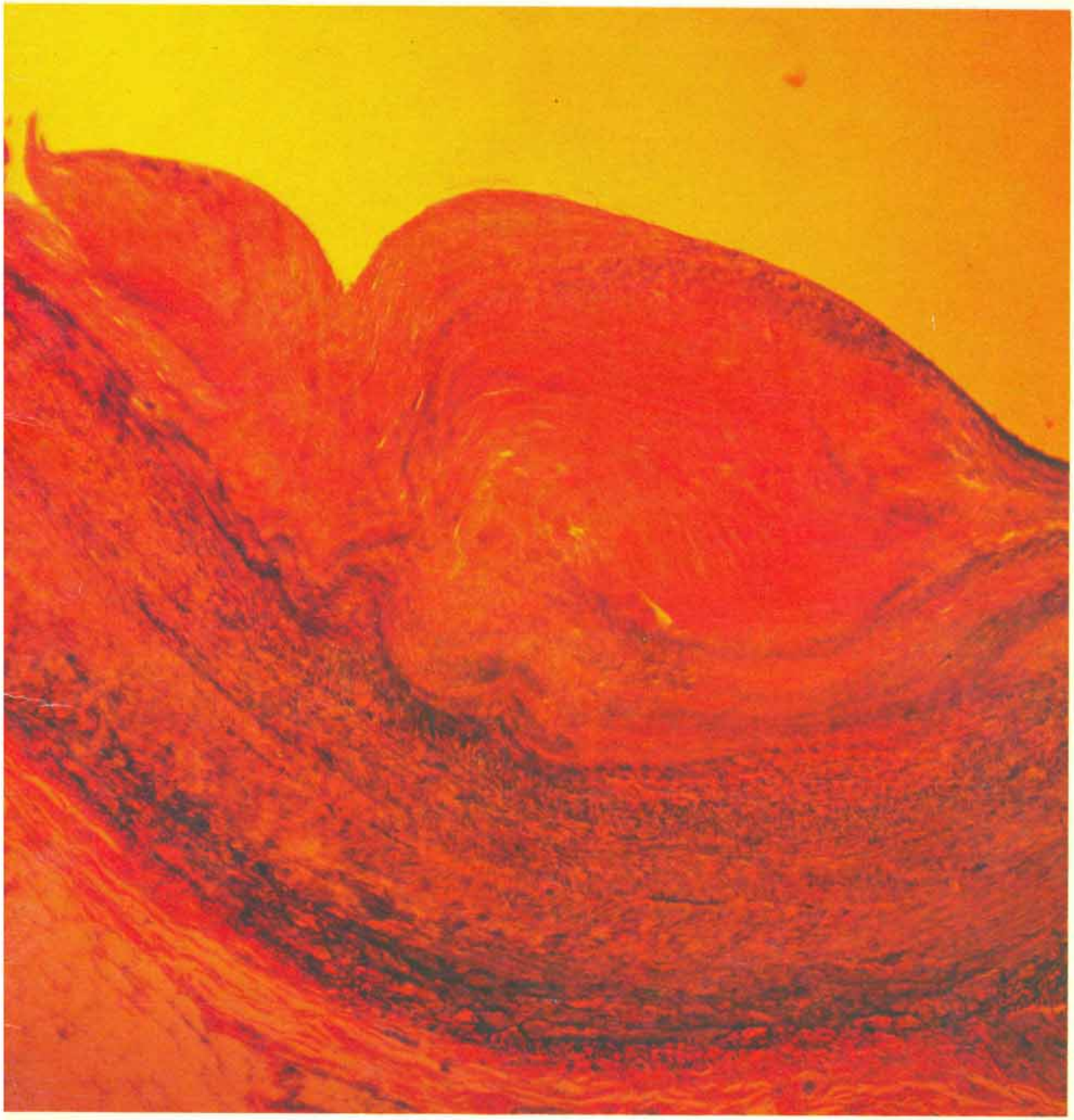
Research Annual Report 1981/82



Baker Institute
Alfred Hospital

Annual Report 1981/82 Baker Medical Research Institute

affiliated with Alfred Hospital and Monash University

The second Annual Report of
THE BAKER MEDICAL
RESEARCH INSTITUTE

Thirty-third Annual Report of the
CLINICAL RESEARCH UNIT
ALFRED HOSPITAL

Twenty-fifth Annual Report of the
EWEN DOWNIE METABOLIC UNIT
ALFRED HOSPITAL

Our Cover:
Cross section of diseased human coronary artery showing atherosclerotic plaque

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HISTORY

Thomas Baker

The Baker Institute was founded in 1926 as a result of a bequest of Thomas Baker, his wife Alice and his sister-in-law Eleanor Shaw. Thomas Baker had established a business for manufacturing photographic materials in partnership with J. J. Rouse. This eventually became Kodak Australasia (Pty) (Ltd). Thomas and Alice Baker and Eleanor Shaw made an agreement with the Board of Alfred Hospital to assume financial responsibility for establishing a Biochemical Laboratory in the new Institute. Most importantly, this laboratory was to be used for medical research. The Biochemical Laboratory grew into the Baker Institute which subsequently became an autonomous institution. But its close affiliation with Alfred Hospital has continued throughout its existence.

Unfortunately Thomas Baker was not destined to see the fulfilment of his vision of a major medical research Institute. He died in 1928, soon after the establishment of the Baker Institute.

Thomas Baker

First Directors

Under its first two Directors Dr W. J. Penfold (1926-1938) and Dr A. B. Corkhill (1938-1948) a high proportion of the work done in the Institute provided clinical pathology services for Alfred Hospital, though there was always some research. After World War II the Hospital established separate service departments for clinical pathology and since then the Baker Institute became fully engaged in medical research. At that time Dr Thomas E. Lowe became the Director of both the Baker Institute and the newly established Clinical Research Unit at Alfred Hospital. This ensured close cooperation of basic and clinical research which has continued ever since. During Dr Lowe's term as Director from 1948-74 the Institute was active in several different fields of medicine including cardiovascular research, haematology, gastroenterology, diabetes and other metabolic disorders, and cancer research.

Monash University Affiliation

In 1965 the Institute became affiliated with Monash University for the purposes of promoting the teaching and encouraging research of undergraduate and postgraduate medical students at the University. This was an important development, which allowed the Institute to participate in the University's Post-graduate Research Training Programme for higher degrees. Between 1966-69 the present modern building of the Baker Institute was built, providing a great boost to its research capacity. Professor Paul Korner became Director of the Institute at the beginning of 1975. Since that time the research effort has been entirely in the field of cardiovascular medicine.

RESEARCH OBJECTIVES

The Baker Institute is Australia's largest cardiovascular research centre. Its main objective is to discover the causes of the two major cardiovascular diseases in our community — high blood pressure and atherosclerosis of the large arteries. These disorders are so deadly because they cause strokes, heart failure, heart attacks and kidney failure. Together they account for over half of Australia's deaths each year and for a large amount of serious illness.

The causes of high blood pressure and atherosclerosis are believed to be due to disorders of the body's complex control systems. Those regulating blood pressure include the nervous system and various hormones, the kidney and the contractile properties of the heart and blood vessels. In addition, the control systems important in the formation of atherosclerotic plaques which obstruct the large blood vessels of the body include mechanisms important in the metabolism and nutrition of the cells of the arterial wall and other body tissues. Of particular importance here are nutritional factors, especially those concerned with the metabolism of cholesterol and other fats.

The objective of our work is to discover the main factors that lead to permanent malfunctioning of these control systems and how to best treat them by medical and surgical means and by changes in lifestyle.

Mr J. C. Habersberger

PRESIDENT'S REPORT

On behalf of the Board of Management, I have much pleasure in presenting the Second Annual Report of the Baker Medical Research Institute under its new constitution since the proclamation of the Baker Medical Research Institute Act, 1980. Our history, of course, goes back well over 50 years. The Institute was established in 1926 under a Deed of Trust by Thomas Baker, his wife Alice and his sister-in-law Eleanor Shaw. Some of the high spots of our history are outlined in the opening pages of this report.

The Baker Institute is now Australia's premier cardiovascular research institute. We have been fortunate that under the leadership provided by Professor Korner, Dr. Nestel and Professor Ludbrook we have attracted a remarkable group of first-class young scientists to the Institute working predominantly in the fields of hypertension research and atherosclerosis research. Our work is held in high regard internationally. One indicator of this is the fact that the International Society of Hypertension recently bestowed the Volhard Award and Lectureship on Professor Paul Korner, which is a signal honour in the field of hypertension research.

Funding

The developments at the Institute during the last 7-8 years have of course required considerable financial support and our Board has worked very hard to provide the means to allow the scientists to carry on their work. To-day successful medical research depends on a combination of good science, entrepreneurial skills and cooperation between government and private sector. The morale amongst our scientists has been extraordinarily high and, perhaps because they are less securely tenured than within Universities, they realise what a great privilege it is to be able to do research. Our major battles have been to secure the necessary finance for our programme.

By far the largest income at present comes from the Federal Government which has given us support through a variety of different grants. Because of our scientific standing, the National Health & Medical Research Council recently recommended to the Government that our grants should be consolidated into a single Institute Block Grant to start in 1983, with a modest increase in the total level of funding. This measure is long overdue and all members of our Board and I, sincerely hope that the Federal Government will now give us this type of support which appears of critical importance in the present stage of our development.

The Institute also receives good support from the Victorian State Government, from the National Heart Foundation of Australia, the Life Insurance Medical Research Fund and numerous other bodies. I want to pay particular tribute to the undeviating support we have received from the Thomas Baker Trust. It may not be well known that this Trust is not synonymous with the Baker Institute and that they are legally only obliged to support us at a very modest level. However, in accordance with the stated wishes of Thomas Baker they have always supported us to their maximum capacity. In 1981 we received $527,758, the greatest sum ever given to us and we are most grateful to the Trustees for rallying to our needs.

To increase our fundraising effort the Board of the Institute recently formed a Development Council under the chairmanship of Sir Laurence Muir. I am particularly grateful to all its members for their tireless efforts on the Council:— Professor R. R. Andrew, Dr C. M. Deeley, Mr S. M. Godfrey, Mr T. W. Kinchington, Mr J. D. Milne, Mr I. T. Perkins, Sir John Reid and Mr K. O. Wilks and of course to our Financial Director — Mr Michael Downes. In 1981 we raised $335,799 from Companies, Trusts and from 3,500

individual donors. It is this effort in particular that allows us to fill existing gaps in our funding and from time to time to embark upon new ventures as scientific opportunities arise.

A full account of our financial position is disclosed in the Financial Statements of this report. I want to draw attention to the small deficit of $25,323 that we incurred in our financial year. Considering the inflationary pressures and salary rises this can be regarded as reasonably satisfactory.

Changes in Volunteer Leaders

In 1981 we restored our traditional link with Kodak Australia Pty. Ltd. on our Board. Mr Don Hogarth, Chairman of Kodak (A/sia) Pty Ltd agreed to join our team and we look forward to his involvement in our affairs for many years to come. It is very pleasing that this historic link between the Institute and Kodak, first started by Thomas Baker and the Rouse family should again be restored.

I want to use this opportunity of registering our sincere and heartfelt thanks to the former Honorary Treasurer Mr George O'D. Crowther, who held this position for many years. Mr Crowther recently tended his resignation which the Board received with regret. In his place I welcome our new Treasurer Mr John Milne, who is Managing Director of the A.N.Z. Banking Group and who has agreed to serve as Honorary Treasurer. He has already worked for us on the Development Council and his financial expertise will be of great value in the future.

Edgar Rouse Fellow

I now want to draw attention to some of the scientific highlights, particularly in the international arena. This year we have been fortunate to have had two very senior scientists from the United States working at the Institute. The first was Dr. Irwin J. Kopin, Chief of the Laboratory of Clinical Science of the National Institutes of Health and one of America's most distinguished biochemical pharmacologists. He has been our first Edgar Rouse Visiting Fellow and his visit will keep alive the memory of Edgar Rouse, who did so much for the Institute. The second visitor was Professor William E. Connor of the University of Oregon, one of America's leading nutritionists. He has been here as Warren McDonald Overseas Fellow of the National Heart Foundation. Both our distinguished visitors contributed greatly to the research of the Institute and collaborated with our staff. Details of their work here are described elsewhere in this report. We have of course also scientists from other countries including Germany, Japan, India and the United States and in 1982 we will greet for the first time a visitor from the Chinese Peoples Republic.

I want to express my sincere thanks for their continuous support to other members of the Board, particularly my Vice President Professor Rod Andrew and Mr Hogarth, Dr. Kay, Professor Korner, Mr McPherson, Mr Moir, Sir Laurence Muir, Sir John Reid, Professor Schofield and the Treasurer Mr Milne and of course our Secretary Dr. Trevor Wood.

This report would not be complete unless I record also the sincere appreciation of our Board for the magnificent work of the Director, Professor Paul Korner and all members of his staff.

Ladies and Gentlemen I have much pleasure in moving the adoption of this report.

Sir Laurence Muir, Chairman of the Development Council

Prof. P. I. Korner

DIRECTOR'S REPORT

In 1981 the Baker Institute completed its first year under its new constitution. I am pleased to report that the scientific work of the Institute continues to make good progress as judged by the usual criteria:— all our research groups are publishing numerous scientific papers and chapters in prestigious international journals and books. Several have given recent 'state of art' lectures at international conferences. Some of the world's leading scientists have started a number of collaborative programmes with us. More young postdoctoral scientists from overseas are finding the Baker Institute a worthwhile place to work and to extend their research experience.

Prof. J. Ludbrook

Last year I reported briefly that Professor John Ludbrook had joined our staff as Associate Director and Head of the Cardiovascular Surgery Research Unit. For him this has meant a change from managing a busy clinical department to running an even busier research laboratory. His surgical skills have been put to very good use devising methods for investigating nervous control of autonomic function, particularly by the changes evoked through alterations in the blood volume of the heart and lungs and by changes in some of their other properties.

Amongst our distinguished international visitors we welcomed Dr. Irwin J. Kopin as our First Edgar Rouse Visiting Fellow and Professor William E. Connor, from the University of Oregon who is spending a sabbatical with us as Warren McDonald International Research Fellow of the National Heart Foundation of Australia. In addition visiting scientists from Germany, Japan, and India are working at the Institute. We are expecting our first visitor from China to arrive shortly to work with Dr. Julie Campbell on research related to cell biology.

I am pleased to report that the financial side of 1981 turned out better than it looked at the start of 1981. Through a record effort our new Development Council under Sir Laurence Muir and our Financial Director Mr Michael G. Downes have managed to fill some of the gaps in our funding. This made it possible to buy several items of equipment, essential for our current research programme. These included a high pressure liquid chromatography unit for our work in biochemical pharmacology, and additional and much needed computer facilities which will increase our data processing capacity and save us money currently spent on the rather too costly facilities of the computer centres at Monash and Melbourne Universities. One interesting application has been the installation of a small computer for non-invasive measurement of cardiac output in our Clinical Research Unit. This is essential for one of our most exciting new research projects on human hypertension which we hope will provide really new insights into its causes (see section on Human Hypertension).

In my previous Annual Report I stressed the inadequacy of long range funding to the Baker Institute from the Federal Government through the National Health and Medical Research Council (N.H. & M.R.C.). At present there are three categories of grants awarded by N.H. & M.R.C.:— *Project Grants* for 1-3 year short-term support of specific projects; *Program Grants* for longer term (5 year) support for a broad area of research involving several investigators; *Institute Block Grants* for longer term (5 year) support of broad, multi-disciplinary research programmes involving even larger groups.

The Baker Institute now receives two Program Grants and several Project Grants and has made application for an Institute Block Grant, similar to that received by the Walter and Eliza Hall and Howard Florey Institutes. This resulted in a site

Federal Funding

visit in May 1981 by a special Ad Hoc Committee of the N.H. & M.R.C., charged to review medical research institutes throughout Australia. They looked at the quality and scope of the research work, the international standing of the research workers and the adequacy or otherwise of the existing levels of financial support. This Committee consisted of medical scientists mostly from outside Victoria under the chairmanship of Professor R. J. Walsh, Dean of the Faculty of Medicine, University of New South Wales. They recommended that the Baker Institute should receive a Block Institute Grant. Their report states:
Of the nine institutes nominated by Council and reviewed by the Committee, the Baker Medical Research Institute is recommended for a Block grant of the Institute type at this time. For this purpose additional funds will have to be sought for the Medical Research Endowment Fund to make provisions for a total grant of $0.925 million (in 1981 Dollars).

This recommendation was accepted by the Medical Research Advisory Committee of the National Health and Medical Research Council and subsequently by the full Council of the N.H. & M.R.C. This has now gone to the Federal Government as part of the N.H. & M.R.C. 'Case for Funds for Medical Research for 1983' which is to be considered by the Federal Government later in 1982 in relation to the 1982/1983 Budget.

We have some grounds for optimism. At the laying of the foundation stone for the new building of the Hall Institute the Prime Minister said: "*It is now 120 years since the first medical school was founded in Melbourne, and the Walter and Eliza Hall Institute together with the Florey and the Baker Institutes, are premier medical research institutions in Australia.*" He added "*It will not surprise you greatly to hear me say that government funds are scarce, but we believe there are some research areas where we must strive for excellence and try to make sure that the people involved are not short of funds.*"

It is very much to be hoped that the Government will agree to the N.H. & M.R.C.'s recommendation about an Institute Block Grant for the Baker Institute. We have no doubts that our work is a national asset and will provide new insights into the causes of the two most deadly diseases in Australia which, in turn, will lead to improvements in health care.

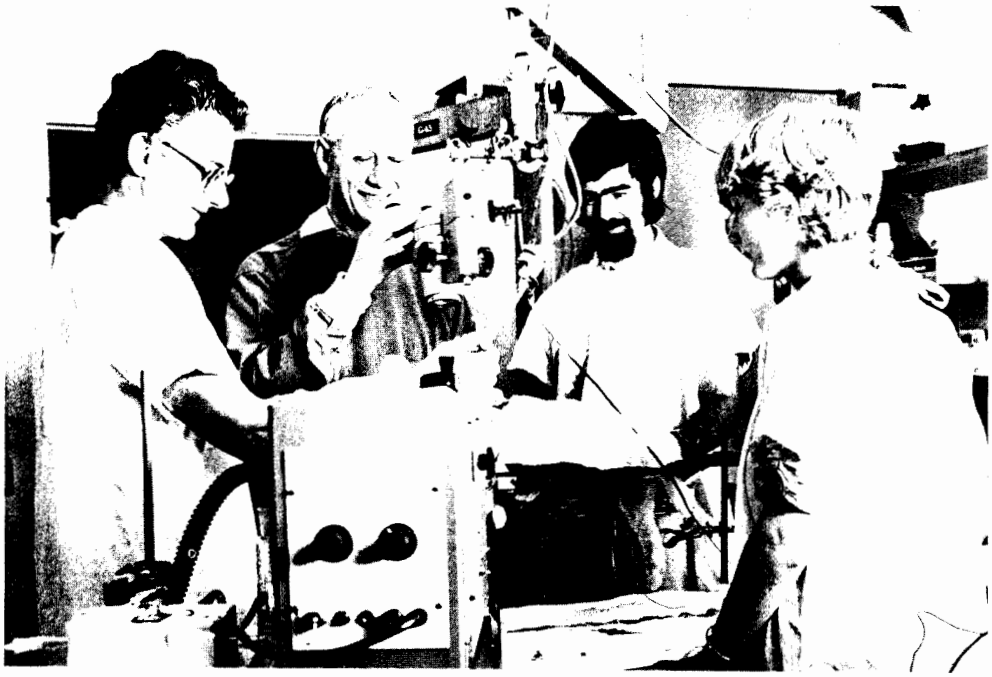
A *centre of excellence* such as the Baker Institute brings many outstanding scientists in different scientific disciplines under one roof. Complex problems related to hypertension, central nervous control of the circulation, and atherosclerosis are best approached from several directions, if answers are to be provided. The brilliant individual research worker is often far more effective as a member of a research team and certainly does not lose his identity there. Inter-disciplinary research centres provide maximum economy in the use of expensive equipment but above all they provide an environment which maximises the chances of reaching research objectives in a relatively short space of time. I very much hope that the Government will give this clear recommendation of the Council relating to the Baker Institute its highest priority in the new medical research initiatives for 1983.

To maintain our success in cardiovascular research will require continuing effort on our part. Recent insights gained through out research in hypertension make it clear that we should become more 'molecular' in our analysis of basic physiological mechanisms, particularly those related to membrane receptors and other processes at the endings of sympathetic nerves. We need to extend our efforts in cellular biology of the enlarging heart, vascular smooth muscle and in electrical mechanisms of disturbances of heart rhythm. These form natural extensions of some of our current areas of work.

On the other hand, although the Baker Institute played an important role in introducing Clinical Pharmacology at Alfred Hospital, this discipline in the hospital must become increasingly concerned with areas outside the cardio-vascular field. Probably the time is close at hand when the hospital should take greater responsibility for Clinical Pharmacology, which will allow us to make new developments at the Institute.

Optimism about the future is justified only if we continue our efforts at 'self help'. Scientists are very much dependent on goodwill and understanding of the community that supports their efforts. They must be able to explain their results, achievements and future objectives and respond to questions and criticisms. I

believe that what has made the major Australian research institutes so successful, has been their acceptance of continuing public accountability as one of the facts of life.



J. Oliver, Prof. Korner, Dr G. Head and R. Smith

DR IRWIN J. KOPIN First Edgar Rouse Visiting Fellow

Edgar Rouse was a Trustee of the Baker Institute from 1942 to 1974 and Chairman of its Board from 1944 to 1974. He provided much of the drive that led to the building of the Baker Institute's new premises in the 1960's and 1970's and thus played a major role of its eventual transformation into a major national cardiovascular research centre. He stood for close cooperation between Institute and Hospital and for the closest integration of basic and clinical research.

To honour his memory and unremitting efforts for medical research the Board of the Baker Institute established the Edgar Rouse Visiting Fellowship, to bring a distinguished international medical scientist to work at the Institute.

This year the Edgar Rouse Visiting Fellowship was awarded for the first time to Dr. Irwin J. Kopin, Chief, Laboratory of Clinical Science, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland, U.S.A. He was with us in January-February 1982.

He was born in New York and educated at McGill University in Montreal. He has been at the National Institutes of Health since 1961. The staff of his laboratory includes the Nobel Laureate Dr. Julius Axelrod and many distinguished researchers have trained and worked there. One of our present staff, Dr. Peter Blombery, trained with Dr. Kopin in 1979/80 whilst an Overseas Research Fellow of the National Heart Foundation. Dr. Kopin has been one of the outstanding contributors to the field of catecholamine research. Catecholamines are the chemical messengers released from the peripheral sympathetic nerves that constrict blood vessels and increase heart rate; they are also released from nerve cells in the brain where they play an important role in the regulation of appetite, other aspects of behaviour and in the control of blood pressure.

During his visit here he worked with Dr. Jim Angus, Dr Alex Bobik and Dr Graham Jackman investigating the role of presynaptic receptor mechanisms at the sympathetic nerve endings. These alter the amount of transmitter released with each nerve impulse. Dr Kopin helped us establish several methods in which he had extensive experience. These complement the techniques developed at the Baker Institute for investigating these important modulators of sympathetic function.

Dr Irwin Kopin

One of the highlights of his visit was a 'Workshop on Catecholamines'. This had 70 participants from interstate, from other research centres in Melbourne and from members of the Baker Institute staff. The topics dealt with were *'Methods in Catecholamine Research', 'Adrenergic Receptors', Noradrenaline Turnover, Plasma and Tissue Catecholamine and Metabolites'* and *'Clinical Physiology and Pharmacology of Adrenergic Neurons'*. The Workshop allowed informal discussions by the participants of the various methodological and biological problems.

PROFESSOR W. E. CONNOR
Warren McDonald International Visiting Research Fellow

Prof. W. E. Connor

Professor Bill Connor spent 4 months' sabbatical leave during 1982 with Dr. Nestel's group. He is Professor of Medicine at the University of Oregon, Portland, USA and has been a leading clinical investigator for the best part of 20 years. His main interest is the nutritional regulation of lipoproteins. Dr. Connor and his wife Sonya, who is Assistant Professor of Clinical Nutrition, had spent their previous sabbatical at the Australian National University. Their elder son was born in Canberra. We regard them as 'honorary' Australians.

Professor Connor has discovered many 'firsts' on the influence of dietary factors plasma cholesterol. Some of these were discovered through researches conducted in the hospital-laboratory environment, whilst other insights came from field studies on the diet of the Tarahumora Indians of Mexico. His current interest, is the remarkable lipid-lowering property of certain highly polyunsaturated fatty (w3) acids found in fish from the cold oceans. The previous immunity of Eskimos to atherosclerosis is being attributed to their high consumption of such fish. This has stimulated a new line of research at the Baker Institute and Sue Wong, one of our PhD. Scholars will be continuing the work.

Professor Connor has had considerable influence on nutrition policy in the United States. He has been a consultant to several programs including the Heart Program Project, Diet and Heart Study Programs and an advisor to the U.S. Senate Select Committee on Nutrition. He has been President of the American Society for Clinical Nutrition, Chairman of the Council on Arteriosclerosis of the American Heart Association and Editor of the Journal of Laboratory and Clinical Medicine. In Australia he has helped spread the National Heart Foundation's nutritional message during National Heart week.

EDWARD WILSON MEMORIAL FELLOWSHIP

The Edward Wilson Charitable Trust has long played an important role in the history of both Alfred Hospital and the Baker Institute. This is described in Ann Mitchell's book 'The Hospital South of the Yarra' published in 1977, and in Thomas Lowe's book 'The Thomas Baker, Alice Baker and Eleanor Shaw Medical Research Institute — The First 50 Years' published in 1974.

The Edward Wilson Memorial Fellowship is the premier fellowship award of the Alfred Hospitals Research Fund. It is tenable not only in the hospital, but also at the Baker Institute and has now been used over many years to bring outstanding researchers to these institutions for periods up to two years.

Since the Baker Institute became a cardiovascular research centre there have been three Edward Wilson fellows — Dr. Jennifer Angell-James, Dr. Frank Rosenfeldt and Dr. Kerin O'Dea.

Edward Wilson Fellows

With all three the Edward Wilson Fellowship award allowed us to introduce new approaches and techniques to the Baker Institute. Dr. Jennifer Angell-James was here in 1975/6 and helped establish our Laboratory of Cardiovascular Neurophysiology. She returned to England and is now Reader in Physiology at St. Barthomolew's Medical College in London. Without the Edward Wilson Fellowship we would not have been able to induce Frank Rosenfeldt to return to Australia, where he started Australia's first laboratory in Experimental Cardiac Surgery. It also allowed us to maintain Dr. Kerin O'Dea's Nutrition Laboratory during 1981. Both Frank Rosenfeldt and Kerin O'Dea are now senior staff members of the Institute, working in N.H. & M.R.C.-supported positions.

The Board of the Baker Institute acknowledges gratefully the important role of the Edward Wilson Fellowship in starting a number of new research ventures.

EMILY STEWART BEQUEST

The late Mrs Emily Elsie Elizabeth Stewart of Glen Iris died in 1976. She was in her mid-eighties and widowed.

Mrs Stewart had no children and so in her will she provided legacies to relatives and friends, and a fund to assist students at Scotch College and Presbyterians Ladies College. She directed that the income from half of her estate be paid to the Baker Medical Research Institute for the work of its Kidney Laboratory. Her will was framed in such a way that the Institute will eventually receive the whole of the income from her estate in perpetuity provided it continues to conduct kidney research.

The estate currently has a value of about $700,000 and the Executors, Perpetual Trustees advise that their investment policy is to provide for continued growth of both capital and income.

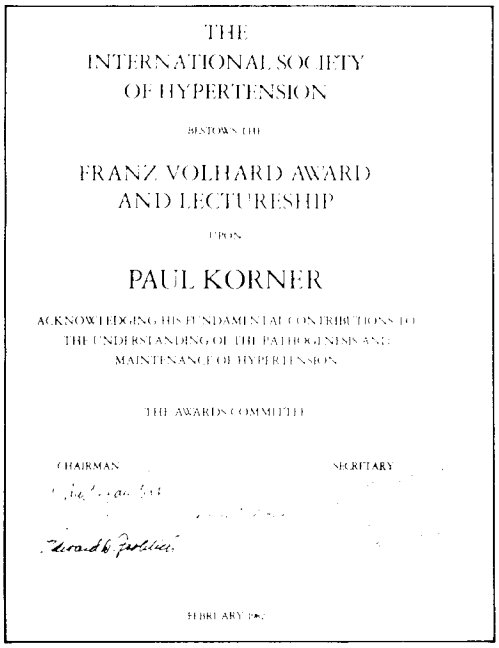
The income is providing substantial support for the maintenance of the Kidney Laboratory which is supervised by Dr Warwick Anderson.

Their work is explained in detail in the Scientific Section of this report.

The Board of Management, Director and Staff are indebted to the late Mrs Stewart for her foresight and generosity in planning this substantial assistance for the Institute.

VOLHARD AWARD

Prof. Davis (left) presents the Volhard Award to Prof. Korner



THE
INTERNATIONAL SOCIETY
OF HYPERTENSION

BESTOWS THE

FRANZ VOLHARD AWARD
AND LECTURESHIP

UPON

PAUL KORNER

ACKNOWLEDGING HIS FUNDAMENTAL CONTRIBUTIONS TO
THE UNDERSTANDING OF THE PATHOGENESIS AND
MAINTENANCE OF HYPERTENSION

THE AWARDS COMMITTEE

CHAIRMAN SECRETARY

FEBRUARY 1982

The Citation

Volhard Lecture

The International Society of Hypertension recently bestowed the prestigious Franz Volhard Award and Lectureship on Professor Paul Korner for his 'fundamental contributions to the understanding of the pathogenesis and maintenance of hypertension'.

Professor Korner delivered the Volhard Lecture at the recent meeting of the International Society which was held in Mexico City in February 1982. The topic of the Lecture was 'Causal and Homeostatic Factors in Hypertension'.

In his lecture Professor Korner said:— *'Many of the ideas on the development of hypertension would never have emerged without the help and stimulus of my collaborators in this work. I am particularly indebted to W. Anderson, J. Angus, A. Bobik, A. Broughton, M. Esler, P. Dorward, P. Fletcher, G. Jennings, J. Oliver and M. West who have worked with me over the last 6-10 years, mostly at the Baker Medical Research Institute'.* We feel therefore that the award recognises the work of the entire Hypertension Group at the Baker Institute.

Scientific Report

Hypertension and Circulatory Control Research Unit

HUMAN HYPERTENSION-VASCULAR LABORATORY
CIRCULATORY CONTROL LABORATORY
CARDIOVASCULAR PHARMACOLOGY
KIDNEY LABORATORY
BIOCHEMICAL PHARMACOLOGY
CLINICAL PHARMACOLOGY

General Summary

The word *hypertension* means high blood pressure (not nervous tension) and our main objectives are to find out its causes and how best to treat it. As shown schematically in Fig H1, the level of blood pressure depends on properties of the heart and blood vessels, on the kidney's role in the regulation of salt and fluid balance, and on the functions of the central nervous system and various hormones. The modern classification of high blood pressure subdivides hypertension into 'secondary' hypertension where the cause is known, and 'primary' hypertension (also called 'essential' hypertension) where the cause or causes are not known.

In man 'secondary' types of hypertension include stenosis (narrowing) of the renal artery, tumours of the adrenal gland and several other disorders. We recognise a causal relationship between the pathology and hypertension, since renal artery narrowing or removal of the tumour usually cures the high blood pressure. Unfortunately all types of secondary hypertension between them account for only about 5% of patients with high blood pressure. In most types of secondary hypertension we do not know the sequence of steps by which the underlying pathological cause eventually leads to elevation of blood pressure. Such knowledge is basic to the understanding of the general interrelationships between the various components of the blood pressure control system.

In 95% of all patients with high blood pressure the cause is unknown and we

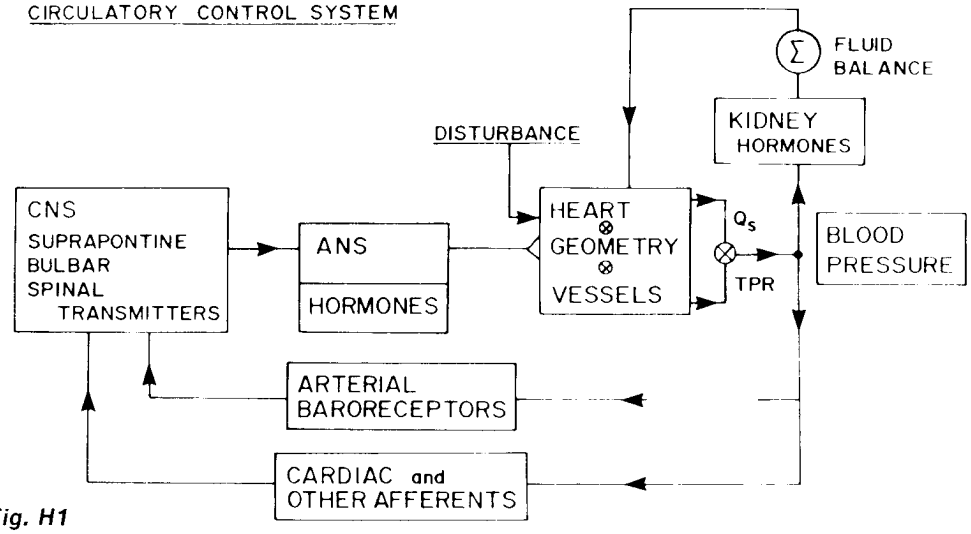


Fig. H1
Schema with components of control system important in circulatory homeostasis. One major difference between normal and hypertensive circulation is that of 'Geometry' due to hypertrophy of heart and vessels. CNS = central nervous system; ANS = autonomic nervous (effector) system; Q_s = systemic flow (cardiac output); TPR = total peripheral resistance.

