Research

# Annual Report 77

Baker Institute
Alfred Hospital


## ANNUAL REPORT 1977

# Baker Medical Research Institute

affiliated with Monash University

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| Fifty-first Annual Report of | **THE THOMAS BAKER, ALICE BAKER and ELEANOR SHAW MEDICAL RESEARCH INSTITUTE** |
| Twenty-ninth Annual Report of | **THE ALFRED HOSPITAL CLINICAL RESEARCH UNIT** |
| Twenty-first Annual Report of | **THE EWEN DOWNIE METABOLIC UNIT** |
| Report of | **C. J. OFFICER BROWN CARDIOTHORACIC SURGICAL UNIT** |

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## CIRCULATORY CONTROL AND HYPERTENSION RESEARCH UNIT

| | |
|---|---|
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| **Scientific Staff:** | W. P. ANDERSON, B.Sc., Ph.D. (Adel), Senior Research Officer, National Health & Medical Research Council |
| | A. BROUGHTON, M.B., B.S. (Syd), M.R.A.C.P., Research Fellow, Life Insurance Medical Research Fund of Australia |
| | PATRICIA K. DORWARD, M.A. (Cantab), Ph.D. (Monash), Senior Research Officer, Life Insurance Medical Research Fund of Australia and New Zealand |
| | M. D. ESLER, M.B., B.S. (Melb), B.Med.Sci. (Melb), Ph.D. (ANU), Research Fellow, National Health & Medical Research Council |
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| **Visiting Scientist:** | PROFESSOR MASAMI IRIKI, M.D., Department of Physiology, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan. |
| **Technical Staff:** | ELIZABETH ANDERSON<br>MARGOT CLARK (till April 1977)<br>JUDI CSICSMANN<br>PAMELA GRAHAM<br>ANNE HEAL<br>DIANNE KELLEHER<br>M. LE DUC |

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**Head:** DR. P. J. NESTEL, M.D., B.S. (Syd), F.R.A.C.P.

**Scientific Staff:**

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N. E. MILLER, M.B., Ch.B., B.Sc., M.Sc. (Manchester), Ph.D. (ANU), Research Fellow, National Health & Medical Research Council

M. REARDON, B.Sc. (Hons), Ph.D. (ANU), Research Officer, Life Insurance Medical Research Fund of Australia & New Zealand

T. ISHIKAWA, M.D., Postdoctoral Fellow, National Heart Foundation of Australia

ANDREA POYSER, B.Sc., Research Assistant, Alfred Hospital Scholarship

ELAINE FAGARAZZI, B.Sc., Research Assistant

MARGARET O'CONNOR, B.Sc., Research Assistant, National Heart Foundation of Australia

JANE MA, B.Sc., Research Assistant, National Health and Medical Research Council

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**Head:** DR. J. E. MALONEY, B.Sc. (Syd), M.Sc. (NSW), Ph.D. (Syd), F.A.I.P.

**Scientific Staff:**

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T. M. ADAMSON, M.B., B.S. (Melb), F.R.A.C.P., Senior Research Associate; Senior Lecturer, Department of Paediatrics, Monash University (Queen Victoria Hospital)

A. M. WALKER, M.Sc., Ph.D. (Mon), Senior Research Officer, National Health & Medical Research Council

M. WILKINSON, B.E. (Mon), Senior Research Officer

DAINE ALCORN, M.Sc. (Melb), Senior Research Associate; Senior Demonstrator, Department of Anatomy, University of Melbourne

J. J. SMOLICH, B.Med. Sci., M.B., B.S. (Melb), Research Associate

J. CANNATA, B.Sc. (Melb), Research Assistant

G. BOWES, M.B., B.S. (Mon), Postgraduate Research Scholar

R. YARDLEY, B.Med.Sci., M.B., B.S. (Mon), Postgraduate Research Scholar

R. HAYLLAR, Bioengineering Student, Swinburne College of Advanced Education

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MARGARET H. DOWLING, E.P.T.A.
R. J. SMITH, Department of Medicine, Monash University

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JUDITH DODS
ANTONIA LOPEZ
ROSE BALDI (till April 1977)
ANNE CAHILL

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S. HART
LINDA LUNT
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D. SALAHDRIS
D. THEODOROKOPOULOS

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(Alfred Hospital)

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**Officer-in-Charge:** A. BONS

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A. GIULIANI
D. HARRISON
P. JONES
M. MOOR
E. TURNBULL

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CONTENTS

*Professor P. I. Korner*

# Director's Report for 1977

The year has been one of consolidation and of some changes at the Baker Institute. It marks the first full year of operation of our new Cardiovascular Metabolism and Nutrition Research Unit under the leadership of Dr. Paul Nestel. The major thrust of its research is in the field of lipid metabolism and coronary artery disease. We are greatly indebted to the Government of Victoria for providing $90,000 in 1976/77 to help equip the biochemical and tissue culture laboratory developed by the Unit. Another tangible sign relating to the arrival of Dr. Nestel's group has been the establishment of a Heart Risk Evaluation Clinic in the Institute which is operated in association with the Victorian Division of the National Heart Foundation of Australia and supported also by ICIANZ Pty. Ltd. The presence of the Clinic in the Institute has been an important bridge between theoretical cardiovascular research and its practical application to community needs.

The work of the Cardiovascular Metabolism and Nutrition Research Unit relates mainly to the study of abnormalities in fat metabolism in man. This has added greatly to the clinical activities of the Clinical Research Unit. Dr. Nestel's group has been one of the first to draw attention to the possibility that the risk of heart disease may not just be simply a matter of high cholesterol but that it depends on the ratio of low density lipoproteins (LDL)/high density lipoproteins (HDL). A relatively high concentration of LDL tends to promote the deposition of fatty plaques whilst the high concentration of HDL promotes removal.

The activities of the Hypertension and Circulatory Control Unit continue to flourish. We have made particularly interesting new advances in three areas as outlined later in the Annual Report. The first relates to improved understanding about the function of some of the chemical transmitters connecting the different brain centres which control the circulation. The second relates to an important new role of the renin-angiotensin system during narrowing of the renal artery. The third is the first unequivocal demonstration that part of the blood pressure lowering effect of beta-blocking drugs is through their effects on the central nervous system. All these projects were begun since our group's arrival at the Baker Institute.

The clinical research activities of the Hypertension Unit have been greatly strengthened with the arrival of Dr. Murray Esler, appointed in 1977 to a five-year National Health & Medical Research Council supported Research Fellowship. His work deals in a quite novel way with the important question of whether there really is abnormality of sympathetic nervous function in patients with essential hypertension.

Towards the end of 1977 Dr. John Maloney, Head of the Developmental Biology Research Unit, accepted an offer from Monash University to move his group to the Queen Victoria Hospital where it could collaborate more closely with the research group in the University Department of Obstetrics and Gynaecology and the Department of Paediatrics. The Unit will be in its new location from February 1978. Dr. Maloney has been at the Baker Institute for a period of four years. During the last two of these the staff of his Unit has expanded considerably in numbers and the work appears to be flourishing. The main research interests of the group have focused more and more on special problems important in neonatal paediatrics, particularly the pathophysiology underlying cot death. The new

location of the Unit will provide a good opportunity to pursue those particular research interests.

During 1977 three new Trustees joined the Board of Trustees of the Baker Institute. Mr. K. E. Allen, Managing Director, Kodak (Australia) Pty. Ltd., Dr. H. B. Kay, representing the Board of the Alfred Hospital, and Professor Graham Schofield, Dean of Medicine, Monash University.

It is with the most profound regret that I must record Mr. Allen's sudden death on 4th December 1977. In the short time that he was a member of our Board he gave a great deal of time and energy to our problems and gave his services quite unsparingly. His death is a grim reminder of the enormous burdens that often lie on senior company executives. It emphasises also the great economic losses to companies and to the nation caused by premature death of gifted people in their prime of life and at the height of their intellectual powers. It reinforces the need for promoting research programmes that will improve understanding of underlying causation as a basis for rational preventitive medicine.

With the increasing complexity and scope of the scientific work and business management of the Institute, the Trustees have decided to take steps that will eventually lead to enlargement of the Board of Trustees of the Institute. Several ways in which this can be done are at present under consideration. In the meantime, because of our immediate need for a greater range of expert advice it has been decided to establish a Business and Management Advisory Committee under the Chairmanship of Mr. J. C. Habersberger, the Chairman of Trustees. I have pleasure in announcing that Sir John T. Reid, Mr. L. M. Muir, Mr. W. D. McPherson and Mr. J. D. Moir have consented to serve on the Committee which will meet for the first time in February 1978.

The end of 1976 marked the retirement of Mr. Gordon Canham who had served the Institute long and well as Secretary to the Board of Trustees. His successor is Dr. Trevor Wood, Chief Executive Officer of the Alfred Hospital, who has shown a sympathetic understanding of our many problems. Another important new development has been the decision by the Trustees to appoint Mr. Michael Downes as Financial Director. Mr. Downes has had extensive business experience. His arrival will relieve me of some of the administrative work and will also help to make known our activities to a wider public forum.

During 1977 our annual budget expenditure exceeded $1m for the first time in the Institute's history. We are particularly grateful to the Victorian State Government who made possible the purchase of almost all the equipment of the new Cardiovascular Metabolism and Nutrition Research Unit. We have also been fortunate in obtaining good project grant support from the National Health and Medical Research Council, the Life Insurance Medical Research Fund of Australia and New Zealand and the National Heart Foundation of Australia, as well as Alfred Hospital Research Grants. Overseas grant support from the United States National Institute of Health and the United States Sugar Association is gratefully acknowledged, as is the support from our many local well-wishers. Of particular importance in this regard is the Alan Williams Trust, established by Mr. and Mrs. Williams to support the research effort of the Institute.

The total income from external grants-in-aid is at the present time the same as the total budget of the Institute for the year 1974, only four year's ago. Nevertheless we will continue to be in serious financial difficulties, indeed the present situation is likely to get worse, until we receive a type of Institute Grant from the Commonwealth Government through the National Health and Medical Research Council similar to that currently given to our sister Research Institutes in this city — the Walter and Eliza Hall and the Howard Florey Institutes. At present the N. H. & M. R. C. appears reluctant to provide Institute funding along these lines to another institution, apparently because the amounts involved are too great in terms of its total budget. It is to be hoped that the main research units of the Baker Institute will eventually receive Programme Grants which are expected to start shortly. Provided that these are sufficient to cater for the scientific costs of each unit, including a reasonable fraction of the staff and equipment costs, they are a potentially workable alternative to Institute grants. They should permit some long range planning and are therefore welcome, since such planning is almost impossible under

the present system of project grants. Programme Grants appear to have many features common to the United Kingdom Medical Reseach Council's Unit funding scheme. They will be tenable not only in research institutes but also in universities, and are therefore more flexible than Institute Grants. Increased Commonwealth support for medical research is today needed as never before. With overall health care expenditure in the Australian community now well in excess of $5,000m it is more than ever necessary to find new approaches to disease and health maintenance. This can only be done by fostering many imaginative new programmes which utilize the numerous talents in this country. It would therefore be entirely justifiable in the national interest for the Commonwealth Government to support the main units in the Baker Institute and many others elsewhere in the country.

There are a number of building projects that need to be tackled as a matter of urgency. The first is an expansion of the animal facilities available to us. The Animal House is owned by the Alfred Hospital but the Baker Institute is the largest user. This facility has coped with a large expansion of work through the dedication of Dr. Neville Walden, our Veterinary Consultant, and Mr. Adrian Bond, the Officer-in-Charge of the Animal House. However, the facilities need to be considerably expanded to cope with the increased need created by the Experimental Cardiac Surgical Unit and the anticipated requirements of Pharmacology. An estimated expenditure of nearly $300,000 will be necessary to finance this project. Another building project that needs to be completed in the near future is the unfinished part on the lower ground floor of the Institute. This will accommodate our new Pharmacology Unit.

One new laboratory to start during 1978 includes an Experimental Cardiac Surgery Laboratory. This will be established by Dr. Franklin Rosenfeldt, an Adelaide graduate now working at St. Thomas' Hospital, London, who will arrive early in 1978 as Edward Wilson Fellow. He will work at the Baker Institute but will have the support of the C. J. Officer-Brown Cardiothoracic Surgical Unit of the Alfred Hospital. Historically, the Baker Institute contributed much laboratory know-how to the establishment of open-heart surgery in Australia about twenty years ago. I have high hopes that this role is about to be renewed. Dr. Rosenfeldt will work on methods of minimizing the degree of myocardial damage during open-heart surgery, particularly in hearts with a compromised coronary circulation.

The New Year will also see the arrival of Dr. Gordon Campbell and his wife, Dr. Julie Campbell, who have recently been overseas in Britain and the USA on Overseas Research Fellowships of the National Heart Foundation and the Life Insurance Medical Research Fund. They will develop a Morphology and Cell Biology Laboratory which will add a much needed dimension to the physiological side of our work. Another new arrival will be Dr. Kerin O'Dea who is coming to the Institute after extensive overseas experience in France and the United States, and a period at the Royal Children's Hospital. Her presence will expand the range of activities of the Cardiovascular Metabolism and Nutrition Research Unit.

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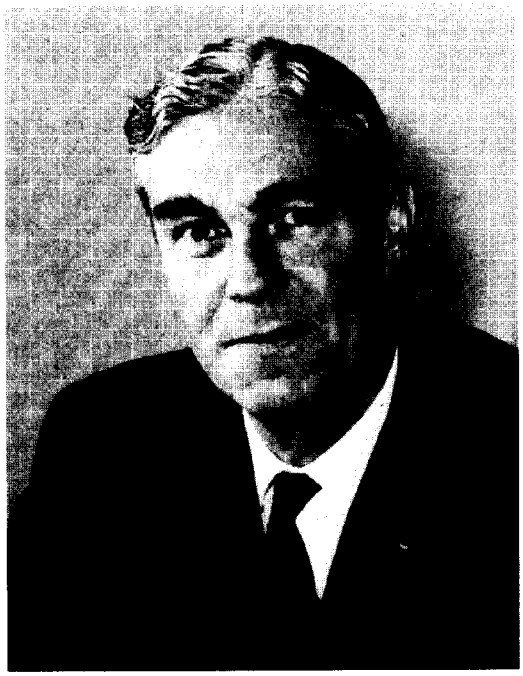
During 1977 we have increased our activities in the field of research training and education. We had a successful two-day course on cardiovascular physiology, biochemistry and medicine attended by 70 Monash and Melbourne University students. Four PhD and four honours students are enrolled to work in the Institute for 1978.

To summarize our activities for 1977:— the Hypertension and the Cardiovascular Metabolism Units have continued to expand their activities and continue to attract able young scientists. The effect of the departure of Dr. Maloney's group will be to permit some expansion of their activities, and will allow housing of our new laboratories without requiring immediate development of the imcompleted areas of the Baker Institute. Above all it has had the effect that the scientific interests and activities of our research groups are now all broadly related to cardiovascular medicine.

# People



*Mr J. C. Habersberger*
*Chairman, Board of Trustees*

**Our Chairman — J. C. Habersberger**

John Cobell Habersberger's long association with the Baker Medical Research Institute began during his employment with Kodak over 37 years. He was secretary of the Company 1944-59, Financial Director 1959-63 and Joint Managing Director 1963-76.

Under the Chairmanship at Kodak of Mr Edgar Rouse, Mr Habersberger was first introduced to the Baker Trust in 1961. He became a Trustee of the Institute in 1966 and its Chairman in 1972.

He was also appointed to the Alfred Hospital Board of Management in 1966, was Vice-President in 1973 and has been President of the Hospital since 1975.

He has held a variety of other important positions over the years including a long association with Melbourne University.

He has played a key role in guiding the affairs of the Institute during the last three years when it has become an entirely cardiovascular research centre. This has been a period of unprecedented expansion and the Institute owes much of its success and standing to his wise counsel over this period.

*Dr. T. J. Wood*
*Secretary to the Trustees*

**Dr. Trevor Wood — Secretary to the Trustees**

Dr. Trevor Wood, Chief Executive Officer of the Alfred Hospital, was appointed Secretary to the Trustees of the Baker Medical Research Institute from January 1977. From that time he has been heavily involved in the management of property and the financial affairs of the Institute.

Dr. Wood has had a long experience in medical administration. In his previous position, he was the Director of Medical Administration at a group of teaching hospitals in Sydney.

He has been a major contributor to the development of the profession as the Censor-in-Chief of the College of Medical Administration.

His interest in teaching and research is of great assistance to the Trustees and to the Institute.

# People

*Mr Michael Downes*
*Financial Director*

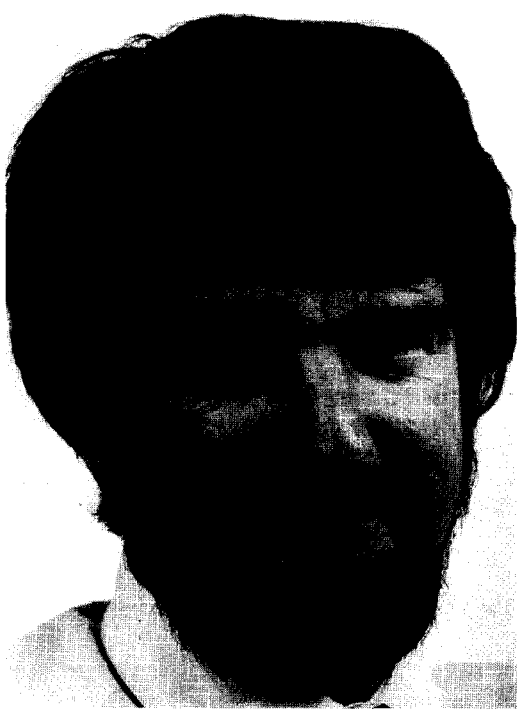
**Michael Downes**

In the latter half of 1977, the Trustees decided to appoint a senior administrator to manage the general business and finances of the Institute and help promote its work to business leaders and the public.

Michael Downes was subsequently appointed Financial Director. He joined the Institute after nineteen years in the advertising business, the last nine as a principal in his own agency. During this recent period, the business which he and his partners started in 1969 grew into an Australia-wide concern of which Mike was Managing Director.

He is a Fellow of the Advertising Institute of Australia (Diploma) and an affiliate member of the Australasian Fund Raising Institute.

Mike is married with two children, and lives in a quiet setting at Plenty. To fill in the time he has left after being father and Financial Director, he is Victorian Commissioner for Scouts and is responsible for 15,000 boys in the section.



*Dr. Gordon Campbell*
*"Morphology"*

**Gordon Campbell**

Gordon Campbell has joined the Baker Institute after holding an overseas Research Fellowship of the National Heart Foundation. This allowed him to work in University College London, and as a visiting lecturer in the Department of Pharmacology, University of Iowa, and in the Department of Pathology, University of Washington, U.S.A.

He graduated BSc (Honours 1) in 1969 and was awarded his PhD in 1974 at the University of Melbourne. His research interests developed during post doctoral experience here and abroad are in the factors affecting the proliferation of smooth muscle cells in diseases. He is expert in the use of techniques involving electronmicroscopy, cell culture, histochemistry and autoradiography.

With his wife Julie, Gordon has established the Morphology and Cell Biology Section at the Institute.

For those moments when he is not involved with his work Gordon likes playing tennis and squash, or taking to the mountains to ski and hike.

# People

*Dr. Julie Campbell*
*"Tissue Culture"*

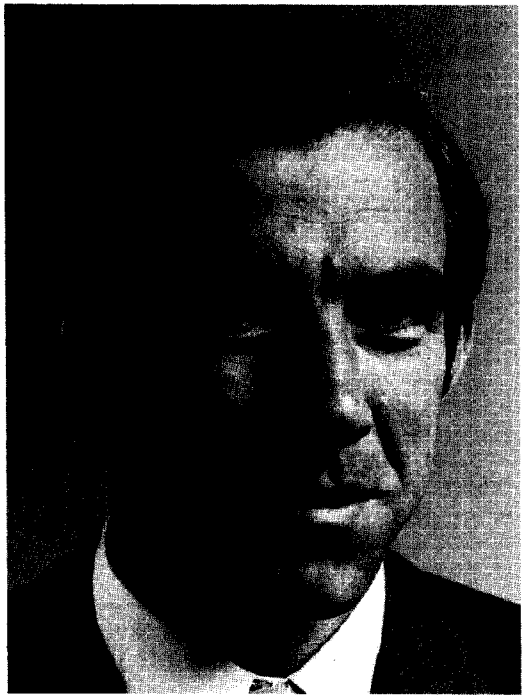
**Julie Campbell (formerly Chamley)**

Julie Campbell graduated BSc (Honours 1) in 1968 at the University of New South Wales. She earned her PhD in 1973 for her work in the Zoology Department, University of Melbourne and her thesis on 'Autonomic neurons and their effector organs in tissue culture'.

She was John Halliday Life Insurance Medical Research Fund Travelling Fellow 1976/78. This is one of the prestige awards made by the fund. She worked overseas in the Department of Anatomy and Embryology, University College London, in the Department of Pharmacology, University of Iowa, and in the Department of Pathology, University of Washington, U.S.A.

Her work and current research thus involves the role of smooth muscle cells in the aetiology of hypertension and atherosclerosis.

Julie is a tennis player, jogs, is interested in yoga and plays International rules Basketball with the "BAKER BOMBERS".



*Dr. Frank Rosenfeldt*
*"Cardiac Surgery"*

**Franklin L. Rosenfeldt**

We are fortunate to have Mr Franklin L. Rosenfeldt, an Australian surgeon just returned from St. Thomas' Hospital, London, join the Institute to lead our new project in Cardiac Surgical Research.

Dr. Rosenfeldt was a medical graduate at Adelaide University with Credit and the General Practitioners' Prize in 1963. He was admitted as Fellow of the Royal College of Surgeons (Edinburgh) 1969 and qualified M.D., Adelaide December 1975.

He has been studying improvements in techniques designed towards preventing damage to the heart muscle during cardiac surgery and will continue this work at the Baker Institute.

Dr. Rosenfeldt is married with three children, enjoys swinging a cricket bat or tennis racquet and has been known to "tickle the key board" of a piano from time to time. We look forward to hearing Frank sing at our next Baker Institute Review.

# People

*Dr. Kerin O'Dea*
*"Maturity onset Diabetes"*

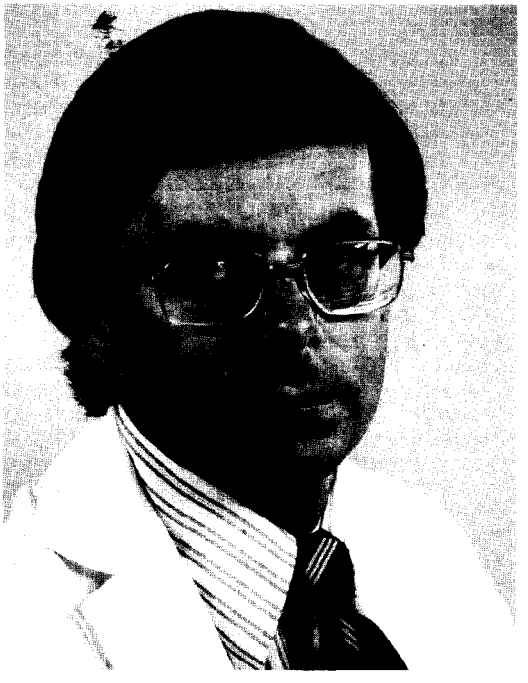
**Kerin O'Dea**

After graduating B.Sc. in 1967 at Melbourne University, and obtaining her PhD in 1971, Kerin travelled overseas to join the Institut fur Pharmakologie, BAYER AG, West Germany. In 1973 she worked with Prof. Philippe Meyer in PARIS, and a year later joined the Cleveland Clinic in the U.S.A.

Before joining the Baker Institute, she was Senior Research Officer at the Research Foundation, Royal Children's Hospital, Melbourne.

Her research interests are around obesity and maturity onset diabetes with relation to coronary disease. She has done a great deal of work with aborigines in the far North West looking at the incidence of these diseases in a people whose lifestyle has been rapidly changed from a primitive culture to urban existence.

Kerin plays tennis, squash, likes bushwalking and is a film critic. She also enjoys travelling as her history shows.



*Dr. Murray Esler*
*"Hypertension in Man"*

**Murray Esler**

Murray Esler graduated in 1967 from Melbourne University with first class honours in Medicine. He obtained his PhD in 1973 from the Australian National University for studies on the pathophysiology of human hypertension.

