membership of the Anti-Cancer Council, National Heart Foundation, Alfred Hospital Board, Australian Opera, Australian National University Council, Parliament House Construction Authority and he is Chairman of the Microsurgery Foundation, Australian Olympic Team Fund (Victorian Committee), State Library and National Museum Buildings Committee.

In his University days he was a member of University Blacks A Grade premiership football teams and represented Victoria.

People



Dr. Allan McLean
Clinical Pharmacology

Allan McLean

Allan McLean has returned to the Baker Institute and Clinical Research Unit after studying Clinical Pharmacology in U.S.A. and Canada while holding a N.H. & M.R.C. Clinical Sciences Fellowship. He was Medical Registrar to the Clinical Research Unit and Research Fellow with the Baker Institute before going overseas.

He graduated B.Sc. (Med) in 1966 after a Pharmacology Honours year at Monash University, then MB.BS (Honours Class I) in 1968. He obtained his MRACP while CRU Registrar and was awarded his Ph.D. through Monash Physiology in 1976.

Basic research interests centre on the pharmacology and local control of blood vessels with continuing interest in using vasodilator drugs as research tools into vascular contractile mechanisms.

Relaxations include tennis, cross-country skiing, bicycling with his wife and three sons, and continuing service as an untreated control for the Lipid Metabolism and Clinical Nutrition Unit.

Dr. Mohammed Fahim
Visiting Scientist

Mohammed Fahim

Dr Mohammed Fahim came to the Baker Institute for a period of 12 months from the Vallabhai Patel Chest Institute, University of Delhi, India. Originally a graduate in physics he changed to physiology and graduated Ph.D. from the University of Delhi, working in Professor Autar Paintal's laboratory. Whilst at the Baker Institute, he worked on the role of dietary salt in experimental hypertension and on its effect on cardiovascular reflexes.

Dr Fahim returned to India in May 1979.

People

Dr. Murray Huff
Visiting Scientist

Murray Huff

We are pleased to have Murray Huff with us for a period of two years as a visiting scientist. Murray holds a post-doctoral fellowship from the Medical Research Council of Canada.

He is Canadian-born and graduated with B.Sc. (Honours) in Biochemistry at McMaster University, Hamilton, Ontario. He received his Ph.D. in 1978 from the University of Western Ontario.

Murray's research interests are the relationship between nutrition and cardiovascular disease and he is working with Dr. Nestel's Unit on this question. His wife and six months' old daughter are with him in Australia.

Dr. Noel Fidge
Lipoprotein Studies

Noel Fidge

Noel graduated from Adelaide University (B.Sc. Honours) in Biochemistry and then completed a Ph.D. on lipid synthesis in macrophages. He was awarded a Life Insurance Medical Research Fund Overseas Fellowship 1966-68 and worked with Dr. De Witt Goodman at Columbia University, New York on Vitamin A Metabolism.

After returning to Australia, he spent a short time at Melbourne University before joining Paul Nestel in the Clinical Science Department at the John Curtin School of Medical Research, Canberra. Together they combined a biochemical and clinical approach to investigate the role of lipoproteins in cardiovascular disease which has continued at the Baker Institute since 1977.

Those who remember Noel playing piano at the recent Baker Revue, will agree that he is a brilliant musician who must have once had a difficult decision whether to follow a professional career in music or science. We're glad we won.

People

Dr. Patricia Dorward
Neurophysiology

Patricia Dorward

Patricia, much travelled daughter of a RAMC Surgeon, obtained her BA at Cambridge (Natural Science Tripos) in 1961. She received her Ph.D. from the Physiology Department, Monash University in 1966 for neurophysiological studies on mechano-receptors and subsequent work with Professors McIntyre and Holman. After the birth of her two daughters, she continued as part-time demonstrator and tutor at Monash.

In 1977 she joined the Baker Institute to help set up a neurophysiology laboratory with the aim of recording electrical activity in baroreceptor and sympathetic nerves. These techniques are important for studying the role central noradrenergic neurons play in the control of blood pressure.

Patricia lives with her family on a small property in Warrandyte and when she is not at work or driving to and fro, she is interested in breeding horses, riding with her daughters and renovating the homestead.

Dr. Walter Riedel
Visiting Scientist

Walter Riedel

Walter Riedel is a visiting fellow at the Institute with particular research interests on autonomic nervous control of temperature homeostasis.

He graduated M.D. at the Vienna University in 1962 and then spent 8 years in clinical medicine at Salzburg, Vienna, Dundee (Scotland), Nicosia (Cyprus). Since 1970 he has worked at the Max-Planck Institute for Physiological and Clinical Research in West Germany. He also teaches Physiology at the University of Giessen.

His many travels on joint research work have taken him to the University of Kiel (1975), and Tokyo Metropolitan Institute of Gerontology (1978). We welcome him now at the Baker Institute.

Walter is married with three children and enjoys mountain and rock climbing as well as skiing.

People

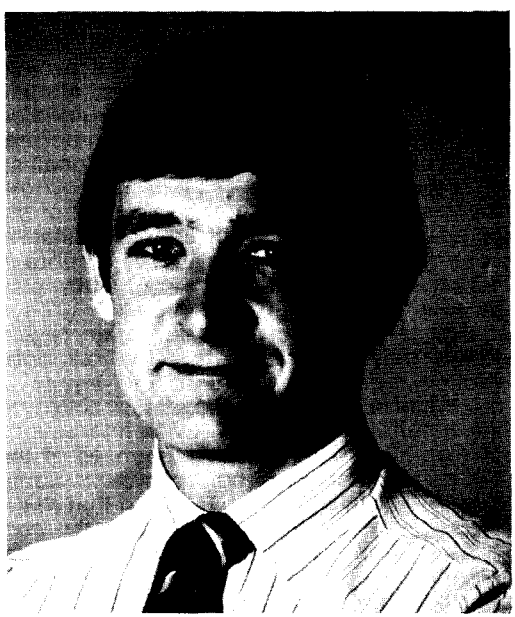
Dr. Warwick Anderson
Renal Hypertension

Warwick Anderson

Warwick graduated B.Sc. (Honours 1) in Physiology from the University of New England N.S.W., in 1968 and obtained a Ph.D. from the University of Adelaide in 1973. He worked for over two years at Harvard Medical School and then joined the Hallstrom Institute in Sydney to work with Professor Korner. He arrived at the Baker Institute with the others of that group in 1975.

His research interests centre on the Kidney and its control of blood pressure. In a period of seven weeks during 1978 he presented his work at many major centres in the U.S.A. with considerable success.

Warwick keeps fit playing squash and bicycle riding but then probably undoes it all wine drinking. This is a subject about which he is quite knowledgeable. He produced our two theatrical productions at the Institute in 1976 and 1978, and intends doing it again in 1979.



Dr. Jim Angus
Pharmacology

Jim Angus

Jim graduated B.Sc., Ph.D. in Department of Pharmacology, Sydney University and first joined Professor Korner's research group at the Hallstrom Institute in 1973. He moved with those who migrated to the Baker Institute when Professor Korner was appointed Director in 1975.

In 1977, Jim Angus was awarded the prestigious C. J. Martin travelling Fellowship of the National Health and Medical Research Council. He used this to study and work with Professor James Black, of University College, London. In 1978 he moved with Professor Black to the Wellcome Research laboratories in Kent to direct his Explanatory Research Group. Jim returned to the Baker Institute in January this year to establish a basic Pharmacology Unit with interests in neuro-humoral transmission and cardio-vascular histamine receptors.

Jim is married, with three children and enjoys golf, fishing and the odd work out on a bicycle.

Hypertension and Circulatory Control Research Unit

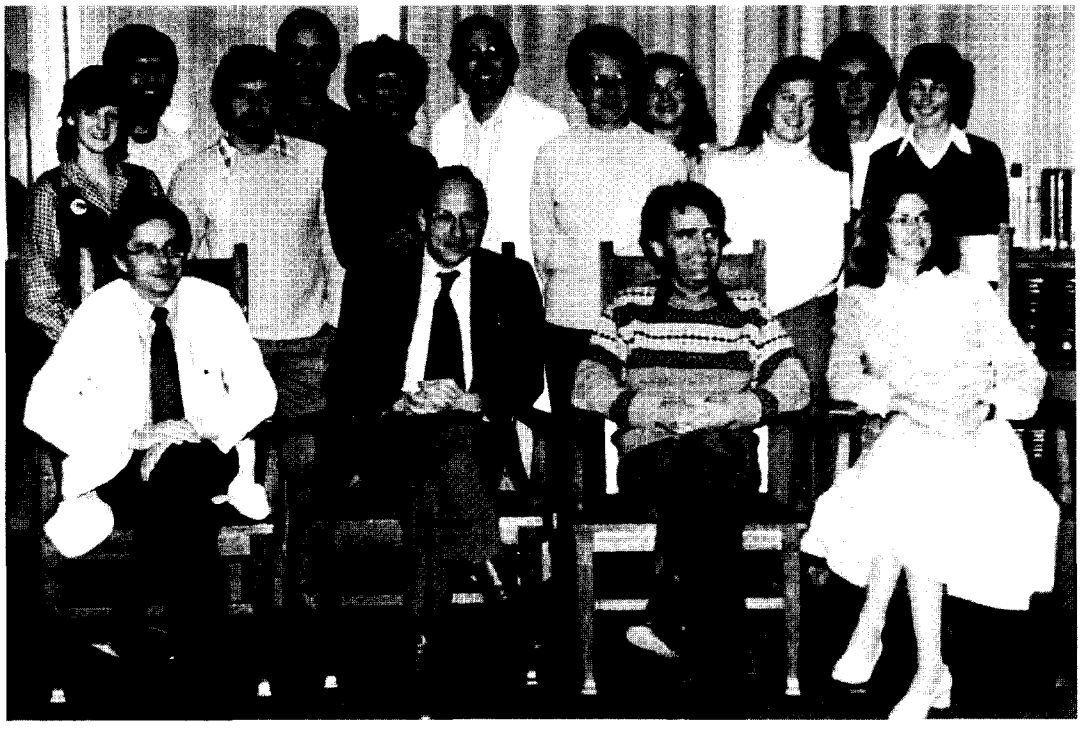
* NERVOUS CONTROL OF THE CIRCULATION
* KIDNEY AND HIGH BLOOD PRESSURE
* ROLE OF SALT
* HEART AND HYPERTENSION

Nervous Control of the Circulation

One of the theories about the causation of essential hypertension in man has been the view that overactivity of the sympathetic nervous system is the trigger mechanism in the elevation of blood pressure. Until recently the chief techniques available have been comparisons of a variety of reflex responses between hypertensive and normotensive subjects. These methods examine the degree of vascular narrowing induced by a given change in blood pressure. Information about blood pressure changes in the body reaches the nervous system from several groups of pressure-sensitive receptors located in the main arteries and in the chambers of the heart. These alter the activity of several circulatory 'centres' in different regions of the brain which in turn influence the rate of discharge of the sympathetic nerves going to the blood vessels and heart. The above studies have suggested that the vessels of hypertensive patients may constrict more than those of normotensive subjects in response to a particular stimulus. However, the main reason for such over-reactivity are structural changes in the vessels themselves, with hypertrophy of the media in response to chronic load produced by the high blood pressure. It is not possible to conclude by using the above methods whether the over-reactivity is entirely due to structural factors or whether there is also a component of increased sympathetic activity.

Because of the above limitations and because it is difficult to record sympathetic neural activity directly in man attempts have been made to characterize the degree of sympathetic activity from the analysis of the plasma concentration of the chemical transmitter — noradrenaline — released at the sympathetic nerve ending. Some workers have found that in a proportion of patients with essential hypertension plasma noradrenaline is elevated and they have considered this as evidence of sympathetic overactivity. However, this interpretation is somewhat simplistic. The plasma noradrenaline concentration is the resultant between the amount of transmitter released, and its rate of removal from the bloodstream. Drs. Murray Esler, Alex Bobik and Graham Jackman and other members of the biochemical pharmacology staff have developed assays over the last two years which allow the separate determinations of the apparent 'secretion' rate of noradrenaline into the bloodstream and its rate of removal. Determination of the noradrenaline 'secretion' rates in normal subjects and in patients with essential hypertension has shown that this is raised in about one-quarter of the hypertensives. Studies are in progress attempting to determine whether this elevation is causally related to the raised blood pressure or whether it is a secondary consequence of hypertension. This is a challenging and difficult question. In addition, we are studying a simpler and more practical question — whether the subset of patients with enhanced 'secretion' of noradrenaline respond better to drugs which depress sympathetic nerve function than those patients with hypertension in whom sympathetic overactivity is absent.

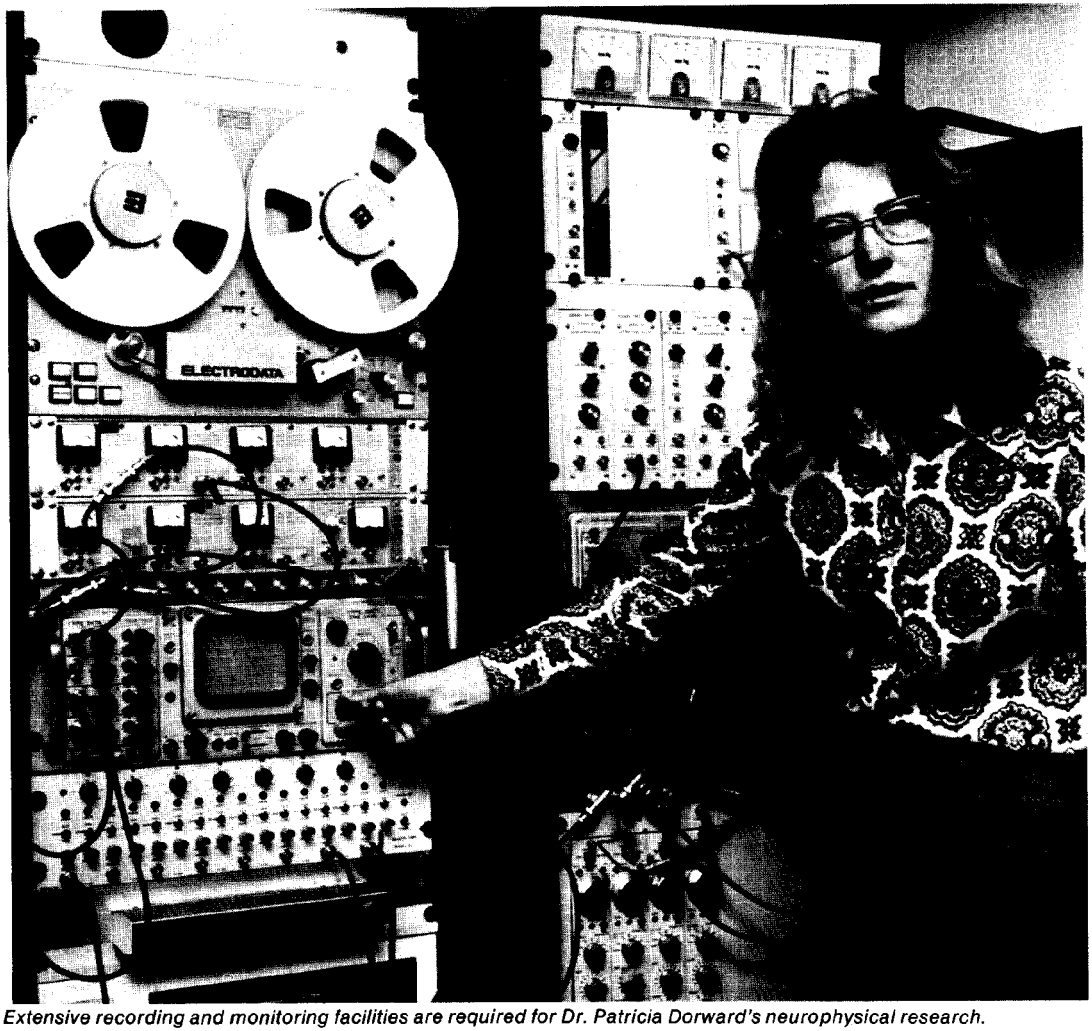
The methods available for studying autonomic nervous function in man are much more limited than insights available from studies in animal experiments, where detailed neurophysiological and neuropharmacological analysis has allowed us to develop more elaborate models about the operation of the central nervous system in circulatory control. In our laboratory the effects of different environmental disturbances on the circulation and the evoked autonomic responses have been studied mostly in unanaesthetized instrumented preparations. With each stimulus information from several receptor groups signalling changes in the internal and external environment activate many different regions of the central nervous system including circulatory centres located in spinal cord, hindbrain, hypothalamus and cortex. Frequently projections from two or more receptor groups converge onto one particular brain region where they interact so that the response evoked by altering one of the inputs is markedly influenced by the level of activity in the other input channels. Such interactions can greatly influence the responses of the body's blood pressure control system. Some of our earlier studies have shown that many of the so-called higher centres in the nervous system participate in the normal regulation of the circulation. The pathways subserving reflex circulatory functions come into close contact with neural pathways subserving certain types of behaviour.



Back (left to right): Gillian Love, Geoff Head, Matthew Le Duc, Dr. Archer Broughton, Aina Martin, Dr. Duncan Blake, Judy Oliver, Kerrie-Anne Hare, Vicki Lukins, Paul Leonard, Sandra Wallace. Seated: Dr. Murray Esler, Professor Paul Korner, Dr. Warwick Anderson, Dr. Patricia Dorward.

Behavioural factors may themselves serve as an input to the circulatory control system and alter its properties.

To examine possible mechanisms involved in the interactions and the 'resetting' of reflex properties by different inputs and by behavioural changes we have begun studies on the role of different transmitters released from 'circulatory' neurons on different circulatory control processes and different types of behaviour. To-date we have concentrated on the analysis of the different brain amine transmitter systems. The brain amines studied are noradrenaline and serotonin which are located in distinctive groups of cells in brain regions known to be important in circulatory control. Much of our work to-date has been related to studying the role of noradrenergic neurons. The studies have involved analysis of the acute and chronic effects of 6-hydroxydopamine (6-OHDA) which is actively taken up by the nerve endings, releases transmitter and eventually produces destruction of the endings. Our studies have shown that the noradrenergic neurons make a definite contribution to each reflex studied though the effects have been small and have required specially sensitive methods to produce unequivocal evidence of their involvement. Destruction of these noradrenergic neurons has much greater effects on feeding and drinking behaviour than on the different reflexes. As far as each particular reflex is concerned, noradrenergic neurons make a distinctive contribution to each reflex, enhancing some responses and depressing others. Distinctive effects on each reflex are also produced through serotonergic neurons which also influence feeding and drinking behaviour. The model about these different transmitter systems that emerges is that each group of neurons with a distinct transmitter contribute one link in a long chain of many different neuron groups. At the present time it is a matter of conjecture why the central nervous pathways subserving circulatory reflexes should contain such a wealth of different transmitter systems. A simplistic explanation is that this provides a safety factor for these important homeostatic functions. Another possibility is that each transmitter system may go either to or from one particular integrative circulatory 'centre' and that different integrative processes utilize distinctive transmitter systems.



Extensive recording and monitoring facilities are required for Dr. Patricia Dorward's neurophysical research.

Other questions being studied relate to the site of action of beta-blocking drugs that are important in lowering blood pressure. An analysis performed in collaboration with Dr. Pat Dorward and Mr. Gregory Frean has shown how propranolol lowers blood pressure in the rabbit. At low plasma concentration it blocks the cardiac beta-receptors and thus prevents effects due to peripheral cardiac sympathetic nerve activity. The fall in cardiac output that occurs has relatively minor effects on the blood pressure because of compensatory peripheral vasoconstriction. At high blood concentration this compensatory vasoconstriction is prevented through the central action of propranolol and permits the development of a much greater fall in blood pressure. It seems likely that a similar mechanism operates in man. Another question important in anaesthesiology has been tackled by Dr. Duncan Blake. He has compared the effect of three anaesthetic agents, thiopentone, althesin and ketamine on the baroreceptor-heart rate reflex and the Valsalva constrictor reflex in the rabbit. Studies have been performed in each animal without anaesthesia and under light anaesthesia produced by each particular agent.

The major differences relate to the vagolytic effects of the different anaesthetics which are very pronounced with thiopentone and with ketamine but are less marked, though still significant, with althesin a new steroid anaesthetic. Only ketamine appears to alter greatly the responsiveness of sympathetic constrictor reflexes.

Kidney and Hypertension

Studies on renal artery stenosis performed by Dr. Warwick Anderson and reported last year showed that in conscious instrumented dogs narrowing of the renal artery was associated with lowering of the distal renal artery pressure and renal blood flow. Distal renal artery pressure became rapidly restored through the intrarenal constrictor action of angiotensin II. This restoration was independent of the activity of the autonomic nervous system and was prevented by infusing converting enzyme inhibitor or competitive angiotensin II antagonists. With mild and moderate narrowing of the renal artery hypertension did not develop and the increased levels of plasma renin activity and angiotensin II concentration returned to normal once the renal artery pressure had been restored. With more severe stenosis hypertension did develop and there was elevation of plasma renin activity and angiotensin II concentrations even after renal artery pressure was restored. These studies have provided support for the view that renin secretion is controlled by two renal mechanisms — a pressure-sensitive renal 'barostat' and another mechanism probably signalling changes in tubular fluid composition and probably located in the macula densa. Systematic elevation of the blood pressure appears to occur only in response to renal artery stenosis that is severe enough to have brought both control mechanisms into play. With milder degrees of narrowing the renin angiotensin system is activated only transiently and is turned off once renal artery pressure has been restored.

The above studies have been extended in order to evaluate the importance of the vascular tone of the kidney on the renal and systemic effects produced by a given degree of renal artery stenosis. In conscious dogs the renal artery was narrowed to lower the distal renal blood pressure to a particular value after the kidney had been either dilated or constricted by infusions into the renal artery of appropriate drugs. The constrictor device was then clamped and the drugs discontinued and the kidney allowed to regain its 'normal' tone. It was found that when the cuff was applied with the kidney constricted, the gradient between the aortic pressure and the distal renal artery pressure remained large, renin production remained high and the systemic blood pressure rose much more than when the cuff was applied with the kidney dilated. This is in accord with the theoretical prediction that to lower the blood pressure distal to the stenosis to a particular value (or to lower blood flow) it is necessary to narrow the renal artery diameter more when the bed is constricted than when it is dilated. In the same way it was found that reducing the distal renal artery pressure to the same level in the conscious dog produced a smaller increase in plasma renin activity and less elevation of the systemic blood pressure than when the narrowing was produced under anaesthesia. Under the latter conditions the renal bed is constricted due to the increased sympathetic activity but it dilates subsequently when the animal recovers from the anaesthetic. These studies have provided evidence that the state of tone of the distal vascular bed supplied by the artery renders an arterial stenosis more or less 'critical' from the point of view of organ blood flow or perfusion pressure. Most vascular beds vasodilate in response to stenosis and this has also been the initial response of the renal bed. The kidney is unique in relation to other beds in that reduction of its perfusion pressure provides a stimulus to the angiotensin II production which constricts the dilated bed thereby making a given degree of stenosis less critical.

The site of action of angiotensin II important in the restoration of the distal renal artery pressure in stenosis appears to be on the efferent arteriole. Its effect is to maintain glomerular filtration rate and the filtration function of the kidney. We have been investigating whether this mechanism may be of more generalised importance. It has long been known that one of the actions of catecholamines is to increase the renal filtration fraction, and studies performed by infusing small concentrations of noradrenaline into the kidney before and after giving converting enzyme inhibitors have shown that this effect on the renal efferent anteriole, is again mediated by the production of angiotensin II. The possibility that the neural input into the kidney affects vascular tone not only through its actions on the vascular smooth muscle but indirectly through the release of local hormones is a matter of great interest and importance, but the physiological circumstances under which it occurs and the types of transmitters involved remain to be defined.

Salt and Hypertension

Previous studies performed in collaboration with Dr. Peter Fletcher provided no definite evidence of any difference in elevation in blood pressure or in cardiac output when renal hypertension was induced by cellophane wrapping in rabbits chronically maintained on different dietary salt intake. Salt varied from high (about 50 mM/day) to low (about 1-2 mM/day). Comparisons in

this series were entirely between animals in the different groups and each animal was maintained on a given dietary salt regime before the induction of hypertension. This year Prof. Korner, Miss Judy Oliver and Dr. M. Fahim have studied the effects of *changing* dietary salt intake in each animal once hypertension had become established. Each rabbit was maintained for two weeks on either high salt, normal or low salt diets as above. On the low diet blood pressure was on average 10-15 mmHg lower than on the high salt diet. What was of particular interest was that the effect was almost entirely on the cardiac output. This was significantly lower in hypertensive animals on the low salt diet than when the diet was composed of either normal or high salt. There was no difference in the degree of vascular narrowing on the different diets. By contrast, in sham-operated control rabbits the same variations in dietary salt intake did not alter cardiac output or blood pressure. These studies suggest that in animals with established renal wrap hypertension body fluid volumes tend to be elevated on normal and high salt diets and become restored to normal when the dietary salt intake is greatly reduced.

In rabbits with normal renal function similar changes in salt intake appear to produce maintenance of the body fluid volumes between much narrower limits.

Heart and Hypertension

Two studies have been performed in this area. In one, Dr. Alex Bobik has assessed the role of sympathetic activity in hypertension on the number of beta-adrenoceptors on the cells membranes of the heart. The study was performed in normal rabbit hearts and in hearts in which hypertrophy has been induced by several weeks of chronic renal hypertension. The beta-receptors are specific receptors on the cell membranes of the heart that respond to the noradrenaline released from the sympathetic nerve endings and to circulating catecholamines. In each group of rabbits three subgroups were studied in which the level of sympathetic activity was either subnormal, normal or enhanced. In the normal heart there was an inverse relationship between the density of beta-adrenoceptors and the level of sympathetic activity. A similar inverse relationship was found between the level of sympathetic tone and the activity of the adenylate cyclase system — an enzyme system which forms a link between the receptor and the contractile and metabolic machinery of the heart muscle cell. These findings indicate that there are sensitive cellular control systems which respond to the level of tonic sympathetic nerve activity. In the hypertrophied heart the beta-receptor density was depressed significantly but the total number of beta-receptors per heart was less markedly affected. In these hearts a reciprocal relationship between receptor density (and activity of the adenylate cyclase system) and the level of sympathetic activity was not observed. An important factor determining the greater decrease in beta-receptor density than in beta-receptor numbers is probably the increase in surface area of the cell membrane. Whether there is also a tonic increase in resting sympathetic activity is uncertain. What is of particular interest is that under conditions of enhanced sympathetic activity the rabbit's myocardial catecholamine stores were much more depleted than in normal animals. The findings resembled those observed in heart failure and suggest that chronic over-stimulation in the hypertensive heart is much less well tolerated in the hypertensive heart than in the normal heart.

A related set of studies in the intact heart has been performed by Dr. Archer Broughton. The long-term aim of the study is to determine the alterations of contractile performance of the hypertrophied heart and to relate them to biochemical indices such as the changes in membrane receptors and alterations in metabolism. All our work to-date has been concerned with the analysis of what is the optimum index of myocardial contractile performance. Therefore, most studies have been performed up to the present in normal hearts. Much work has been done in the past on the question of what constitutes the best index of contractile performance but there is little unanimity as to the result. All these indices measure the rate of left ventricular pressure development at different times in the cardiac cycle. Three indices have been studied:— (1) maximum rate of left ventricular pressure (dP/dt)max; (2) rate of left ventricular pressure development at a left ventricular pressure of 40 mmHg — which occurs earlier in the cardiac cycle; (3) the index (dP/dt/total left ventricular pressure)max which occurs still earlier. On the basis of experiments performed largely under basal conditions most workers believe that there is little to choose between these indices. Each index has been considered to be a rather variable entity subject to many extraneous factors.

Since the cardiologist wishes to measure contractile performance to tell him something about the heart muscle itself rather than about the operation of the heart

Dr. Arch Broughton studies heart muscle function and over-enlargement of the heart.

and vessels and autonomic nervous system, we have used a controlled preparation in which the influences of the autonomic nervous system are eliminated. We have also used a steady-state analysis of the changes in contractility which differs from the transient type of analysis used in most previous work. Under basal conditions there was indeed little to choose between the indices at normal blood pressures but at blood pressures slightly below normal the most commonly used clinical index (dP/dt)max underestimates contractility by about 5-10%. The underestimation of contractility becomes markedly accentuated under conditions of enhanced contractility and it may be 100% in error under conditions of maximum inotropic stimulation at levels of blood pressure such as those normally observed during exercise. Such underestimation does not occur with the other indices. However, problems associated with their use relate to the time of the cardiac cycle at which they occur. If the index falls into too early a part of the cardiac cycle it will no longer reflect the 'active state' or the total contractile potential of the muscle. On balance, the index dP/dt at a developed left ventricular pressure of 40 mmHg provides the best estimate of contractile state under widely varying conditions of contractile performance from basal to maximum.