General Summary

say they have primary (essential) hypertension. In Australia 1 person in 6 has essential hypertension, i.e. 2.5 million Australians. The proportion of hypertensive patients in the U.S.A. and Britain is the same as in Australia. But in Japan it is considerably larger, whilst in the highlands of Papua and New Guinea or amongst the Eskimos it is much smaller. Epidemiological evidence suggests that both genetic and environmental factors contribute to the development of high blood pressure. We do not know for certain whether patients with essential hypertension constitute a homogenous group or whether there are several subsets of patients with different causal mechanisms, but our current working hypothesis is that there are several subsets. The strongest candidates as basic causes are sympathetic overactivity or a 'fault' in the body's handling of salt.

In both secondary and primary hypertension the high blood pressure leads to enlargement of the muscle cells of the heart and arteries, because they have to bear a greater pressure load. The enlarged heart and vascular muscle in turn amplify all kinds of stimuli that normally cause contraction. For example in experimental renal artery stenosis, where the basic cause of the high blood pressure is the narrowing of the renal artery. We have found that its resistance to blood flow accounts for only about one-third of the rise in blood pressure. The rest is due to the amplification of normal levels of sympathetic activity, effects of pressor hormones and the rise in blood volume, provided by the enlargement of the heart and vessels (Fig. H2). These can all be regarded as 'compensatory' mechanism in this type of hypertension for maintaining good kidney function. But this benefit to the organism is offset by the greater susceptibility to stroke and heart failure.

Normally, when an environmental disturbance causes a change in blood pressure it can readily be brought back to normal by a variety of regulators the body's circulatory control system (Fig. H1), much as we regulate room temperature by means of a thermostat. However, the type of defect which leads to a chronic permanent rise in blood pressure, is one that is not readily susceptible to the type of negative feedback control suggested in Fig. H1. Obviously, if we have a very narrow renal artery the body's regulatory systems cannot permanently compensate for this.

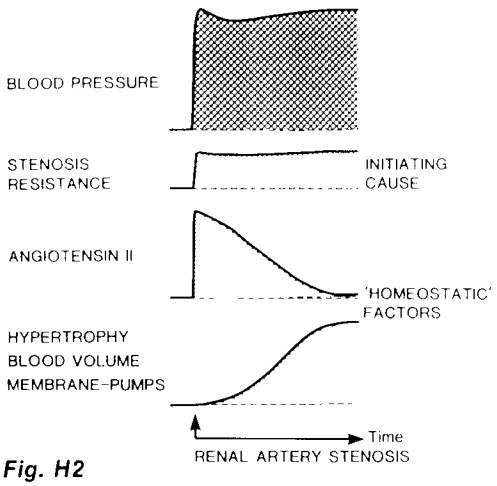


Fig. H2

Schematic representation of different 'causes' of Goldblatt renovascular hypertension. Only the basic initiating cause (stenosis resistance) contributes throughout; other 'homeostatic' mechanisms vary in their contribution at different times — important early role of angiotensin (AII) is later supplanted by cardiovascular 'amplifiers' and other homeostatic factors.

This is probably also the case in essential hypertension, where the 'fault' is a functional equivalent of renal artery stenosis. The 'fault' in essential hypertension may involve cellular transport 'pumps' that are important in the re-uptake of transmitter released at sympathetic nerve endings, or 'pumps' that transport salt in and out of various cells in the body.

What strategy can we employ to find out what causes hypertension? One of our main difficulties is that the contribution to the elevation of blood pressure by the amplification provided by enlargement of the heart and vessels is usually considerably greater than the contribution of the 'basic' fault in blood pressure control. An important study from the Baker Institute, published in the Lancet in 1980, suggests a way out of this impasse. We showed that prolonged treatment of high blood pressure for a 12 month period reversed the hypertrophy of the vessels and heart, and when treatment was discontinued the high blood pressure redeveloped over the next few weeks. Treatment thus removed the effects of the biological amplifiers on the blood pressure, but did not affect the basic causes of hypertension. A 'longitudinal' sequential study of the development of

hypertension throughout life is logistically almost impossible. But a study of the redevelopment of hypertension in individuals over a period of several weeks or months gives us a chance to determine the basic cause in particular patients. We have been tooling up over the last 2 years for a longitudinal study using non-invasive methods, with minimum discomfort to the patients. This will get under way in the beginning of 1982.

We have become convinced of the value of longitudinal studies from our analysis of experimental renovascular hypertension in animal experiments. Our hope is that sequential analysis of redevelopment of high blood pressure in patients with essential hypertension will yield very valuable information which, hopefully, will produce more specific therapy of hypertension in individual patients.

In our programme of hypertension research we use a multi-disciplinary approach to study the individual components of the control system in Fig. H1. For example, our research programme on the sympathetic nervous system investigates the role of peripheral blood pressure sensors and their projections to different parts of the brain on cardiovascular reflexes. But we are also investigating the fundamental membrane mechanisms by which the chemical transmitter is released from sympathetic nerve endings and acts on other types of membrane receptors in the heart and blood vessels. Similarly, our work on the kidney ranges from analysis of the complex hydraulics of narrowing of the renal artery to understanding the hormone and cell membrane transport mechanisms which control the movements of sodium. An inter-disciplinary approach to basic questions is a best way of ensuring that our programme will yield insights of real clinical value.

HUMAN HYPERTENSION LABORATORY

M. D. Esler, P. A. Blombery, G. L. Jennings, P. I. Korner, B. Heinzow, K. O'Dea

Human Hypertension

List of Projects

Studies of noradrenaline kinetics
Effects of drugs which block noradrenaline uptake and metabolism
Effects of antihypertensive drugs
Effects of dietary salt intake on sympathetic activity
Effects of caloric intake on sympathetic activity
Regional release rates of noradrenaline
Autonomic insufficiency

Sympathetic Nervous System and Hypertension

At one time it was thought that all patients with essential hypertension had overactivity of their sympathetic nervous system, because the amplifying role of the enlarged heart and vessels had not yet been recognised. These amplifiers even enhance the responses to *normal* levels of sympathetic nerve activity. To overcome this problem various biochemical indices of sympathetic function have been developed. The biochemical indices include plasma noradrenaline and adrenaline concentrations, but on average these are not grossly different in patients with hypertension and in normal subjects.

At the Baker Institute Dr. Murray Esler and colleagues developed the noradrenaline 'spillover' rate determination as an additional index of sympathetic function. This is done by infusing noradrenaline labelled with minute amounts of a radioactive tracer. The 'spillover' rate is only a minute fraction of the total noradrenaline released at the nerve endings, because much of it gets taken back again into the terminal.

Recent findings by Peter Blombery and Birger Heinzow suggest that it is valid to consider the 'spillover' rate as proportional to the total amount noradrenaline released. They measured the spillover rate in the coronary circulation in dogs in which the sympathetic nerves to the heart were electrically stimulated, and found that spillover rate was highly correlated to total sympathetic nerve activity.

Esler has found that in about 20% of patients with essential hypertension the noradrenaline spillover rate is increased above values found in any normal subject (Fig. H3), because the reuptake of transmitter back into the terminal is defective.

This type of abnormality could be genetically based and is the kind of 'fault' which could lead to chronic elevation of high blood pressure. It seems a reasonable hypothesis to suggest at this

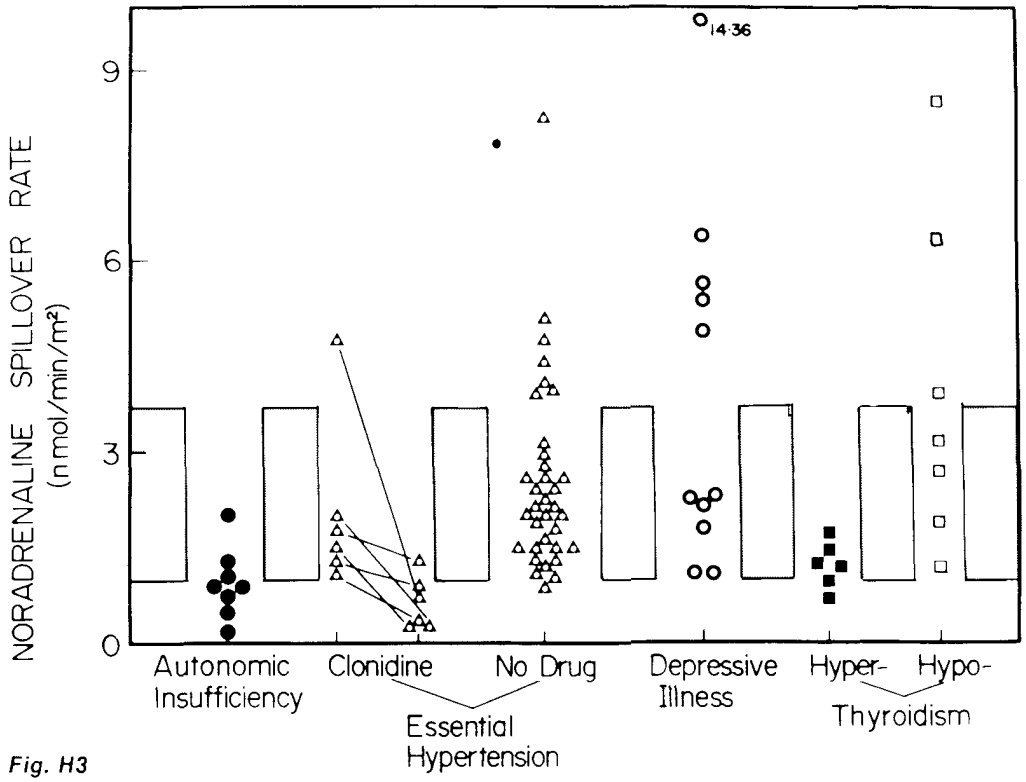


Fig. H3

The rates of spillover of noradrenaline into plasma. The range of values found in 34 healthy subjects is indicated by the bars. Noradrenaline spillover was increased in 20% of patients with essential hypertension, but also in some patients with depressive illness and hypothyroidism in whom blood pressure was normal.

time that in about 20% of the hypertensive population there is some evidence of sympathetic overactivity.

But paradoxically, increased noradrenaline spillover to plasma was also observed in patients with depressive illness and in others with thyroid gland underactivity—two disorders in which blood pressure is typically normal. We do not know whether the noradrenaline release in these disorders came from sympathetic nerves to other structures than the heart and blood vessels. This highlights the need to study *regional* noradrenaline release in hypertensive patients, by organs such as the heart and kidney which have a central role in blood pressure regulation. This type of investigation has begun (Fig. H4).

Dietary Salt

Fig. H4

Total and renal noradrenaline release in four patients with essential hypertension.

Effect of Dietary Salt Intake and Calories

The value of dietary salt restriction in treating essential hypertension, and of calorie restriction ("reducing diets") in obese hypertensives is well known. We have recently found that placing patients on a low salt diet increased noradrenaline release by approximately 50%. This indicates that dietary salt restriction lowers blood pressure by mechanisms other than the inhibition of sympathetic nervous activity.

By contrast we found considerable correlation between sympathetic nerve activity and calories in the diet. A 400 calorie diet reduced both the blood pressure and noradrenaline release.

Helen Skews at the centrifuge

Systolic BP was 16% lower on a low than a high calorie diet, while noradrenaline release was decreased by 50% with undereating. These effects were noticed within a week or so of commencing the diet, and prior to significant weight loss. These findings suggest that part of the blood pressure-lowering effect of low calorie diet is due to inhibition of sympathetic nervous system tone, independent of any loss of weight.

CIRCULATORY CONTROL LABORATORY

P. I. Korner, P. K. Dorward, G. A. Head, J. Gipps, J. R. Oliver, S. L. Burke, B. K. Evans, J. Clevers, E. Badoer

Circulatory Control

List of Projects

Rapid resetting of the arterial baroreceptors
Cardiovascular functions of central brain amine neurons
Hypothalamus and cardiovascular control
The renal sympathetic baroreflex
Angiotensin II and autonomic function
Comparison of central effect of clonidine and α-methyldopa
Hypertension and baroreflexes

Operation of the Central Nervous System (CNS)

The autonomic nervous system alters the force and rate of the heart through changes in activity of the vagus and cardiac sympathetic nerves. In addition, the small arteries and veins are constricted through increased sympathetic constrictor nerve activity and through secretion of catecholamines from the adrenal gland. This is brought about during environmental disturbances and behavioural stimuli through changes in activity of a large number of pressure-sensitive receptors. These signal changes in blood pressure in the arteries, in the heart chambers and lung vessels, and through other types of receptors that are sensitive to changes in chemical composition of the blood, lung movement, pain etc.

The sensory nerves carrying these signals ultimately project to many different regions of the brain, which process the information and produce appropriate autonomic effector response patterns in the light of all the incoming information. Autonomic patterns can be evoked, not only by peripheral stimuli, but can also occur due to signals from specific 'command' areas in the brain, for example, at the onset of exercise. The nerve cells involved in the central pathways controlling autonomic function release many different types of chemical transmitters at their endings. We have been particularly interested in the role of the central noradrenergic and serotonergic nerve cells which play a role not only in the control of blood pressure, but also in the regulation of appetite and various other aspects of behaviour. In addition, some of the well known anti-hypertensive drugs act on these cells or alter their metabolism.

Arterial Baroreceptors and Baroreflexes

Pat Dorward and Mike Andresen recently found that the threshold at which individual baroreceptor units fire is rapidly reset, whenever there is a sustained change in the arterial blood pressure, (Fig. H5). The arterial baroreceptors have therefore a poor longterm 'memory' for any absolute level of the blood pressure but short term changes in pressure can evoke reflex responses about virtually any level of blood pressure. Rapid receptor resetting appears to be due to the elastic properties of the arterial wall and occurs within minutes of sustained changes

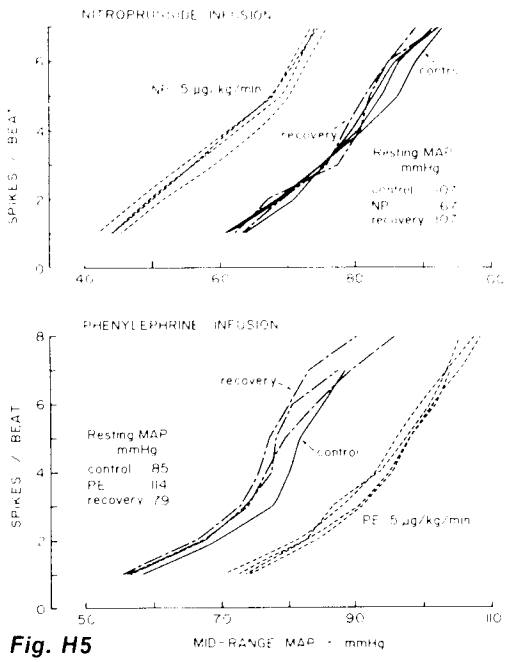


Fig. H5

Relationship between mid-range MAP (mm Hg) and unit activity (spikes/beat) in two units obtained from different rabbits given nitroprusside (upper) and phenylephrine (lower). Responses to repeated pressure ramps were obtained during control (solid lines). 1 h drug infusion (interrupted lines) and recovery period (dot-dashed lines). Resting MAP for each period shown in inserts.

in resting blood pressure.

The nerves arising from the arterial baroreceptor units are so fine that their activity can only be recorded in immobilised anaesthetised animals. However, Dr. Dorward and colleagues have developed a method of recording renal sympathetic nerve activity in conscious animals, using a special electrode which allows the nerve to remain alive for periods between 1-2 weeks. A lot of data analysis from a large number of measurements is required to study renal sympathetic nerve responses to blood pressure changes. A computer program now provides the information, thanks to the work of Mrs. Judy Gipps.

Currently we are examining the effects of blood pressure changes induced by various vasoactive agents and haemorrhage on the resetting of the renal sympathetic nerve responses.

With nitroprusside the threshold for producing inhibition of renal sympathetic nerve activity fell with the fall in blood pressure, but gain (sensitivity) did not alter. All the above changes could be completely accounted for by rapid resetting of the arterial baroreceptors. On the other hand, when the mean arterial pressure was raised with phenylephrine the threshold for inhibiting renal sympathetic nerve activity was not reset, possibly owing to central nervous system interactions involving arterial and cardio-

Dr Geoff Head, Rosemary Smith and Emilio Badoer at an experiment

pulmonary baroreceptors. With severe haemorrhage the resting rate of sympathetic nerve discharge increased, as expected, but the *range* of the baroreflex renal sympathetic nerve changes and the *gain* of the baroreflex were both considerably reduced.

Central Nervous System

CNS Studies

In the central nervous system we are studying cardiovascular functions of a number of chemical transmitter systems. To date most work has been on the properties of the central noradrenergic and serotonergic nerve cells, and the mechanisms of the actions of centrally acting antihypertensive drugs. More recently, we have begun to examine the anatomical and functional organisation of the hypothalamus and other 'higher' brain centres.

Transmitters

The noradrenergic and serotonergic nerve cells are named after the transmitters released at their nerve endings. Each type of cell is present in distinctive groups in the hindbrain region and sends fibres both to the higher centres of the brain and to the spinal cord. In previous years we have used neurotoxic drugs 6-hydroxydopamine and 5,6-dihydroxytryptamine injected into the cerebrospinal fluid to study these cells: (i) during the phase of acute transmitter release soon after injection of these drugs and (ii) chronically following destruction of the specific neurons. These studies have shown both groups of cells play an important role in the regulation of blood pressure and heart rate, and that a number of centrally acting anti-hypertensive drugs alter blood pressure by acting on these neurons. Each group of neurons is present in about 8-10 discrete hindbrain nuclei and this year we have begun to examine the functions of particular cell groups. This has been done by inserting fine electrodes under anaesthesia into one particular nucleus and destroying most of its nerve cells by passing an electric current. The responses to intracisternal injections of the neurotoxin are then tested 1-2 weeks later, when the animals have fully recovered from the surgical procedure.

To date we have studied noradrenergic nuclei A_1 or A_2. We found that after placing lesions in the A_1 area which destroyed about 90% or noradrenergic cells, or after making similar lesions in the A_2 nucleus, the responses to 6-hydroxydopamine (the specific neurotoxin) were not altered. The results therefore suggest that the endings from noradrenergic cells belonging to these particular nuclei were not responsible for the hypertension or bradycardia, or that complete degeneration of the terminal (and disappearance of transmitter) had not occurred.

Prof. Korner and Judy Oliver discussing results

Antihypertensive Drugs

We have previously shown that noradrenergic neurons are important for the cardiac slowing which follows centrally administered clonidine, an important antihypertensive drug. We tested the responses after A_1 and A_2 lesions. We found that after A_1 lesions the response to clonidine (1μg/kg i.c.) reduced the fall in heart rate to about half that observed in sham operated animals. These results therefore suggest that A_1 neurons may contribute to the heart rate responses to clonidine. On the other hand after A_2 lesions there were no differences in the responses to i.c. clonidine or to i.c. alpha-methyldopa compared with the responses of sham operated rabbits.

Another antihypertensive drug that we are studying is alpha-methyl dopa (Aldomet). This drug is thought to be converted into an active metabolite alpha-methyl noradrenaline (and possibly others) after its uptake into noradrenergic nerves. Subsequent release of alpha-methyl noradrenaline during nerve activity then produces a fall in blood pressure and cardiac slowing. It is generally considered that the drug acts on the same central receptor sites as clonidine. Both are thought to stimulate central alpha-adrenoceptors.

We have compared the effects of intracisternal (i.c.) with intravenous (i.v.) administration of alpha-methyldopa. The dose ratio required to produce blood pressure falls is 1/400 by the i.c. route when compared with the i.v. route, which is a much greater dose ratio than with clonidine and may be due to physical differences of the two drugs. Alpha-methyldopa lowers blood pressure and heart rate after about 2.5 and 4 hours after injection. This is much longer than after clonidine and can be explained by the biotransformation to an active metabolite.

We have for the first time studied how alpha-methyldopa affects the properties of the baroreceptor-heart rate reflex, and have found the same changes as occur with clonidine. With both drugs the range of heart rate responses and the reflex gain were significantly increased. Currently studies are in progress to determine any differences in cardiovascular responses to the two drugs after chronic destruction of noradrenergic and serotonergic neurons.

Hypothalamus

This is part of an investigation to find out how some of the higher centres of the brain modify cardiovascular responses. The hypothalamus plays a role in many types of behaviour, in the control of the autonomic nervous system and in the secretion of various hormones important in salt and fluid balance. We have found that in rabbits it affects the different sympathetic constrictor outflows in a very

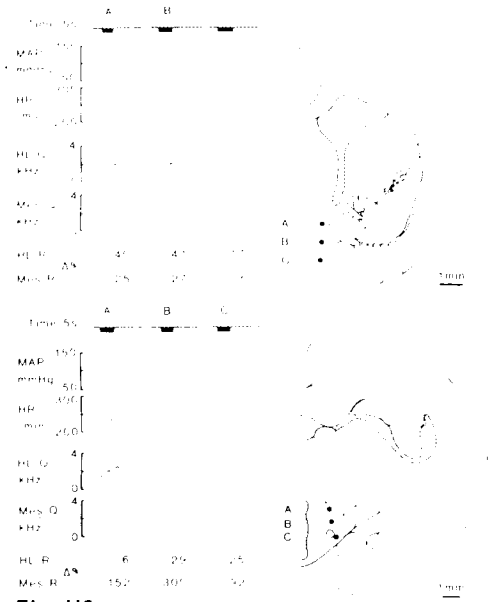
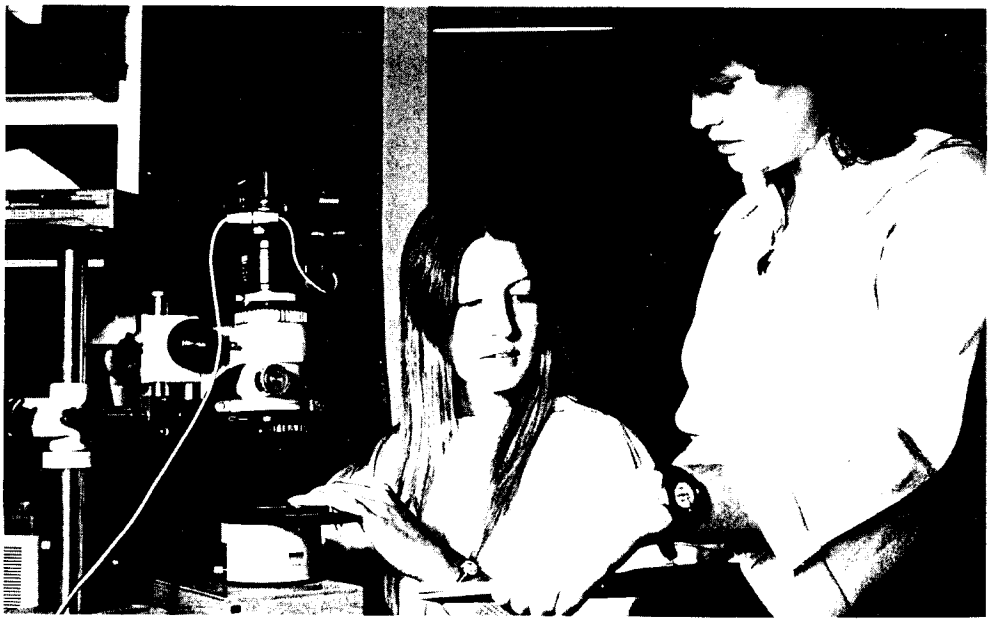


Fig. H6

Electrical stimulation (bars) of anterior (top) and posterior (bottom) hypothalamus and evoked circulatory responses:— MAP = blood pressure, HR = heart rate; HLQ & R = hindlimb flow and resistance, Mes Q & R = mesenteric flow and resistance.



Christine Duch (left) and Judy Aberdeen (right) photographing stained sections of a rabbit hypothalamus

specific manner. Thus electrical stimulation of almost every site either produces varying amounts of constriction of the gastrointestinal blood vessels or no response, (Fig. H6). Similarly, stimulation of the different regions leads to varying degrees of dilation of the blood vessels to the skeletal muscle bed or no response. As far as a given sympathetic outflow was concerned we could not change its response from constriction to dilatation by electrical stimulation of different hypothalamic regions. These studies suggest that there are distinctive connections between the hypothalamus and individual autonomic motoneuron pools.

Modulation by Angiotensin

There has been considerable interest in the question whether the peptide hormone angiotensin II can produce longterm changes in autonomic function. This hormone can be increased in the blood stream, when salt is reduced, or during administration of vasodilator drugs. We have found that during an increase of plasma angiotensin II concentration by as little as 20 pg/ml the vagal nerve activity to the heart is inhibited, so that with transient rises in blood pressure there is less increase in vagal activity and less slowing of the heart than under normal conditions. This has been the first demonstration that angiotensin II does modulate cardiovascular autonomic function under *physiological* conditions. Previously there had been suggestions of similar effects during the administration of large pharmacological doses of the drug, but the postulated effect has always been thought to be mediated through the central nervous system. We have found that angiotensin acts peripherally on a specific angiotensin II receptor related to the vagus. Due to this action there is less release of the transmitter substance acetyl choline per vagal nerve impulse than under normal circumstances. We do not know at this time whether this type of modulation of transmitter release by peptide hormones occurs at other nerve terminals at which acetyl choline is released, which includes some of the autonomic pathways of the central nervous system.

CARDIOVASCULAR PHARMACOLOGY LABORATORY

J. A. Angus, R. Brazenor, T. Cocks, P. I. Korner, M. Le Duc, M. Lew, C. Wright

List of Projects

Actions of ergot derivatives in isolated coronary arteries
Neurogenic vascoconstriction of large coronary arteries
Effect of slow calcium channel blocking drugs on constricted coronary arteries and myocardium
Role of endothelium in vasodilator responses
Apparent frequency dependent effect of clonidine on cardiac sympathetic nerve transmission
Failure of clonidine to inhibit cardiac vagal transmission: evidence against presynaptic alpha-adrenoceptors on vagal varicosities
Action of angiotensin II at vagal varicosities
Are any beta-andrenoceptors agonist selective for the uterus compared with the cardiovascular system?

Coronary Spasm

One research area deals with coronary

Pharmacology Staff: (standing L-R) Dr Tom Cocks, Dr Jim Angus, Michael Lew, (seated) Christine Wright and Matthew Le Duc.

Coronary Artery Spasm

artery spasm and its treatment. Coronary artery spasm, sometimes called vasospastic angina (Prinzmetal's angina), causes cardiac pain, much as does atherosclerotic coronary artery disease. However, in contrast to the latter there are either no lesions, (or only minimal lesions), in the arteries of patients with vasospastic angina. In endeavouring to pinpoint the membrane-receptor mechanisms which cause coronary artery spasm we have studied isolated coronary artery rings placed in organ baths under highly controlled conditions. We have measured the force developed by their smooth muscle to various stimulants and pharmacological antagonists. This allows precise characterisation of the membrane receptors contributing to the production of spasm. In the organ bath the increase in force is measured isometrically, i.e. without allowing the muscle to shorten. However, we also require information concerning the degree of narrowing of the arterial diameter that occurs when the vascular muscle shortens as is the case in the intact heart.

We have developed a new preparation that allows us to measure drug-induced decreases in coronary artery diameter by means of an ultrasonic device called a sonomicrometer, where we measure the changes in diameter under conditions when the blood flow and the distal resistance of the segment of large coronary artery are held constant in an *in vivo* preparation (Fig. H7). This combination of *in vitro* and *in vivo* techniques in the study of the possible causes and treatment of coronary vasospasm are used in our assessment of the actions of drugs that cause or relieve vasospasm.

We have found that ergometrine, which constricts the coronaries of patients with variant angina (and is therefore used to diagnose this during cardiac catheterisation), does this by acting on serotonin receptors. Possibly serotonin, released from platelets may be a trigger factor in coronary vasospasm. We have found that a number of antagonists block the ergometrine-induced constriction of the coronary arteries, but unfortunately they all tend to constrict the artery in their own right. The degree of constriction is not as great as that produced by serotonin, and is spoken of as a partial agonist action. It would be useful to develop specific serotonin antagonists without this property.

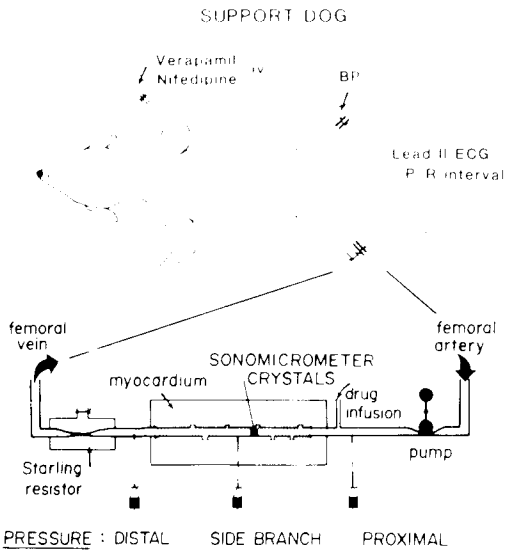


Fig. H7

Schematic diagram of the technique used to measure changes in external coronary artery diameter under conditions of controlled flow and distal resistance. The left anterior descending coronary artery from a donor dog heart is perfused with heparinised blood from a support dog.

The calcium ion antagonists are effective inhibitors of inotropic (contractile) responses in heart muscle, yet they are relatively weak inhibitors of the constriction induced by serotonin or noradrenaline in the large coronary arteries. We showed that verapamil inhibited the inotropic response to sympathetic stimulation or to added noradrenaliane in guinea pig left atria at one tenth the concentration required to relax dog coronary arteries constricted by noradrenaline. These results suggest that the requirement for extracellular calcium by coronary vascular smooth muscle stimulated by noradrenaline is considerably less than in cardiac muscle.

We also examined the cardiovascular effects of verapamil and nifedipine (both slow calcium channel blockers) in anaesthetized dogs and their ability to inhibit the constrictor response to serotonin in the blood-perfused coronary artery preparation. This has allowed us to observe simultaneously the vasodilator response to these antagonists on the constricted large coronary arteries, their effects on atrio-ventricular (A-V) conduction and on systemic vascular resistance and heart rate. Our results show that concentrations of verapamil

that inhibit serotonin-induced coronary vasoconstriction cause prolongation of the P-R interval or 2nd degree A-V conduction block, as well as marked bradycardia and hypotension. By contrast, nifedipine was almost without effect on atrial conduction but caused a similar vasodilation as verapamil of the large coronary artery. These studies suggest that nifedipine may be better than verapamil for the treatment of vasospasm and emphasize that there are marked differences between drugs classified as *slow calcium ion channel blockers*. The effectiveness of verapamil in variant angina is probably due to a decrease in myocardial oxygen requirement through causing a decreased contractility and reduction in blood pressure rather than through the direct abolition of spasm of the large coronary artery.

One of our most recent findings has been that large coronary arteries may either constrict or dilate during noradrenaline release from sympathetic nerve stimulation. There is a change from constriction to dilatation as one goes along the length of the artery indicating that the receptor types subserving these responses (alpha or beta-adrenoceptors) are not uniform in their distribution along the vessel (Fig. H8). Beta-adrenoceptor block always led to vasoconstrictor responses of much greater magnitude than without block suggesting that neurogenic spasm in patients may be aggravated by propranolol. We are now looking at some of the factors which amplify constrictor responses in coronary vessels. These include lumen encroachment from arterial lesions or from generalised medial hypertrophy as in hypertension. In collaboration with Dr. Greg Dusting (Austin Hospital) we are investigating the role of prostacyclin (produced by the pericardium) in dilating large coronary arteries.

Dr. Tom Cocks, in collaboration with Drs. Julie and Gordon Campbell, is examining the role of the endothelium in large arteries. Some substances dilate large blood vessels when normal endothelium is present but are potent constrictors when endothelium is removed.

Adrenergic transmission

The second problem deals with analysis of the role of presynaptic adrenoceptors on the sympathetic nerve endings. Stimulation of these receptors alters the

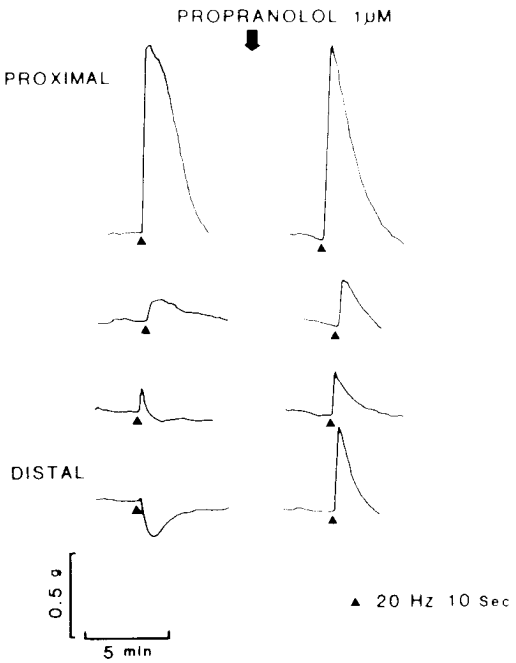


Fig. H8

Records of four small ring segments of a dog circumflex coronary artery in response to electrical field stimulation. Sympathetic stimulation caused a variety of responses; only constriction, only dilatation or biphasic responses. After propranolol (β-adrenoceptor block) only constriction was observed.

amount of transmitter released with each nerve impulse. We have used the isolated guinea pig atrium for this work. When suitably stimulated in the presence of atropine (to block the vagus nerves) the sympathetic fibres release noradrenaline from their endings in the sino-atrial node of the right atrium to produce a rise in heart rate.