He joined the University of Michigan, U.S.A. and spent 4 years in hypertension research and clinical medicine. He was Assistant Professor of Internal Medicine 1975-76.

In February 1977, Murray joined the Baker Institute and is currently developing new and improved methods for studying the role of the sympathetic nervous system in the development of hypertension.

He is married with two children and kept sane by a wife who is a psychiatrist. Hobbies are beach and trout fishing and hiking.

# People

*Mr Michael Percy*
*"Electronics"*

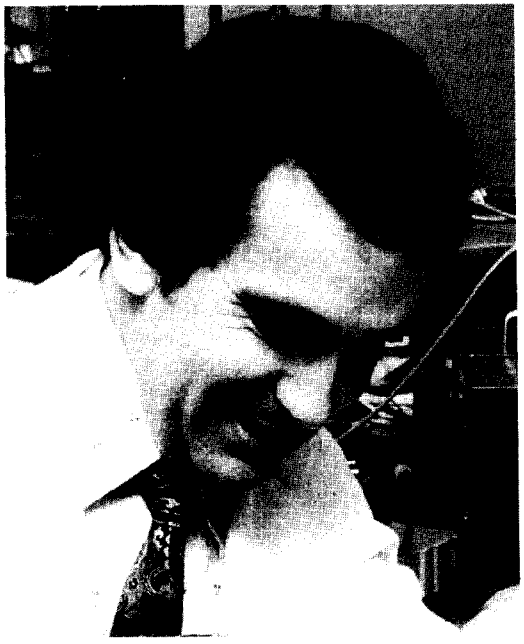
**Michael Percy**

Mike heads the Electronics and Engineering Workshop at the Institute.

He graduated in Electrical Engineering at Melbourne University in 1972 and worked for 2 years at L. M. Ericsson's in Power Supply. He then joined Victorian Railways to design various equipment in the Signals and Communication fields. One such item of equipment was a train speed monitor which will be used in the Melbourne Underground loop.

In October, 1977, Mike came to the Baker replacing Ron Wall who moved to the Alfred Hospital to become Duty Electronics Engineer.

Mike lists his leisure activities as house and car renovation, bush walking and occasional golf. One notes however he drives a campmobile to work, so he obviously gets away from it all on a regular basis.



*Mr Ron Wall*
*"Electronics"*

**Ron Wall**

In October Ron Wall, our Electronic Engineer, transferred to the Alfred Hospital as their Deputy Electronic Engineer, a position in which much that had been learned at the Baker Institute could be put into clinical practice.

As Deputy Electronic Engineer he is responsible for the supervision of the Medical Electronic Department's technical staff, for the design of specialised electromedical equipment, for assisting and advising medical staff on close procedures employing electromedical equipment and by means of lectures the continuing education of medical personnel on matters relating to electromedical equipment. With electromedical equipment playing an ever increasing role in health care, it is vital that medical staff are given prompt and competent support by those of an engineering discipline.

**Kenneth Edward Allen**

On the 4th December, 1977, the Baker Institute suffered a serious loss by the untimely death of one of its Trustees, Kenneth Edward Allen.

As Chairman and Managing Director of Kodak (A/Asia) Pty. Ltd. Mr Allen had a deep knowledge of and interest in the history and work of the Institute well before he became a Trustee.

Although he had been a Trustee for a short time only, his outstanding business acumen, broad scientific knowledge and feeling for people had already been a significant help to the Institute and his fuller participation in the general management of the Institute was eagerly awaited. His tragic death at the relatively early age of forty-seven deprived the Institute of his great potential.

The Trustees extend their deepest sympathy to Mrs Allen and family.

# Hypertension and Circulatory Control Research Unit

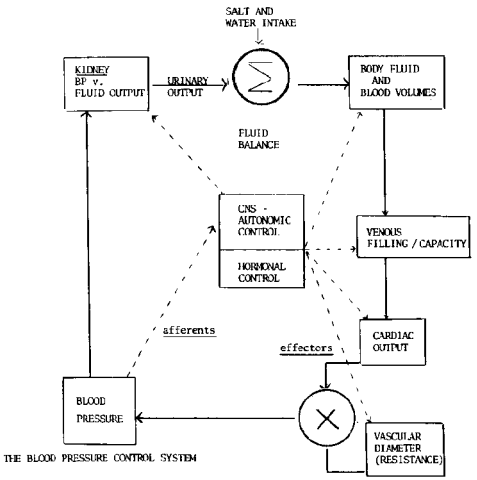
## MAIN TOPICS

- CENTRAL NERVOUS CONTROL OF BLOOD PRESSURE
- KIDNEY AND HYPERTENSION
- SALT AND HYPERTENSION
- BETA-BLOCKING DRUGS AND HYPERTENSION

## GENERAL SUMMARY

### Blood Pressure Control System

High blood pressure is widely prevalent in our community and its presence greatly increases the risk of death or serious incapacity from strokes and heart attacks. Despite the enormous research effort that has been made in many parts of the world the exact factors causing high blood pressure are still poorly understood. This applies particularly to the commonest type of hypertension found in man — essential hypertension. Our knowledge is only marginally more satisfactory, however, in most groups of secondary hypertension with a defined pathological cause. Secondary hypertensions include renal artery stenosis (narrowing) and several types of tumour of the adrenal gland and several other 'causes'. These can often be 'cured' when the underlying pathology is removed, for example, by surgical repair of the renal artery or by removal of the adrenal tumour. In virtually none of the different types of secondary hypertension are we, however, clear about the exact sequence of physiological disorders which lead to elevation of the blood pressure. These are not likely to be all the same but point to various mechanisms by which the blood pressure can be permanently altered. They also highlight the great complexity of the 'system' controlling the body's blood pressure.



THE BLOOD PRESSURE CONTROL SYSTEM

The diagram shows that:
*Blood pressure = Cardiac output x Vascular resistance*

Cardiac output depends on the capacity of the blood volume available for venous filling. The blood volume in turn depends on the function of the kidney. The diagram shows that the central nervous system through the various peripheral autonomic nerves can alter the activity of the heart, the degree of constriction of the small arteries that help to distribute blood to the tissues and the calibre of the veins. Vascular diameter can also be influenced by certain hormones, some of which are also important in the control of salt composition and fluid balance of the body.

High blood pressure is regarded as a disorder of the circulatory control system. Probably the 'cause' of essential hypertension is not the same in every patient and there are several factors that may contribute. Suggestions that have been made are that high blood pressure may be the result of (1) hyperactivity of the sympathetic nervous system; (2) some abnormality of the way in which the kidney handles salt and water, or (3) some abnormality in the contractile mechanisms of the vascular smooth muscle itself.

The block diagram showing the circulatory control system represents a gross oversimplification of what actually happens in the body. However, it emphasises that in a system with so many interacting variables it is often a matter of great difficulty to find out whether a particular component of the system is working satisfactorily or not. A primary disturbance of, for example, the central nervous system will tend to affect in time all the components of the blood pressure control system. Thus it may lead to changes in the distribution of blood flow, changes in the function of the kidney and many other effects which in turn may lead to secondary changes in nervous activity and body hormone balance. These many interactions are what have made the unravelling of the primary disturbance of essential hypertension so difficult in man. If ever a disorder calls for a multiplicity of approaches involving several components of the cardiovascular control system it is hypertension.

## Autonomic Nervous System and Control of Blood Pressure

### Essential Hypertension

There has been much speculation whether or not overactivity of the sympathetic nervous system is a trigger mechanism in the causation of essential hypertension in man. It is an important question whether the stress of modern living, or abnormal processing by the nervous system of the information it receives, may lead to high blood pressure. We now know that in something like 20-30% of young patients with mild essential hypertension the rise in blood pressure is associated with signs of sympathetic overactivity. One of the strongest pointers of sympathetic overactivity to date has been the demonstration in many of these patients of an increased concentration of noradrenaline in their plasma. Noradrenaline is the transmitter released from the sympathetic nerve endings during a nerve impulse. The released noradrenaline produces constriction of blood vessels and stimulates the heart. The transmitter acts on receptors in the heart and vessels to produce these effects. Some of the noradrenaline is then again taken up again by the nerve ending, and some spills over into the circulation. The blood concentration of oradrenaline thus is the resultant of two simultaneously occurring processes:— (i) release of noradrenaline from sympathetic nerves; (ii) removal from tissues after release. Either of these processes could be abnormal in patients with essential hypertension, and it is important to know something about each process.

During the year Dr Murray Esler has developed methods designed to find out whether transmitter release and/or removal are altered in hypertension. These methods involve determination of the clearance from the plasma of minute amounts of radioactively labelled noradrenaline by means of standard pharmacokinetic analysis. Preliminary results have shown that compared with normal subjects clearance of noradrenaline from the plasma is *increased* in something like 30-40% of young hypertensive patients and is normal in the remainder. These results suggest that when the noradrenaline plasma levels are raised in patients with hypertension this is the result of increased transmitter release from the nerve terminals and not of defective clearance. Methods have been developed for measuring apparent noradrenaline

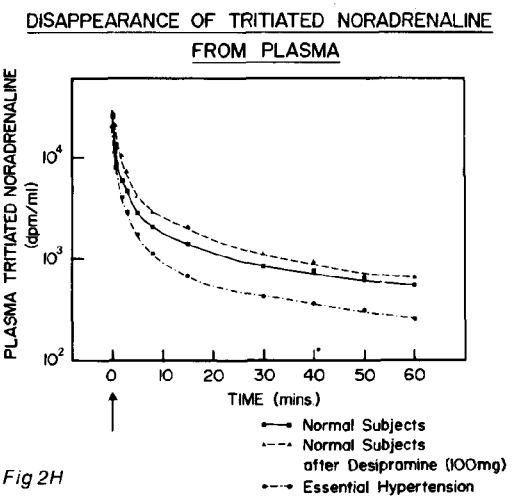



*Fig 2H*

*The rate of removal of tritiated noradrenaline from the circulation was increased in patients with essential hypertension.*

secretion rate directly and for studying differences in the properties of the amine 'pump' important in the re-uptake of noradrenaline. The latter is measured in the blood platelets of hypertensive patients and normal subjects. Blood platelets serve in this instance as a convenient model of cellular processes at the sympathetic nerve terminal. If there were genetic abnormalities in membrane processes of the hypertensive patient they will probably become apparent in the platelet model. These techniques are now established at the Baker Institute and will provide important tools in helping characterise a subset of hypertensive patients with possible abnormality of sympathetic function. It should then be possible to find out whether this abnormality is a primary event or is secondary to other changes occurring in the blood pressure control system.

### Central Nervous Transmitters

The nervous control of blood pressure involves many sites in the brain which integrate information received from the nervous system. The nerves connecting the different centres release small packets of chemicals called transmitters at their endings (much as described above for the peripheral sympathetic nerves) which alter the activity of the centres to which the nerves project. Our work has tried to define the role of the nerve cells within the central nervous system which release noradrenaline at endings in different parts of the brain.

The noradrenaline-containing nerve cells are closely associated with many regions of the brain known to be involved in the control of blood pressure. However, there is relatively little knowledge available about what the noradrenergic pathways do. There has even been a recent controversy whether stimulation of the 'noradrenergic' pathways excites or whether it inhibits the nerve cells in the spinal cord which give rise to the peripheral sympathetic fibres.

One particular difficulty in the analysis is that the pathways containing noradrenaline in the brain are only *one* of several transmitter systems. There are other nerves in parallel with the noradrenergic nerve cells using different transmitters including serotonin, dopamine and probably many others. This multiplicity of transmitter systems has made the study of interrupting only one component of the nervous pathways a particular difficult one. However, the group working on this problem, including Professor Korner, Dr. Reynoldson, Miss Oliver and Mr. Head have made much progress during the year and we are now a good deal clearer about the role of noradrenaline as a central transmitter.

The work has been done in rabbits and has involved studying the circulatory and behavioral effects which follow injection into the cerebrospinal fluid of a chemical substance, 6-hydroxydopamine, which destroys the central noradrenergic neurones. The substance is actively taken up by the nerve endings causing release of noradrenaline from the storage vesicles and eventually destruction of the central noradrenergic neurones. In the first few hours after injecting 6-hydroxydopamine the observed responses depend partly on the effect of this release of noradrenaline on other nerve cells, and partly on the effects of blockade. The late effects after destruction of the ending depend on the loss of the noradrenergic nerve cells.

Last year we reported that after injection of 6-hydroxydopamine there is a marked reduction in the intake of food and water in the animals for a period of 7-9 days after injection, which results in a loss of 10-15% of their body weight. The effect appears to be a fairly specific alteration in behaviour, with the animals alert and without any other impairment of their motor function. The effect of increased activity of the noradrenergic pathway going from the lower brainstem to the 'higher' cardiovascular centres is excitation of sympathetic nervous activity. On the other hand, increased activity of the descending pathways from the lower brainstem to the spinal cord inhibits sympathetic constrictor activity. These opposing influences have undoubtedly been the cause of much previous confusion regarding the function of the noradrenergic neurones of the brain. We used a combination of anatomical and chemical lesions to sort out this problem. One week after giving noradrenaline in the intact animal, blood pressure is significantly reduced probably due to the loss of influences from the higher cardiovascular centres which contribute to the tonic control of blood pressure. The level of the blood pressure thus is dependent on the overall excitatory and inhibitory effects of the central nervous noradrenergic pathways. Certain drugs such as *clonidine* used in the treatment of hypertension lower blood pressure by producing disproportionate stimulation of the lower brainstem inhibitory pathway of the noradrenergic neurones.

We have studied the effects of destruction of the noradrenergic neurones on a whole battery of reflexes involving a large range of distinctive pathways in the central nervous system. Small but significant alterations in reflex properties were observed in all reflexes tested as detailed later in this report. This indicates that the noradrenergic pathways play a role in many of the moment-to-moment adjustments of the circulation by the central nervous system. Perhaps the most important point was that despite extensive destruction of the noradrenergic neurones involving a lowering of spinal cord catecholamine content by 70-80% the effect on all the reflex pathways tested were only *small*. In fact they would have not been readily detected had we not utilised very sensitive methods for assessing changes in reflex properties. The most likely explanation is that some of the nerves utilising transmitters other than noradrenaline compensate to a large degree for the loss of noradrenergic pathways.

**Kidney and Hypertension**

Narrowing of the renal artery is one of the relatively common causes of 'secondary' hypertension in man, and is also one of the oldest methods of experimentally produc-

ing hypertension in animals. Studies performed by Dr. Warwick Anderson in collaboration with Professor C. I. Johnston and Professor P. I. Korner have demonstrated an important new intrarenal role of the renin-angiotensin system in the restoration of renal perfusion pressure soon after experimental induction of renal artery stenosis. The study highlights how much there is still to be learnt about the 'known' causes of hypertension.

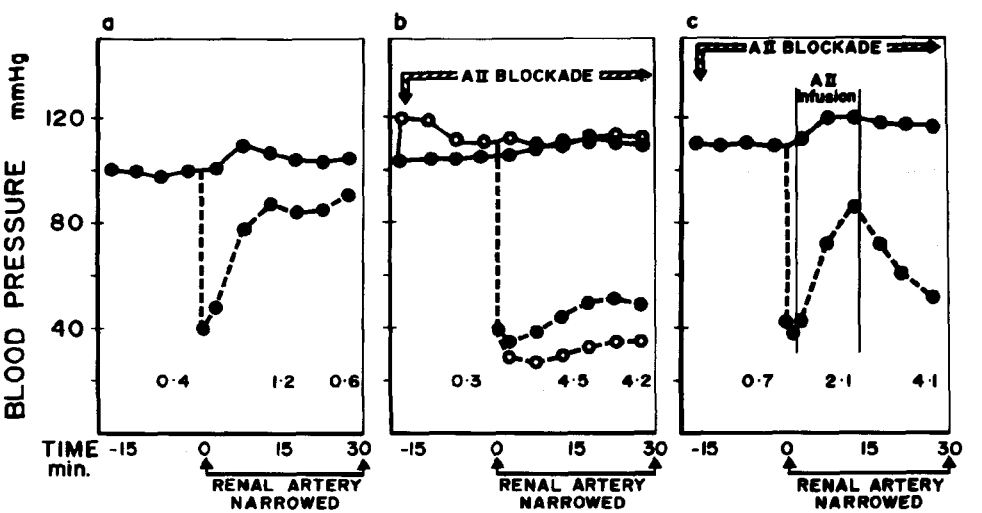
In experiments performed in trained instrumented dogs graded renal artery stenosis was induced by inflating a cuff that had been placed around the renal artery. The dogs also had instruments for measuring changes in blood flow to the kidney and the pressure in the renal artery distal to the cuff as well as the general level of the blood pressure. Narrowing of the renal artery by inflating the cuff so that it would alter the diameter by about 75% produced a transient reduction in pressure and blood flow and a large dilatation of the small blood vessels of the kidney. The reduction in pressure in the renal artery results in the increased release by the kidney of an enzyme called renin. Renin acts on a component of the proteins in the blood plasma to produce another substance, angiotensin I, which in turn is converted to another peptide, angiotensin II, which is a powerful constrictor of blood vessels. Angiotensin II acts to overcome the dilatation in the small arteries of the kidney originally produced by the renal artery narrowing and helps to restore the distal renal artery pressure very close to normal. One important effect of this restoration of pressure is that it helps to maintain the normal filtering function of the kidney. The increased secretion of renin and its return upon restoration of pressure is accomplished through a renal 'barostat' — a receptor that is sensitive to renal artery pressure changes. Restoration of the distal renal artery pressure after stenosis can be prevented by giving inhibitors of angiotensin II formation or angiotensin II blocking drugs. The kidney's ability to maintain distal renal artery pressure and almost normal excretory function can be maintained after narrowing the diameter of the renal artery by as much as about 80-85%. For milder degrees of narrowing restoration of the renal blood pressure occurs very rapidly in about 30 minutes, but with greater narrowing it takes about 1-2 days.

***LEGEND***
***(Fig 3H)***

***Recovery of pressure distal to a stenosis of the renal artery***

*Arterial blood pressure (solid lines), renal artery pressure (broken line) and plasma renin activity (numbers at bottom of each graph) changes following renal artery narrowing. (a) Normal response showing recovery of pressure distal to the stenosis; (b) Response in dogs with prior blockade of the renin-angiotensin system (open circles, Sar¹,Ile⁸ AII; closed circles, AI converting enzyme inhibitor) # recovery of renal artery pressure is abolished; (c) Simulation of normal recovery of renal artery pressure, by infusion of angiotensin II into the renal artery of dogs pretreated with converting enzyme inhibitor.*

*In all cases, the renal artery narrowing was achieved by inflation of a cuff around the renal artery to lower pressure distally to 40 mmHg over 30 seconds (at first vertical arrow). This degree of artery narrowing was then maintained (by clamping the cuff tubing) until the end of the experiment.*



As long as the renal artery pressure can be restored through the renal barostat mechanism high blood pressure does not develop. The action of the renin-angiotensin system under these conditions is responsible for normal maintenance of the filtering function of the kidney. When the renal artery is narrowed by about 90% restoration of renal artery pressure cannot be accomplished through this mechanism alone and the general blood pressure of the body then goes up. Although eventually renal blood pressure returns to its initial value secondarily to this rise in the body's blood pressure it no longer can turn the renin-angiotensin system off completely, nor does it completely restore renal excretory function.

Stronger stimulation brings other control mechanisms of renin secretion into play in response to the greater degree of renal impairment. Hence development of high blood pressure probably helps to provide reasonable renal function. With still greater renal impairment colossal quantities of aniotensin are formed in so-called malignant hypertension which produces such high blood pressures as to result in rapid demise. With the less severe degrees of stenosis the presence of this powerful action of the renin-angiotensin system in the kidney helps to explain why renovascular hypertension in man occurs in only a small proportion of patients with renal artery stenosis.

**Beta-Blocking Drugs and Blood Pressure Control**

There has been much debate on how beta-blocking drugs lower blood pressure. There is general agreement that part of the effect is mediated by peripheral blockade of the cardiac beta receptors but these cannot fully explain the hemodynamic effect in a proportion of patients. A question that has therefore arisen is whether these drugs also block central nervous beta-receptors. If this were so one might expect an effect rather similar to that of the central $\alpha$-agonist drug, clonidine, which produces attenuation of vasoconstrictor reflexes. Dr. Pat Dorward and Professor Korner have recently obtained evidence of a small central beta-blocking action of propranolol, one of the most commonly employed beta blocking drugs in the treatment of high blood pressure. Renal sympathetic nerve activity was recorded in anaesthetized animals and the effect of the drug on the renal baroreflex was investigated, i.e. on the normal relationship between efferent sympathetic nerve discharge and blood pressure. Normally as blood pressure increases there is inhibition of sympathetic activity and the opposite occurs as blood pressure decreases from the resting value. With propranolol the threshold for inhibition of renal sympathetic activity is lower than normal so that over a range of blood pressure there is less sympathetic nerve discharge after beta-blockade than under control conditions before block. We have found that these effects on the reflex cannot be explained by the effects of the drug on the baroreceptors themselves and it is most likely to be a central nervous effect of the drug. This mechanism is probably of therapeutic significance.

**Visit by Professor Iriki**

During the year one notable event was the return visit from Professor Masami Iriki from the Tokyo Metropolitan Institute of Gerontology. He introduced to us the technique of Ninomiya and colleagues of recording sympathetic nerve activity in unanaesthetized animals. This is done by means of a special collagen fibre electrode. The technique promises to be a particularly valuable one. We are greatly indebted to Professor Ishio Ninomiya whose appointment to become Chairman of Physiology in a new Cardiovascular Research Institute in Osaka, Japan, prevented a personal visit. We are, as always, indebted to Professor Iriki who has contributed much over the last two years to the Neurosciences Laboratory of the Institute.

**Other Studies**

During the last year Dr. Jeffrey Hutchinson has done much work on the so-called brain renin-angiotensin system. Several years ago Ganten, Hutchinson and Schelling discovered large concentrations of a renin-like material in many parts of the brain. Interest in this material became very great when it was found that injecting drugs which antagonise the action of angiotensin II lowered the blood pressure of rats with spontaneous genetically determined hypertension. After the initial enthusiasm, however, the pendulum has swung hard against the brain renin-angiotensin system. Several workers have been unable to find significant concentration of immunoreactive angiotensin in brain tissue and previously observed high brain angiotensin levels in many different brain regions are now considered to be largely a methodological artefact. Dr. Hutchinson

has critically examined the brain renin system methodology. He has developed a new method, apparently free of previous artefacts which suggests that there is indeed a brain renin-angiotensin system, though it is located in only a few sites in the brain and is not nearly as widely distributed as suggested by the earlier work. Dr. Hutchinson has accepted an appointment at the Department of Medicine, Austin Hospital, and will be continuing the studies there.

Another study performed in collaboration with Dr. Peter Fletcher relates to the role of salt in the development of renal hypertension. Previously we had found that despite a 25-fold variation in dietary salt intake there was no difference in the magnitudes of renal hypertension produced by bilaterally wrapping both kidneys in cellophane. This year we have studied the renal hypertension after cellophane wrapping in rabbits with only one kidney. In contrast to animals with both kidneys where the plasma renin activity increased by a normal amount in response to low salt in their diet, the animals with only a single kidney have a blunted renin response to low salt. In many ways their responses are not unlike those of 'low-renin' hypertension in man.

A new project was started in collaboration with Dr. A. Bobik and Dr. A. Broughton to examine the mechanisms underlying the altered response of the hypertrophied heart during increased sympathetic stimulation. This has involved physiological analysis of the mechanisms setting limits on contractile performance of the enlarged heart. We are examining whether myocardial hypertrophy is associated with changes in the number of beta-adrenoreceptors on the membrane of the heart muscle, and the various factors which determine the intracellular concentration of cyclic AMP, a substance which is of particular importance in bringing calcium ions to the contractile proteins of the heart.

***Back (left to right):*** *Matthew Le Duc, Dr. Murray Esler, Dr. Jim Reynoldson, Dr. Warwick Anderson, Aina Martin, Pam Graham, Dr. Arch Broughton, Ann Heal, Judi Csicsmann, Dr. Jeff Hutchinson.* ***Seated:*** *Libby Anderson, Judy Oliver, Professor Paul Korner, Dr. Patricia Dorward, Dianne Kelleher.*

## DETAILS OF PROJECTS

### 1. Rate of removal of noradrenaline from plasma in normal and hypertensive men

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

There is a longstanding viewpoint that overactivity of the sympathetic nervous system underlies the blood pressure elevation in at least a proportion of patients with essential hypertension. This idea has been strengthened by recent reports that the plasma concentration of noradrenaline, the chemical transmitter of the sympathetic system, is elevated in many hypertensive patients. But the plasma level of noradrenaline is determined by two simultaneous processes, secretion rate and removal rate. It is not clear whether the higher plasma concentration noted in hypertensive patients truly reflects an elevated rate of noradrenaline release from sympathetic nerves (sympathetic 'overactivity') or whether it results from slower noradrenaline removal from plasma after release.