DETAILS OF PROJECTS

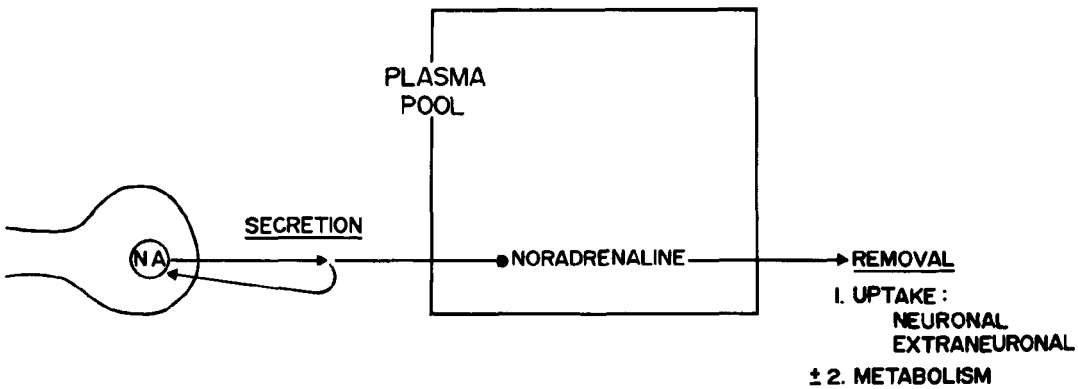
1. Noradrenaline Kinetics in Essential Hypertension

M. Esler, P. Korner, A. Bobik, G. Jackman, D. Kelleher & G. Jennings.

The demonstration of an elevated concentration of the sympathetic transmitter, noradrenaline, in the plasma of some patients has been considered to-date to be one of the strongest pointers to sympathetic nervous overactivity in essential hypertension. But the plasma noradrenaline concentration provides only limited information about sympathetic nervous system activity when the rate of removal of noradrenaline from the circulation in hypertensive patients is not known. The blood level is the resultant of two simultaneous processes — (i) release of noradrenaline from sympathetic nerves; and (ii) removal from the blood after release. (Fig. 1.) It might be that in patients with essential hypertension removal from the circulation is slow, so that the rate of release from sympathetic nerves could be quite normal. Since noradrenaline is a local and not a circulating hormone, and the plasma concentration of noradrenaline is not sufficient, even in hypertensive patients, to raise blood pressure directly, it is important to make this distinction between release rate and removal rate of noradrenaline.

We measured the rate of removal of noradrenaline from the blood-stream in 15 patients with essential hypertension and in 15 healthy subjects. A small dose of radiolabelled noradrenaline (0.3 μg, 80 μCi) was injected intravenously, and the rate of disappearance from plasma was followed. In normal subjects the disappearance of the noradrenaline was rapid. Among hypertensive patients, in no case was noradrenaline removal slowed, indicating that the high plasma noradrenaline level in hypertension is not due to defective clearance from that blood stream.

Since these results point to increased noradrenaline release as the basis for high plasma noradrenaline levels in some patients with essential hypertension, this was estimated directly in 14 patients and in 12 healthy subjects with normal blood pressure. The method involves the intravenous infusion of radio-labelled noradrenaline at a constant, known rate, until the level reached in the blood plasma levels off. By measuring this concentration of radiolabelled noradrenaline, and the concentration of the patient's own noradrenaline, noradrenaline release rate is calculated. In 6/14 patients with essential hypertension the plasma concentration of noradrenaline was



elevated and in 5 out of these 6 patients the rate of release of noradrenaline was elevated.

The findings indicate that sympathetic nervous system overactivity is present in a proportion of patients with essential hypertension, and the question arises whether it is the cause of their high blood pressure. Studies are being planned to see if it is possible to determine the cause of sympathetic nervous overactivity in the above patients. An additional question is, given we know the level of sympathetic activity, can this be utilized to improve the existing treatment of hypertension in different subsets of patients?

There is an attempt throughout the world to provide optimum treatment in different groups of patients. The problem has been that to date the basis on which the patients have been classified into different groups has not found any general acceptance. It would be anticipated that patients with sympathetic nervous overactivity classified according to the criteria established by the present techniques would respond more to the blood pressure-lowering effects of drugs that suppress sympathetic neural activity than patients in whom such overactivity could not be demonstrated.

2. Simultaneous Determination of Plasma Noradrenaline Concentration. Clearance and Relative Secretion Rate into Plasma in Man.

G. Jackman, M. Esler, H. Skews, V. Carson & A. Bobik.

Elevated 'steady-state' plasma concentrations of noradrenaline in some patients have been considered to be one of the strongest pointers to sympathetic overactivity in essential hypertension. However, 'steady-state' plasma concentrations represent the resultant effects of 'spillover' from sympathetic nerves and its ultimate removal from the plasma compartment. To-date there has been no attempt to examine the degree to which these two factors influence 'steady-state' noradrenaline plasma concentrations in man. Hence, the aim of the present study was to develop suitable methodology which could be used to simultaneously determine plasma noradrenaline concentration, apparent noradrenaline clearance and hence the relative rate of noradrenaline secretion into the plasma pool.

The method requires a constant intravenous infusion of a tracer dose of levo-noradrenaline-^{3}H until 'steady-state' plasma noradrenaline specific activity is attained (~2 hours). The resultant specific activity is then determined from a knowledge of the radioactivity in plasma due to noradrenaline-^{3}H and the noradrenaline plasma concentration. Briefly, plasma catecholamines and catechol-^{3}H metabolites of noradrenaline-^{3}H are absorbed onto alumina at pH 8.6. Catecholamines (including noradrenaline-^{3}H) are selectively eluted from alumina with 0.1N perchloric acid. Catechol-^{3}H metabolites are retained on the alumina under these mild

acidic conditions. The recovery of noradrenaline-^{3}H from plasma averages 60%. Catecholamines in the perchloric acid eluate are subsequently converted to their tritiated methoxy derivatives with COMT in the presence of S-adenosyl-L-methionine and Mg^{++}. Normetanephrine-^{3}H from this reaction is purified prior to quantitation by selective solvent extraction, thin layer chromatography and conversion to vanillin-^{3}H. No corrections are required for the contribution of radioactivity from the 0-methylation of levo-noradrenaline-^{3}H since this value represents less than 2% of the total radioactivity in the radio-enzymatic determination of plasma noradrenaline.

3. How Propranolol Lowers Blood Pressure

Patricia Dorward, G. Frean and P. Korner

In both sodium pentobarbital-anaesthetized and conscious rabbits propranolol at high plasma concentrations (320 ± 20 ng/ml) lowered the threshold pressure for inhibiting renal sympathetic neural activity. This was not due to changes in the arterial baroreceptor input, and was not related to vagal afferent activity. Hence, the effect was considered to be due to a CNS action of propranolol, probably on central beta-adrenoceptors. In accordance with the neurophysiological experiments propranolol at plasma concentrations of 168 ± 35 ng/ml and 240 ± 33 ng/ml attenuated the rise in total peripheral resistance (TPR) evoked during a Valsalva-like manoeuvre in conscious rabbits. The role of CNS 'resetting' of constrictor reflexes by propranolol on the fall in resting blood pressure was also studied in conscious rabbits. After 1 hour control observations each animal was infused on a different day with one of the following 4 treatments, each for a period of 3 hours: 0.9% NaCl; propranolol at 5 μg/kg/min (P_1); 15 μg/kg/min (P_2) and 50 μg/kg/min (P_3). Propranolol elicited significant reductions in heart rate and cardiac output with the responses similar in each animal at all three infusion rates of drug. However, greater reduction in blood pressure than during 0.9% NaCl infusion occurred only at levels P_2 and P_3 (90 ± 8.9 and 290 ± 15.2 ng/ml) but not at level P_1 (39 ± 2.7 ng/ml). At the former levels CNS 'resetting' of constrictor reflexes probably prevents 'compensatory' rises in TPR and allows the effects of peripheral cardiac beta-blockade on cardiac output to lower blood pressure. This does not occur at the lowest plasma concentrations studied which are in the lower part of the human therapeutic range.

4. Effect of 6-hydroxydopamine on Baroreceptor-Heart Rate and Nasopharyngeal Reflexes

P. I. Korner, J.A. Reynoldson, G. Head, Judy Oliver & Val Carson.

The baroreceptor-heart rate reflex was studied in conscious rabbits by deriving sigmoid mean arterial pressure (MAP) — heart period (HP, pulse interval) curves before and at different times after intracisternal (i.c.) injection of either vehicle or 6-hydroxydopamine (6-OHDA). Each curve was characterized by the HP range (HPR) between upper and lower HP plateau levels, median blood pressure (BP_{50}) and average gain ($\bar{G}$) about BP_{50}. Vehicle was without effect on these parameters at 2 and 4 hours and on day 7 after injection. (Fig. 2.) After giving 400 or 600 μg kg^{-1} 6-OHDA there were similar significant rises at 2 and 4 hours in HPR and $\bar{G}$ to about 200% of control, and a rise in BP_{50} of about 10 mmHg. In pontine (decerebrate) rabbits there were similar rises in HPR and $\bar{G}$ but BP_{50} decreased. Chronic changes after 6-OHDA included a rapid weight loss necessitating artificial feeding. After 400 μg kg^{-1} weight was regained by day 7 and BP_{50} and threshold for eliciting bradycardia increased signifi-

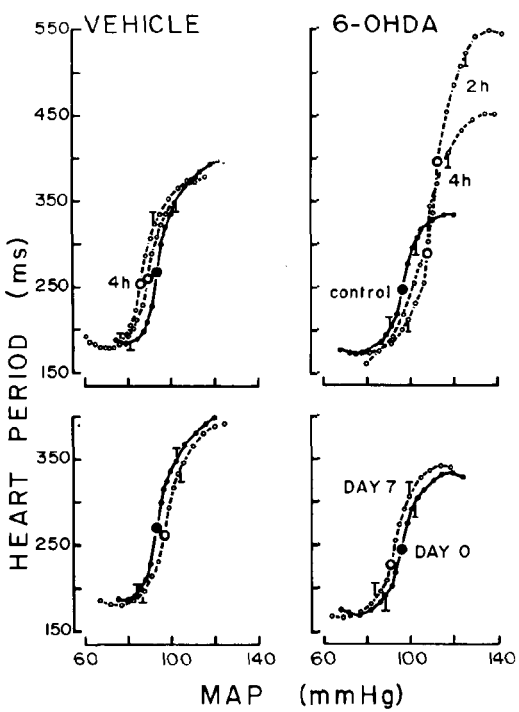


FIG. 2
Barocurve responses to injection of 6-hydroxydopamine or saline vehicle intracisternally.

cantly by 13.7 ± 2.3 mmHG. Absence of significant parameter changes after 600 μg kg^{-1} on day 7 was considered to be due to residual fluid balance disturbances in this group. These appeared to be no longer present in 6 rabbits given a second i.c. dose of 600 μg kg^{-1} on day 7 and studied 1 week later, when changes in reflex properties consisted of a rise in BP_{50} (10.9 ± 3.7 mmHg), reduction in $\bar{G}$ to 52 ± 17.8% of control, a small reduction in HPR and impairment in the cardiac sympathetic component of the HP response studied after vagal block.

The nasopharyngeal reflex consisting of a rise in HP and maintenance of MAP close to resting was evoked by graded inhalation of formalin vapour. The responses were not significantly altered after i.c. vehicle. After 600 μg kg^{-1} 6-OHDA MAP was significantly less well maintained at 2 and 4 hours and on day 7 than before injection and there were also significant changes in HP response. Neither MAP or HP responses were further impaired by a second dose of 6-OHDA on day 7, and both had become virtually restored 1 week later. The results suggest that catecholaminergic neurons normally participate in the baroreceptor-heart rate reflex and the naso-pharyngeal heart rate and constrictor reflexes and that different groups of neurons probably modulate each response.

5. Effect of 6-hydroxydopamine on Circulatory Responses to Clonidine

J.A. Reynoldson, G.A. Head & P.I. Korner

The effects of intracisternal injection (i.c.i.) or clonidine (1 μg kg^{-1}) on blood pressure and heart rate were studied in conscious rabbits with an implanted catheter in the cisterna magna. Each animal was studied under control conditions and 7 days after i.c.i. of 6-hydroxydopamine (6-OHDA) (1 μg kg^{-1}; n = 10) or ascorbic acid vehicle (n = 6). In the control experiments blood pressure and heart rate began to fall 1-2 minutes after i.c.i. of clonidine, with maximum falls at 10-20 minutes averaging 18 ± 2 mmHg and 45 ± 8 beats/min and almost complete recovery by 90 minutes. After vehicle pretreatment neither response was significantly altered. (Fig. 3.) After 6-OHDA the early component of the bradycardia was abolished and only a late fall in heart rate developed 30 minutes after i.c.i. clonidine. (Fig. 3.) The magnitude of the hypotension was unaffected but the onset was slightly delayed, probably owing to the abolition of the bradycardia. The dose of 6-OHDA reduced spinal cord catecholamines to about 20% of the level observed after vehicle. Central catecholaminergic pathways are thus important in the early predominantly vagal component of the clonidine induced bradycardia, but play little role in the hypotensive response.

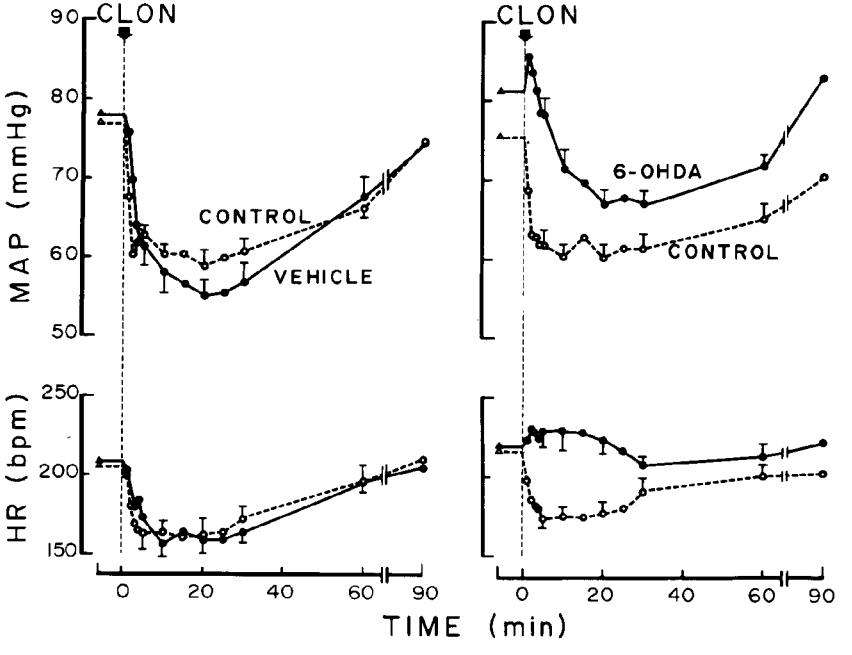


FIG. 3

6-hydroxydopamine alters the blood pressure and heart rate responses to intracisternal injections of clonidine.

6. Operation of The Central Nervous System in Circulatory Control
P.I. Korner

The circulatory response to a disturbance is the sum of autonomic neural + adrenal catecholamines + direct local effects. Suprapontine and bulbo-spinal pathways of the CNS both contribute to the differentiation of the neural response patterns and to the adrenal catecholamine secretion rates. Arterial hypoxia, CO-hypoxia and hemorrhage each at a severity that produced similar direct local circulatory effects in autonomically 'de-efferented' rabbits, have differing patterns of vagal activity, regional sympathetic neural activity and adrenal catecholamine secretion. In prolonged disturbances the latter are important peripheral modulators of neural effects. In disturbances involving simultaneous changes in activity of several groups of afferents the autonomic responses are often non-linear, in that the effects of altering one input are markedly altered by the level of activity of one or more of the others. Non-linear chemoreceptor-ventilatory interactions account for species circulatory response differences to arterial hypoxia and for the qualitative heart rate response differences of the rabbit in mild and severe hypoxia. Non-linear interactions can greatly alter the responses of arterial baroreceptor reflexes to arterial pressure changes. Such 'resetting' can be produced by activation of other afferents, central command factors and drugs acting at specific sites in the CNS. 'Resetting' produced by interactions with projections from the chemoreceptors and cardiopulmonary baroreceptors greatly enhance the apparent gain of the blood pressure control system, permitting more effective compensation for the effects of large disturbances. Non-linear interactions provide the organism with a variable reference servo-control system of circulatory regulation that allows a greater range of adjustments to environmental and behavioral stimuli than if control occurred through an array of autonomous reflexes.

7. Effects of Thiopentone, Ketamine and Althesin on Cardiovascular Reflexes
D.W. Blake & P.I. Korner

Baroreceptor-heart rate reflexes were studied in (1) conscious instrumented rabbits; (2) in the same animals after light anaesthesia induced by one of the above anaesthetic agents on a given day. Every anaesthetic was studied in each animal on different days. The sigmoid baroreflex function curves were characterized in the usual way by (i) the heart period range (HPR) between upper and lower HP plateau levels; (ii) median blood pressure (BP_{50}); and (iii) average gain or sensitivity. All anaesthetics depressed HPR and gain from the values observed in the same animal without anaesthesia. After thiopentone (dose 0.8 mg/kg/min) and ketamine (0.65 mg/kg/min) the effects were similar for each parameter and averaged 39% and 38% of the value observed in the absence of anaesthesia, but after althesin (0.1 mg/kg/min) the effect was 61% of control, i.e. significantly less depressed than with the other agents. Each anaesthetic increased BP_{50} and threshold for eliciting bradycardia, with the increase greater for thiopentone (11 mmHg) and ketamine (16 mmHg) than for althesin (3 mmHg). The cardiac sympathetic component of the reflex response was altered little by thiopentone and althesin, but HPR and gain were depressed by ketamine.

8. Acute Angiotensin II-Mediated Restoration of Distal Pressure Following Renal Artery Stenosis and Its Relationship to the Development of Sustained Hypertension in Conscious Dogs.
W.P. Anderson, P.I. Korner, C.I. Johnston & D.J. Casley

The effects of graded renal artery stenosis on renal and systemic haemodynamics and plasma renin activity (PRA) were studied in conscious, chronically instrumented dogs. In mild and moderate stenosis (following rapid reduction in distal renal artery pressure to 60 or 40 mmHg) there was initial vasodilation followed by prompt restoration of renal artery pressure and vascular resistance (within 5-30 minutes) with minimal changes in mean aortic pressure (MAP). ΔPRA and Δ renal artery pressure were reciprocally related, the relationship probably representing renal 'barostat' control of renin secretion in the conscious dog. Restoration of renal artery pressure was prevented by giving converting enzyme inhibitor. With more severe stenosis produced by lowering renal artery pressure to 20 mmHg the latter took 2-3 days to become fully restored. MAP rose 18.2 ± 2.5 by the 30 minutes but had declined to control by day 2-3. ΔPRA during the first hour of stenosis was greater than accounted for by the fall in renal artery pressure, but by day 2-7 PRA appeared to be predominantly under renal 'barostat' control. With still more severe stenosis ΔPRA remained above control over the 7 day period despite restoration of renal artery pressure suggesting that it was controlled by factors additional to the 'barostat' mechanism. The rise in renal artery pressure was now mainly determined by the increase

in systemic MAP. Renal 'barostat' mediated increase in renin-angiotensin activity is thus the main mechanism restoring renal artery pressure with mild stenosis, whilst in severe stenosis this is only accomplished by development of systemic hypertension.

9. The Influence of Renal Vascular Tone on the Haemodynamic and Humoral Events Following Acute Renal Artery Stenosis in Conscious Dogs

W.P. Anderson, P.I. Korner & C.I. Johnston

We have previously shown that following mild and moderate stenosis of the renal artery in conscious, chronically instrumented dogs, renal artery pressure distal to the stenosis was restored back to near normal values by a mechanism dependent on angiotensin II (AII). Calculation of the effective resistance to blood flow of the stenosis in these experiments showed that the stenosis behaved in a complex manner. (Fig 4.) This year we have further evaluated the hydraulic behaviour of the renal artery stenoses, and the significance of this behaviour for the renal response to stenosis. The experiments were performed in conscious dogs prepared at a preliminary operation with a Doppler flowmeter and inflatable renal cuff around the renal artery, and catheters in the renal artery and aorta (with unilateral nephrectomy).

In one series of dogs we used a wire snare to narrow the renal artery instead of the usual inflatable cuff. Identical responses were found. We have also investigated the effect of the prevailing renal haemodynamics on the events during and subsequent to the induction of stenosis. In random order, an infusion into the renal artery of a vasodilator (acetycholine, 1 μg/kg/min), a vasoconstrictor (AII, 2.5 ng/kg/min or methoxamine, 3 μg/kg/min), or saline was commenced 1-2 minutes prior to stenosis induction. In all instances, the cuff was inflated to lower distal renal artery pressure to 40 mmHg, and the renal artery infusion turned off 1 minute later. More severe narrowing of the vessel was required to achieve a distal pressure of 40 mmHg when the kidney was vasoconstricted, and subsequently systemic arterial pressure and plasma renin activity rose more and the aorta-renal artery pressure gradient was maintained for a longer period.

Experimental stenosis of the renal artery is most commonly performed at surgery in anaesthetized animals. However, renal

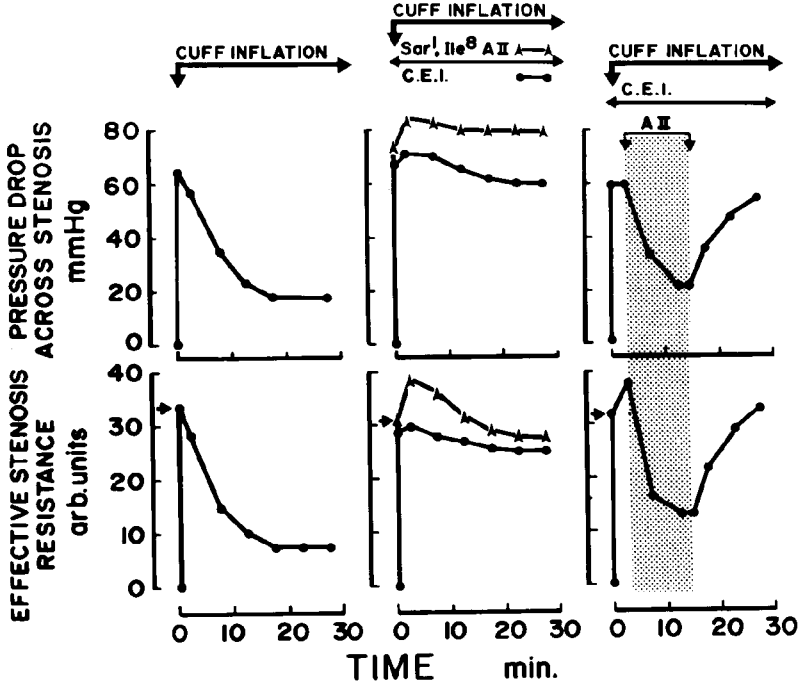


FIG. 4

The effective resistance of the renal artery stenosis is not fixed, but varies in response to changes in renal vascular resistance. It stays high when renal vasoconstriction is prevented (with AII blockers, middle panel), but fall when the endogenous (left panel) or exogenous (right panel) angiotensin III vasoconstricts the kidney.

vascular resistance rises during anaesthesia surgery, and the results of the study described in the above paragraph suggests that a greater narrowing of the renal artery would be required under these conditions. A study has been commenced to compare the effects of renal artery stenosis in dogs either anaesthetized with pentobarbitone or conscious. Stenosis is induced by creating an aorta-renal artery gradient of 50 mmHg in each case. Preliminary results show a hypertension of 10-25 mmHg 24 hours after stenosis induction in anaesthetized dogs, but no significant rise in blood pressure in conscious dogs. The results show that under anaesthesia a more severe stenosis of the renal artery is required to produce the same nominal reduction in distal pressure as in the resting conscious dog and provides further evidence that stenosis of the renal artery has to be very severe before hypertension can be produced acutely when the animal is conscious.

10. Angiotensin II Mediates Some of the Effects of Noradenaline Infusion into the Renal Artery of the Conscious Dog

S. Selig, W.P. Anderson & P.I. Korner

Starling first suggested that adrenaline acts predominantly on the efferent arterioles of the kidney in 1912, and many investigators have since shown that both noradrenaline and adrenaline tend to raise glomerular filtration fraction (FF) and rate (GFR). Most of these studies were performed before it was known that the catecholamines were potent stimulators of renin release from the kidney. Moreover, the angiotensin II produced is a potent constrictor of the efferent arteriole. We have therefore tested whether some of the effects of noradrenaline on the kidney were secondarily mediated by the stimulated renin-angiotensin system.

The expermiments were performed in trained conscious dogs prepared at a preliminary operation with aortic, renal artery and vena caval catheters, and a Doppler flowmeter around the renal artery.

Noradrenaline was infused into the renal artery at 0.02, 0.05 and 0.1 μg/kg/min. Each dog was studied twice, with and without angiotensin I converting enzyme inhibitor (SQ 20 881) infusion (0.12 mg/kg bolus; 0.04 μg/kg/min infusion i.v.). Noradrenaline produced a dose related rise in plasma angiotensin II concentration that was blocked by SQ 20 881. Inhibition of AII formation also greatly attenuated the rise in GFR in response to noradrenaline. Filtration fraction rose with noradrenaline infusion, but SQ 20 881 changed this response into a reduction. SQ 20 881 also attenuated the rise in arterial pressure that occurred with noradrenaline infusion. Thus, the renal effects of noradrenaline appear to be mediated to an important extent by the concomitant stimulation of the renin-angiotensin system.

11. Plasma Vasopressin Responses to Dehydration, Haemorrhage and Renal Artery Stenosis in the Conscious Dog

P.T. Pullan, W.P. Anderson & C.I. Johnston

We had previously shown that, in the absence of autonomic cardiovascular reflexes, vasopressin has vasoactive properties at plasma levels of about 30 pg/ml and above. Normal resting levels were about 5-8 pg/ml. We have now performed a series of experiments to test whether plasma levels of this hormone may be elevated into this vasoactive range.

All experiments were performed in conscious dogs prepared with aortic and vena caval catheters, including a large venous catheter (lower vena cava) for haemorrhage.

While dehydration (produced by 48 hours water deprivation) resulted in only a small rise in plasma vasopressin concentration (+ 2.3 pg/ml), mild non-hypertensive haemorrhage elevated vasopressin into vasoactive concentrations (48 ± 21 pg/ml), and more severe haemorrhage raised plasma concentrations more than 100-fold (775 ± 357 pg/ml). Goldblatt hypertension produced by severe renal artery stenosis (mean arterial pressure elevated 39 ± 14 mmHg after 1 week) was associated with only a doubling of vasopressin concentration, and in normal dogs, subpressor infusions of vasopressor were not found to potentiate the pressor effects of angiotensin II. It is concluded that vasopressin may play an important pressor role in haemorrhage but not in moderate dehydration or Goldblatt hypertension.

12. Influences of Adrenergic Sympathetic Neural Activity on Cardiac Beta-Adrenoreceptors and the Adenylate Cyclase System in Normal and Hypertrophied Hearts

A. Bobik, P.I. Korner, V. Carson & J. Oliver

One of the major complications of long-standing hypertension is the development of myocardial hypertrophy. The hypertrophied heart is often subnormal in its responses to sympathetic stimulation. Whether this is due to changes in beta-adrenoreceptor numbers or activities of en-

zymes controlling intracellular 3,5-cyclic AMP concentrations is at present unknown. Furthermore, the effect of chronic increases or decreases in cardiac sympathetic neural activity *in vivo* on beta-adrenoreceptors and the adenylate cyclase system in unknown. Several workers have suggested that beta-adrenoreceptors may be regulated by the extracellular concentration of noradrenaline, the transmitter released from sympathetic nerve endings. For example, *in vitro* incubation of lymphocytes with isoprenaline diminishes the responsiveness of the beta-adrenoreceptor adenylate cyclate system and the reverse effects have been observed after removal of sympathetic influences. Hence the aim of the present study is to characterise biochemically the regulatory properties of cardiac beta-adrenoreceptors and the adenylate cyclase system in sarcolemma-enriched fractions from cardiac muscle which have been subjected for some time *in vivo* to different levels of sympathetic activity.

In normal rabbits and in hypertensive rabbits with marked myocardial hypertrophy induced by bilateral renal cellophane wrapping the following levels of sympathetic neural activity were studied:- (1) diminished sympathetic activity produced by blocking transmission by twice daily intramuscular administration of large doses of guanethidine over a period of two weeks sufficient to greatly lower cardiac catecholamines; (2) 'normal' activity and; (3) increased sympathetic activity produced by sectioning of the carotid sinus and aortic nerves two weeks previously.

In normotensive rabbits reduction in sympathetic activity by guanethidine-treatment induced a significant increase (17%) in the density of beta-adrenoreceptors in sarcolemma enriched fractions of the heart. No change in the dissociation constant for the antagonist (dihydroalprenolol-^{3}H) was observed. Basal adenylate cyclase activity was increased by 33% without any alteration in activity produced by sodium fluoride stimulation. An additional effect of guanethidine was a small but significant increase in sarcolemma protein yield obtained per gm ventricle. In the normal rabbits with section of the sino-aortic nerves there was slight elevation of blood pressure, tachycardia but no increase in heart weight. In these rabbits there was little change in beta-adrenoreceptor density and adenylate cyclase activity.

Although the studies with hypertrophied animals are not yet complete, we have been able to demonstrate that during marked hypertrophy there is a significant reduction averaging 34% in beta-adrenoreceptor density with no significant change in the antagonists affinity for the receptor. Sodium fluoride stimulated adenylate cyclase activity was unaltered in hypertrophy. The experiments to-date suggest that both beta-adrenoreceptor density and basal adenylate cyclase activity may be at least partially modulated by sympathetic neural activity and cardiac hypertrophy induced by renal wrap.

13. Hormonal Regulation of Cardiac Muscle Beta-Adrenoreceptors and Their Effects on the Adenylate Cyclase System

V. Carson, J. H. Campbell, A. Bobik & G. R. Campbell

Alterations in hormone membrane receptor number or affinity are important mechanisms by which cells may regulate the magnitude of hormone mediated responses. To-date both the turkey and frog erythrocyte cells have been used as model systems of the beta-adrenoreceptor-adenylate cyclase system for the study of factors involved in the regulation of beta-adrenergic receptor mediated responses. Recent evidence has shown that the behaviour of these models do not reflect those of cardiac beta-receptors.

We have found cultured spontaneously beating cardiac cells isolated from the ventricles of 11 day old chick embryos to offer a convenient method of studying the effects of various catecholamines on the beta-adrenoreceptor-adenylate cyclase system. This system is highly responsive to beta-agonist stimulation. Thus a 5 minute 37°C incubation of intact cells with isoprenaline (10^{-5}M) produces an average increase of 310% in the intracellular 3',5'-cyclic AMP concentration. Continual stimulation of the beta-receptor-adenylate cyclase system of cardiac cells in culture results in a reduction in the beta-receptor mediated response. *In vitro* studies using membranes isolated from these cells indicate that this reduction in beta-receptor mediated response is due to specific alteration(s) in the properties of the beta-adrenoreceptor-adenylate cyclase system. Activation of adenylate cyclase via beta-adrenoreceptors is impaired. However, adenylate cyclase may still be activated directly with sodium fluoride and phosphoiesterase activity of these cells is similar to control cells.