The sympathetic nerve endings have an alpha-adrenoceptor on which alpha-adrenoceptor stimulant drugs, such as clonidine, act to diminish the amount of transmitter released by each sympathetic nerve impulse. The produces a smaller rise in heart rate than normal. A hypothesis called the auto-inhibitory feedback hypothesis is at present much in vogue. It suggests that release of noradrenaline itself acts on the presynaptic alpha-receptor to modulate subsequent release in much the same way as produced by clonidine. However, experiments on which this hypothesis is

based used rather strong stimuli. Angus and Korner showed in 1980 that such modulation did not occur with more physiological stimuli. Recent experiments suggest that when neuronal uptake is inhibited by desipramine (0.1 μM), autoinhibitory feedback is enhanced. Probably neuronal uptake lowers the noradrenaline concentration to a level below threshold for stimulation of the presynaptic α adrenoceptors. In the guinea-pig atrium the presynaptic α-adrenoceptor appears to be extrasynaptic, *ie* some distance from the nerve-muscle junction (Fig. H9). At this site very strong nerve stimulation would be necessary to provide an adequate concentration of transmitter at the presynaptic receptor. Autoinhibitory feedback of transmitter is probably not of much physiological importance, but the presynaptic alpha-receptor is easily accessible to circulating drugs such as clonidine or may be influenced by circulating catecholamines.

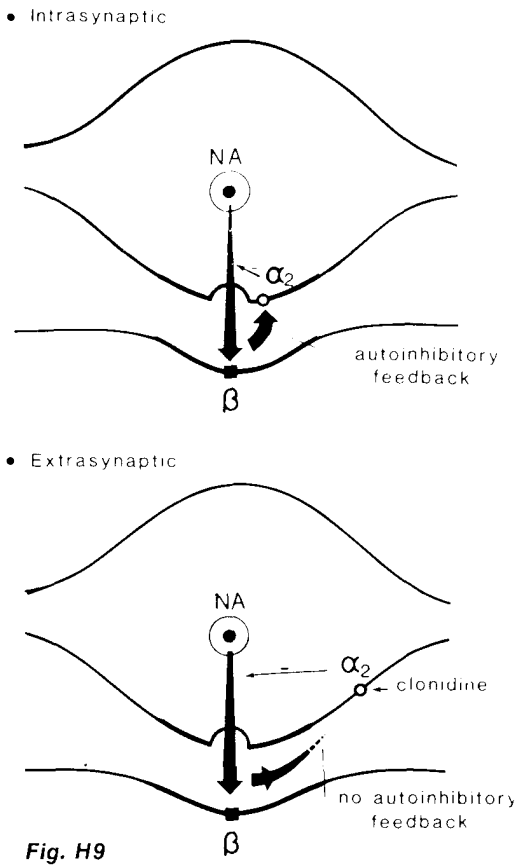
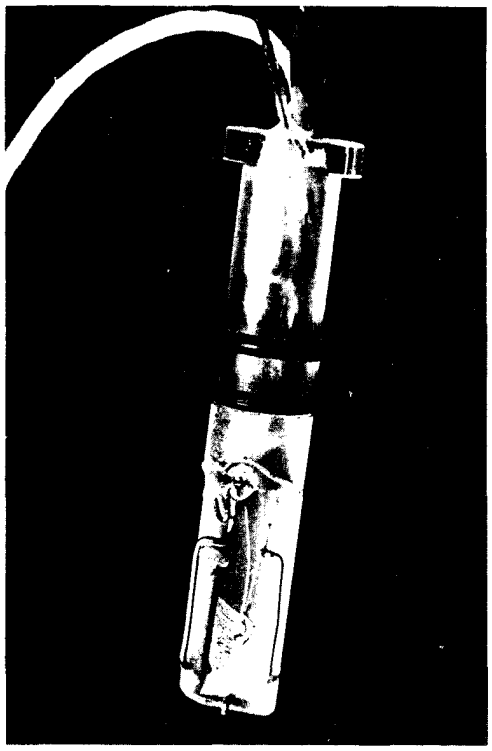


Fig. H9
Schematic diagrams of the proposed locations of presynaptic alpha$_2$-adrenoceptors. Receptors located intrasynaptically (top) or extrasynaptic (bottom).



Photograph of the minature flow-through cell for correlating tissue response (tachycardia) with noradrenaline release during electrical field stimulation of guinea pig right atria. This apparatus was made in the Baker Institute.

Since Dr. Irwin Kopin's visit (see Edgar Rouse Fellowship) we are relating the physiological responses to sympathetic stimulation to chemical measurements of transmitter release. We have developed a tiny flow-through cell (800 μl volume) where we can quantify release of noradrenaline and its metabolites from the effluent under controlled conditions of flow and temperature and relate them to the magnitude of the heart rate changes.

KIDNEY LABORATORY

W. P. Anderson, S. Selig, P. I. Korner, K. Denton, P. J. Bartley
Outside Collaborators: Professor G. Ryan, D. Alcorn, B. Kemp, Professor C. I. Johnston.

List of Projects

Is angiotensin II a trigger mechanism in Goldblatt hypertension?

Factors causing hypertension following renal artery stenosis

Renal blood flow and glomerular filtration rate during development of renal 'wrap' hypertension

Aspirin and indomethacin as inhibitors of renal cyclooxygenase in dogs

Effects of indomethacin on renal protein kinase and cyclooxygenase

Role of renal prostaglandins kinins and renal blood flow control

Renal Artery Stenosis

Our main research has been to analyse the mechanisms of renovascular hypertension and to determine the sequence of steps by which renovascular hypertension causes elevation of blood pressure. This has been studied in instrumented conscious dogs, by rapidly narrowing the renal artery (renal artery stenosis) and analysing the factors important in the production of hypertension. We have found that the hydraulics of renal artery stenosis are complex, and that narrowing of the arterial diameter of about 90% is necessary to produce chronic hypertension. The narrowed renal artery contributes only about 25-30% of the rise in total peripheral resistance in this type of hypertension. The renal artery stenosis can be considered the 'basic' mechanism of hypertension, but many other compensatory or 'homeostatic' mechanisms are brought into play. One important mechanisms contributing to the early rise in blood pressure is the spillover of angiotensin II (AII) into the systemic circulation which, through the elevation of blood pressure, helps to maintain glomerular filtration rate and renal excretary function. Initially the constriction of the systemic blood vessels outside the kidney produced by AII contributes about 65-70% of the rise in total peripheral resistance. Later on plasma AII concentration returns to normal, probably through reflex autonomic mechanisms, and its function in maintaining high blood pressure and normal renal function is taken over by the rise in blood volume in the body and by the amplifying effect of the enlarged heart and smooth muscle of the blood vessels which were referred to earlier.

Experiments performed in the mid-1970's suggested that this potent hormone may be an essential 'trigger'

Members of the Kidney Laboratory: (L-R) Kate Denton, Dr Warwick Anderson, Steve Selig, Diana Dalling and David Harrison.

Renal Artery Stenosis

mechanism of chronic hypertension. This hypothesis was based on experiments by A. C. Barger and co-workers reported in 1975. They found in dogs, that during continuous infusion of an inhibitor of AII production, the development of hypertension during renal artery stenosis was completely prevented for the 3-4 days' duration of the experiment.

At that time the complexity of the hydraulics of renal artery stenosis were not fully appreciated. We now know that one of the most important actions of AII is to constrict the vessels within the kidney. More narrowing of the renal arterial diameter is needed to produce a given reduction in the distal pressure or in blood flow if the renal bed is constricted than if it is dilated. Thus in a normal dog which constricts its renal vessels with AII a given reduction in arterial perfusion pressure requires more narrowing of the renal artery, than after pretreatment with an AII inhibitor, when the renal vascular bed remains dilated.

We have developed a method of standardising the amount of narrowing of the renal artery. We find that hypertension still develops if the renal artery is narrowed by exactly the same amount (93%) both before and after administration of an AII inhibitor.

However, in the presence of an AII inhibitor the rise in blood pressure is only about 1/3 of that occurring in the intact animal. Although hypertension can still develop under these circumstances, the importance of AII as a homeostatic factor in the maintenance of renal function is evident from the fact that in the presence of the inhibitor glomerular filtration rate is much lower than in the intact dog (Fig. H 10). The systemic vasoconstriction and subsequent hypertension produced by AII is thus a most important mechanism for ensuring adequate renal function in acute renal artery stenosis.

We have also studied another type of experimental renovascular hypertension, produced by wrapping the kidney of rabbits in cellophane. Here again angiotensin II appears to play an important intrarenal role since in the presence of AII inhibitor glomerular filtration rate is reduced more than in the normal animal.

Prostaglandins

We have also studied the role of prostaglandins (i) in the control of the renal circulation and (ii) on the formation

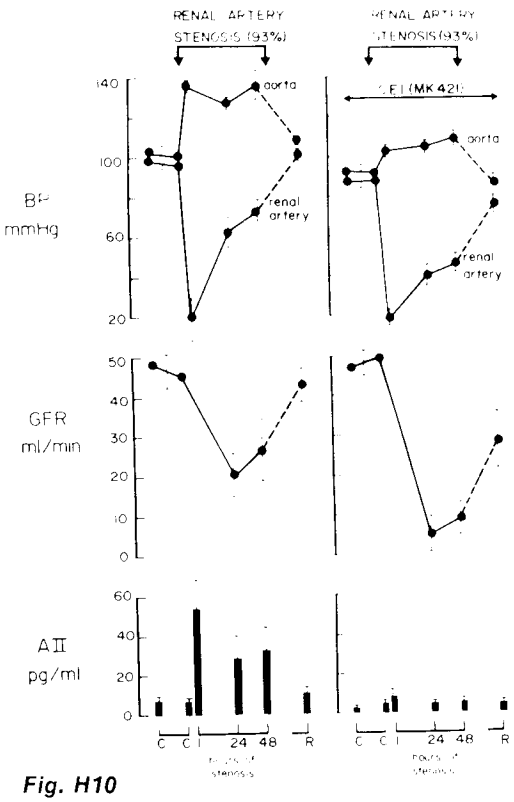


Fig. H10
Effect of 48 hours stenosis on aortic and renal artery pressures, glomerular filtration rate and AII plasma concentration produced by rapid injecting 93% of renal artery cuff volume required for complete occlusion in 6 conscious dogs. (Left) *normal response;* (Right) *after 5 days pretreatment with converting enzyme inhibitor (MK 421). BP = blood pressure; GFR = glomerular filtration rate; C = control day; R = recovery 24 hr after releasing cuff (Anderson, Selig and Korner, unpublished data).*

of AII. Prostaglandins are an important class of substances present in all cell membranes. They are known to be important in blood coagulation and in reproductive physiology. A considerable number of claims have been made about their contributions in circulatory control. For example, prostaglandins have been thought to play a role in renin release, and to alter the effects on renal blood flow of constrictor stimuli such as AII, catecholamines, haemorrhage or mechanically-induced ischaemia. All the studies on which these hypotheses are based, have been performed in anaesthetised preparations, frequently

after a considerable amount of acute surgical trauma. It therefore seemed worthwhile to examine them again in the conscious dog.

To date most of our findings have been negative. We have found that drugs such as aspirin, which inhibit prostaglandin synthesis, have no effect on renin release in renal artery stenosis. Nor do they modify the renal blood flow and vascular resistance responses to haemorrhage or noradrenaline infusion. In the conscious animal prostaglandins either play little role in regulating the circulation of the normal kidney or in altering the activity of the renin-angiotensin system, or their effects are masked by other mechanisms.

BIOCHEMICAL PHARMACOLOGY LABORATORY

A. Bobik, G. Jackman, P. Little, K. Oddie, P. Scott, H. Skews, J. Snell, P. Snow

Biochemical Pharmacology

Projects

Regulation of adrenoceptor function on smooth muscle cells in culture

Influence of prolonged exposure to partial beta-adrenergic agonist on cardiac beta-receptor function

Modulation of cardiac beta-adrenoceptor responses during phospholipase AII activation

Cardiac noradrenaline metabolism in renal hypertension

Effect of monoamine oxidase inhibition on cardiac noradrenaline stores

Electrochemical estimation of tissue and plasma dihydroxyphenylglycol

Effect of central methyldopa administration on plasma noradrenaline concentrations

Much of our research is related to analysis of basic cellular mechanisms involved in the function of the autonomic nervous system. On the applied side we are involved in several problems related to the clinical pharmacology of cardiovascular drugs which are described in the report of the Clinical Research Unit.

Adrenergic Receptors

In studies involving the binding of labelled antagonists to specially purified cell membrane preparations we have determined the number of beta adrenoceptors in the heart, and how this is altered in hypertension. Another approach is to study heart cells under the controlled conditions of tissue culture and to determine the sequence of steps linking the membrane receptor to the cellular biochemical machinery, which is

Biochemical Pharmacology Laboratory: (standing L-R) Dr P. Little, Dr A. Bobik, H. Skews, Dr G. Jackman, (seated L-R) K. Oddie, L. Rowlands, P. Scott and J. Snell.

involved in the particular cellular response.

In heart muscle cells in tissue culture we have studied the effects of prolonged beta receptor stimulation with isoprenaline. In the heart the cells rapidly become unresponsive to further stimulation. The mechanism appears to involve some uncoupling between the membrane receptor and the rest of the cellular machinery.

Beta receptors are also present on the membrane of vascular smooth muscle, where their stimulation normally causes vasodilatation. Smooth muscle membrane beta receptors also rapidly become unresponsive during prolonged stimulation by catecholamines. The reason for this is different in the smooth muscle cells than in heart muscle and appears to be due to a loss in the capacity of the receptor to bind catecholamines and beta receptor antagonists.

The most important membrane receptors on blood vessels are the alpha-adrenoceptors which produce constriction of vessels when stimulated by catecholamines. The large arteries and veins contain two subtypes of alpha adrenoceptors (alpha$_1$ and alpha$_2$-subtypes), which may be detected by their capacity to bind labelled specific antagonists e.g. tritiated yohimbine and prazosin on the surface membrane. We are at present studying the distribution of these receptors on the different arteries and veins to the various main organs of the body. This is part of an investigation to see how vascular hypertrophy in hypertension affects receptor numbers and vascular responses under normal conditions and during chronic sympathetic stimulation.

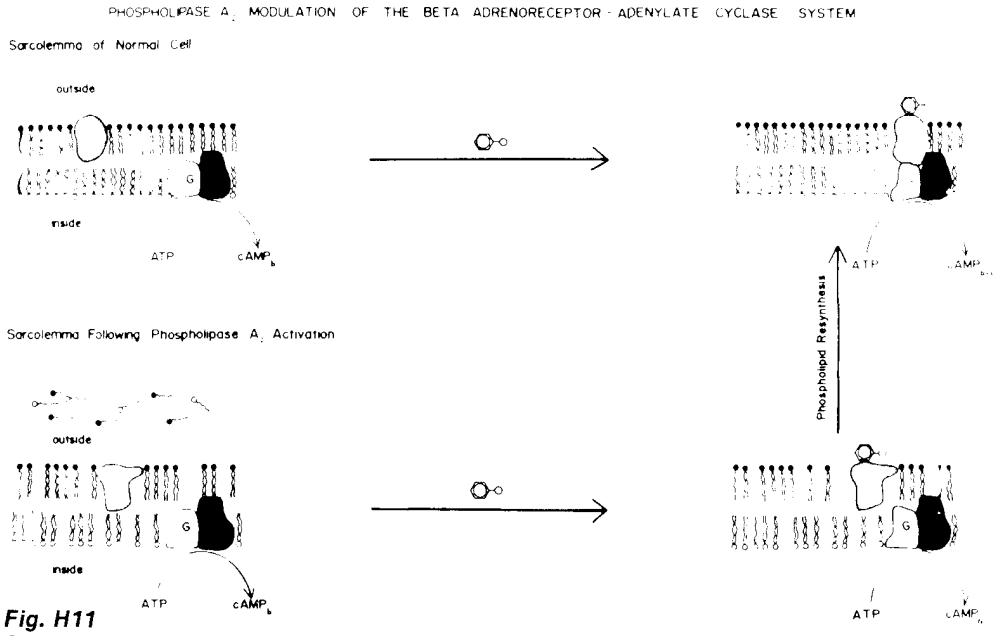


Fig. H11

Schematic representation of the mechanism by which phospholipase A$_2$ activation in the cell membrane affects heart cell beta adrenoceptor function.

Under normal circumstances the beta adrenoceptor ( ) residing in the phospholipid structure ( ) of the cell membrane interacts with catecholamines ( ) thereby changing cell membrane fluidity which allows the complex to interact with the enzyme adenylate cyclase ( ) and increase 3,5-cyclic AMP production (c AMP$_{b+c}$) from adenosine triposphate (ATP).

Following phospholipase A$_2$ activation in the cell membrane a proportion of the phospholipids (about 0.5 to 1%) are hydrolysed to lysophospholipids ( ) and free fatty acids which are released from the cell membrane. Under these circumstances cell membrane integrity is impaired and whilst the binding properties of the beta adrenoceptor to catecholamines is not impaired, this complex cannot interact with adenylate cyclase. Providing cell membrane damage due to phospholipid depletion is not severe. resynthesis of phospholipids restores the beta adrenoceptor response.

At present most of our work on the effects of sympathetic stimulation has been in relation to the sympathetic endings of the heart. We have found that chronic sympathetic stimulation depresses the cardiac catecholamine stores, to levels previously reported in cardiac failure. We are investigating the effects of sympathetic stimulation on other metabolites to determine the mechanisms by which transmitter stores are reduced in hypertension.

Lastly, we are examining the effects on beta receptor function of the heart of the enzyme (catalyst) phospholipase A_2 which is present in many parts of the cell including its surface membrane, (Fig. H11). This enzyme increases its activity when heart cells are deprived of oxygen or nutrients, which is likely to occur during a heart attack. We have found that increased activity of the enzyme depresses beta receptor function, which would make the cell less responsive to sympathetic stimulation. We are at present studying some of the cellular mechanisms involved in the regulation of the activity of this enzyme.

Presynaptic Alpha-Receptors on the Sympathetic Endings

The biochemical correlates of transmitter release and metabolism with the tissue responses are discussed in the 'Cardiovascular Pharmacology Laboratory' section. From the biochemical viewpoint the introduction of the high pressure liquid chromatography assays with electrochemical detection have been the major factors in making this work possible. Without the sensitivity of the assays provided by this equipment we could not measure the small amounts of noradrenaline and its major metabolite dihydroxyphenylethylene glycol, which provide us with clues about what happens to the released noradrenaline.

CLINICAL PHARMACOLOGY LABORATORY

A. McLean, A. Somogyi, B. Heinzow

List of Projects:

Hepatic blood flow and extraction of high clearance drugs

Influence of cirrhosis and decompressive shunt surgery on hepatic blood flow

Influence of alcoholic and non-alcoholic liver disease on the absorption and metabolism of ethyl alcohol

Metronidazole usage in surgical patients and patients with hepatic and renal disease

Influence of renal blood flow on renal clearance of drugs

Mechanisms of clearance of basic drugs by the kidney

The activities of the Clinical Pharmacology Laboratory are aimed predominantly at defining those factors which influence the delivery of drug molecules to target tissues in the body and in translating these findings into clinical practice.

Our principal experimental interest centres on defining the mechanisms which govern hepatic extraction of rapidly metabolised (high clearance) drugs particularly at the time when these drugs are being absorbed from the gut into portal blood, i.e. presystemic ("first pass") extraction. In these studies we use the antihypertensive, beta-adrenoceptor blocking drug, propranolol, as it is representative of the general group of highly extracted drugs. Previously we have described large increases in the peak concentration and concentration-time integral of propranolol in the peripheral circulation of normal volunteers when this drug was coadministered with food or the antihypertensive vasodilator, hydralazine, (Fig. H12). Both food and hydralazine increase blood flow through the gut and liver. The role of these and other factors required analysis in animal experiments, using techniques not applicable to humans.

Over the past year we have investigated the influence of absorption rate and drug concentrations in portal blood and the effects of alteration in rate of blood flow through the liver, and the possible effects of metabolic inhibition on the process of

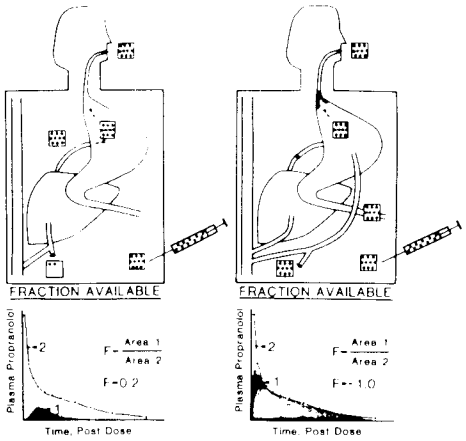


Fig. H12
The effect of liver disease and blood shunts on oral drugs.

Blood shunts

first-pass extraction in conscious or anaesthetised dogs, as appropriate. These studies have pointed to the general principle that shunting of blood may be an important determinant of oral dosing with high clearance drugs even in normal livers, and that this process may provide a basis for variation in patient response to treatment and drug interactions.

We have completed our study on the influence of cirrhosis of the liver on the use of high clearance drugs, and conclude that oral doses of this class of drugs should be reduced to at least 50% of normal in patients with mild clinical signs, and that as little as 10% of normal doses will suffice in patients with advanced disease. Examination of current literature on the use of beta blockers for control of portal hypertension indicates that these principles are not always appreciated by the specialist gastroenterologist. Similar conclusions apply to dosing of patients who have undergone surgical shunting. However, oral doses should not exceed 30% of normal in these patients. A prospective study has confirmed that the distal lienorenal shunt produces equivalent effects on oral drug bioavailability to the mesocaval shunt. We propose to continue this work in a more experimental manner to attempt to resolve the apparent paradox of similar degrees of shunting of blood, but measurably better clinical results in patients with distal lienorenal shunts. We suspect that the state of arterial perfusion postoperatively will provide at least part of the explanation, but this hypothesis can only be tested in experimental animals. We look forward to Mr William Johnson, Monash Department of Surgery, Alfred Hospital joining our group in 1982 to collaborate in these studies.

Our studies in patients with liver disease have been extended to low clearance drugs because of observations in our propranolol study which indicated

Clinical Pharmacology Staff: (standing L-R) S. Edwards, Dr A. Somogyi, Dr B. Heinzow, Dr A. McLean, (seated L-R) A. Tonkin, L. Demos and C. Cahill

that there may be a qualitative change in the enzymic capacity of the hepatocyte mass. We are using ethanol as a means of testing this hypothesis, as analysis of plasma concentration-time profiles will allow estimates of enzyme constants (Vmax, Km).

We have also carried out a study of the effects of intra-abdominal pathology (eg. biliary inflammation, intra-abdominal sepsis) and surgery on requirements for the antibacterial agent, metronidazole. It has been shown that absorption of rectal suppositories is almost complete (≈80%), that fluctuations in plasma concentrations are minimised on rectal delivery and that surgical patients require lower doses than normally recommended. Preliminary studies on the influence of liver and kidney disease indicate that dosage regimens need in future to take these factors into account. Liver disease causes accumulation of parent drug, while renal disease results in accumulation of an active metabolite. These findings have been translated almost completely into practise in our hospital and affiliated hospitals through the educational efforts of our ward pharmacists. This has resulted in a measurable improvement in the efficiency and economy of usage of this antibiotic in surgical patients.

Renal mechanisms of drug handling are of importance, but largely neglected by our group with the single exception of previous studies on sulphonamide pharmacokinetics and N-acetylation phenotype. We are interested to explore the influence of changes in blood flow on renal clearance because of preliminary observations that atenolol clearance is changed by vasodilators. Additionally, Dr. Somogyi has an established interest in the handling of cimetidine and other bases (eg. procainamide) by the kidney, and mechanisms underlying high renal clearance will be studied.

Our studies on the application of drug assays and a clinical pharmacokinetics service to drug use have been focussed on a collaborative study in the Neurology Out-patient Clinic. By providing assay results on a "same-day" basis before the clinician interviews the patient, we have demonstrated that the information obtained is put to immediate use. Such pharmacokinetic guidelines have to date been provided for two of the major antiepileptic drugs—phenytoin (Dilantin) and carbamezapine (Tegretol). There is a strong trend towards a decline in the incidence of side-effects, and compliance of patients with medication was improved during the course of the study. We have concluded that the use of drug assays is most valuable when the results are readily available to clinicians at the time of management and prescribing decisions.

The active collaboration of several Hospital Departments and of their Heads is gratefully acknowledged. We have been particularly indebted to Dr. Frank Dudley, Director of Gastroenterology; and Dr. John Spicer, Director of Microbiology.

Cardiovascular Metabolism and Nutrition Research Unit

LIPOPROTEIN AND NUTRITION LABORATORY
LIPOPROTEIN BIOCHEMISTRY LABORATORY
NUTRITION AND DIABETES LABORATORY

General Summary

We are studying the regulation of lipoproteins and the role of nutrition in relation to lipid disorders, diabetes and energy control.

A major emphasis in our basic research is the study of the protein moieties of the lipoproteins. Each of the four major lipoprotein classes carries its specific complement of proteins, the functions of which relate to the secretion, transport and catabolism of these large lipid-carrying macromolecules. As yet, only a few of these proteins have been shown to have unique functions and the absence or deficiency of several are known to result in abnormal lipoprotein transport. Of particular interest is the likelihood that some forms of hyperlipidaemia, and atherosclerosis itself, might be due to abnormal concentrations of one or more of these proteins or to an abnormal interaction of the proteins with components of the arterial wall.

The main advances in this area during the year have included the first measurements in man of the metabolism of an apoprotein, A IV; further definition of the role of the C apoproteins in triglyceride transport; the initial demonstration of multiple specific binding sites for lipoproteins in the intestine; the development of a technique that separates triglyceride-rich lipoproteins into functionally different classes; the demonstration of over-production of small cholesterol-rich

The Cardiovascular Metabolism and Nutrition Research Unit: (standing L-R) G. Collier, J. Cohn, K. Chisholm, J. Turton, S. Wong, A. Ward, A. Leonard-Kanevsky, J. Bazelmans, H. Edelsbacher, E. Faehse, P. Nugent, Dr M. Reardon, (seated L-R) Dr N. Fidge, Mrs S. Connor, Dr T. Billington, Dr P. Nestel, Prof. W. Connor and Dr K. O'Dea.

lipoproteins with high cholesterol diets; the observation of an association between such particles (intermediate density lipoproteins IDL) and coronary artery disease; the concept of IDL over-production as a major cause of hyper-lipoproteinaemia. There has been an expansion in the studies of lipoprotein protein metabolism in a number of isolated, cultured cell preparations and the development of techniques to study the role of apoprotein E in human lipoprotein metabolism.

In the area of nutrition we have carried out studies on the value of fibre and carbohydrate-rich diets on insulin sensitivity; the relationship of obesity to defective thermogenesis; the possibility that vegetable protein lowers plasma lipids.

LIPOPROTEIN AND NUTRITION LABORATORY

P. J. Nestel, M. F. Reardon, N. H. Fidge, T. Billington, M. Huff, K. O'Dea, J. Bazelmans, C. Nolan.

Lipoprotein and Nutrition

Projects:

Apolipoprotein C metabolism in man

Metabolism of sub-species of very low density liproprotein

Dietary cholesterol effects on intermediate density lipoprotein production

Relationships between apoprotein E-3 and coronary heart disease

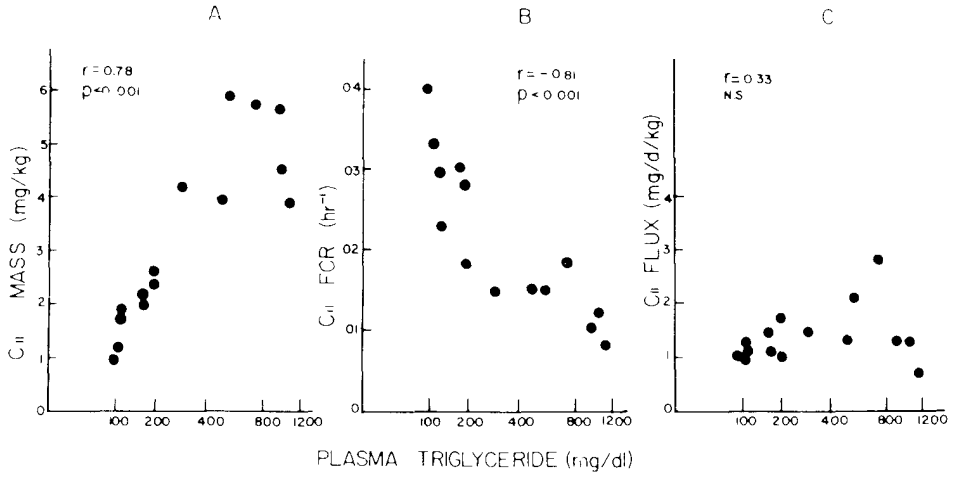
Effect of diet on insulin and glucose kinetics

Regulation of triglyceride metabolism by insulin

Utilization of glucose with exercise

Apolipoprotein C metabolism

The C apoproteins comprise at least four peptides, CI, CII, $CIII_1$ and $CIII_2$, are found in triglyceride-rich lipoproteins (TRL) and in high density lipoproteins (HDL), and are related to the catabolism of TRL. We have been first to develop the techniques for measuring the amounts of C proteins produced and metabolised each day. The similarity in the catabolic rate of each of the proteins showed that the C proteins interact with TRL in an integrated manner. We have found abnormalities in C protein metabolism in hypertriglyceridaemic subjects. Although in these subjects the amounts of C proteins present in TRL are increased, the daily synthesis rate of the proteins is not increased. By contrast when hyper-triglyceridaemia was induced in normal subjects with carbohydrate-rich diets, C protein production increased markedly. This might explain the transient nature of hypertriglyceridaemia in the normal subjects in contrast to its persistence in the hyperlipidaemic subjects. Further, in the most severely hypertriglyceridaemic subjects, with defective removal of TRL, the catabolism of the C proteins was



Relationship between plasma triglyceride concentration and total mass of exchangeable apolipoprotein CII (A), fractional catabolic rate of apolipoprotein CII (B), and flux of apolipoprotein CII (C).

markedly abnormal. Whereas normally C proteins are transferred quantitatively from TRL to HDL as triglyceride is hydrolyzed, in these patients C proteins were not conserved within HDL but largely removed directly from the circulation. This might explain the defective catabolism of TRL in severe hyperlipidaemia.

VLDL

Metabolism of VLDL subspecies

Lipoproteins are usually separated by their flotation characteristics during ultracentrifugation. We have now shown that this technique does not adequately separate functionally discrete populations of particles. We have succeeded in this with heparin affinity chromatography. By combining this with metabolic studies in which labelled VLDL or subfractions are reinjected into subjects, we have identified within VLDL, newly secreted lipoproteins and the catabolized remnants derived from the VLDL. Subjects with hypertriglyceridaemia and those eating cholesterol-rich diets have higher proportions of these remnants within the VLDL fraction which by conventional techniques has been considered devoid of remnants. The importance of this is that remnants or IDL (intermediate density lipoproteins) are probably atherogenic.

Dietary cholesterol stimulates IDL production

We have studied the effects of cholesterol loading in man, seeking changes in VLDL that may define a subpopulation of particles that may be atherogenic. Using heparin affinity chromatography to isolate such particles we have found a significant increase in cholesterol-rich IDL in the plasma within two weeks of cholesterol loading. Interestingly this occurred even in the absence of a rise in plasma total cholesterol. Measurements of synthesis rates (by reinjecting labelled IDL) showed a significant increase in the secretion rate of IDL. This probably reflects retransport of dietary cholesterol from the liver through the circulation.

E-3 apoprotein concentration and coronary heart disease

We have established quantitation procedures for the E-3 apoprotein. A survey carried out by us in Melbourne has indicated that approximately 20 percent of the population has a deficiency of E-3 apoprotein. However not all people found with this deficiency have an accumulation of remnants. It appears that the expression of type III hyperlipoproteinaemia requires the presence of

Fig. A

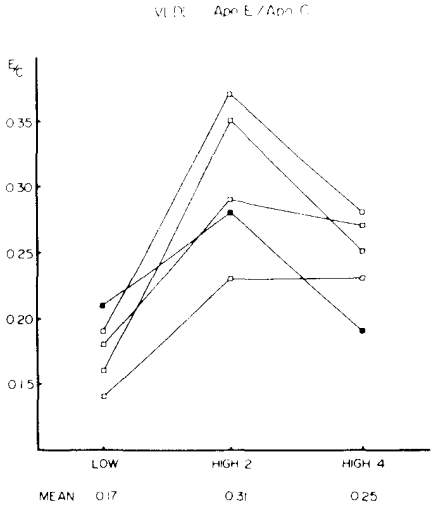
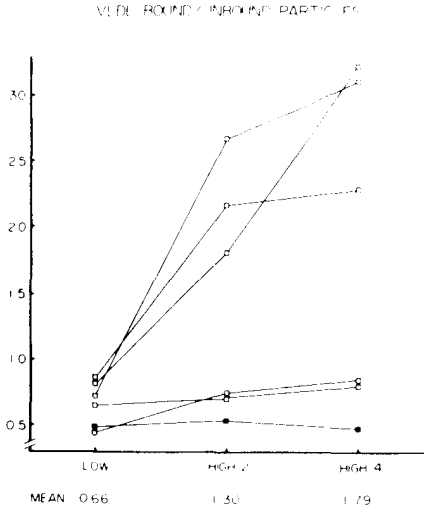
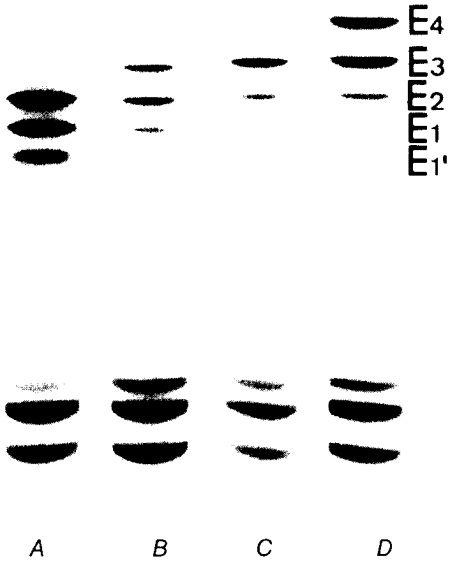


Fig. B



When dietary cholesterol intake is increased from a low (200 mg/day) to a high level (1,700 mg/day), small intermediate density lipoproteins, which are thought to be atherogenic, accumulate in the circulation. In figure A, this is shown by an increase in the ratio of apoprotein E to apoprotein C which together with the higher cholesterol content and the higher affinity to heparin (figure B) strongly suggest the production of a more atherogenic particle into the circulation in response to the increased intake of dietary cholesterol.

a second metabolic perturbation (either of familial or environmental origin) before the remnant accumulation is observed. The nature of these secondary stimuli are at present being examined. We have also compared remnant lipoprotein concentrations (as indicated by remnant B apoprotein levels) in people with or without known coronary heart disease. In two age and sex-matched populations with normal lipids, it was found that remnant lipoprotein concentrations were 2-3 fold higher in the group with coronary heart disease. We are now extending these studies to ascertain the importance of the E-3 apoprotein in the pathogenesis of coronary heart disease. These studies clearly indicate the emerging relevance of apoprotein quantitation in evaluating risk for coronary heart disease.