The rate of removal of noradrenaline from plasma was studied in healthy men and male patients with untreated essential hypertension. A small bolus dose of radiolabelled noradrenaline was injected intravenously (0.3 $\mu$g, 0.08 mCi), and the rate at which the noradrenaline was cleared from the plasma was followed over 60 minutes with sequential sampling of arterial blood from a brachial artery catheter.

The rate of removal was extremely rapid in normal subjects, only 5% of the total dose remaining in the circulation 5 minutes after injection. The tricyclic antidepressant disipramine, which inhibits the active transport system for cellular uptake of noradrenaline, in a single oral dose of 100 mg reduced the removal rate of noradrenaline by approximately 50% (Fig. 2H).

In patients with essential hypertension, tritiated noradrenaline was removed from the circulation more quickly than in normal subjects, at about double the normal rate. Since the plasma concentration of noradrenaline is often elevated in patients with essential hypertension the secretion rate of noradrenaline must often be high in face of the increased rate of removal from plasma which we describe here. Sympathetic overactivity is thus present in these patients and may be the cause of the blood pressure elevation.

*Dr. Garry Jennings.*

### 2. CNS Pathways Involved in the Rise in Blood Pressure and Fall in Heart Rate after Intracisternal Injection of 6-hydroxy-dopamine

P. I. Korner, J. R. Oliver, J. A. Reynoldson, G. A. Head, V. Carson and M. R. Walker

Instrumented rabbits were given 6-hydroxydopamine or ascorbic acid vehicle while anaesthetised with propranidid, an ultra-short acting anaesthetic. 6-hydroxydopamine resulted in a rise in blood pressure of 26 ± 3.7 (s.e.m.) mmHg, and a fall in heart rate of 59 ± 11 beats/min and there were no significant effects in animal given vehicle. Maximal changes occurred about 2.5 h after injection. The effects were virtually identical when 6-hydroxydopamine was injected without anaesthesia through a special implanted polyvinyl chloride cannula.

The rise in blood pressure was due to marked systemic vasoconstriction involving predominantly the renal and splanchnic beds but with little change in the muscle bed as assessed from distribution of injected microspheres. This suggests that the pressor response was not mediated through the central nervous baroreceptor pathways. The distribution of the vascular resistance changes resembles the effects of electrical stimulation of the hypothalamic pressor regions. To test whether the rise in blood pressure was mediated through suprapontine pathways 6-hydroxydopamine was injected in pontine preparations with only the lower brainstem and spinal

cord centres intact. This results in an immediate fall in blood pressure which was maximal after ½ h and was associated with a variable heart rate response. Therefore, in animals with intact CNS the acute rise in blood pressure after 6-hydroxydopamine is mediated through suprapontine pathways.

The acute hypertension after 6-hydroxydopamine probably resulted partly from noradrenaline release since it was diminished after central administration of the blocking drug phentolamine.

The results suggest that the suprapontine noradrenergic pathways controlling blood pressure are mainly excitatory and that bulbo-spinal pathways exert inhibitory effects.

**3. Behavioral and Reflex Changes after intracisternal injection of 6-hydroxydopamine**

P. I. Korner, J. R. Oliver, J. A. Reynoldson, G. A. Head and V. Carson

After injection of 600 *u*g of 6-hydroxydopamine rabbits did not eat and hardly drank for 7-9 days after injection and lost on average 10-15% of their body weight. To avoid non-specific cardiovascular effects on the various reflexes the animals were artifically fed through a permanent gastrostomy tube which greatly reduced the weight loss.

We studied (i) the baroreceptor-heart rate reflex; (ii) a Valsalva-like reflex; (iii) the reflex response to arterial hypoxia; (iv) the nasopharyngeal reflex. Each of these reflexes involves distinct afferent mechanisms so that the battery of tests examines the role of noradrenergic neurones on different CNS pathways. Our previous afferent analysis in the rabbit has shown that the baroreceptor-heart rate reflex is mediated predominantly through the carotid baroreceptors with the aortic baroreceptors playing a much smaller role. The reflex response to arterial hypoxia is mediated through the arterial chemoreceptors, arterial baroreceptors and through lung inflation receptors. The nasopharyngeal reflex is mediated through trigeminal and arterial baroreceptor afferents and only minimally through the arterial chemoreceptors. The Valsalva reflex is mediated through aortic (but only minimally carotid) baroreceptors and through cardiopulmonary baroreceptors.

The baroreceptor-heart rate and nasopharyngeal reflexes were tested for the

*Operating to implant flowmeters in a rabbit, Dr. Jim Reynoldson.*

first few hours after injecting 6-hydroxydopamine (or vehicle) and 7 days after injection. After 6-hydroxydopamine the baroreceptor-heart rate reflex was reset about the higher resting blood pressure and there was enhancement of the range of heart period changes. After 7 days the reflex had recovered completely in animals with brain intact. However, in decerebrate rabbits the range of heart rate changes and the sensitivity of the baroreceptor-heart rate reflex was about 30% less than in vehicle-treated decerebrate rabbits. The latter suggests functional impairment in the bulbo-spinal component of the noradrenergic pathway which is masked in animals with all pathways intact.

The effects of the nasopharyngeal reflex consisted of less satisfactory maintenance of blood pressure during stimulation compared with control but with no changes in cardiac slowing during the first few hours after injection. The effects were still present 7 days after injecting the drug.

The Valsalva-like reflex was studied 7 days after injection. After 6-hydroxydopamine the cardiac output fell more for a given rise in intrathoracic pressure and blood pressure was less well maintained. The reason for this greater fall in cardiac output is probably a somatic deficit rather than an autonomic one. There appeared to be less tensing of limb musculature during application of Valsalva pressure with loss of muscle pump action and a greater

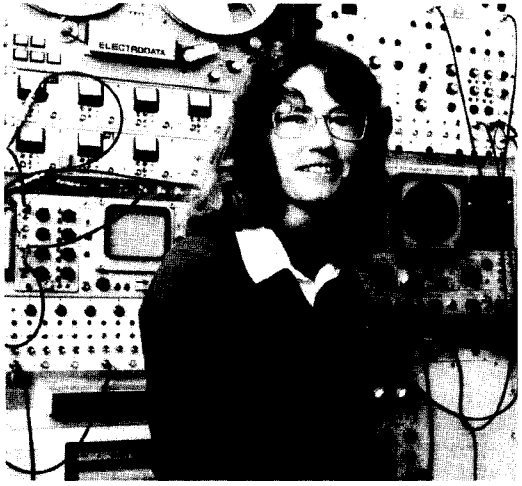
displacement of blood from the thorax and abdomen to the limbs in 6-hydroxydopamine treated animals. It was not observed in decerebrate preparations pre-treated with the drug, in which somatic muscle tone was greater. There was also some impairment in the heart rate response to the Valsalva reflex. There was only slight attenuation in the cardiovascular response to arterial hypoxia.

The results have indicated behavioral and cardiovascular effects mediated through noradrenergic central autonomic pathways. The results of the reflex analysis suggest that noradrenergic pathways are only one of the transmitter systems involved and that after depletion there is compensation through pathways using other transmitters.

**4. Effect of Propranolol on Renal Sympathetic Baroreflex Properties and Aortic Baroreceptor Activity**
Patricia Dorward and P. I. Korner

Sigmoid renal baroreflex curves relating mean arterial pressure to integrated renal sympathetic nerve activity were obtained in anaesthetised rabbits with previously implanted balloons to raise and lower blood pressure. Control curves were obtained during saline infusions and propranolol was given to reach plasma levels over 300 ng/ml over the period of measurement. This reduced blood pressure by 9.6 ± 1.1 mmHg but had no effect on resting sympathetic discharge. Proprano ol lowered threshold of the renal baroreflex. Median blood pressure was reduced by 15.4 ± 1.9 mmHg, but there was no change in gain or sympathetic activity range. Thus, at a given blood pressure there was diminution of sympathetic discharge compared with control. Similar changes in baroreflex curves occurred after giving a low dose of clonidine intravenously. However, 'non-specific' reduction in blood pressure produced by bleeding or nitroprusside infusion produced no resetting of the baroreflex curves, though the resting sympathetic discharge increased.

The effects of propranolol (plasma levels 137 and 348 ng/ml) on arterial baroreceptor discharge were studied in separate experiments. Mean arterial pressure-integrated aortic nerve activity curves were derived and at the two levels of propranolol there was a small reduction of aortic nerve discharge averaging about 7% of control. Single unit analysis showed a small reduction in firing frequency/sec near the threshold, which was sufficient to explain the changes in integrated aortic nerves discharge. Since the changes in input from the aortic baroreceptors do not account for the reduction in threshold of the renal baroreflex, we conclude that the latter is due to the central nervous action of propranolol.




*Dr. Patricia Dorward surrounded by electronic equipment used for recording electrical activity on nerves.*

**5. Chemoreceptor and Baroreceptor Influences on Sympathetic Efferents to the Ear**
*M. Iriki, P. I. Korner and Patricia Dorward

The efferent sympathetic nerves to the ear of the rabbit play an important role in temperature control. Whether this particular pool of autonomic neurones is under the control of the arterial baroreceptors has not been previously defined. In the present study mass ear sympathetic nerve discharge was recorded in anaesthetised rabbits and blood pressure raised and lowered by the usual method of inflating aortic and vena caval perivascular balloons. In intact rabbits there was no change in the ear sympathetic efferent discharge during large changes in blood pressure whilst the animals were breathing air. However, during arterial hypoxia there was pronounced inhibition of sympathetic activity and there was now a small rise in efferent discharge with increasing blood pressure. The latter was abolished by vagotomy, and the evidence suggested that it was due to cardiopulmonary-chemoreceptor interaction. The inhibition during arterial hypoxia was

abolished by cutting the carotid sinus and aortic nerves indicating that it was mediated through the arterial chemoreceptors. We conclude that there is virtually no arterial baroreceptor representation in the ear sympathetic motor neurone pool. The chemoreceptor pathways can, however, influence its activity and its influence is similar to that previously observed in the cardiac sympathetic. In addition, the ear sympathetic can be influenced through cardiopulmonary baroreceptor pathways.

*Visiting Scientist: Professor of Physiology, Tokyo Metropolitan Institute of Gerontology

**6. Recording of Sympathetic Nerve Discharge in Unanaesthetised Animals**
M. Iriki and Patricia Dorward

During the year we learnt the technique originally introduced by Ninomiya and associates of recording sympathetic efferent activity and arterial baroreceptor discharge in unanaesthetised animals. The recording is done by means of a collagen fibre electrode which is implanted at a preliminary operation several days before the experiment. To-date we have used this successfully for recording renal sympathetic and aortic nerve mass discharge. We have obtained renal baroreflex function curves and mean arterial pressure-aortic nerve discharge curves by raising and lowering blood pressure in these animals with our standard method of inflating perivascular balloons. We have examined renal baroreflex resetting of the renal sympathetic discharge in arterial hypoxia and also the effect of the nasopharyngeal (smoke) reflex. One interesting finding, not obvious from our previous cardiorespiratory analysis, has been the observation that the latter reflex is terminated by a long inhibitory 'silent' period similar to that generally observed in somato-sympathetic reflexes.

**7. Brain Renin System**
J. S. Hutchinson and J. Csicsmann

During the year the work has consisted of developing methods which will permit detection of brain renin-angiotensin that is free of the artefacts of previous methods. The method is a dialysis exchange method which does not have the angiotensinase artefacts of previous methods. The immunoreactive angiotensin I and II are found in highest concentration in the pituitary gland and the thalamus and the hypothalamus. These are regions which have previously been shown to be important sites in the central nervous system for the actions of angiotensin on blood pressure and release of anti diuretic hormone. The presence of brain angiotensin has been observed in previously nephrectomized rats, showing that it comes from brain and not from kidney.

The most recent work we have done has involved the development of a method that is simpler than the time-consuming dialysis technique.

Because the angiotensin I is bound to protein a centrifugation method which uses effective enzyme inhibitors has been developed. This yields more immunoreactive angiotensins than the dialysis method and should simplify future biochemical and biological characterisation.

**8. Acute Renal Haemodynamic and Renin-Angiotensin System Responses to Graded Renal Artery Stenosis and their Relationship to the Development of Hypertension in Conscious Dogs.**
W.P. Anderson, P. Korner, *C.I. Johnston and *C.J. Casley

Graded renal artery stenosis was studied in conscious instrumented dogs with one remaining kidney. Stenosis was induced by rapidly inflating a renal cuff over 30 sec to lower distal renal artery pressure to 60, 40 or 20 mmHg and then maintaining stenosis for 1 hour in the first two grades and for six days in the third grade. In the first two grades mean arterial pressure hardly changed, but in the third it had increased by 18 ± 2.5 mmHg by the end of 1 hour. Soon after stenosis distal renal artery pressure, renal blood flow and renal vascular resistance fell significantly and plasma renin activity (PRA) and angiotensin II (AII) rose all in proportion to the severity of stenosis. Renal artery pressure, renal vascular resistance, PRA and AII became almost completely restored in less than 1 hour in the two mildest grades and in 2-3 days in the third grade. In the latter, blood pressure also returned to normal and plasma creatinine did not change. However, renal blood flow was significantly reduced in all groups even after return of distal renal artery pressure, suggesting that 'critical' stenosis had been exceeded in all our experiments. In dogs pretreated with converting enzyme inhibitor or AII antagonists restoration of renal artery pressure and renal vascular resistance was abolished, suggesting that in the normal dog the restoration was mediated

through renal effects of AII. Moreover, their restoration was a major factor in turning off renin secretion through the renal barostat. (Fig. 3H) This is suggested by the reciprocal nature of the renal haemodynamic and hormonal changes in normal dogs and by the small effects of renal vascular resistance when converting enzyme inhibitor was infused late in stenosis.

More severe stenosis was induced by rapidly lowering distal renal artery pressure to 20 mmHg four times over one hour and maintaining stenosis for the next 6 days. Mean arterial pressure showed a sustained increase of 35 ± 11 mmHg. PRA reached a maximum after 1 hour, falling to a steady level of about 2.5 x control and remained high despite eventual restoration of renal artery pressure. Plasma creatinine was 156% of control suggesting diminished glomerular filtration. Sustained 'one-kidney' hypertension appears to require stenosis severe enough to overtax the capacity of the renal barostat to restore renal artery pressure and renal vascular resistance and thus maintain renal function.

*Monash University Department of Medicine

**9. Role of Vasopressin in Blood Pressure Control and Hypertension**

*P. Pullan, *C.I. Johnston, W.P. Anderson and P.I. Korner

Vasopressin (antidiuretic hormone) is vasoactive and it has been suggested that it is important in the control of blood pressure. The pressor sensitivity to vasopressin was determined by infusing 6 conscious dogs intravenously with arginine vasopressin before and after total autonomic blockade (dose range 1-25 mu/kg/min). We measured their blood pressure, pulse rate and plasma vasopressin levels. Before autonomic blockade the pressure threshold was achieved after the plasma vasopressin concentration had risen from a basal level of 7.3 ± 1.7 to 150 pg/ml and was linear over the range 100-10,000 pg/ml. However, bradycardia was evident at plasma levels of 30 pg/ml. By contrast, in the autonomically blocked dog pressor sensitivity was greatly increased and significant rises in blood pressure of 9 mmHg occurred with the lowest infusion rate which produced a rise in plasma vasopressin averaging 23 pg/ml. The dose response curve was steeper than in intact dogs and was shifted to the left.

In six dogs with a single remaining kidney acute renal hypertension was induced by constricting their renal artery with a perivascular balloon cuff. These dogs had rises in blood pressure, plasma renin activity and angiotensin concentration and a rise in plasma vasopressin from basal levels of 6.9 ± 0.7 to a maximum of 10.2 ± 0.9 pg/ml ($P > 0.01$) over the next five days. However, immediately upon renal artery constriction over the first hour of stenosis though blood pressure, plasma renin activity and angiotensin II increased, there was no change in plasma angiotensin and vasopressin in the acute state suggesting that the rise in vasopressin in the chronic part of the study is not related to changes in renin-angiotensin system activity. In general, the results support the view that vasopressin under certain circumstances may contribute to the control of blood pressure.

**10. Regional Blood Flow and Vascular Resistance in Rabbits with Chronic Renal Hypertension**

P. J. Fletcher and P. I. Korner

Regional blood flow and cardiac output were compared in six hypertensive rabbits in which one kidney had been removed 10 weeks before and the other kidney wrapped in cellophane, and six normotensive rabbits where one kidney had been removed and the other subjected to sham-operation. Mean arterial pressure was 137 ± 4.4 mmHg in the wrap animals and 97 ± 2 mmHg in the sham treated group. Cardiac output was reduced by 30% in wrapped animals compared with the normotensive sham-operated group. Blood flow to skeletal muscle was greatly reduced in wrapped animals (5.2 ± 0.7 ml/min/100g) compared with the control group (10.2 ± 1.5 ml/min/100g. This difference was sufficient to account entirely for the reduction in cardiac output. Blood flow to all other organs studied (heart, kidney, brain, skin, small intestine and adrenal glands) was similar in both groups. Total peripheral resistance in the wrapped animals was increased by 95% and the increase in resistance was greatest in skeletal muscle (170%). The results show that increase in regional vascular resistance in this type of hypertension is not uniform and may either present a primary haemodynamic abnormality in renal wrap hypertension or be the result of impairment of arterial baroreflex function in these animals.

**11. Comparison of Renin and Blood Pressure Responses to Different Dietary Sodium Intakes in Hypertensive Rabbits due to Bilateral Cellophane Wrapping of the Kidneys or Cellophane Wrapping of a Single Remaining Kidney.**

P. J. Fletcher and P. I. Korner

The rise in blood pressure was the same in bilaterally cellophane wrapped rabbits as in wrapped rabbits with a single remaining kidney. In both groups the effect was entirely accounted for by a rise in total peripheral resistance. In bilaterally cellophane wrapped rabbits the rise in plasma renin activity (PRA) and plasma renin concentration (PRC) was the same when the animals were placed on a low salt diet as in a corresponding group of sham-operated animals. On the other hand, in wrapped animals with only one remaining kidney the renin response was blunted and there was a smaller rise in plasma renin activity and plasma renin concentration than in corresponding sham-operated rabbits with only a single kidney.

When bilaterally wrapped animals were on a low sodium diet they had the same blood pressure as on a high salt diet. By contrast wrapped rabbits with only one kidney had a small but significant reduction in blood pressure when placed on a low salt diet. The reason could have been the attenuated renin response providing less effective compensation for the fall in body fluid volume when only one kidney is present.

**12. Measurement of Cardiac Contractility**

A. Broughton and P. I. Korner

Left ventricular performance may be assessed by measuring pumping capacity where cardiac output or stroke volume are related to filling pressure, or in terms of muscle mechanics such as the maximum rate of pressure rise during the isovolumetric phase of systolic dP/dt max. Ventricular filling pressure approximates the preload on the heart and mean aortic pressure approximates the afterload. The influence of these loading factors on the performance of the ventricle has often been studied in the past, but controversy remains regarding the relationship of the afterload to cardiac output and dP/dt max. Some authors have found that cardiac output was almost independent of aortic pressure over a large pressure range whilst others have found an inverse relationship between cardiac output and arterial pressure. There is similar uncertainty regarding the relationship between afterload and dP/dt max, and most workers have concluded that there is a positive correlation between them. In most studies left ventricular filling pressure during the changes in afterload has not been controlled.

We have developed a preparation in anaesthetised dogs in which left ventricular preload and afterload could be controlled independently and the effects of changes in autonomic activity during pressure changes eliminated. In this preparation dP/dt max was recorded by means of a catheter tip micromanometer and electronic differentiator, and cardiac output was measured by thermodilution. In this preparation altering aortic pressure whilst maintaining preload constant has shown that dP/dt max is virtually independent of aortic diastolic pressure provided the latter exceed 70-80 mmHg. However, under conditions where contractile activity was doubled by infusing Calcium, dP/dt max was pressure-independent at aortic diastolic pressure greater than about 100-110 mmHg but below this level there was a small decline, presumably due to limitation of coronary blood flow. When left atrial pressure was varied from 8-30 mm Hg whilst holding arterial pressure constant, there was a plateau of dP/dt max at left atrial pressures between 15-25 mmHg; at 30 mmHg there was a small decline suggesting some fall off in contractility at these large cardiac dimensions.

There was an almost linear relationship between cardiac output and aortic blood pressure with cardiac output declining as blood pressure increased. Cardiac output-arterial pressure curves with different left atrial filling pressures lay approximately parallel to one another with large cardiac output at higher filling pressures. The relationship of stroke volume to left atrial pressure was curvilinear but stroke volume had not levelled off up to pressures of 30 mmHg. This differs from the conventional ventricular function curves where the outflow becomes limited by a fixed Starling peripheral resistance.

# CARDIOVASCULAR METABOLISM AND NUTRITION RESEARCH UNIT

***Back (left to right):*** *Jane Ma, Andrea Poyser, Lyn Taylor, Andrew Gross, Denise Winter, Dr. Michael Reardon, Elaine Fagarazzi, Margaret O'Connor;* ***Seated:*** *Dr. Timothy Billington, Dr. Paul Nestel, Dr. Noel Fidge.*

**Major Research Interests**

- LIPOPROTEIN METABOLISM
- CHOLESTEROL METABOLISM
- EPIDEMIOLOGY OF HYPERLIPIDAEMIA AND CORONARY DISEASE
- DIETS IN HYPERLIPIDAEMIA

**General Summary**

The Unit has been in operation for one full year. The staff comprised three senior research scientists, two post-doctoral fellows (one from Japan), and support staff of four science graduates, a dietitian, one laboratory technician and a secretary.

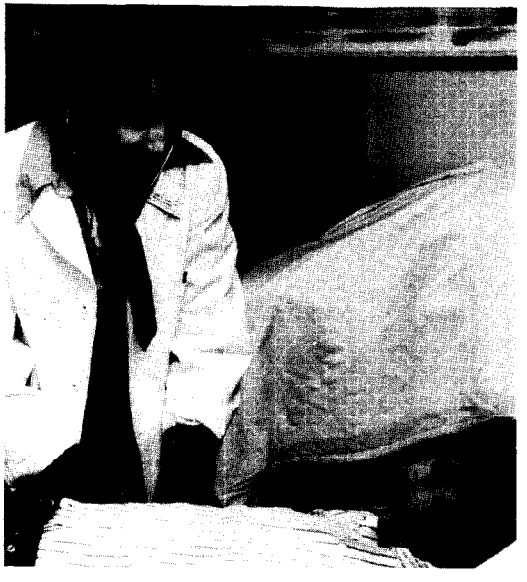
The research during the year has concentrated on studies of lipid metabolism, mostly in human subjects. Clinical service has been combined with clinical investigation through the establishment of a Heart Risk Evaluation Service (in association with the Victorian Division of the National Heart Foundation and I.C.I. Australia) in the Institute itself, a new Lipid Outpatient Clinic at the Alfred Hospital and through the Clinical Research Unit. A tissue culture laboratory has been established and collaborative studies have been initiated with other groups at the Adelaide Children's Hospital, the Royal Children's Hospital in Melbourne and the Cardiac Diagnostic Service, Alfred Hospital.

**The Heart Risk Evaluation Service**

This clinic was established as a community service to enable healthy individuals to have their blood pressure and serum lipids measured. It has also provided us with a clear picture of the extent of the coronary risk problem. About 1600 subjects were seen during the year, a high proportion of whom showed hyperlipidaemia (25% of men and 33% of women) or hypertension (15%). Those found to be affected and willing to be treated are being offered specialised dietary advice and other forms of treatment if needed. Hypertensive subjects were usually referred to their own doctors for treatment.

The proof that screening procedures of this sort, if followed by adequate treatment of discovered risk factors, will lower the number of heart attacks in the community, remains to be established. But the likelihood of this being the case is high and our optimism is based on the following grounds: 1. The high prevalence of hyperlipidaemia in our community (about one quarter of middle-aged men and women). 2. The established association between hyperlipidaemia and coronary disease. 3. Emerging evidence that lowering plasma lipids may prevent the development of clinical coronary disease, at least in middle-aged and younger people. 4. The effectiveness of treating hyperlipidaemia in specialised clinics. 5. The enthusiastic response of people to the establishment of similar clinics elsewhere in Australia and overseas indicating an increasing awareness in the community of preventive health care.