The reduction in beta-receptor mediated response of these cells is related to the functional amount of beta agonist at the beta-adrenergic receptor. The process is reversible and on removal of the beta-agonist from the incubation culture medium, the beta-

receptor mediated response returns to within 20% of control by 24 hours.

These results indicate that beta-adrenoreceptor mediated effects of catecholamines on cardiac cells may be regulated by changes in the properties of the beta-receptor-adenylate cyclase system. Studies in progress are aimed at investigating the mechanisms by which this regulatory process occurs.

14. The Influence of Heart Rate and Aortic Pressure on Maximum Left Ventricular Performance During Catecholamine Infusion

A. Broughton & P.I. Korner

During isoprenaline administration declining arterial pressure due to β_2 adrenoreceptor stimulation and chronotropic effects may significantly modify the β_1 adrenoreceptor mediated increase in left ventricular contractility. This study reports findings in 10 anaesthetized open chest vagotomized dogs.

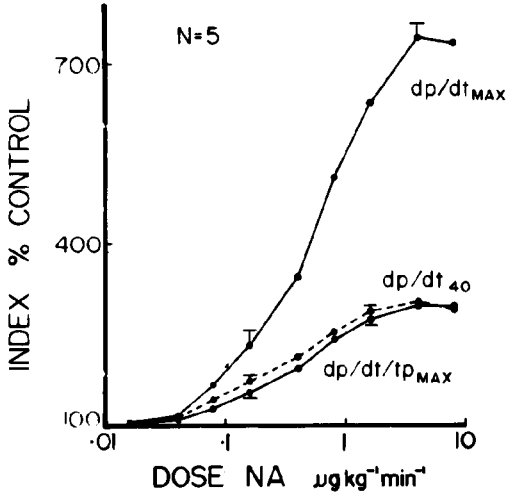


FIG. 5
Comparison of the increases in three isovolumic indices of cardiac contractility during noradrenaline infusion.

During cumulative infusion of noradrenaline (0.016-8 μg/kg/min) in 5 dogs at constant preload, the increase in left ventricular (dP/dt)max was sigmoid shaped with an upper plateau about 16000 mmHg sec^{-1} representing a six-fold increase above its basal value. (Fig. 5.) Initially heart rate was permitted to rise, increasing from 150 to about 225 beats/minute while mean aortic pressure (MAP) rose from about 150 to 240 mmHg. However, when heart rate was controlled by left atrial pacing at 150/minute during noradrenaline infusion, the increase in (dP/dt)max was still 4-5-fold with an upper plateau around 12,000 mmHg sec^{-1} ($P < 0.01$). Thus, chronotropic effects contribute about 20% of the increase in (dP/dt)max during noradrenaline infusion when heart is uncontrolled.

In contrast to the results of noradrenaline administration, when isoprenaline was infused in five dogs, MAP fell progressively below resting values, to as low as 75 mmHg and the rise in (dP/dt)max was only about five-fold. However, when MAP was then elevated above control by methoxamine and the infusion continued, further increases in (dP/dt)max were seen to reach levels comparable to those during noradrenaline infusion.

The initial low plateau in (dP/dt)max during isoprenaline infusion probably represented both limitation due to early aortic valve opening and a true plateau in contractility, because two other isovolumic indices of contractility dP/dt at developed ventricular pressure to 40 mmHg and (dP/dt/total ventricular pressure)max which are computed early in isovolumic systole were significantly affected by methoxamine. (dP/dt)max is thus a less reliable index of contractility during maximal enhancement of contractile state than the other two indices except at blood pressures well above normal.

Cardiovascular Metabolism and Nutrition Research Unit

Major Research Interests

- LIPOPROTEIN METABOLISM
- CHOLESTEROL METABOLISM
- INSULIN AND CARBOHYDRATE METABOLISM
- EPIDEMIOLOGY OF HYPERLIPIDAEMIA AND CORONARY DISEASE
- OBESITY — METABOLIC DERANGEMENTS
- MANAGEMENT OF HYPERLIPIDAEMIA AND OBESITY

General Summary

The Unit has grown during its second year of operation. It has been joined by Dr. Kerin O'Dea, a biochemist with a major interest in nutrition, especially in relation to obesity and insulin and carbohydrate metabolism. Dr. Noriko Tada, a physician from Tokyo, has come for 2 years to work on lipoprotein proteins and Dr. Timothy Billington has replaced Dr. Reardon who is spending two years in Toronto. Three scholars worked in the Unit, Gillian Martin obtaining an MSc, Andrew Gross honours in biochemistry and Bruce Watson beginning a PhD course. Early in 1979, Dr. Murray Huff will join from Canada for two years.

The staff now comprises three senior research scientists, three post-doctoral fellows, three graduate scholars and support staff of three science graduates, three technicians, one dietitian and one secretary.

A. Lipoprotein Metabolism

As described in detail later our major research is in the area of lipoproteins. Studies of lipoprotein metabolism are being carried out in healthy and hyperlipidaemic subjects. The protein moieties of lipoproteins are labelled with radioiodine, reinjected and the specific radioactivity curves of the lipoprotein proteins analyzed to provide measures of pool size, production and removal rate. The major purpose of the studies is to define the regulation of lipoprotein transport which is closely related to atherosclerosis and coronary disease. In particular, since the three major classes of lipoproteins, the very low density (VLDL), low density (LDL) and high density (HDL) are metabolically closely interrelated and since VLDL and LDL promote atherosclerosis while HDL appears to retard it, the main emphasis has been to study the turnover of the lipoproteins as an integrated system.

The lipoproteins are mixtures of lipids and proteins, designed to transport the water-insoluble fats, triglyceride and cholesterol, through the aqueous medium of the plasma. This is accomplished through the detergent properties of some of the proteins. The lipoprotein proteins have other unique functions, some of which are structural while others activate enzymes that allow the larger lipoproteins to be dismantled and reformed into smaller species that can be removed.

Of the 4 major classes of lipoproteins, two, the chylomicrons and very low density lipoproteins (VLDL) serve to transport triglyceride, the body's major source of fuel, from sites of formation to sites of storage. The removal of triglyceride requires the participation of HDL that contain proteins that initiate the lipolysis of the triglyceride and subsequently incorporate the remaining surface material within the HDL, where the excess cholesterol from the large lipoproteins is retained as cholesteryl esters. The smaller remnants of the chylomicrons and VLDL are either removed rapidly from the circulation, probably by the liver, or reformed into the still smaller cholesterol-rich LDL. Lipoprotein metabolism therefore represents a complex series of sensitively regulated biochemical and physico-chemical interactions.

The major lines of research in the lipoprotein area have been as follows:

1. Much effort has been spent on the function of HDL since this lipoprotein is central to total lipoprotein metabolism and appears to protect against coronary disease.
   a. The kinetics of HDL protein transport have been defined in man.
   b. The formation and catabolism of HDL have been studied in disorders such as alcoholic hepatitis, in which HDL metabolism is disturbed.
   c. The relationship of HDL formation to fat feeding (since HDL may be derived from chylomicrons) is being studied in the rat.
   d. The effects of different diets and of physical exercise on HDL levels and kinetics are being pursued.
   e. The important role of HDL in the transport of cholesterol from cells to sites of removal has been studied in several different experiments.

2. The metabolism of VLDL has been studied in man by compartmental analysis and in vitro with cultured lymphocytes. The main findings have been that hypertriglyceridaemic subjects generally secrete excess VLDL but that

Back (left to right): Jane Ma, Geoff Harrison, Dr. Kerin O'Dea, Bruce Watson, Patricia Astwood, Dr. Timothy Billington, Lyn Cannon, Lynne Antonoff, Margaret O'Connor, Hubert Edelsbacher, Dr. Norio Tada, Penny Snow. Seated: Dr. Murray Huff, Dr. Paul Nestel, Dr. Noel Fidge.

this becomes critical only in those who also show impaired clearance. In vitro studies showed that VLDL from hypertriglyceridaemic subjects were taken up by cells at an increased rate, suggesting a mechanism for the development of atherosclerosis in hypertriglyceridaemia.

3. Cholesterol metabolism was studied to answer two major questions:
   1. The effect of cholesterol consumption on cholesterol production and excretion in children with hypercholesteroleamia;
   2. The influence of high circulating HDL concentrations on cholesterol transport in man.

B. The Heart Risk Evaluation Clinic

This clinic has operated for two years as a community service that enables healthy individuals to have their serum lipids and blood pressure measured. Of the 3,500 subjects seen, the proportion requiring some dietary counselling is about one quarter. Our new dietitian, Sylvia Pomeroy, has developed several techniques for group sessions that have lifted the success rate to over 75%, judged as the lowering of serum lipids to normal within 4 months.

There clearly is a demand for a service of this kind that is accessible, simple and quick and that provides advice about coronary risk factor prevention.

C. Studies relating to Diabetes and Obesity

a. Urbanization of Australian Aborigines. A pilot study has been carried out by Dr. O'Dea to examine the effects of urban living on the development of diabetes.

Recent epidemiological studies have revealed a high prevalence of maturity onset diabetes (and obesity and coronary heart disease) in certain populations which have undergone rapid transition from a primitive to an urban lifestyle. Examples are the Pima Indians in the U.S., Central Pacific Islanders and South Australian Aborigines. However, there are other communities (Eskimos, Yemenite Jews, African Bantus and Melanesians) which respond to western influence by developing disease incidence patterns similar to those of Caucasians,

suggesting that environmental factors interact with a pre-existing genotype resulting in high incidences of maturity onset diabetes in particular populations.

Thirteen full blood Aborigines from near Derby, W.A., were studied both in their urban setting and after a 3 month period in the bush when they had returned to their traditional way of life, which increased their consumption of meat, fish and vegetables, led to much more exercise and eliminated alcohol and processed food. Measurements included glucose and insulin changes after a starch meal and fasting plasma lipids. The main metabolic advantages of the traditional lifestyle were: lowered weight, lowered triglyceride and a lower insulin response to the starch load. However in comparison with Caucasians, the Aborigines secreted more insulin even during the traditional lifestyle. The change from traditional to urban environment was accompanied by metabolic changes consistent with the development of obesity and diabetes.

b. The relationship of refined carbohydrate to the development of obesity and maturity onset diabetes.

Epidemiological and experimental observations have suggested that the low fibre content of diets in Western societies may be linked to obesity and diabetes.

We are working on the hypothesis that any factor which lowers the rate of hydrolysis of starch in the intestine and thus slows the rate of absorption of glucose will result in lower glucose and insulin concentrations after eating starch. Preliminary results suggest that the same load of starch can elicit quite different metabolic responses depending on the form in which it is ingested, e.g. ground rice is absorbed much more quickly than whole rice. The total insulin secretion after ground rice is double that after unground rice, the peak value reached being 3 times higher.

Inhibitors of α-amylase have been found in extracts of some cereals, legumes and fruits. Removal of these inhibitors during refining of carbohydrate may be metabolically disadvantageous. We have set up an in vitro method for measuring the rate of release of glucose from starch and are comparing a range of refined and unrefined sources of starch. The in vitro findings may enable us to predict which foods will elicit the smallest changes in glucose and insulin levels in vivo and thereby design diets for the treatment of diabetes and obesity. These will be tested in short and long term studies. An attempt will be made to relate in vivo changes in insulin sensitivity to the in vitro binding of insulin to receptors.

SCIENTIFIC PROJECTS

1. High Density Lipoprotein Metabolism

N. Fidge, P. Nestel, T. Ishikawa, N. Tada, M. Reardon, M. O'Connor.

a. HDL Kinetics

Since HDL appear to be central to lipoprotein metabolism, a study of HDL protein metabolism was undertaken to determine the formation and removal of the two major proteins AI and AII in normal and hyperlipidaemic subjects. The kinetics were calculated from the pattern of removal of reinjected autologous protein-labelled HDL. Both major proteins AI and AII, were distributed in two pools but were removed at different rates showing that HDL was not catabolized as an intact particle. The formation of HDL was stimulated by being overweight. A link between the turnover of the two lipoproteins, HDL and VLDL, was seen in hypertriglyceridaemic individuals who showed increased formation of both VLDL and HDL. These findings suggest that whenever triglyceride transport is high as in obesity or hypertriglyceridaemia, the increased formation and catabolism of the large VLDL stimulates the production of HDL. This may reflect the formation of HDL from VLDL surface material or the requirements for additional HDL proteins to regulate VLDL catabolism.

In contrast, in subjects with the inherited form of hypercholesterolaemia, the catabolism of HDL (as well as of LDL) was impaired. Whether this effect on HDL is detrimental and predisposes to the accumulation of cholesterol in arterial tissues is speculative. Finally, subjects with high levels of HDL in the plasma showed normal formation but reduced removal rates of HDL proteins.

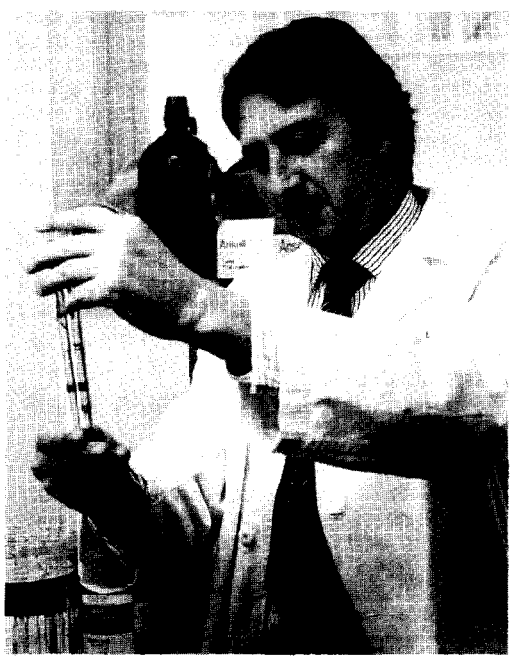
b. HDL in Alcoholic Hepatitis

Highly interesting changes in lipoproteins occur in severe alcoholic liver disease. Species of lipoproteins and lipoprotein proteins that are normally absent from plasma have been observed in patients studied so far. In contrast, normal HDL proteins are greatly reduced in concentration. The abnormal lipoproteins appear to be partly catabolized chylomicrons and VLDL, that in the absence of normal HDL, cannot be cleared from the plasma. Measurement of HDL turnover in these subjects has revealed marked instability of HDL resulting in rapid breakdown and removal of

the lipoprotein. This in turn interferes with the normal catabolism of the other lipoproteins. This system is being studied in detail to further our understanding of lipoprotein metabolism.

c. HDL and physical exercise
(with Dr. M. Podkolinski of the Antarctic Division).

Physical exercise is another factor known to influence lipoprotein levels and has been reported to raise HDL concentrations in particular. The opportunity to study extreme degrees of physical exertion on HDL levels was made possible on subjects climbing the Himalayan mountains. Blood samples were collected at the base camp, at the peak and on return to the camp. HDL protein levels were measured by immunoassay. Unusually high HDL protein levels observed before the final ascent were consistent with physical fitness, but these rose even further to extremely high concentrations at the end of the 5-week climb. The reason for this phenomenon is not known but may lie in the high rate of VLDL-triglyceride utilization by exercising muscles. The apparently beneficial effects of exercise and of high HDL levels in preventing coronary disease may stem from the more efficient utilization of the triglyceride-rich lipoproteins, since these may also be atherogenic.



Dr. Noel Fidge engaged in lipoprotein research examines proteins identified with dyes.

2. Very Low Density Lipoprotein Metabolism
P. Nestel, A. Everitt, B. Watson, T. Billington, N. Fidge, M. Reardon.

a. A large series of experiments has been concluded measuring the kinetics of VLDL B-protein, which is a marker of the fate of the lipoprotein particle. Both overproduction and diminished removal characterized most studies in hypertriglyceridaemic subjects. Overweight was a major cause of reduced removal and is being pursued in studies of markedly obese subjects.

b. The other major proteins of VLDL are the C group, of which CII is of prime importance being the activator of lipoprotein lipase, the enzyme that initiates VLDL removal by hydrolyzing the triglyceride within the lipoprotein. The methodology for isolating and quantifying each of the C proteins has been difficult but has now been accomplished. We have therefore been able to carry out simultaneous kinetic studies of the C and B apoproteins. The C proteins remain in the circulation much longer than the B protein, indicating that the C proteins are transferred to new VLDL (as well as to HDL), after the initial VLDL particle has been removed.

c. The effects of different diets are also being investigated. Eating excessive sugar disturbed lipoprotein levels in some but not all people. In those affected, VLDL (and triglyceride) rose, whereas HDL and LDL (and cholesterol) fell. In a study of normal subjects in whom the transport rates of VLDL and LDL were calculated by injecting labelled VLDL, the reasons for these disparate effects were shown. In those who showed an accumulation of VLDL and triglyceride in the plasma, the removal rate of VLDL was slowed; in others who showed no increase or even a fall in VLDL, removal mechanisms were stimulated during the feeding of sucrose, and compensated adequately for the increased rate of formation. The molecular basis for the effects of sucrose on VLDL removal are now being studied. In all subjects, the fall in cholesterol was due to an increased removal of LDL.

d. Studies of VLDL metabolism are being carried out simultaneously in vivo as described and in vitro using cultured lymphocytes. The findings so far show an increased uptake by cells of VLDL derived from hypertriglyceridaemic than from normal subjects. This may be relevant to the increased incidence of atherosclerosis in hypertriglyceridaemic subjects. Since partly catabolized VLDL were taken up more readily than intact VLDL, the greater removal of VLDL from hypertriglyceridaemics suggests

structural differences in the VLDL and these are being investigated. By labelling the B and C apoproteins separately we have shown that the uptake of VLDL into cells can occur without an initial breakdown of the particle.

3. Other Lipoprotein Research
N. Fidge, N. Tada, B. Watson, J. Ma, P. Nestel, M. O'Connor.

a. Immunochemical methods are being developed and electroimmunoassay has emerged as a most powerful tool for quantitating apoproteins. Monovalent antisera have been produced against human B, AI, AII, CII and E apoproteins. The availability of pure antisera has enabled us to measure accurately total plasma apoprotein concentrations in normal and hyperlipoproteinaemic patients; to estimate the alteration in apoprotein composition induced by dietary changes and to assist with the chemical identification of apoproteins and their complexes.

b. Chylomicrons are being analyzed for their protein composition. Newer proteins are being investigated both in lymph chylomicrons obtained from humans and rats. The role of these proteins is unknown, but it is clear that they are associated with fat absorption and are quickly removed when the alimentary particles enter the plasma. The origin and turnover characteristics of these proteins is being studied by reinjecting radio-labelled chylomicron proteins.

Studies are also being carried out on recently described particles that appear in the circulation after cholesterol feeding, independently of a rise in the plasma cholesterol concentration. These particles are highly atherogenic in animals.

c. Lipoprotein studies are being carried out with cultured skin fibroblasts to complement metabolic studies in vivo. The possibility that the cholesterol-lowering effect of polyunsaturated fatty acids is due to an increased removal of LDL was tested. LDL were obtained from subjects who had been fed, in turn, diets rich in saturated and polyunsaturated fats. However, fibroblasts metabolized both varieties of LDL similarly. An alternative possibility, that changes in the fatty acid composition of the cells might lead to different rates of LDL uptake was also tested but found not to apply.

d. Fibroblasts were obtained from a child with a very rare disorder in the metabolism of a precursor of cholesterol. This has provided an opportunity to study a less well described pathway of cholesterol synthesis originating from the amino acid, leucine.

Dr. Norio Tada

4. Epidemiology of Lipoproteins
P. Nestel, N. Miller, in association with T. J. Boulton, Children's Hospital, Adelaide, and T. Dwyer, Div. Human Nutrition, C.S.I.R.O., Adelaide.

The possibility that the birth concentrations of HDL or of LDL might predict future coronary disease was tested by obtaining case histories of cardiovascular disease in the families of several hundred infants in whom HDL and LDL were measured at birth. Multiple logistic function analysis in which several lipid variable were tested showed that raised LDL levels were associated with excess coronary disease among grandparents and great-grandparents. HDL at birth was unrelated to familial coronary disease, suggesting that the apparent protective effect of HDL against coronary disease is not genetically determined.

5. Cholesterol Metabolism
P. Nestel, A. Everitt, N. Miller, G. Martin, T. Billington, M. Reardon.

a. Dietary Cholesterol

The studies of cholesterol metabolism during cholesterol feeding in infancy and childhood have been completed. These are the first reported studies showing that the changes in serum cholesterol levels and in cholesterol synthesis and excretion that follow changes in cholesterol intake, are similar in children and adults, indicating that compensatory mechanisms come into play

in early infancy. Additional studies in children with familial hypercholesterolaemia showed normal responses in cholesterol metabolism to increased consumption of cholesterol. Dietary factors do not contribute importantly to the development of familial hypercholesterolaemia, (in contrast to their importance in the much commoner sporadic hypercholesterolaemia).

b. Cholesterol transport in relation to circulating lipoproteins

Coronary heart disease almost always develops as the result of atherosclerosis in the artery, an invariable component of which is the accumulation of cholesterol. The deposition of this cholesterol is influenced by the amount of cholesterol in the circulating lipoproteins.

Previous studies, including our own, have shown that high density lipoprotein (HDL) is closely linked to tissue cholesterol content: circulating HDL levels were inversely related to tissue cholesterol mass and to the degree of atherosclerosis. By contrast, elevated VLDL and LDL led to more cholesterol deposition and atherosclerosis. This was demonstrated in subjects with coronary disease in whom the severity of atherosclerosis was estimated by angiography and the tissue cholesterol content measured in pieces of heart atrium obtained later at surgery.

These findings suggested that HDL had a vital role in removing cholesterol from cells. It had been previously shown by others and by ourselves that when cultured cells such as skin fibroblasts were incubated with LDL, the cholesterol content of the cells rose, but fell in the presence of HDL. It was necessary to show this in vivo in man and appropriate experiments were devised in obese subjects who were losing weight rapidly. Weight loss leads to the movement of cholesterol out of fat cells and by prelabelling that cholesterol with radioisotopic cholesterol, it was possible to show that HDL was the preferred acceptor of cholesterol leaving cells.

The subsequent fate of that cholesterol is important since only the liver and intestine have the capacity tc excrete cholesterol. Others had previously considered that HDL might transport cellular cholesterol directly to the liver for excretion. Two kinds of experiments were therefore devised. In the first series, cholesterol metabolism was studied in subjects with the unusual inherited disorder of hyperalphalipoproteinaemia, or excess HDL. If a function of HDL is to shuttle cholesterol from cells to the liver then these individuals might be expected to show a high turnover of cholesterol in their tissues, increased cholesterol transport through the blood within HDL, and a high rate of excretion of cholesterol and of bile acids which are derived from cholesterol. However, all

Mrs. Andrea Everitt at work in the Lipid Research Laboratory.

Dr. P. J. Nestel, Deputy Director

measurements of cholesterol transport and excretion were normal, suggesting an alternative mode of disposal of HDL cholesterol. One important finding was made in these subjects with high HDL: the amount of cholesterol in tissue pools, calculated from data obtained after injecting radio-labelled cholesterol, was significantly less than normal, confirming the ability of high concentrations of HDL to reduce the cholesterol content of tissues.

Further experiments showed that HDL cholesterol as cholesteryl esters, was preferentially transferred to the other lipoproteins, the VLDL and LDL and in this manner cellular cholesterol that had been initially transferred to HDL could be made reavailable to the cells through LDL. These findings were made by injecting HDL in which the cholesteryl esters had been labelled and observing the almost quantitative transfer initially to VLDL and then to LDL. The eventual transport of cholesterol for excretion might therefore occur through VLDL and LDL, the role of HDL being to scavenge excess cholesterol derived from cellular membranes and that shed from cholesterol-rich surface material of catabolized, larger, triglyceride-carrying lipoproteins.

6. Metabolic Consequences of Obesity
K. O'Dea, P. Nestel, T. Billington.

A distinction between obesity beginning in childhood and that beginning in adulthood has been suggested as an explanation for the variability in metabolic derangements found in obesity. Studies are in progress in which some commonly occurring metabolic changes such as hyperlipidaemia and insulin resistance are being investigated by lipoprotein turnover measurements and insulin binding kinetics. The prevalence of these will be related to the morphology of the obesity, defined from adipocyte size and number.

7. Glucose-insulin responses to refined and unrefined carbohydrates
K. O'Dea, P. Nestel.

Studies have been carried out in normal subjects to determine differences in glucose absorption and insulin secretion following identical loads of carbohydrate given in the unrefined or more refined forms. Comparisons of brown rice versus white rice, wholemeal flour versus white flour have not revealed major differences in glucose-insulin responses. However when the structure of the grain is disrupted, as by grinding rice, glucose absorption is much more rapid and insulin secretion exaggerated. As outlined above, such responses may predispose to overweight and diabetes mellitus.

8. Insulin receptor studies
K. O'Dea.

Insulin receptors on circulating human monocytes probably have the same characteristics as insulin receptors in muscle cells, adipocytes and hepatocytes. Alterations in insulin receptor binding characteristics have been found in several clinical states of altered insulin sensitivity. The number of insulin receptors has been shown to be inversely correlated with the chronic circulating level of the hormone, e.g. the chronic hyperinsulinaemia of obesity is associated with low insulin receptor number which seems to explain the well documented insulin insensitivity of obesity. Changes in affinity of the receptor follow meals. Changes in receptor number appear to reflect chronic changes in the circulating level of the hormone, whereas acute changes influence receptor affinity.

We are conducting a series of studies on the binding of insulin to its receptors on human monocytes:

1. In obesity before and after weight loss.
2. Childhood onset obesity as compared to adult onset obesity.
3. Hyperlipidaemias — particularly the carbohydrate-dependent ones.
4. Dietary changes: high carbohydrate diet where the carbohydrate is predominantly either refined or unrefined.
5. Aborigines: urban and traditional environments.

Lipid Service and Studies

Subjects with hyperlipidaemia are being seen by consultation in the lipid clinic in the outpatient department. Those requiring detailed investigation of lipoprotein metabolism or evaluation of dietary management are studied in the C.R.U. Obese subjects are also being admitted to the C.R.U. for investigations of insulin and lipid metabolism prior to treatment.

Many of these studies can be carried out on an outpatient basis under the close supervision of the Unit's dietitian, Miss Sylvia Pomeroy.

Overseas Visits:

Dr. N. Fidge and Dr. P. Nestel attended the American Heart Association meeting in Dallas and presented some of the Unit's work in two papers: "High density lipoprotein AI and AII Kinetics" and "Overproduction and reduced removal of very low density lipoprotein B-apoprotein in hypertriclyceridemia".

Dr. O'Dea visited several laboratories in England and Europe.

Local Lectures

Dr. P. Nestel and A. Everitt presented papers relating to cholesterol metabolism at the annual meetings of the Australian Nutrition Society and the Australian Society for Medical Research. Dr. Nestel presented a paper on lipoprotein metabolism to the Cardiac Society of Australia and New Zealand. Drs. Fidge, Tada and Nestel each presented a paper at the meeting of the Australian Atherosclerosis Group. Dr. O'Dea presented her findings on carbohydrate and insulin metabolism in Aborigines at the International Congress for Child Psychiatry and Allied Professions and at A.N.Z.A.A.S.

Morphology and Cell Biology Laboratory

Major Research Interests

* THE ROLE OF SMOOTH MUSCLE CELLS AND NON-MUSCLE CELLS IN ATHEROGENESIS.
* BIOLOGY OF THE SMOOTH MUSCLE CELL.
* ARTERIAL CHANGES IN HYPERTENSION

General Outline of Work

The word atherosclerosis is derived from the Greek *athera* (gruel) and *sclerosis* (hardening), and this disease is characterized by the formation of focal intimal lipid deposits in the artery wall. In the early stages of atherosclerosis smooth muscle cells migrate from the media of the artery to localized areas in the intima where they proliferate and produce large amounts of connective tissue. These focal intimal deposits are termed atheromatous plaques. A plaque can develop with time to such a size that it occludes the artery, or a more common and equally harmful effect is that it predisposes the artery to occlusion by thrombosis. In later stages of lesion development cells become engorged with lipid to become what are called "foam cells". Swollen foam cells disintegrate forming a poltaceous mass within the plaque. Although it is known that smooth muscle cells can take up lipid and develop a foam cell-like appearance, the role of other cell types from the intima and blood in the formation of foam cells is not known.

A greater understanding of the biology of the smooth muscle cell must therefore be included as an important part of research into atherosclerosis. We have been investigating factors influencing the phenotypic modulation of smooth muscle cells from their normal contractile state to one in which proliferation and the synthesis of connective-tissue are the major functions of the cell (Phenotypic modulation is the reversible change of cell expression without any concommitant change of type-specific character). This phenotypic modulation occurs when smooth muscle cells migrate from the media to the intima in the initial stages of an atheromatous plaque and can be detected under the electron microscope by a change in the cells' morphology. Contractile state smooth muscle cells have large numbers of myofilaments within their cytoplasm, while modulated smooth muscle cells lack most of the myofilaments (and therefore cannot contract) and are filled with synthetic apparati.

An approach we have employed to determine the factors involved in the modulation of smooth muscle is to grow isolated contractile smooth muscle cells in culture. This technique allows the controlled manipulation of the cells' environment thereby enabling an assessment of the relative importance of individual factors on the process of modulation. We believe that these studies may lead to a greater understanding of how atheromatous plaques form, which in turn will eventually lead to ways to prevent or reverse their development.