Isoelectric focussing gels of very low density lipoprotein apoproteins demonstrating the four basic patterns for E aproprotein (A to D, from left to right). A — VLDL from a patient homozygous for type III hyperlipoproteinaemia showing a complete absence of the E — 3 apoprotein. B — VLDL from a patient heterozygous for type III HLP (20% of the population) showing a deficiency of E — 3 apoprotein. The deficiency of this apoprotein is confirmed by densitometric scans. C, D — VLDL from normal patients showing the presence of E — 3 apoprotein and in (D) the presence of E — 4 apoprotein.

Dietary influence on insulin sensitivity and glucose turnover

Since diets rich in unrefined carbohydrate and in fibre appear to be beneficial for diabetics, we examined the effects of such diets on glucose production and turnover and on total body insulin sensitivity. Healthy lean men were tested with 10-day diets containing either 20g or 100g fibre daily as part of a high unrefined carbohydrate intake.

Glucose production, measured by the constant infusion of ^{3}H-glucose technique, was uninfluenced by dietary fibre. Insulin sensitivity was determined by the "glucose clamp" method in which insulin is infused to raise the concentration in plasma 5 to 10-fold, while maintaining euglycaemia (constant plasma glucose concentration) through a variable glucose influsion. Insulin sensitivity was high with the carbohydrate-rich diet, but was not augmented by fibre derived from cereals, legumes, fruits and vegetables.

Role of insulin in triglyceride production and removal

Plasma insulin, triglycerides, glucose tolerance and body weight are closely correlated. The precise role of insulin is uncertain and we have used the glucose-insulin infusion technique to study this question. In 37 experiments, plasma triglyceride fell significantly when plasma insulin levels were raised moderately. The fall in triglyceride was significantly correlated to insulin sensitivity (glucose utilization during the insulin infusions). Multiple correlation analysis showed that

Dr Mike Reardon, Patricia Nugent and Elizabeth Faehse preparing samples

this was strongly related to body weight: as weight increases, the utilization of both glucose and triglycerides falls. This reflects diminishing triglyceride removal (less re-esterification of tissue fatty acids) and increasing triglyceride production (from released fatty acids).

Improved glucose utilization with exercise

Exercise is being proposed as part of health programs. A benefit of physical fitness on glucose utilization would improve the management of diabetics. We have studied this in a 3-months controlled comparison of supervised exercise in middle-aged men. This project is being carried out in collaboration with Dr. A. Kretsch from the Preventive Medicine Clinic, Fitzroy and Dr. R. Brinkert from the Preston Institute.

In the exercising group, glucose disposal after oral glucose improved and the glucose-induced rise in plasma insulin concentration was reduced, implying improved insulin sensitivity. This improvement correlated with the number of exercise sessions undertaken rather than with improvement in aerobic fitness. Since body weight did not change, the finding suggests that in the context of improved physical fitness, improved glucose utilization is related to increased energy intake.

LIPOPROTEIN BIOCHEMISTRY LABORATORY

N. H. Fidge, M. F. Reardon, P. J. Nestel, N. Suzuki, M. O'Connor, J. Yin, J. Cohn.

Projects:

Chylomicron catabolism and HDL formation—use of the A-IV apoprotein

Metabolic consequences of apoprotein E-3 deficiency of man

Abnormal lipoproteins in diseased states

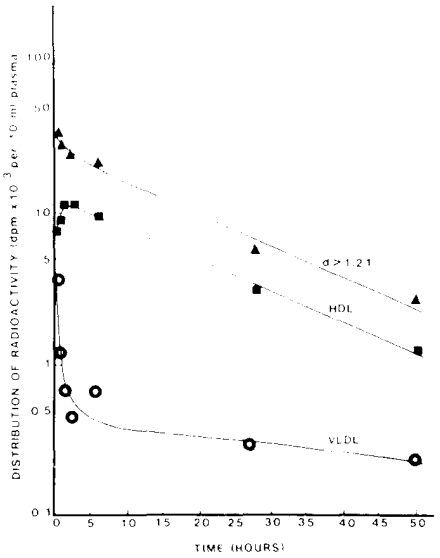
Metabolism of high density lipoproteins by the intenstine and liver

The role of apoproteins in the recognition of lipoproteins by various tissues.

The in vivo metabolism of AIV apolipoprotein in human subjects

The A IV protein is a major constituent of chylomicron protein and its function is therefore likely to be related to the transport of dietary fat. In plasma however A IV is mostly not associated with lipoproteins. The possibility exists that A IV is transferred from plasma into the gut during fat absorption and then returns to the plasma reservoir after the chylomicrons enter the plasma. This was

studied by reinjecting labelled A IV within either chylomicrons, lipoprotein free plasma or HDL. The nature of the kinetics supported the above metabolic pathway. A IV is probably first secreted without lipoproteins and then redistributed to chylomicrons and HDL. Catabolism of A IV occurred independently from each of the three fractions.



Redistribution of labelled AIV apoprotein when administered intravenously as a component of chylomicrons. The AIV rapidly transfered to the lipoprotein-free (d > 1.21) and HDL fractions.

The metabolic basis of type III hyperlipoproteinaemia

Type III hyperlipoproteinaemia, a disorder where remnant lipoproteins accumulate in the circulation, is known to be associated with a total absence (homozygous form) or partial deficiency (heterozygous form) of a plasma protein (termed E-3 apoprotein). The absence of this protein was thought to result in a delayed catabolism of remnants due to a lack of recognition of the remnants by tissue receptors. However, kinetic studies carried out by us have established the presence of an unusual biosynthetic pathway for remnant production in type III hyperlipoproteinaemics. This pathway results in an overproduction of remnant particles and so an increased concentration in the circulation. We have shown that this pathway is potentially reversible by treatment with thyroxine or oestrogen. The nature of the biochemical deregulation causing this pathway to be expressed is now being investigated.

Lipoprotein Biochemistry Laboratory Staff: (L-R) J. Cohn, A. Leonard-Kanevsky, Dr N. Suzuki, M. O'Connor, H. Edelsbacher and Dr N. Fidge

Abnormal lipoproteins in renal disease

Patients with chronic renal failure who survive through dialysis have an increased risk of dying from vascular complictions. This has been attributed to their mild hyperlipidaemia. We have carried out a more systematic analysis of their lipoproteins and have found them to have grossly abnormal protein profiles. The VLDL contain increased amounts of apoprotein E and A IV and the B_{48} protein which is a uniquely gut protein. The LDL also contain increased apoprotein E. The presence of remnants of alimentary particles suggests a defect in lipoprotein removal and the enrichment with E protein is thought to confer potential for atherogenicity.

Metabolism of high density lipoproteins (HDL) by the intestine and liver

Cholesterol homeostasis within cells is thought to be regulated largely by plasma lipoproteins, low density lipoproteins (LDL) delivering cholesterol to the cells and HDL removing excess surface cholesterol. The intestine utilizes substantial amounts of cholesterol for dietary fat transport and we have therefore studied the interactions of intestinal cells with several species of LDL and HDL. We have shown for the first time the preferential binding of HDL to rat gut cells and have produced evidence that this is mediated through a specific binding site. Furthermore the cells internalize and catabolize the HDL so providing cholesterol. The specific binding site resides in cell membranes other than the brush border. The intestine is therefore an important organ for the catabolism of HDL from which it preferentially obtains cholesterol.

NUTRITION AND DIABETES LABORATORY

K. O'Dea, P. J. Nestel, G. Collier, A. Ward, S. Wong
Outside Collaborators: R. M. Spargo, Kimberley Health Dept., Derby, W.A.
A. Sinclair, Veterinary Research Institute, Parkville, Vic.

Projects:

The relationship between urbanisation and diabetes in Australian aborigines

Lipid composition of traditional aboriginal foods

Metabolic response to food

Rate of hydrolysis of starch in leguminous foods

Dietary treatment of type 2 diabetes

Exercise and insulin sensitivity

Diet and insulin sensitivity

Infrequent meal ingestion

It is now generally accepted that the most common form of diabetes, variously referred to as "Type 2" or "non-insulin dependent" or "maturity onset" diabetes, is associated with the western lifestyle. It is rare or nonexistent in traditionally living or under-developed societies and is one of the first diseases to emerge as these societies urbanise. Although the *susceptibility* to type 2 diabetes appears to be genetically determined, whether or not susceptible individuals actually develop the disease depends upon the presence of a number of lifestyle-associated external trigger factors related to diet and physical activity level.

The aims of this laboratory's program are to define, firstly, the metabolic characteristics which may identify people susceptible to diabetes and, secondly, the particular aspects of our western lifestyle which could act as environmental triggers. These questions are being approached experimentally from three directions:

(i) The study of the metabolic responses of a high risk population (Aborigines) in different environmental and nutritional conditions.

(ii) Metabolic studies in type 2 diabetic and normal subjects to determine which factors are important for the effective dietary treatment of diabetes: high complex carbohydrate, low fat, high fibre, type of fibre or a

combination of some of these factors.

(iii) Animal studies aimed to elucidating the mechanisms underlying the changes in insulin secretion and insulin sensitivity occurring in response to dietary change and long-term physical training.

Diabetes in Aborigines

Urbanisation and diabetes in Aborigines

Numerous surveys of Aboriginal communities around Australia have shown that diabetes is up to 10 times more common in urbanised Aborigines than in Australians of European origin. The study of such communities can provide insight into both the metabolic characteristics of susceptible people and the environmental factors operating to precipitate diabetes in these people.

Over the past 5 years we have conducted a series of metabolic studies on Aborigines from the Kimberleys in W.A. with particular reference to the degree of urbanisation and the effects of temporary reversions to traditional hunter-gatherer lifestyle. From this work we are able to draw some tentative conclusions:

(i) The metabolic characteristics of these people highly susceptible to type 2 diabetes are mild impairment of glucose tolerance and an unusually high insulin response to glucose even when young and lean. This could have favoured survival in the traditional lifestyle by facilitating efficient fat deposition on either a feast-or-famine pattern of food intake or a low carbohydrate diet.

(ii) The widespread occurrence of obesity in Aboriginal communities precedes the development of diabetes.

(iii) Temporary reversion to traditional lifestyle with its high level of physical activity and high protein, low carbophydrate, low fat diet leads to weight loss, and improvement in glucose tolerance and insulin sensitivity in these people and may prove an effective way of treating/preventing diabetes in fringe dwelling Aboriginal communities in remote areas of Australia.

In 1982 we plan to put this to the test by monitoring a group of diabetic Aborigines before and after two months reversion to traditional lifestyle.

Lipid composition of traditional Aboriginal foods

High dietary fat intake in western societies has been implicated in the

Members of the Nutrition and Diabetes Laboratory: (L-R) Dr Kerin O'Dea, Angela Ward, Greg Collier, Janice Turton and Kerin Chisholm

pathogenesis of a number of "diseases of affluence" including obesity, diabetes and coronary heart disease. Much of the fat eaten in a western diet is derived from animal foods (meat and dairy products). Although the traditional diets of many Aboriginal communities in Australia were high in animal foods, there is reason to believe that they were not high in fat. We have analysed kangaroo and found it to be polyunsaturated, low fat, low cholesterol meat. Similarly, our recent analyses of a wide range of seafood have indicated that these also have a low fat content and a high proportion of polyunsaturated fatty acids (PUFA). This has particular relevance since it has been suggested that certain of these PUFA may play an important role in protecting against coronary heart disease.

The information gained from our analyses of wild animal foods may eventually allow the design of polyunsaturated, low fat diets which are not necessarily low in animal products and, as such, have far reaching implications for public health generally.

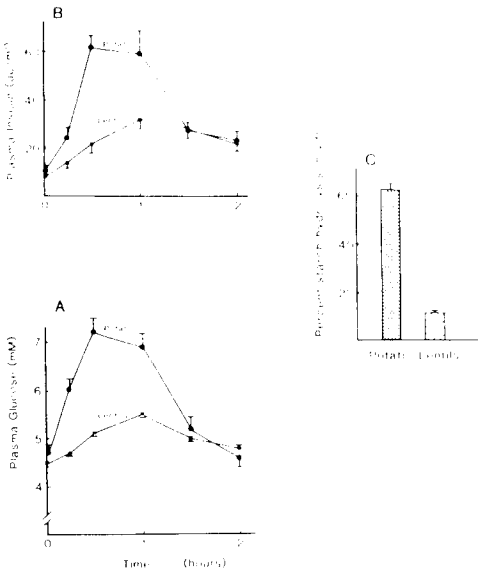
Metabolism and Food

Metabolic responses to food

In view of the association between type 2 diabetes and the consumption of diets high in refined carbohydrate and fat, we have examined the metabolic responses to different types of carbohydrate in the presence and absence of fat. Our results suggest that the presence of fat in some way reduces the sensitivity of peripheral tissues to insulin even in the short-term and that this effect is most pronounced when fat is ingested with carbohydrates which are rapidly digested and absorbed. We are pursuing these findings in longer term studies on rats in which we will measure insulin sensitivity, glucose utilization and insulin receptor binding in skeletal muscle in rats fed diets of varying fat/carbohydrate content.

Rate of hydrolysis of starch in leguminous foods

Carbyhydrate foods of leguminous origin give rise to very flat postprandial glucose and insulin responses and, for this reason, it has been suggested that they would be of benefit in the dietary treatment of diabetes. The mechanisms by which the digestion and absorption of carbohydrate is delayed has been attributed to the presence of certain leguminous fibres increasing the viscosity of intestinal contents. We have made an



Carbohydrate foods which are slowly digested (such as lentils) are absorbed much more slowly onto the bloodstream than foods which are rapidly digested (such as patatoes) (A). As a result of this slow absorption slowly digested foods provoke a much smaller insulin than do rapidly digested foods (B). We have developed a simple in vitro test to measure the rate of starch hydrolysis in carbohydrate foods which is being used to screen foods for their use in diabetic diets (C).

extensive study of factors affecting the rate of digestion of carbyhydrate in legumes by incubating food samples with digestive enzymes and measuring the rate of appearance of the products of digestion. Legumes are hydrolysed extremely slowly in this system. However, their rate of hydrolysis is greatly increased by increasing their surface area (i.e. grinding finely before cooking), but is unaffected by rapid shaking during incubation. These observations are inconsistent with viscosity being the factor responsible for the very slow rate of digestion of legumes. They suggest that, as for other complex carbohydrates, physical availability of the starch is the critical factor, and that in their natural form the starch in legumes is extremely well "insulated" from the digestive enzymes.

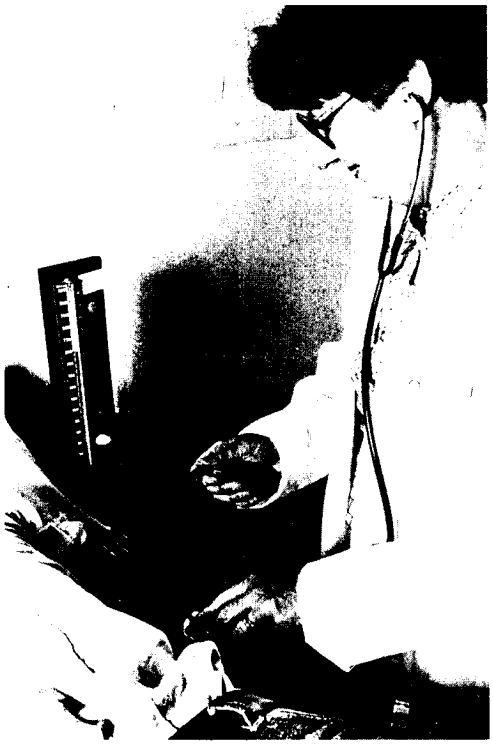
AUSTRALIAN NUTRITION FOUNDATION

The office of the Victorian Division, of which Dr. Nestel is Chairman, is situated at the Institute. The Foundation's main functions have been to provide information and promote education in nutrition. The automatic telephone information service has continued to receive hundreds of calls each week. In June, a dietitian telephone information service was set up to complement the automatic service, by offering personal advice to the public on two afternoons each week. The personal service has been an outstanding success with 12 enquiries on average each afternoon. Many requests are received from health professionals, teachers, students and the general public for articles and pamphlets published by the Foundation. The Executive Officer is Mrs Lydia Nestel. The Foundation is being supported largely by a grant from the Sir Robert Menzies National Foundation.

THE HEART RISK EVALUATION CLINIC

The risk factor prevalence study is a major area of investigation currently being undertaken by the Heart Risk Evaluation Clinic in conjunction with the National Heart Foundation and the Commonwealth Department of Health. The study will provide a detailed profile of the major heart risk areas which will enable us to plan and target community education activities. Later, these activities will be assessed to determine the success of the programme. There is an enormous community interest in the clinic and individuals have their blood pressure, weight and blood cholesterol and triglyceride levels measured. Subjects who demonstrate the presence of one or more risk factors are then advised how to reduce this risk and about 50% of individuals with hyperlipidaemia have been fully corrected within twelve months. They are cheerfully cared for by Sr. Joan List and most people have no hesitation in returning to the Clinic for follow-up measurements.

Repeated surveys of the risk factors will be carried out in 1983 and 1986, but even now, the study has generated a wide cross section of interested people and organisations. It would appear that, at least in the area of cardiovascular disease, the community has at last recognized the importance of preventative medicine in reducing major illness.



Sister Joan List of the Heart Risk Evaluation Clinic

Cell Biology Laboratory

Projects

Accumulation of cholesteryl esters in smooth muscle: dependence on phenotype.

Binding kinetics of ^{125}I-LDL by smooth muscle cells in the contractile versus synthetic state.

Morphometric analysis and population dynamics of the smooth muscle cells of diffuse intimal thickenings.

Endothelial-smooth muscle interactions.

Smooth muscle-smooth muscle interactions.

Collagen and glycosaminoglycan production by smooth muscle cells in culture.

Cell biology of the conduction system (Purkinje fibres) of the heart.

General Summary

Endothelial-smooth muscle interactions

An atherosclerotic plaque consists of a mass of proliferated smooth muscle cells in which fat may accumulate and where extracellular matrix (collagen and glycosaminoglycans) has been laid down.

The question is what stimulates smooth muscle cells to undergo these changes? We have previously shown that before smooth muscle cells proliferate in response to substances in the blood they must first undergo a change in phenotype (Fig. CB1) from their usual contractile state to a so-called 'synthetic' state. This alteration is associated with distinctive changes in appearance which can be readily observed in cell culture (Fig. CB1). The alteration takes about seven days.

We have recently found that in the presence of a confluent layer of endothelial cells, which normally line the arterial wall, the smooth muscle cells do not undergo a change in phenotype but remain in the contractile state (Fig. CB2). Synthetic state smooth muscle cells grown in the presence of the same feeder layer of endothelium are totally inhibited from proliferating in response to serum 'mitogens', i.e. substances which normally bring about proliferation. Other studies have shown that the smooth muscle itself may under certain circumstances cause the endothelial lining cells to proliferate. From this a picture has emerged that the cellular components of the arterial wall are in a functional equilibrium. It is a disturbance of this equilibrium that is

Dr Julie Campbell, Janet Rogers and Lucy Popadynec harvesting cultured endothelial cells

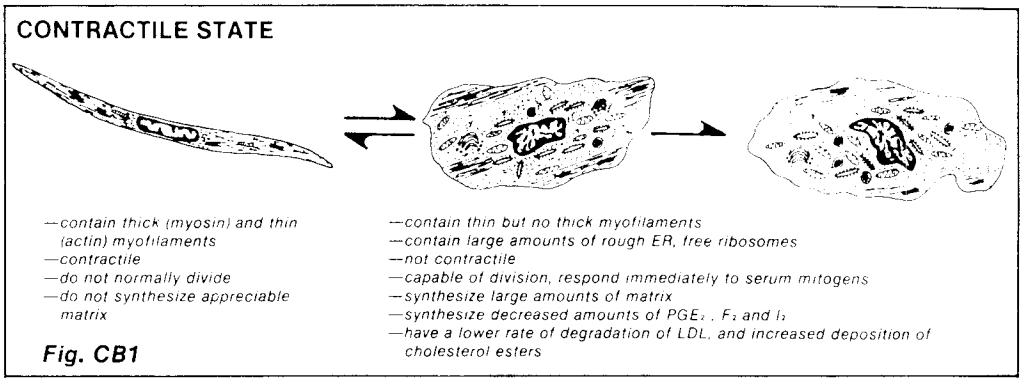


Fig. CB1

associated with the type of proliferation which leads to atherosclerosis.

Lipoprotein receptor binding by smooth muscle cells

During 1981 we studied the binding, uptake and degradation of low density lipoproteins (LDL) by arterial smooth muscle cells in culture. We studied the characteristics of contractile smooth muscle cells and compared them with those of cells in the synthetic state. We found that the receptor binding characteristics were not altered in the two cellular phenotypes. However, the ability of the synthetic state cells to metabolise LDL was significantly lower than that of cells in the contractile state. This resulted in an increased deposition of cholesteryl esters in cells of the synthetic state. The exact basis of these metabolic effects are not clear but they may be related to the changes in a particular enzyme system (lysosomal cholesteryl ester hydrolaze) in synthetic state cells.

Cell biology of the conducting system of the heart

The specialised conduction pathways of the heart ensure rhythmic and synchronized excitation and contraction.

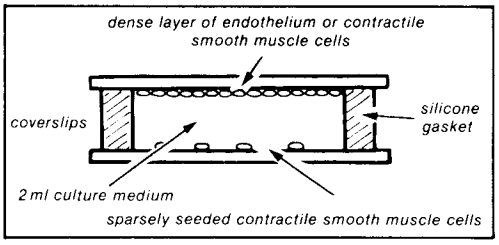
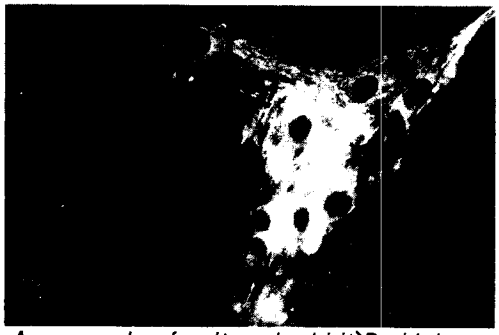


Fig. CB2

Cell culture system (Rose Chamber) used to demonstrate the capacity of endothelial cells to inhibit the modulation of smooth mucle cells contractile to synthetic states.

Any disturbance within this system, either at the site of origin or along the conduction pathways, can lead to cardiac arrhythmias. There are many different types of arrhythmias, but one of the most extreme examples is ventricular fibrillation which results in sudden death after heart attacks. Ventricular fibrillation often arises from a 'focus' of very irritable muscle fibres in the border zone around the dead muscle cells of a myocardial infarct.

We have recently developed a method for growing the conducting tissue (Purkinje fibres) of the heart in cell culture. This is an exciting development which will allow us to study some of the properties of this tissue under highly controlled conditions. To date we have determined that these cells contain large amounts of myosin muscle protein, which is immunologically identical to that in contractile heart muscle cells. However, in the Purkinje fibres it is not arranged in a sarcomere configuration similar to that of working myocardial cells.



An example of cultured rabbit Purkinje fibres stained with fluoresceinated antibodies to cardiac myosin. Studies of these cultured fibers are allowing new insight into the relationship between the conducting and working systems of the heart.

Cardiovascular Surgical Research Unit

General Summary

Projects

Optimal temperature for myocardial preservation

Surgical treatment of cardiac arrhythmias

Hospital costs and return to work after coronary bypass surgery

Treatment of infection in the pleural cavity

Antibiotic prophylaxis after coronary bypass surgery

Release of creatine kinase isoenzyme after coronary bypass surgery

Measurement of myocardial perfusion using hydrogen desaturation

Effect of lesions of the NTS on circulatory control in conscious rabbits

Contribution of vagally-innervated intrathoracic receptors, and carotid sinus baroreceptors, to the control of heart rate and renal nerve activity

Contrasting effects on heart rate of inflating caval, ascending aortic, and descending aortic cuffs

The unit's activities are in two principal fields: research and development in cardiac surgery (Dr. Rosenfeldt), and control of the circulation in the setting of surgery and resuscitation (Dr. Ludbrook).

Cardiac Surgery

During cardiac surgery a heart-lung machine (pump oxygenator) takes over the function of the heart and lungs. The blood flow through the heart can then be cut off, to provide the surgeon with a bloodless field, and the heart muscle is placed in a state of suspended animation (cardioplegia) by perfusing it with an iced solution containing potassium and other ions. The ions in the solution cause the heart to stop beating, and cooling the heart reduces its oxygen requirements, so that under ideal conditions the heart can safely remain in this protected state for two or more hours.

It is cooling which provides the main protection for the heart, and hence over the last few years we have investigated the theoretical and practical aspects of its

Anne Heal, Phillip Henenberg and Prof. Ludbrook studying baro-receptor reflexes in a rabbit

use in heart surgery. Our previous work has refuted the notion that the heart would be damaged by temperatures as low as 4-10 °C. However the view still prevails that during surgery cooling the heart from body temperature (37 °C) to room temperature (20 °C) provides adequate protection against damage. Recently we have shown in isolated dog hearts that further protection is achieved if the heart is cooled to 4 °C. The recirculating cooling circuit which has been developed at the Baker Institute enables the surgeon to cool the heart to 4-10 °C, and thus increases the margin of safety between damage and full recovery, particularly in long operations in the previously damaged heart.

Rhythm Disorders

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 arrhythmia may cause the patient suddenly to collapse and even die. Most of these rhythm irregularities can be controlled by drugs, but some patients continue to suffer disabling symptoms. In recent years some of these refractory cases have been successfully treated by operations to modify or interrupt the conducting system or, in some instances, to replace it by an implanted pacemaker. Alternatively, the area giving rise to abnormal impulses can be removed or electrically isolated from the rest of the heart. We now have a team to develop this surgical approach comprising cardiologists, surgeons and electronic engineers.

In 1981 an important advance was made, in that the team began to tackle the Wolff-Parkinson-White (WPW) Syndrome. Here the key to success is accurate localisation of abnormal conducting fibres by electrical mapping of the heart at operation. The design and testing of the mapping equipment was a joint venture between the Electronics Department of the Alfred Hospital and the Baker Institute. The initial design came from Dr. John Uther in Sydney. Following a period of testing of the equipment in dogs, during which members of the team gained skill in mapping the heart, the clinical program of operating on patients with the WPW syndrome was begun. In 1981 ten patients were treated and nine completely cured of their arrhythmias.

Costs of Coronary Surgery

An area of concern to the government and the public has been the escalating cost of health care. It is estimated that in 1980 there were 3800 coronary bypass graft procedures performed in Australia. In a collaborative venture with the Victorian Health Commission we assessed the cost to the Alfred Hospital of a coronary bypass procedure and the rate of return to work by patients 1-2 years after surgery. The cost to the hospital was calculated to be $4,700 per operated patient. The return-to-work survey of 100 patients aged 55 years and under, showed that before surgery 56 were working but only 16 at full capacity, compared with 77 working with 63 at full capacity after surgery.

Cardiovascular Control

Surgeons have much practical interest in circulatory control. Dr. Ludbrook is continuing his research on the way in which the arterial baroreceptors detect *changes* in blood pressure and are able to control the circulation during blood loss, over-transfusion, and in excessive dilution of the blood with blood substitutes. He is also studying the control of the circulation by these arterial baroreceptors in man and in rabbits during exercise. During 1981 in collaboration with Dr. Dorward, the work on arterial baroreceptors has been extended to study the effects on the activity of the sympathetic constrictor nerves to the kidney in a variety of circumstances.

To date much effort has gone into developing new techniques for elucidating how receptors in the heart, which sense changes in cardiac function, affect the circulation. Like the arterial baroreceptors these receptors, too, respond to changes in tension in the wall of the structures in which they lie. They are thus affected by changes in pressure in the heart chambers and by changes in blood volume. They are of potential importance in helping to resist the effects of blood loss, or of circulatory overload. Both problems occur with some frequency in the setting of clinical surgery and intensive care. They have not previously been studied with any precision in conscious animals or in man.

We have started work on this problem in conscious rabbits, following our previous finding that after arterial baroreceptor denervation it is still possible to elicit a pronounced

bradycardia by steep increases in blood pressure, and that in an isolated carotid sinus preparation the bradycardic response to elevation of systemic blood pressure greatly exceeds that to local elevation of carotid sinus pressure. This suggested that receptors in the left ventricle are still active in the conscious rabbit.

A method has been devised for determining the threshold of this reflex in conscious, baroreceptor-intact, rabbits. Inflatable cuffs placed on the ascending as well as the descending thoracic aorta, permit the left ventricular receptors and arterial baroreceptors to be differentially loaded. Catheters in the ear artery and ascending aorta permit determination of the degree of loading (or unloading) of the receptors. Catheters in the left atrium or ventricle indicate changes in left ventricular end-diastolic pressure. The animals can be studied with all receptors intact and, after arterial baroreceptor denervation, and immediately after cervical vagotomy.

Preliminary results indicate close correlations between onset of the bradycardia and the changes in arterial pressure, left atrial pressure and left ventricular end-diastolic pressure. It appears that a rise in ventricular blood pressure elevation with the physiological range evokes the left ventricular-heart rate reflex.

Ross Jacobs, Jenny Griffiths, Dr. Frank Rosenfeldt and Janet Ness of the Cardiac Surgical Research Laboratory.

Computer Services

The Institute acquired a PDP 11/23 computer in 1980 and also the invaluable services of Judy Gipps as programmer and statistician. In the first instance the computer has been used mainly for the needs of the neurophysiological laboratory where the problem of converting physiological signals into numbers and then into mathematically-defined curves has been greatest.

Mrs Judy Gipps (right) computing data with Dr Pat Dorward (left) and Sandra Burke

At present the facility is being adapted to allow some 'on line' facilities for data processing in the neurophysiological laboratory, but to make it available to others. This involves establishing satellite terminals, which will in the long run save money, since it will greatly reduce our usage of the Monash and Melbourne University Computer Centre facilities.

Biomedical Engineering Services

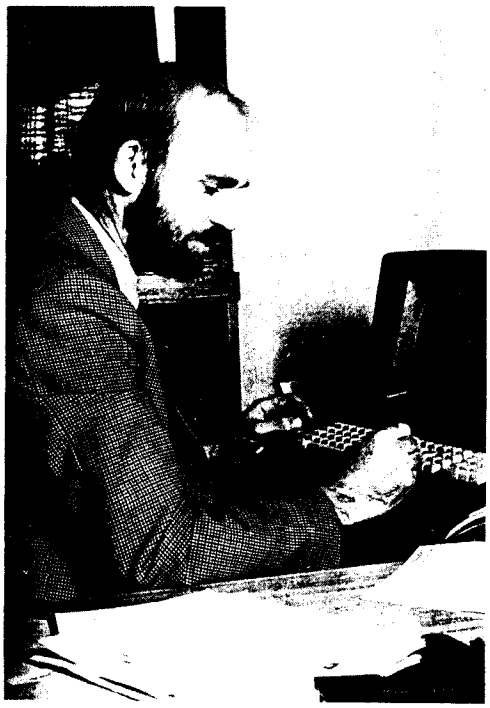
The electronics laboratory and mechanical workshop develop and build electronic and mechanical equipment that is not available commercially, and services equipment purchased overseas, when such a service is not locally provided. This type of facility is far more important in an Australian research institute than, for example, in a U.S. institute.

Falk Hannemann (Electronics Design Engineer) is in charge of the unit; other senior staff members are Kerin Harvey (Electronics Engineer) and John Baird (Instrument Maker). In addition Andrew Fry and David Bell are two apprentices. Major achievements during the past 12 months include the development of a computer controllable instrument for the measurement of cardiac output for non-invasive studies in the Clinical Research Unit; a mobile stereotaxic operating table and electronic support system for Professor Korner and Geoff Head's studies on brain stereotaxic mapping and lesions; pressure regulator for a roller pump (Cardiac Laboratory); a thermodilution cardiac output computer with digital display providing a direct readout (Kidney Laboratory) and a substantial improvement of the sonomicrometer for measurements of artery diameter by pulsed high-frequency ultrasound (Pharmacology Laboratory). Both electronic and mechanical improvements have been made in the design of several items of equipment, e.g. transducer amplifiers, heart period meters, integrators, and the Doppler blood flow measuring system in response to changing needs. The electronics laboratory has been much involved in making the present computer facility operational and in establishing the extended network of terminals and satellites.

Members of the Electronics Laboratory and Workshop: (L-R) Kevin Harvey, John Baird, Andrew Fry and Falk Hannemann (Head).