This approach, as an alternative to advising the entire population to change its eating habits, may be more effective in that treatment of, and compliance by an individual are likely to be more thorough if the risk has been clearly identified. Screening also allows for the assessment of other risk factors — an important consideration — since the potential benefit from reduction of the serum cholesterol level is thought to be even greater when other risk factors are present. Thus, whilst on average there is a one in 20 risk of a symptom-free middle-aged Australian man developing coronary disease within a five year period, the presence of three major risk factors (high cholesterol, high blood pressure and smoking) increase this chance to one in two.



*Heart Risk Evaluation Clinic where Sister Liz Leembruggen examines patient.*

In order to be effective, screening procedures need to be simple, acceptable, diagnostically sensitive and inexpensive. Appropriate treatment must be readily available, effective, and likely to be adhered to. These principles must be shown to be applicable to programmes that seek to identify and treat hyperlipidaemia by dietary means. Our experience so far has shown that these criteria can be met. Of all the hyperlipidaemic individuals that were given dietary advice during the year (usually in the form of a group discussion) 68% reduced their blood fat levels to normal and maintained this improvement for six months. The challenge is to find new ways of persuading the others.

**Lipid Metabolism and Coronary Disease**

Most of the long-term studies are related to the causation of hyperlipidaemia and the manner in which this predisposes to coronary heart disease.

As an example of our approach to the problem, it is possible to measure the amounts of different lipids such as cholesterol and triglyceride which are produced each day. We can measure the amounts of cholesterol that are absorbed, synthesised, excreted and disposed of in other ways each day. It is then possible to determine whether a person with hypercholesterolaemia suffers from this disorder because of: 1. An inherited defect in clearing cholesterol (within low density lipoprotein) from the blood; 2. Overproduction of cholesterol in body tissues; 3. Inefficient compensation for dietary cholesterol, e.g. insufficient reduction in cholesterol synthesis. It is often worthwhile to establish this in a subject who does not respond readily to conventional treatment. We can also define the ways in which specific diets and drugs contribute to or overcome hyperlipidaemia.

Our most important effort this year has been to establish sophisticated methods for studying lipoprotein protein metabolism. There are various proteins

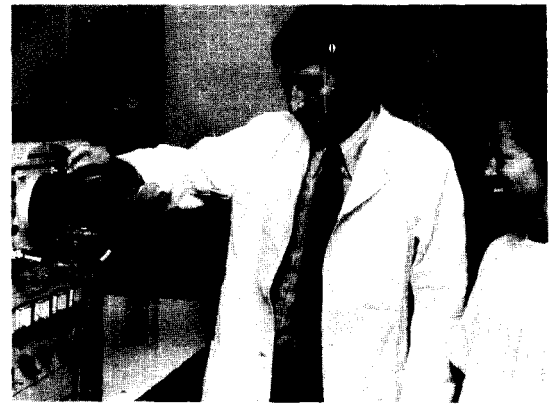
associated with the blood lipids (so called lipoproteins) that control the formation and disposal of the lipids. We have developed techniques for measuring the behaviour of these proteins in man as well as in isolated cells. The three major classes of lipoproteins (other than the chylomicrons that transport dietary fat) are the very low density lipoproteins (VLDL), the low density lipoproteins (LDL) and the high density lipoproteins (HDL). The VLDL are secreted by the liver as triglyceride-rich particles with at least one obligatory protein, the B-protein. In the plasma, the VLDL immediately acquire additional proteins from the HDL, the C and E group of proteins, that initiate and possibly control the catabolism of the lipoprotein: triglyceride is hydrolysed and removed and the particle becomes relatively enriched in esterified cholesterol. In this way VLDL become converted to smaller, intermediate density lipoproteins (IDL), and finally to the cholesterol-rich LDL; during this process the C and E series of proteins are partly returned to HDL. The LDL are removed mainly in extrahepatic tissues and provide the cholesterol requirements of most cells. HDL are probably secreted from both the liver and gut and their functions include the uptake and transport of cellular cholesterol and the orderly breakdown of VLDL to smaller lipoproteins through the provision of the C and E proteins. The major proteins of HDL, the A proteins, stimulate the efflux of cellular cholesterol, promote the esterification of cholesterol and the transfer of this lipid to sites of excretion.

Our group has been active in developing some of these aspects:

* Measurements of the synthesis, turnover and catabolism of the major lipoproteins.
* The regulation of cellular cholesterol by lipoproteins especially high density lipoproteins.
* Development of specific immunoassays for quantitative measurements of individual lipoprotein proteins for kinetic studies.
* Study of effects of diets and drugs on lipoproteins.
* Relating the degree of atherosclerosis to the type and severity of hyperlipoproteinaemia.

Another theme which is being pursued is the regulation of the cholesterol content of tissues and how this is influenced by the composition and relative concentrations of the different plasma lipoproteins. Particular attention is being paid to the high density lipoproteins (HDL); tissue culture and clinical studies have demonstrated an important role for HDL in transporting cholesterol out of cells, including the cells that make up the atherosclerotic plaque. Cholesterol is deposited in those cells from the cholesterol-rich low density lipoprotein (LDL) of plasma. The balance between cholesterol moving in and out of cells may therefore be a function of these two lipoproteins. Interest in HDL in this regard was recently stimulated by our observation that the amount of cholesterol in the tissues of man was inversely related to the plasma HDL cholesterol concentration, suggesting that the efficiency with which cholesterol is removed from tissues depends on the amount of HDL in plasma. Attention was subsequently drawn to the presence of low HDL concentrations in patients with existing clinical coronary disease, raising the possibility that a low HDL concentration might be an important unrecognised factor in accelerating the progression of coronary artery disease. We are studying this interesting new area by metabolic studies in hypercholesterolaemic subjects and also in isolated cells grown in culture systems.

We are also conducting surveys of HDL levels in specific populations and relating this to the incidence of coronary disease.



*Dr. Noel Fidge with Research Assistant Margaret O'Connor.*

## SCIENTIFIC PROJECTS

### 1. Lipoprotein Protein Kinetics

#### a. Very low density lipoproteins

M. Reardon, N. Fidge, P. Nestel, E. Fagarazzi

The kinetics of these triglyceride-rich lipoproteins have been studied in healthy and hypertriglyceridaemic subjects. We have defined the multiexponential nature of the turnover of the VLDL B-apoprotein (the protein required for the synthesis of VLDL). We have also demonstrated a major alternative pathway of VLDL catabolism — whereas in normal subjects all VLDL is degraded to LDL (which is subsequently cleared from the circulation), in hypertriglyceridaemic individuals, the bulk of VLDL is cleared at an earlier stage as a larger particle (IDL). This may be a consequence of the overproduction of VLDL that we have observed in most hypertriglyceridaemic subjects and the failure of LDL turnover to accommodate the increased flux of VLDL. Since IDL are likely to be atherogenic, the increased formation of this particle and its direct removal by tissues may contribute to the atherosclerosis associated with hypertriglyceridaemia.

#### b. High density lipoproteins

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

The kinetics of the two major HDL proteins ($A_1$ and $A_2$) are being studied in man. Each protein is catabolised within a 2-pool system, but at different fractional rates suggesting that the HDL particle may not be removed intact.

Since HDL are involved in the orderly catabolism of VLDL we are combining our studies of HDL turnover with those of the other lipoproteins. The kinetics of the VLDL C proteins which are responsible for initiating the "lipoprotein cascade" of catabolic events are also being defined in human subjects. When combined with those of the B protein in VLDL, IDL and the A proteins of HDL, a complete lipoprotein turnover profile is obtained. Comprehensive studies of this sort are being carried out in normal and hyperlipidaemic individuals to define the interrelationships of the various lipoproteins and points of disturbed regulation. Although single gene defects, giving rise to unique disturbances in the metabolism of single lipoproteins, are known, it is more likely that most hyperlipidaemic states will show a disturbance of several lipoproteins.

#### c. Lipoprotein kinetics in response to diets

The effects of high sucrose diets, which lead to hypertriglyceridaemia, are being studied. Two kinds of responses have been observed. In some subjects, the sugar diet stimulates the removal of lipoproteins (VLDL and IDL) and so the lipoprotein pools do not increase. However in those who do not increase the clearance of VLDL B-protein, there is an expansion of the VLDL and IDL pools. This is a further example of the heterogeneous response to dietary overload, showing the capacity of some individuals, but not of others, to make full compensatory metabolic adjustments. (Nestel, Reardon, Fagarazzi).

Similar studies are being carried out in rats, which show a pattern of lipoprotein metabolism that differs in some important aspects from that in man (Fidge, Ishikawa, O'Connor).

*Andrea Poyser testing blood samples.*

### 2. High Density Lipoproteins and Cholesterol Metabolism

P. J. Nestel, N. Miller, A. Poyser

a. We have established for the first time in vivo that cholesterol leaving tissues is immediately and primarily transferred to HDL in plasma. This confirms a major postulated role of HDL in the regulation of cellular cholesterol. The observations were made in obese subjects undergoing weight loss, which we had shown previously leads to the efflux of cholesterol from adipocytes.

b. We have examined the influence of lipoproteins on the cellular content of cholesterol in a study carried out in collaboration with the Cardiac Diagnostic Service and the cardiac surgeons of the Alfred Hospital. Cholesterol accumulated significantly in cardiac atrial tissue in subjects with either elevated levels of plasma LDL or elevated plasma VLDL and/or lowered plasma HDL. This again demonstrates the interaction of the various lipoproteins in promoting cholesterol influx on the one hand (LDL and VLDL), and cholesterol efflux on the other (HDL).

c. The amounts of cholesterol in body tissues can be measured in vivo by compartmental analysis of injected radio-cholesterol. We have used this technique previously to show an inverse correlation between the mass of body cholesterol and the plasma HDL concentration. This study is being extended to subjects with unusually high HDL levels as occur in familial hyperalphalipoproteinaemia.

**3. Tissue Culture Studies of Lipoprotein Metabolism**

**a. Fibroblasts**

N. Miller, J. Ma.

Studies with cultured fibroblasts have confirmed that such cells take up and degrade LDL by a specific receptor-mediated process, thereby increasing their cholesterol content, and that HDL reduces cellular cholesterol content by enhancing cholesterol excretion. Two effects of HDL on LDL metabolism by fibroblasts have been studied. An acute inhibitory effect, due to binding of HDL to the cell membrane, has been found to be reversed during prolonged incubations by an increase in LDL number. This latter effect reflects a rise in LDL receptor synthesis, occurring in response to the increase in cellular cholesterol efflux induced by HDL. In other experiments evidence has been obtained for the participation of specialised subcellular structures, known as microfilaments and microtubules, in the regulation of LDL receptor function and in the endocytosis of LDL following its binding to the receptor. Membrane stabilising agents in common clinical usage have been found to profoundly modify lipoprotein metabolism by fibroblasts.

**b. Lymphocytes**

P. Nestel, A. Poyser, M. Reardon

Fresh and cultured lymphocytes are being used to study the in vitro catabolism of VLDL and IDL. Both lipoproteins are readily taken up by lymphocytes in a manner suggesting the involvement of high affinity receptors. Double-labelled VLDL (in the B and C apoproteins respectively) suggest that the lipoprotein is removed intact.

*Librarian, Mary Dellafield, assisting Dr. Norman Miller with journals.*

**4. Epidemiologic Studies of Lipoproteins and Coronary Disease**

P. Nestel, N. Miller, A. Poyser, P. Jenkins, N. Fidge, T. Ishikawa.

a. The epidemiologically observed inverse correlation between HDL cholesterol concentration and incidence of coronary disease has been extended by demonstrating that this relationship holds also for HDL particles by measuring the A-proteins of HDL in subjects from a Norwegian study. The samples of plasma were obtained from a prospective study of coronary heart disease being carried out in Tromsø, Norway.

b. In collaboration with the Cardiac Diagnostic Service, the extent of atherosclerosis in the coronary arteries has been quantified and found to be significantly related to raised levels of VLDL triglyceride and LDL cholesterol (positively) and negatively to reduced levels of HDL cholesterol. Multivariate analysis showed that low HDL cholesterol gave the best independent index of the severity of coronary atherosclerosis (correlation coefficient of -0.5). Whereas other studies have established that low HDL cholesterol was an important risk

factor for clinical coronary events this is the first demonstration of this in relation to the extent of the underlying atherosclerotic process.

c. Another epidemiological survey seeking a role for HDL in protecting against coronary disease is being carried out in association with Dr. Boulton of the Adelaide Children's Hospital. Cord blood HDL measurements have been made in several hundred new-born children and details of familial cardiovascular disease are being sought among the relatives. To date, significantly more events have occurred in relatives of infants with low HDL levels than with high HDL levels.

**5. Cholesterol Metabolism**
P. J. Nestel and A. Poyser

This area of investigation utilises two techniques of sterol balance. 1. the measurement of cholesterol synthesis and excretion and of bile acid synthesis through the chemical analysis of sterol excretion in the faeces; 2. the calculation of the turnover of cholesterol after radiolabelling of body cholesterol.

**a. Effect of dietary cholesterol and fat**

The response of infants to dietary fat and cholesterol. The changes in the serum cholesterol and in the sterol balance have been completed in 10 infants during two diets. The rise in serum cholesterol when the diet was changed from a polyunsaturated fat — low cholesterol, to a more saturated — high cholesterol intake was similar to that seen in adults. Cholesterol feeding suppressed endogenous cholesterol synthesis as in adults, but polyunsaturated fats stimulated the excretion of bile acids to a much greater extent in the infants. Infants were studied because of previous suggestions that the control of cholesterol homeostasis is less efficient at this age than later in life and that in consequence, the serum cholesterol rises to a greater height when cholesterol is fed. Our studies have not confirmed this hypothesis: the changes in the serum cholesterol and in cholesterol synthesis resembled those we observed previously in adults (study conducted with Dr. Boulton, Adelaide Children's Hospital).

**b. Studies in children with familial hypercholesterolaemia**

This study is being carried out with Jillian Martin (Royal Children's Hospital, Melbourne). This disorder is due in part to a deficiency of the receptor for LDL B-protein, which leads to diminished clearance of LDL from the circulation. It is not clear from studies carried out in adults whether there are additional defects in the regulation of cholesterol itself. We have therefore chosen to study children with this disorder and are measuring the synthesis, turnover and excretion of cholesterol and the response to dietary cholesterol.

**c. Cholesterol metabolism in hypertension**

Sterol balances are being carried out in hypertensive subjects because of the epidemiological association of blood pressure and serum cholesterol.

The effects of diet on blood pressure are also being studied (Nestel, Esler, Winter). Suitable subjects attending the Risk Evaluation Clinic who have both hypertension and hyperlipidaemia are taking part in a trial comparing the effects of a low-fat and a normal-fat intake on blood pressure. Recent overseas data suggest a benefit from low-fat diets.

**General Information**

Members of the Unit were successful in obtaining research grants from the National Health and Medical Research Council, the National Heart Foundation, the Life Insurance Medical Research Fund of Australia and New Zealand, the Alfred Hospital Research Fund and the U.S. Sugar Association. The Victorian Government and the Hospitals and Charities Commission generously provided an establishment grant that included provision for a lipid diagnostic service for Victorian Hospitals.

During the year Dr. Nestel and Dr. Miller were invited to attend several conferences and present reviews at the International Conference on Obesity (Washington), International Conference on Atherosclerosis (Milan) and the Symposium on High Density Lipoproteins (Brussels). The work of the Unit was also presented by other members at various Australian conferences. Dr. Ishikawa returned to Tokyo (Keio Medical School) in December.

The staff during 1978 will be increased by three post-doctoral fellows (including one each from Canada and Japan) and two graduate scholars.

# Developmental Biology Research Unit

**Main Topics**

- Cot Death — Studies on the development of the respiratory system in the fetus and newborn.
- Development of the control of cardiac function in the fetus and newborn.
- Management of heart and lung disorders in the human infant.

**General Outline of Work:**
Periods when breathing stops are often observed in premature infants and become more frequent in the youngest group of these babies. At term these periods are reduced in number and continue to decrease as the baby grows. On the other hand some babies, who are otherwise healthy, suddenly stop breathing completely and need to be resuscitated. These children are considered 'near-miss' infants, and particularly in the United States of America, have come under close study as subsequently some have died in their cots unexpectedly. The causes of cot death are unknown at the present time as are the reasons for breath-less periods in premature and term infants. The possibility that many of these problems may arise 'in utero' has caused the Development Biology Research Unit to study life before birth, particularly the growth and maturation of the Cardiovascular and Respiratory Systems. Not only are these systems studied in the fetus but also throughout birth and in the newborn period. The hope that insight into the fundamental development of cardiovascular and respiratory regulatory systems might elucidate some of the most pressing paediatric clinical problems stimulated research in this area. Studies within the unit are not confined to experimental preparations but include a detailed analysis of breathing patterns in the clinical situation of a Neonatal Special Care Nursery in conjunction with the Monash Department of Paediatrics. Within this nursery respiratory and cardiovascular functions may be studied in prematurely born infants and babies at term. Problems of special interest in this area are cot death, recurrent periods of non-breathing particularly in the premature baby and early detection of the failure of the heart and respiratory systems.

When an infant is born prematurely, survival is largely controlled by the degree of maturity of the major biological systems. This maturity is seen at two levels, a structural one and a functional one. Because of the close interrelation between structure and function, any project involved in a developmental biological question must examine both areas.

The Developmental Biology Unit with this in mind, has initiated a series of interdisciplinary studies on the development of the heart and respiratory systems during 'in utero' (fetal) life and out into the newborn period. Although the principal aims of the projects as outlined are concerned with human problems, answers to these would by necessity be limited if the studies were confined only to the human baby. Some of our research therefore involves studies on laboratory animals and some of it involves investigations of human infants born either normally at term or prematurely. The animal studies up to this stage have constituted the main part of our effort and have given considerable new information at both the structural and functional level. This includes also the study of the circadian and ultradian rhythms of the fetal and newborn cardiovascular and respiratory systems.

**STRUCTURAL DEVELOPMENT**
**Animal Studies:**

Over the past three years we have evolved a much clearer concept of how the lung develops 'in utero'. From very early in fetal life the lung acts as a gland secreting a fluid which we have shown plays a vital role in its own development. Continual removal of this fluid gives rise to a small under-developed lung, while blocking its flow causes gross lung distention. As seen in the report on functional development, the muscles involved in air-breathing are not silent 'in utero', but have distinct periods of sustained activity. Such activity may be akin to "jogging" and are fundamental for normal development at both a functional and structural level. Studies in fetal lambs have shown that if the nerves to these muscles are damaged then lung growth is affected, the lungs being small and immature. Obviously similar studies cannot be performed in man and as a consequence these animal studies are important in that they help to explain some of the lung abnormalities found in human infants, and elucidate some of the factors which control normal lung growth.

*Left to right: John Cannata, Dr. John Maloney, Margaret Dowling, Bob Smith, Vojta Brodecky, Dr. Adrian Walker.*

**FUNCTIONAL DEVELOPMENT**
**Animal Studies:**

The functional development of the respiratory system has been studied intensively, particularly during the last one third of 'in utero' life, with the use of specially designed recording devices. Newly developed computer based methods of analysis have been used to process the data from these studies. Early results suggest that the baby 'in utero' has a specific pattern to its breathing movements. This pattern can be followed as it changes during development 'in utero', through the crucial birth process and into early infancy. The ability of the infant to produce and sustain a rhythmic pattern of breathing is essential for survival following birth.

The control of the breathing movements has also been actively investigated. By changing the amount of oxygen and carbon dioxide in the lamb's blood, alterations of the breathing pattern can be produced. It would appear from these studies that the lamb 'in utero' responds differently to the newborn lamb when subjected to the changes in oxygen and carbon dioxide. Oxygen deprivation in the awake newborn gives rise to an increase in breathing activity. However the 'in utero' lamb ceases breathing movements following this stimulus. Such variations in response to oxygen lack may help to explain how an immature or maldeveloped respiratory control system may precipitate clinical disorders.

The influence which the brain has over breathing movements also is being investigated in the lambs by measuring electrical activity from the brain by recording devices placed on the brain's surface. These studies suggest that the pattern of breathing activity is determined to a large extent by whether the lamb is awake or asleep.

From these studies of breathing movements made by lambs 'in utero' and during newborn life the following picture has emerged. The breathing pattern changes progressively during development suggesting changes in the control mechanisms. Further work is drawing more closely together the structural and functional changes. Human studies with less invasive and more sophisticated techniques will continue to follow on from the lamb studies in the attempt to more clearly understand the clinical respiratory disorders.

Many human circadian rhythms are not apparent in the newborn, but develop over the first weeks of life, so that it might be assumed that such rhythms are not manifest in the fetus 'in utero'. Alternatively fetal circadian rhythms may develop during gestation, be disrupted at birth, then reappear slowly in the neonatal period. The objective of this study is to examine the fetal lamb cardiovascular and respiratory systems for evidence of cir-

cadian and ultradian variability. Fetal rhythms, if present, have clear implications for the design and evaluation of studies in developmental biology, just as adult circadian rhythms have considerable practical importance in addition to their inherent interest.

**Human Studies:**
Recurrent periods of non-breathing (apnoea) are one of the major problems encountered in the neonatal intensive care area. Monitors are currently used in these units which sound an alarm when breathing ceases for a defined period, but as yet such events cannot be predicted and hence prevented. With this in mind projects are under way in the neonatal nursery in which breathing patterns of a wide group of infants, both normal and abnormal, are recorded for long periods and their patterns analysed using the similar data processing to those of the animal studies. As with animal studies the breathing patterns of normal infants show considerable variation determined partly by whether the infant is awake, asleep, and in what type of sleep. Until this range of normality is defined and understood abnormality cannot be defined. However with the experience obtained in data handling from our animal studies, it is anticipated that these limits should shortly be defined in the human infant.

A basic analytical problem is to provide quantitative descriptions of the developmental patterns of the respiratory system, cardiovascular system and their interaction. To do this we are using a PDP-11/34 digital computer (see Fig. 1). A number of data acquisition, editing, processing, and display programs have been developed in this laboratory and additional software, written in both higher level and assembler language, is in the developmental stage. Data is collected over epochs of specific duration, e.g. studies of one hour (drawn from two hour recording periods composed of, e.g. one hour control, one hour stress epochs), and seventy-two hours. From this data, population statistics and measures of temporal variability are computed. These are employed to characterise natural developmental patterns of cardiac and respiratory control and to examine the responses to stress.

*Fig. I*
*The PDP 11/34 Computer with Dr. J. Maloney (left) and bioengineer, Mr Malcolm Wilkinson (right). This computer is being used to analyse cardiac and respiratory function 'in utero', throughout birth and in the newborn period. The computer also assists in an analysis of data from human premature and full term babies with our hope of being able to predict impending respiratory and cardiovascular collapse.*

**PROJECTS**

**1. Morphological effects of chronic tracheal ligation and drainage in the fetal lamb lung.**
D. Alcorn, *T. M. Adamson, * T. F. Lambert, J. E. Maloney, B. C. Ritchie, and **P. M. Robinson.

The relationship between lung liquid flow and fetal lung development has been studied at the cellular level using ultrastructural techniques. Continuous 'in utero' tracheal ligation and drainage (over a period of 21-28 days) both result in malformations of the developing fetal lamb lung. Ligated lungs are larger, and drained lungs are smaller, than normal lungs at a similar gestational age.

* In collaboration — Monash University Department of Paediatrics.
** In collaboration — University of Melbourne, Department of Anatomy.

These changes are not merely due to altered lung liquid volume, but actual tissue growth has been affected. Future alveolar wall thinning is enhanced in ligated lungs and inhibited in drained lungs, whilst the presence of differentiated alveolar type II cells (probably related to surfactant production) is decreased in ligated lungs and markedly enhanced in drained lungs. These results indicate the importance of fetal lung liquid in the regulation of pulmonary development in the fetus.

**2. Baroreflex Activity in conscious fetal and newborn lambs.**

John E. Maloney, John Cannata, Margaret H. Dowling, Wendy Else, and Blair Ritchie.