A characteristic feature of long term hypertension is an increase in the thickness and rigidity of arteries, which is due, at least in the aorta, to an increase in the size of the smooth muscle cells and the amount of connective tissue between them. This increase in thickness and rigidity means an increased work-load for the heart with a resultant hypertrophy of cells. We are examining 1) the role of the sympathetic nervous system in the etiology of hypertension; 2) the evolution and regression of vascular changes induced by hypertension and their involvement in atherogenesis; 3) the effect of reversal of hypertension on blood vessels, with particular emphasis on those smooth muscle cells present in the intima.

Hypertension has been developed in rabbits by bilaterally cellophane wrapping their kidneys, and a colony of spontaneous hypertensive (genetic) rats (Okamoto-Aoki strain) has recently been established within the Institute.

SPECIFIC PROJECTS

1. **Muscle and Non-muscle Cells in Atherosclerotic Plaques: Staining with FITC-labelled Antibodies to Muscle-specific Proteins**
   J. H. Campbell, G. R. Campbell, U. Gröschel-Stewart*, D. Vesselinovitch* and R. W. Wissler*.

While it is generally considered that smooth muscle cells constitute the major cell type in atherosclerotic plaques, some authors maintain that monocyte-derived macrophages play a major role. Clear ultrastructural classification of the cells in lesions is difficult due to their general mesenchymal appearance, especially after lipid accumulation.

In order to determine the proportion of smooth muscle cells to non-muscle cells in atherosclerotic plaques, 4μm frozen sec-

Standing (left to right): Dr. Gordon Campbell, Paul Shallard. Seated: Lucy Popadynec, Dr. Julie Campbell, Janet McConnell.

tions of monkey lesions were stained with FITC-labelled antibodies to actin, myosin and tropomyosin from chicken gizzard smooth muscle. These antibodies stain smooth muscle proteins but not the corresponding proteins from non-muscle cells such as fibroblasts, endothelial cells or monocytes.

It was found that greater than 95% of the cells in intimal lesions stained intensely with the antibodies to actin and tropomyosin indicating that they are of smooth muscle origin. The same cells stained with the antibody to smooth muscle myosin, however the reaction was weak compared with that of the smooth muscle cells of the media and those immediately next to the internal elastic lamina on the luminal side, suggesting that the smooth muscle cells in the body of the lesion have lost myosin and undergone a phenotypic modulation.

2. Antibody Staining of 10nm (100Å) Filaments in Cultured Smooth, Cardiac and Skeletal Muscle Cells.

G. R. Campbell, J. H. Campbell, U. Groschel-Stewart*, J. V. Small* and P. Anderson*.

Round smooth-surfaced filaments approximately 10nm in diameter (range 8-12nm) are now generally recognised as a ubiquitous and distinct class of cytoplasmic filaments. These filaments, commonly referred to as 10nm or 100Å filaments, have been observed in a large number of different cell types including fibroblasts, leukemia cells, Hela cells, epithelial cells, endothelial cells, skeletal muscle, cardiac muscle, Purkinje fibres and nerve. Their morphological identity with tonofilaments of epithelial cells early suggested their involvement in structural support although they have also been implicated in processes such as intracellular transport of organelles and in axoplasmic transport in neurons. An increase in the numbers of 10nm filaments in some cells in pathological conditions such as cardiac myxomas, neuroblastoma, human breast tumours, hypertrophied smooth muscle caused by stenosis of the ileum, rhabdomyoblastomas and leiomyosarcomas has been observed.

Antibodies were prepared against the SDS denatured 10nm filament protein "skeletin" extracted from chicken gizzard. The specificity of the antibody to the 10nm filament protein was shown by immunodiffusion before and after purification of the protein on SDS gels by the enzyme-linked immunoabsorbent assay (ELISA) and by its specific absorption with purified skeletin. In immunofluorescence (where preimmune sera and antigen-absorbed antisera give negative results), cultured cardiac, skeletal and smooth muscle cells and endothelial cells stained intensely.

Dr. Julie Campbell changing medium of a culture.

No staining was observed in fibroblasts present in these cultures, nor was there staining in glial cells or nerve cell bodies and fibres from sympathetic ganglion and Auerbach's plexus cultures. Smooth muscle cells (regardless of their source and phenotypic state) and endothelial cells stained intensely in the perinuclear region and in a fine filamentous network that existed throughout the cytoplasm. In both chick and rat skeletal and cardiac muscle (cultures and frozen sections) filamentous network staining was observed, while in rat muscle the antibody was additionally localized in a regular pattern in the region of the Z-disc, and in the case of cardiac muscle associated with the intercalated disc. The addition of 10^{-6}M colchicine to the culture medium of smooth and striated muscle and endothelial cells resulted in an aggregation of the filaments in the nuclear region.

Cultured smooth and striated muscle and endothelial cells and freshly isolated smooth muscle cells extracted of actomyosin and tubulin by high and low ionic strength solutions gave a staining pattern similar to non-extracted cells and in the electron microscope exhibited filaments of predominantly 10nm diameter.

This antibody will provide further information on the role of non-muscle cells in the etiology of atherosclerosis, as we can distinguish smooth muscle and endothelial cells from fibroblasts and blood-borne cells. In conjunction with antibodies to native actin, myosin and tropomyosin from smooth muscle which distinguish smooth muscle cells from non-muscle cells such as endothelial cells and fibroblasts, the antibodies will be used to stain frozen serial sections of lesions in different developmental stages to determine the proportion of muscle to non-muscle in the lesions and from where these cells are derived.

3. Modulation of Monkey Vascular Smooth Muscle In Culture and Response to Platelet Factor

J.H. Campbell, G.R. Campbell and R. Ross*.

It has been suggested that serum factors, in particular a factor derived from platelets, are the cause of migration and proliferation of smooth muscle cells in the formation of atheromatous plaques.

We have shown that isolated smooth muscle cells from the adult monkey aorta modulated from the contractile functional state to the synthetic and proliferative state after 8 days in culture, irrespective of the concentration of monkey whole blood serum (WBS) in the culture medium. Once modulation occurred the cells in 0 and 0.5% WBS did not proliferate, while those in 1.5 and 10% WBS responded in a dose dependent manner over the next 7 days. When cells were placed in the same concentrations of platelet-deficient serum (PDS), modulation occurred at day 8 but this was not followed by a significant increase in cell number at any serum concentration by day 15. When platelet factor was added to PDS to bring its concentration back to that in WBS the mitogenic activity of the serum on modulated cells was restored. This demonstrated that i) platelet factor does not cause, inhibit or stimulate the process of modulation; ii) platelet factor is a mitogen of modulated smooth muscle cells, but cannot stimulate contractile state smooth muscle cells to divide.

4. LDL Metabolism In Modulating Smooth Muscle Cells

J.H. Campbell, J. Ma, L. Popadynec, G.R. Campbell and P. Nestel.

The uptake of low density lipoprotein (LDL) into smooth muscle cells has been implicated in the formation of atheromatous plaques.

We have been studying changes in LDL metabolism during modulation of smooth muscle from the contractile to synthetic state. The model which we used was cultured rabbit aortic smooth muscle cells which modulate on days 7 to 8. It was found that LDL binding, internalization and degradation was high in the contractile state cells, decreased sharply on modulation, then slowly increased over the next few days. There was no change in the *de novo* synthesis of cholesterol before, during or after modulation.

5. Antibody to Human Uterine Myosin
J.H. Campbell, G.R. Campbell and U. Gröschel-Stewart*

Myosin was prepared from surgical specimens of gravid and non-gravid human myometrium, and antisera produced in rabbits. The IgG-enriched fraction of the immune-sera was used in the FITC double antibody technique to stain fresh frozen sections and cells in culture and compared with that obtained using antibodies to chicken gizzard myosin.

Uterine and gizzard myosin antibodies intensely stained cryostat sections and cultures of contractile state smooth muscle cells of various origins. However, differences in staining intensities were noted when the reactivity of the two antibodies was compared on modulated smooth muscle cells, fibroblasts and blood platelets. Whereas modulated smooth muscle cells reacted weakly or not at all with the gizzard myosin antibody, the uterine myosin antibody still gave a strong reaction but with a diminution in intensity as compared with that of contractile smooth muscle cells. Fibroblasts did not stain with the gizzard myosin antibody, but gave a moderate reaction with the uterine antibody. Similarly, platelets stained with the uterine antibody while the gizzard antibody did not stain the platelets beyond the pre-immune serum level. When the uterine anti-myosin was twice absorbed on crude platelet actomyosin it no longer gave a reaction with blood platelets or fibroblasts but still stained smooth muscle cells.

This suggests that the uterine IgG fraction not only contained an antibody to smooth muscle contractile myosin but also to non-muscle or cytoplasmic myosin.

6. Identification of Cardiac Muscle in the Media of Rat Azygos Vein.
J.H. Campbell and G.R. Campbell

Cell culture of azygos vein from the neonatal and adult rat produced fusiform-shaped cells which with phase contrast microscopy resembled smooth muscle. They contracted spontaneously at a rate of 5 to 120 per minute with a contraction cycle lasting 120 ± 20 msec. In contrast, smooth muscle cells from veins such as the saphenous contracted spontaneously at less that 1 per minute and with a contraction cycle of 10 to 20 seconds.

Staining of azygos vein cultures with FITC-labelled antibodies to smooth muscle myosin gave no reaction, while staining with antibodies to cardiac myosin revealed the presence of ordered A-bands typical of cardiac muscle. Serial sectioning of the whole azygos vein and examination under the electronmicroscope showed that the media of the vein from the heart to below the fifth rib consisted entirely of cardiac muscle. Beyond this region smooth muscle cells began to appear in a separate inner layer increasing in proportion until at the point of bifurcation of the vein the cardiac muscle layer had disappeared.

Cultures of rat aorta are used by several laboratories in the study of the functional characteristics of isolated vascular smooth muscle cells. The cardiac cells of the azygos vein are very likely the same cells described by some of these workers as "high-shortening velocity smooth muscle cells". Since the azygos vein can be as close as 1μm to the aorta and is enclosed in the same fascia, our studies emphasize that extreme care must be taken as to cell origin when using culture as a model in physiological experiments.

7. Trophic Interactions Between Nerve and Vascular Smooth Muscle In Transplants to the Anterior Eye Chamber
G.R. Campbell, J.H. Campbell, N.A. Short*, R. Robinson* and K. Hermsmeyer*.

To date it is not clear whether the increase in peripheral resistance observed in essential hypertension is due to increased sympathetic nerve activity, an alteration in the properties of the vascular smooth muscle, or a combination of the two. The spontaneously hypertensive rat (SHR) of the Okamoto strain is widely used as a model of essential hypertension. Recently, it has been demonstrated that the membrane potential (E_m) of vascular smooth muscle cells of the caudal artery of SHR have a less negative E_m than those from matched Kyoto normotensive rats (KNR) at 16°C, but not at 36°C over a range of $(K^+)_o$ from 2.7 mM to 150 mM. This altered E_m electrogenesis correlates with greater responses to midrange concentrations of norepinephrine by SHR caudal artery strips than KNR.

The anterior chamber of the eye is used as a site for transplantation as it is an immunologically privileged site bathed by the aqueous humour which acts as a nutrient medium minimizing degeneration while the tissue attaches to the host iris and becomes vascularized at day 3 or 4. We have shown that reinnervation of the transplant by autonomic nerves of the host iris begins at 1 to 2 weeks and functional neuromuscular transmission comparable to that in the normal tissue can be observed by 4 weeks.

Changes in E_m electrogenesis at 16°C of 2 week KNR caudal artery smooth muscle transplanted to the anterior eye chamber of adult SHR and reinnervated by sympathetic nerves of the host iris were examined.

Caudal artery transplanted into the anterior eye chamber attached to the host iris, became vascularized then functionally reinnervated by host sympathetic nerves.

When caudal artery from adult SHR was transplanted into a KNR host, the E_m of the reinnervated muscle cells was not altered after 6-16 weeks. Similarly, the E_m of adult KNR caudal artery was not altered in a SHR host. However, if caudal artery was taken from 2 week old rats (in which hypertension and the E_m differences between adult KNR and SHR had not yet developed) and cross-transplanted into adult hosts for 6-12 weeks, then the artery from the SHR strain developed the higher E_m values characteristic of the KNR strain. Likewise, artery from 2 week KNR transplanted into an adult SHR host and reinnervated by its nerves developed the low E_m values characteristic of the SHR strain. That is, a potentially KNR caudal artery developed the properties of a SHR in a SHR host and a potentially SHR caudal artery developed the properties of a KNR in a KNR host. The results suggested that whatever factors affect membrane properties of the SHR, they were present at least some, if not all the time, in the adult animal.

The results provide evidence that the E_m alteration of the SHR caudal artery is independent of structural changes which occurred in the artery as a result of extra stress on the walls due to increased blood pressure as the transplants are not subject to these changes. The differences between the SHR and KNR are not genetic in origin since the two week KNR caudal artery placed in a SHR environment develops properties consistent with the SHR. This suggests that altered E_m electrogenesis is not the factor initiating hypertension, but rather the smooth muscle cells are responding to an external factor. This factor could be either altered neural influences or circulating humoral agents acting at a certain stage of development which may induce hypertension through a mechanism such as increased norepinephrine sensitivity due to an altered E_m.

Dr. Gordon Campbell and Paul Shallard at the Electron microscope.

8. Arterial Changes In Spontaneously Hypertensive rats

G.R. Campbell and J.H. Campbell

The ultrastructure of the caudal artery of spontaneously hypertensive rats (SHR) of the Okamoto-Aoki strain has been examined.

In the 12-16 week animal the caudal artery demonstrated both hyaline arteriosclerosis and hyperplastic arteriosclerosis. The intimal proliferation of smooth muscle cells was localized to regions which appeared intermittently throughout the length of the vessel. These areas were initially observed about three weeks after the onset of hypertension in these rats (i.e. at about seven weeks of age). In older animals the intimal proliferative areas were enlarged and often contained large numbers of small smooth muscle cells oriented parallel to the long axis of the artery (i.e. at right angles to the smooth muscle cells of the media). In most of these smooth muscle cells the major portion of cytoplasm was filled with myofilaments although some contained a

large number of organelles usually associated with synthesis. Irregular-shaped cells occurred, many with an appearance which previously has been termed "moth-eaten". Between cells were long strands of material resembling basal lamina and a large number of electron-dense granules and membranous figures. The regions of artery between proliferative areas appeared relatively normal in young animals. However, in older SHR interspersed between areas of intimal proliferation were regions in which there was an interrupted or completely absent internal elastic lamina. Smooth muscle cells from this region were often separated by a wide extracellular space which contained reduplicated layers of basal lamina-like material and many electron-dense granules.

9. Transplantation of Arteries to the Anterior Eye Chamber

G.R. Campbell and J.H. Campbell

Rat caudal artery transplanted to the anterior eye chamber attaches to the iris and becomes vascularized within a few days. Nerves grow in and by 6 weeks the transplant resembles the *in vivo* caudal artery. Transplants of aorta, however, demonstrate little re-innervation which is consistent with their normal innervation pattern. It is not known whether this specific reinnervation pattern is due to a mechanical phenomenon (such as the density of connective tissue) inhibiting the ingrowth of nerves or to an innate property of the respective arteries. However, electrophysiological analyses of fetal rat hippocampus, cerebellum and heart transplanted to the anterior eye chamber suggest the target organ (in this case transplant) plays an important role in determining the type and pattern of reinnervation. Further evidence for target organ influence in the case of arteries comes from experiments in which sympathetic nerves and isolated medial smooth muscle cells from rabbit thoracic aorta (sparsely innervated) or rabbit ear artery (densely innervated) were grown in joint culture, the nerve fibres forming long-lasting associations with many of the muscle cells from the ear artery but only transitory relationships with cells from the aorta.

10. Lack of Effect of Receptor Blockers on the Formation of Long-lasting Associations Between Sympathetic Nerves and Cardiac Muscle Cells in Vitro.

G.R. Campbell, J.H. Campbell and G. Burnstock*.

It was shown previously that sympathetic nerves form long-lasting associations with cardiac muscle cells in culture. Nerve fibres palpate all cells in the culture for about 50 min. after making the initial contact; if the target cell is a fibroblast the nerve moves on, but if it is a muscle cell it forms an intimate relationship with it that can persist for many days. The synapses formed become functional and stimulation of sympathetic nerves produces either a decrease or increase in the rate of spontaneous contraction of the muscle cells. The inhibitory response is blocked by the muscarinic antagonist hyoscine, and it seems likely that the excitatory response is mediated by β-adrenoceptors since it is well known that these mediate the action of noradrenaline released from sympathetic nerves to the heart.

The mechanism by which sympathetic nerves 'recognise' muscle cells (as opposed to fibroblasts) is unknown. The object of the experiments was to see if receptor sites are involved in the process of 'recognition'. In particular, the interactions of sympathetic nerves with cardiac muscle cells were studied in the presence of propranolol and hyoscine to determine whether long-lasting association still takes place. In the presence of 10^{-8} to 5×10^{-5} g/ml dl-propranolol hydrochloride or (-) scopolamine hydrobromide nerve fibres from the sympathetic ganglion explants grew over the cells. Whenever they contacted the muscle cells, the fibres branched and formed fine varicose networks. The attachments which formed between the nerve and muscle appeared to be very firm since with every contraction the nerve fibres moved. They were also long-lasting and were frequently observed for up to 6 days. By contrast, all nerve associations with non-muscle cells were transitory.

We conclude from these experiments that receptors to the neurotransmitters acetylcholine or noradrenaline released from sympathetic nerves are not involved in the mechanism of 'recognition' of cardiac muscle cells by sympathetic nerves, *or* that the interaction of nerve and target cell involved sites on the receptor molecules which are not identical to the sites of transmitter binding. This is consistent with the claim that acetylcholine (nicotinic) receptors are not necessary for the formation of skeletal neuromuscular junctions *in vitro*.

CARDIAC SURGERY GROUP: (Left to right) — Michelle Bebbington, Sr. Jan Dixon, Dr. Franklin Rosenfeldt, Christine Boyes, Andrew Fambiatos.

Cardiac Surgical Research Unit

Investigation of the problems of cardiovascular surgery was begun in the Baker Institute in 1945 by C. J. Officer-Brown, the first cardiac surgeon at the Alfred Hospital. In 1956 a pump oxygenator similar to one used by American surgeons was developed and tested in the Institute. This paved the way for the first successful open heart operation in Australia which was performed in the Alfred Hospital in 1957. Over the succeeding years surgeons at the Alfred Hospital have continued investigative work at the Institute to deepen their understanding of the physiology of cardiac surgery and to improve the practice of cardiac surgery in the hospital.

March 1978 saw the arrival of Dr. Franklin Rosenfeldt and the establishment of a Cardiac Surgical Research Unit as a department of the Institute. Equipment necessary for investigations in animals involving heart-lung bypass was set up and a research programme commenced. Dr. Rosenfeldt has been joined by Andrew Fambiotis, a Science graduate from Melbourne University. Work in the animal operating theatre has been greatly facilitated by the experience of Sr. Jan Dixon and her staff and by the assistance of Mr. Ben Smith, a heart-lung perfusionist from the Alfred Hospital. A feature of the research programme from the beginning has been a close working relationship with the cardiac surgeons and cardiologists in the Hospital, enabling improvements in surgical techniques developed in the Institute to be immediately applied for the benefit of patients.

RESEARCH INTERESTS

* Myocardial Preservation During Heart Surgery
* Cardiopulmonary Bypass
* Coronary Artery Surgery
* Surgical Treatment of Cardiac Arrhythmias
* Treatment of Intrapleural Infection

GENERAL SUMMARY

Myocardial Preservation

Over the last 10 years mortality rates for open-heart surgery in most hospitals have fallen from 10-15% to 1-5%. This dramatic reduction has been accompanied by a similar reduction in the incidence of myocardial infarction (heart attack) occurring during heart surgery. These improvements have resulted to a large extent from better appreciation of the vulnerability of the pumping muscle of the heart to damage during operations and from refinements in the means of protecting against this damage.

The pump oxygenator can take over the function of the heart and lungs during surgery but to provide the surgeon with a quiescent heart in an almost bloodless field, the coronary blood flow to the heart muscle is interrupted. The muscle is then placed in a state of "suspended animation" (cardioplegia) by perfusing it with an iced cardioplegic solution containing potassium and other ions. The ions produce immediate cardiac standstill and cooling of the heart reduces its oxygen requirements so that under optimal conditions the heart can remain in this protected state for two or more hours and subsequently return to normal function. The most important aspect of the cold cardioplegic technique is the maintenance of a low cardiac temperature. It is this aspect of the technique which has been the subject of the initial investigations in the Cardiac Surgical Research Unit during 1978.

Arrhythmia Surgery

The regular beat of the heart is generated by the cardiac pacemaker and the system of conducting fibres throughout the heart. In certain disease states this regular beat becomes disordered and bursts of rapid beating may cause the patient suddenly to collapse and even die. Most of these rhythm irregularities can be satisfactorily controlled by drug treatment but there are a group of patients who continue to suffer disabling symptoms in spite of maximal drug treatment. Over the last 10 years some of these refractory cases have been successfully treated by operations to modify or interrupt the conducting system and in some instances to replace it by an implanted artificial pacemaker. This new branch of cardiac surgery has developed mainly in the United States, but has also been taken up at the Royal Prince Alfred Hospital in Sydney and now is being introduced at the Alfred Hospital with help from the Baker Institute.

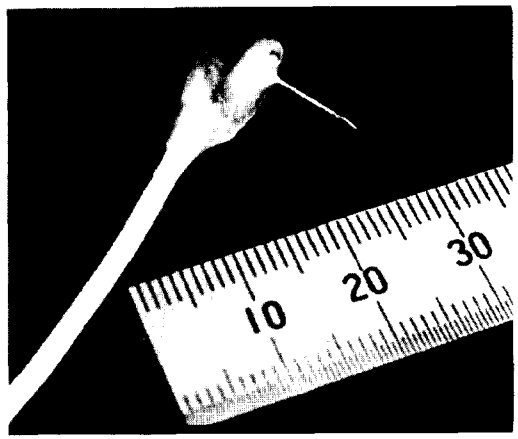


Fig. 1. Miniature sensor to measure the temperature of the heart during surgery.

PROJECTS

1. Development of Miniature Cardiac Temperature Probe

In collaboration with the Department of Communication Engineering at the Royal Melbourne Institute of Technology and the Baker Institute Workshop a miniature needle probe has been developed for measuring the temperature of the heart during open-heart surgery. The semiconductor sensor has a more linear output than a thermistor and being of microscopic size can be fitted into a hypodermic needle fine enough to be inserted safely into the human heart at the time of surgery. This probe has proved convenient and safe and is currently being used in the Alfred Hospital to provide the surgeon with a continuous readout of cardiac temperature while he operates. The feasibility of producing this probe commercially is being examined. The availability of these probes has made possible two projects concerned with improvements in techniques of cooling the heart, namely the use of the cardiac spacer and the recirculating cooler. The initial work on these projects was done by a National Heart Foundation Vacation Scholar, Richard Davey.

2. Cardiac Spacer

The heart is kept cold during surgery by irrigating its surface with cold fluid. Occasionally, particularly if the heart is enlarged, the cold fluid fails to circulate freely between the back of the heart and the chest wall. The inadequately cooled region of the heart may thus be damaged. In collaboration with Bly's Industries, a Sydney based plastics firm, a mesh pad (spacer) has been produced to lift the heart forwards and allow free flow of cooling fluid on all surfaces of

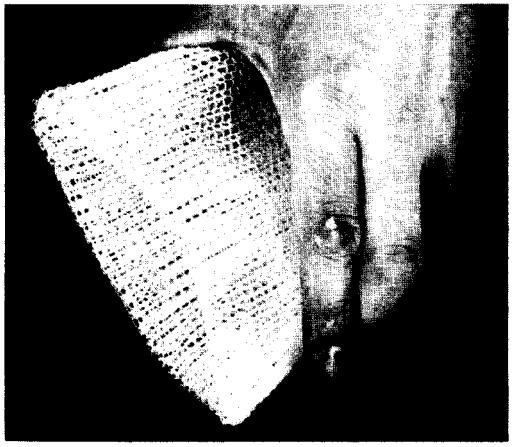


Fig. 2. Mesh spacer used to improve cooling of the heart.

the heart. A trial is being conducted during heart surgery at the Alfred Hospital. In one group of patients the spacer is used and temperature measurements from two regions of the heart are compared with comparable measurements in a second group in which the spacer is not used.

3. Recirculating Cooler

The usual source of cold fluid to irrigate the heart during operations is a bottle of sterile intravenous fluid from a refrigerator. Often this fluid is not properly cooled before use and also prolonged operations may require 20 or more bottles of fluid. A British cardiac team have developed a recirculating cooling system whereby the cold fluid is sucked out from around the heart, re-cooled by a heat exchanger and refrigeration unit and returned to the heart. We have simplified this system and replaced the heat exchanger and refrigerator by a long coil of thin walled plastic tubing packed in a freezing mixture. Initial results indicate that this system provides a greater flow of fluid at a lower temperature than the system using multiple bottles. At present a trial is being conducted in patients to compare the heart temperature attained by the recirculating cooler with that attained by the bottle techniques.

4. Hypothermic Damage

Some investigators have suggested that if the rat heart is cooled to below 10°C, permanent damage may result. Efficient cooling techniques in the human may result in at least the outer layers of the heart being as cold as 4°C and therefore susceptible to this form of damage if it exists. Thus, it is important to determine the optimal temperature for cardioplegia. This information has great importance in the field of human heart transplantation. When the donor heart is transported to a distant recipient it is usually stored in fluid at 4°C and could thus be damaged. The problem is being studied in dog hearts removed from the body and supported by the circulation of another dog. The hearts are deprived of their blood supply and cooled to various temperatures. The function, composition and microscopic structure of the heart muscle is compared before and after cooling.

5. Surgical Treatment of Disturbances of Heart Rhythm

In collaboration with the Cardiac Diagnostic Service and the Electronics Department of the Alfred Hospital and Baker Institute, equipment has been assembled to map out precisely the conducting system of the heart at operation. In the Institute, tests were done in dogs of a technique new to Australia in which parts of cardiac conducting system are blocked by a cryosurgical (freezing) probe. Following these tests, sufficient confidence was gained to begin mapping out and operating on the conducting system in man. By the end of 1978 two patients had been successfully treated and more operations are planned for 1979.

6. Treatment of Intrapleural Infection

An empyema is an abscess in the pleural space between the lung and the chest wall. It is seen as a complication of lung abscess, severe pneumonia and occasionally follows surgery for removal of lung tissue or operations on the oesophagus. The conventional method of treating this condition is to administer antibiotics and insert a drainage tube through the chest wall to allow the pus to escape until the abscess heals. This process usually takes 2-3 months. We have developed an alternative method of treatment in which the infected area is irrigated cyclically with dilute antiseptic solution through a specially designed double lumen tube. Once the infection is eradicated the tube is removed and the wound sealed. Some mild side effects were noted in patients having this treatment due to absorption of the antiseptic into the bloodstream. This led to a study at St. Thomas' Hospital, London, of the absorption of antiseptic from the pleural space. A modified form of this treatment has been successfully used in one patient in the Alfred Hospital with no evidence of significant absorption of antiseptic into the bloodstream. Further studies are planned of the absorption of antiseptics from the pleural space in animals and in man.

Standing (left to right): Dr. Allan McLean, Dr. James Angus, Peter Cahill. Seated: Elizabeth Anderson, Cheryl Isbister.

Pharmacology Unit

MAJOR RESEARCH INTERESTS

* RECEPTOR PHARMACOLOGY OF CARDIAC AND VASCULAR TISSUES
* EXPERIMENTAL AND APPLIED PHARMACOLOGY OF DRUGS USED TO TREAT CARDIOVASCULAR DISEASES
* THERAPEUTIC MONITORING

GENERAL SUMMARY

Both experimental pharmacology and applied (clinical) pharmacology laboratories have been established over the last six months.

The aim of the experimental animal pharmacology laboratory is to assess the mode of action of drugs in isolated tissues and in intact animal experiments. In isolated tissue experiments pieces of heart muscle on blood vessels are removed from experimental animals and placed in warmed oxygenated physiological salt solution. The tissue responses to drugs can thus be examined directly without the influences of autonomic neural reflexes, changes in blood flow or circulating hormones. This approach also allows a known bath concentration of drug to come into equilibrium with the tissue without significant drug metabolism.

In experiments in intact rabbits and dogs, various physiological parameters can be monitored using blood flow meters, pressure catheters and radioactive microspheres. In these whole animal preparations, drug action on circulation can be investigated before and after surgical modification of the circulation (e.g. renovascular hypertension, portacaval shunts) or blockade of the autonomic nervous system.

In the clinical pharmacology laboratory initial efforts were directed towards the establishment of analytical facilities to support clinical and investigational efforts. Drug clearance measurements have been developed as a means of defining the functional state of the liver and a study has been made of effects of perturbations in blood flow following food, vasodilator drugs or portacaval shunting.

DETAILS OF PROJECTS

1. **Pharmacology of Vascular Smooth Muscle and Vasodilator Drugs**
   A.J. McLean, A. Bobik and J.A. Angus

The responsiveness of arterial and venous smooth muscle to a range of vasodilator drugs varies considerably and correlates with the efficacy of these agents in lowering blood pressure. The vasodilator drugs represent useful probes for exploring the differences in smooth muscle activation in normotensive and hypertensive animals.

This is of particular interest since vasodilators appear to cause a net decrease in intracellular calcium after a contractile stimulus.

We will explore the question of differential reactivity of vasodilators quantitatively in humans, intact animals and in isolated tissue experiments. The cellular mechanism of action of vasodilators particularly in calcium handling and in cyclic nucleotide fluxes will be examined.

2. Modulation of Cardiac Autonomic Transmission
J.A. Angus

Receptors located on sympathetic nerve terminals may be physiologically important in modulating the release of transmitter noradrenaline, particularly at low frequency of stimulation. A number of antihypertensive drugs have been shown to modify the overflow or release of noradrenaline in pharmacological experiments. Therefore, clinical responses to these drugs have been considered in the light of both pre- and post-junctional effects.