Secretarial Staff: (standing L-R) Clare Harwood, Kim Howard, Wendy Coleman, Karen Kerr, (seated L-R), Seah Lian-Kee, Marjorie Nicholson and Susan Weir

Librarian Mary Delafield with Ellison Rickards



Mr Ian Dodds, Finance Officer at the Accounts Computer

Laboratory Supervisor Chris Lewis (right) and his assistant Rohan Vaughan

Publications

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CARDIOVASCULAR SURGICAL RESEARCH UNIT

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SUMMER VACATION STUDENTSHIPS

Each summer vacation we have post-graduate and post-doctoral training programs. In order to give prospective students an introduction to medical research the Institute offers a number of summer vacation studentships.

With support from the National Heart Foundation or the Australian Kidney Foundation, 20 studentships were offered to science or medical students in the 1981/82 summer vacation period. These awards provided financial support for a six weeks' period during which time the students were able to participate in one of the current research projects. This year the students submitted a report of their research work and four prizes were awarded for the best contributions. The overall standard of the reports was high and showed considerable appreciation of the research problem. The students made useful and significant contributions within the laboratory. Best reports this year come from Andrew Byrne, Russell Bourne, Sophie Constanides and David Hillis.

The advantage of these studentships is that it gives them a taste for research in this field, and what may be involved in an honours year or in a postgraduate research programe.

Staff activities and overseas visits

HYPERTENSION AND CIRCULATORY CONTROL

Dr. J. Angus—visited the Wellcome Research Laboratories in April, 1981; the International Pharmacological Congress in Tokyo (July, 1981) and a satellite on 'Molecular Pharmacology of Neurotransmitter-Receptor Systems' in Hiroshima.

Dr. W. Anderson—visited the meeting of the American Council of High Blood Pressure Research, Cleveland (September, 1981), the Division of Renal Medicine, Colorado and the Department of Physiology, University of Mississippi.

Dr. M. Esler—attended meeting of International Society of Hypertension in Milan (May, 1981) and Workshop on Adrenergic Receptors in Basel (June, 1981); meeting of International Society of Hypertension (Mexico City, February, 1982).

Dr. G. Jennings—attended Symposium on Hypertension, London (May, 1981) and meeting of International Society of Hypertension in Milan (May, 1981).

Professor P. Korner—attended Symposium on Hypertension, London (May, 1981), International Society of Hypertension (Mexico City, 1982), Satellite on Alpha-receptors (Palm Springs, California), and visited the Havard Medical School, the University of Mississippi, the Cardiovascular Center of the University of Iowa and the Cardiovascular Research Institute of the University of California at San Francisco.

Professor Korner has been much involved as President of the International Physiological Congress to be held in Sydney August/September, 1983.

CARDIOVASCULAR METABOLISM AND NUTRITION RESEARCH UNIT

Dr. N. Fidge—attended the meeting of the Council on Arteriosclerosis, American Heart Association in Dallas, Texas (November, 1981) and visited the Department of Medicine, University of Texas, Cardiovascular Research Institute, University of California and the Gladstone Research Foundation in San Francisco.

Dr. P. Nestel—participated in the First International Symposium on Acarbose in Montreux, Switzerland (October, 1981); Council on Arteriosclerosis, American Heart Association meeting in Dallas, Texas (November, 1981); International Symposium on Nutritional Aspects of Atherosclerosis in Tokyo (February, 1982). He visited laboratories in the University of Texas Health Sciences Center, Dallas as well as the Cardiovascular Research Institute, University of California and the Gladstone Research Foundation in San Francisco.

Dr. K. O'Dea—visited the Department of Medicine, University of Dusseldorf, laboratories of INSERM in Paris, Department of Gastroenterology, Central Middlesex Hospital. She attended the First International Symposium on Acarbose in Montreux, Switzerland (October, 1981).

Dr. M. Reardon—attended the American Heart Association meeting in Dallas, Texas (November, 1981) and visited the Department of Medicine, University of Texas in Dallas and the Departments of Medicine and Nutrition, University of Toronto.

CARDIOVASCULAR SURGICAL RESEARCH UNIT

Dr. J. Ludbrook—attended the International Society of Hypertension in Milan (June, 1981); the International Congress of Nephrology in Athens (June, 1981); the International Surgical Group meeting in Uppsala, Sweden (September, 1981) and the International Vascular Symposium in London (September, 1981).

SPECIAL SEMINARS — 1981

8 April	Antibodies to insulin and β - adrenoceptors: application to study of receptor structure and function	Dr. L. Harrison, Royal Melbourne Hospital
14 July	Science for heroes	Prof. B. Morris, John Curtin School of Medical Research, ANU.
10 August	Cerebral aneurysms	Prof. W. E. Stehbens, Dept. of Pathology, Wellington Clinical School, N.Z.
12 August	CNS organisation of cardiovascular pathways	Dr. R. Dampney, Dept. of Physiology, University of Sydney
1 September	Functional organisation of pre- and post-ganglionic vasoconstrictor system supplying skin and skeletal muscle	Prof. W. Jänig, Dept. of Physiology, Christian-Albrechts University, Kiel, German Fed. Rep.
14 September	Hydrophilicity of β -blocking drugs and β_1-selectivity	Dr. J. Cruickshank, ICI, U.K.

BAKER INSTITUTE IN-HOUSE SEMINARS—1981

23 March	Therapeutic implications of dihydroergotamine kinetics in man	Dr. P. Little, C.R.U.
13 April	Smooth muscle reactivity and atherogenesis — LDL metabolism and response to serum mitogens differ according to phenotype	Dr. Julie Campbell, Baker Institute
27 April	Liver, blood flow and drug clearance	Dr. A. McLean, Baker Institute
25 May	Influence of high cholesterol and high carbohydrate diets on apolipoprotein C kinetics	Dr M. Huff, Baker Institute
22 June	Control of transmitter release at cardiac nerve terminals	Dr J. Angus, Baker Institute
13 July	Blood volume and baroreceptor reflexes	Dr. J. Ludbrook, Baker Institute
27 July	A new lipoprotein synthetic pathway responsible for the development of type III hyper-lipoproteinaemia	Dr. M. Reardon, Baker Institute
10 August	Metabolic response to low carbohydrate/high protein diet (traditional diet) in Australian Aborigines	Dr. Kerin O'Dea, Baker Institute
24 August	The relationship between temperature and the degree of myocardial protection during heart surgery	Dr. F. Rosenfeldt, Baker Institute

BAKER INSTITUTE/PRINCE HENRY'S HOSPITAL JOINT HYPERTENSION SEMINARS — 1981

2 March	Potential mechanisms producing coronary artery spasm	Dr. J. Angus, Baker Institute
16 March	Potentiation by captopril of vasodilatation produced by nitroprusside	Dr. G. Jennings, C.R.U.
30 March	First-pass hepatic extraction of propranolol in man is not stereo-selective	Dr. G. Jackman, C.R.U.
6 April	Kinins and renal haemodynamics	Dr. B. Clappison, P.H.H.
4 May	Prostaglandins and renal blood flow and renin release	Dr. W. Anderson, Baker Institute
29 June	Role of central monoamines in reflex circulatory control	Dr. G. Head, Baker Institute

6 July	The kallikrein-kinin system in acute renal failure	Dr. G. Mathews, P.H.H.
31 August	CNS alpha-receptors in experimental hypertension	Dr. M. Morris, P.H.H.
7 September	The causes of hypertension	Prof. P. Korner, Baker Institute
21 September	Studies in autonomic insufficiency	Dr's G. Jennings, A. Bobik and M. Esler, Baker Institute and C.R.U.
5 October	Calcium antagonists in coronary vasospasms	Dr's J. Angus and R. Brazenor, Baker Institute
19 October	Catecholaminergic and dopaminergic nerves and the kidney	Dr. B. McGrath, P.H.H.
16 November	Release of creatine kinase MB isoenzyme after cardiac bypass surgery	Dr. F. Rosenfeldt, Baker Institute
30 November	A new angiotensin converting enzyme inhibitor	Dr. B. Jackson, P.H.H.
7 December	Regional noradrenaline release in dogs and humans	Dr's P. Blombery and M. Esler

BAKER INSTITUTE — FLOREY INSTITUTE WORKSHOP 24 JULY 1981

The research efforts of our two research institutes complement each other and this really comes across in the joint workshop. Members of one institution selected the speakers from the other and we learned a great deal about each other's techniques and approach. The meeting lasted the whole afternoon and was followed by a buffet meal at the Baker Institute.

The programme was as follows:—

Genes and Environment
(Chairman — D. Denton)
H. Niall:— Evolution of peptide hormones
K. O'Dea:— Diseases of affluence and the Australian Aborigines
J. Coghlan:— DNA probes and hybridization histochemistry
P. Nestel:— Lipoprotein genotype and fat transport

Hormones and Receptors
(Chairman — P. Korner)
R. D. Wright:— Parathormone
A. Bobik:— Cellular actions of catecholamines
B. Kemp:— Cellular actions of peptides
M. Reardon:— Cellular actions of apoproteins
M. Wintour-Coghlan:— ADH in the foetus
R. Brazenor:— 5HT receptors in coronary artery
B. Hudson:— Inhibin
W. Anderson:— Renal prostaglandins

Hypertension and Circulatory Control
(Chairman — B. Scoggins)
P. Korner:— Hypertension research, 1981
B. Scoggins:— Steroids in hypertension
M. Esler:— Sympathetic nervous system in human hypertension
R. Weisinger:— Central nervous control of salt appetite
J. Ludbrook:— Saline ≠ blood

VISIT OF PROFESSOR ROBERT WISSLER

Prof. R. Wissler

Professor Robert W. Wissler recently visited Australia as guest of the National Heart Foundation's Sixth Triennial Conference. Subsequently he spent several days at the Baker Institute as guest of our Cellular Biology group. Professor Wissler is Donald N. Pritzker Distinguished Service Professor of Pathology at the University of Chicago. He is also Director of their Atherosclerosis Center of Research.

On the occasion of his visit a workshop was held on 24 February 1982 on 'Cellular Pathobiology of Atherosclerosis'. Speakers at this meeting included Professor Bill Connor (who discussed lipid turnover in atherosclerotic plaques), Professor Allan Day (platelet-macrophage-lipoprotein interactions), Professor David Penington (platelets in vascular disease), Dr. Julie Campbell (smooth muscle-endothelial interactions), Professor Jack Martin (regulation of endothelial cell activity), A/Professor Barry Gow (endothelial changes in post-stenotic dilatation) and Dr. J. A. Angus (pharmacological intervention).

BAKER MEDICAL RESEARCH INSTITUTE

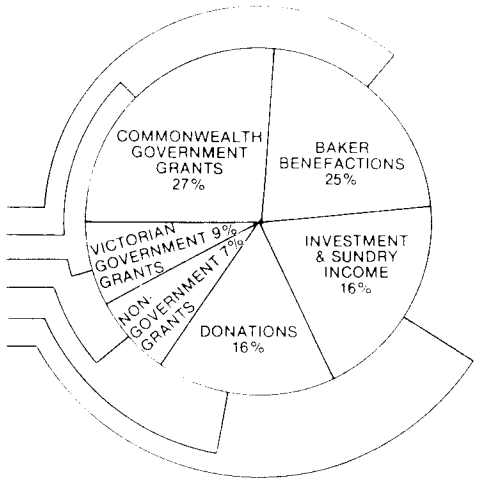
YEAR ENDED 31 DECEMBER 1981

FINANCIAL REPORTS

Income and Expenditure at a glance

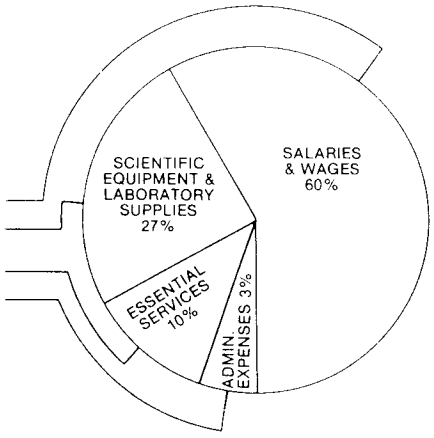
INCOME DERIVED FROM THE FOLLOWING SOURCES:

1980 000's	1980 %		1981 000's	1981 %
356	22	Baker Benefactions	517	25
421	26	Government Grants— Commonwealth	574	27
140	9	Government Grants—Victorian	185	9
138	9	Non-Government Grants	137	7
233	15	Donations	336	16
310	19	Interest from Investments and Sundry Income	343	16
1598	100		2092	100



EXPENDITURE DISTRIBUTED AS FOLLOWS:

1980 000's	1980 %		1981 000's	1981 %
1041	64	Salaries & Wages	1284	60
362	23	Scientific Equipement and Laboratory Supplies	569	27
164	10	Essential Services	209	10
48	3	Administrative Expenses	54	3
1615	100		2116	100



BAKER MEDICAL RESEARCH INSTITUTE

BALANCE SHEET AT 31 DECEMBER 1981

ACCUMULATED FUNDS AND LIABILITIES	1981	1980
OPERATING FUND		
Accumulated (deficit)—Page 71	**(116,924)**	(91,601)
Bank overdraft	**35,822**	57,590
Sundry creditors and accrued expenses	**177,105**	131,930
	96,003	97,919
ENDOWMENT FUND		
Accumulated fund—Page 72	**1,225,122**	1,283,566
RESEARCH SCHOLARSHIP AND OTHER FUNDS		
Restricted fund—Page 72	**59,068**	15,618
Edgar Rouse Memorial Fellowship Fund—Page 73	**77,713**	67,230
Laura Nyulasy Scholarship Fund—Page 73	**2,875**	3,405
William Buckland Research Fund—Page 73	**31,712**	31,337
Lang Research Scholarship Fund	**4,852**	4,852
	176,220	122,442
	$1,497,345	$1,503,927

These Accounts should be read in conjunction with the notes on page 74.

ASSETS			1981	1980
OPERATING FUND ASSETS				
Cash on hand			**300**	300
Sundry debtors			**35,703**	56,119
Short term deposits (at cost) held by Trustees of the Institute—			**60,000**	41,500
			96,003	97,919
ENDOWMENT FUND ASSETS				
Investments (at cost)—Note 3				
Held by Trustees of the Institute				
Freehold properties	40,000			40,000
Government and semi-government stock	83,124			86,124
Shares and debentures in companies	157,756			145,197
Short term deposits	26,500			14,000
Mortgage loans	345,000			356,000
		652,380		641,321
Held by the Trustees, Executors & Agency Co Ltd—				
Shares in companies	69,158			67,335
Trust units	84,000			548,719
Short term deposits	7,200			7,200
Mortgage loans	402,050			
		562,408		623,254
Cash at bank		10,334		18,991
			1,225,122	1,283,566
RESEARCH SCHOLARSHIP AND OTHER FUND ASSETS				
Investments (at cost):— Note 3				
Held by Trustees of the Institute				
Shares in companies		4,852		8,817
Short term deposits		59,000		59,000
		63,852		67,817
Held by The Trustees, Executors & Agency Co Ltd—				
Shares in companies	8,937			4,852
Trust units	25,504			25,204
Short term deposits	2,947			2,800
		37,388		32,856
Cash at bank		74,980		21,769
			176,220	122,442
			$1,497,345	$1,503,927

BAKER MEDICAL RESEARCH INSTITUTE

YEAR ENDED 31 DECEMBER 1981

STATEMENT OF INCOME AND EXPENDITURE — OPERATING FUND

INCOME —		1981	1980
DONATIONS FROM BAKER BENEFACTIONS			
Statutory amount	11,569		11,569
Transfers from Endowment Fund	505,258		344,911
		516,827	356,480
OTHER DONATIONS (Net of transfers)		**335,799**	233,374
GRANTS-IN-AID OF RESEARCH PROJECTS			
Life Insurance Medical Research Fund of Australia and New Zealand	30,000		40,178
National Health and Medical Research Council	574,164		420,518
National Heart Foundation of Australia	71,143		94,971
		675,307	555,667
OTHER GRANTS			
The James and Elsie Borrowman Research Trust	9,500		Nil
The William Buckland Research Fund	2,461		2,500
Victorian State Government	185,000		140,000
Laura Nyulasy Research Scholarship Fund	945		Nil
Clive & Vera Ramaciotti Foundations	11,842		
Australian Associated Brewers	11,032		
		220,780	142,500
INTEREST FROM INVESTMENTS			
Held by Trustees of The Baker Institute Grant Trust	4,590		3,461
Other investment income	186,674		173,412
		191,264	176,873
OTHER INCOME			
Rentals	7,180		12,013
Sundry sales, recoveries and refunds	144,113		120,966
		151,293	132,979
Deficit for the year		**25,323**	17,616
		$2,116,593	$1,615,489

These Accounts should be read in conjunction with the notes on page 74.

EXPENDITURE—	1981	1980
Salaries and wages	**1,284,224**	1,040,640
Laboratory supplies and isotopes	**174,889**	148,695
Additional equipment and building costs	**291,310**	116,385
Library Maintenance	**30,773**	18,817
Postage and telephone	**15,736**	12,673
Printing and stationery	**27,202**	24,674
Light and power	**63,216**	46,145
Insurance	**19,080**	15,678
Repairs and renewals	**39,046**	34,385
Animal house contribution	**9,000**	9,000
Collaborative Grant — NH & MRC Programme	**55,000**	54,000
Travelling expenses	**43,306**	35,439
Public relations	**10,276**	5,637
Stanhope Court	**3,080**	1,131
Fund raising expenses	**40,477**	41,476
Sundries	**9,978**	10,714
	2,116,593	1,615,489

STATEMENT OF MOVEMENT IN ACCUMULATED FUND

OPERATING FUND		
Deficit for year	**25,323**	17,616
Accumulated deficit as at 1/1/1981	**91,601**	73,985
Accumulated deficit as at 31 December—Page 68	**$116,924**	$91,601

BAKER MEDICAL RESEARCH INSTITUTE

YEAR ENDED 31 DECEMBER 1981

STATEMENT OF MOVEMENT IN ACCUMULATED FUNDS

		1981	1980
ENDOWMENT FUND			
Balance at 31 December 1980		**$1,283,566**	$1,498,617
Donations—Baker Benefactions	527,758		393,359
—Victorian State Government			90,000
Interest	365		—
Profit on sale of shares	10,597		—
Other income	119		378
		538,839	483,737
		1,822,405	1,982,354
Bank Interest and Overdraft Charges	38		1,054
Transfer to Operating Fund	505,258		344,911
Loss on sale Common Fund	62,669		—
Adjustment to Share Investments	567		—
Building maintenance and renovations	13,209		—
Cost of motor vehicles	15,542		—
Biology Research Unit Extension	—		352,704
Transfer to William Buckland Fund	—		119
		597,283	698,788
Balance at 31 December 1981—Page 68		**$1,225,122**	$1,283,566

NOTE: Interest received on Endowment Fund assets is credited direct to the Operating Fund.
Income from the Lang Research Scholarship Fund has been credited directly to the Endowment Fund

RESTRICTED FUND			
Balance at 31 December 1980		**$15,618**	$37,323
Baker Benefactions Statutory Amount 1982	—		11,569
Donations	45,000		7,000
Investment income and bank interest	255		194
Transfer from Operating Fund	3,000		
Grants and scholarships	10,764		
		59,019	18,763
		74,637	56,086
Transfer to Operating Fund			
—Baker Benefactions Statutory Amount 1981	11,569		11,569
Donations, Grants and Other income	4,000		28,899
		15,569	40,468
Balance at 31 December 1981—Page 68		**$59,068**	$15,618

NOTE: Baker Benefactions Statutory amount for 1982 will be credited directly to Endowment Fund.

These Accounts should be read in conjunction with the notes on page 74.

		1981	1980
EDGAR ROUSE MEMORIAL SCHOLARSHIP FUND			
Balance at 31 December 1980		**$67,230**	$58,302
Donations	1,936		2,260
Investment income and bank interest	8,547		6,668
		10,483	8,928
		77,713	67,230
Transfer to Operating Fund—Other Income		**Nil**	Nil
Balance at 31 December 1981—Page 68		**$77,713**	$67,230
LAURA NYULASY SCHOLARSHIP FUND			
Balance at 31 December 1980		**3,405**	2,873
Investment income (net)		**415**	300
Other			232
		3,820	3,405
Transfer to Operating Fund (Scholarship)		**945**	
Balance at 31 December 1981—Page 68		**$2,875**	$3,405
WILLIAM BUCKLAND RESEARCH FUND			
Balance at 31 December 1980		**31,337**	30,757
Investment income (net)		**2,956**	2,739
Transfer from Endowment Fund			119
Other Income		—	222
		34,293	33,837
Purchase of shares	120		
Transfer to Operating Fund	2,461		
		2,581	2,500
Balance at 31 December 1981—Page 68		**$31,712**	$31,337

BAKER MEDICAL RESEARCH INSTITUTE

YEAR ENDED 31 DECEMBER 1981

NOTES TO AND FORMING PART OF THE ACCOUNTS

1. INCORPORATION

On 1 August 1980, The Thomas Baker, Alice Baker and Eleanor Shaw Medical Research Institute was incorporated as the "Baker Medical Research Institute" under the Baker Medical Research Institute Act 1980. At this date the assets and liabilities of the original Institute were vested in the new Baker Medical Research Institute at book value.

2. STATEMENT OF ACCOUNTING POLICIES

The following accounting policies of the Institute, which are consistent with those applied in the previous years, are as follows:

(a) Historical Cost

The accounts of the Institute are prepared on the basis of historical cost and unless otherwise stated do not take into account the effect of changing money values or current valuations of non-current assets.

(b) Institute Funds, Income and Expenditure

The work of the Institute is financed from grants, endowments, donations and bequests of both general and specific natures. Income is taken to specific funds depending on the terms of any relevant covenants applying to that income.

Other income and expenditure is accounted for on an accrual basis. Any deficiency arising therefrom is carried forward in the Operating Fund.

(c) Capital Expenditure and Depreciation

Capital expenditure made by the Institute in respect of buildings, furniture and equipment in present and past periods has been charged against appropriate funds, grants or revenue accounts and expensed in the period in which it was incurred. Accordingly, no depreciation charge appears in the Institute's accounts.

The insurable value of such accumulated capital expenditure, including buildings, to 31 December 1981 was approximately $8,742,000 (1980 $6,550,000).

3. INVESTMENTS

The market value of shares in companies listed on the Australian Stock Exchange at 31 December 1981 was $447,630 (1980 $474,389).

The Trustees, Executors & Agency Co Ltd is the custodian and manager of certain 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.

4. STAFF ENTITLEMENTS

The Institute does not provide for long service leave or holiday pay in the accounts. The liabilities at 31 December 1981 amounted to; holiday pay $85,002 (1980 $28,120) and long service leave $56,508 (1980 $30,574).

5. CONTINGENT LIABILITY

A contingent liability exists where the Institute has indemnified a staff member in a libel action brought against him in circumstances where he was representing the Institute. The action is presently pending and it is the opinion of the solicitors of the Institute and the Board of Management that the result of this action cannot be assessed at this time.

6. ETHEL MARY BAILLIEU FUND

The assets of the Ethel Mary Baillieu bequest, although recorded and accounted for by the Baker Institute, do not form part of these accounts and are not audited by us.

Auditors Report to the Board of Baker Medical Research Institute.

In our opinion the balance sheet, statement of income and expenditure and statements of movement in accumulated funds, as set out on pages 68 to 74 are properly drawn up to show a true and fair view of the state of the Institute's affairs at 31 December 1981.

PRICE WATERHOUSE
E. A. ALEXANDER
A member of the firm,
Chartered Accountants.

Melbourne
16th February 1982

DONATIONS 1981

Victorian State Government	$185,000.00
Estate of Emily E. E. Stewart	63,680.92
Allan Williams Trust Fund	22,000.00
Anonymous	20,000.00
Sandoz Australia Pty. Ltd.	18,265.00
Estate Mrs P. H. Dickie	12,500.00
I.C.I. Australia Ltd.	12,000.00
The Ian Potter Foundation	10,000.00
I.C.I. Australia Ltd.	12,000.00
Clive & Vera Ramaciotti Foundations	11,842.00
Australian Associated Brewers	11,032.00
The Ian Potter Foundation	10,000.00
I.C.I. Research	9,999.99
James & Elsie Borrowman Research Trust	9,500.00
Percy Baxter Charitable Trust	7,000.00
Estate of Mrs Anna White	5,000.00
The Windermere Hospital Foundation	5,000.00
Dame Elisabeth Murdoch	5,000.00
Australian Consolidated Ind. Ltd.	5.000.00
ANZ Banking Group Ltd.	5,000.00
Esso Australia Ltd.	5,000.00
Ciba-Geigy	4,500.00
Boehringer Ingelheim Pty. Ltd.	4,000.00
H. & L. Hecht Trust	4,000.00
The Wm. Angliss (Vic.) Charitable Fund	4,000.00
Australia/Japan Foundation	4,000.00
George Thomas & Lockyer Potter Charitable Trust	3,600.00
Appel Family Bequest	2,800.00
Estate of the Late Edward Wilson	2,500.00
B.H.P. Co. Ltd.	2,500.00
The William Buckland Research Fund	2,461.00
G. J. Coles & Co. Ltd.	2.250.00
Bell Charitable Fund	2,000.00
E. H. Flack Estate	1,825.00
Mrs B. Hewitt	1,250.00
Prof. P. I. Korner	1,050.00
William Paxton Charitable Fund	1,000.00
Kodak (A/Asia) Pty. Ltd.	1,000.00
The Arthur Anderson & Co. Foundation	1,000.00
Ansett Transport Industries Ltd.	1,000.00
Robert Bosch (Aust.) Pty. Ltd.	1,000.00
CRA Services Ltd.	1,000.00
The Chamber of Manufacturers Ins. Ltd.	1,000.00
Mr W. Chin	1,000.00
Comalco Limited	1,000.00
Commercial Bank of Australia Ltd.	1,000.00
Commercial Bank of Australia Ltd.	1,000.00
Charles Davis Limited	1,000.00
EZ Industries Ltd.	1,000.00
Endeavour Resources Ltd.	1,000.00
The Herald & Weekly Times Ltd.	1,000.00
Hooker Corporation Ltd.	1,000.00
Industrial Equity Limited	1,000.00
North Broken Hill Holdings Ltd.	1,000.00
Permewan Wright Cons. Pty. Ltd.	1,000.00
Potter Partners	1,000.00
Rayson Industries Pty. Ltd.	1,000.00
Red Tulip Chocolate Pty. Ltd.	1,000.00
Royal Insurance	1,000.00
David Syme & Co. Ltd.	1,000.00
Sportscraft Consolidated Pty. Ltd.	1,000.00
J. B. Were & Son	1,000.00
George Weston Foods Ltd.	1,000.00
Estate A. H. Cook	1,000.00
E. B. Myer Charity Fund	1,000.00
Laura Nyulasy Research Scholship. Fund	945.00
CBA Travel Services Ltd.	830.00
Clonakilty Pty. Ltd.	800.00
The Shell Co. of Australia Ltd.	650.00
Rev. Leahy	600.00
Estate Mrs C. M. Nesbitt	500.00
Ajax Fasteners Australia Ltd.	500.00
Aust. International Finance Corp. Ltd.	500.00
Acmil Ltd.	500.00
Bank of N.S.W.	500.00
Commonwealth Banking Corporation Ltd.	500.00
Carlton & United Breweries	500.00
Courtaulds Hilton Limited	500.00
Crawfords Productions Pty. Ltd.	500.00
J. Gadsden Australia Ltd.	500.00
Mayne Nickless Ltd.	500.00
McCaughan Dyson & Co.	500.00
McPherson's Limited	500.00
Nabisco Pty. Ltd.	500.00
Reckitt & Coleman Australia Ltd.	500.00
Woolworth's (Vic) Ltd.	500.00
Wormald International Limited	500.00
George Frederick Little Settlement	470.00
Ms. M. A. Simpson	350.00
Blake & Riggall	300.00
Sir Laurence & Lady Muir	300.00
Mrs M. I. Pierce	300.00
McIllwraith-Davey & Co. Pty. Ltd.	250.00
Monsato Australia Limited	250.00
Repco Limited	250.00
Ford Motor Co. of Australia Ltd.	250.00
Messrs. A. C. Goode & Co.	250.00
Mr F. Murphy	250.00
Mr F. K. Alfredson	250.00
Mr A. J. Risstrom	230.00
Mrs G. Ansell	200.00
Mrs K. R. Ansell	200.00
H. & I. Arnhold	200.00
Sir Robert Blackwood	200.00
Makmur Enterprises Pty. Ltd.	200.00
Mr J. Moir	200.00
Mr H. Schreiber	200.00
Mr J. Taylor	200.00
Mrs M. C. Volum	200.00
Mr B. J. Walter	200.00
Barclays International Australia Ltd.	200.00
Cadbury Schweppes Pty. Ltd.	200.00
W. A. Deutscher Pty. Ltd.	200.00
Guthrie Operations Pty. Ltd.	200.00
Hewlett Packard Australia Pty. Ltd.	200.00
Hendersons Industries Ltd.	200.00
Mr H. R. Holdenson	200.00
Dr. H. B. Kay	200.00
Mr J. R. McDonnell	200.00
Oakbridge Limited	200.00
Bly's Industries Pty. Ltd.	200.00
CTM Nominees Pty. Ltd.	200.00
Ms A. P. Kennedy	175.00

Mrs E. Parker	175.00
Mrs M. Vernon	160.00
Mrs A. Bottomley	150.00
Mr & Mrs M. A. Cuming	150.00
Miss H. D. Glascodine	150.00
Mrs E. G. Hunter	150.00
Mrs D. Newton	150.00
Mr K. Oppenheimer	150.00
Messrs. Arthur Robinson & Co.	150.00
Miss M. Stanistreet	150.00
Mr I. D. Swansson	150.00
C.I.G. Medishield	150.00
Mr A. H. Ansell	125.00
Mrs L. Porter	125.00
Norlane Bowling Associates	109.00
Mr H. P. Blaich	100.00
S. Bude	100.00
Mrs M. Y. Bull	100.00
Mr D. P. Chan	100.00
Dr. H. C. Chan	100.00
Mr G. W. Chatfield	100.00
Dr. D. Chong	100.00
Dr E. P. Choo	100.00
Christian Womens Fellowship	100.00
Mr B. T. Corrigan	100.00
Cypress & Sons Pty. Ltd.	100.00
Sir Peter Derham	100.00
Mrs M. A. Dobson	100.00
Mr C. Emery	100.00
Euglo Nominees Pty. Ltd.	100.00
Mr L. K. Farmer	100.00
Mr L. M. Francome	100.00
Mr L. A. Gadsden	100.00
Mr H. H. Gillbank	100.00
Mrs B. L. Glascodine	100.00
Mr A. J. Glasson-Williams	100.00
Mr R. Goldenberg	100.00
Dr J. S. Guest	100.00
Mr & Mrs J. C. Habersberger	100.00
Mr P. Haddad	100.00
Mr B. Halpern	100.00
Mrs H. Handbury	100.00
Mr T. Holden	100.00
Dr S. J. Iceton	100.00
Mr A. P. Kelly	100.00
Mrs E. Korner	100.00
Mr N. R. Korner	100.00
Mr A. Leitch	100.00
Mrs. J. Ling	100.00
Mr R. W. Lister	100.00
Sir James McNeill	100.00
Mr A. J. Marriott	100.00
Mrs D. M. Martin	100.00
Mr E. R. Meagher	100.00
Miss G. B. Murray	100.00
Mr R. E. Nelson	100.00
Dr H. K. Ng	100.00
Mr J. D. Noack	100.00
Mr J. G. Reade	100.00
Mrs B. A. Richardson	100.00
Mr R. A. Ritchie	100.00
Mr K. Rogers	100.00
Mr E. Smorgan	100.00
The Southsiders	100.00
John Stansfield-Smith & Sons	100.00
Mrs A. K. Stewart	100.00
Dr G. Stirling	100.00
Mrs L. L. Sullivan	100.00
Mr S. Sunamura	100.00
Mr H. E. Towers	100.00
Mr A. J. Williams	100.00
Mrs I. M. Willis	100.00
Aberfoyle Limited	100.00
Brash Holdings Limited	100.00
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General Summary

The variety of interests of the Clinical Research Unit which include hypertension, hyperlipidaemia, peripheral vascular disease, clinical pharmacology, postural hypotension and other cardiovascular and metabolic diseases have ensured that 1981 has been a busy and productive year, both for patient care and for clinical research. Progress in some of these fields is outlined in other sections of the Baker Institute Report.

In the field of hypertension we have mainly been involved in improving tests of sympathetic function, using measurement of the apparent rate of secretion of noradrenaline and its reuptake into sympathetic nerve endings, and studying the effects of beta-adrenoceptor simulation as a method of determining receptor sensitivity and number in man. We have made a major effort to validate our non-invasive method of measuring cardiac output by the Indirect Fick Method, as we expect this to play an important part in our future studies of the causes of essential hypertension and on the mechanisms of benefit to the cardiovascular system of physical activity. The method is invaluable in a large number of investigations on the effects of cardiovascular drugs in man.

List of Projects

1. Comparison of the Indirect Fick and thermodilution methods for measurement of cardiac output in man.
2. Pathogenesis and treatment of postural hypotension due to autonomic insufficiency.
3. Haemodynamic effects of prenalterol.
4. Efficacy of a long-acting beta blocker, LT 31-200, in essential hypertension.
5. Drug treatment of pulmonary hypertension.

Comparison of the Indirect Fick and thermodilution methods for measurement of cardiac output in man

G. Jennings, M. Hargreaves

Although the Indirect Fick method has been used for many years as a non-invasive way of determining cardiac output during exercise, it's validity at rest has been questioned. Cardiac output is determined by dividing carbon dioxide production by the arterio-venous difference in carbon dioxide content.