The immediate transient baroreceptor sensitivity was measured in 9 conscious fetal and 7 conscious newborn lambs for periods of at least 35 days following bolus injections of phenylephrine (20-50 g/kg). Mean sensitivities were unchanged throughout gestation from 105 days at 6.7 ± 0.4msec/cm $H_20$ (n = 45) and were insignificantly different from those in the newborn period, 5.9 ± 0.4msec/cm $H_20$ (n = 78). In contrast, baroreflex sensitivities were less in 2 fetuses and 2 newborn lambs when pressures were increased by chronically implanted thoracic aortic balloon cuffs; they were 3.03 ± 0.11 (n = 127) and 0.91 ± 0.11msec/cm $H_20$ (n = 61), respectively. 'Steady-state' heart period-arterial pressure curves indicate that the baroreflex operates down to levels of 40cm $H_20$ in the fetus which is lower than that achieved in the adult of other species, e.g. rabbit and man.

**3. A study of the influence of the drug NA 872 on development of the fetal respiratory system.**

V. Brodecky, Margaret Dowling, J. E. Maloney.

Survival of the newborn baby following premature delivery often depends on the ability of the lung and respiratory system to function effectively. It has been noted that steroids increase lung maturity and other compounds are being tested for their ability to promote lung growth and maturation. Of these the drug NA 872* is of interest because preliminary data on its effects on lungs of several species suggested that it increased cell differentiation and maturation. The unit has made a detailed examination of its effects on the morphological, biochemical and functional development of the lung and respiratory system of the fetal lamb 'in utero'.

Intensive studies have been made on each of eight fetal animals for thirty days from day 100 (term ~147 days). Ninety-six monitoring periods of two hours duration have been undertaken and submitted to analyses to determine if the drug NA 872 had any effect on the dynamics of the respiratory system. In selected animals ultrastructural studies have been undertaken at day 130 and 74 samples of lung liquid taken for electrolyte composition and phospholipid analysis. Preliminary examination of this data indicate that the lungs mature earlier under the influence of the drug NA 872 as does the activity of the respiratory system which suggests the drug also acts on the central nervous system. Lung liquid electrolytes are not significantly altered.

* Boehringer-Ingelheim.

**4. New features in the development of the submucosal gland of the respiratory tract.**

J. J. Smolich, Bernice F. Stratford, J. E. Maloney and B. C. Ritchie.

The development of the submucosal gland was studied with light and scanning electron microscopy in the rat, fetal dog and fetal sheep. From the results obtained, the present concepts about gland formation in man were questioned and an alternative hypothesis proposed.

In scanning electron microscopy, the development of the submucosal gland began with an aggregation of low electron responsive cells. Within such an aggregate, a pit, several microns in diameter, was formed. This pit was usually surrounded, in the rat, by medium electron responsive cells with primary cilia and by low electron responsive cells in the fetal dog. Medium electron responsive cells appeared in other areas of the aggregate preceded, in the rat, by apical elevations on the low electron responsive cells. Further development in the rat led to a disappearance of the low electron responsive cells, differentiation of ciliated and brush cells and enlargement of the gland orifice.

In light microscopy, it was observed that the initial gland buds in both the rat and fetal sheep contained lumina several microns in size. These had not been reported by previous investigations. The bud extended into the underlying tissue and developed many simple tubules. The lumina of these tubules were consistently larger than the channel close to the epithelial surface. The cells of these tubules were also the first to differentiate into mucous and serous cells. The development of glands in the rat, in contrast to the fetal sheep, began after birth. In the fetal sheep, unlike the rat, the lumina of the developing glands were often filled with acidic mucosubstances, even though the cells of these glands were unreactive for such material. Hence, it was suggested that this material was derived

from the mucin-containing cells of the surface epithelium. Thence it was carried into the interior of the developing gland by the fluid present in the respiratory tract during the intrauterine period.

Points covered in the discussion included the nature of low electron responsive cells, the mechanism of pit formation, the differentiation of mucous and serous cells and possible explanations to account for the observations of previous workers.

**5. Age-dependent pattern of autonomic heart rate control during hypoxia in fetal and newborn lambs.**

Adrian M. Walker, John P. Cannata, Margaret H. Dowling, Blair C. Ritchie and John E. Maloney.

Autonomic nervous control of heart rate (HR) during hypoxia was studied longitudinally in nine chronically catheterised fetal lambs (109 days-term) and seven newborn lambs (2-28 days old). Changes in heart rate(△HR) during hypoxia were age-dependent. Before 120 days gestation△HR was insignificant, but between 120 days-term brady-cardia occurred. The newborn response was marked tachycardia. Autonomic influences on HR were quantified using atropine and propranolol blockade. In fetal lambs antagonistic increases in parasympathetic and sympathetic outflows were evident during hypoxia. For example, between 120 days-term, increased parasympathetic outflow was evidenced by greater atropine induced △HR increments in hypoxic than normoxic states (117 ± 11 versus 27 ± 5 beats/min, mean ± SEM). Increased sympathetic influence was shown by greater propranolol induced HR decrements in hypoxic than normoxic states (60 ± 10 versus 11 ± 3 beats/min). Thus in hypoxic lambs 120 days-term net bradycardia reflected predominant parasympathetic cardio-deceleration. In hypoxic lambs before 120 days gestation, both parasympathetic and sympathetic outflows increases, and no net △HR occurred. In newborn lambs synergistic sympathetic and parasympathetic changes contributed to the net tachycardia. Increased sympathetic influence was evidenced by greater propranolol induced △HR in hypoxic than normoxic states (71 ± 10 versus 28 ± 8 beats/min). Decreased parasympathetic HR restraint was shown by smaller atropine induced △HR in hypoxic than normoxic states (22 ± 5 versus 38 ± 8 beats/min). Thus the pattern of autonomic control of HR during hypoxia differs in fetal and newborn lambs. Changes in sympathetic and parasympathetic influences are antagonistic in the fetus, but synergistic in newborn.

**6. Autonomic control of the pulmonary circulation.**

B. C. Ritchie, *B. Davis, J. Cannata and R. J. Smith.

Further studies on the role of the nervous system in controlling the pulmonary circulation have indicated that stimulation of aortic and carotid body chemoreceptors have not changed pulmonary vascular resistance. A delayed rise in resistance has been shown suggesting a possible central chemosensitive centre controlling pulmonary vascular resistance. These findings are consistent with other clinical and experimental findings where brain damage and raised intracranial pressure have induced pulmonary oedema and increased pulmonary vascular resistance. The role of the sympathetic nervous system in mediating these responses has been controversial; our experiments in unanaesthetised sheep where the sympathetic ganglia were previously ablated in one lung showed no change in the distribution of blood flow between each lung in response to alveolar hypoxia.

* In collaboration — member of Thoracic Surgical Unit, Alfred Hospital, Prahran.

**7. The response of the unanaesthetised fetal lamb to hypovolemic shock.**

R. Yardley, J. Cannata, R. J. Smith, A. Walker, and B.C. Ritchie.

The tolerance of the fetus to hypovolemic shock has received little attention; our understanding of this response is important to the clinical situations of premature placental separation, placental rupture and the future prospects of intrauterine corrective surgery. Studies in fetal, newborn and adult sheep have shown that the early reflex response to shock in the fetus and newborn has been tachycardia followed by bradycardia. By contrast the mature animal with comparable blood loss shows a consistent tachycardia. In the short term the fetus tolerates severe and recurrent hypovolemic episodes without detriment. Further studies are in progress to determine the reponses of cardiac output, distribution of blood flow and the effects on the placental circulation.

**8. Morphological effects of phrenectomy in the foetal lamb lung.**
D. Alcorn, T. M. Adamson, J. E. Maloney, B. C. Ritchie, P. M. Robinson.

The role of phrenic innervation of the diaphragm and its effect on intrauterine pulmonary development over the last third of gestation is investigated in this study using chronically phrenectomized foetal lambs. The lungs of the phrenectomized lambs were decreased in weight and volume. This was not accounted for by their diminished lung liquid volume when compared with both sham operated and normal controls of a similar gestational age. Phrenectomized lambs' lungs maintained a lesser percentage of future air spaces and on histological examination this was seen to be a result of thickened interalveolar walls as well as future air space collapse. The proliferation of potential alveoli was reduced. Cellular differentiation, however, had advanced, as indicated by the presence of both the alveolar type I and type II cells. These experiments demonstrate that the integrity of the phrenic nerve is essential for normal pulmonary development. The precise mechanisms of this relationship are not known.

**9. Control of the pulmonary circulation in the fetal and newborn lamb.**
A. M. Walker, J. E. Maloney, J. Cannata and B. C. Ritchie.

The fetal lung is expanded with liquid which is cleared at birth. These studies examined the influence of fetal lung liquid on the fetal and newborn pulmonary vascular bed. Vascular conductance measured in autoperfused fetal lungs increases markedly as liquid is withdrawn to residual volume (RV), and decreases progressively with liquid expansion. Thus the volume of liquid in the fetal lung is likely to affect pulmonary blood flow 'in utero'. The mechanical effects of lung expansion on fetal pulmonary arteries are illustrated by radiographic measurements. Lung expansion from RV first increases the calibre of 300-500$\mu$ arteries but compresses arteries of 1,500-3,000$\mu$. Further lung expansion reduces the calibre of all arteries 300-3,000 $\mu$. Effects on pulmonary blood volume and flow after introducing gas into fetal lungs were studied isotopically in rapid frozen lungs. Pulmonary blood volumes increase after ventilation with air, but not after 3% $O_2$ and 7% $C0_2$ ventilation (arterial blood gases not changed from fetal levels). Thus, ventilation with air, rather than introducing gas into the alveoli increases fetal pulmonary blood volume. In ventilated fetal lungs regional blood flow and aeration are topographically correlated when arterial blood gases are little changed from fetal levels. When $Pa0_2$ rises and $PaC0_2$ falls from fetal levels, the regional distribution of pulmonary blood flow is reversed: blood flow/unit lung volume is greater in the more dense lung regions. Thus two patterns of pulmonary vascular control may operate in the fetal-neonatal transition.

**10. The role of lung liquid in prenatal lung development.**
T. M. Adamson, D. Alcorn, T. F. Lambert, J. E. Maloney, B. C. Ritchie, and P. M. Robinson.

Despite studies on fetal lung liquid secretion its role in prenatal lung development is yet to be defined. Pathological studies suggest a role in fetal lung growth, since congenital atresia of bronchi or trachea is associated with lung expansion. To clarify this concept two groups of fetal lambs were studied, fetuses where the drainage of lung liquid was prevented by tracheal ligation, and fetuses where the liquid was continuously drained away. Both stimuli were present over the same growth period 110-130 days (term 147 days). In each group the lungs were abnormal compared with controls at 130 days. The ligated were large and the drained lungs small. These changes were not explained alone by differences in lung liquid volume, but represented changes in tissue growth. In the ligated lung alveolar wall thinning was enhanced, but inhibited in the drained lungs, whilst the presence of differentiated alveolar type II cells was decreased in ligated, but enhanced in drained lungs. These studies indicate the importance of fetal lung liquid as a regulator of prenatal lung growth.

**11. Autonomic control of heart rate during hypotension in conscious fetal and newborn lambs.**
A. M. Walker, J. Cannata, M. Dowling, B. C. Ritchie and J. E. Maloney.

Development of reflex heart rate (HR) control during hypotension was studied in 3 fetal lambs between 109-141 days gestation (term = 147 days) and in 4 newborn lambs 1-22 days old. Carotid artery and jugular vein catheters, ECG electrodes, and a balloon around thoracic in-

ferior vena cava were implanted 1-49 days before experiments. Graded hypotension lasting 10sec was produced by varied balloon inflation. Sympathetic (S) and parasympathetic (PS) nervous control was assessed by propranolol, (P, 1mg/kg) and atropine (A, 0.2mg/kg). Newborn lambs (N = 99) showed progressive tachycardia as mean arterial pressure (MAP) decreased. HR increased 64 ± 5bpm (mean ± SE) when MAP decreased 39 ± 1cm$H_20$; the HR increase was less after A (33 ± 2bpm, $p < 0.001$) or P (17 ± 3bpm, $p < 0.001$). In fetal lambs (N = 134) no progressive tachycardia occurred. HR increased 11 ± 3bpm when MAP fell 8.3 ± 0.4cm$H_20$, but decreased 11 ± 5bpm when MAP further decreased 23 ± 1cm$H_20$; the bradycardia was reversed by A (HR increase 18 ± 2bpm, $p < 0.005$). Thus, autonomic HR control during hypotension changes at birth. In newborn lambs reduction in parasympathetic plus an increase in cardiac sympathetic activities account for the tachycardia, whereas in fetal lambs the two cardiac autonomic effectors exert antagonistic effects.

**12. Normal development of the fetal respiratory system.**

G. Bowes, B. C. Ritchie, V. Brodecky, M. H. Dowling and J. E. Maloney.

The functional maturation of fetal respiratory system is being studied by measurement of the neural respiratory centre output in chronically instrumented 'in utero' lambs over the last one third of gestation. The electromyographic activity of the diaphragm would appear to be a good index of the output of the neural respiratory centre. The activity is measured by fine electrodes surgically implanted in the fetal diaphragmatic muscle and the data obtained analysed with the help of a digital computer system. Recordings are taken throughout gestation and into the immediate newborn period to follow the patterns of activity of differing developmental stages. The studies this year have involved 15 fetal preparations from which 200 hours of recordings have been taken.

The results indicate that there is a recognisable pattern of respiratory centre output which changes with gestational development. This changing pattern can be seen by examination of a number of the features of the respiratory centre output. At around 100 days gestation (term 145 days) the fetus is making respiratory movements almost continuously and sometimes at very high rates (150-200/min), whereas later in gestation around 135 days, there are periods of up to 20 minutes when no breathing movements are detected. The profile of the inspiratory and expiratory times of the breathing movements also changes with gestation, with the expiratory times becoming longer towards term. Further studies will be carried out to further investigate and analyse this pattern of neural respiratory centre output and to study the pattern at even earlier gestational ages.

**13. The effect of hypoxia on fetal respiratory centre output.**

G. Bowes, B. C. Ritchie, V. Brodecky, M. H. Dowling and J. E. Maloney.

The air-breathing adult animal responds to hypoxia by increasing its rate of breathing and its minute ventilation. Previous studies have indicated that the fetus responds differently to an hypoxic stimulus. By changing the inspired oxygen concentration in the gas breathed by the pregnant ewe the maternal and consequently to fetal $Pa0_2$ can be manipulated. The maternal ewe breathes a gas mixture with 10% oxygen causing a 10mmHg decrease at fetal $Pa0_2$. The hypoxic responses of chronically instrumented 'in utero' fetal lambs are being studied over the last one third of gestation. This year 20 experiments have been carried out on 9 fetal preparations at differing gestational ages. Throughout gestation the response to this isocapnic hypoxia is to cause cessation of breathing movements and respiratory centre output. The rapidity of onset of the response to hypoxia is however variable and may depend on the pattern of respiratory activity present at the time of delivery of the stimulus. This factor and the degree to which the rate of change of $Pa0_2$ exerts an effect are the subjects of continuing study.

The time at which the hypoxic response changes from one of depression to one of excitation of the respiratory centre would appear to be at or after birth but the exact timing and the factors operating in the changeover are yet to be determined.

The persistence of the fetal response to hypoxia in premature neonates may be an important factor in the genesis of the clinical problem of apnea in premature infants.

**14. The effect of hypercapnia on fetal respiratory centre output.**

G. Bowes, B. C. Ritchie, V. Brodecky, M. H. Dowling and J. E. Maloney.

The effect of hypercapnia on the fetal respiratory system has been reported by different investigators to produce either stimulation with an increase in rate and depth of breathing movements or to give little or no effect. This year hyperoxic hypercapnic stimuli have been used in 25 experiments on 9 fetal preparations.

The maternal ewe breathes a gas containing 9% $C0_2$ in oxygen resulting in an 8-10mmHg increase in fetal $PaC0_2$. The rate of breathing movements is not consistently increased during the stimulus period. However a less variable minutely rate is found on most occasions. The change in breathing rate during the stimulus appears dependent on the state of activity of the respiratory centre at the moment the stimulus was delivered. While there seems to be no consistent rate change there would appear to be an increase in size of bursts of electrical activity from the diaphragm, for which a process of data analysis is being developed.

**15. The effect of CNS activity states on fetal respiratory centre output.**

G. Bowes, B. C. Ritchie, V. Brodecky, M. H. Dowling and J. E. Maloney.

Studies elsewhere have demonstrated the strong influence "sleep" or "activity states" have on respiratory centre output in adult animals. The pattern of activity is different in the awake state from the sleep states and the activity varies between the classic sleep states of rapid eye movement (active) and non rapid eye movement (quiet) sleep. The response of the respiratory system to afferent inputs is also affected by the "sleep" state present when the stimulus is given. The respiratory centre output in response to an hypoxic hypercapnic stimulus in the adult is notably attenuated during rapid eye movement (REM) sleep.

In the fetus other studies have shown that the activity state of CNS affects respiratory centre output, with breathing movements occurring during REM sleep and not during non-REM sleep states. Preliminary studies in our group have commenced in this area, in an attempt to define more clearly how the activity state of the fetal CNS influences the changing gestational pattern of respiratory centre output we have observed. In addition we hope to investigate the effect of CNS activity state on the fetal response to chemoreceptor stimuli.

Successful recordings of electrocortical and electroocular activity have been made in 3 chronically instrumented 'in utero' fetal lambs and correlation of this information with respiratory centre output is proceeding at this time.

**16. Development of circadian rhythms 'in utero'.**

A. M. Walker, M. Wilkinson, V. Brodecky, M. Dowling, J. Cannata, R. J. Smith, R. Hayllar, G. Bowes, R. Yardley, T. M. Adamson and J. E. Maloney.

In preliminary studies seven chronically instrumented fetal lambs (Fig. 2) of 105 to 141 days gestation have been studied in twelve recording periods of 19 to 96 consecutive hours duration. Fetal ECG, diaphragm EMG, carotid arterial pressure, amniotic fluid pressure and maternal posture have been measured in six of these studies; fetal ECG and diaphragm EMG have been recorded in the remainder. Because many environmental factors can influence the period, phase and amplitude of mammalian circadian rhythms we have attempted to limit cyclic influences to the daily laboratory schedule and the light-dark cycle. The onset time and duration of the light period approximates the natural day length.

*Fig. 2*
*A photograph of a pregnant ewe carrying a small magnetic tape recorder on its back. This recorder collects information from the fetus 'in utero' for periods of up to 72 hours continuously. Data is being analysed to determine if the fetal cardiovascular and respiratory state change during the monitoring period and to determine the natural functional development of heart and lung 'in utero'.*

Diurnal variation in the activity of the ewe has been a consistent finding; ewes spend a greater proportion of light-time (L) in the standing posture compared to dark-time (D). Circadian variations have been identified in fetal cardiovascular functions. These show a consistent phase relationship to the L-D cycle, though they have not yet been apparent in all fetuses studied. In some cases these cardiovascular variations have not been apparent early in gestation, but appear when the animal has been studied again later in gestation. Fetal heart rate variations which have been identified are an increase in average heart rate in D compared to L and an extended range of heart rate variation in D compared to L. In those fetuses in which heart rate increased in D, there was a coincident increase in mean carotid arterial pressure. No consistent circadian pattern of fetal breathing movements has been identified.

**17. Data acquisition and computing.**
M. Wilkinson, R. Hayllar, A. Walker, R. Yardley, G. Bowes and J. E. Maloney.

During this year the group has taken delivery of a PDP 11/34 digital computer, including an analog/digital subsystem for real time analysis of up to 16 channels of analog data. Softwave has been developed to allow the following types of analysis.

a) Analysis of fetal and newborn respiratory development. Three topics have been investigated:
   (i) Direct conversion of diaphragmatic EMG activity into T (I) and T (E) histograms in order to improve our present understanding of the operation and maturation of the central respiratory pattern generator.
   (ii) Quantitative estimates of the percentage time spent in apnea and the variations which occur over the last third of gestation in the fetus.
   (iii) Power spectral analysis of the EMG activity.

These studies will also form the basis of an automatic pattern recognition system to allow early identification of factors dangerous to fetal well-being.

b) Statistical reduction of experimental data.

Programs have been written to allow calculation of population statistics, regression equations both linear and polynomial and autocorrelation functions. The regression programs incorporate graphics interaction to allow rapid assessment of the most appropriate regression to apply. The graphics capability will be considerably extended next year by the recent purchase of an interactive digital plotter.

c) Analysis of fetal and newborn ECG data.

A modified Oxford "Medilog" 24 hour recording system has been successfully applied to long term monitoring of fetal ECG and diaphragmatic EMG. Preliminary data reduction using Fourier techniques has commenced on this data to establish the presence or otherwise of circadian rhythms. During next year cross correlation techniques will be used to study interactions between the fetal cardiovascular and respiratory system.

**18. Effects of vagal blockade during hypoxia on left ventricular output.**
R. Yardley, J. Cannata, R. J. Smith and A. M. Walker.

Experiments have been conducted on 2 fetal lambs and 1 newborn lamb to this date to examine the effect of hypoxia on left ventricle output heart rate and blood pressure during mild hypoxia.

The fetal animals were instrumented with doppler flow probes, vascular catheters (for pressure recording and drug infusion) and ECG electrodes, around 105 days gestation and experiments conducted after 120 days. Measurements of blood pressure heart rate and left ventricular output were made at 1 minute intervals during a 20 minute control period and then during a 20 minute period of hypoxia ($Pa0_2$ 16-17mmHg).

The animals were allowed to recover for 30 minutes during which time the measured values and blood gas acid-base status had returned to normal. After recovery the animals were subjected to a repeat of the previous experiment only with an infusion of atropine (6 experiments) and propranolol (1 experiment).

The result of the experiments fall into two groups the first set of observations being the effects of hypoxia on the measured variables without drugs.

In general there was a biphasic response to hypoxia there being an initial bradycardia with a change of onset 20 beats/min followed by a slight tachycardia as the hypoxia persisted. There was a small increase in the mean arterial pressure, however the left ventricular output

remained unchanged or increased only slightly during hypoxia as compared with the control period.

The effects of atropine on heart rate, blood pressure, stroke volumes and left ventricular output during hypoxia were more dramatic. After atropine was infused (0.2mg/Kgm/10mins) the heart rate increased about 15-20 beat/min over the original control levels and when the fetus became hypoxic there was a marked elevation of heart rate from 180 beats/min up to about 250 beats/min. The blood pressure fell an average about 3-4mmHg and the left ventricular output increased slightly but there was a marked reduction in left ventricular stroke volume.

The above observations have a number of possible explanations but the simplest is that in the hypoxic state in the fetus both elements of the autonomic nervous system are stimulated simultaneously, and that the parasympathetic system largely balances the heart rate response of the sympathetic system leading to only small changes in the overall heart rate with maintenance of cardiac output. Blocking the effects of the vagus leads to unopposed sympathetic stimulation with massive increase in heart rate (80%) some increase (10%) in left ventricular output but reduction in stroke volume (70%).

This means that there would be a marked increase in cardiac $O_2$ consumption for only a modest increase in left ventricular output if the parasympathetic system were not activiated to maintain heart rate and left ventricular filling within a reasonable range.

Further experiments are needed in this area to elucidate the differing inotropic and chronotropic effects of the sympathetic and parasympathetic transmitters during hypoxia and asphyxia.

**19. Baroreflexes in unanaesthetised fetal and newborn lambs.**

R. Yardley, J. Cannata, R. J. Smith and A. M. Walker.

The baroreceptor-heart reflex has been studied in 70 experiments in five fetal lambs and three of these animals as newborns. An aortic occluding cuff of silastic tubing was implanted on the descending aorta, distal to the ductus anteriosus, at 100 to 105 days gestation. This occluding cuff was used to raise the mean arterial pressure (MAP) in the baorreceptor regions.

Measurements have been made of the MAP and the heart period (HP) at 10 seconds after the beginning of a step increase in pressure in the occluder; at this stage the pressure and response were steady and there was only a minimal change in the blood gas status of the animal (less than 5% fall in $Pa0_2$ and no change in $PaC0_2$).

Using these measurements attempts have been made to derive an input-output relationship which can be used to show if a gestational trend exists in the reflex and the effects of autonomic blocking drugs during hypoxia, asphyxia and anaesthetic administration.

The results to date indicate that the sensitivity of the reflex in the region of the resting level does not change with gestation but that the level at which the reflex saturates increases through gestation and into the newborn period. This is true even when allowance is made for the changing resting levels of MAP and HP throughout gestation.