We have been particularly concerned with developing preparations whereby the cardiac sympathetic nerve fibres can be stimulated selectively without affecting the muscle directly or the synchronism of the contractile state. Guinea pig left atria are stimulated by a punctate electrode to contract 95 times/min. Immediately following the depolarisation pulse from this electrode field electrodes placed either side of the tissue deliver 1-4 pulses during the next 40 ms when the muscle is depolarised. This field stimulus activates the sympathetic nerve fibres in the atria to release transmitter which causes a marked increase in contractile force. Using this technique we will examine the effect of various antihypertensive drugs and agonists such as adrenaline, histamine and angiotensin which have been shown to alter transmitter noradrenaline overflow. We will attempt to establish whether these prejunctional receptors have a physiological role in autonomic transmission.

3. Vascular histamine receptors
J.A. Angus and P.I. Korner

Histamine infusions in the conscious rabbit cause both vasoconstriction and vasodilation. Previously we have defined the receptor subtypes responsible for these actions by the use of selective H_1 and H_2-receptor antagonists. Recently very specific and potent H_2-receptor agonists have become available. Under conditions of autonomic nervous system blockade we will use radioactive microspheres to measure quantitative organ blood flow distribution changes during selective H_1-or H_2-receptor stimulation. These methods will be used to assess the role of H_1-and H_2-receptors in the vascular histamine response and compare with vascular effects of endogenous histamine released by guanethidine.

4. Effect of Hypothermia on Isolated Cardiac Muscle
J.A. Angus and F. Rosenfeldt

Papillary muscles and strips of ventricular wall removed from guinea-pig and dog hearts will be used to assess the effect of hypothermia on cardiac muscle. Under conditions of the isolated organ bath, the contractility of cardiac muscle in response to pacing, calcium, inotropic drugs and hypoxia will be assessed before and after varying periods of hypothermia as produced in 'open-heart' surgical procedures. We will attempt to assess the therapeutic advantage of different cardioplegic solutions in preserving function and later use pieces of human papillary muscle removed during surgery. To compare with the animal tissues from a pharmacological point of view we will assess changes in receptor subtype that is thought to occur during hypothermia.

5. Hepatic Drug Metabolism and Hepatic Blood Flow
A.J. McLean, A. Bobik, G. Jennings and F.J. Dudley

Functional changes in hepatic blood flow are recognised as important in altering the clearance of a variety of important therapeutic agents (e.g. lidocaine, propranolol, propoxyphene). Little account has been taken of the fixed changes in flow which accompany cirrhotic liver disease or functional pertubations known to be associated with the ingestion of food or drugs.

We have undertaken an investigation of these influences both because of their therapeutic importance, and because a combination of such measurements may yield better descriptions of the vascular patterns within the liver.

In initial studies we have established that simultaneous administration of propranolol (1 mg/kg) and hydralazine (25, 50, 100mg) orally results in significant increases in the peak concentration and the amount of propranolol in the general circulation (Fig. 1). Measurements of absorption using ^{14}C-propranolol have shown that gut absorption does not change, while clearance after intravenous administration (0.2 mg/kg) also is little changed. These results indicate an im-

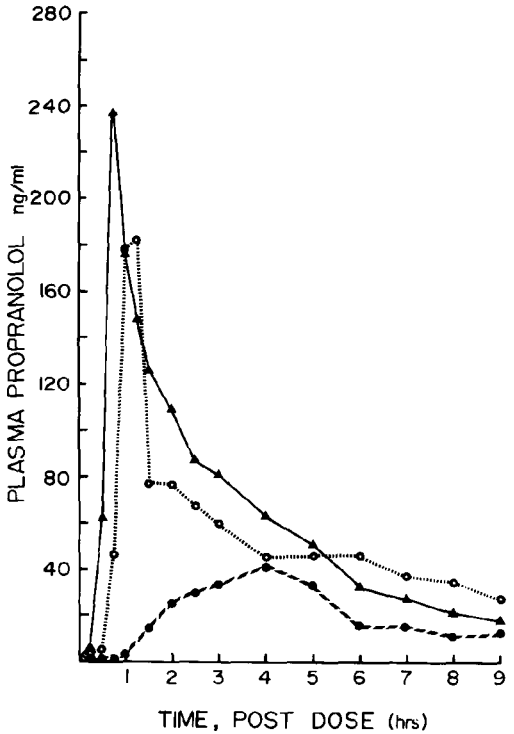


Figure 1

Influence of hydralazine on plasma concentration — time profiles for propranolol
● *Oral propranolol, 1 mg/kg, alone*
○ *Oral propranolol, 1 mg/kg, with 25 mg hydrallazine orally*
▲ *Oral propranolol, 1 mg/kg, with 50 mg hydrallazine orally*

portant drug interaction between propranolol and hydralazine.

Future studies are planned to quantitate changes in blood flow (using IGG clearance measurements) after various stimuli to the splachnic vascular bed on both normal subject and patients with liver disease.

6. Influence of Surgically-Induced Portacaval Shunts on Systemic Availability of Propranolol in Dogs
A.J. McLean, E.I. McInnes and F.J. Dudley

We are exploring the changes in both first-pass clearance and systemic clearance resulting from the creation of Eck (portacaval) shunts in dogs. We have confirmed observations in the literature that post-operatively dogs develop classical neurological sequelae normally observed in subjects with cirrhosis — changes in mood and conscious state, ataxia and hindlimb weakness if meat-feeding is continued even in minor amounts. This model will be used to develop and assess methods of assessing hepatic blood flow in health and disease.

7. Influence of Gastrointestinal and Renal Disease on Sulfamethazine Disposition
A.J. McLean and A. Bobik

The genetically determined capacity of subjects to N-acetylate substrates (acetylator phenotype) is the single important determinant of dosing regimens with major therapeutic substances (e.g. isoniazid, procainamide, hydrallazine). In clinical practice, metabolic clearance is rarely determined, rather a patient is dosed with a model substrate (e.g. sulfamethazine) and then measured of parent substrate and N-acetylated substrate are made in plasma samples or refined urine collections. Recent evidence of non-linear pharmacokinetics in animals and man has led to the predicition that delay in absorption or decreased renal clearance will lead to errors in assignment of phenotype.

Preliminary results in patients with mild to moderate degrees of renal impairment confirm predictions related to renal disease. Studies are proceeding on subjects with various types of malabsorption process.

8. Study of Patterns and Utility of Drug Administration to Hospital In-Patients
C.V. Wellington, C. Guest & A.J. McLean

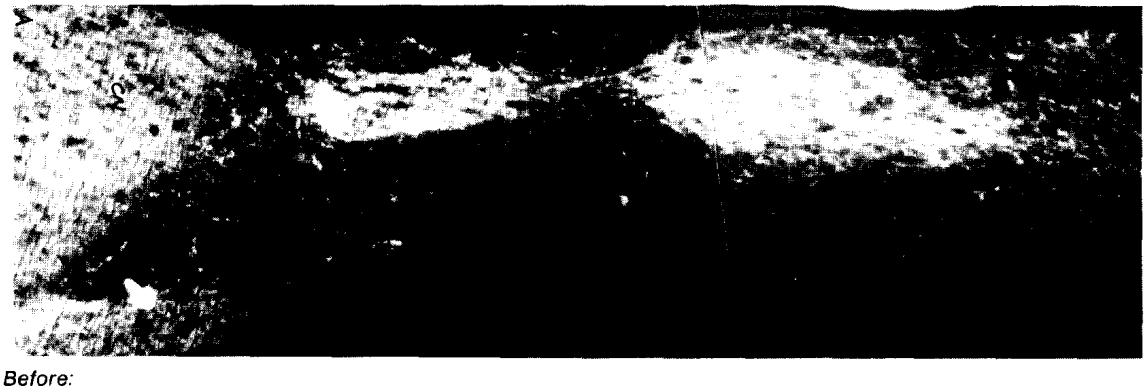
Pharmacokinetically based interpretations of drug concentrations measured in plasma from patients allows an assessment of the adequacy of dosing of the individual patient with reference to an accepted therapeutic range for each drug. A pilot survey on in-patients has been undertaken since November 1978. The preliminary results that the incidence of potentially subtherapeutic and toxid drug concentrations is significant (approximately 30%) and comparable to the results from local and overseas centres. A prospective study is planned with future data retrieval to include relevant details of clinical condition in addition to drug concentration.

FLUORESCENCE HISTOCHEMICAL DEMONSTRATION OF CENTRAL CATECHOLAMINERGIC PATHWAYS

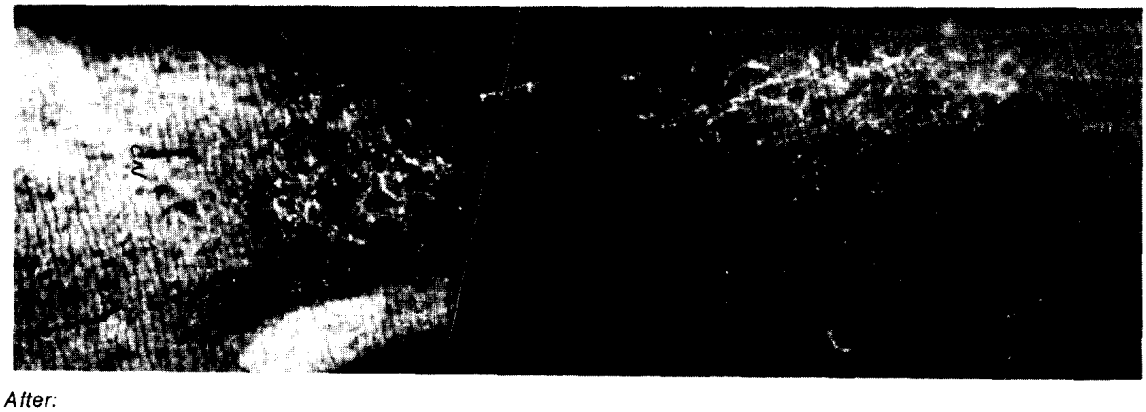
Catecholamine-containing neurons and their processes are closely associated with many regions of the brain which are known to be involved in the regulation of cardiovascular function. Intracisternal injection of 6-hydroxydopamine (6-OHDA), which selectively damages these neurons, produces acute hypertension and modifies the baroreceptor-heart period reflex, the nasopharyngeal reflex, the response to arterial hypoxia and the Valsalva-like reflex. The nature of the damage produced by 6-OHDA makes it very difficult to accurately assess the extent of damage using biochemical assay of noradrenaline levels. Although 6-OHDA can cause degeneration of the entire catecholaminergic neuron, usually only the terminal varicose regions of the nerve fibre degenerate. The cell body remains intact and continues to synthesize noradrenaline which passes down the axon by axonal flow and accumulates proximal to the degenerated terminal region. Distended axons containing high levels of noradrenaline are thus characteristic of 6-OHDA-induced damage (Fig. 1). Also regrowth of terminal processes from the tip of the axon begins 2-4 weeks following 6-OHDA treatment.

The Falck-Hillarp fluorescence histochemical technique of visualizing catecholamine-containing neurons in the rabbit brain has been established. Using this method it is possible to differentiate the initial depletion of transmitter stores and degeneration of terminals by 6-OHDA and the ensuing accumulation of transmitter in axons of damaged neurons and also to identify regrowth of terminal fibres.

The new formaldehyde-glutaraldehyde (FAGLU) perfusion technique has also been carried out using the rabbit brain. It is a very convenient method for fixing the brain for histological and mapping purposes and for the identification of the cell bodies of catecholaminergic-neurons but, for the visualization of terminal network, the Falck-Hillarp method is superior.



Before:



After:

Figure 1: Fluorescent histochemical sections before and after 6-OHDA

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PHARMACOLOGY UNIT

J.A. ANGUS and J.W. BLACK.
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Pharmacological assay of cardiac H_2-receptor blockade by amitriptyline and lysergic acid diethylamide. *Circ. Research Supplement,* 1979 (In press).

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Developments of computer-based estimations of pA_2 values and associated analysis. *J. Pharmacol. exp. Ther.* 207: 705-718, 1978.

A.J. McLEAN, P. du SOUICH AND M. GIBALDI.
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A.J. McLEAN, P. McNAMARA, P. du SOUICH, M. GIBALDI and D. LALKA.
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P. du SOUICH, A.J. McLEAN, D. LALKA, B. JENKINS, K.D. HAEGELE and M.L. McNAY.
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P. du SOUICH, R. SLAUGHTER, A. ELVIN, D. LALKA and A.J. McLEAN.
Mechanisms of non-linear disposition kinetics of sulfamethazine in normal volunteers. *Clin. Pharmacol. Therap.* (In press) 1979.

J. TAYLOR, A.J. McLEAN, R. LEONARD, U. CLIBON, P. du SOUICH, S. HARRIS, D. LALKA, T. LUDDEN, R. TALBERT, N. VIEUNA, C. WALTON and J.L. McNAY.
Initial experience of Clinical Pharmacology and Clinical Pharmacy interactions in a clinical pharmacokinetics consultation service. *J. Clin. Pharmacol.* (In press) 1979.

SEMINAR PROGRAMME — 1978

Date	Title	Lecturer
3 March	Is there a brain renin-angiotensin system?	Dr Jeff Hutchinson Austin Hospital
10 March	Smooth muscle cells in culture — and localization of contractile proteins with fluorescein-labelled antibodies.	Dr Julie Campbell Baker Institute
17 March	High density lipoproteins and cholesterol metabolism.	Dr Paul Nestel Baker Institute
31 March	A variable-pressure implanted carotid sinus capsule for study of arterial baroreceptor reflexes in the rabbit.	Prof John Ludbrook Dept of Surgery University of Adelaide
7 April	An overview of the clinical pharmacology of β-blockers.	Dr Alex Bobik Baker Institute
14 April	Trophic influences of sympathetic nerves in hypertension.	Dr Gordon Campbell Baker Institute
21 April	Studies on the mechanisms of action of growth hormone.	Dr Adrian Herrington Prince Henry's Hospital
28 April	6-OH-dopamine — cardiovascular reflexes and behaviour.	Prof Paul Korner Baker Institute
5 May	Antidiuretic hormone — is it vasopressor, physiologically?	Dr Peter Pullen Medicine, Prince Henry's Hospital, and Dr Warwick Anderson Baker Institute
12 May	Lipoprotein metabolism in man.	Dr Michael Reardon Baker Institute
16 June	Urbanization and maturity onset diabetes: Studies in Aborigines.	Dr K. O'Dea Baker Institute
23 June	Studies on the toad autonomic nervous system.	Prof G. Campbell Zoology Dept. Melbourne University
30 June	The mechanism of insulin secretion.	Dr Richard Larkins Dept of Medicine Repatriation General Hospital
7 July	Permanent behavioural changes caused by action of certain amino acids and inhibitors of protein synthesis on developing chick and rat brain.	Dr Lesley Rogers Pharmacology Dept Monash University
14 July	How to protect the heart from the surgeon.	Dr Frank Rosenfeldt Baker Institute
21 July	Role of central catecholamine neurones in cardiovascular control.	Dr Jim Reynoldson Baker Institute
28 July	Renin-angiotensin system in adrenal insufficiency.	Dr J. Stockigt Alfred Hospital
4.August	Noradrenaline kinetics (secretion rate, clearance from plasma), in normal men and patients with essential hypertension.	Dr Murray Esler Baker Institute
11 August	Clonidine — unravelling its site and mechanism of action.	Dr B. Jarrott Austin Hospital
18 August	Glucocorticoid physiology 1978 — a black hole?	Dr John Funder Medical Research Centre Prince Henry's Hospital
1 September	Pharmacodynamics and mechanism of action of hydralazine and metabolites.	Dr Alan McLean Baker Institute
15 September	Central neurotransmission and ethanol dependence.	Dr Michael Nott Pharmacology Dept. Melbourne University
29 September	Antarctica and megadosage of ascorbic acid.	Dr Peter Gormly Antarctic Division Dept of Science
13 October	The turnover of HDL apoprotein and its relationship to the metabolism of other lipoproteins.	Dr Noel Fidge Baker Institute

27 October	*Neuropeptides.*	Dr Geoff Tregear Howard Florey Institute Melbourne University
10 November	Why do animals lick their wounds?	Dr John Hutson Royal Children's Hospital
24 November	Insulin binding to solubilized receptors from human placenta.	Dr Timothy Billington Baker Institute
8 December	Catabolism of chylomicrons.	Dr Trevor Redgrave Physiology Department Melbourne University

SEMINARS GIVEN BY DISTINGUISHED VISITORS

Date	**Title**	**Lecturer**
22 March	Noradrenaline transmission.	Professor U. S. Von Euler, Karolinska Inst., Sweden
24 February	Hypertension and renal function in human pregnancy.	Dr. Eileen Gallery, North Shore Hospital, Sydney.
29 March	Crooked figures — non-parametric vs. statistics in biological research.	Professor J. Ludbrook, University of Adelaide.
29 September	*Current status of vitamin A metabolism.*	Professor DeWitt Goodman, Columbia University, N.Y.
11 November	Epidemiological study of blood pressure in Infancy.	Dr. Michael De Sweit, Brompton Hospital, London.
15 December	Hormonal regulation of intestinal development of the suckling and weanling rat.	Dr. Susan Henning-Rao, Temple University, Philadelphia.

Dr. A. C. Barger, Professor of Physiology, Harvard Medical School with Professor Korner. Dr. Barger was a speaker in the Ansett Seminar Series during the first half of 1979.

ANSETT SEMINARS

This special Seminar series has allowed us to invite four distinguished Australian scientists to talk on their own field of research. Those working interstate were generously flown to Melbourne by Ansett Airlines of Australia. We are most grateful to Ansett Airlines for making the series possible.

The dates and topics of the four lectures are given below, together with some details about each of the Ansett lecturers.

2.5.1978
Professor G. Thorburn — "Hormonal Regulation of Pregnancy and Parturition"

Professor Thorburn recently returned to Australia after an absence for several years during which he worked at the Nuffield Institute of Medical Research at Oxford. He has returned to become Professor of Physiology at the University of Queensland. Professor Thorburn is well known for his important contribution in the field of fetal endocrinology. Before that, he started his research career in cardiovascular physiology and was one of Professor Korner's first graduate students; subsequently he worked at the University of New South Wales and at C.S.I.R.O. before going to Britain.

4.7.1978
Dr. Donald Metcalf — "Control of Haemopoiesis *in vitro* by Glycoprotein Regulators"

Dr. Metcalf is Assistant Director of the Walter & Eliza Hall Institute and is well known for his work on the regulation of the production of red and white blood cells. He is one of the world's leaders in leukaemia research.

14.9.1978
Professor W. G. Nayler — "The Pharmacological Protection of Hypoxic and Ischaemic Heart Muscle"

Professor Gwen Nayler holds a Personal Chair in the Cardiothoracic Institute of the University of London. She was formerly Associate Director of the Baker Institute and was visiting Australia on this occasion. She is well known for her work on the role of calcium in myocardial contraction and for her contributions to cardiovascular pharmacology.

31.10.1978
Professor D. Curtis — "The Role of Glycine and GABA as Central Inhibitory Transmitters"

Professor David Curtis is Professor of Pharmacology at the John Curtin School of Medical Research at the Australian National University, Canberra. His work probably started the modern period of central nervous neuropharmacology. He is originally a Melbourne graduate and has an indirect association with Alfred Hospital, in that his wife is a sister of Miss Sewell, Director of Nursing.

PAPERS PRESENTED AT INTERNATIONAL MEETINGS IN 1978:-

PROFESSOR P.I. KORNER. International Society of Hypertension (Paris, June). Workshop on "Nervous System & Hypertension" (Hospital Necker).

International Society of Nephrology (Montreal, June). "The role of cardiac output in the pathogenesis of hypertension."

"Angiotensin II: Intrarenal action to minimize the development of experimental hypertension following renal artery stenosis."

Symposium on Spontaneously Hypertensive Rats & Related Studies (Kyoto, September), "How propranolol lowers blood pressure".

4th International Catecholamine Symposium (Asilomar, California, September). "Role of central noradrenergic neurons in cardiovascular reflexes."

DR. P.J. NESTEL. American Heart Association Meeting (Dallas, November). "Overproduction and reduced removal of very Low Density Lipoprotein B-apoprotein in Hypertriglyceridemia."

DR. W.P. ANDERSON. Council for High Blood Pressure Research (Cleveland, October). "Acute angiotensin II — mediated restoration of renal artery pressure following renal artery stenosis and the consequences for development of sustained one-kidney hypertension in conscious dogs".

DR. G.R. CAMPBELL. Cold Spring Harbor Symposium on Quantitative Biology (N.Y., April). "Immunofluorescent localization of 10NM (100A°) filaments in muscle & non muscle cells".

Conference on "Disorders of receptors and membranes" (Seattle, May). Workshop discussions.

3rd Internal Symposium in Vascular Neuroeffector Mechanisms (Brussels, August). "Trophic interactions between renal & vascular smooth muscle in transplants to the anterior eye chamber."

DR. J. CAMPBELL. Conference on "Disorders of receptors and membranes" (Seattle, May). Workshop discussions.

DR. M. ESLER. 4th International Catecholamine Symposium (Asilomar, Cal., September). "Role of removal of norepinephrine from the circulation in healthy men & patients with essential hypertension".

G.L. JENNINGS. 8th World Congress on Cardiology. "The effect of β-blockade in the work ST curve & its prognostic significance for coronary bypass surgery".

DR. N. FIDGE. American Heart Association Meeting (Dallas, November). "High Density lipoprotein AI & AII kinetics".

These staff members also took the opportunity to present research seminars at centres in Europe & North America.

Papers presented at local and National Meetings

PROFESSOR P. I. KORNER. Australian Physiological & Pharmacological Society (Canberra, May).

DR. P. J. NESTEL. Australian Nutrition Society (Adelaide, August).

Australian Society for Medical Research (Cowes, December).

Australian Atherosclerosis Group (Sydney, October).

Cardiac Society of Australia (Sydney, September).

DR. W. P. ANDERSON. Australian Physiological & Pharmacological Society (Flinders University, August).

DR. A. BROUGHTON. Cardiac Society of Australia (Sydney, September).

DR. A. BOBIK. Australasian Society of Clinical & Experimental Pharmacologists (Monash, December).

DR. G. R. CAMPBELL. Australian Society of Experimental Pathology (UNSW, August).

Anatomical Society of Australia & New Zealand (Monash, August).

Australian Society for Medical Research (Cowes, December).

DR. J. CAMPBELL. Australian Anatomical Society (Melbourne, August).

Cell Biology Society (Melbourne, October).

DR. G.L. JENNINGS. Australasian Society of Clinical & Experimental Pharmacologists (Monash, December).

Royal Australian College of Physicians (Sydney, October).

Cardiac Society of Australia (Sydney, September).

General Practitioners Society of Australia (Melbourne, November).

DR. P. DORWARD. Australian Physiological & Pharmacological Society (Canberra, May).

DR. M. ESLER. General Practitioners Society of Australia (Victoria) (Melbourne, November).

DR. N. FIDGE. Australian Atherosclerosis Group (Sydney, October).

DR. A. J. McLEAN. Australian Physiological & Pharmacological Society (Flinders).

Australian Society of Clinical & Experimental Pharmacologists (Monash, December).

DR. K. O'DEA. International Congress for Child Psychiatry (Melbourne, August).

MRS. A. EVERITT. Australian Society for Medical Research (Cowes, December).

DR. J. REYNOLDSON. Australian Physiological & Pharmacological Society (Canberra, May).

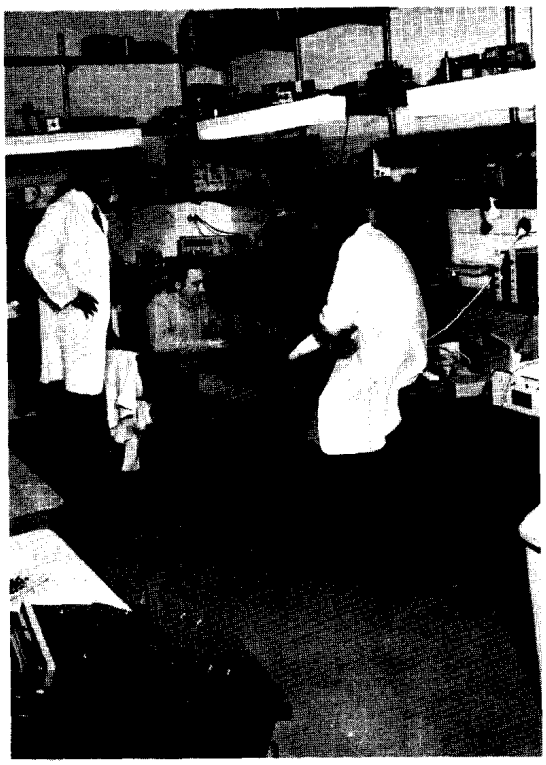
DR. F.L. ROSENFELDT. Cardiac Society of Australia (Syd., Sept.).

DR. N. TADA. Australian Atherosclerosis Group (Sydney, October).

MR. KEVIN HARVEY, MR. J. BAIRD, MR. M. J. PERCY. Society for Medical & Biological Engineering (Vic) (Melbourne, October).

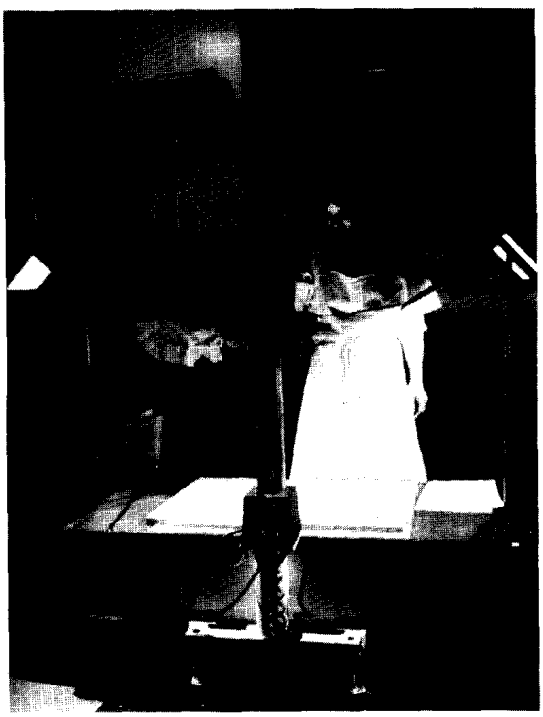
TEACHING

Members of staff gave undergraduate and postgraduate lectures at Monash University in the Departments of Physiology (Prof. Korner, Drs. Broughton & Campbell) and Pharmacology (Prof. Korner, Drs. Anderson & Reynoldson), and at the University of Melbourne in the Departments of Physiology (Prof. Korner, Drs. Nestel & Anderson), Pharmacology (Dr. O'Dea), Anatomy (Dr. G. Campbell) and Medicine (Drs. Nestel & O'Dea). Staff members who participated in the teaching of Monash University Medical students at the Alfred Hospital included Prof. Korner and Drs. Nestel, Broughton, Esler, Jennings, McLean and Rosenfeldt.



Lab Manager, Chris Lewis, with Electronics staff Kevin Harvey and John Baird.

The Staff Room was decorated in 1978 and is a comfortable meeting place for staff.



Anne Langusch, Photographic Technician in the darkroom.

VISITS TO THE INSTITUTE

In February 1978, we introduced the first of our series of VIP Tours and Luncheons at the Institute. These are organised visits, usually once a month, where representatives from government, academic, media and the business community are invited to attend.

We feel it is important that community leaders are aware of the work of the Baker Medical Research Institute in the fields of heart research.

Visitors are given a brief introduction to the Institute, followed by a conducted tour where demonstrations and experiments are carried out. The duration of the tour is about one hour after which visitors have the opportunity to talk with Institute staff at lunch.

Mr. B. M. Warden, Chief Manager of Bank of N.S.W. in Victoria presents a movie projector to Professor Korner.

Members of the Government Health and Welfare Committee visiting the Institute 26th July, 1978. Left to Right: Prof. R. Andrew [Baker Trustee], Dr. T. Wood [Secretary], Senator P. Baume, Mr. R. Johnston M.P., Mr. B. Lloyd M.P. [part hidden], Senator M. Walters, Mr. J. Habersberger [Chairman of Trustees], Dr. P. Nestel [Deputy Director of the Institute—explaining displays in foyer]

Arrangements to visit the Institute may be made by telephoning our Financial Director, Mr. Michael Downes on 520 2194.

During 1978 we were privileged to welcome the following guests:

Mr. R. Anderson, Manager, Repco Health Products

Mr. G.K. Abbott, Technical Manager, The Victorian Egg Marketing Board

Mr. A.B. Anderson, Representative, Trustee Organisation

Senator Peter Baume, L.P. Govt. Health & Welfare Committee, L.P. New South Wales

Mr. I. Baker, Director of Finance, Treasury, Victoria

Mr. R. Baeck, Manager, Radio 3XY

Dr. R. Beanland, Head of Department, Comm. & Electronic Engineering, R.M.I.T.

Mr. M. Brown, Chairman, Public Service Board

Mr. C. F. Barry, Managing Director, Fiber Glass International Pty.

Mr. G.S. Boag, Executive Director, National Heart Foundation

Ms. Elizabeth Bond, Elizabeth Bond Show, Australian Broadcasting Commission

Mr. D. Cornish, Manager, Trustees Executors & Agency

Mr. W. B. Crothers, Managing Director, Midland Milk Pty. Ltd.

Dr. R.G. Downes, Director, Ministry for Conservation

Cr. R.W. Ennis, Councillor, Melbourne City Council

Dr. K. Farrer, Chief Scientist, Kraft Foods

Mr. P. Ferguson, Melbourne Manager, Commercial Bank of Australia

Mr. J. Fitzgerald, Editor, Herald

Mrs. D. FitzGerald, Chairman, Equal Opportunity Board

Dr. R.F. Garrod, Director, Antarctic Division

Mr. D. Grant, Company Manager, Repco Cycle and Health

Mr. D.H. Greig, Director, Greig Brothers Pty. Ltd.