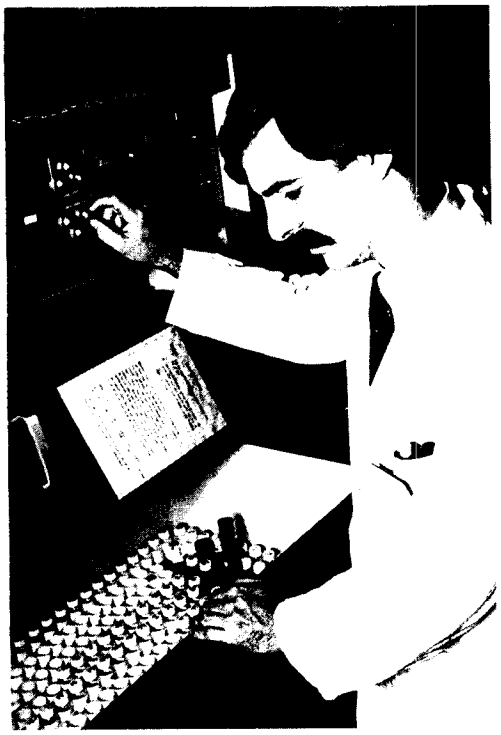
These measurements are controlled by a microcomputer through a system developed in the Baker Institute workshop, aimed at maximising the precision of the method.

In twelve subjects, (of whom five were normal, healthy volunteers and the remainder had a variety of cardiac and respiratory diseases), a close relationship was found between the estimates of arterial and venous carbon dioxide content obtained non-invasively by the new method and those obtained by direct measurement of blood samples. Estimates of cardiac output were similar when measured simultaneously by the Indirect Fick and thermodilution methods During exercise, the non-invasive method was found to be even more reliable. In 1982 we plan to apply this method in our studies on possible causes of essential hypertension in man. The availability of a reliable, non-invasive method for measurement of cardiac output will greatly facilitate these studies. For the first time we will be able to make repeated measurements in patients without subjecting them to cardiac catheterisation. The method is easy to use during exercise, and will be employed in our forthcoming programme to determine how physical exercise benefits the cardiovascular system.

Pathogenesis and treatment of postural hypotension due to autonomic insufficiency

G. Jennings, A. Bobik, M. Esler

Previous studies have suggested that patients with autonomic dysfunction can be divided into those in whom the defect in their sympathetic nervous system is in the central nervous system and those in whom the abnormality is at the peripheral nerve endings. Patients with a central abnormality were usually found to have other evidence of involvement in physical signs on routine examination of the CNS. They also differ from normal subjects and those with peripheral autonomic defects in their noradrenaline concentrations in plasma, response to reflex stimulation and spillover rate. To investigate the categorisation of these patients more fully, we have performed basilic (arm) vein biopsies on a group of subjects with autonomic insufficiency. Histochemistry and electron microscopy have been done by Dr. Gordon Campbell of the Department of Anatomy, Melbourne



Dr Peter Little setting up radio immunoassays

University and by Dr. Greg Willis, Prince Henry's Hospital. Preliminary results suggest that there is marked reduction of catecholamine content in veins from patients with peripheral autonomic dysfunction.

As reported previously, our patients with autonomic insufficiency have received marked benefit from high doses of dihydroergotamine, a new way of treating this condition. Several of our patients have now received this drug for four years and continue to have excellent relief of symptoms without evidence of toxicity.

Beta-adrenoceptor responses in autonomic dysfunction

G. Jennings, A. Bobik, M. Esler

We have studied the responses of cylic AMP to isoprenaline incubation of lymphocytes from six patients with autonomic dysfunction and severe postural hypotension. Three patients had the Shy-Drager syndrome (central pattern), characterised by central nervous system symptoms and signs and normal plasma noradrenaline (average 250 ± 26 pg/ml

which was similar to the values of 250 ± 27 pg/ml in eleven age-matched, control subjects). The other three subjects had idiopathic orthostatic hypotension (peripheral pattern) with no central nervous system signs, but a low plasma noradrenaline (average 160 pg/ml). In the patients with Shy-Drager syndrome, there was a greater cyclic AMP response at each concentration of isoprenaline than in seven normal subjects. However, the patients with autonomic dysfunction of the peripheral pattern, had normal lymphocyte cyclic AMP responses, suggesting that diminished sympathetic tone and low levels of plasma catecholamines at rest are not always associated with enhanced beta-adrenoceptor responsiveness. We also found differences between heart rates in our patients with autonomic insufficiency and those in normal subjects after isoprotenerol administration. However, care should be taken in interpreting results in subjects with intact circulatory reflexes, and in those without them, since response to isoprenaline in normal subjects is partly determined by the efficiency of circulatory reflexes and is altered by pharmacologic autonomic block.

Patients with autonomic insufficiency provide a yardstick for assessing the sympathetic nervous system in man and the biochemical findings related to catecholamines in these patients have important implications for evaluating the results obtained in other illnesses such as hypertension, depression, thyroid disease.

Haemodynamic responses to prenalterol

G. Jennings, K. Oddie, M. Hargreaves, A. Bobik

Prenalterol is a new drug which is thought to selectively stimulate the beta-adrenoceptors of the heart, resulting mainly in an increase in cardiac contractility. It is hoped that this drug will provide an alternative to digoxin as a stimulant for the failing heart. We have studied the effects of intravenous and oral administration of prenalterol in six normal subjects. Heart rate, blood pressure, cardiac output and plasma concentration of prenalterol were measured at various times up to ten hours after administration of 2.5 mg i.v. and 10mg oral prenalterol. At the time of peak effect it was found that prenalterol caused a small rise in heart rate (5-10 beats/min) with a much larger increase in cardiac output of approximately 25%. Blood pressure remained unchanged in subjects with intact circulatory reflexes. These acute responses suggest that the drug is capable of markedly increasing cardiac contractility without causing undue tachycardia such as occurs with the non-selective beta-stimulant, isoprenaline. The effects of prenalterol were compared with those of isoprenaline before and after autonomic blockade with clonidine 300 μg, atropine 0.04 mg/kg and phentolamine 10mg in the same subjects. Before autonomic block, isoprenaline caused a dose-related increase in heart rate and fall in mean arterial pressure after bolus administration. After autonomic block, the same doses of isoprenaline caused a smaller change in heart rate, but a greater fall in blood pressure suggesting that the arterial baroreflex was contributing to tachycardia caused by isoprenaline when the drug was given before autonomic block. Prenalterol, after autonomic block, caused a much greater rise in heart rate than had been present at the same dose before block. In contrast to isoprenaline, however, there was no fall in blood pressure even at the highest doses. This finding suggests that prenalterol is indeed highly selective in man for cardiac beta-receptors and that unlike isoprenaline very little stimulation occurs of peripheral beta-receptors.

Efficacy of LT 31-200, a long acting beta-adrenoceptor blocker, in patients with moderate essential hypertension

G. Jennings, K. Oddie, A. Bobik

LT 31-200 is a beta-adrenoceptor blocker which *in vitro* is at least 10-20 times more potent than pindolol, which is presently the most potent commercially available beta blocker. Preliminary studies have suggested that the drug is very well tolerated and that provided sufficient dosage is given, effects last for several days. The present study was designed to determine whether LT 31-200 was suitable for administration in a once weekly dose.

Following a run-in period, patients received 1 mg daily for two weeks followed by a wash-out period, then 8 mgs once weekly for the next two weeks. Measurements were made throughout the day at the beginning and end of each

week of plasma concentration, haemodynamics, blood pressure and heart rate at rest and during exercise. Three subjects have completed the study so far and a significant fall in arterial blood pressure was observed in each patient. The fall was mainly due to reduction in cardiac output, both after the first dose and after two weeks of administration. The duration of action of the 8 mg dose was found to be up to five days, but further patients will be required to complete the study before it can be assessed whether the duration is as long as one week.

Metronidazole pharmacokinetics and rectal availability in post-operative surgical patients

Lisa Ioannides, A. Somogyi, J. Spicer, B. Heinzow, N. Tong, A. McLean

The rectal bioavailability and intravenous disposition of metronidazole was studied in 8 surgical patients on a fixed post-operative regimen of metronidazole 500 mg 8 hourly. Plasma concentrations were studied over 8 hour dosing intervals on consecutive days. Assays were performed using high pressure liquid chromatography and biological techniques.

Rectal bioavailability (F) was almost complete; F = 78.3 ± 11.1% (mean ± SD), range 59.3 - 94.0%, and the mean steady-state plasma concentration (C_{SS}) was 16.4 ± 5.6 μg/ml. Clearance (Cl_S) of the parent drug was 52.2 ± 19.8 ml/min, range 35.2 - 86.8 ml/min, while the estimated mean plasma half-life ($t_{1/2}$) was 12.4 ± 7.2 hr, range 4.3 - 26.2 hr.

Variation in metronidazole disposition indicates the need to individualise therapy. However rectal suppositories represent an adequate, safe and economical means of administration of metronidazole in patients following abdominal and pelvic surgery with or without significant postoperative complications.

Clinical pharmacy monitoring and utilization of enteral and parenteral metronidazole in a general hospital

Lisa Ioannides, A. Somogyi, N. Tong, J. Spicer, A. McLean

Pharmacokinetic data indicating adequate rectal bioavailability of metronidazole in surgical patients was used as a basis for hospital policy, restricting intravenous metronidazole usage to patients with proven anaerobic infections, or patients unable to take oral medications in circumstances where rectal therapy was inappropriate. Clinical pharmacists screened patients according to these criteria and reminded or informed medical staff of the results of bioavailability studies and existing hospital policy.

The use of intravenous metronidazole (500 mg) decreased from an average of 228 ± 48 vials/month (mean ± S.D.) in the year prior to the study to an average of 77 ± 57 vials/month in the current year with a minimum of 55 vials/month at the time of this review.

The use of rectal suppositories increased from 290 ± 200 suppositories/month to 815 ± 251 suppositories/month over the same time periods. Wound isolation rates did not alter.

The value of active utilization monitoring has been confirmed, and an education liaison role for clinical pharmacists has been demonstrated with substantial cost-benefit gains in antibiotic usage.

PUBLICATIONS
(see also Baker Institute Report)

G. JENNINGS, A. BOBIK and M. ESLER
Beta-Receptors in Orthostatic Hypotension—Letter to the Editor, New Eng. J. Med., Vol. 305, 17: 1019, 1981.

G. JENNINGS, A. BOBIK, M. ESLER and P. KORNER
Contribution of cardiovascular reflexes to differences in beta-adrenoceptor-mediated responses in essential hypertension. Clin. Sci. 61 (in press), 1981

G. JENNINGS, A. BOBIK and P. KORNER
Influence of intrinsic sympathomimetic activity of beta-adrenoceptor blockers on the heart rate and blood pressure responses to graded exercise. Br. J. Clin. Pharmac. 12: 355-362, 1981.

G. L. JENNINGS, J. S. GELMAN, J. R. STOCKIGT and P. I. KORNER
Accentuated hypotensive effect of sodium nitroprusside in man after captopril. Clin. Sci. 61:521-526, 1981.

Ewen Downie Metabolic Unit

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INTRODUCTION

During 1981 the Unit has continued its dual role as a clinical service and research department of the hospital. While providing a broad clinical service in endocrinology and diabetes, our laboratory work has again been directed towards thyroid and adrenal diseases. As well as studies done from this hospital, we receive samples from interstate and from as far away as Malaysia and Hong Kong.

Visitors

In the past year we have enjoyed visits from a number of guests. Dr. Harald Meinhold, from the Thyroid Research Group at Klinikum Steglitz, Freie Universität Berlin, worked here as a Visiting Scientist for the first half of 1981. During this time he established a valid method for measurement of thyroid hormone binding to lymphocytes. Dr. John Baxter of University of California, San Francisco, Dr. Kevin Catt from the National Institutes of Health, Bethesda, and Dr. Sidney Ingbar of Harvard Medical School also visited the department and gave seminars here.

During 1981 we continued to enjoy valued collaboration with the Baker Institute and Clinical Research Unit, Medical Research Centre Prince Henry's Hospital, Monash University Department of Medicine, Howard Florey Institute University of Melbourne, as well as with Departments of Endocrinology at University of California, San Francisco.

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

Estate of the late Vincenza Acton
Estate of the late H. Vistaline
G. M. Rollason Trust
Vivian Hill Trust
Alfred Hospital Whole-time Medical Specialists' Private Practice Fund
Research support from the National Health and Medical Research Council and the Alfred Hospital Medical Research Committee is also acknowledged.

General Summary

GENERAL ACCOUNT OF RESEARCH

Thyroid Hormone Pathophysiology

We have now done further work on a new hereditary thyroid hormone binding abnormality and have demonstrated that this condition is due to a greater than normal affinity of thyroxine for circulating albumin. It appears that a subtle inherited difference in the structure of albumin allows thyroxine to bind more tightly than normal to this protein. In order to maintain a normal level of the active (or free) fraction of thyroxine, affected subjects need about double the normal total hormone level in the blood. It is this biochemical abnormality which puts them at risk of a false diagnosis of hyperthyroidism.

We have now determined the number and affinity (strength) of thyroxine binding-sites on albumin prepared from the serum of affected subjects and have shown that these binding sites are reversibly altered if the sulphur-sulphur linkages of albumin are modified by reducing agents.

In order to find out the prevalence of this condition, now known as familial euthyroid T_4 excess, we have established a screening assay for abnormal binding which allows 10 samples to be screened in a single tube. Although we have so far identified six affected kindreds in Australia, it appears that the condition has a low prevalence in this community.

We have also evaluated a number of commercial free thyroxine assays in this condition and have found that some give misleading results which appear to confirm thyroid overactivity.

During severe illness there are numerous changes in the physiology of the endocrine glands. While many of these responses are beneficial, others may have adverse effects during prolonged illness. Further, these changes in circulating hormone levels may create diagnostic confusion, suggesting disease where it is absent, or obscuring important diagnostic information where a true hormone abnormality exists. Among the most difficult areas in Clinical and Laboratory Endocrinology at present, is the understanding of thyroid hormone changes during severe non-thyroidal illness. There is ample evidence for altered stimulation of the thyroid by the pituitary, for altered plasma binding of hormones in the circulation, for decreased removal of iodine from the thyroxine molecule and for altered tissue uptake of hormone. Many dilemmas remain. Which changes are important in particular patients? Which severely ill patients have genuine thyroid disease? Which patients, without underlying thyroid disease, would benefit from an alteration in their thyroid status?

We have approached these problems in

several ways. A follow-up study of thyroid function after recovery from severe prolonged illness showed that thyroid hormone levels returned to normal. However, it was also shown that severe illness could normalize the elevation in thyroid stimulating hormone, one of the cardinal diagnostic features of true primary thyroid deficiency.

The circulating levels of the three normal thyroid hormone binding proteins may vary widely during severe illness. It has so far been uncertain whether the observed changes in total and apparent free level can be attributed to these changes. By calculating the anticipated free level after assuming a normal binding affinity for each protein, we have demonstrated that the measured and calculated free levels are usually in good agreement. However, in some severely ill subjects there is a marked difference which is so far unexplained.

The presence of circulating inhibitors of thyroid hormone binding to plasma proteins has recently been suggested. We have been unable to show stable high molecular weight inhibitors, but have recently developed methods to detect short-lived unstable compounds which modify hormone binding or hormone delivery to tissues. After extensive preliminary studies, a system has been developed which allows equilibrium binding and hormone dissociation studies to be completed within 20 minutes of blood sampling.

Steroids, Adrenal Disease, Hypertension

It need hardly be re-stated that the various classes of steroid hormones: glucocorticoids, mineralocorticoids, oestrogens, androgens and progestogens each have very diverse actions which are still poorly defined at the cellular level. Each group of steroids is widely used therapeutically, either to correct a hormone deficiency or to alter some body process e.g. contraception, vasoconstriction in the skin, salt retention, anti-inflammatory action. Furthermore, there has been extensive development of modifications of the steroid molecule in order to produce compounds which block normal effects by interacting with the specific receptor, filling it with an inert substance which then prevents the subsequent attachment of the active steroid. The differences between various classes of steroid, and the contrast between agonist and antagonist, often depend on minute structural differences, for example a single OH or CH_3 group in the whole 4-ring molecule. With the objective of gaining further insight into the subtle relationships between steroid structure and function, Dr. Ken Wynne has been exploring the effect of chemical modifications on receptor binding and tissue action.

In a collaborative study with the Medical Research Centre, Prince Henry's Hospital we have compared the effect of various replacement steroids in adrenal insufficiency. Our findings suggest that conventional therapy is probably not optimal in congenital hyperplasia or in subjects adrenalectomized for Cushing's disease.

Renin assays are now widely used in the investigation of patients with hypertension, but, until now samples have required a complicated collection procedure. By re-examining assay conditions we have validated a simple technique which allows routine heparinized samples to be transported and processed at room temperature. Using this simplified assay we have gained information on the value of renin measurement in the long-term management of adrenal insufficiency, mineralocorticoid hypertension, Bartter's syndrome and refractory heart failure.

LIST OF PROJECTS

1. Thyroid Hormone Physiology
   a. Familial euthyroid thyroxine excess
      —Characterization of the binding abnormality in terms of affinity, capacity and specificity
      —Determination of prevalence
      —Disulphide-dependence of binding
      —Molecular basis for binding abnormality
   b. Studies in non-thyroidal illness
      —Assessment of serum binding
      —Modified hormone delivery to tissues
      —Comparison of methodological differences in free hormone measurement
      —Central control of thyroid function
      —Studies after recovery from severe illness
   c. Studies of thyroid hormone dissociation and delivery to tissues
   d. Studies of T_4-analogue binding to lower affinity proteins in plasma
2. Steroids, Renin, Hypertension
      —Mechanisms of glucocorticoid-

induced vasoconstriction
—Simplified renin methodology
—Effect of Indomethacin during mineralocorticoid replacement
—Long-term studies of glucocorticoid-responsive hypertension
—Evaluation of glucocorticoid and mineralocorticoid replacement therapy

3. Collaborative projects (Dr. K. N. Wynne)
—Metabolism of aldosterone by kidney: relevance to modulation of hormone action
—Endocrine effects of Ginseng
—Catecholestrogens and thyroid function
—Mineralocorticoid activity of METEC (methyl ester of testosterone 17α ethynyl carboxyllic acid)

ABSTRACTS

Familial Euthyroid Thyroxine Excess

J. W. Barlow, E. L. White, J. Csicsmann, P. Taft, J. R. Stockigt

Abstracts

Our recently published studies have demonstrated that the excess of circulating thyroxine (T_4) in this condition is appropriate to maintain a normal free T_4 level in the face of increased plasma protein binding of T_4. The abnormal high-capacity T_4 binding site in the sera of affected subjects was separable from prealbumin and thyroxine-binding globulin, but multiple techniques failed to separate this binding site from albumin. Hence, we compared T_4 binding to albumin preparations isolated from the sera of normal and affected subjects. By equilibrium dialysis, affected subjects showed an extra T_4 binding site ($K_d \sim 50$ nM) in addition to the T_4 binding sites of normal albumin ($K_d \sim 4\,\mu M$). Capacity studies indicated that about one third of circulating albumin molecules contained the extra binding site. Estimates of capacity and affinity suggest that the abnormal binding site accounts for the observed doubling of normal total T_4 in order to maintain a normal free level.

Studies with the disulphide reducing agent, dithiothreitol, indicate that disulphide bonds are critical in maintaining the abnormal T_4-albumin association. Low concentrations of dithiothreitol (~ 1 mM) lead to a reversible decrease in the T_4 affinity of albumin without a change in capacity. This system may provide an important model for disulphide-dependent changes in hormone attachment to specific binding sites.

A screening test for this condition has been developed so that samples from ten subjects can be tested in a single tube. This procedure involves assessment of ^{125}I T_4 binding under conditions where the concentration of unlabelled T_4 is 100-fold greater than normal. The very high capacity of the abnormal binding site allows one abnormal sample to be detected amongst ten. Preliminary results suggest that familial euthyroid T_4 excess has a prevalence of between 1:10,000 and 1:30,000 in an Australian population of predominantly European background.

Studies in collaboration with Dr. Harald Meinhold demonstrated that specific T_3 receptors on lymphocytes were almost identical in normal and affected subjects, providing evidence against the suggestion that this condition represents a new type of hormone resistance.

Thyroid Function After Recovery from Hypothyroxinaemia of Severe Non-thyroidal Illness

P. J. Fuller, J. W. Barlow, E. L. White, D. M. Hurley, J. R. Stockigt

We have examined the possibility that impairment of compensatory TSH hypersecretion might be one cause of thyroid hormone deficiency during severe illness. Low levels of triiodothyronine (T_3) are frequently found during non-thyroidal illness, but it is now established that serum thyroxine (T_4) may also become subnormal. The latter finding is associated with high mortality. The free T_4 index (FT_4I) is usually low, but free T_4 levels have varied widely, depending on methods. It has been suggested that measurement of reverse T_3 (rT_3) may distinguish between hypothyroidism (low rT_3) and changes due to non-thyroidal illness (normal or high rT_3).

The possibility of transient illness-related secondary hypothyroidism must also be considered, in view of the recent demonstration that pituitary TSH secretion is depressed during severe illness. If such suppression occurred in patients who had diminished thyroid reserve before the onset of severe illness, thyroid hormone deficiency might be anticipated. A prospective study of this possibility is clearly not feasible. We therefore assessed thyroid function four to 24 months after recovery from severe prolonged illness associated with hypo-

thyroxinaemia. The ten patients reported (4 males, aged 28-75; 6 females, aged 53-71) were studied during and after recovery from renal failure, prolonged sepsis, severe pneumonia, burns or liver failure.

We found resolution of the low T_4, FT_4I and T_3 after recovery in nine of ten patients. At that time neither basal TSH nor its response to TRH was excessive, indicating that underlying thyroid function was probably normal. By contrast, one patient showed clear evidence of primary subthyroidism after recovery, although the previous TSH level during illness had not been increased. Serum rT_3 was subnormal during severe illness in two patients who subsequently had normal thyroid function. In fact, in only one case was the rT_3 elevated.

Conclusions: (i) Although associated with a poor prognosis, low T_4 during severe prolonged illness is compatible with survival. (ii) Studies after recovery suggest that underlying diminished thyroid reserve is uncommon in patients who survive severe illness associated with low T_4. (iii) Our findings in one case suggest that severe illness may impair the TSH hypersecretion of primary subthyroidism. (iv) During severe illness there may be great difficulty in identifying patients with underlying hypothyroidism or diminished thyroid reserve.

Endocrine Effects of Ginseng

K. N. Wynne, J. R. Stockigt, P. Pearce†, J. W. Funder†
†Medical Research Centre, Prince Henry's Hospital

Ginseng is an extract of the root of Panax ginseng, and is one of the oldest and most valued Chinese medicines. Recently, it has become widely available in the western world as a herbal tonic. Some modern studies have suggested that ginseng has an anti-stress effect due to an interaction with the hypothalamo-pituitary-adrenal axis and that over-use can cause side-effects of an endocrine nature. For these reasons, a concentrated mixture of ginsenosides (saponins of ginseng which are believed to be the active constituents) has been examined for ability to compete for classical steroid receptors.

Ginsenosides (2 mg/ml) from Red Korean Ginseng did not displace estrogen from estrogen receptors nor androgen from androgen receptors. However, this solution diluted 1 to 500, effectively competed with dexamethasone for glucocorticoid receptors and similarly, at 1:100 dilution, with aldosterone for mineralocorticoid receptors. A 1:6 dilution competed with R5020 for progesterone receptors. Work is proceeding to isolate the ten or eleven ginsenosides from ginseng by means of preparative high performance liquid chromatography so that further studies may be carried out.

Catecholestrogens and Thyroid Function

K. N. Wynne, I. Ekkel, J. R. Stockigt

Estrogens are oxidised in the human to either catecholestrogens or estriols. It has been reported that thyroid status influences the relative proportions of these metabolites. A catecholestrogen-antigen was synthesized and high titre antisera raised in sheep, allowing us to develop a specific radioimmunoassay for 2-hydroxy-catecholestrogens in plasma and acid-hydrolysed urine.

Consecutive urine specimens from normal subjects were assayed for catecholestrogens and estriol; and the ratio of the two metabolites was found to be reasonably constant for an individual but varied widely between individuals. Samples from subjects with thyroid disorders gave ratios within the range of normal variation. However, when the catecholestrogen to creatinine ratio was examined, most healthy subjects were within the range 1-3 nmoles 2-hydroxyestrone/mmole creatinine and the hypothyroid subjects so far studied were above this range. Further studies are in progress to determine whether such measurements give a valid index of diminished thyroid hormone action.

OVERSEAS AND AUSTRALIAN MEETINGS

During 1981, papers were presented at both meetings of the Endocrine Society of Australia, at the European and American Thyroid Association meetings and at the meeting of the Australian Association for Clinical Biochemists.

Dr. Stockigt presented a review of our studies of thyroid hormone binding at the Annual Seminar Conference of the Endocrine Society of Australia in Leura. Our findings in familial euthyroid T_4 excess were presented at the European and American Thyroid Association meetings, as well as forming part of

invited lectures in Rotterdam and Berlin. Dr. Fuller presented our work on thyroid function after recovery from severe illness in Christchurch. Mr John Barlow attended the American Thyroid Association meeting in Minneapolis and visited laboratories in San Francisco, Boston and Los Angeles. Ms. Judith Csicsmann attended the European Thyroid Association meeting in Pisa and visited research centres in Berlin and Budapest. Dr. Taft attended the International Symposium on Insulin Delivery Systems in Assisi in September. Dr. Douglas Lording was a guest lecturer at the III General Medical Conference in Bali and Singapore. Members of the Unit also gave lectures and presentations in Colac, Mildura, Launceston, Swan Hill, Traralgon, and Hamilton during 1981. At the Australian Association of Clinical Biochemists meeting papers were presented by Ms. Elizabeth White, Judith Csicsmann and Marianne DeGaris.

TEACHING AND SEMINARS

Seminars

Drs. Breidahl, Taft, Lording and Stockigt gave lectures and seminars in the 6th year Clinical School Teaching Programme and participated in the teaching of general medicine, diabetes and endocrinology to 4th, 5th and 6th year students.

Postgraduate teaching sessions were held weekly during the first half of the year. In addition, clinical lunchtime seminars were held twice monthly throughout the year. The following topics were presented during 1981:—

1. Bartter's syndrome
2. Androgen-producing adrenal adenoma
3. Electrocardiographic changes in diabetic ketoacidosis
4. Contrast media and thyroid function
5. CT scanning of prolactinomas
6. Therapeutic decisions in Cushing's disease
7. Hereditary abnormalities of thyroxine binding globulin
8. Adult hypophosphatasia
9. Potassium disturbances in haematological malignancy
10. Mineralocorticoid hypertension; localization of adrenal lesions
11. Management of hypoparathyroidism
12. Amiodarone and thyroid function
13. Hypercalcaemia due to occult sarcoidosis
14. Munchausen's syndrome in a diabetic
15. Differentiated thyroid carcinoma

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HOW TO SUPPORT MEDICAL RESEARCH INTO HEART AND VASCULAR DISORDERS

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- BEQUESTS
- GIFTS
- LEGACIES

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

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.....

bequeath to the Baker Medical Research Institute, Commercial Rd., Prahran, in the State of Victoria, to advance the work of the Institute, the sum of $..... free of all duties, for which the written acknowledgement of the Financial Director shall be sufficient discharge.

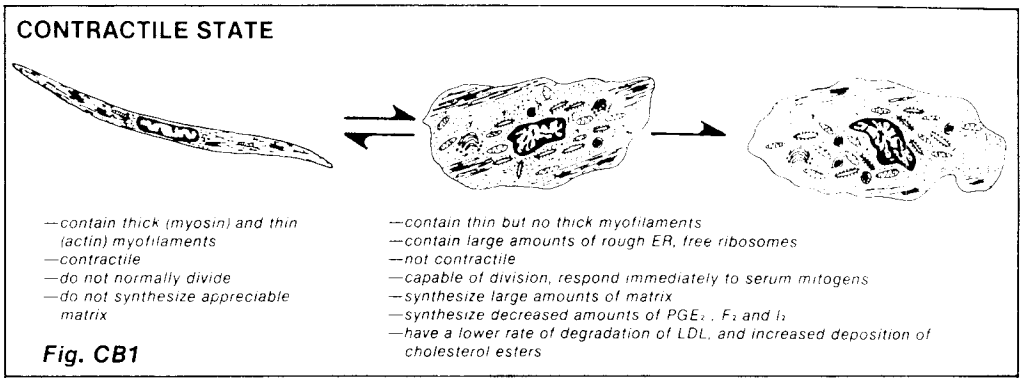


Fig. CB1

associated with the type of proliferation which leads to atherosclerosis.

Lipoprotein receptor binding by smooth muscle cells

During 1981 we studied the binding, uptake and degradation of low density lipoproteins (LDL) by arterial smooth muscle cells in culture. We studied the characteristics of contractile smooth muscle cells and compared them with those of cells in the synthetic state. We found that the receptor binding characteristics were not altered in the two cellular phenotypes. However, the ability of the synthetic state cells to metabolise LDL was significantly lower than that of cells in the contractile state. This resulted in an increased deposition of cholesteryl esters in cells of the synthetic state. The exact basis of these metabolic effects are not clear but they may be related to the changes in a particular enzyme system (lysosomal cholesteryl ester hydrolaze) in synthetic state cells.

Cell biology of the conducting system of the heart

The specialised conduction pathways of the heart ensure rhythmic and synchronized excitation and contraction.

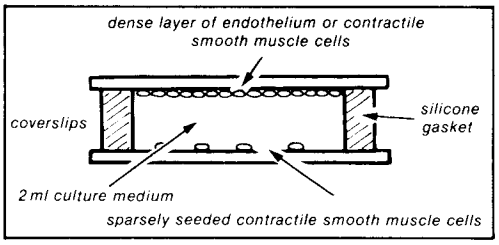
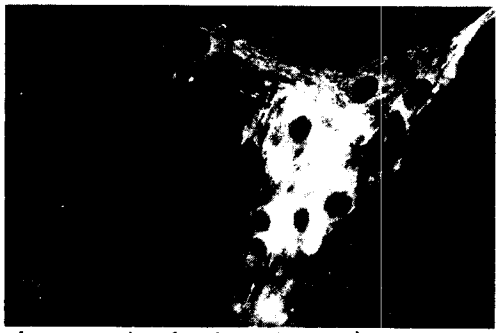


Fig. CB2

Cell culture system (Rose Chamber) used to demonstrate the capacity of endothelial cells to inhibit the modulation of smooth mucle cells contractile to synthetic states.

Any disturbance within this system, either at the site of origin or along the conduction pathways, can lead to cardiac arrhythmias. There are many different types of arrhythmias, but one of the most extreme examples is ventricular fibrillation which results in sudden death after heart attacks. Ventricular fibrillation often arises from a 'focus' of very irritable muscle fibres in the border zone around the dead muscle cells of a myocardial infarct.

We have recently developed a method for growing the conducting tissue (Purkinje fibres) of the heart in cell culture. This is an exciting development which will allow us to study some of the properties of this tissue under highly controlled conditions. To date we have determined that these cells contain large amounts of myosin muscle protein, which is immunologically identical to that in contractile heart muscle cells. However, in the Purkinje fibres it is not arranged in a sarcomere configuration similar to that of working myocardial cells.



An example of cultured rabbit Purkinje fibres stained with fluoresceinated antibodies to cardiac myosin. Studies of these cultured fibers are allowing new insight into the relationship between the conducting and working systems of the heart.

Cardiovascular Surgical Research Unit

General Summary

Projects

Optimal temperature for myocardial preservation

Surgical treatment of cardiac arrhythmias

Hospital costs and return to work after coronary bypass surgery

Treatment of infection in the pleural cavity

Antibiotic prophylaxis after coronary bypass surgery

Release of creatine kinase isoenzyme after coronary bypass surgery

Measurement of myocardial perfusion using hydrogen desaturation

Effect of lesions of the NTS on circulatory control in conscious rabbits

Contribution of vagally-innervated intrathoracic receptors, and carotid sinus baroreceptors, to the control of heart rate and renal nerve activity

Contrasting effects on heart rate of inflating caval, ascending aortic, and descending aortic cuffs

The unit's activities are in two principal fields: research and development in cardiac surgery (Dr. Rosenfeldt), and control of the circulation in the setting of surgery and resuscitation (Dr. Ludbrook).

Cardiac Surgery

During cardiac surgery a heart-lung machine (pump oxygenator) takes over the function of the heart and lungs. The blood flow through the heart can then be cut off, to provide the surgeon with a bloodless field, and the heart muscle is placed in a state of suspended animation (cardioplegia) by perfusing it with an iced solution containing potassium and other ions. The ions in the solution cause the heart to stop beating, and cooling the heart reduces its oxygen requirements, so that under ideal conditions the heart can safely remain in this protected state for two or more hours.

It is cooling which provides the main protection for the heart, and hence over the last few years we have investigated the theoretical and practical aspects of its

Anne Heal, Phillip Henenberg and Prof. Ludbrook studying baro-receptor reflexes in a rabbit

use in heart surgery. Our previous work has refuted the notion that the heart would be damaged by temperatures as low as 4-10 °C. However the view still prevails that during surgery cooling the heart from body temperature (37 °C) to room temperature (20 °C) provides adequate protection against damage. Recently we have shown in isolated dog hearts that further protection is achieved if the heart is cooled to 4 °C. The recirculating cooling circuit which has been developed at the Baker Institute enables the surgeon to cool the heart to 4-10 °C, and thus increases the margin of safety between damage and full recovery, particularly in long operations in the previously damaged heart.