The reflex then matures in two of three aspects: (1) the operating level changes; (2) there is a marked increase in the percentage change in pressures that can be applied before saturation appears in late gestation as compared with the younger fetuses, however (3) the gain remains unchanged. The MAP-HP reflex in the fetal sheep was largely abolished by giving atropine indicating that most of the slowing of the heart is due to vagal efferents and little or no reduction in resting sympathetic tone. Some experiments have been conducted with the fetus in an hypoxic state while the reflex was tested but further work in this area will be required before any conclusions can be made regarding a gestational trend and interactions of the baroreflex with chemoreceptor stimulation.

# Publications

## HYPERTENSION AND CIRCULATORY CONTROL RESEARCH UNIT
## Published or Accepted for Publication

W. P. ANDERSON, P. I. KORNER, A. BOBIK and J. P. CHALMERS.
Leakage of dl-propranolol from cerebro-spinal fluid to the bloodstream in the rabbit. *J. Pharmacol. & Exptl. Therapeutics*, Vol. 202, No. 2, 320-325, 1977.

W. P. ANDERSON, P. I. KORNER, C. I. JOHNSTON, J. A. ANGUS and D. J. CASLEY.
Intrarenal action of angiotensin II in restoring renal artery pressure after acute renal artery stenosis. *Clin. & Exptl. Pharmacol & Physiol.* (In Press)

W. P. ANDERSON, P. I. KORNER and C. I. JOHNSTON.
Angiotensin II: Intrarenal action to minimize the development of experimental hypertension following renal artery stenosis. *Kidney International.* (In Press)

JAMES A. ANGUS and PAUL I. KORNER.
Regional vascular resistance and heart rate responses mediated through $H_1$- and $H_2$- histamine receptors in the unanaesthetised rabbit. *Europ. J. Pharmacol.*, 45: 45-53, 1977.

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M. de B. DALY, P. I. KORNER, J. E. ANGELL-JAMES and J. R. OLIVER.
Cardiovascular-respiratory interactions between carotid bodies and upper airways receptors in the monkey. *Am. J. Physiol.*, 234 , H293-H299, 1978.

M. de B. DALY, P. I. KORNER, J. E. ANGELL-JAMES and J. R. OLIVER.
Cardiovascular and respiratory effects of carotid body stimulations in the monkey. *Clin. Exptl. Pharmacol. & Physiol.* (In Press)

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J. S. HUTCHINSON, J. CSICSMANN, P. I. KORNER and C. I. JOHNSTON.
Characterization of immunoreactive angiotensin in canine cerebrospinal fluid as des-asp$^1$-Angiotensin II. *Clin. Sci. Mol. Med.* 54, 147-151, 1978.

M. IRIKI, PATRICIA DORWARD and P. I. KORNER.
Baroreflex 'resetting' by arterial hypoxia in the renal and cardiac sympathetic nerves of the rabbit. *Pflugers Archiv.*, 370: 1-7, 1977.

PAUL I. KORNER and PETER J. FLETCHER.
Role of the heart in causing and maintaining hypertension. *Cardiovascular Medicine,* 139-155, 1977.

P. I. KORNER
Central nervous control of autonomic cardiovascular function. In: *Handbook of Physiology,* ed. Robert M. Berne, Section 2, Circulation, Vol. 1, Am. Physiol. Soc., Washington. (In Press).

P. I. KORNER.
Role of the autonomic nervous system in reflex cardiovascular control In: *Progress of Cardiology,* ed. Paul N. Yu and John F. Goodwin, Vol. 8, Lea & Febiger, Philadelphia. (In Press)

P. I. KORNER, A. M. TONKIN and J. B. UTHER.
Valsalva constrictor and heart rate reflexes in subjects with essential hypertension and with normal blood pressure. *Clin. Exptl. Pharmacol & Physiol.* (In Press)

P. PULLAN, C. I. JOHNSTON, W. P. ANDERSON and P. I. KORNER.
Role of vasopressin in blood pressure control and hypertension. *Clin. Sci. Mol. Med.* (In Press)

**Submitted for Publication**

W. P. ANDERSON, PAUL I. KORNER, COLIN I. JOHNSTON and DAVID J. CASLEY.
Acute renal hemodynamic and renin-angiotensin system responses to graded renal artery stenosis and their relationship to the development of 'one-kidney' hypertension in conscious dogs.

W. P. ANDERSON, P. I. KORNER, C. I. JOHNSTON, J. A. ANGUS and D. J. CASLEY.
Intrarenal action of angiotensin II in restoring renal artery pressure after acute renal artery stenos.

PATRICIA K. DORWARD and PAUL I. KORNER.
Effect of dl-propranolol on renal sympathetic bareoreflex properties and aortic baroreceptor activity.

J. S. HUTCHINSON and J. CSICSMANN
The distribution of immunoreactive angiotensin I and II extracted from rat brain.

## CARDIOVASCULAR METABOLISM AND NUTRITION RESEARCH UNIT

**Published or accepted for publication:**

N. H. FIDGE and P. POULIS.
Metabolic heterogeneity in the formation of low density lipoprotein from very low density lipoprotein in the rat. Evidence for the independent production of a low density lipoprotein subfraction. *J. Lipid Res.* (in press).

T. ISHIKAWA, N. FIDGE, D. S. THELLE, O. H. FORDE and N. E. MILLER.
The Tromso Heart Study. Serum apolipoprotein AI concentration in relation to future coronory heart disease. *Europ. J. Clin. Invest.* (In press).

N. E. MILLER.
Induction of low density lipoprotein receptor synthesis by high density lipoprotein in cultures of human skin fibroblasts. *Biochim. Biophys. Acta* (In press).

G. J. MILLER and N. E. MILLER.
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G. J. MILLER and N. E. MILLER.
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P. J. NESTEL and N. E. MILLER.
Mobilization of adipose tissue cholesterol in high density lipoprotein during weight reduction in man. In: *"High Density Lipoproteins and Atherosclerosis"*. Gotto A.M., Miller, N. E. and Oliver M. F. (Editors), Elsevier/North-Holland Biomedical Press, Amsterdam, The Netherlands , 1978.

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P. J. NESTEL, N. QUINLIVAN and H. ROXBURGH.
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P. J. NESTEL, A. POYSER, R. L. HOOD, S. C. MILLS, M. R. WILLIS, L. J. COOK and T. W. SCOTT.
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P. J. NESTEL, T. ISHIKAWA and R. GOLDRICK.
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P. J. NESTEL and N. E. MILLER.
High density lipoprotein and cholesterol metabolism. In: *"High Density Lipoproteins"* C. E. Day (Editor) Plenum Press, New York (In press).

P. J. NESTEL and P. VIJAYAGOPAL.
Metabolism of lipoproteins by human lymphocytes. Possible defects of very low density lipoprotein catabolism in subjects with hypertriglyceridaemia. *Artery* 3:456-471, 1977.

P. POULIS and N. H. FIDGE.
The effect of a short term saturated fat diet on the apoprotein composition and radioiodination properties of rat very low density lipoproteins. *Lipids* 12:288-292, 1977.

M. F. REARDON, N. H. FIDGE and P. J. NESTEL.
The catabolism of very low density lipoprotein B apoprotein in man. *J. Clin. Invest.* 61:850-860, 1978.

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M. L. WAHLQVIST, N. H. FIDGE and F. LOMAS.
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M. WHYTE, P. J. NESTEL and A. MacGREGOR.
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## DEVELOPMENTAL BIOLOGY RESEARCH UNIT

**Papers published or accepted for publication**

ALCORN, D., ADAMSON, T. M., LAMBERT, T. F., MALONEY, J. E., RITCHIE, B. C., and ROBINSON, P. M.
Morphological effects of chronic tracheal ligation and drainage in the fetal lamb lung. *J. Anat. (Lond). 123:* 649-660, 1977.

ALCORN, D., ADAMSON, T. M., MALONEY, J. E., RITCHIE, B. C., and ROBINSON, P. M.
Morphological effects of phrenectomy on the foetal lamb lung. *J. Anat. (Lond).* (In press).

CHEZ, R. A., EHRENKRANZ, R. A., OAKES, G. K., WALKER, A. M., HAMILTON, L. A., BRENNAN, S. C., and McLAUGHLIN, M. K.
Effects of adrenergic agents on ovine umbilical and uterine blood flows. In Longo, L. D. (Ed.): *Circulation in the fetus and newborn.* New York, Garland Publishing, 1977. (In press).

EHRENKRANZ, R. A., HAMILTON, L. A., BRENNAN, S. C., OAKES, G. K., WALKER, A. M., and CHEZ, R. A.
Effects of salbutamol and isoxsuprine on uterine and umbilical blood flow in pregnant sheep. *Amer. J. Obstet. & Gynecol. 128:* 287-293, 1977.

EHRENKRANZ, R. A., WALKER, A. M., OAKES, G. K., HAMILTON, L. A., and CHEZ, R. A.
Effect of Fenoterol (Th1165a) infusion on uterine and umbilical blood flow in pregnant sheep. *Amer. J. Obstet. & Gynecol. 128:* 177-182, 1977.

MALONEY, J. E., CANNATA, J., DOWLING, MARGARET H., ELSE, WENDY and RITCHIE, B.
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MALONEY, J. E., BAIRD, J., BRODECKY, V., and DIXON, JAN.
A technique for the direct observation of the unanaesthetised foetal sheep. *Am. J. Obstet. & Gynecol.* (In press).

MALONEY, J. E.
The perinatal development of the respiratory system in the foetus. *Proc. Aust. Physiol. Pharmacol. Soc. Symposia.* (In press).

OAKES, G. K., WALKER, A. M., EHRENKRANZ, R. A., and CHEZ, R. A.
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SMOLICH, J. J., STRATFORD, BERNICE F., MALONEY, J. E., and RITCHIE, B.C.
Development of the upper respiratory epithelium of the rat. *J. Anat.* (In press).

SMOLICH, J. J., STRATFORD, BERNICE F., MALONEY, J. E., and RITCHIE, B. C.
Glandular development in the neonatal rat trachea. *J. Anat. (Lond).* (In press).

WALKER, A. M., CANNATA, J., DOWLING, MARGARET, RITCHIE, B. C., and MALONEY, J. E.
Development of autonomic influence on the heart rate of conscious foetal and neonatal lambs. *Biol. Neonate.* (In press).

WALKER, A. M., OAKES, G. K., EHRENKRANZ, R., McLAUGHLIN, M., and CHEZ, R. A.
Twenty-four hour rhythms in uterine and umbilical blood flows of conscious pregnant sheep. *Gynecol. Invest.,* 1977. (In press).

**Submitted for publication**

WALKER, ADRIAN M., CANNATA, JOHN P., DOWLING, MARGARET H., RITCHIE, BLAIR C., and MALONEY, JOHN E.
Age dependent pattern of autonomic heart rate control during hypoxia in fetal and newborn lambs. (Submitted).

**Abstracts**

ADAMSON, T. M., ALCORN, D., LAMBERT, T. F., MALONEY, J. E., RITCHIE, B. C., and ROBINSON, P. M.
The role of lung liquid in prenatal lung development. Proc. International Union of Physiological Sciences. *12:* 389, 1977.

ALCORN, D., ADAMSON, T. M., MALONEY, J. E., RITCHIE, B. C., and ROBINSON, P. M.
Morphological effect of phrenectomy in the foetal lamb lung. Proc. 27th Congress I.U.P.S. *13:* 17, 1977.

ALCORN, D., ADAMSON, T. M., MALONEY, J. E., RITCHIE, B. C., and ROBINSON, P. M.
A synopsis of fetal lung development. J. Anat. (Lond). (In press).

MALONEY, J. E., BRODECKY, V., CANNATA, J., DOWLING, MARGARET, ELSE, WENDY and RITCHIE, B. C.
Control of arterial blood pressure in unanaesthetised fetal and newborn lambs. Aust. Paed. J. *12:* 229, 1976.

MALONEY, J. E.
Breathing before birth — experimental studies. Proc. 48th A.N.Z.A.A.S. Conference. *1:* 256, 1977.

WALKER, A. M., CANNATA, J., DOWLING, M. H., RITCHIE, B. C., and MALONEY, J. E.
Sympathetic and parasympathetic control of heart rate in unanaesthetised fetal and newborn lambs. Proc. Aust. Physiol. Pharmacol. Soc. *8:* 155P, 1977.

WALKER, A. M., MALONEY, J. E., and RITCHIE, B. C.
Control of the pulmonary circulation in the fetal and newborn lamb. Proc. 27th Congress I.U.P.S. *12:* 332, 1977.

WALKER, A., CANNATA, J., DOWLING, M., RITCHIE, B. C., and MALONEY, J. E.
Autonomic control of heart rate during hypotension in conscious fetal and newborn lambs. Proc. 27th Congress I.U.P.S. *13:* 798, 1977.

WALKER, A. M., CANNATA, J., DOWLING, MARGARET, and RITCHIE, B. C.
Autonomic components of the heart rate response to hypoxia in the foetal and newborn lamb. Aust. Paed. J. (In press).

## SPECIAL SEMINARS

1. A course of six postgraduate seminars in Clinic Pharmacology of the Cardiovascular System were held, in particular to candidates preparing for the first part F.R.A.C.P. and to advanced trainees in cardiology. These lectures were presented by Professor Korner, Drs. Nestel, Jennings, Esler, Fletcher and Miller. Professor Korner also presented a series of four seminars on CNS Control of the Circulation.

2. Sister Elizabeth Leembruggen of the National Heart Foundation/Baker Institute Risk Evaluation Clinic presented a film on Risk Factors Related to Coronary Heart Disease and a demonstration on cardiovascular resuscitation.

3. Dr. Michael de Swiet, Brompton Hospital, London, gave a seminar on 'Epidemiological Study of Blood Pressure in Infancy'.

4. The Electronics Laboratory, in conjunction with the Alfred Hospital, presented a course of monthly seminars on electronic engineering. Apart from the staff of the Baker Institute and Alfred Hospital there were guest speakers from Tektronics Pty. Ltd., Prince Henry's Hospital, S.E.C. and Hewlett Packard Australia Pty. Ltd.

## SEMINAR PROGRAMME — 1977

| Date | Title | Lecturer |
|---|---|---|
| 4 February | Cholesterol metabolism in man. | Dr. Paul Nestel<br>Baker Institute |
| 18 February | Localization of the central nervous region mediating the cardiovascular responses to cerebral ischaemia in the rabbit. | Dr. Roger Dampney<br>Department of Physiology<br>University of Sydney |
| 4 March | An investigation of beta adrenergic receptors. | Dr. E. Woodcock<br>Department of Medicine<br>Prince Henry's Hospital |
| 18 March | Clinical and experimental studies of metabolic intervention during myocardial ischaemia. | Dr. Norman Miller<br>Baker Institute |
| 1 April | Increased sympathetic nervous system activity in essential hypertension — fact or April Fool's Day fancy. | Dr. Murray Esler<br>Baker Institute |
| 15 April | Studies of apolipoproteins and their roles in fat transport. | Dr. Noel Fidge<br>Baker Institute |
| 29 April | Hypertension — an endocrine disease? | Prof. Colin Johnston<br>Department of Medicine<br>Monash University |
| 13 May | Recent advances in thyroid hormone metabolism. | Dr. Jim Stockigt<br>Ewen Downie Metabolic Unit<br>Alfred Hospital |
| 21 May | Tranquillizer-like actions of narcotic analgesics. | Dr. Jim Reynoldson<br>Baker Institute |
| 10 June | Haemodynamic changes in hypertensive pregnancy. | Prof. W. A. W. Walters<br>Department of Obstetrics & Gynaecology<br>Queen Victoria Hospital |
| 24 June | Myocardial metabolism in the conscious dog. | Dr. Mark Wahlqvist<br>Prince Henry's Hospital |
| 8 July | Experimental models of steroid hormone induced hypertension. | Dr. Bruce Scoggins<br>Howard Florey Institute |
| 22 July | The microsphere technique for measuring peripheral blood flow distribution. | Dr. Peter Fletcher<br>Baker Institute |
| 12 August | Exercise testing in the assessment of surgical and medical interventions in ischaemic heart disease. | Dr. Garry Jennings<br>Clinical Research Unit<br>Alfred Hospital |
| 26 August | Methods of approach to the study of human growth. | Dr. D. Cheek<br>Royal Childrens' Hospital |
| 23 September | Foetal lung growth — factors controlling it. | Dr. Michael Adamson<br>Visiting Fellow<br>Baker Institute |
| 7 October | Single cell nerve activity in man. | Dr. Henry Kranz<br>Val Cleef Foundation<br>Alfred Hospital |
| 21 October | Pressor and depressor responses to Saralasin (1-Sar-8-Ala AII) in man. | Dr. Barry McGrath<br>Prince Henry's Hospital |
| 28 October | Central respiratory pattern generation in the foetus. | Dr. Glenn Bowes<br>Baker Institute |
| 4 November | Neuromuscular transmission in arterioles. | Dr. G. Hirst<br>Department of Physiology<br>Monash University |
| 11 November | Renal vascular mechanisms in hypertension. | Dr. Warwick Anderson<br>Baker Institute |
| 18 November | How do beta- blockers lower blood pressure? | Prof. Paul Korner<br>Baker Institute |
| 2 December | Reflex control of the foetal and newborn heart. | Dr. Bob Yardley<br>Baker Institute |
| 16 December | Interactions between lipoproteins and cultured fibroblasts. | Dr. Norman Miller<br>Baker Institute |

## AUGUST VACATION COURSE ON BASIC SCIENCE OF THE CARDIOVASCULAR SYSTEM

During the University August vacation this year a two-day course on cardiovascular physiology, pharmacology and biochemistry was held at the Institute. The course was open to all Third and Honour year science students. The aim was to introduce these students to some of the current research being performed at the basic science level into the diseases of hypertension and atherosclerosis. The students were taught some of the mechanisms of both normal control blood pressure and lipoprotein metabolism and present understanding of the pathogenesis of hypertension and atherosclerosis. In particular, emphasis was placed on how research is conducted in these two areas and on new insights recently gained. On the afternoon of the second day the students visited demonstrations in all laboratories.

Sixty students attended the course. We held lectures in the library, the only room large enough to hold this number. A smorgasbord dinner was provided at the conclusion of the course. The great success of the venture has encouraged us to hold further courses of this nature in 1978.

**Lectures Presented**

| | |
|---|---|
| Professor Paul Korner | Control of the Circulation |
| Dr. Paul Nestel | Atherosclerosis & Lipoproteins — clinical, experimental & metabolic aspects |
| Dr. Warwick Anderson | Kidney and Hypertension |
| Dr. Archer Broughton | Cardiac Function |
| Dr. Noel Fidge and Dr. Norman Miller | Biochemistry and Physiology of Lipoproteins and Atherosclerosis |
| Dr. Murray Esler and Dr. Garry Jennings | High Blood Pressure in Man |
| Dr. John Maloney | Cardiovascular Development in Foetus and Newborn. |

## LOCAL LECTURES

Papers were presented at the Annual Meeting of the Australasian Society of Clinical and Experimental Pharmacologists held in Sydney by Professor P. I. Korner and Dr. J. A. Reynoldson; at the Cardiac Society of Australia & New Zealand Annual Meeting by Drs. W. P. Anderson and P. J. Fletcher, where Professor P. I. Korner was invited to present the Kempson Maddox Lecture; and at the ANZAAS Meeting by Dr. M. Esler and Professor P. I. Korner.

Drs. P. J. Nestel, M. Reardon and Andrea Poyser presented abstracts at the Annual Meeting of the Australian Society for Medical Research and Drs. P. J. Nestel and N. Fidge presented papers at the Annual Meeting of the Australian Atherosclerosis Society in Melbourne.

Drs. J. E. Maloney, A. M. Walker, B. C. Ritchie and G. Bowes gave lectures on various aspects of fetal respiration and circulation at Monash and Melbourne Universities, and participated at an ANZAAS Symposium on Breathing before Birth, and an APPS Symposium on Control of Fetal and Neonatal Respiration.

## OVERSEAS VISITS

During July Professor P. I. Korner attended the Physiological Society Meeting Oxford, U.K., participated in a satellite symposium in Berlin on 'Central interactions between respiratory and cardiovascular control systems', and presented a communication entitled 'Valsalva constrictor reflex in rabbits — role of aortic and carotid baroreceptors' at the 27th International Congress of Physiological Sciences in Paris.

Dr. P. J. Nestel attended by invitation of the National Institutes of Health the 2nd International Congress on Obesity in Washington. Also in October Dr. P. J. Nestel and Dr. N. Miller presented papers in Brussels on 'Mobilisation of adipose tissue cholesterol in high density lipoprotein during weight reduction in man' and 'Do high density lipoprotein protect against coronary atherosclerosis?' Dr. Nestel presented a communication on 'Low density lipoprotein protein metabolism in man' in Milan during November.

Drs. T. M. Adamson and A. M. Walker and Diane Alcorn presented invited papers at the 27th Congress of the International Union of Physiological Sciences in Paris from 18-23 July 1977. Dr. J. E. Maloney at-

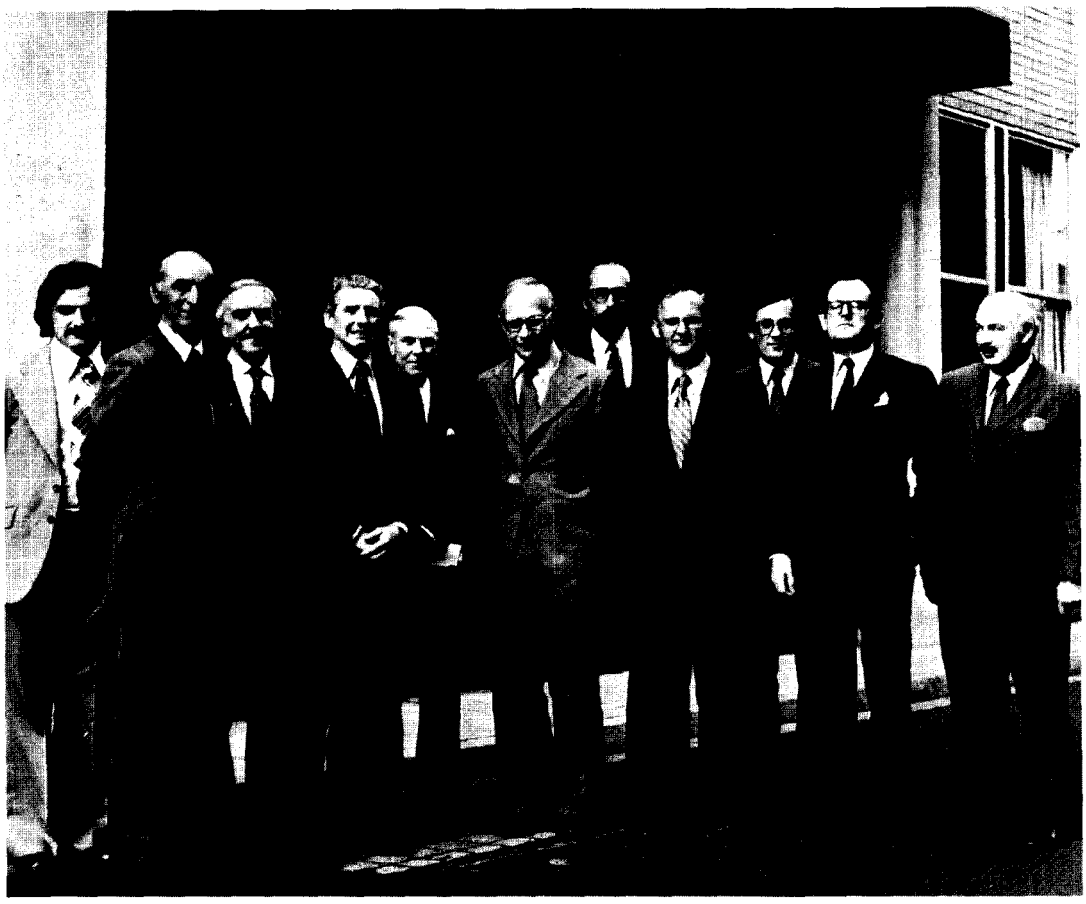
tended by invitation a Sudden Infant Death Research Planning Workshop held by the National Institute of Health in Washington, D.C., U.S.A.

## VISITS TO THE INSTITUTE

In March the Board of Directors of the Victorian Division of the National Heart Foundation visited the Baker Institute. The tour included all facets of research carried out at the Institute as well as the Clinical Research Unit.