Mr. R.H. Greig, Director, Greig Brothers Pty. Ltd.

The Hon. V. Houghton, Minister for Health

Mr. D. Hall, National Marketing Director, Dairy Research

Mr. R. Hart, Director, Direct Marketing Group

Mr. R.F. Haase, Publicity & Fundraising Adviser

Mr. M.R. Ham, Solicitor, Mallesons

Mr. D. Hutchison, Company director

Mr. F. Hodel, Senior Manager, Credit & Lending Department

Dr. S.C. Joy, State Manager, National Bank of Australasia

Mr. Roger Johnston, L.P. Govt. Health & Welfare Committee, L.P. Hotham

Mr. J. Kolm, Research Director, ICI Australia

Mr. F. Kubis, Managing Director, Perpetual Finance Ltd.

Mr. S.M. Kimpton, Chairman, Kimpton Minifie McLennan Ltd.

Mr. R. Kingston, Relieving Regional Manager, Bank of New South Wales

Mr. J. Layton, Manager, CBA Insurance Services Ltd.

Professor D.G. Lampard, Chairman, Dept. of Electrical Engineering, Monash University

Mr. Bruce Lloyd, N.C.P., Chairman, N.C.P. Murray

Mr. B. Mansfield, ATV Channel 0

Mr. J. McCahon, National Heart Foundation

Mr. H. Morom, Victorian Manager, Colonial Mutual Life Insurance Soc. Ltd.

Mr. P. Moore, Assistant Secretary, Broken Hill Pty. Ltd.

Senator J.I. Melzer, The Parliament, Commonwealth of Australia

Professor R. Martin, Vice Chancellor, Monash University

Mr. G. Niall, Chairman, National Mutual Life Association of Australasia Ltd.

Mr. A. Osborne, Marketing Manager — Medical, CIG Medishield

Mr. J.O. Reynolds, Manager — Corporate Planning, Western Mining Corporation Ltd.

Mr. T.W. Roper, M.P. Parliament House

Councillor P. Rayson, Councillor, City of Prahran.

Dr. N. Snow, Technical & Planning Director, Dairy Research

Mr. J.H. Stephens, Assistant Manager, Trustees Executors & Agency

Mr. D.W. Stride, Managing Director, Commercial Bank of Australia

Mr. R. Simmons, General Manager, Perpetual Executors & Trustees

Mr. B.M. Schmitzer, Chief Executive, CIG Medishield

Mr. D. Sawer, Manager — Public Affairs, Broken Hill Pty. Ltd.

Mr. J.R. Serpell, Manager — Victoria & Tas. Qantas Airways

Mr. J.H. Screen, Victorian Manager, Bank of New South Wales

Mr. G. Taylor, Editor, The Age

Mr. A.J. Teale, Director — Corporate Relations, General Motors-Holden's Ltd.

Mr. A.P.J. Trevena, Administrator, Kraft Foods

Ms. J. Tuxen, Executive Director, Yooralla Society of Victoria

Mr. R.W. Van Niel, Finance Director, Kodak (Australasia) Pty. Ltd.

Mr. M. Van Den Wittenboer, Retail Manager, Shell Co. of Australia

Mr. A.F. Warburton, Managing Director, Australian Eagle Insurance

Mr. E.A. Witts, Director of Industrial Relations, Ford Motor Co. of Aust. Ltd

Mr. H.P. Walter, Manager, Bank of New South Wales

Mr. R.G. Webster, State Co-ordinator of Works, Treasury Department.

Mr. B. Wilson, General Manager, FML Assurance Ltd.

Mr. A.B. Wenzel, Director, Wenzel Fabrics Pty. Ltd.

Dr. S. Wheildon, Director of Medical Services, Queen Victoria Medical Centre

Senator Mary Walters, L.P. Govt. Health & Welfare Committee, L.P. Tasmania.

SIR RICHARD STAWELL ORATION: Research and Development

Delivered by Prof. P. I. Korner to Victorian Branch, Australian Medical Association, 2 May 1979. Reprinted by permission of the Sir Richard Stawell Victorian Trustees.

We are here tonight to honour the memory of Sir Richard Stawell, a very great Australian physician. Born in Kew in Victoria in 1864 he graduated in Medicine from the University of Melbourne in 1886. He did his residency at the Melbourne Hospital, and this was followed by a period of work at the Children's Hospital. He obtained his MD degree but advanced clinical training was available only overseas. So Richard Stawell went to London and worked at the Great Ormond Street and Queen's Square Hospitals. He returned to Melbourne via the United States where he made brief visits to some of the leading medical centres. He established himself in private practice in Collins Street and became a member of the honorary medical staff at the Children's Hospital and later the Melbourne Hospital, where in time he became the Senior Physician.

The pattern of development of the clinical schools of our teaching hospitals owes much to Sir Richard Stawell and his contemporaries, and many of its marks are still with us to-day. When he began his career in medicine the first need in Australia was to have competent doctors with highly developed clinical skills. The first professors in our medical schools taught in anatomy, physiology and pathology — the pillars of scientific medicine of those days. Often they had to 'profess' in more than one discipline. With no money for staff and equipment, their major concern was to teach rather than to do research, and it is a marvel than any was done at all. Clinical teaching was done by honorary physicians and surgeons. The first full-time professors of medicine and surgery in Australia — Charles Lambie and Harold Dew — did not assume their chairs in Sydney till 1930, five years prior to Sir Richard Stawell's death. The Sydney model was not followed in Melbourne and Adelaide where full-time clinical professors were not appointed till after World War II. It is a fact that throughout our history Australia's teaching hospitals have been 'town' rather than 'gown' orientated and have lacked the strong academic tradition characteristic of American university hospitals. This has changed to some extent in the most recently established medical schools. However, all Australian clinical schools still tend to emphasize predominantly the vocational aspects of clinical training, and to underemphasize the importance of medical research programmes in our quest for a better health service. By contrast, doctors in countries with academically orientated clinical schools are more attuned to the need for vigorous pursuit of medical research and medicine has tended to be more innovative.

In this talk I want to discuss some of the contributions that medical research has made recently to some of the main health problems of our community in the cardiovascular field. My theme is that a greater national medical research effort is necessary. The level of our medical costs is high — in the last financial year it exceeded $6 billion. One of the goals of an increased research effort is to obtain new insights into the causes of the different diseases which affect the health of our community, so that we may prevent them or at any rate delay their arrival during the prime of life. There is little doubt that preventive medicine would be cheaper than the cure of established diseases. Other goals of research are, of course, better detection and treatment.

THE CHANGING OUTLOOK IN CARDIOVASCULAR DISORDERS

In Australia cardiovascular disorders — mainly complications of hypertension and coronary artery disease — account for about 60,000 deaths per annum, over 50% of all deaths and in addition contribute to much serious chronic illness and economic loss. Cancer accounts for 20% of all deaths, and all other causes account for the rest. There are, of course, many non-fatal illnesses that are major health problems, such as disorders of mental health.

Amongst the killer diseases our understanding of the basic causes of high blood pressure, coronary atherosclerosis and cancer is still inadequate. This is the case despite the very great increase in the research efforts made in many countries. Australia too has played an important role in research in these areas. Although the basic causes are unknown we have nevertheless learned a great deal about the body's normal functions, giving us good hope that these problems will ultimately be solved. As

Johnathan Miller writes "what distinguishes the medicine of the past twenty-five years is not that its practitioners are equipped with an arsenal of antibiotics and antiseptics, but that they are furnished with a comprehensive and unprecedented understanding of what the healthy body is and how it survives and protects itself."

In the cardiovascular field it was recognized that in addition to basic research it was necessary to see if current knowledge could be applied more effectively once the magnitude of the problems of hypertension and coronary disease had been fully defined. Therefore, over the last 20-25 years an increased effort was made to obtain epidemiological data. Studies such as those carried out in Framingham in the United States, in Busselton in Western Australia and in Albury in New South Wales have provided us with a solid data base.

From studies such as these we have learned that in Australia one person in six has high blood pressure, mostly without other symptoms or signs. They have confirmed the results, based on analysis of life insurance data obtained more than 50 years ago by Dublin and Lotka, that the probability of developing strokes, heart failure or renal failure bore a direct relationship to the level of the blood pressure.

The epidemiological surveys also identified several factors predisposing to the development of coronary disease. They showed that the 'risk' of developing coronary atherosclerosis increased with elevation of blood cholesterol, hypertension, obesity, smoking and if diabetes was present. The 'risk' was compounded if several of the above factors were present simultaneously in a given individual.

In the field of hypertension an exciting development following these surveys has been the institution of large scale clinical trials, with randomization of patients on active drugs and on placebo. One well-known study performed several years ago by the Veterans Administration in the United States showed that active drug treatment provided a rapid benefit for patients with severe hypertension and those with moderate elevation of their blood pressure. In Australia the National Blood Pressure Study, sponsored by the National Heart Foundation and other organisations, has just been completed, though not all results are available at this time. The study has been concerned with the treatment of milder hypertension than the Veterans Administration Study and is the first of its kind to be completed in the world. The preliminary results have indicated that treatment exerts a definite rapid benefit in patients with diastolic blood pressure of 100mm Hg or more, but that little benefit was demonstrable over the trial period with milder elevation of blood pressure. This does not mean that ultimately there might not be some benefit, but the results suggest that with current drugs the benefit will be small. An important implication is that whilst treatment of moderate elevation of blood pressure does produce great benefits, the outlook for the patient is still not as good as that of a person with a normal blood pressure. In other words, the problems of treatment of hypertension have only been partly solved.

In addition, there have been several intervention trials to look at the effects of reducing the 'risk' factors which predispose to coronary disease. The data relating to the elimination of 'risks' is less firmly based than the studies on hypertension. When smoking stops there appears to be a relatively rapid reduction of 'risk' associated with this factor. Lowering blood cholesterol through dietary changes also appears to be beneficial, but evidence is still inconclusive on some of the other factors. In Australia there has been an educational campaign sponsored by the National Heart Foundation which has encouraged people on the grounds of prudence to alter their life style and reduce the coronary 'risk' factors.

What has been of particular interest is that there has been a definite reduction in mortality from the major cardiovascular diseases in Australia during the last 10 years. There has been a lowering of the death rate from strokes associated with hypertension, and there seems little doubt that the campaign for improved detection and adequate therapy of high blood pressure amongst both public and doctors has been largely responsible. There has also been a small but definite decline of about 5% in mortality from coronary artery disease since 1968. It is fair to say that the reasons for this decline are not yet clear, though everyone in the field would like to take some credit. In the United States there has also been a fall in mortality from coronary disease, and a recent detailed analysis by the U.S. National Heart, Lung and Blood Institute suggests that the decline is real and is not due to altered incidence or changes in diagnostic criteria. There has been considerable discussion whether the reduced mortality is due to changes in diet or smoking habits, or through better medical care as in coronary care units, or through as

yet unidentified factors. What encourages us to believe that it has occurred in response to some of the active measures that have been taken, is that reduction in mortality has not occurred in every country in the world, but only in those with active programmes for the reduction of 'risk' factors. Thus it is interesting that at the same time that the mortality from coronary disease fell in Australia it has risen by about 5% in New Zealand where the powerful dairy lobby has opposed any major campaign to reduce the dietary intake of fats.

In the cancer field steps have, of course, also been taken to improve detection and apply more vigorous treatment. However, in this area these changes have not yielded as spectacular success as in the cardiovascular field. It should not be forgotten that the achievements in the cardiovascular fields, though definite and encouraging, are still small in relation to the problems which remain. Community expectations that, given enough money, all these problems can be instantly solved are unreasonable. New insights necessary for their solutions require a great effort in basic research and often a good deal of time. Serendipity — defined as looking for a needle in a haystack and coming out with the farmer's daughter — also requires a lot of luck.

BASIC AND APPLIED RESEARCH

Medical research involves two types of activity. Firstly, there is *basic research* that contributes to new knowledge in the health sciences. There is also *applied research* such as the epidemiological surveys and clinical trials that I have discussed, or new technological developments. There has been much argument whether too much money is being spent on basic research and whether a greater proportion of available funds should be expended in applied so-called mission-orientated research. Such a policy has been strongly advocated even by some eminent scientists. One of the strongest advocates in recent years has been Lord Rothschild in Britain, who argued the case in his well known report "A Framework for Government Research and Development" published in 1971. The British Government was impressed with the arguments and made considerable funds available to the Department of Health, amounting in 1977 to about half the funds given to the Medical Research Council for all its activities. The idea was that the Department should identify major health research priorities and themselves allocate the funds needed to solve them. A recent assessment of the scheme by a working party established by the Nuffield Foundation has suggested that Lord Rothschild's scheme has been a failure and has resulted in much waste of public funds. They considered that however worthy the objectives of a given project might be, open competition with other research projects was the only method of ensuring a high quality level of execution.

Basic research offers the only hope for finding new solutions to scientific problems. Our understanding of the fundamental causes of cardiovascular disorders, cancer, mental disorders and many other problems is still very imperfect. However, we have learned a tremendous amount about the various control processes that normally regulate blood pressure, that transport fats into and out of cells, and that control cellular division. We are learning a great deal about the properties of the nervous system. It has become apparent how complex the blood pressure control system is and how many factors influence the blood pressure, including kidney, body fluid volumes, heart, vascular structures, nervous and hormonal mechanisms. Our ability to lower blood pressure by a variety of drugs involve non-specific manipulations of the system which have been, so to speak, by-products of some of the basic studies.

There often is a long latent period before possible practical applications of fundamental discoveries are recognized. Frequently the aims of the study by the original investigator are completely different from their ultimate practical application. Julius Comroe has made this point very clearly, illustrating some of the discoveries without which modern open-heart surgery could never have got off the ground. The indispensable basic discoveries included the discovery of blood groups and avoidance of incompatible transfusion reactions, advances in the field of blood coagulation and discovery of anticoagulants, the discovery of X-rays, the discovery of how to measure pressures and flow and many others. The latencies between discovery and application ranged from 15 to 50 years!

Let me hazard a guess of the fate of a patient with poliomyelitis, if funds had been available only for applied research. The patient would now get about in a mobile, computer-controlled respirator — the ultimate product of sophisticated 20th century technology! Instead the disease has been eliminated owing to the basic discoveries that resulted in the development of the Salk and Sabin vaccines. At present it seems unlikely that similar almost total prevention will occur with the major cardiovascular disorders.

However, if we can retard their development by 10-15 years this too will be a major achievement.

There is no choice to be made between supporting basic or applied research — we have to support both. The criterion for support has to be excellence of the project determined by ranking through peer review by expert committees and working parties. Most grant-giving bodies in Australia operate under such a system. However, what determines the overall research effort are the funds available. At present Australia spends over $6 billion per annum on the cost of health services. Only 0.25% of this is spent on all types of medical research supported by the National Health and Medical Research Council, and about 0.4% of the costs if all other funds are added. The per capita expenditure on medical research in Australia is only about one-tenth of that in the United States, and about half of that in Great Britain, France, Sweden and West Germany. This is an inadequate performance in a wealthy country.

The case for expanding the medical research effort in Australia is one of national self interest and self respect, like the argument why we should develop our industrial resources. Australia must no longer rely on the importation of all its scientific know-how as it had to do in the early colonial days. As an advanced industrialized nation we must make our contribution to knowledge and explore our own particular needs. We must not be like the foolish virgins of the biblical parable and rely on other people's efforts, particularly as we have our own distinctive problems and aspirations which are not identical with those of the United States, Britain or Europe. In addition, scientific research provides the manpower needed for the critical appraisal of new developments and their adaptation to our needs. The level of medical research support in Australia should be high and politicians who have our long-term national aspirations at heart should not hesitate to give it the highest priority. Medical research deserves steadily increasing long-term support. It is not valid to use short-term cost-benefit arguments, as has been done by economists and treasury experts — cynics who know the price of everything and the value of nothing.

MEDICAL RESEARCH IN AUSTRALIA

At present the top 3% of Australia's school leavers enter our faculties of medicine. It seems highly desirable that our young people with the best intellectual equipment should join in the exciting quest for new insights into the functioning of the body and the causes of disease. However, in recent years, with the greater financial temptations of medical practice only a handful of medical graduates have entered medical research. The number has been decreasing to a degree that has alarmed those of us that are convinced of the need for an increased research effort in Australia. What is worse, in the absence of good local opportunities, some of those that train here will be offered employment in countries with more expansive research policies. The biblical parable of the talents is as true about human resources as it is about wise investments! Part of the problem is that not all graduates who wish to participate in medical research want to burn, so to speak, their clinical bridges. The training courses for basic and advanced clinical training by the various specialist Colleges are long and inflexible and almost totally vocationally orientated. This is probably a legacy of the Australian teaching hospital of Sir Richard Stawell's day, but it no longer fulfils the useful function that it did then. After their long vocational training courses our registrars and residents are in their early thirties and few are willing to start another specialist course in a particular field of medical research which involves them in financial sacrifices. We must remember that medical research can't be done automatically by most doctors after a few months work in a scientific laboratory. It requires just as much training as any other major specialty. There should be much more flexibility in our College programmes to allow our best graduates to get greater exposure to academic medicine in lieu of some vocational training. It is worth remembering that the reasons why the United States has achieved so much in clinical research is because of the strength of its basic biomedical science and the much stronger academic orientation of its teaching hospitals.

Australia has a proud record in medical research, and the quality of its clinical and basic research is well regarded internationally. I need not remind you that we have two medical Nobel prize winners in medicine, and our scientists are in the vanguard in the fields of circulatory control and hypertension, lipid disorders and metabolism, immunology and cancer, endocrinology, neurophysiology, pharmacology and many others. Our clinicians too have made major contributions by noting unexpected and unusual associations, such as the discoveries of Gregg, of Campbell and of McBride. The main things wrong with

Australia's current effort is the total level of funds, and the inadequate number of really major centres of excellence on the scale of the John Curtin School of Medical Research, the Hall and Florey Institutes and the Baker Institute. Research institutes provide opportunities for approaching a particular set of problems from many viewpoints. In universities medical research efforts are often unduly fragmented and compartmentalized because of the incorrectly perceived need to represent every discipline relevant to the different vocational teaching requirements. There is much to be said for concentrating effort in particular areas of excellence in universities and for a greater number of reasonably funded research groups.

In concluding, I believe Sir Richard Stawell would have accepted the need for change in the organisation of the teaching hospital of our day. I am sure he would have supported the sentiments with which the Commonwealth Minister for Health opened the first session of the National Health and Medical Research Council, which has played such an important role in the development of Australia's medical research effort. The year was 1937 and the minister was none other than William Morris Hughes, who had put Australia on the international map in other ways many years earlier. Mr. Hughes said "The first objective of the Council is to raise the standard of health in the community. By health, I do not mean a relative condition, the mere freedom from active disease — but that state of abounding energy that makes one rejoice to be alive." This is the goal of preventive medicine that we hope to reach some day through our scientific efforts.

Grants and Donations

Victorian State Government	130,000.00
Sandoz Research	14,000.00
Utah Foundation	12,437.00
Alan Williams Trust Fund	10,000.00
Beckworth Court Pastoral Co.	9,900.00
The Ian Potter Foundation	9,786.00
The Felton Bequest	7,800.00
The James & Elsie Borrowman Research Trust	6,000.00
Broken Hill Co. Pty. Ltd.	5,000.00
The George Thomas Lockyer Charitable Trust	4,375.00
The William Angliss (Vic.) Charitable Trust	4,000.00
H. & L. Hecht Trust	4,000.00
Merck, Sharp & Dohme (Aust.) Pty. Ltd.	4,000.00
Estate Edward Wilson	2,500.00
The Appel Family Bequest	2,000.00
Percy Baxter Charitable Trust	2,000.00
The Bell Charitable Trust	1,250.00
The Marian & E.H. Flack Charitable Trust	1,245.00
A. Buchanan	1,000.00
Ciba-Geigy Aust. Ltd.	1,000.00
Estate R. V. Hall	1,000.00
Smith Kline & French Laboratories (Aust.) Ltd.	1,000.00
A. E. Stansen & Co. Pty. Ltd.	1,000.00
J. B. Were & Son	1,000.00
Repco Ltd.	600.00
Carlton & United Breweries Ltd.	500.00
Commercial Bank of Australia Ltd.	500.00
David Syme & Co. Ltd.	
The George F. Little Trust	475.00
C.B.A. Travel	400.00
Mrs. L. Hewgill	400.00
S.M. Kimpton	360.00
A. Dobell	250.00
Ford Motor Co. of Australia Ltd.	250.00
Pethard Tarax Charitable Trust	250.00
The Shell Co. of Australia Ltd.	250.00
C.I.G. Medishield	200.00
Robert Davies	200.00
Alan Edwards	200.00
Kraft Foods	200.00
M. O'Sullivan	200.00
Wengel Pty. Ltd.	200.00
Professor P.I. Korner	166.00
A.H.S. Australia	100.00
Cypress & Sons Pty. Ltd.	100.00
G.R.E. Insurance Ltd.	100.00
Mrs. R. Houghton	100.00
Ramsay Surgical Ltd.	100.00
Specialty Hardware Service Pty. Ltd.	100.00
Western Mining Corporation Ltd.	100.00
K. Harvey	78.00
Seigfried Myer	75.00
Alfred Anderson	50.00
Judith Bates	50.00
Robert Clemence	50.00
R. Goldenberg	50.00
Robert Howden	50.00
Jenglass Products	50.00
P.C. Johnstone	50.00
Meeco Pty. Ltd.	50.00
Millipore Pty. Ltd.	50.00
Selbys Scientific Ltd.	50.00
R.S. & E.M. Spear	40.00
C. Lewis	38.00
J. Baird	30.00
Valerie Carson	30.00

M.G. & M.I. Downes	30.00
Shirley Druhan	30.00
Aina Martin	30.00
Thomas Warburton Pty. Ltd.	30.00
L. Young	30.00
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Paramedics Pty. Ltd.	25.00
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Barry Dunbar	20.00
F. Forgione	20.00
Kain, Hearnes & Kain	20.00
L.H. Moon & Son Pty. Ltd.	20.00
Mr. and Mrs. P. Shaw	20.00
George White & Co. Pty. Ltd.	15.00
Physiologists Institute	12.40
Susan Evans	10.00
G.M.T. Agencies Pty. Ltd.	10.00
H.C.F. Constructions	10.00
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J.A. & G. Neylan	10.00
Precision Fasteners & Engineering Supplies	10.00
Richmond Textile Co.	10.00
I. & J. Scott	10.00
Ungar Metal Co.	10.00
C. Von Ton	10.00
Eleanor Coburn	8.00
P.T. Greenhalgh	8.00
R. Holdenson	5.00
Johns Professional Products	5.00
D. Kane	5.00
Linds Hospital Supplies	5.00
Mrs. R. Ritchie	5.00
Rapitype Contac	2.00
	$244,790.40

Further contributions were received from —
Australian Eagle Insurance Co. Ltd., 2/14 Australian Field Regiment Association, Brian and Judy Bainbridge, R.M.V. Blakemore, Peter Bolton, Vincent & Pam Bulton, K.J. & D.P. Brewster, Miss N.E. Cameron, Winnifred Chambers, Mrs. Elizabeth Cooper, G.J. Daw, Mrs. A.R. Findley, Nancy & Barbara Funder, Garfield Red Cross, Miss M. Gilbert, H.B. & D.M. Goetze, Mrs. Donna Habersberger, Roger Harrison, J.W. Hatfield, Mrs. C. Holper, Mrs. T.S. Howell, Jean Jeffrey, N.B. Johnson, Miss E.B. Jones, Miss W.D. Jones, Miss W.D. Jones, Kodak (A'Asia) Pty. Ltd., Dorothy Lear, K. Lesh, Beverley Marshall, D.L. Meggitt, Miss J. MacDonald, Mr. & Mrs. G.A. McGarvie, National Heart Foundation, K.A. Ness, Mrs. J. Robertson, Mrs. J. Scott, R. Smith, St. Matthews Ladies Fitness Class, Geraldine L. Syker, H.C. Trinick, L.B. Williams, Windsor Primary School Staff Association, Women's Auxiliary Garfield R.S.L.

In Memory of —
Mr. A.R. (Reg.) Angliss, Margaret Byrne, Mary Ann Byrne, Dr. Arnold Cooper, Margaret Date, Lindsay J. Forbes, a Friend, Mrs. Henrietta Golding, Senator Ivor Greenwood, Miss Ethel Hamilton, J.S.N. Harris, Mrs. Harrison, Mr. J. Hopkins, Mrs. Heather Johnson, Lucy Law, Mrs. E. McLean, Mr. R.G. Mills, Evelyn Moore, Mr. H. Ogilvie, Mrs. C. Pearson, Mrs. Constance May Pugsley, Reefton (Harry Spicer), Samuel Riddiford, A.L. Silverson, Tasman Smith, Mr. J.G. Taylor, Neville C. Thrum, Mr. Raymond G. Venn.
TOTAL: $16,809.00

The Thomas Baker, Alice Baker and Eleanor Shaw Medical Research Institute

Statement of Movement in Maintenance Fund for the Year Ended 31 December 1978

EXPENDITURE

Salaries and wages	739,841
Laboratory supplies and isotopes	134,644
Additional equipment and building costs	148,173
Library maintenance	20,186
Postage and telephone	11,383
Printing and stationery	18,039
Light and power	36,939
Insurance	19,485
Repairs and renewals	35,153
Animal house contribution	9,000
Sundries	9,550
Travelling expenses	25,959
Public relations	4,766
Stanhope Court	14,257
	$1,227,375

INCOME

Donations from Baker Benefactions		
Statutory amount	11,569	
Transfers from Endowment Fund	295,000	306,569
Donations other		128,199
Grants-In-Aid of Research Projects		
Life Insurance Medical Research Fund of Australia and New Zealand	52,648	
National Health and Medical Research Council	207,165	
National Heart Foundation of Australia	89,233	
Department of Health, Education and Welfare (USA)	2,478	
Sugar Association (USA)	5,404	356,928
Other Grants		
The James and Elsie Borrowman Research Trust	6,000	
The William Buckland Research Fund	2,200	
Victorian State Government	130,000	138,200
Interest from Investments		
Held by Trustees of The Baker Institute Grant Trust	4,419	
Other investment income	144,794	149,213
Other Income		
Rentals	28,015	
Sundry sales, recoveries and refunds	100,440	128,455
Deficit for the year		19,811
		$1,227,375

Auditors' Report to the Trustees of The Thomas Baker, Alice Baker and Eleanor Shaw Medical Research Institute.

In our opinion, the balance sheet and statements of movements in accumulated funds, as set out on pages 68–71, are properly drawn up to show a true and fair view of the state of the Institute's affairs at 31 December 1978.

PRICE WATERHOUSE & CO.
M.J. McNULTY,
A member of the firm,
Chartered Accountants.

Melbourne
20th February 1979.

Deficit for year	19,811
Accumulated deficit as at 1 January 1978	30,456
Accumulated deficit as at 31 December 1978	$50,267

The Thomas Baker, Alice Baker and Eleanor Shaw Medical Research Institute

Balance Sheet at 31 December 1978

ACCUMULATED FUNDS AND LIABILITIES

Maintenance Fund		
Accumulated (deficit)	(50,267)	
Sundry creditors and accrued expenses	171,848	
	121,581	
Endowment Fund		
Accumulated fund	1,446,707	
	1,446,707	
Research and Scholarship Funds		
Restricted fund	73,083	
Edgar Rouse Memorial Fellowship Fund	54,145	
Laura Nyulasy Scholarship Fund	2,864	
William Buckland Research Fund	29,218	
Lang Research Scholarship Fund	4,852	
	164,162	
	$1,732,450	

MAINTENANCE FUND ASSETS

Cash on hand	300	
Sundry debtors	22,075	
Short term deposits (at cost) held by Trustees of the Institute	40,000	
Cash at bank	59,206	
		121,581
Endowment Fund Assets		
Investments at cost		
Held by Trustees of the Institute		
Freehold properties	40,000	
Government and semi-government stock	86,124	
Shares and debentures in companies	122,204	
Short term deposits	104,968	
Mortgage loans	442,500	
	795,796	
Held by the Trustees, Executors & Agency Co. Ltd.		
Shares in companies	63,708	
Trust units	548,719	
Short term deposits	7,200	
	619,627	
Cash at bank	31,284	
		1,446,707
Research and Scholarship Fund Assets		
Investments (at cost):		
Held by Trustees of the Institute		
Shares in companies	4,852	
Short term deposits	104,000	
	108,852	
Held by the Trustees, Executors & Agency Co. Ltd.		
Shares in companies	7,741	
Trust units	2,800	
Short term deposits	24,340	
	34,881	
Cash at bank	20,429	
		164,162
		$1,732,450

The Thomas Baker, Alice Baker and Eleanor Shaw Medical Research Institute

Notes to the Balance Sheet at 31 December 1978

1. Expenditure made in present and past periods on fixed assets including laboratory equipment, motor vehicles, buildings, improvements and furniture and fittings has been charged against appropriate funds, grants or revenue accounts, and expensed in the year in which it was incurred.
   The insured value of all assets at 31 December 1978 including the building, totalled $5,700,000 (1977 $5,042,200).
   Capital Commitments at 31 December 1978 amounted to $220,000 for the redevelopment of the animal house and renovations being carried out on the "Future Area".
2. The Laura Nyulasy Research Scholarship Fund and the William Buckland Scholarship Fund are both managed by the Trustees, Executors & Agency Co. Ltd.
3. The market value of shares in companies listed on the Australian Stock Exchange at 31 December 1978 was $46,969 (1977 $24,703) above the amount at which they are stated in the accounts.
4. Income and expenditure is accounted for on an accrual basis.
5. The Trustees, Executors & Agency Co. Ltd. is the custodian and manager of some of the investments of the Institute. These investments are included in the balance sheet of the Institute in accordance with statements provided by the custodian company giving details of the Institute's entitlements in securities held by the custodian company in its own name.