Rhythm Disorders

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 arrhythmia may cause the patient suddenly to collapse and even die. Most of these rhythm irregularities can be controlled by drugs, but some patients continue to suffer disabling symptoms. In recent years some of these refractory cases have been successfully treated by operations to modify or interrupt the conducting system or, in some instances, to replace it by an implanted pacemaker. Alternatively, the area giving rise to abnormal impulses can be removed or electrically isolated from the rest of the heart. We now have a team to develop this surgical approach comprising cardiologists, surgeons and electronic engineers.

In 1981 an important advance was made, in that the team began to tackle the Wolff-Parkinson-White (WPW) Syndrome. Here the key to success is accurate localisation of abnormal conducting fibres by electrical mapping of the heart at operation. The design and testing of the mapping equipment was a joint venture between the Electronics Department of the Alfred Hospital and the Baker Institute. The initial design came from Dr. John Uther in Sydney. Following a period of testing of the equipment in dogs, during which members of the team gained skill in mapping the heart, the clinical program of operating on patients with the WPW syndrome was begun. In 1981 ten patients were treated and nine completely cured of their arrhythmias.

Costs of Coronary Surgery

An area of concern to the government and the public has been the escalating cost of health care. It is estimated that in 1980 there were 3800 coronary bypass graft procedures performed in Australia. In a collaborative venture with the Victorian Health Commission we assessed the cost to the Alfred Hospital of a coronary bypass procedure and the rate of return to work by patients 1-2 years after surgery. The cost to the hospital was calculated to be $4,700 per operated patient. The return-to-work survey of 100 patients aged 55 years and under, showed that before surgery 56 were working but only 16 at full capacity, compared with 77 working with 63 at full capacity after surgery.

Cardiovascular Control

Surgeons have much practical interest in circulatory control. Dr. Ludbrook is continuing his research on the way in which the arterial baroreceptors detect *changes* in blood pressure and are able to control the circulation during blood loss, over-transfusion, and in excessive dilution of the blood with blood substitutes. He is also studying the control of the circulation by these arterial baroreceptors in man and in rabbits during exercise. During 1981 in collaboration with Dr. Dorward, the work on arterial baroreceptors has been extended to study the effects on the activity of the sympathetic constrictor nerves to the kidney in a variety of circumstances.

To date much effort has gone into developing new techniques for elucidating how receptors in the heart, which sense changes in cardiac function, affect the circulation. Like the arterial baroreceptors these receptors, too, respond to changes in tension in the wall of the structures in which they lie. They are thus affected by changes in pressure in the heart chambers and by changes in blood volume. They are of potential importance in helping to resist the effects of blood loss, or of circulatory overload. Both problems occur with some frequency in the setting of clinical surgery and intensive care. They have not previously been studied with any precision in conscious animals or in man.

We have started work on this problem in conscious rabbits, following our previous finding that after arterial baroreceptor denervation it is still possible to elicit a pronounced

bradycardia by steep increases in blood pressure, and that in an isolated carotid sinus preparation the bradycardic response to elevation of systemic blood pressure greatly exceeds that to local elevation of carotid sinus pressure. This suggested that receptors in the left ventricle are still active in the conscious rabbit.

A method has been devised for determining the threshold of this reflex in conscious, baroreceptor-intact, rabbits. Inflatable cuffs placed on the ascending as well as the descending thoracic aorta, permit the left ventricular receptors and arterial baroreceptors to be differentially loaded. Catheters in the ear artery and ascending aorta permit determination of the degree of loading (or unloading) of the receptors. Catheters in the left atrium or ventricle indicate changes in left ventricular end-diastolic pressure. The animals can be studied with all receptors intact and, after arterial baroreceptor denervation, and immediately after cervical vagotomy.

Preliminary results indicate close correlations between onset of the bradycardia and the changes in arterial pressure, left atrial pressure and left ventricular end-diastolic pressure. It appears that a rise in ventricular blood pressure elevation with the physiological range evokes the left ventricular-heart rate reflex.

Ross Jacobs, Jenny Griffiths, Dr. Frank Rosenfeldt and Janet Ness of the Cardiac Surgical Research Laboratory.

Computer Services

The Institute acquired a PDP 11/23 computer in 1980 and also the invaluable services of Judy Gipps as programmer and statistician. In the first instance the computer has been used mainly for the needs of the neurophysiological laboratory where the problem of converting physiological signals into numbers and then into mathematically-defined curves has been greatest.

Mrs Judy Gipps (right) computing data with Dr Pat Dorward (left) and Sandra Burke

At present the facility is being adapted to allow some 'on line' facilities for data processing in the neurophysiological laboratory, but to make it available to others. This involves establishing satellite terminals, which will in the long run save money, since it will greatly reduce our usage of the Monash and Melbourne University Computer Centre facilities.

Biomedical Engineering Services

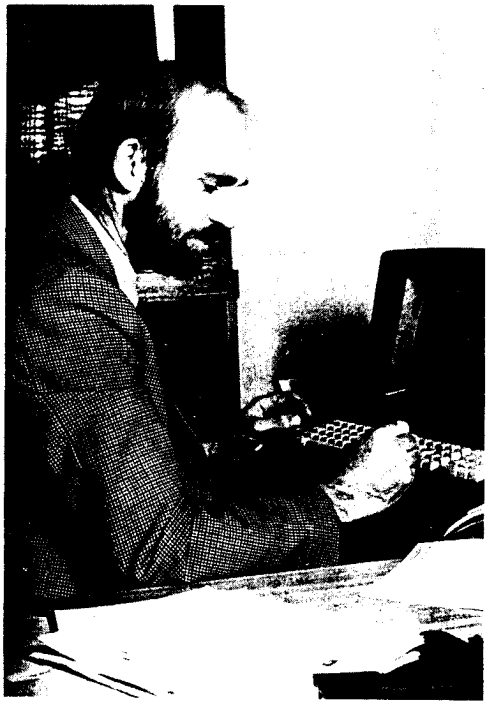
The electronics laboratory and mechanical workshop develop and build electronic and mechanical equipment that is not available commercially, and services equipment purchased overseas, when such a service is not locally provided. This type of facility is far more important in an Australian research institute than, for example, in a U.S. institute.

Falk Hannemann (Electronics Design Engineer) is in charge of the unit; other senior staff members are Kerin Harvey (Electronics Engineer) and John Baird (Instrument Maker). In addition Andrew Fry and David Bell are two apprentices. Major achievements during the past 12 months include the development of a computer controllable instrument for the measurement of cardiac output for non-invasive studies in the Clinical Research Unit; a mobile stereotaxic operating table and electronic support system for Professor Korner and Geoff Head's studies on brain stereotaxic mapping and lesions; pressure regulator for a roller pump (Cardiac Laboratory); a thermodilution cardiac output computer with digital display providing a direct readout (Kidney Laboratory) and a substantial improvement of the sonomicrometer for measurements of artery diameter by pulsed high-frequency ultrasound (Pharmacology Laboratory). Both electronic and mechanical improvements have been made in the design of several items of equipment, e.g. transducer amplifiers, heart period meters, integrators, and the Doppler blood flow measuring system in response to changing needs. The electronics laboratory has been much involved in making the present computer facility operational and in establishing the extended network of terminals and satellites.

Members of the Electronics Laboratory and Workshop: (L-R) Kevin Harvey, John Baird, Andrew Fry and Falk Hannemann (Head).

Secretarial Staff: (standing L-R) Clare Harwood, Kim Howard, Wendy Coleman, Karen Kerr, (seated L-R), Seah Lian-Kee, Marjorie Nicholson and Susan Weir

Librarian Mary Delafield with Ellison Rickards



Mr Ian Dodds, Finance Officer at the Accounts Computer

Laboratory Supervisor Chris Lewis (right) and his assistant Rohan Vaughan

Publications

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CARDIOVASCULAR SURGICAL RESEARCH UNIT

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SUMMER VACATION STUDENTSHIPS

Each summer vacation we have post-graduate and post-doctoral training programs. In order to give prospective students an introduction to medical research the Institute offers a number of summer vacation studentships.

With support from the National Heart Foundation or the Australian Kidney Foundation, 20 studentships were offered to science or medical students in the 1981/82 summer vacation period. These awards provided financial support for a six weeks' period during which time the students were able to participate in one of the current research projects. This year the students submitted a report of their research work and four prizes were awarded for the best contributions. The overall standard of the reports was high and showed considerable appreciation of the research problem. The students made useful and significant contributions within the laboratory. Best reports this year come from Andrew Byrne, Russell Bourne, Sophie Constanides and David Hillis.

The advantage of these studentships is that it gives them a taste for research in this field, and what may be involved in an honours year or in a postgraduate research programe.

Staff activities and overseas visits

HYPERTENSION AND CIRCULATORY CONTROL

Dr. J. Angus—visited the Wellcome Research Laboratories in April, 1981; the International Pharmacological Congress in Tokyo (July, 1981) and a satellite on 'Molecular Pharmacology of Neurotransmitter-Receptor Systems' in Hiroshima.

Dr. W. Anderson—visited the meeting of the American Council of High Blood Pressure Research, Cleveland (September, 1981), the Division of Renal Medicine, Colorado and the Department of Physiology, University of Mississippi.

Dr. M. Esler—attended meeting of International Society of Hypertension in Milan (May, 1981) and Workshop on Adrenergic Receptors in Basel (June, 1981); meeting of International Society of Hypertension (Mexico City, February, 1982).

Dr. G. Jennings—attended Symposium on Hypertension, London (May, 1981) and meeting of International Society of Hypertension in Milan (May, 1981).

Professor P. Korner—attended Symposium on Hypertension, London (May, 1981), International Society of Hypertension (Mexico City, 1982), Satellite on Alpha-receptors (Palm Springs, California), and visited the Havard Medical School, the University of Mississippi, the Cardiovascular Center of the University of Iowa and the Cardiovascular Research Institute of the University of California at San Francisco.

Professor Korner has been much involved as President of the International Physiological Congress to be held in Sydney August/September, 1983.

CARDIOVASCULAR METABOLISM AND NUTRITION RESEARCH UNIT

Dr. N. Fidge—attended the meeting of the Council on Arteriosclerosis, American Heart Association in Dallas, Texas (November, 1981) and visited the Department of Medicine, University of Texas, Cardiovascular Research Institute, University of California and the Gladstone Research Foundation in San Francisco.

Dr. P. Nestel—participated in the First International Symposium on Acarbose in Montreux, Switzerland (October, 1981); Council on Arteriosclerosis, American Heart Association meeting in Dallas, Texas (November, 1981); International Symposium on Nutritional Aspects of Atherosclerosis in Tokyo (February, 1982). He visited laboratories in the University of Texas Health Sciences Center, Dallas as well as the Cardiovascular Research Institute, University of California and the Gladstone Research Foundation in San Francisco.

Dr. K. O'Dea—visited the Department of Medicine, University of Dusseldorf, laboratories of INSERM in Paris, Department of Gastroenterology, Central Middlesex Hospital. She attended the First International Symposium on Acarbose in Montreux, Switzerland (October, 1981).

Dr. M. Reardon—attended the American Heart Association meeting in Dallas, Texas (November, 1981) and visited the Department of Medicine, University of Texas in Dallas and the Departments of Medicine and Nutrition, University of Toronto.

CARDIOVASCULAR SURGICAL RESEARCH UNIT

Dr. J. Ludbrook—attended the International Society of Hypertension in Milan (June, 1981); the International Congress of Nephrology in Athens (June, 1981); the International Surgical Group meeting in Uppsala, Sweden (September, 1981) and the International Vascular Symposium in London (September, 1981).

SPECIAL SEMINARS — 1981

8 April	Antibodies to insulin and β - adrenoceptors: application to study of receptor structure and function	Dr. L. Harrison, Royal Melbourne Hospital
14 July	Science for heroes	Prof. B. Morris, John Curtin School of Medical Research, ANU.
10 August	Cerebral aneurysms	Prof. W. E. Stehbens, Dept. of Pathology, Wellington Clinical School, N.Z.
12 August	CNS organisation of cardiovascular pathways	Dr. R. Dampney, Dept. of Physiology, University of Sydney
1 September	Functional organisation of pre- and post-ganglionic vasoconstrictor system supplying skin and skeletal muscle	Prof. W. Jänig, Dept. of Physiology, Christian-Albrechts University, Kiel, German Fed. Rep.
14 September	Hydrophilicity of β -blocking drugs and β_1-selectivity	Dr. J. Cruickshank, ICI, U.K.

BAKER INSTITUTE IN-HOUSE SEMINARS—1981

23 March	Therapeutic implications of dihydroergotamine kinetics in man	Dr. P. Little, C.R.U.
13 April	Smooth muscle reactivity and atherogenesis — LDL metabolism and response to serum mitogens differ according to phenotype	Dr. Julie Campbell, Baker Institute
27 April	Liver, blood flow and drug clearance	Dr. A. McLean, Baker Institute
25 May	Influence of high cholesterol and high carbohydrate diets on apolipoprotein C kinetics	Dr M. Huff, Baker Institute
22 June	Control of transmitter release at cardiac nerve terminals	Dr J. Angus, Baker Institute
13 July	Blood volume and baroreceptor reflexes	Dr. J. Ludbrook, Baker Institute
27 July	A new lipoprotein synthetic pathway responsible for the development of type III hyper-lipoproteinaemia	Dr. M. Reardon, Baker Institute
10 August	Metabolic response to low carbohydrate/high protein diet (traditional diet) in Australian Aborigines	Dr. Kerin O'Dea, Baker Institute
24 August	The relationship between temperature and the degree of myocardial protection during heart surgery	Dr. F. Rosenfeldt, Baker Institute

BAKER INSTITUTE/PRINCE HENRY'S HOSPITAL JOINT HYPERTENSION SEMINARS — 1981

2 March	Potential mechanisms producing coronary artery spasm	Dr. J. Angus, Baker Institute
16 March	Potentiation by captopril of vasodilatation produced by nitroprusside	Dr. G. Jennings, C.R.U.
30 March	First-pass hepatic extraction of propranolol in man is not stereo-selective	Dr. G. Jackman, C.R.U.
6 April	Kinins and renal haemodynamics	Dr. B. Clappison, P.H.H.
4 May	Prostaglandins and renal blood flow and renin release	Dr. W. Anderson, Baker Institute
29 June	Role of central monoamines in reflex circulatory control	Dr. G. Head, Baker Institute

6 July	The kallikrein-kinin system in acute renal failure	Dr. G. Mathews, P.H.H.
31 August	CNS alpha-receptors in experimental hypertension	Dr. M. Morris, P.H.H.
7 September	The causes of hypertension	Prof. P. Korner, Baker Institute
21 September	Studies in autonomic insufficiency	Dr's G. Jennings, A. Bobik and M. Esler, Baker Institute and C.R.U.
5 October	Calcium antagonists in coronary vasospasms	Dr's J. Angus and R. Brazenor, Baker Institute
19 October	Catecholaminergic and dopaminergic nerves and the kidney	Dr. B. McGrath, P.H.H.
16 November	Release of creatine kinase MB isoenzyme after cardiac bypass surgery	Dr. F. Rosenfeldt, Baker Institute
30 November	A new angiotensin converting enzyme inhibitor	Dr. B. Jackson, P.H.H.
7 December	Regional noradrenaline release in dogs and humans	Dr's P. Blombery and M. Esler

BAKER INSTITUTE — FLOREY INSTITUTE WORKSHOP 24 JULY 1981

The research efforts of our two research institutes complement each other and this really comes across in the joint workshop. Members of one institution selected the speakers from the other and we learned a great deal about each other's techniques and approach. The meeting lasted the whole afternoon and was followed by a buffet meal at the Baker Institute.

The programme was as follows:—

Genes and Environment
(Chairman — D. Denton)
H. Niall:— Evolution of peptide hormones
K. O'Dea:— Diseases of affluence and the Australian Aborigines
J. Coghlan:— DNA probes and hybridization histochemistry
P. Nestel:— Lipoprotein genotype and fat transport

Hormones and Receptors
(Chairman — P. Korner)
R. D. Wright:— Parathormone
A. Bobik:— Cellular actions of catecholamines
B. Kemp:— Cellular actions of peptides
M. Reardon:— Cellular actions of apoproteins
M. Wintour-Coghlan:— ADH in the foetus
R. Brazenor:— 5HT receptors in coronary artery
B. Hudson:— Inhibin
W. Anderson:— Renal prostaglandins

Hypertension and Circulatory Control
(Chairman — B. Scoggins)
P. Korner:— Hypertension research, 1981
B. Scoggins:— Steroids in hypertension
M. Esler:— Sympathetic nervous system in human hypertension
R. Weisinger:— Central nervous control of salt appetite
J. Ludbrook:— Saline ≠ blood

VISIT OF PROFESSOR ROBERT WISSLER

Prof. R. Wissler

Professor Robert W. Wissler recently visited Australia as guest of the National Heart Foundation's Sixth Triennial Conference. Subsequently he spent several days at the Baker Institute as guest of our Cellular Biology group. Professor Wissler is Donald N. Pritzker Distinguished Service Professor of Pathology at the University of Chicago. He is also Director of their Atherosclerosis Center of Research.

On the occasion of his visit a workshop was held on 24 February 1982 on 'Cellular Pathobiology of Atherosclerosis'. Speakers at this meeting included Professor Bill Connor (who discussed lipid turnover in atherosclerotic plaques), Professor Allan Day (platelet-macrophage-lipoprotein interactions), Professor David Penington (platelets in vascular disease), Dr. Julie Campbell (smooth muscle-endothelial interactions), Professor Jack Martin (regulation of endothelial cell activity), A/Professor Barry Gow (endothelial changes in post-stenotic dilatation) and Dr. J. A. Angus (pharmacological intervention).

BAKER MEDICAL RESEARCH INSTITUTE

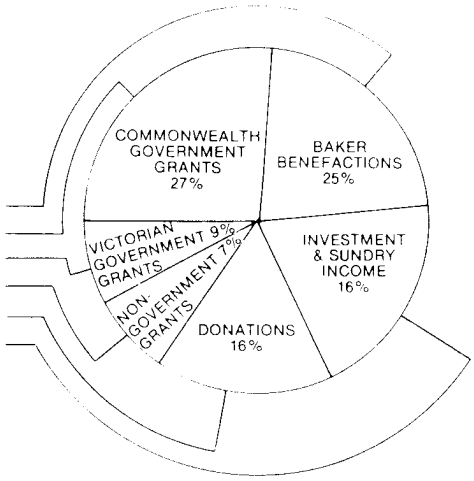
YEAR ENDED 31 DECEMBER 1981

FINANCIAL REPORTS

Income and Expenditure at a glance

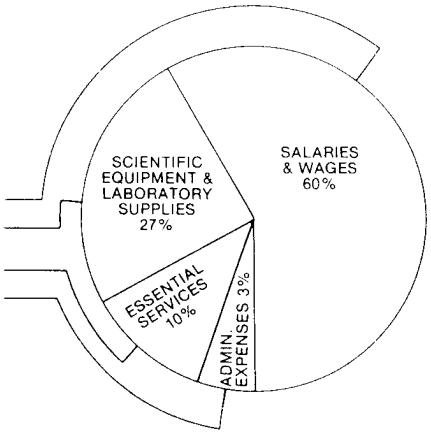
INCOME DERIVED FROM THE FOLLOWING SOURCES:

1980 000's	1980 %		1981 000's	1981 %
356	22	Baker Benefactions	517	25
421	26	Government Grants— Commonwealth	574	27
140	9	Government Grants—Victorian	185	9
138	9	Non-Government Grants	137	7
233	15	Donations	336	16
310	19	Interest from Investments and Sundry Income	343	16
1598	100		2092	100



EXPENDITURE DISTRIBUTED AS FOLLOWS:

1980 000's	1980 %		1981 000's	1981 %
1041	64	Salaries & Wages	1284	60
362	23	Scientific Equipement and Laboratory Supplies	569	27
164	10	Essential Services	209	10
48	3	Administrative Expenses	54	3
1615	100		2116	100



BAKER MEDICAL RESEARCH INSTITUTE

BALANCE SHEET AT 31 DECEMBER 1981

ACCUMULATED FUNDS AND LIABILITIES	1981	1980
OPERATING FUND		
Accumulated (deficit)—Page 71	**(116,924)**	(91,601)
Bank overdraft	**35,822**	57,590
Sundry creditors and accrued expenses	**177,105**	131,930
	96,003	97,919
ENDOWMENT FUND		
Accumulated fund—Page 72	**1,225,122**	1,283,566
RESEARCH SCHOLARSHIP AND OTHER FUNDS		
Restricted fund—Page 72	**59,068**	15,618
Edgar Rouse Memorial Fellowship Fund—Page 73	**77,713**	67,230
Laura Nyulasy Scholarship Fund—Page 73	**2,875**	3,405
William Buckland Research Fund—Page 73	**31,712**	31,337
Lang Research Scholarship Fund	**4,852**	4,852
	176,220	122,442
	$1,497,345	$1,503,927

These Accounts should be read in conjunction with the notes on page 74.

ASSETS			1981	1980
OPERATING FUND ASSETS				
Cash on hand			**300**	300
Sundry debtors			**35,703**	56,119
Short term deposits (at cost) held by Trustees of the Institute—			**60,000**	41,500
			96,003	97,919
ENDOWMENT FUND ASSETS				
Investments (at cost)—Note 3				
Held by Trustees of the Institute				
Freehold properties	40,000			40,000
Government and semi-government stock	83,124			86,124
Shares and debentures in companies	157,756			145,197
Short term deposits	26,500			14,000
Mortgage loans	345,000			356,000
		652,380		641,321
Held by the Trustees, Executors & Agency Co Ltd—				
Shares in companies	69,158			67,335
Trust units	84,000			548,719
Short term deposits	7,200			7,200
Mortgage loans	402,050			
		562,408		623,254
Cash at bank		10,334		18,991
			1,225,122	1,283,566
RESEARCH SCHOLARSHIP AND OTHER FUND ASSETS				
Investments (at cost):— Note 3				
Held by Trustees of the Institute				
Shares in companies		4,852		8,817
Short term deposits		59,000		59,000
		63,852		67,817
Held by The Trustees, Executors & Agency Co Ltd—				
Shares in companies	8,937			4,852
Trust units	25,504			25,204
Short term deposits	2,947			2,800
		37,388		32,856
Cash at bank		74,980		21,769
			176,220	122,442
			$1,497,345	$1,503,927

BAKER MEDICAL RESEARCH INSTITUTE

YEAR ENDED 31 DECEMBER 1981

STATEMENT OF INCOME AND EXPENDITURE — OPERATING FUND

INCOME —		1981	1980
DONATIONS FROM BAKER BENEFACTIONS			
Statutory amount	11,569		11,569
Transfers from Endowment Fund	505,258		344,911
		516,827	356,480
OTHER DONATIONS (Net of transfers)		**335,799**	233,374
GRANTS-IN-AID OF RESEARCH PROJECTS			
Life Insurance Medical Research Fund of Australia and New Zealand	30,000		40,178
National Health and Medical Research Council	574,164		420,518
National Heart Foundation of Australia	71,143		94,971
		675,307	555,667
OTHER GRANTS			
The James and Elsie Borrowman Research Trust	9,500		Nil
The William Buckland Research Fund	2,461		2,500
Victorian State Government	185,000		140,000
Laura Nyulasy Research Scholarship Fund	945		Nil
Clive & Vera Ramaciotti Foundations	11,842		
Australian Associated Brewers	11,032		
		220,780	142,500
INTEREST FROM INVESTMENTS			
Held by Trustees of The Baker Institute Grant Trust	4,590		3,461
Other investment income	186,674		173,412
		191,264	176,873
OTHER INCOME			
Rentals	7,180		12,013
Sundry sales, recoveries and refunds	144,113		120,966
		151,293	132,979
Deficit for the year		**25,323**	17,616
		$2,116,593	$1,615,489

These Accounts should be read in conjunction with the notes on page 74.

EXPENDITURE—	1981	1980
Salaries and wages	**1,284,224**	1,040,640
Laboratory supplies and isotopes	**174,889**	148,695
Additional equipment and building costs	**291,310**	116,385
Library Maintenance	**30,773**	18,817
Postage and telephone	**15,736**	12,673
Printing and stationery	**27,202**	24,674
Light and power	**63,216**	46,145
Insurance	**19,080**	15,678
Repairs and renewals	**39,046**	34,385
Animal house contribution	**9,000**	9,000
Collaborative Grant — NH & MRC Programme	**55,000**	54,000
Travelling expenses	**43,306**	35,439
Public relations	**10,276**	5,637
Stanhope Court	**3,080**	1,131
Fund raising expenses	**40,477**	41,476
Sundries	**9,978**	10,714
	2,116,593	1,615,489

STATEMENT OF MOVEMENT IN ACCUMULATED FUND

OPERATING FUND		
Deficit for year	**25,323**	17,616
Accumulated deficit as at 1/1/1981	**91,601**	73,985
Accumulated deficit as at 31 December—Page 68	**$116,924**	$91,601

BAKER MEDICAL RESEARCH INSTITUTE

YEAR ENDED 31 DECEMBER 1981

STATEMENT OF MOVEMENT IN ACCUMULATED FUNDS

		1981	1980
ENDOWMENT FUND			
Balance at 31 December 1980		**$1,283,566**	$1,498,617
Donations—Baker Benefactions	527,758		393,359
—Victorian State Government			90,000
Interest	365		—
Profit on sale of shares	10,597		—
Other income	119		378
		538,839	483,737
		1,822,405	1,982,354
Bank Interest and Overdraft Charges	38		1,054
Transfer to Operating Fund	505,258		344,911
Loss on sale Common Fund	62,669		—
Adjustment to Share Investments	567		—
Building maintenance and renovations	13,209		—
Cost of motor vehicles	15,542		—
Biology Research Unit Extension	—		352,704
Transfer to William Buckland Fund	—		119
		597,283	698,788
Balance at 31 December 1981—Page 68		**$1,225,122**	$1,283,566

NOTE: Interest received on Endowment Fund assets is credited direct to the Operating Fund.
Income from the Lang Research Scholarship Fund has been credited directly to the Endowment Fund

RESTRICTED FUND			
Balance at 31 December 1980		**$15,618**	$37,323
Baker Benefactions Statutory Amount 1982	—		11,569
Donations	45,000		7,000
Investment income and bank interest	255		194
Transfer from Operating Fund	3,000		
Grants and scholarships	10,764		
		59,019	18,763
		74,637	56,086
Transfer to Operating Fund			
—Baker Benefactions Statutory Amount 1981	11,569		11,569
Donations, Grants and Other income	4,000		28,899
		15,569	40,468
Balance at 31 December 1981—Page 68		**$59,068**	$15,618

NOTE: Baker Benefactions Statutory amount for 1982 will be credited directly to Endowment Fund.

These Accounts should be read in conjunction with the notes on page 74.

		1981	1980
EDGAR ROUSE MEMORIAL SCHOLARSHIP FUND			
Balance at 31 December 1980		**$67,230**	$58,302
Donations	1,936		2,260
Investment income and bank interest	8,547		6,668
		10,483	8,928
		77,713	67,230
Transfer to Operating Fund—Other Income		**Nil**	Nil
Balance at 31 December 1981—Page 68		**$77,713**	$67,230
LAURA NYULASY SCHOLARSHIP FUND			
Balance at 31 December 1980		**3,405**	2,873
Investment income (net)		**415**	300
Other			232
		3,820	3,405
Transfer to Operating Fund (Scholarship)		**945**	
Balance at 31 December 1981—Page 68		**$2,875**	$3,405
WILLIAM BUCKLAND RESEARCH FUND			
Balance at 31 December 1980		**31,337**	30,757
Investment income (net)		**2,956**	2,739
Transfer from Endowment Fund			119
Other Income		—	222
		34,293	33,837
Purchase of shares	120		
Transfer to Operating Fund	2,461		
		2,581	2,500
Balance at 31 December 1981—Page 68		**$31,712**	$31,337

BAKER MEDICAL RESEARCH INSTITUTE

YEAR ENDED 31 DECEMBER 1981

NOTES TO AND FORMING PART OF THE ACCOUNTS

1. INCORPORATION

On 1 August 1980, The Thomas Baker, Alice Baker and Eleanor Shaw Medical Research Institute was incorporated as the "Baker Medical Research Institute" under the Baker Medical Research Institute Act 1980. At this date the assets and liabilities of the original Institute were vested in the new Baker Medical Research Institute at book value.

2. STATEMENT OF ACCOUNTING POLICIES

The following accounting policies of the Institute, which are consistent with those applied in the previous years, are as follows:

(a) Historical Cost

The accounts of the Institute are prepared on the basis of historical cost and unless otherwise stated do not take into account the effect of changing money values or current valuations of non-current assets.

(b) Institute Funds, Income and Expenditure

The work of the Institute is financed from grants, endowments, donations and bequests of both general and specific natures. Income is taken to specific funds depending on the terms of any relevant covenants applying to that income.

Other income and expenditure is accounted for on an accrual basis. Any deficiency arising therefrom is carried forward in the Operating Fund.

(c) Capital Expenditure and Depreciation

Capital expenditure made by the Institute in respect of buildings, furniture and equipment in present and past periods has been charged against appropriate funds, grants or revenue accounts and expensed in the period in which it was incurred. Accordingly, no depreciation charge appears in the Institute's accounts.

The insurable value of such accumulated capital expenditure, including buildings, to 31 December 1981 was approximately $8,742,000 (1980 $6,550,000).

3. INVESTMENTS

The market value of shares in companies listed on the Australian Stock Exchange at 31 December 1981 was $447,630 (1980 $474,389).

The Trustees, Executors & Agency Co Ltd is the custodian and manager of certain 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.

4. STAFF ENTITLEMENTS

The Institute does not provide for long service leave or holiday pay in the accounts. The liabilities at 31 December 1981 amounted to; holiday pay $85,002 (1980 $28,120) and long service leave $56,508 (1980 $30,574).

5. CONTINGENT LIABILITY

A contingent liability exists where the Institute has indemnified a staff member in a libel action brought against him in circumstances where he was representing the Institute. The action is presently pending and it is the opinion of the solicitors of the Institute and the Board of Management that the result of this action cannot be assessed at this time.

6. ETHEL MARY BAILLIEU FUND

The assets of the Ethel Mary Baillieu bequest, although recorded and accounted for by the Baker Institute, do not form part of these accounts and are not audited by us.

Auditors Report to the Board of Baker Medical Research Institute.

In our opinion the balance sheet, statement of income and expenditure and statements of movement in accumulated funds, as set out on pages 68 to 74 are properly drawn up to show a true and fair view of the state of the Institute's affairs at 31 December 1981.

PRICE WATERHOUSE
E. A. ALEXANDER
A member of the firm,
Chartered Accountants.