We also had the pleasure of having the Directors of the Life Offices Association tour the Baker Institute in October. Here again demonstrations of work performed by different divisions of the Institute were shown.

*Above: Dr. N. Fidge demonstrates a point on the relationship between fats and heart disease to Messrs. Jones, Kimber, Bienvenu and Chappell.*



*Top: The visitors and hosts (l to r): Messrs. D. Phillips (FML), R. L. Bienvenu (NML), M. S. Mainprize (CML), E. K. Jones (Scot. Amic.), J. C. Habersberger (Baker Institute), Prof. P. I. Korner (Baker Institute), Messrs. D. J. Kimber (R.-G.), J. C. Chappell (T&G), D. J. Slee (U&I), J. N. Baylis (Swiz.), N. E. Renton (LOA).*

## NEW COMPUTER LINK

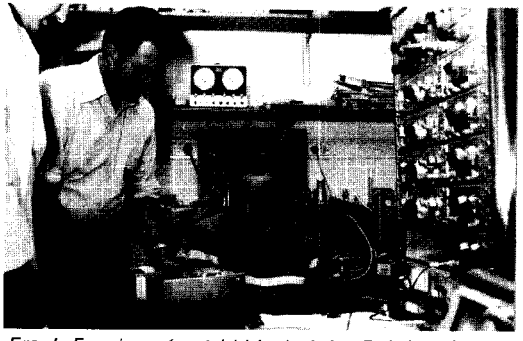
During the year a donation was received from the Potter Foundation which enabled the Institute to purchase two Texas 733 Electronic Data Terminals. Each terminal is linked to the Monash Computer Centre using a standard Telecom line. They are capable of sending and receiving information, and printout at speeds of up to 30 characters per second. The terminals incorporate a twin cassette system for writing, editing and storage of programs within the Institute.

A large amount of data is generated during the course of our research work and this requires an enormous amount of statistical analysis. The terminals remove much of the drudgery of analysis and provide an efficient service with clear copies of results.

Many statistical tests are common to research workers so a special program has been written incorporating the common features. This program is stored on disc at Monash University and can be called at any time through our terminal system.

Apart from the service to researchers, our computers also efficiently store administration data which includes all personnel records.

*Chief Accountant, Hec McConnell and Laboratory Supervisor, Chris Lewis.*



*Frank Forgione (part hidden), John Baird and Kevin Harvey in the Electronics Workshop.*

*New CANDE computer terminals provided by the Ian Potter Foundation. Pictured at terminal, Michael Percy, head of Electronics Workshop.*

## GRANTS AND DONATIONS

| | |
|---|---|
| Victorian State Government | 135,000.00 |
| Ciba-Geigy (Aust) Pty. Ltd. | 14,000.00 |
| Sandoz (Aust) Pty. Ltd. | 12,000.00 |
| Allan Williams Trust Fund | 10,000.00 |
| Boehringer Ingleheim Pty. Ltd. | 8,000.00 |
| The James and Elsie Borrowman Research Trust | 5,500.00 |
| The George Thomas Lockyer Potter Charitable Trust | 5,500.00 |
| The William Anglis (Vic) Charitable Trust | 4,000.00 |
| Estate of D. A. Parker | 3,383.37 |
| The Felton Bequest | 3,250.00 |
| H. L. Hecht Trust | 3,000.00 |
| William Ritchie Food Stores Pty. Ltd. | 3,000.00 |
| Kodak (Australia) Pty. Ltd. | 2,500.00 |
| Estate of Edward Wilson | 2,500.00 |
| The Ian Potter Foundation | 2,250.00 |
| Dr. B. Ritchie | 2,000.00 |
| Australian Academy of Science | 1,974.00 |
| The Appel Family Bequest | 1,800.00 |
| The Bell Charitable Trust | 1,250.00 |
| Estate of Marian & E. H. Flack | 1,155.00 |
| Merck, Sharpe & Dohme (Aust) Pty. Ltd. | 1,000.00 |
| The Percy Baxter Charitable Trust | 1,000.00 |
| J. B. Were & Son | 1,000.00 |
| The Truby & Florence Williams Charitable Trust | 1,000.00 |
| The George F. Little Trust | 929.00 |
| The Alfred Edments Trust | 850.00 |
| Carlton United Breweries Ltd. | 500.00 |
| Mrs. Winifred Crane | 500.00 |
| Pethard Tarax Charitable Trust | 250.00 |
| Mrs. L. P. Hewgill | 200.00 |
| General Motors Holden | 150.00 |
| Dr. H. B. Kay | 150.00 |
| J. Godey | 100.00 |
| Professor P. I. Korner | 100.00 |
| Dr. J. Maloney | 100.00 |
| Mr. H. D. Stewart | 100.00 |
| Seigfred Meyer | 75.00 |
| Mrs. E. Cooper | 50.00 |
| Alan F. Drayton | 25.00 |
| Miss N. E. Cameron | 20.00 |
| P. J. & P. A. Shaw | 20.00 |
| Mrs. M. Le Duc | 5.00 |
| | $230,186.37 |

**Further contributions were received from —**
• Miss J. Hall; • Miss N. E. Cameron; • Mr & Mrs M. Mollaghan; • Baker Benefactions, Kodak (Aust) Pty. Ltd.; • Kodak (Aust) Pty. Ltd.; • Mrs E. Rumble; • K. B. Allen; • 2/14 Australian Field Regiment Association; • J. C. HabersBerger; • Mr & Mrs A. Mitchell; • Misses D. & J. & Mr R. Jeffrey, J. Whitty, Thomas Baker (Kodak) Alice Baker & Eleanor Shaw, Australian Eagle Insurance Co. Ltd., Herbert Allen.

**In Memory of —**
• Gerald T. Collins; • John Andrew McQualter; • Wayne Robert Cowley; • Albert George Walton; • William John Hayes; • Mr A. McGee; •Mrs Dawn Warlow; • John Constantine Black; • Mr A. O'Brien; • Mr J. H. Castle; • Mr Overend; • Mrs Doris Dawe; • Rohan Rivett; • Mrs Mollie Wotherspoon; • Mrs Ruby Vera Green; • Mrs J. Macartney; • Mr K. E. Allen; • Alec Whatmore; • John Derrick
TOTAL $682.00

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

## Revenue account for the year ended 31st December, 1977

| EXPENDITURE | |
|---|---|
| Salaries and wages | 695,914 |
| Laboratory supplies and isotopes | 111,405 |
| Additional equipment and building costs | 105,890 |
| Library maintenance | 15,059 |
| Postage and telephone | 8,465 |
| Printing and stationery | 12,223 |
| Light and power | 30,815 |
| Insurance | 41,647 |
| Repairs and renewals | 26,172 |
| Animal house contribution | 8,000 |
| Sundries | 8,361 |
| Travelling expenses | 12,138 |
| Public relations | 1,040 |
| Stanhope Court | 4,664 |
| | $1,081,793 |

| INCOME | | |
|---|---|---|
| **Donations from Baker Benefactions** | | |
| Statutory amount | 11,569 | |
| Transfers from Endowment Fund | 282,100 | 293,669 |
| Donations other | | 77,369 |
| **Grants-in-Aid of Research Projects** | | |
| Anti-Cancer Council | 354 | |
| Life Insurance Medical Research Fund of Australia and New Zealand | 50,985 | |
| National Health and Medical Research Council | 174,372 | |
| National Heart Foundation of Australia | 35,654 | |
| Department of Health, Education and Welfare (USA) | 33,368 | |
| Sugar Association (USA) | 8,353 | 303,086 |
| **Other Grants** | | |
| The James and Elsie Borrowman Research Trust | 5,500 | |
| The William Buckland Research Fund | 1,649 | |
| Victorian State Government | 135,000 | 142,149 |
| **Interest from Investments** | | |
| Held by Trustees of The Baker Institute Grant Trust | 4,419 | |
| Other investment income | 141,306 | 145,725 |
| **Other Income** | | |
| Rentals | 28,085 | |
| Sundry sales, recoveries and refunds | 73,204 | 101,289 |
| Deficit for the year | | 18,506 |
| | | $1,081,793 |

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

The Trustees, Executors & Agency Co. Ltd. is the custodian and investment manager of some of the investments of the Institute. These investments included in the balance sheet of the Institute are in accordance with statements provided by the custodian company giving details of the Institute's entitlement in securities held by the custodian company in its own name but it has not been practicable for us to carry out normal audit procedures to confirm those investments or the income arising therefrom.

Subject to the above reservations in our opinion, the balance sheet together with the notes thereto, as set out on schedules 2 to 8 is properly drawn up to show a true and fair view of the state of the Institute's affairs at 31 December 1977.

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

Melbourne
14 February, 1978

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

## Balance Sheet as at 31st December, 1977

### ACCUMULATED FUNDS AND LIABILITIES

| | | |
|---|---|---|
| **Maintenance Fund** | | |
| Accumulated deficit brought forward | (11,950) | |
| Deficit for year | (18,506) | |
| Accumulated deficit | | (30,456) |
| Bank overdraft | | 28,473 |
| Sundry creditors and Accrued expenses | | 29,153 |
| | | 27,170 |
| **Endowment Fund** | | |
| Accumulated fund | | 1,398,502 |
| | | 1,398,502 |
| **Research and Scholarship Funds** | | |
| Restricted fund | | 31,150 |
| Edgar Rouse Memorial Fellowship Fund | | 41,247 |
| Laura Nyulasy Scholarship Fund | | 2,864 |
| William Buckland Research Fund | | 22,297 |
| Lang Research Scholarship Fund | | 4,852 |
| | | 102,410 |
| | | $1,528,082 |

### MAINTENANCE FUND ASSETS

| | | |
|---|---|---|
| Cash on hand | | 200 |
| Sundry debtors | | 26,970 |
| **Endowment Fund Assets** | | |
| Investments at cost | | |
| Held by Trustees of the Institute | | |
| Government and semi-government stock | 86,124 | |
| Shares and debentures in companies | 121,280 | |
| Short term deposits | 75,688 | |
| Mortgage loans | 529,000 | |
| Sundry debtor | 175 | |
| | | 812,267 |
| Held by The Trustees, Executors & Agency Co. Ltd. | | |
| Shares in companies | 63,356 | |
| Trust units | 473,719 | |
| Short term deposits | 7,200 | |
| | | 544,275 |
| Cash at bank | 41,960 | |
| | | 1,398,502 |
| **Research and Scholarship Fund Assets** | | |
| Investments (at cost): | | |
| Held by Trustees of the Institute | | |
| Shares in companies | 4,852 | |
| Short term deposits | 48,000 | |
| | 52,852 | |
| Held by The Trustees, Executors & Agency Co. Ltd. | 27,960 | |
| Cash at bank | 21,598 | |
| | | 102,410 |
| | | $1,528,082 |

**Notes to the Balance Sheet at 31st December 1977**

1. Expenditure included in present or past periods on fixed assets including laboratory equipment, motor vehicles, buildings, improvements and furniture and fittings has been charged against appropriate funds, grants or revenue accounts.
   The insured value of all assets at 31 December 1977, including the building, totalled $5,042,200 (1976 $3,500,000).
   Commitment for the balance of the future purchase of investment in quoted shares amounted to $Nil (1976 $691).
2. The Laura Nyulasy Research Scholarship Fund and the William Buckland Scholarship Fund are both managed by the Trustees, Executors & Agency Co. Ltd.
   In 1976 the investments in shares held by the Trustees of the Institute included amounts of $20,023 for shares and $934 for debenture stocks at probate value being a bequest from the Estate of W. H. Wylie (deceased). This year the above investments have been included in shares held by the Baker Medical Research Institute.
3. The market value fo shares in companies listed on the Australian Stock Exchange at 31 December 1977 was $24,703 (1976 $1,975) above the amount at which they are stated in the accounts.
4. Income and expenditure are accounted for on an accrual basis. In 1976 income was accounted for on a cash basis only. Had last year's policy been followed the deficit for the year would have been increased by $16,646.

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

## Year Ended 31st December 1977

| | | | |
|---|---|---|---|
| **RESTRICTED FUND** | | | |
| Balance at 31st December, 1976 | | | 121,126 |
| Baker Benefactions Statutory Amount 1977 | | 11,569 | |
| Donations | | 56,050 | |
| Investment and bank interest | | 3087 | |
| Patient's fees | | 3,586 | |
| | | | 74,292 |
| | | | 195,418 |
| Transfer to Maintenance 'Statutory Amount' 1977 | | 11,569 | |
| Transfer to Maintenance National Health and Medical Research Council Grant 1977 | | 75,955 | |
| Transfer to Maintenance Specific Donations | | 75,394 | |
| | | | 162,918 |
| Transfer to Melbourne University (Dr. G. Hand Project) | | 1,099 | |
| Travel grant (Dr. Walker) | | 251 | |
| | | | 1,350 |
| | | | $31,150 |
| **OTHER FUNDS** | | | |
| Held by Trustees, Executors & Agency Co. Ltd. | | | |
| William Buckland Research Fund | | 22,296 | |
| Laura Nyulasy Research Scholarship Fund | | 2,864 | |
| | | | 25,160 |
| Held by Trustees of the Institute | | | |
| Lang Scholarship Research Fund (shares at cost) | | 4,852 | |
| Edgar Rouse Memorial Fellowship Fund | | | |
| Short term deposit — GMAC | 35,000 | | |
| Short term deposit — T.E. & A. | 2,800 | | |
| Cash at bank | 3,447 | | |
| | | 41,247 | |
| | | | 46,099 |
| | | | $71,259 |
| **ENDOWMENT FUND** | | | |
| Balance at 31st December, 1976 | | | 1,357,012 |
| Donations to date | | 321,996 | |
| Interest | | 1,070 | |
| Accretion SEC stock | | 28 | |
| Proceeds sale of shares (T.E. & A.) | | 497 | |
| | | | 323,591 |
| | | | 1,680,603 |
| Transfer to maintenance account | | | 282,100 |
| | | | $1,398,503 |
| | | | $1,500,912 |

# CLINICAL RESEARCH UNIT

## STAFF

| | |
|---|---|
| **Director** | PROFESSOR P. I. KORNER, M.D., B.S., M.Sc (Syd), F.R.A.C.P., F.A.A. |
| **Deputy Director** | DR. P. J. NESTEL, M. D, B.S. (Syd), F.R.A.C.P. |
| **Staff Physician** | G. L. JENNINGS, M.B., B.S., M.R.C.P. (U.K.), F.R.A.C.P. |
| **Clinical Assistants** | P. A. BLOMBERY, M.B., B.S., B.Sc, (Med), F.R.A.C.P. (Till April 1977)<br>A. BROUGHTON, M.B., B.S., F.R.A.C.P.<br>M. ESLER, M.B., B.S., Ph.D. (ANU), M.R.A.C.P., Senior Clinical Research Fellow,<br>P. J. FLETCHER, M.B., B.S., B.Sc. (Med), F.R.A.C.P. (Till June 1977)<br>N. E. MILLER, M.B., Ch.B., B.Sc., M.Sc. (Manchester), Ph.D. (ANU) |
| **Biochemical Pharmacology** | A. BOBIK, B. Pharm., M.Sc., Ph.D. (Syd), Officer-in-Charge<br>V. CARSON, M.Sc.<br>G. JACKMAN, B.Sc., Ph.D. (Lond), A.R.A.C.I., A.R.C.S. |
| **Dietitian** | DENISE WINTER |
| **Technical Staff** | P. ASHLEY, B.Sc.<br>M. BANGAH, B.Sc.<br>SUE ELLETT<br>URSULA GREGOREK, B.Sc. (Till 9/12/77)<br>FRANCIS HOPKINS<br>JULIE NEALE (Till 7/1/77)<br>HELEN SKEWS, B.Sc.<br>MARGARET STONEHAM, B.Appl.Biol. (Till 25/2/77) |

## WARD STAFF

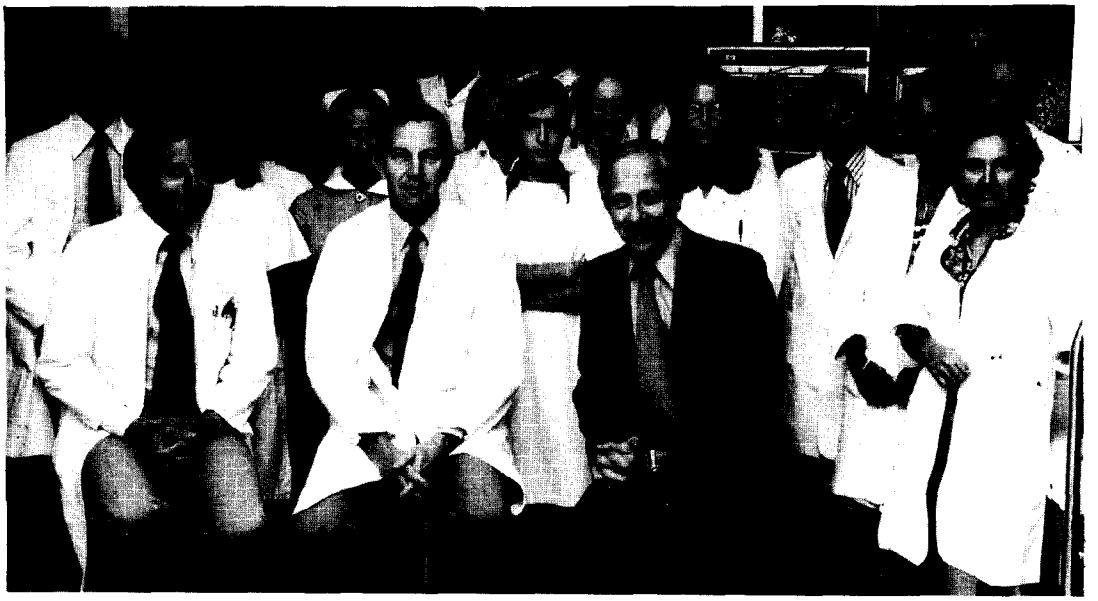
| | |
|---|---|
| **Registrar** | P. JENKINS, M.B., B.S., F.R.A.C.P. (Part 1) |
| **Resident Medical Officers** | B. KONG, M.B., B.S.<br>P. POON, M.B., B.S.<br>H. TEICHTAHL, M.B., B.S.<br>A. WU, M.B., B.S. |
| **Ward Sisters:** | Sr. SUE SCEALEY<br>Sr. PRU COX |
| **Hypertension Clinic** | Sr. HELEN HALL (Baker Institute) |

# Director's Report

During 1977 the activities of the Clinical Research Unit have increased greatly. It is important to stress the very considerable clinical service function performed by the Unit. This includes running the Hospital's Hypertension Evaluation Clinic with Dr. Garry Jennings the Staff Physician in charge. Dr. Paul Nestel, Deputy Director of C.R.U., has established the Hospital's Lipid Clinic for diagnosis and management of patients with disordered lipoprotein metabolism. The scope and activities of the Clinic are described by Dr. Nestel later in this report. Other service functions performed by the Unit include plasma catecholamine assays, quantitative exercise tests, ambulatory blood pressure monitoring and other tests which are performed as a Hospital service when required.

The research activities are closely integrated with the activities of the Hypertension and Circulatory Control Research Unit and the Cardiovascular Metabolism and Nutrition Research Unit and the Cardiovascular Metabolism and Nutrition Research Unit of the Baker Institute. Some of the basic studies performed in C.R.U. in collaboration with the Baker Institute are outlined in the Baker Medical Research Institute section of this report. It is important to stress that questions such as whether there really is sympathetic overactivity in essential hypertension can only be found out in man. Animal models only outline *potential* mechanisms but not what actually happens. One important aspect of the work has been pharmacokinetic studies of beta-blocking drugs and their effectiveness in inhibiting exercise tachycardia. Clinical trials to establish a rational once-a-day dosage regime using timolol and a diuretic have been completed during the year. This type of applied research is important since it contributes to the more rational use of drugs in hypertension and better treatment of the hypertensive patients. It has also great practical value in the training of residents though at present they receive insufficient training in this field in our teaching hospitals. There is little doubt that many more well planned clinical trials should at present be undertaken in Australian teaching hospitals.

An important event towards the latter part of 1977 has been the move of the Clinical Research Unit into the new Ward Block.



***Clinical Research Unit: Standing (left to right):*** *Dr. Arch Broughton, Sue Ellett, Sr. Helen Hall, Sr. Sue Scealey, Moham Bangah (part hidden), Sr. Pru Cox, Judith Dods, Peter Ashley, Dr. Peter Jenkins, Francis Hopkins, Dr. Peter Poon, Dr. Graham Jackman (part hidden), Helen Skews, Dr. Murray Esler, Dianne Kelleher, Dr. Alex Bobik, Val Carson.* ***Seated:*** *Dr. Garry Jennings, Dr. Paul Nestel, Professor Paul Korner.*

This has greatly improved the clinical laboratory facilities which are available to the Unit. We have good accommodation for performing haemodynamic, exercise and metabolic studies. The 10 beds of the Unit are in close proximity to the main medical cardiological beds in the Hospital. We hope that our bed numbers will soon be increased to 15. This is important in relation to a projected new Clinical Research activity with the return from the United States of Dr. Allan McLean half way through 1978 to establish a Clinical Cardiovascular Pharmacology Laboratory.

During the year we received a donation by the National Heart Foundation Australia (Victorian Division) to allow us to purchase equipment for non-invasive cardiac output measurements. This has now been assembled and will allow us to measure maximum pumping capacity of the heart in patients with different types of heart disease. Of particular interest will be to find out whether patients with high blood pressure, with some evidence of cardiac enlargement, suffer a permanent limitation of their maximum cardiac pumping performance even after satisfactory treatment.

**Lipid Service**

Although most hyperlipidaemic subjects have been managed through the Outpatient Lipid Clinic and the Heart Risk Evaluation Clinic, a substantial number were admitted into the CRU for metabolic studies in two broad categories, diagnostic and investigational.

Hyperlipidaemia denotes raised plasma lipids, generally cholesterol or triglyceride or both. It is a broad and imperfect description of complex and varied biochemical derangements. While the majority of hyperlipidaemic individuals can be managed as outpatients on the empirical assumption that these disorders most commonly reflect poor eating habits, 20-25% of affected subjects do not respond to dietary changes. There may then be reasons for carrying out special studies. The problems usually fall into one of the following categories:

1. The differentiation between primary and secondary hyperlipoproteinaemia. This has been commonly seen in diabetic patients with severe hyperlipidaemia, where the problem lay in inadequate insulin therapy, the presence of obesity or the development of complications such as renal impairment that in turn also produces hyperlipidaemia. Other examples included alcoholism and impaired liver function, each of which leads to hyperlipidaemia though through separate processes; the association of pancreatitis, diabetes and fat-inducible hyperlipidaemia where the defect may lie primarily in the failure to clear chylomicrons from the blood or be a secondary manifestation of diabetes; hypothyroidism obesity and hyperlipidaemia occurring together, and so on. These difficulties have usually been clarified in hospital where each factor could be studied in turn.
2. The evaluation of multiple dietary factors or possible failure to adhere to dietary instruction. The hyperlipidaemias due to overproduction from carbohydrate or ethanol or the failure to clear dietary fat have been studied by either removing or administering the food in question, by measuring the turnover of circulating lipoproteins during these dietary manouvres, and by measuring the relevant enzymes.
3. Unusual or rare forms of hyperlipoproteinaemia requiring specialised diagnostic studies including biopsies for tissue culture diagnosis.

The investigational studies have been mainly directed towards an understanding of the dietary control of lipoprotein protein metabolism. Healthy volunteer subjects have been admitted for periods of four to six weeks and given diets of varying proportions of fats and carbohydrates. Comparisons of lipoprotein turnover at the end of each dietary period have defined the relative importance of increased production versus diminished removal as the major reason for the development of hyperlipidaemia in a given individual. These studies will assist in our management of hyperlipidaemic individuals.

Many studies of lipid metabolism could be carried out without hospitalization but rather through the facilities of our clinical laboratory adjacent to the metabolic ward area where supervision by our dietitian and specially trained nurses was available. Quite complex and prolonged metabolic studies have been performed successfully in this way. These have included measurements of the production rates and tissue distribution of cholesterol that entail studies of six months' duration; analysis of lipoprotein protein kinetics that required daily visits for 2-3 weeks; the

effects of specialized foods that were prepared and packaged in the laboratory, etc. The close supervision of patients undergoing unusual dietary treatments is also best handled in a clinical laboratory; this included, for instance, obese subjects on very low caloric intakes.