The Thomas Baker, Alice Baker and Eleanor Shaw Medical Research Institute

Year Ended 31 December 1978

Statement of Movement in Accumulated Funds

RESTRICTED FUND		
Balance at 31 December 1977		31,150
Patients' Fees	6,731	
Baker Benefactions Statutory Amount 1979	11,569	
Donations	55,526	
Investments and bank interest	2,952	
Baker Institute History	30	
Royal Perth Hospital (sale Flowmeter)	4,500	
AMP Insurance (Dr N. Miller)	894	
NIH (USA) (Dr J. Maloney)	24,738	
Antarctic Rental 1979/80 (part)	40,899	
		147,839
		178,989
Transfer to maintenance	79,668	
Transfer to Monash University (Dr J. Maloney)	24,738	
Gratuities (sale Flowmeter)	1,500	
		105,906
		$73,083
Represented by:		
Term deposits — Euro-Pacific	57,000	
Cash at bank	16,083	
		$73,083
ENDOWMENT FUND		
Balance at 31 December, 1977		1,398,502
Donations	348,817	
Interest	1,977	
		350,794
		1,749,296
Transfer to maintenance	295,000	
Transfer to Edgar Rouse Memorial Fellowship Fund	7,589	
		302,589
		$1,446,707
Represented by:		
Freehold properties	40,000	
Inscribed stocks and bonds	86,124	
Shares in Companies	185,912	
Mortgages	442,500	
TE & A Common Fund No. 4	473,719	
Term deposit — Euro-Pacific	104,968	
Term deposit — TE & A	7,200	
TE & A Common Fund No. 20	75,000	
		1,415,423
Cash at bank		31,284
		$1,446,707

CLINICAL RESEARCH UNIT

STAFF

Director
P. I. KORNER, M.D., B.S., M.Sc.(Syd), F.R.A.C.P., F.A.A.

Deputy Director
P. J. NESTEL, M.D., B.S.(Syd), F.R.A.C.P.

Staff Physician
G. L. JENNINGS, M.B., B.S., M.R.C.P.(UK), F.R.A.C.P.

Clinical Assistants
A. BROUGHTON, M.B., B.S., F.R.A.C.P.
M. ESLER, M.B., B.S., B.Med.Sci., F.R.A.C.P., Ph.D.(ANU).
A. J. McLEAN, B.Sc(Med), M.B., B.S., M.R.A.C.P., PhD.(Monash).

Biochemical Pharmacology
A. BOBIK, B.Pharm.,M.Sc., Ph.D.(Syd), Officer-in-Charge.
V. CARSON, M.Sc.
G. JACKMAN, B.S., Ph.D.(Lond), A.R.A.C.I., A.R.C.S.

Dietitian
DENISE WINTER (till May).
SYLVIA POMEROY, M.Sc.

Scientific and Technical Staff
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M. BANGAH, B.Sc.
JANET BROWN
PAULINE COOPER, B.Sc.
SUE ELLETT
M. SANDERS
HELEN SKEWS, B.Sc.

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ROMAYNE HOLMES, M.B., B.S.
VICTOR KALFF, M.B., B.S., F.R.A.C.P.(Part 1)

Residents
B. HARRISON, M.B., B.S., F.R.A.C.P.(Part 1)
B. KATZ, M.B., B.S.
B. A. K. KHALID, M.B., B.S., B.Med.Sci.
Y. L. LIM, M.B., B.S., Ph.D., F.R.A.C.P.(Part 1)

Ward Sister
SUE SCEALEY

Hypertension Clinic
SR. HELEN HALL (Baker Institute)

Standing (left to right): Dr. Murray Esler, Peter Ashley, Sue Ellett, Mohan Bangah, Val Carson, Mark Sanders, Dr. Alex Bobik, Dr. Archer Broughton, Helen Skews, Dr. Graham Jackman, Sr. Sue Scealey. Seated: Dr. Allan McLean, Professor Paul Korner, Dr. Paul Nestel, Dr. Garry Jennings.

CLINICAL RESEARCH UNIT

Director's Report

The location of the new Unit in the Ward 2A area provides us with much more satisfactory accommodation. The Unit now has 15 beds, we have a regular admitting day and as part of our service commitment provide two Outpatient Clinics for the Hospital. These are the Hypertension Evaluation Clinic, run by Dr. Garry Jennings, and the Lipid Clinic, run by Dr. Paul Nestel. The clinical laboratory area is also functioning satisfactorily, but the alterations required to produce a catheterisation laboratory for our use jointly with the Cardiovascular Diagnostic Service were deferred till 1979 because of lack of funds in the Hospital during 1978. It is important both for us and for C.D.S. that this should be finished as soon as posssible.

Details of our studies performed by Dr. Murray Esler and collaborators on noradrenaline pharmacokinetics and secretion rate in hypertensive patients and normal subjects has been described in detail in the Baker Institute Report. A study by Dr. Garry Jennings has recently been completed in which not only blood pressure changes but those in cardiac output and total peripheral resistance were studied in a group of hypertensive patients after one year's 'ideal' treatment. Before treatment the vascular resistance of these patients was elevated and was higher than in normal subjects even after complete autonomic block. The mechanism of this non-autonomic increase in total peripheral resistance is probably due to structural hypertrophy of the small blood vessels. These play an important role in the 'over-reactivity' of the hypertensive patients to nervous stimuli. Dr. Jennings' work suggests that these structural changes are reversible with good treatment. The implication is that good treatment not only restores blood pressure but may also restore the distribution of the blood flow in all the tissues towards normal. The reversibility depends on continued administration of active drugs and when treatment is discontinued there is rapid elevation of blood pressure back to original levels.

Drs. Jennings and Esler, through their interest in the role of autonomic overactivity, have also studied a group of patients with marked underactivity of their autonomic nervous system. The study has examined the haemodynamic and biochemical indices in patients with autonomic insufficiency. Such patients are literally brought to their knees by the autonomic dysfunction which can produce a large fall in blood pressure whenever they assume the upright posture. The introduction of a new drug, dihydroergotamine, which constricts veins preferentially has proved a very valuable adjunct in the management of these patients.

Clinical pharmacology has become established in the Unit with the arrival of Dr. Allan McLean. His interest has been how the pharmacokinetics of therapeutically important drugs are altered in patients with heart, kidney and liver disease. Since arriving he has developed a new method of measuring the amount of blood flowing to the liver and the amount of blood flow that is shunted past the liver in patients with chronic liver disease. The method depends on determining the clearances of two classes of drugs, one with the high clearance by the liver and one with the low clearance. The work has resulted in collaboration between Dr. McLean and Dr. Frank Dudley, Director of the Gastroenterology Service at the Hospital. The method is non-invasive and therefore appears likely to be of great value in the investigation of patients with certain types of liver disease. Dr. McLean's arrival has also contributed to the more rational use of drugs in the Hospital and he is making considerable contributions to a number of drug committees.

PROJECTS

Effects of Treatment of Hypertension on the Non-autonomic Component of Peripheral Vascular Resistance

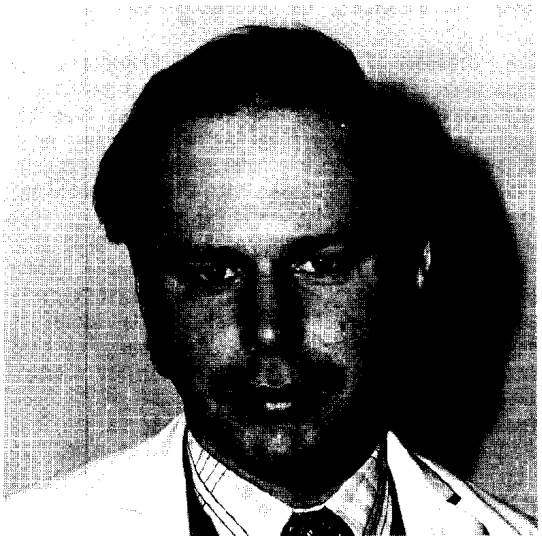
G. L. Jennings, M. Esler, S. Ellet & P. I. Korner

Patients with essential hypertension have elevation of their total peripheral resistance (TPR) due mainly to hypertrophy of muscle in their arterial walls. Whether these structural changes can be reversed by treatment of hypertension is being investigated in the present study. TPR is measured after pharmacologically removing the influences of the autonomic nervous system before treatment and after one year of careful control of each patient's blood pressure in the Hypertension Evaluation Clinic. Results of the first eight patients to complete the study have indicated a marked reduction in TPR post-blockade after successful treatment (average 57%) indicating reversal of the structural changes in their resistance vessels.

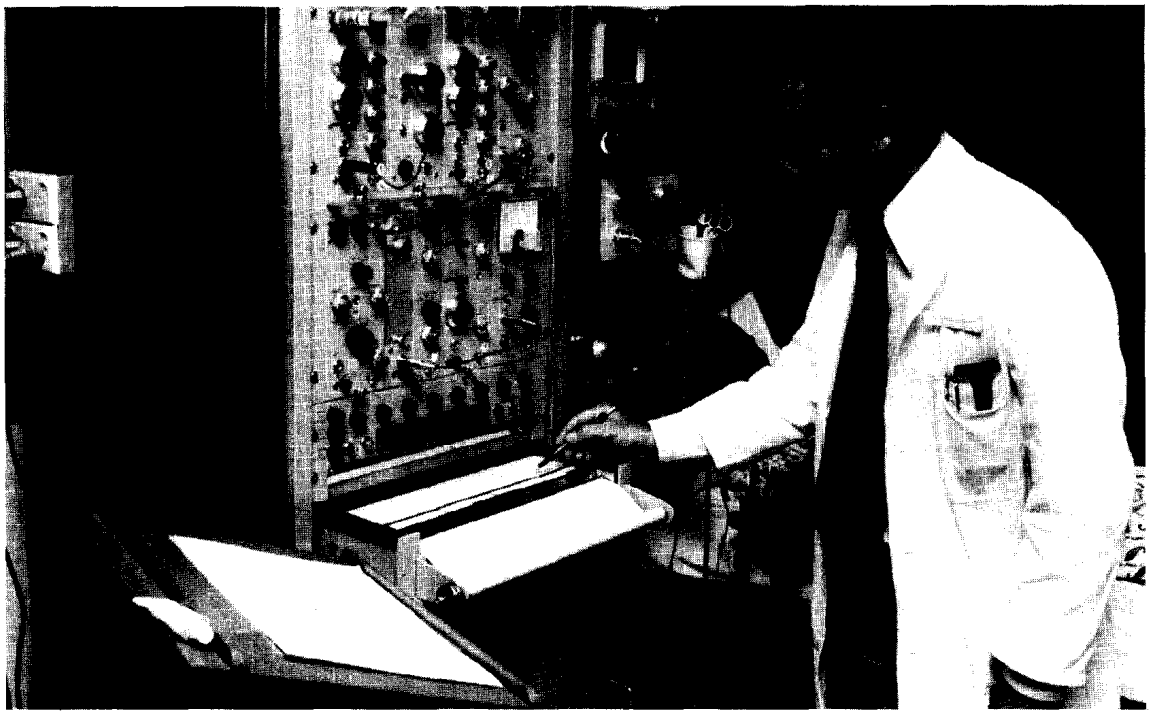
Measurement of β-Receptor Numbers and Sensitivity in Man

G. L. Jennings, A. Bobik, M. Bangah, S. Ellet, H. Hall & P. I. Korner

Recent studies using *in vitro* methods have suggested that in certain states, e.g. chronic beta-blockade, thyroid disease, the number or sensitivity of beta-receptors is altered. This is being investigated in man *in vivo* using isoprenaline-heart rate dose-response curves with measurement of isoprenaline concentration in the blood at the time of maximum effect on heart rate after bolus injections of isoprenaline. The plateau of the sigmoidal relationship obtained between log concentration of isoprenaline and heart rate is related to the total number of beta-receptors stimulated, and the slope of the relationship gives an indication of their affinity. In the same subjects measurement of adenylate cyclase stimulation after lymphocyte receptors is performed *in vitro* and the results correlated with those *in vivo*. Studies performed in man, and rabbits, have so far indicated that the change in heart rate after isoprenaline given in this way is not affected by reflexes aimed at minimising the fall in blood pressure which occurs as similar absolute heart rates are achieved with isoprenaline given before or after vagal blockade. Thus the method would appear to be a valid way of assessing effective beta-receptor numbers and affinity. Studies are under way to investigate the effects of age, hyper-



Dr. Alex Bobik.



Dr. Garry Jennings studying print out at the Exercise Testing Centre.

tension and thyroid disease on beta-receptors. This technique is also used to determine whether the number of beta-receptors determines the responsiveness of different individuals to beta-blocking drugs.

Non-Invasive Measurements of Cardiac Output

G. L. Jennings, J. Baird & P. I. Korner

As a result of a donation from the family of Senator Ivor Greenwood through the National Heart Foundation we were fortunate to receive equipment during the year which will be used to measure cardiac output by the 'Indirect Fick' method. The measurement of inspired and expired 0_2 + CO_2, and of mixed venous P_{CO_2} by a rebreathing technique allows calculation of cardiac output without requiring catheterisation of the subject. Studies can thus be performed repeatedly in the same subject after various interventions, and problems associated with the measurement of cardiac output in normal, or near-normal subjects using invasive techniques are avoided. It is proposed to use the technique to measure maximum cardiac pumping capacity (i.e., cardiac output at maximum exercise) as a sensitive index of cardiac function in patients with hypertension on and off therapy, in patients with angina who have coronary bypass operations, and in normal subjects undergoing fitness programmes, etc. Validation studies are currently underway comparing the method with standard methods.

Exercise Testing for the Detection of Ischaemic Heart Disease in Asymptomatic Subjects

G. L. Jennings, H. B. Kay, S. Ellet, R. Holmes & V. Kalff

Approximately one-half of the people dying each year from coronary artery disease die suddenly and in about half of these people sudden death is the first manifestation of their disease. Treatment of symptomatic coronary disease is expensive and in some forms of the disease has no effect on subsequent mortality. Clearly the identification of people with coronary disease before they get symptoms, combined with improved methods of treating this 'latent' phase of the disease is an important community problem.

Exercise testing has been widely used for this purpose, but has come under severe criticism because of the large number of subjects who are found to have abnormalities on their exercise test, but do not have obvious coronary artery disease on subsequent investigation. We have been applying a more quantitative exercise protocol to those previously used, in an attempt to reduce the number of 'false

positives'. The only abnormality considered likely to be due to ischaemic heart disease using this protocol is flat ST segment depression, the magnitude of which is work-related. Another requirement is that this abnormality should persist (although usually diminished in magnitude) after acute beta-blockade. A total of 331 'normal' subjects have had exercise tests. Of these 20% have had some deviation from the normal response. However, the rigorous criteria of abnormality have applied to only 1.5% of subjects, which is similar to the usual incidence of coronary artery disease in the 'normal' population of this age range. The group is to be followed up using standard questionnaires so that the accuracy of the test can be determined.

Dihydroergotamine in the Management of Postural Hypotension

G. Jennings, M. Esler & R. Holmes

Patients with autonomic nervous system failure often suffer from incapacitating postural hypotension. They are unable to reflexly increase vascular resistance, and maintain blood pressure, to compensate for the venous pooling and fall in cardiac output that occurs with standing. Dihydroergotamine, an ergot alkaloid which selectively constricts veins, has been evaluated by us in this condition. In six patients, intravenously administered dihydroergotamine minimized venous pooling with head-up tilting. Central blood volume fell little and normal blood pressure was maintained. Four patients then were given the drug by mouth, each for two months or more. At a dose of 30-40 mg daily, prolonged benefit was noted. Systolic blood pressure while standing was maintained above 100 mmHg, and all were free of postural dizziness. Dihydroergotamine appears to be a significant advance in the management of this condition.

Comparison of Effectiveness of Timolol Administered Once Daily and Twice Daily in the Control of Blood Pressure in Essential Hypertension

G. L. Jennings, H. Hall, A. Bobik & P. I. Korner

The effects of timolol given either as a single dose or in two equally divided doses were compared in a double blind trial in 15 patients with essential hypertension. The timolol given per day remained constant for each patient, but different patients received from 10-30 mg/day. The dose for each patient was determined from the blood pressure response during the eight weeks open phase of the trial when each received a constant dose of diuretic throughout and amounts of timolol adequate to produce a specified hypotensive response. In the double blind phase there were four randomized test periods of six weeks each. Supine mean blood pressures during the four test periods were 122 mmHg (placebo), 115 (diuretic once/day), 106 (diuretic once/ day + timolol once/day) and 108 (diuretic once/day + timolol twice/day). Differences between treatment periods were similar for sitting, standing and causal blood pressures. Ambulatory blood pressures over the waking hours were closely similar to clinical standing blood pressures at the different treatment periods. Timolol + diuretic produced similar lowering of blood pressure in patients requiring 10, 20 or 30 mg timolol/day when given as one dose or in two equal doses. Plasma concentrations, after taking the various tablets, were high enough to be a major contributing factor to the long duration of the hypotensive response.

Pindolol Pharmacokinetics in Relation to Time Course of Inhibition of Exercise Tachycardia

G. L. Jennings, A. Bobik, E. T. Fagan & P. I. Korner

Pharmacokinetics of pindolol were studied in normal subjects given 5, 10 and 20 mg orally and 3 mg i.v. Plasma half time was 2.9 $\pm$ 0.3 (s.e. mean) /hour for both routes; peak drug levels occurred 1-2 hours after ingestion and bioavailability was 53%. Plasma protein binding was 38% and was independent of plasma concentration; the drug was not concentrated in the red cell.

Work-heart rate regression lines were calculated from resting heart rate and three grades of 'steady-state' exercise standardized for the maximum work capacity (W_{max}) of each subject. The equation was characterized by slope and HR_{50} (calculated heart rate at $0.5W_{max}$). After giving 5 mg i.v. pindolol to produce maximum cardiac β - adrenoceptor blockade there were differences in inhibition of resting heart rate, slope HR_{50} and maximum heart rate suggesting differences in sympathetic components. However, estimates of the degree of inhibition were closely similar for each variable when determined before and after atropinization indicating that the accuracy of estimation was independent of the level of vagal activity.

After oral pindolol peak inhibition of resting heart rate, slope and HR_{50} coincided with peak plasma concentration. Peak reduction of resting heart rate was greatest at the lowest dose, but inhibition of slope and

HR_{50} were similar at all doses. The different heart rate parameters recovered at different rates. After 24 hours slope had returned to control, and the residual inhibition of HR_{50} reflected residual β-adrenoceptor blockade of resting heart rate, as demonstrated by a shift in isoprenaline-heart rate relationship. Inhibition of HR_{50} and other exercise parameters were 20% less in the concentration range 5-20 ng/ml than peak inhibition obtained in the range 21-160 ng/ml. The higher potency of pindolol compared with propranolol can be accounted for by the difference in protein binding.

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CLINICAL RESEARCH UNIT

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EWEN DOWNIE METABOLIC UNIT

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Technical Staff
IDA EKKEL, A.A.I.M.T.
JULIE LLOYD (until February, 1978)
ANN McCLELLAND (from February, 1978)
FREDERICKE RABOLD

Secretary
BRENDA ROACH (until June, 1978)
MARILYN TAYLER (from May, 1978)

GENERAL SUMMARY

During 1978 there were a number of changes in the staff of the Unit and also in its clinical, laboratory and office facilities. Early in 1978 Dr. Pincus Taft, Physician-in-Charge since 1963, relinquished this position and was appointed Visiting Endocrinologist, thus allowing a continuation of his major role in the Department's activities. He joins Dr. Hal Breidahl as a senior appointee on the Visiting Medical Staff. Dr. Jim Stockigt, Deputy Director since 1973, was appointed Director and took up this position in April. Dr. Douglas Lording, clinical assistant since 1976, was appointed Assistant Endocrinologist at the end of his advanced training in Endocrinology, which completed the requirements for F.R.A.C.P.

Remodelling of the Unit's laboratory and office facilities was completed early in 1978 and has increased the laboratory space by about 25%. This work was made possible by a generous bequest from the Estate of the late G.E. Gillet. The ward area was transferred to the adjacent portion of Level 5 of the Main Ward Block, making the former ward available as office space.

The Unit continues to provide a clinical service in Endocrinology and Diabetes and to run an Endocrine Laboratory with routine and research functions. Our major laboratory commitments are in the areas of Thyroid Disease and Endocrine Hypertension. Principal research projects are concerned with structure-activity relationships of steroid hormones, receptor-binding of steroids, the relationship between steroid hormones and the renin-angiotensin system, effects of systemic illness on thyroid hormone production and studies of situations in which there is dissociation between the production of thyroxine and triiodothyronine.

During 1978, a joint project was begun with the Medical Research Centre, Prince Henry's Hospital, which enabled Dr. Ken Wynne, a steroid biochemist, to join the staff of the Unit to work in collaboration with Drs. John Funder and Jim Stockigt and Mr. John Barlow. For the initial year his work was supported by temporary funds from each Unit, but, commencing in 1979, Dr. Wynne has obtained grant support from the National Health and Medical Research Council for a period of three years as a Senior Research Officer. Additional equipment for this work has been funded, in part, by a grant from the Alfred Hospital Whole-time Medical Specialists' Private Practice Fund, and laboratory space has been provided in the special purposes laboratory area on Level 5 of the Main Ward Block.

Dr. Jim Stockigt, Director Ewen Downie Metabolic Unit.

As in previous years, we have continued to enjoy valued collaboration with numerous colleagues, particularly from the Howard Florey Institute of Experimental Medicine and Physiology, from the Baker Institute and from the Endocrine Unit and Medical Research Centre, Prince Henry's Hospital.

We have been fortunate in receiving financial support, either direct, or in the form of equipment or travel support from the following benefactors:

Estate of the late Vincenza Acton
Estate of the late H. Vistaline
G.M. Rollason Trust
Mr. Alan Pay
In Memory of Jack Bartlett
Merck Sharp and Dohme (Australia)
Alfred Hospital Whole-Time Medical Specialists' Private Practice Fund.

Travel and Meetings

Dr. Breidahl visited Sydney, Hobart, Adelaide and Perth in his capacity as President of the Diabetes Federation of Australia. He presented the symposium paper "Diabetes in Pregnancy" at the 6th Asia and Oceania Congress of Endocrinology in Singapore in January 1978, and also attended the meetings of the Australian Diabetes Society and the Royal Australasian College of Physicians in October. His marriage to Dr. Margot Bailie, Director of Biochemistry in May, completed an eventful year.

In Singapore in January 1978, at the 6th Asia & Oceania Congress of Endocrinology, Dr. Taft presented a paper on the effect of biguanide withdrawal. In London, in September, he attended the Scientific Meeting

of British Diabetes Association and visited the Administrative Headquarters of the Association to discuss problems related to diabetes education within and outside hospital diabetes clinics. In Paris he visited the diabetes services of Professors Attau and Leubetsky before attending, as an invited participant, the Post-graduate Course in Diabetes conducted by the European Association for the Study of Diabetes in Zagreb, Yugoslavia. This was followed by the 14th Annual Scientific Meeting of this Association where he presented the paper "Lactate accumulation with biguanide: a comparison of the effect of phenformin and metformin". He gave the symposium paper "Management of diabetes — present and future controversies" at a combined plenary session of the Australian Diabetes Society and Royal Australasian College of Physicians meeting in Sydney in October. Dr. Taft was elected President of the Australian Diabetes Foundation for 1978.

Dr. Stockigt presented the symposium paper "Role of Mineralocorticoids in Endocrine Hypertension" at the 6th Asia and Oceania Congress of Endocrinology in Singapore in January, 1978. In September he attended the European Thyroid Association Meeting in Berlin and the American Thyroid Association Meeting in Portland, Oregon. He has been appointed Secretary of the Programme Organising Committee for the VIII International Thyroid Congress (Sydney, February 1980), and attended meetings of this Committee at both the European and American meetings. En route he visited San Francisco, to discuss collaborative work at the University of California.

Mr. John Barlow, who completed his M.Sc. (Monash) in 1978, attended the 60th Annual Meeting of the American Endocrine Society in Miami in June 1978, where he presented the paper "Dexamethasone binding in bovine tissue: a novel glucocorticoid receptor?" En route, he visited the laboratories of Drs. John Baxter and Isidore Edelman in San Francisco and Dr. Beverley Pearson-Murphy in Montreal. He also presented papers at the annual meetings of the Endocrine Society of Australia and the Australian Society of Medical Research.

Dr. Duncan Topliss has continued his second year of advanced training in Endocrinology with the Unit during 1978. He is developing a major interest in thyroidology and presented the paper: "Isolated thyroxine excess: an ambiguous finding" at the Sixth Asia and Oceania Congress of Endocrinology in Singapore in January 1978. In addition to his clinical duties, his more recent work has been on the effect of steroid deficiency on the pituitary-thyroid axis, on screening methods to detect endogenous thyroid hormone antibodies in serum and on the pathogenesis of a unique familial syndrome of isolated thyroxine excess without hyperthyroidism. He will continue his advanced training in association with Dr. Robert Volpé in Toronto from July 1979, so as to add a training in Clinical Immunology to his background in Endocrinology. Support from the Royal Australasian College of Physicians in the form of the Beecham Travelling Fellowship, and additional support from an Alfred Hospital Fellowship and a Searle Travel Grant will assist him in his work.

Seminar Programme

The programme of Monday lunchtime Seminars, held alternately at the Alfred Hospital and at Prince Henry's Hospital, continued during 1978. Topics presented by the Unit were:-

1. Atypical Manifestations of Hypothyroidism: Polymyositis, Anaemia, Neuropathy.
2. Management of Pituitary Tumours.
3. Hyperosmolar Coma.
4. Hypertension and Renal Ischaemia: Renal Artery Stenosis, Hepatitis-associated Polyarteritis.
5. 11 β hydroxylase deficiency.
6. Follicular Carcinoma of the Thyroid.
7. Primary Aldosteronism: Surgical and Medical Management.
8. Pituitary-Thyroid Failure during Catastrophic Illness.
9. Diverse Causes of Hypoglycaemia.
10. Hypocalcaemia: Infantile and Adult.
11. Mechanisms of Acute and Chronic Renal Failure in Diabetics.
12. Pituitary Tumours and Prolactin Excess.
13. Surgical Options in the Management of Morbid Obesity.
14. Arrhythmias in Hyperthyroidism.
15. Effects of Iodine on the Thyroid.

STEROIDS AND BLOOD PRESSURE REGULATION

The important relationship between steroid hormones and high blood pressure is obvious in conditions like Cushing's syndrome and primary aldosteronism. The occasional hypertension of oestrogen excess adds a further mechanism which cannot be explained by simple renal sodium retention — as is indeed the case in Cushing's and Conn's syndrome, where studies in the chronic phase show increased peripheral resistance, rather than excessive extracellular salt and water, as the dominant abnormality.

Hence, it is necessary to broaden our views of the effects of steroid hormones on blood pressure by considering their influence on conventional pressor mechanisms, on vascular reactivity and vascular permeability, as well as their effect on renal sodium retention. In contrast to the hypertension of steroid hormone excess, the profound circulatory failure of severe corticosteroid deficiency in Addison's disease indicates that steroid hormones are vital in maintaining normal blood pressure. None of these effects have yet been defined in terms which link steroid structure, receptor binding or tissue response, to a measurable effect which influences blood pressure.

Steroid hormones, unlike the peptides, are synthesized (and metabolized) in a series of discrete sequential changes in structure which profoundly alter biological activity. The molecular biology of these changes is poorly understood and in some instances is hard to define in terms of the classical (perhaps archaic) classification of steroids into mineralocorticoid, glucocorticoid, oestrogen, androgen and progestogen. The recent demonstration at the Howard Florey Institute that hydroxylated progesterones may influence blood pressure, not directly, but by an action synergistic with conventional corticosteroids, has stimulated interest in the effect of novel classes of steroid hormones on blood pressure. Hence, the relevance of studies which examine the physiology of hydroxylated progesterones and which attempt to define the effect of structural modifications on tissue binding and biological activity. So far, our work has been directed towards evaluating the influence of the 19 methyl group on corticosteroid activity and to studies which compare the binding and metabolism of hydroxylated progesterones with conventional glucocorticoids and mineralocorticoids in bovine tissues.

Dr. Ken Wynne

The Synthesis of 19-Nor Aldosterone and Receptor Binding of 19-Nor Steroids

K.N. Wynne, J. Mercer*, J.W. Funder* and J.R. Stockigt

**Medical Research Centre, Prince Henry's Hospital*

It has recently been reported that absence of the 19 methyl group from deoxycorticosterone (19-nor DOC) enhances affinity for mineralocorticoid receptors so much that 19-nor DOC has a higher affinity than aldosterone (Funder *et al* Endocrinology 103: 1456, 1978). This finding suggested the possibility that 19-nor aldosterone might be a "super-mineralocorticoid" if the same effect occurred. Because analogues lacking the 19 methyl group were available only for deoxycorticosterone, cortisol and progesterone, we had to synthesize 19-nor corticosterone and 19-nor aldosterone *de novo*, in order to examine the general effects of this structural modification.

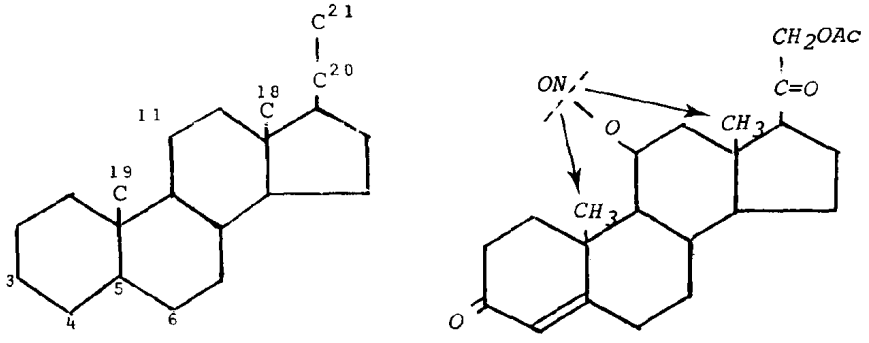

Fig. 1
The direction of migration of the nitrosyl radical in the photolysis of the 11 beta nitrite of corticosterone acetate to form a mixture of the C18 and C19 oxime derivatives. This is the key reaction in the preparation of 19-nor aldosterone.