Melbourne
16th February 1982

DONATIONS 1981

Victorian State Government	$185,000.00
Estate of Emily E. E. Stewart	63,680.92
Allan Williams Trust Fund	22,000.00
Anonymous	20,000.00
Sandoz Australia Pty. Ltd.	18,265.00
Estate Mrs P. H. Dickie	12,500.00
I.C.I. Australia Ltd.	12,000.00
The Ian Potter Foundation	10,000.00
I.C.I. Australia Ltd.	12,000.00
Clive & Vera Ramaciotti Foundations	11,842.00
Australian Associated Brewers	11,032.00
The Ian Potter Foundation	10,000.00
I.C.I. Research	9,999.99
James & Elsie Borrowman Research Trust	9,500.00
Percy Baxter Charitable Trust	7,000.00
Estate of Mrs Anna White	5,000.00
The Windermere Hospital Foundation	5,000.00
Dame Elisabeth Murdoch	5,000.00
Australian Consolidated Ind. Ltd.	5.000.00
ANZ Banking Group Ltd.	5,000.00
Esso Australia Ltd.	5,000.00
Ciba-Geigy	4,500.00
Boehringer Ingelheim Pty. Ltd.	4,000.00
H. & L. Hecht Trust	4,000.00
The Wm. Angliss (Vic.) Charitable Fund	4,000.00
Australia/Japan Foundation	4,000.00
George Thomas & Lockyer Potter Charitable Trust	3,600.00
Appel Family Bequest	2,800.00
Estate of the Late Edward Wilson	2,500.00
B.H.P. Co. Ltd.	2,500.00
The William Buckland Research Fund	2,461.00
G. J. Coles & Co. Ltd.	2.250.00
Bell Charitable Fund	2,000.00
E. H. Flack Estate	1,825.00
Mrs B. Hewitt	1,250.00
Prof. P. I. Korner	1,050.00
William Paxton Charitable Fund	1,000.00
Kodak (A/Asia) Pty. Ltd.	1,000.00
The Arthur Anderson & Co. Foundation	1,000.00
Ansett Transport Industries Ltd.	1,000.00
Robert Bosch (Aust.) Pty. Ltd.	1,000.00
CRA Services Ltd.	1,000.00
The Chamber of Manufacturers Ins. Ltd.	1,000.00
Mr W. Chin	1,000.00
Comalco Limited	1,000.00
Commercial Bank of Australia Ltd.	1,000.00
Commercial Bank of Australia Ltd.	1,000.00
Charles Davis Limited	1,000.00
EZ Industries Ltd.	1,000.00
Endeavour Resources Ltd.	1,000.00
The Herald & Weekly Times Ltd.	1,000.00
Hooker Corporation Ltd.	1,000.00
Industrial Equity Limited	1,000.00
North Broken Hill Holdings Ltd.	1,000.00
Permewan Wright Cons. Pty. Ltd.	1,000.00
Potter Partners	1,000.00
Rayson Industries Pty. Ltd.	1,000.00
Red Tulip Chocolate Pty. Ltd.	1,000.00
Royal Insurance	1,000.00
David Syme & Co. Ltd.	1,000.00
Sportscraft Consolidated Pty. Ltd.	1,000.00
J. B. Were & Son	1,000.00
George Weston Foods Ltd.	1,000.00
Estate A. H. Cook	1,000.00
E. B. Myer Charity Fund	1,000.00
Laura Nyulasy Research Scholship. Fund	945.00
CBA Travel Services Ltd.	830.00
Clonakilty Pty. Ltd.	800.00
The Shell Co. of Australia Ltd.	650.00
Rev. Leahy	600.00
Estate Mrs C. M. Nesbitt	500.00
Ajax Fasteners Australia Ltd.	500.00
Aust. International Finance Corp. Ltd.	500.00
Acmil Ltd.	500.00
Bank of N.S.W.	500.00
Commonwealth Banking Corporation Ltd.	500.00
Carlton & United Breweries	500.00
Courtaulds Hilton Limited	500.00
Crawfords Productions Pty. Ltd.	500.00
J. Gadsden Australia Ltd.	500.00
Mayne Nickless Ltd.	500.00
McCaughan Dyson & Co.	500.00
McPherson's Limited	500.00
Nabisco Pty. Ltd.	500.00
Reckitt & Coleman Australia Ltd.	500.00
Woolworth's (Vic) Ltd.	500.00
Wormald International Limited	500.00
George Frederick Little Settlement	470.00
Ms. M. A. Simpson	350.00
Blake & Riggall	300.00
Sir Laurence & Lady Muir	300.00
Mrs M. I. Pierce	300.00
McIllwraith-Davey & Co. Pty. Ltd.	250.00
Monsato Australia Limited	250.00
Repco Limited	250.00
Ford Motor Co. of Australia Ltd.	250.00
Messrs. A. C. Goode & Co.	250.00
Mr F. Murphy	250.00
Mr F. K. Alfredson	250.00
Mr A. J. Risstrom	230.00
Mrs G. Ansell	200.00
Mrs K. R. Ansell	200.00
H. & I. Arnhold	200.00
Sir Robert Blackwood	200.00
Makmur Enterprises Pty. Ltd.	200.00
Mr J. Moir	200.00
Mr H. Schreiber	200.00
Mr J. Taylor	200.00
Mrs M. C. Volum	200.00
Mr B. J. Walter	200.00
Barclays International Australia Ltd.	200.00
Cadbury Schweppes Pty. Ltd.	200.00
W. A. Deutscher Pty. Ltd.	200.00
Guthrie Operations Pty. Ltd.	200.00
Hewlett Packard Australia Pty. Ltd.	200.00
Hendersons Industries Ltd.	200.00
Mr H. R. Holdenson	200.00
Dr. H. B. Kay	200.00
Mr J. R. McDonnell	200.00
Oakbridge Limited	200.00
Bly's Industries Pty. Ltd.	200.00
CTM Nominees Pty. Ltd.	200.00
Ms A. P. Kennedy	175.00

Mrs E. Parker	175.00
Mrs M. Vernon	160.00
Mrs A. Bottomley	150.00
Mr & Mrs M. A. Cuming	150.00
Miss H. D. Glascodine	150.00
Mrs E. G. Hunter	150.00
Mrs D. Newton	150.00
Mr K. Oppenheimer	150.00
Messrs. Arthur Robinson & Co.	150.00
Miss M. Stanistreet	150.00
Mr I. D. Swansson	150.00
C.I.G. Medishield	150.00
Mr A. H. Ansell	125.00
Mrs L. Porter	125.00
Norlane Bowling Associates	109.00
Mr H. P. Blaich	100.00
S. Bude	100.00
Mrs M. Y. Bull	100.00
Mr D. P. Chan	100.00
Dr. H. C. Chan	100.00
Mr G. W. Chatfield	100.00
Dr. D. Chong	100.00
Dr E. P. Choo	100.00
Christian Womens Fellowship	100.00
Mr B. T. Corrigan	100.00
Cypress & Sons Pty. Ltd.	100.00
Sir Peter Derham	100.00
Mrs M. A. Dobson	100.00
Mr C. Emery	100.00
Euglo Nominees Pty. Ltd.	100.00
Mr L. K. Farmer	100.00
Mr L. M. Francome	100.00
Mr L. A. Gadsden	100.00
Mr H. H. Gillbank	100.00
Mrs B. L. Glascodine	100.00
Mr A. J. Glasson-Williams	100.00
Mr R. Goldenberg	100.00
Dr J. S. Guest	100.00
Mr & Mrs J. C. Habersberger	100.00
Mr P. Haddad	100.00
Mr B. Halpern	100.00
Mrs H. Handbury	100.00
Mr T. Holden	100.00
Dr S. J. Iceton	100.00
Mr A. P. Kelly	100.00
Mrs E. Korner	100.00
Mr N. R. Korner	100.00
Mr A. Leitch	100.00
Mrs. J. Ling	100.00
Mr R. W. Lister	100.00
Sir James McNeill	100.00
Mr A. J. Marriott	100.00
Mrs D. M. Martin	100.00
Mr E. R. Meagher	100.00
Miss G. B. Murray	100.00
Mr R. E. Nelson	100.00
Dr H. K. Ng	100.00
Mr J. D. Noack	100.00
Mr J. G. Reade	100.00
Mrs B. A. Richardson	100.00
Mr R. A. Ritchie	100.00
Mr K. Rogers	100.00
Mr E. Smorgan	100.00
The Southsiders	100.00
John Stansfield-Smith & Sons	100.00
Mrs A. K. Stewart	100.00
Dr G. Stirling	100.00
Mrs L. L. Sullivan	100.00
Mr S. Sunamura	100.00
Mr H. E. Towers	100.00
Mr A. J. Williams	100.00
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General Summary

The variety of interests of the Clinical Research Unit which include hypertension, hyperlipidaemia, peripheral vascular disease, clinical pharmacology, postural hypotension and other cardiovascular and metabolic diseases have ensured that 1981 has been a busy and productive year, both for patient care and for clinical research. Progress in some of these fields is outlined in other sections of the Baker Institute Report.

In the field of hypertension we have mainly been involved in improving tests of sympathetic function, using measurement of the apparent rate of secretion of noradrenaline and its reuptake into sympathetic nerve endings, and studying the effects of beta-adrenoceptor simulation as a method of determining receptor sensitivity and number in man. We have made a major effort to validate our non-invasive method of measuring cardiac output by the Indirect Fick Method, as we expect this to play an important part in our future studies of the causes of essential hypertension and on the mechanisms of benefit to the cardiovascular system of physical activity. The method is invaluable in a large number of investigations on the effects of cardiovascular drugs in man.

List of Projects

1. Comparison of the Indirect Fick and thermodilution methods for measurement of cardiac output in man.
2. Pathogenesis and treatment of postural hypotension due to autonomic insufficiency.
3. Haemodynamic effects of prenalterol.
4. Efficacy of a long-acting beta blocker, LT 31-200, in essential hypertension.
5. Drug treatment of pulmonary hypertension.

Comparison of the Indirect Fick and thermodilution methods for measurement of cardiac output in man

G. Jennings, M. Hargreaves

Although the Indirect Fick method has been used for many years as a non-invasive way of determining cardiac output during exercise, it's validity at rest has been questioned. Cardiac output is determined by dividing carbon dioxide production by the arterio-venous difference in carbon dioxide content.

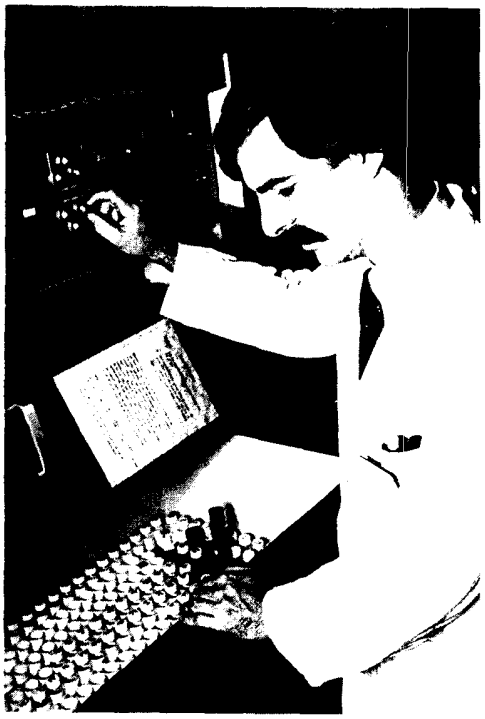
These measurements are controlled by a microcomputer through a system developed in the Baker Institute workshop, aimed at maximising the precision of the method.

In twelve subjects, (of whom five were normal, healthy volunteers and the remainder had a variety of cardiac and respiratory diseases), a close relationship was found between the estimates of arterial and venous carbon dioxide content obtained non-invasively by the new method and those obtained by direct measurement of blood samples. Estimates of cardiac output were similar when measured simultaneously by the Indirect Fick and thermodilution methods During exercise, the non-invasive method was found to be even more reliable. In 1982 we plan to apply this method in our studies on possible causes of essential hypertension in man. The availability of a reliable, non-invasive method for measurement of cardiac output will greatly facilitate these studies. For the first time we will be able to make repeated measurements in patients without subjecting them to cardiac catheterisation. The method is easy to use during exercise, and will be employed in our forthcoming programme to determine how physical exercise benefits the cardiovascular system.

Pathogenesis and treatment of postural hypotension due to autonomic insufficiency

G. Jennings, A. Bobik, M. Esler

Previous studies have suggested that patients with autonomic dysfunction can be divided into those in whom the defect in their sympathetic nervous system is in the central nervous system and those in whom the abnormality is at the peripheral nerve endings. Patients with a central abnormality were usually found to have other evidence of involvement in physical signs on routine examination of the CNS. They also differ from normal subjects and those with peripheral autonomic defects in their noradrenaline concentrations in plasma, response to reflex stimulation and spillover rate. To investigate the categorisation of these patients more fully, we have performed basilic (arm) vein biopsies on a group of subjects with autonomic insufficiency. Histochemistry and electron microscopy have been done by Dr. Gordon Campbell of the Department of Anatomy, Melbourne



Dr Peter Little setting up radio immunoassays

University and by Dr. Greg Willis, Prince Henry's Hospital. Preliminary results suggest that there is marked reduction of catecholamine content in veins from patients with peripheral autonomic dysfunction.

As reported previously, our patients with autonomic insufficiency have received marked benefit from high doses of dihydroergotamine, a new way of treating this condition. Several of our patients have now received this drug for four years and continue to have excellent relief of symptoms without evidence of toxicity.

Beta-adrenoceptor responses in autonomic dysfunction

G. Jennings, A. Bobik, M. Esler

We have studied the responses of cylic AMP to isoprenaline incubation of lymphocytes from six patients with autonomic dysfunction and severe postural hypotension. Three patients had the Shy-Drager syndrome (central pattern), characterised by central nervous system symptoms and signs and normal plasma noradrenaline (average 250 ± 26 pg/ml

which was similar to the values of 250 ± 27 pg/ml in eleven age-matched, control subjects). The other three subjects had idiopathic orthostatic hypotension (peripheral pattern) with no central nervous system signs, but a low plasma noradrenaline (average 160 pg/ml). In the patients with Shy-Drager syndrome, there was a greater cyclic AMP response at each concentration of isoprenaline than in seven normal subjects. However, the patients with autonomic dysfunction of the peripheral pattern, had normal lymphocyte cyclic AMP responses, suggesting that diminished sympathetic tone and low levels of plasma catecholamines at rest are not always associated with enhanced beta-adrenoceptor responsiveness. We also found differences between heart rates in our patients with autonomic insufficiency and those in normal subjects after isoprotenerol administration. However, care should be taken in interpreting results in subjects with intact circulatory reflexes, and in those without them, since response to isoprenaline in normal subjects is partly determined by the efficiency of circulatory reflexes and is altered by pharmacologic autonomic block.

Patients with autonomic insufficiency provide a yardstick for assessing the sympathetic nervous system in man and the biochemical findings related to catecholamines in these patients have important implications for evaluating the results obtained in other illnesses such as hypertension, depression, thyroid disease.

Haemodynamic responses to prenalterol

G. Jennings, K. Oddie, M. Hargreaves, A. Bobik

Prenalterol is a new drug which is thought to selectively stimulate the beta-adrenoceptors of the heart, resulting mainly in an increase in cardiac contractility. It is hoped that this drug will provide an alternative to digoxin as a stimulant for the failing heart. We have studied the effects of intravenous and oral administration of prenalterol in six normal subjects. Heart rate, blood pressure, cardiac output and plasma concentration of prenalterol were measured at various times up to ten hours after administration of 2.5 mg i.v. and 10mg oral prenalterol. At the time of peak effect it was found that prenalterol caused a small rise in heart rate (5-10 beats/min) with a much larger increase in cardiac output of approximately 25%. Blood pressure remained unchanged in subjects with intact circulatory reflexes. These acute responses suggest that the drug is capable of markedly increasing cardiac contractility without causing undue tachycardia such as occurs with the non-selective beta-stimulant, isoprenaline. The effects of prenalterol were compared with those of isoprenaline before and after autonomic blockade with clonidine 300 μg, atropine 0.04 mg/kg and phentolamine 10mg in the same subjects. Before autonomic block, isoprenaline caused a dose-related increase in heart rate and fall in mean arterial pressure after bolus administration. After autonomic block, the same doses of isoprenaline caused a smaller change in heart rate, but a greater fall in blood pressure suggesting that the arterial baroreflex was contributing to tachycardia caused by isoprenaline when the drug was given before autonomic block. Prenalterol, after autonomic block, caused a much greater rise in heart rate than had been present at the same dose before block. In contrast to isoprenaline, however, there was no fall in blood pressure even at the highest doses. This finding suggests that prenalterol is indeed highly selective in man for cardiac beta-receptors and that unlike isoprenaline very little stimulation occurs of peripheral beta-receptors.

Efficacy of LT 31-200, a long acting beta-adrenoceptor blocker, in patients with moderate essential hypertension

G. Jennings, K. Oddie, A. Bobik

LT 31-200 is a beta-adrenoceptor blocker which *in vitro* is at least 10-20 times more potent than pindolol, which is presently the most potent commercially available beta blocker. Preliminary studies have suggested that the drug is very well tolerated and that provided sufficient dosage is given, effects last for several days. The present study was designed to determine whether LT 31-200 was suitable for administration in a once weekly dose.

Following a run-in period, patients received 1 mg daily for two weeks followed by a wash-out period, then 8 mgs once weekly for the next two weeks. Measurements were made throughout the day at the beginning and end of each

week of plasma concentration, haemodynamics, blood pressure and heart rate at rest and during exercise. Three subjects have completed the study so far and a significant fall in arterial blood pressure was observed in each patient. The fall was mainly due to reduction in cardiac output, both after the first dose and after two weeks of administration. The duration of action of the 8 mg dose was found to be up to five days, but further patients will be required to complete the study before it can be assessed whether the duration is as long as one week.

Metronidazole pharmacokinetics and rectal availability in post-operative surgical patients

Lisa Ioannides, A. Somogyi, J. Spicer, B. Heinzow, N. Tong, A. McLean

The rectal bioavailability and intravenous disposition of metronidazole was studied in 8 surgical patients on a fixed post-operative regimen of metronidazole 500 mg 8 hourly. Plasma concentrations were studied over 8 hour dosing intervals on consecutive days. Assays were performed using high pressure liquid chromatography and biological techniques.

Rectal bioavailability (F) was almost complete; F = 78.3 ± 11.1% (mean ± SD), range 59.3 - 94.0%, and the mean steady-state plasma concentration (C_{SS}) was 16.4 ± 5.6 μg/ml. Clearance ($C1_S$) of the parent drug was 52.2 ± 19.8 ml/min, range 35.2 - 86.8 ml/min, while the estimated mean plasma half-life ($t_{1/2}$) was 12.4 ± 7.2 hr, range 4.3 - 26.2 hr.

Variation in metronidazole disposition indicates the need to individualise therapy. However rectal suppositories represent an adequate, safe and economical means of administration of metronidazole in patients following abdominal and pelvic surgery with or without significant postoperative complications.

Clinical pharmacy monitoring and utilization of enteral and parenteral metronidazole in a general hospital

Lisa Ioannides, A. Somogyi, N. Tong, J. Spicer, A. McLean

Pharmacokinetic data indicating adequate rectal bioavailability of metronidazole in surgical patients was used as a basis for hospital policy, restricting intravenous metronidazole usage to patients with proven anaerobic infections, or patients unable to take oral medications in circumstances where rectal therapy was inappropriate. Clinical pharmacists screened patients according to these criteria and reminded or informed medical staff of the results of bioavailability studies and existing hospital policy.

The use of intravenous metronidazole (500 mg) decreased from an average of 228 ± 48 vials/month (mean ± S.D.) in the year prior to the study to an average of 77 ± 57 vials/month in the current year with a minimum of 55 vials/month at the time of this review.

The use of rectal suppositories increased from 290 ± 200 suppositories/month to 815 ± 251 suppositories/month over the same time periods. Wound isolation rates did not alter.

The value of active utilization monitoring has been confirmed, and an education liaison role for clinical pharmacists has been demonstrated with substantial cost-benefit gains in antibiotic usage.

PUBLICATIONS
(see also Baker Institute Report)

G. JENNINGS, A. BOBIK and M. ESLER
Beta-Receptors in Orthostatic Hypotension—Letter to the Editor, New Eng. J. Med., Vol. 305, 17: 1019, 1981.

G. JENNINGS, A. BOBIK, M. ESLER and P. KORNER
Contribution of cardiovascular reflexes to differences in beta-adrenoceptor-mediated responses in essential hypertension. Clin. Sci. 61 (in press), 1981

G. JENNINGS, A. BOBIK and P. KORNER
Influence of intrinsic sympathomimetic activity of beta-adrenoceptor blockers on the heart rate and blood pressure responses to graded exercise. Br. J. Clin. Pharmac. 12: 355-362, 1981.

G. L. JENNINGS, J. S. GELMAN, J. R. STOCKIGT and P. I. KORNER
Accentuated hypotensive effect of sodium nitroprusside in man after captopril. Clin. Sci. 61:521-526, 1981.

Ewen Downie Metabolic Unit

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INTRODUCTION

During 1981 the Unit has continued its dual role as a clinical service and research department of the hospital. While providing a broad clinical service in endocrinology and diabetes, our laboratory work has again been directed towards thyroid and adrenal diseases. As well as studies done from this hospital, we receive samples from interstate and from as far away as Malaysia and Hong Kong.

Visitors

In the past year we have enjoyed visits from a number of guests. Dr. Harald Meinhold, from the Thyroid Research Group at Klinikum Steglitz, Freie Universität Berlin, worked here as a Visiting Scientist for the first half of 1981. During this time he established a valid method for measurement of thyroid hormone binding to lymphocytes. Dr. John Baxter of University of California, San Francisco, Dr. Kevin Catt from the National Institutes of Health, Bethesda, and Dr. Sidney Ingbar of Harvard Medical School also visited the department and gave seminars here.

During 1981 we continued to enjoy valued collaboration with the Baker Institute and Clinical Research Unit, Medical Research Centre Prince Henry's Hospital, Monash University Department of Medicine, Howard Florey Institute University of Melbourne, as well as with Departments of Endocrinology at University of California, San Francisco.

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

Estate of the late Vincenza Acton
Estate of the late H. Vistaline
G. M. Rollason Trust
Vivian Hill Trust
Alfred Hospital Whole-time Medical Specialists' Private Practice Fund
Research support from the National Health and Medical Research Council and the Alfred Hospital Medical Research Committee is also acknowledged.

General Summary

GENERAL ACCOUNT OF RESEARCH

Thyroid Hormone Pathophysiology

We have now done further work on a new hereditary thyroid hormone binding abnormality and have demonstrated that this condition is due to a greater than normal affinity of thyroxine for circulating albumin. It appears that a subtle inherited difference in the structure of albumin allows thyroxine to bind more tightly than normal to this protein. In order to maintain a normal level of the active (or free) fraction of thyroxine, affected subjects need about double the normal total hormone level in the blood. It is this biochemical abnormality which puts them at risk of a false diagnosis of hyperthyroidism.

We have now determined the number and affinity (strength) of thyroxine binding-sites on albumin prepared from the serum of affected subjects and have shown that these binding sites are reversibly altered if the sulphur-sulphur linkages of albumin are modified by reducing agents.

In order to find out the prevalence of this condition, now known as familial euthyroid T_4 excess, we have established a screening assay for abnormal binding which allows 10 samples to be screened in a single tube. Although we have so far identified six affected kindreds in Australia, it appears that the condition has a low prevalence in this community.

We have also evaluated a number of commercial free thyroxine assays in this condition and have found that some give misleading results which appear to confirm thyroid overactivity.

During severe illness there are numerous changes in the physiology of the endocrine glands. While many of these responses are beneficial, others may have adverse effects during prolonged illness. Further, these changes in circulating hormone levels may create diagnostic confusion, suggesting disease where it is absent, or obscuring important diagnostic information where a true hormone abnormality exists. Among the most difficult areas in Clinical and Laboratory Endocrinology at present, is the understanding of thyroid hormone changes during severe non-thyroidal illness. There is ample evidence for altered stimulation of the thyroid by the pituitary, for altered plasma binding of hormones in the circulation, for decreased removal of iodine from the thyroxine molecule and for altered tissue uptake of hormone. Many dilemmas remain. Which changes are important in particular patients? Which severely ill patients have genuine thyroid disease? Which patients, without underlying thyroid disease, would benefit from an alteration in their thyroid status?

We have approached these problems in

several ways. A follow-up study of thyroid function after recovery from severe prolonged illness showed that thyroid hormone levels returned to normal. However, it was also shown that severe illness could normalize the elevation in thyroid stimulating hormone, one of the cardinal diagnostic features of true primary thyroid deficiency.

The circulating levels of the three normal thyroid hormone binding proteins may vary widely during severe illness. It has so far been uncertain whether the observed changes in total and apparent free level can be attributed to these changes. By calculating the anticipated free level after assuming a normal binding affinity for each protein, we have demonstrated that the measured and calculated free levels are usually in good agreement. However, in some severely ill subjects there is a marked difference which is so far unexplained.

The presence of circulating inhibitors of thyroid hormone binding to plasma proteins has recently been suggested. We have been unable to show stable high molecular weight inhibitors, but have recently developed methods to detect short-lived unstable compounds which modify hormone binding or hormone delivery to tissues. After extensive preliminary studies, a system has been developed which allows equilibrium binding and hormone dissociation studies to be completed within 20 minutes of blood sampling.

Steroids, Adrenal Disease, Hypertension

It need hardly be re-stated that the various classes of steroid hormones: glucocorticoids, mineralocorticoids, oestrogens, androgens and progestogens each have very diverse actions which are still poorly defined at the cellular level. Each group of steroids is widely used therapeutically, either to correct a hormone deficiency or to alter some body process e.g. contraception, vasoconstriction in the skin, salt retention, anti-inflammatory action. Furthermore, there has been extensive development of modifications of the steroid molecule in order to produce compounds which block normal effects by interacting with the specific receptor, filling it with an inert substance which then prevents the subsequent attachment of the active steroid. The differences between various classes of steroid, and the contrast between agonist and antagonist, often depend on minute structural differences, for example a single OH or CH_3 group in the whole 4-ring molecule. With the objective of gaining further insight into the subtle relationships between steroid structure and function, Dr. Ken Wynne has been exploring the effect of chemical modifications on receptor binding and tissue action.

In a collaborative study with the Medical Research Centre, Prince Henry's Hospital we have compared the effect of various replacement steroids in adrenal insufficiency. Our findings suggest that conventional therapy is probably not optimal in congenital hyperplasia or in subjects adrenalectomized for Cushing's disease.

Renin assays are now widely used in the investigation of patients with hypertension, but, until now samples have required a complicated collection procedure. By re-examining assay conditions we have validated a simple technique which allows routine heparinized samples to be transported and processed at room temperature. Using this simplified assay we have gained information on the value of renin measurement in the long-term management of adrenal insufficiency, mineralocorticoid hypertension, Bartter's syndrome and refractory heart failure.

LIST OF PROJECTS

1. Thyroid Hormone Physiology
   a. Familial euthyroid thyroxine excess
      —Characterization of the binding abnormality in terms of affinity, capacity and specificity
      —Determination of prevalence
      —Disulphide-dependence of binding
      —Molecular basis for binding abnormality
   b. Studies in non-thyroidal illness
      —Assessment of serum binding
      —Modified hormone delivery to tissues
      —Comparison of methodological differences in free hormone measurement
      —Central control of thyroid function
      —Studies after recovery from severe illness
   c. Studies of thyroid hormone dissociation and delivery to tissues
   d. Studies of T_4-analogue binding to lower affinity proteins in plasma
2. Steroids, Renin, Hypertension
      —Mechanisms of glucocorticoid-

induced vasoconstriction
—Simplified renin methodology
—Effect of Indomethacin during mineralocorticoid replacement
—Long-term studies of glucocorticoid-responsive hypertension
—Evaluation of glucocorticoid and mineralocorticoid replacement therapy

3. Collaborative projects (Dr. K. N. Wynne)
—Metabolism of aldosterone by kidney: relevance to modulation of hormone action
—Endocrine effects of Ginseng
—Catecholestrogens and thyroid function
—Mineralocorticoid activity of METEC (methyl ester of testosterone 17α ethynyl carboxyllic acid)

ABSTRACTS

Familial Euthyroid Thyroxine Excess

J. W. Barlow, E. L. White, J. Csicsmann, P. Taft, J. R. Stockigt

Our recently published studies have demonstrated that the excess of circulating thyroxine (T_4) in this condition is appropriate to maintain a normal free T_4 level in the face of increased plasma protein binding of T_4. The abnormal high-capacity T_4 binding site in the sera of affected subjects was separable from prealbumin and thyroxine-binding globulin, but multiple techniques failed to separate this binding site from albumin. Hence, we compared T_4 binding to albumin preparations isolated from the sera of normal and affected subjects. By equilibrium dialysis, affected subjects showed an extra T_4 binding site ($K_d \sim 50$ nM) in addition to the T_4 binding sites of normal albumin ($K_d \sim 4\,\mu M$). Capacity studies indicated that about one third of circulating albumin molecules contained the extra binding site. Estimates of capacity and affinity suggest that the abnormal binding site accounts for the observed doubling of normal total T_4 in order to maintain a normal free level.

Studies with the disulphide reducing agent, dithiothreitol, indicate that disulphide bonds are critical in maintaining the abnormal T_4-albumin association. Low concentrations of dithiothreitol ($\sim$1 mM) lead to a reversible decrease in the T_4 affinity of albumin without a change in capacity. This system may provide an important model for disulphide-dependent changes in hormone attachment to specific binding sites.

A screening test for this condition has been developed so that samples from ten subjects can be tested in a single tube. This procedure involves assessment of ^{125}I T_4 binding under conditions where the concentration of unlabelled T_4 is 100-fold greater than normal. The very high capacity of the abnormal binding site allows one abnormal sample to be detected amongst ten. Preliminary results suggest that familial euthyroid T_4 excess has a prevalence of between 1:10,000 and 1:30,000 in an Australian population of predominantly European background.

Studies in collaboration with Dr. Harald Meinhold demonstrated that specific T_3 receptors on lymphocytes were almost identical in normal and affected subjects, providing evidence against the suggestion that this condition represents a new type of hormone resistance.

Thyroid Function After Recovery from Hypothyroxinaemia of Severe Non-thyroidal Illness

P. J. Fuller, J. W. Barlow, E. L. White, D. M. Hurley, J. R. Stockigt

We have examined the possibility that impairment of compensatory TSH hypersecretion might be one cause of thyroid hormone deficiency during severe illness. Low levels of triiodothyronine (T_3) are frequently found during non-thyroidal illness, but it is now established that serum thyroxine (T_4) may also become subnormal. The latter finding is associated with high mortality. The free T_4 index (FT_4I) is usually low, but free T_4 levels have varied widely, depending on methods. It has been suggested that measurement of reverse T_3 (rT_3) may distinguish between hypothyroidism (low rT_3) and changes due to non-thyroidal illness (normal or high rT_3).

The possibility of transient illness-related secondary hypothyroidism must also be considered, in view of the recent demonstration that pituitary TSH secretion is depressed during severe illness. If such suppression occurred in patients who had diminished thyroid reserve before the onset of severe illness, thyroid hormone deficiency might be anticipated. A prospective study of this possibility is clearly not feasible. We therefore assessed thyroid function four to 24 months after recovery from severe prolonged illness associated with hypo-

thyroxinaemia. The ten patients reported (4 males, aged 28-75; 6 females, aged 53-71) were studied during and after recovery from renal failure, prolonged sepsis, severe pneumonia, burns or liver failure.

We found resolution of the low T_4, FT_4I and T_3 after recovery in nine of ten patients. At that time neither basal TSH nor its response to TRH was excessive, indicating that underlying thyroid function was probably normal. By contrast, one patient showed clear evidence of primary subthyroidism after recovery, although the previous TSH level during illness had not been increased. Serum rT_3 was subnormal during severe illness in two patients who subsequently had normal thyroid function. In fact, in only one case was the rT_3 elevated.

Conclusions: (i) Although associated with a poor prognosis, low T_4 during severe prolonged illness is compatible with survival. (ii) Studies after recovery suggest that underlying diminished thyroid reserve is uncommon in patients who survive severe illness associated with low T_4. (iii) Our findings in one case suggest that severe illness may impair the TSH hypersecretion of primary subthyroidism. (iv) During severe illness there may be great difficulty in identifying patients with underlying hypothyroidism or diminished thyroid reserve.

Endocrine Effects of Ginseng

K. N. Wynne, J. R. Stockigt, P. Pearce†, J. W. Funder†
†Medical Research Centre, Prince Henry's Hospital

Ginseng is an extract of the root of Panax ginseng, and is one of the oldest and most valued Chinese medicines. Recently, it has become widely available in the western world as a herbal tonic. Some modern studies have suggested that ginseng has an anti-stress effect due to an interaction with the hypothalamo-pituitary-adrenal axis and that over-use can cause side-effects of an endocrine nature. For these reasons, a concentrated mixture of ginsenosides (saponins of ginseng which are believed to be the active constituents) has been examined for ability to compete for classical steroid receptors.

Ginsenosides (2 mg/ml) from Red Korean Ginseng did not displace estrogen from estrogen receptors nor androgen from androgen receptors. However, this solution diluted 1 to 500, effectively competed with dexamethasone for glucocorticoid receptors and similarly, at 1:100 dilution, with aldosterone for mineralocorticoid receptors. A 1:6 dilution competed with R5020 for progesterone receptors. Work is proceeding to isolate the ten or eleven ginsenosides from ginseng by means of preparative high performance liquid chromatography so that further studies may be carried out.

Catecholestrogens and Thyroid Function

K. N. Wynne, I. Ekkel, J. R. Stockigt

Estrogens are oxidised in the human to either catecholestrogens or estriols. It has been reported that thyroid status influences the relative proportions of these metabolites. A catecholestrogen-antigen was synthesized and high titre antisera raised in sheep, allowing us to develop a specific radioimmunoassay for 2-hydroxy-catecholestrogens in plasma and acid-hydrolysed urine.

Consecutive urine specimens from normal subjects were assayed for catecholestrogens and estriol; and the ratio of the two metabolites was found to be reasonably constant for an individual but varied widely between individuals. Samples from subjects with thyroid disorders gave ratios within the range of normal variation. However, when the catecholestrogen to creatinine ratio was examined, most healthy subjects were within the range 1-3 nmoles 2-hydroxyestrone/mmole creatinine and the hypothyroid subjects so far studied were above this range. Further studies are in progress to determine whether such measurements give a valid index of diminished thyroid hormone action.

OVERSEAS AND AUSTRALIAN MEETINGS

During 1981, papers were presented at both meetings of the Endocrine Society of Australia, at the European and American Thyroid Association meetings and at the meeting of the Australian Association for Clinical Biochemists.

Dr. Stockigt presented a review of our studies of thyroid hormone binding at the Annual Seminar Conference of the Endocrine Society of Australia in Leura. Our findings in familial euthyroid T_4 excess were presented at the European and American Thyroid Association meetings, as well as forming part of

invited lectures in Rotterdam and Berlin. Dr. Fuller presented our work on thyroid function after recovery from severe illness in Christchurch. Mr John Barlow attended the American Thyroid Association meeting in Minneapolis and visited laboratories in San Francisco, Boston and Los Angeles. Ms. Judith Csicsmann attended the European Thyroid Association meeting in Pisa and visited research centres in Berlin and Budapest. Dr. Taft attended the International Symposium on Insulin Delivery Systems in Assisi in September. Dr. Douglas Lording was a guest lecturer at the III General Medical Conference in Bali and Singapore. Members of the Unit also gave lectures and presentations in Colac, Mildura, Launceston, Swan Hill, Traralgon, and Hamilton during 1981. At the Australian Association of Clinical Biochemists meeting papers were presented by Ms. Elizabeth White, Judith Csicsmann and Marianne DeGaris.

TEACHING AND SEMINARS

Seminars

Drs. Breidahl, Taft, Lording and Stockigt gave lectures and seminars in the 6th year Clinical School Teaching Programme and participated in the teaching of general medicine, diabetes and endocrinology to 4th, 5th and 6th year students.

Postgraduate teaching sessions were held weekly during the first half of the year. In addition, clinical lunchtime seminars were held twice monthly throughout the year. The following topics were presented during 1981:—

1. Bartter's syndrome
2. Androgen-producing adrenal adenoma
3. Electrocardiographic changes in diabetic ketoacidosis
4. Contrast media and thyroid function
5. CT scanning of prolactinomas
6. Therapeutic decisions in Cushing's disease
7. Hereditary abnormalities of thyroxine binding globulin
8. Adult hypophosphatasia
9. Potassium disturbances in haematological malignancy
10. Mineralocorticoid hypertension; localization of adrenal lesions
11. Management of hypoparathyroidism
12. Amiodarone and thyroid function
13. Hypercalcaemia due to occult sarcoidosis
14. Munchausen's syndrome in a diabetic
15. Differentiated thyroid carcinoma

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ABSTRACTS

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