The procedure was an interesting elaboration of the elegant synthesis of aldosterone devised by the Nobel Laureate, Derek Barton in 1961. He and his colleagues showed that a nitrite group on a steroid molecule will, with intense light, exchange with a neighbouring hydrogen atom and thus open the way to substitutions in positions hitherto unreactive with conventional reagents. With corticosterone acetate, photolysis of the 11 beta nitrite will create an oxime on the C18 and C19 angular methyl groups (Fig. 1). Because the position of the double bond influences the proportion of C18 to C19 oxime, the 3,20-bisethylene acetal of corticosterone acetate, which has a 5-6 double bond, was the chosen starting material for the synthesis of 19-nor aldosterone. A brief outline of this multistep synthesis is shown in Fig. 2. We are grateful for the assistance of the C.S.I.R.O. departments of Applied Organic Chemistry and Protein Chemistry in some steps of the synthesis by the provision of specialized reagents and equipment. Mass spectroscopy of the final material has been carried out by Mr. G. Joannou of the Department of Biochemistry, Royal Prince Alfred Hospital, Sydney.

Receptor studies demonstrated that 19-nor modification of various steroids had no uniform effect on specific binding. For example, with deoxycorticosterone, progesterone and cortisol, this modification enhanced specific mineralocorticoid binding, as measured by competition with ^{3}H aldosterone in rat kidney slices, while no difference in affinity was found between corticosterone and 19-nor corticosterone. By contrast, 19-nor aldosterone showed less than 1% the affinity of aldosterone for mineralocorticoid receptors. Similarly, the 19-nor modification of aldosterone abolished its affinity for glucocorticoid receptors. These findings suggest that absence of the C19 methyl group may enhance receptor binding of 11-deoxysteroids, but that no consistent effect can be predicted with other steroids. Therefore, it seems very unlikely that 19-nor aldosterone is a "super-mineralocorticoid".

Hydroxylated Progesterones: Binding and Metabolism in Bovine Liver

J.W. Barlow, K.N. Wynne, J.R. Stockigt and J.W. Funder*

**Medical Research Centre, Prince Henry's Hospital*

The hydroxylated progesterones may have a role in blood pressure regulation, but the mechanism of action of these steroids is undefined, although they are known not to act via conventional glucocorticoid or mineralocorticoid receptors. We have previously identified a high affinity dexamethasone binding-site in bovine tissue which differs from classical steroid hormone receptors. Because the natural steroid which competes best for this site is 17 alpha hydroxy progesterone (17OHP), we have examined this binding to define factors which influence the interaction of hydroxylated progesterones with their possible receptors.

In these studies, bovine liver cytoplasmic extract was prepared by homogenisation of tissue and high-speed centrifugation. The resulting supernatant contained steroid

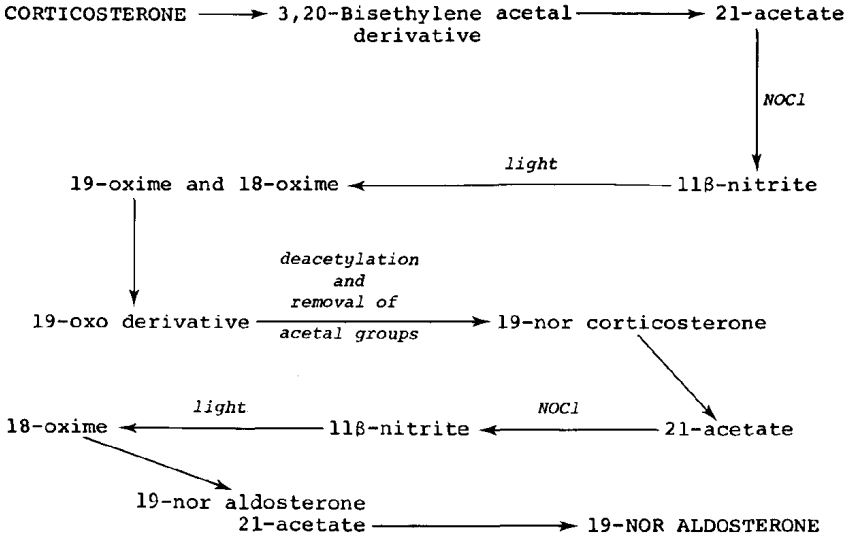

Fig.2
Summary of the reactions involved in the preparation of 19-nor aldosterone from corticosterone.

John Barlow

binding proteins (receptors, albumin and transcortin) and probable steroid metabolising enzymes. Labelled steroid in physiologic amounts, either tritiated dexamethasone (^{3}HDM) or tritiated 17 hydroxy-progesterone (^{3}H 17OHP) was added to the cytoplasmic extract. After incubation the proportion of ^{3}HDM or ^{3}H 17OHP specifically bound to macromolecules was measured. These studies have shown that the ^{3}H 17OHP binding-site is a protein which has a high affinity and limited capacity with extremely rapid binding kinetics.

To examine the possible effect of tissue enzymes on these steroids, tritiated compounds were assessed by thin layer chromatography after incubation with bovine liver. When ^{3}H 17OHP was incubated with bovine liver for 90 minutes, the radioactive steroid migrated with authentic 17OHP on the thin layer chromatogram (Fig.3, top panel). However, if the coenzyme NADPH (1mM) was added, the picture was markedly different (Fig.3, lower panel), because all the radioactivity migrated with 17, 20-dihydroxy-progesterone rather than with 17OHP suggesting that the steroid had been modified by an NADPH-dependent enzyme. Studies of tracer binding also showed the effects of steroid metabolism, because specific ^{3}H 17OHP binding, present without NADPH was completely abolished in the presence of NADPH. The fact that ^{3}HDM, which shares the same binding site, was not metabolised in the same manner and did not compete with 17OHP for the enzyme, suggests that binding and metabolism of 17OHP are two different phenomena.

Physiologic responses to hydroxylated progesterones, particularly those related to

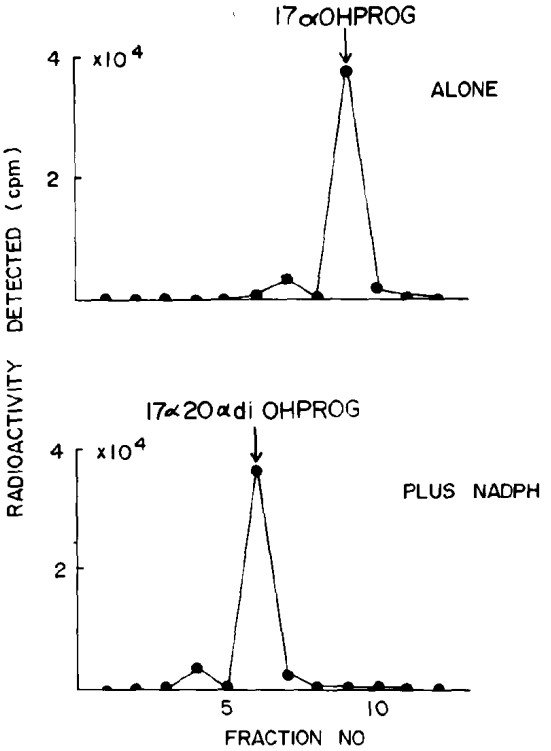

Fig.3
The influence of the coenzyme NADPH (1mM) on the metabolism of ^{3}H 17 OH Progesterone by bovine liver cytoplasmic extract is shown by thin layer chromatography after incubation of tracer alone (upper panel), or in the presence of NADPH (lower panel). In the presence of NADPH the steroid tracer is modified to a more polar compound corresponding in mobility to 17, 20 dihydroxy-progesterone.

blood pressure, still remain to be defined, but the interaction with the type of binding site identified in bovine tissues could be the first step in this response. The activity of a metabolising enzyme which is modulated by cofactors may in turn limit this first binding step. If so, responses could be controlled not only by hormone level and receptor, but by cofactor regulation of local tissue metabolism of the steroid. Such interaction between receptor binding and local modification of hormone structure may have wide implications in determining hormone action.

The Importance of Renin Substrate Depletion in Addison's Disease and its Relationship to Glucocorticoid Deficiency

J.R. Stockigt, M.J. Hewett, D.J. Topliss and P. Taft.

Increased activity of the renin-angiotensin system has been proposed as an important pressor mechanism in adrenal insufficiency. While renin release is clearly increased, animal studies have shown marked

depletion of renin substrate in severe glucocorticoid lack. Hence, there may be opposite influences of the enzyme and substrate which jointly determine the rate of angiotensin II formation. To further define these changes in man, plasma renin concentration, activity and substrate were measured before and after treatment in nine patients with Addison's disease who showed varying degrees of cortisol and aldosterone deficiency. Plasma angiotensin II was also measured in some studies. With severe deficiency of both steroids there was a huge increase in renin concentration (200 times normal) but substrate was reduced to about 100 ng/ml (less than 10% of normal) so that renin activity and angiotensin II were only modestly increased (5-8 times normal, Fig.4). After 2-4 days treatment with glucocorticoid and saline infusion, renin concentration had decreased 10-fold, but renin activity and angiotensin II *doubled* as renin substrate reached low-normal levels. Before treatment, substrate was positively correlated with plasma cortisol ($r=0.95$, $p<0.005$, $n=9$), but renin concentration and renin activity showed no correlation with cortisol or aldosterone.

In predominant glucocorticoid deficiency, severe depletion of substrate, to less than 20% of normal, occurred without excessive renin concentration, while substrate remained normal in predominant mineralocorticoid deficiency, despite greatly increased renin concentration. There was no depletion of substrate in high renin states without glucocorticoid deficiency (diabetic ketoacidosis, accelerated hypertension).

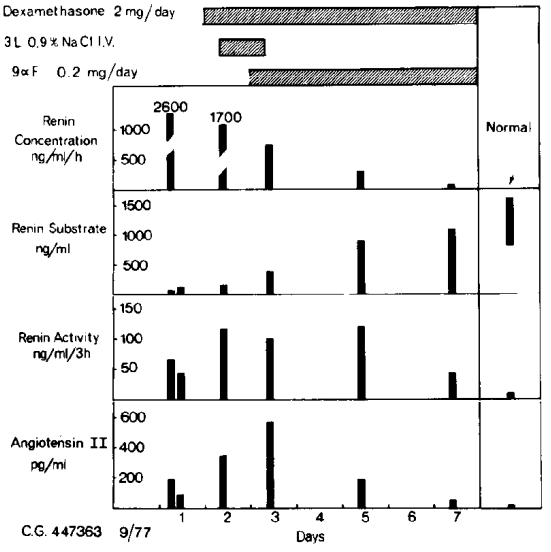

Fig.4
Effect of treatment in severe Addison's disease on renin concentration, renin substrate, renin activity and plasma angiotensin II. In severe uncorrected steroid deficiency, there is gross depletion of renin substrate, so that renin activity and angiotensin II fail to fully reflect the degree of renin excess. Normal range for renin concentration is 5-20 ng/ml/h.

These findings suggest that: (i) Severe deficiency of renin substrate to less than 10% of K_m can limit the homeostatic role of the renin-angiotensin system in adrenal failure despite an appropriate renin response. (ii) As previously demonstrated in animals, glucocorticoid is critical in preventing depletion of substrate in man. (iii) Substrate depletion can result from decreased production without increased utilization in selective glucocorticoid deficiency. (iv) No single parameter adequately describes the renin-angiotensin system in adrenal failure, because renin concentration may overestimate the level of angiotensin II, while renin activity can underestimate renal renin release. (v) Substrate depletion could contribute to circulatory failure in severe glucocorticoid deficiency.

STUDIES OF THYROID FUNCTION

It is generally assumed that blood levels of thyroid hormones are relatively free of short-term fluctuations, and that analysis of a single blood sample will usually define a patient's thyroid status. While this is generally true of serum T_4, which has a long half-life of about 7 days, it is now clear that potentially misleading fluctuations in both serum T_3 and T_4 can occur in non-thyroidal illness. Starvation, febrile illness, surgical stress and exposure to some radiographic contrast media may lower T_3 sufficiently to be diagnostically misleading in hyperthyroidism. However, the presence of T_4 excess with normal serum T_3 does not necessarily imply hyperthyroidism, because the stress of illness and iodine exposure may each increase T_4 temporarily into the hyperthyroid range. It is particularly in situations of severe non-thyroidal illness that great reliance is placed on laboratory assessment of thyroid status. Hence, it is critical to define potential artefacts clearly so that both false positive and false negative diagnoses may be minimized. To this end, we have now evaluated thyroid function during and after numerous surgical and medical stresses.

Assessment is further complicated by the recent demonstration that all measurable thyroid hormones may decrease to extremely low levels in some patients with prolonged severe illness. It remains uncertain whether this is due to cessation of normal pituitary

Elizabeth White, John Barlow and Mary Egan at work in the new routine laboratory.

TSH secretion, to failure of central TRH production, to unresponsiveness of the thyroid or to abnormalities of protein binding. Further, it is still uncertain whether this is a true state of thyroid hormone deficiency where substitution therapy might be beneficial. Given the slow offset of thyroid hormone action and our inability to assess it by tissue responses in patients with severe illness, this question will be very difficult to resolve.

Thyroid Function during Catastrophic Illness

D.J. Topliss, E.L. White, J.R. Stockigt and P. Taft.

There are several recent reports of extremely low levels of thyroxine (T_4) in euthyroid patients during prolonged severe illness. Conventional assessment of plasma protein binding by resin uptake and related techniques, suggests that free T_4 may also be very low, indicating a possible transient state of hormone deficiency. In order to further assess this important possibility, serial assessments of total and free hormone levels and thyroxine binding globulin (TBG) have been carried out in patients with severe prolonged illness. Free T_4 was measured by kinetic radioimmunoassay using antibody immobilized on glass beads (Corning) and TBG was measured both by conventional radioimmunoassay (CEA, Sorin) and by a sandwich assay, dependent on TBG binding capacity (Corning).

One representative study is summarized in Table 1 showing mean hormone levels before, during and after catastrophic illness. An elderly woman with gout, hypertension, renal failure, renal stones, gallbladder disease, previous intrahepatic abscess and recurrent sepsis, showed low levels of circulating thyroid hormones after postoperative haemorrhage following nephrectomy. The level of T_4 was subnormal during the most severe phase of illness, without evidence of TSH excess to indicate primary subthyroidism. Binding correction by T_3 resin uptake suggested that free T_4 was also low, but direct assessment of free T_4 showed a *higher* level during illness. Measurements of both TBG mass and capacity gave slightly lower levels during illness. The close correlation between changes in TBG mass and capacity did not support the previous suggestion (Chopra, 1978) that the discrepancy between total and free T_4 may be due to a circulating inhibitor of T_4 binding during severe illness. Reciprocal changes in T_3 and reverse T_3 were seen as previously reported, with very low levels of T_3 during the severe illness.

During the 3 week period of severe complications, the subnormal level of T_3 was associated with hypothermia to 34°C, brady-

TABLE 1
EFFECT OF SEVERE PERIOPERATIVE COMPLICATIONS ON THYROID HORMONES AND BINDING PROTEINS (MEAN VALUES)

Total T_4 nmol/l	Free T_4 Index	Free T_4 pmol/l	Total T_3 nmol/l	Total Reverse T_3 nmol/l	Thyroxine Binding Globulin *Immuno-assay ug/ml	Thyroxine Binding Globulin †Sandwich Assay ug/ml	TSH mU/l
Before and After Complications (mean of 7 samples)							
69	69	12	1.00	0.36	13.9	15.5	<5
During Severe Complications (mean of 12 samples)							
33	38	16	<0.2–0.4	0.79	9.3	12.2	<5
p<.001	<.001	<.01	<.001	<.001	<.05	‡N.S.	‡N.S.
Normal Range:							
60–145	50–140	10–27	1.1–2.7	0.2–0.8	10–27	12–30	<5

* Dependent on mass of TBG.
† Dependent on capacity of TBG.
‡ N.S.: Not significant.

cardia and hypotension. Treatment with T_3 substitution, 20 μg daily, was given (in conjunction with many other therapeutic manoeuvres) and was associated with recovery. Thyroid and pituitary function was shown to be normal after recovery.

These findings confirm that estimation of free thyroxine index gives spuriously low values for circulating free T_4 during very severe illness, probably due to inherent deficiencies in the T_3 resin uptake technique. Studies of TBG mass and capacity, in high dilution, show no evidence of a circulating competitive inhibitor of T_4 binding to TBG, but a serum factor which interferes with the binding of ^{125}I T_3 to resin *in vitro* has not so far been ruled out.

This spurious deficiency of T_4 is associated with a true lack of T_3, the major calorigenic hormone. The development of hypothermia during prolonged severe illness with a possible response to T_3 substitution, supports the possibility that a transient state of functional thyroid deficiency can occur in subjects without thyroid disease. Cautious therapeutic use of T_3 may be appropriate in such situations. We have so far found no evidence that a central defect in TRH or TSH secretion or thyroid unresponsiveness to TSH occurs in severe illness.

Familial Thyroid Hormone Excess without Hyperthyroidism: Hormone Resistance or Abnormal Thyroxine Deiodination?

D.J. Topliss, J.R. Stockigt, M.J. Martin and E.L. White

These studies were initiated after it was shown that two unrelated, clinically-euthyroid, non-goitrous subjects had persistently elevated serum T_4 (196±7 SEM nmol/l; N: 60-145) over a period of 1-2 years, without associated illness, exposure to iodine excess or tendency towards remission or progression of the abnormality. Serum T_3 was persistently normal (2.1±0.1 nmol/l; N: 1.0-2.7) as were the levels of reverse T_3 and 3-3'T_2.

That T_4 excess was not due to increased protein binding was demonstrated by free thyroxine index, measurement of free T_4 and estimation of thyroxine-binding globulin by its capacity and by radioimmunoassay. Endogenous T_4 antibody was ruled out by comparison of different assay separation methods. Plasma TSH, its response to thyrotropin-releasing hormone (TRH) and Basal Metabolic Rate (BMR) showed no evidence of excessive effects of thyroid hormone. Basal TSH was in the high-normal range (3.3±0.6 mU/l; N:<4). After TRH 200μg IV the maximum TSH response was 10-23 mU/l; N:<25 and mean serum T_3 rose from 2.2 to 2.8 nmol/l after 120 min. In both subjects BMR was at the lower limit of normal (-15% and -10%) and radio-iodine uptake was normal (6% and 20% at 4 hours).

One of these patients is being studied extensively and has so far been shown to have a

pituitary-thyroid axis which is normally responsive to exogenous T_3 and T_4. Administration of successive increments of oral T_3 40, 80 and 160μg daily, resulted in a decline of serum T_4 with a half-life of 7 days, and progressive suppression of the TSH response to TRH. Fourteen days of oral T_4 0.25 mg reduced ΔTSH to 2 mU/l at which time T_4 was 265 nmol/l, T_3 2.6 nmol/l and reverse T_3 0.6 nmol/l (Fig.5). Six weeks of oral T_4, 0.4 mg daily, raised T_4 to 370-390 nmol/l and abolished the TSH response to TRH, but T_3 remained 2.7-2.8 nmol/l Fig.5). BMR increased to only +5% during high dose T_4 treatment for 6 weeks.

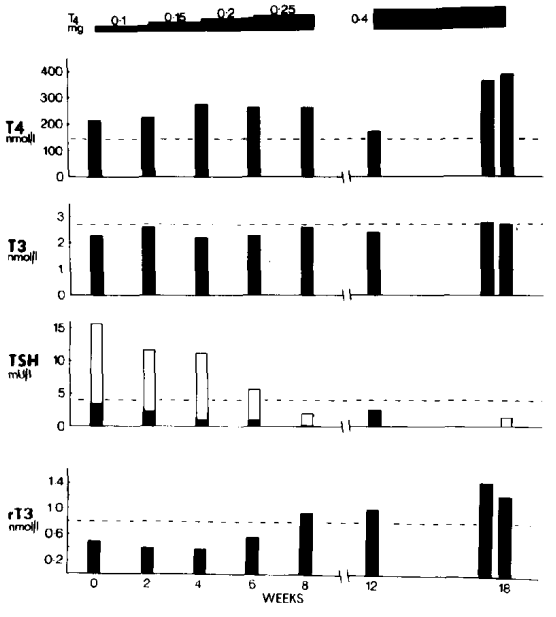

Fig.5
Effect of successive increments of oral T_4 on thyroid hormone levels and on the TSH response to TRH in a subject with persistent isolated T_4 excess, showing that the pituitary-thyroid axis is responsive to exogenous T_4. Basal TSH is shown by the solid bars and the maximum response after TRH by the open bars. Serum T_3 shows only a minimal response to the increasing levels of T_4 but the TSH response to TRH is greatly diminished.

This subject is excessively sensitive to the anti-thyroid effects of exogenous iodide, as is found in subjects with diminished thyroid reserve. After potassium iodide, 240 mg daily for 14 days, basal TSH rose to 14 mU/l, with ΔTSH 78 mU/l after TRH 400μg. Iodide caused a marked decline in both serum T_3 and T_4. This is in contrast to the effect in normal subjects, where iodide in this dose, causes a small decrease in thyroid hormone levels and a slight increase in TSH which usually remains within the normal range.

This led us to the initial hypothesis that the findings represented an adaptation to impaired thyroxine deiodination in peripheral tissues, but subsequent studies demonstrate a familial abnormality which is more suggestive of a new syndrome of thyroid hormone resistance. This patient's mother and two siblings have isolated T_4 excess, while two other siblings have T_3 excess with normal T_4. None has any evidence of hyperthyroidism or any of the other stigmata associated with the known syndromes of thyroid hormone resistance. Hormone ingestion has been ruled out by uptake studies.

Recognition of this new type of familial thyroid abnormality will avoid unnecessary treatment for spurious hyperthyroidism and may ultimately provide new information on thyroid hormone action and interconversion.

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C.J. OFFICER BROWN CARDIAC SURGERY UNIT

Director:	Mr. George R. Stirling
Cardiac Surgeons:	Mr. Eric Cooper
	Mr. Bruce B. Davis
	Mr. Gil Shardey
Research Fellow:	Mr. Franklin Rosenfeldt

During 1978, 544 cardiac operations were carried out in the Unit, of these 379 were open heart procedures. Operations for coronary artery disease increased to a total of 211 for the year, valve operations were little changed but there has been a significant fall in the number of patients with congenital heart disease referred for surgery.

The restricted availability of both beds and operating theatres have limited growth but it is hoped that these constraints will be removed in 1979. In December 1978 the New Ward Block was commissioned and the whole Unit is now well accommodated, albeit temporarily, on the third floor of that building. The new operating suites are expected to be commissioned in early 1979.

The plans for the final accommodation of the Unit in the Centre Block of the Hospital are now completed and approved. The Unit has assisted the Hospital in a successful public appeal for funds for this and other developments. The Health Commission Co-ordinating Committee of the Unit met in November and decided that growth of the Unit to meet a case load of 550 open heart cases per year should be supported.

Mr. Frank Rosenfeldt joined the Unit in January 1978 as a career investigator in cardio-thoracic surgery. Mr. Rosenfeldt has been awarded the Edward Wilson Fellowship for 1978 and 1979 and, with strong support from Professor Paul Korner and the Baker Medical Research Institute, has established a vigorous programme in experimental cardio-thoracic surgery. The major research interest of the group headed by Mr. Rosenfeldt is in the preservation of the myocardium during surgery and studies at both the laboratory and clinical level are proceeding. Mr. Andrew Fambiatos, research assistant to Mr. Rosenfeldt, has made a valuable contribution. The techniques of surgery for electro-physiological disturbances of the heart have been another area for development by Mr. Shardey and Mr. Rosenfeldt and our clinical programme in surgery for cardiac arrhythmia has been successfully started. We are grateful to donors from any sources in enabling this work to proceed and, in particular, B.H.P. Co. Ltd. which contributed $5,000. Many patients and relatives continue to donate generously to the Unit's research activities.

Dr. Peter Newland joined the Unit in October as a full time Cardiac Anaesthetist with additional responsibilites for cardio-pulmonary perfusion and intensive care. Miss E. Anne Shanahan is leaving the Unit, Dr. Alan Cameron retired from his anaesthetic duties during the year and we are grateful for their contribution and wish them well.

A comparison of the changing experience in the different disease groups is presented in the table.

CASE TYPE	1974	1975	1976	1977	1978
Coronary Disease	98	115	166	177	211
Valve Disease	134	160	141	150	139
Congenital Disease	41	50	62	44	16
Miscellaneous	18	13	4	8	13
Total Open Heart	270	289	336	361	379
Open Heart Mortality	4.8%	8.3%	3.6%	5.8%	3.7%
Pacemakers	69	90	101	122	148
Closed Procedures	21	30	33	30	17
Total Operations	360	409	470	513	544

Coronary artery surgery was carried out in 55% of operations, valve surgery remained rather stationary and congenital heart referrals have fallen. Pacemaker surgery continues to grow in volume. The overall mortality for open heart surgery was 3.7%.

SURGERY FOR CORONARY ARTERY DISEASE

Increasing confidence in elective myocardial revascularisation has resulted in more referrals and some widening of the indications so that the question of bearing of angiographically demonstrated severe disease on the question of longterm survival of the patient is, with increasing frequency, influencing the decision for operation. One hundred and eighty five simple revascularisation operations were carried out with 3 deaths.

The tendency towards using more grafts in each operation continues and over two thirds of the cases had 3 or more grafts. Cardioplegia has been frequently used in this group, as in others, and a study is in progress to determine whether this has

helped to reduce the incidence of intra-operative myocardial infarction. Aneurysmectomy was carried out in 25 cases with an 8% mortality. The major factors in mortality in operations for coronary artery disease were:

1. operation during evolving myocardial infarction (2 cases) and
2. the presence of severe renal and respiratory impairment (2 cases), coronary artery embolism after aneurysmectomy (1 case) and post-operative aortic dissection (1 case).

VALVE DISEASE

Valve surgery was carried out in one hundred and forty-four cases with an overall mortality of 5.8%. The mortality for single valve replacement is less than 2%, perhaps due to better techniques of myocardial preservation, but there were 2 deaths in twenty-four cases of multiple valve replacement. Closed mitral valvotomy was used in a small, highly selected group of five cases and we remain satisfied with this technique. Associated coronary artery grafting was carried out in a quarter of the cases undergoing valve replacement without an apparent increase in risk.

The Bjork-Shiley prosthesis was favoured in most cases but porcine xenografts were used in some where anticoagulants were contra-indicated and a continuing hazard of prosthetic thrombosis when the Bjork-Shiley valve has been used in the atrio-ventricular valve position has influenced us to return to the use of the Starr-Edwards ball valve prosthesis in a significant group of patients for atrio-ventricular valve replacement. Both the Carpentier and the De Vega techniques of repair were used for functional tricuspid regurgitation. The major factors in mortality following valve replacement were operative haemorrhage (2 cases), continuing septicaemia (2 cases), drug anaphylaxis (1 case) and presumed late arrhythmia (1 case).

CONGENITAL HEART DISEASE

Our experience with congenital heart disease is small, 21 cases in all comprising 17 open cases and 4 closed. There was only 1 death, a patient with a seemingly adequate Hardy repair for Ebstein's disease died post-operatively from extensive pneumonia and septicaemia possibly caused by aspiration following too recent dental extraction.

COMPLICATIONS

The frequency of re-operation for haemorrhage has been reduced from 8% in 1977 to 5.5% in 1978 possibly due to the use of techniques of measuring activated clotting times with resultant improvement in the use of Heparin and Protamine. There has also been a reduced need for inotropic support after surgery (5.2%) which may be related to superior myocardial preservation. The problem of post-operative renal failure, usually in those patients with serious pre-operative renal impairment, remains serious. Eighteen patients suffered from serious post-operative renal failure (4.8%) of which 4 required dialysis. Three of the latter died.

The high morbidity from post-operative haemorrhage, respiratory complications, arrhythmia and renal failure might have been responsible for a higher mortality had it not been for the dedicated and skilled attention of our nursing, physiotherapy, and resident medical staff, including the co-operation of anaesthetists and the staff of the Renal Unit. To all of these and many others we extend our congratulations and thanks.

How to support medical research into heart and vascular disorders

The Baker Medical Research Institute is Australia's only research institute now devoted entirely to research into disorders of the heart and blood vessels. We depend very much on non-government support in the form of grants, donations and legacies. Our task is to seek new knowledge in these important areas which at present are the cause of so much human suffering and loss. We also provide training for Australians for vocations in medicine and science.

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- DONATIONS
- BEQUESTS
- GIFTS
- LEGACIES

- DONATIONS

ALL DONATIONS ARE DEDUCTIBLE FOR INCOME TAX PURPOSES

It is important to recognize that immediate savings can be achieved if funds intended as a bequest are given as a donation deductible from income. The purpose of the donation can be stipulated, as for a bequest, and may be spread over several years for maximum benefits. All donations ARE USED SOLELY FOR MEDICAL RESEARCH, not for administrative costs.

- BEQUESTS

The donor may wish to specify the purpose for which the bequest (capital or income) is to be used, and the Baker Institute is very pleased to accept such a bequest. It is important to realise that it is not necessary to specify a definite area of research for using the bequest, since all funds of this type are used for research in cardiovascular medicine. Under the latter conditions to facilitate the handling of investments capital sums will be incorporated into the Endowment Fund and the income used as directed.

- LEGACIES AND GIFTS

— ALL LEGACIES AND GIFTS OF RESIDUE ARE EXEMPTED FROM FEDERAL ESTATE DUTY

— THERE IS AT PRESENT EXEMPTION FROM STATE PROBATE DUTIES IN VICTORIA, WESTERN AUSTRALIA AND QUEENSLAND

In estates of moderate size legacies and gifts to the Institute of part of residue can reduce the rate of duty applicable to the whole estate, with relatively little diminution of the share to go to beneficiaries other than the Institute. For further advice you may wish to contact the Institute or consult your solicitor.

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