**1. Pharmacokinetics of Timolol in Man**
A. Bobik, G. L. Jennings, P. Ashley and P. I. Korner

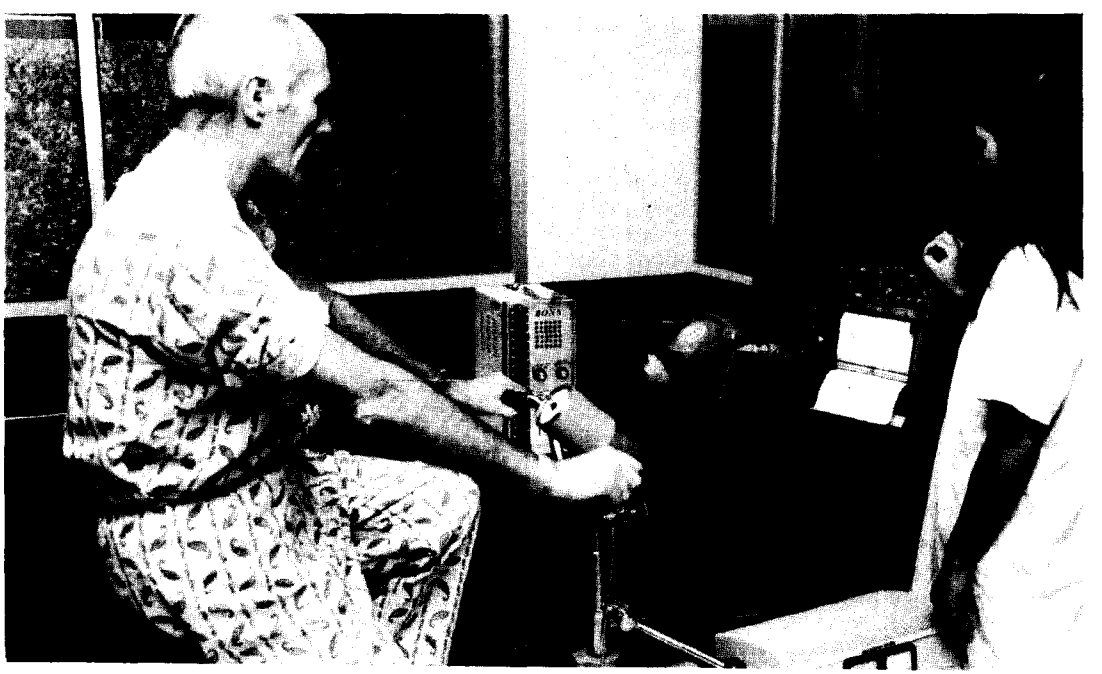
The pharmacokinetics of timolol, a betaadrenergic antagonist was examined following acute and chronic oral administration in varying doses to healthy volunteers. Following the administration of 5, 10 and 20 mg, timolol was well absorbed by all subjects. Maximal plasma levels occurred between 0.5 and 2.5 hr after administration and varied by approximately five-fold. The elimination half-life determined from the post absorptive phase was 3 hr (s.e.m. = 0.3) and is independent of the administered dose. The systemic bioavailability of timolol is directly proportional to the orally administered dose indicating no appreciable saturable 'first pass effect'. Chronic administration (one week) of various doses of timolol (5 mg qid, 10 mg bd and 20 mg daily) resulted in no measurable accumulation of the drug or change in its pharmacokinetic parameters.

We conclude that timolol pharmacokinetics follow simple linear rate processes.

**2. Plasma Timolol Concentrations and their Relationships to Changes in Heart Rate and Blood Pressure at Rest and During Exercise**
A. Bobik, G. L. Jennings, P. I. Korner and P. A. Ashley

Timolol is a beta adrenoreceptor blocking agent recently introduced for the treatment of hypertension and ischaemic heart disease. It differs from other beta-blockers in that it is administered as the levo isomer and not a racemic mixture. To date there is no published data on dose-response relationships with this drug in man.

We have studied the relationship between plasma concentration of this drug and its effects on heart rate and blood pressure at rest and during exercise. After administration of 5, 10 and 20 mg timolol heart rate and blood pressures were significantly reduced and could be related to the plasma concentrations. Timolol produced complete blockade of endogenous sym-



*The new Exercise Laboratory within Ward 2A at the Alfred Hospital.*

pathetic tone to the heart at plasma concentrations below 2.5 ng/ml. Resting systolic blood pressure was also significantly reduced at these low timolol plasma concentrations. At higher plasma timolol concentrations (20-40 ng/ml) the reduction was maximal. The relationships during exercise were of a curvilinear nature with approximately 50% of maximal response occurring between 2.5-5 ng/ml and maximal response between 20-40 ng/ml.

From this study we conclude that the therapeutic half-life of timolol depends on the administered dose and may be predicted from the plasma concentration — effectrelationships and pharmacokinetic parameters for this drug.

### 3. A Comparison of Single Daily and Divided Dose Regimes of Oral Timolol

G. L. Jennings, A. Bobik, S. Ellett, P. Ashley and P. I. Korner

The effects of different dose regimes of timolol on resting heart rate, systolic blood pressure and the response of these variables to graded bicycle exercise standardised in terms of each subject's maximum work capacity were studied in 10 volunteers. The effects were studied after timolol 5, 10 and 20 mg in a single oral dose. The maximum effects of the three doses were identical on resting heart rate, slope of the heart rate-work relationship and the absolute heart rate at a given rate of exercise ($HR_{50}$). The main effect of the larger doses was to depress the exercise tachycardia for longer. Similarly the hypotensive effect of timolol was more prolonged at the higher dose.

The drug was also given following pretreatment for one week with timolol 5 mg qid, 10 mg bd and 20 mg as a single daily dose. A test performed prior to administration of the last chronic dose showed that resting heart rate and $HR_{50}$ were significantly lower than the placebo values, the latter variable being similar at 20%, 23.3% and 15.6% in the three regimes. HR and BP responses to dosage after pretreatment did not difffer from the acute responses.

The regimes were similar in their effect on systolic blood pressure but once daily timolol 20 mg did not reduce the slope of the heart rate response over the 24 hour period to the same extent as the divided dose regimes.

### 4. Bioavailability of Oxprenolol Administered as Standard and Slow Release Tablets

P. A. Ashley, A. Bobik, G. L. Jennings, G. Jackman and P. I. Korner

It is now recognised that poor patient compliance may be a significant factor contributing to failure of antihypertensive therapy. Thus in recent years attempts have been made to increase patient compliance by reducing the frequency of administration of antihypertensive drugs. For beta-blockers (the plasma half-lives of which are relatively short), the dosage interval may be prolonged by administering larger than usual doses or by the use of sustained release preparations. Oxprenolol is a beta-blocking drug which is well established as a useful agent in the management of hypertension and ischaemic heart disease. However, because of the drug's short plasma half-life administration is currently recommended three times daily.

We compared the bioavailability, plasma levels and pharmacological effects of 160 mg of oxprenolol administered as a standard tablet and as slow-release (SR) preparation in healthy volunteers. Administration of oxprenolol in SR form reduced peak plasma levels and delayed the time to reach the peak in comparison with the ordinary tablet. The area under the plasma concentration curves (AUC) was about 10-20% less in the SR preparation. Administration of oxprenolol in the SR form did not significantly influence the urinary recovery of oxprenolol (about 4% of the dose). However, there was a significant difference in the 24 hour excretion of oxprenolol-o-glucuronide (normal 54.0 ± 7.7 mg and SR 31.6 ± 2.8 mg;$P < 0.025$).

The elimination half-life determined from the post absorptive phase of the standard tablet was 2.05 ± 0.25 hr. The effect on the resting and exercise heart rates and blood pressures were similar and declined at the same rates in the post absorptive phase for each formulation. The relatively high plasma concentrations attained with both formulations did not allow a study of plasma concentration — effect relationships. Despite substantial differences (100%) between the peak plasma levels of the ordinary and SR formulations, both types of tablets induced similar maximal effects on resting and exercise heart rates and blood pressure over the 24 hour study period.

There was significant inhibition of resting heart rate and exercise tachycardia 24 hours after both oxprenolol regular ($P < .01$) and oxprenolol slow release ($P < .05$). This suggests that the dose of oxprenolol used in the study is above that required to provided maximum cardiac beta blockade and sufficient to prolong the effect of the standard preparation to 24 hours.

In summary, the present study indicates that SR formulation has no apparent benefits in its pharmacological effectiveness over an equivalent normal formulation. The more prolonged action is somewhat offset by slightly smaller absorption of drug. However, the reduction in peak plasma levels may possibly aid in reducing the incidence of side-effects with these drugs.

**5. The Effect of Propranolol on the Valsalva Constrictor Reflex**
G. L. Jennings and P. I. Korner

The way in which beta-blockers reduce blood pressure is at present unknown. One mechanism which has been suggested, however, is that there is an action on the central nervous system. Clonidine, a drug which is known to exert its hypotensive action through the central nervous system, attenuates sympathetic constrictor reflexes. Whether propranolol affects the Valsalva constrictor reflex has been studied in 7 patients with mild to moderate essential hyptertension. During the 'steady-state' period of the normal Valsalva reflex there is a graded increase in total peripheral resistance which is related to expiratory pressure. This increase was found to be attenuated by 15-20% ($P < .005$) after propranolol. This change could be caused by a central effect on the reflex arc by propranolol. However, the effect appeared to be related to less fall in cardiac output at a given expiratory pressure during the Valsalva manoeuvre. This may be due to the effects of propranolol on cardiac dimensions or on venous compliance in these young mild hypertensive patients. The results in hypertensives are currently being compared with those in a similar group of normal subjects in order to clarify this problem.

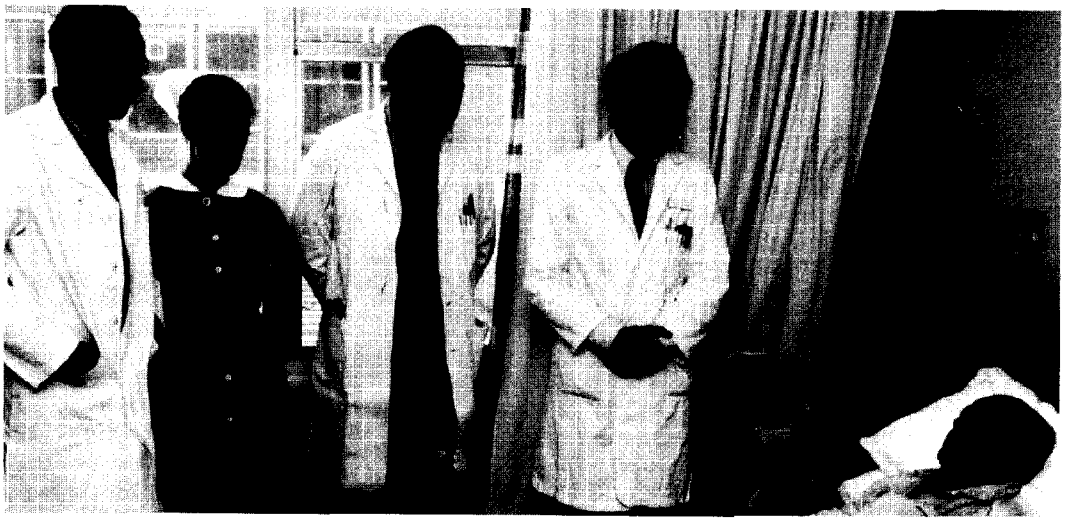
*Dr. Alex Bobik of CRU.*

**6. Pharmacokinetics of Pindolol and the Time Course of Inhibition of Exercise Tachycardia.**
G. L. Jennings, A. Bobik, E. T. Fagan and P. I. Korner

Pharmacokinetics of pindolol were examined after giving 5, 10 and 20 mg orally and 3 mg intravenously. Bioavailability averaged 53%, plasma half-life 2.9 hours and plasma protein binding 38%. Peak plasma concentration after oral dosage coincided with maximum reduction of resting heart rate, slope and $HR_{50}$ (heart rate at 50% maximum work capacity) of the work-heart relationship during exercise 1-2 hours after administration. After 24 hours there was still 28% and 31% of peak inhibition of resting heart rate and $HR_{50}$, but slope had recovered. Inhibition of $HR_{50}$ was about 20% less at plasma pindolol concentrations 5-20 ng/ml than in the range of maximum inhibition 21-160 ng/ml.

**7. The Effect of Beta-Blockade on the Work- ST Curve and its Prognostic Significance for Coronary Bypass Surgery**
G. L. Jennings, *G. Stirling, **A. Pitt and P. I. Korner

In 41 subjects with coronary disease the effect of 3 mg i.v. pindolol on the work-ST segment depression ( ST) curve were investigated. In 36 subjects (group A) the work- ST curve was shifted to the right, with less ST at a given workload ($P < .001$). In 5 subjects (group B) the curve was shifted to the left. Maximum work capacity (Wmax) did not alter significantly in either group (average 677 ± 33 kpm before and 679 ± 26 kpm after pindolol). In 26 group A subjects and all 5 group B subjects coronary bypass surgery was performed,



*On a ward round,* ***from left,*** *Dr. Nestel, Sr. Sue Scealey, Professor Korner and Dr. Jennings.*

and the other 10 group A patients were treated medically. In the latter group the work- ST curve remained unchanged at 3 and 12 months.

In the 26 group A patients there was one death; the work – ST relationship in the other 25 after 3 and 12 months was even more to the right than with pindolol ($P \doteq .01$) and Wmax had increased by 32 ± 6% ($P < .001$); most patients were asymptomatic. In the 5 group B subjects there was a further shift to the left in work- ST relationship, 2 late deaths and 3 non-fatal infarcts. We suggest that the direction of shift by beta-blockade of the work- ST curve has progostic significance for subsequent coronary artery surgery.

* C. J. Officer-Brown Cardio-Thoracic Surgical Unit
** Cardiovascular Diagnostic Service

### 8. Effects of Treatment on the Non-autonomic Component of Peripheral Vascular Resistance in Hypertension

G. L. Jennings and P. I. Korner

As outlined in the previous Baker Medical Research Institute Report a long-term study is currently under way investigating the reversibility of the structural changes due to medial hypertrophy in patients with hypertension. Total peripheral resistance (TPR) is measured before and after pharmacological total autonomic blockade in previously untreated or poorly controlled hypertensive patients.

They are then managed in the C.R.U. Hypertension Evaluation Clinic with careful control of blood pressure over the following 12 months. TPR measurements before and after total autonomic blockade are then repeated so that any regression of the structural 'non-autonomic' component of the elevated TPR found in hypertension can be assessed. Seventeen patients have completed their initial study and are now in the treatment phase. So far only 3 patients have completed the study.

### 9. The Diagnosis and Treatment of Circulatory Autonomic Dysfunction

G. L. Jennings and M. Esler

Dysfunction of the autonomic nervous system may be idiopathic, or is a common accompaniment of diabetes mellitus, of several neurological conditions and the use of a large number of drugs.

The major symptom is often postural dizziness related to inadequate peripheral vasoconstriction on standing which results in pooling of blood in the lower limbs and hypotension. In severe cases this symptom may be extremely debilitating. Existing therapy is largely supportive and of variable efficacy. A number of patients with suspected abnormality of cardiovascular autonomic control have been investigated. The use of biochemical indices of autonomic function such as urinary and plasma noradrenaline measurements as well as testing of a variety of circulatory

autonomic reflexes such as tilting and the Valsalva reflex allow more precise localisation of the lesions and assessment of therapy.

A study of the response of patients to dihydroergotamine (D.H.E.) a new agent used in this condition is in progress. Patients who had previously failed to respond to existing medical therapy have been given intravenous dihydroergotamine with marked reduction in the postural fall with tilting. Chronic oral therapy has also led to improvement in these patients despite problems in choosing the correct dose in each patient related to the drugs' poor bioavailability. A double blind controlled study comparing placebo, D.H.E. and fludrocortisone (the most effective standard therapy), used both alone, and in combination is under way.

**10. An improved Simultaneous Assay of Norepinephrine, Dopamine and 5-Hydroxy-Tryptamine in Discrete Brain Areas**

V. Carson

Alterations in central catecholamines and 5-hydroxy-tryptamine stores in the brain following depletion with 6-hydroxydopamine, 5, 6-dihydroxytryptamine or other drugs have usually been assessed by fluorimetric methods. Shellenberger and Gordon (1971) modified established fluorimetric methods so that catecholamines (norepinepnrine and dopamine) and 5-hydroxy-tryptamine could be assayed simultaneously on a single brain sample. However, the method is relatively insensitive, particularly to dopamine and is unsuitable for the study of catecholamine levels in discrete brain areas following drug-induced depletion. Recently introduced radio-enzymatic techniques greatly improve the sensitivity of the catecholamine assay and have been combined with the fluorimetric method for 5-hydroxy-tryptamine to achieve an improved simultaneous assay of the three momoamines from a single sample.

Brain monoamines are extracted into perchloric acid and 5-hydroxy-tryptamine separated from the catecholamines by alumina chromatography. 5-hydroxy-tryptamine is estimated as described by Shellenberger and Gordon. The catecholamines are eluted from the alumina with perchloric acid and an aliquot (100 *u* or less) is reacted with catechol-O-methyl transferase and s-adenosyl methionine-$^{3}$H in the presence of $Mg^{3}++$ and Tris buffer, pH8.9. The O-methylated products so formed are isolated by selective solvent extraction, 3-methoxy-tyramine-$^{3}$H is separated from the metanephrines-$^{3}$ by oxidation of the latter with sodium periodate. Selective solvent extraction completes the separation.

Product formation is linearly related to substrate concentration over the range 2-20 ng/ml. The assay is sensitive to approximately 20 pg norepinephrine and 200 pg dopamine. Tissue eluates show no inhibitory effect on the enzymatic reaction, thus eliminating the need for internal standardization.

Norepinephreine and dopamine show no cross-reaction in the respective assays. All results are corrected for the recovery of a radioactive tracer added to the original perchloric acid extract and results obtained are in excellent agreement with those obtained by the fluorimetric method.

**Reference:**

1. Schellenberger, M. Kent and Gordon, J. H. (1971), Anal. Biochem. *39,* 356-372.

**11. Biochemical Studies with Cardiac Sarcolemma**

A. Bobik, P. I. Korner, V. Carson and J. R. Oliver

It is well known that the hypertrophied heart is often subnormally responsive to sympathetic stimulation. Whether cardiac membrane receptors such as beta-adrenergic receptors and related enzymes such as adenylate cyclase are abnormally responsive during hypertrophy is however unknown. Furthermore, the effect of chronic increases or decreases in cardiac sympathetic neural activity on such membrane receptors and adenylate cyclase is unknown. Recent work by Lefkowitz and co-workers using purified frog erythrocytes *in vitro* suggest that beta-adrenoreceptor number may be regulated by the extracellular concentration of beta-adrenergic agonist.

In order to study the properties of cardiac beta-adrenoreceptors and the adenylate cyclase system during such pathological conditions it has been necessary to develop techniques for the preparation of a relatively pure sarcolemma fraction from cardiac muscle. Heart sarcolemma is isolated from the ventricle of rabbit heart

by a combination of homogenisation, hypotonic shock and 0.4M LiBr treatments. Mitochrondrial contamination of the sarcolemma fraction as judged by cytochrome C oxidase activity is negligible. The sarcolemma fraction (1000 xg) contained $Nat/^{+}$ $K^{+}$ — ATPase (5.9 *u* moles P/mg protein/h), $Mg^{++}$ — ATPase (13.5*u* moles P/mg protein/h) and $Ca^{++}$ — ATPase (12.3 *u* moles P/mg protein/h). Basal & denylate cyclase activity was 105 *p* moles/mg protein/ min and $10^{-4}$M isoprenaline and 8mM NaF caused 53 and 209% stimulation respectively. $^{3}$H-Alprenolol bound specifically (162 pmoles/mg protein) to this sarcolemma preparation with high affinity (Kd = 9 nM).

Current studies in rabbits are directed towards evaluating the effects of chronic neurogenic hypertension produced by buffer nerve denervation and chronic presynaptic adrenergic blockade on beta receptor number, affinity and the related adenylate cyclase system.

**Clinical Research Unit Laboratory**

The C.R.U. Clinical Laboratory has been used in 1977 for a wide variety of diagnostic and research activities. These have included exercise testing in the evaluation of ischaemic heart disease, ambulatory blood pressure and E.C.G. monitoring, pharmacokinetic and pharmacodynamic studies of beta-blocking drugs, the assessment of patients with autonomic dysfunction, and haemodynamic studies in hypertensive patients.

# Publications

**Published or Accepted for Publication**


A. J. BARNETT, A. BOBIK, V. CARSON, J. S. KORMAN and A. J. McLEAN.
Pharmacokinetics of Methyldopa. Plasma levels following single intravenous, oral and multiple oral dosage in normotensive and hypertensive subjects. *Clin. Exptl. Pharmacol. & Physiol.*, 4: 331-339, 1977.

A. BOBIK and A. J. McLEAN.
Drug analysis in the overdose patient. Its application to clinical toxicology. *Med. J. Aust.*, 1: 367-369, 1977.

A. BOBIK and G. L. JENNINGS.
Therapy with beta adrenergic blocking drugs: Pharmacological considerations. *Sandoz Therapeutic Quarterly*, 4:(4), 1-13, 1977.

A. BOBIK, E. A. WOODCOCK, C. I. JOHNSTON and W. J. FUNDER.
The preparation and purification of 3-(4-Iodophenoxy)-1-isopropyl-amino-2-propranolol-$^{125}$ I, a beta adrenergic antagonist. *J. Labld. Compds. & Radiopharm.*, 13: (14), 605-610, 1977.

A. BOBIK, G. M. HOLDER and A. J. RYAN.
Inhibitors of hepatic mixed function oxidase 3. Inhibition of hepatic microsomal aniline hydroxylase and aminopyrine demethylase by 2,6- and 2,4-dihydroxyphenyl alkyl ketones and related compounds. *J. Med. Chem.*, 20: 1194-1199, 1977.

A. BOBIK, G. L. JENNINGS and P. I. KORNER.
Plasma pindolol levels and their significance in the assessment of cardiac beta blockade. *Med. J. Aust.*, 2: (suppl. 2), 3-5, 1977.

G. L. JENNINGS, A. BOBIK and P. I. KORNER.
Pindolol, exercise testing and angina. *Med. J. Aust.*, 2: (suppl. 2), 6-7, 1977.

G. JENNINGS, N. ZAINAL, B. JONES, D. MODEL, P. TURNER, EM.M. BESTERMAN and P. H. KIDNER:
Disopyramide in the treatment and prevention of arrhythmias following myocardial infarction. *J. Int. Med. Res.*, 4: (suppl. 1), 71, 1977.


## LECTURES AND MEETINGS

A. BOBIK. Paper to the Australian Association of Hospital Pharmacists entitled "The clinical pharmacokinetic of beta-blocking drugs",

Paper to the International Symposium on Visken entitled "Plasma pindolol levels and their significance in the assessment of cardiac beta-blockade".

G. L. JENNINGS. Paper to the International Symposium on Visken entitled "Pindolol in the management of angina".

Conducted medical seminars at the University of Tasmania on "Exercise testing in ischaemic heart disease".

***DR. EWEN DOWNIE*** *(1902-1977)*
*Ewen Downie died in August 1977. A man of vision and energy, he was responsible in 1955 for the establishment of the Diabetic and Metabolic Unit which now fittingly bears his name. The ward and laboratory facilities in which the Unit works, completed in 1957, are the result of his efforts. He was an outstanding physician, a dedicated medical educator, a pioneer in clinical investigation in this country and he was committed to the fostering of youthful aspirants to advancement in Endocrinology. The Ewen Downie Metabolic Unit is testimony to his endeavours and is committed to his ideals and example.*

# EWEN DOWNIE METABOLIC UNIT

## Annual Report

## STAFF

| | |
|---|---|
| **Physician-in Charge** | PINCUS TAFT, M.D., F.R.A.C.P. |
| **Deputy Director** | J. R. STOCKIGT, M.D., F.R.A.C.P. |
| **Visiting Physician** | H. D. BREIDAHL, M.D., F.R.C.P., F.R.A.C.P. |
| **Honorary Consulting Physicians** | EWEN DOWNIE, M.D., F.R.A.C.P. (Deceased, August 1977)<br>BRYAN HUDSON, M.D., F.R.A.C.P. |
| **Honorary Consulting Biochemist** | JOSEPH BORNSTEIN, D.Sc., M.D., F.R.A.C.P. |
| **Clinical Assistants** | D. W. LORDING, M.B., B.S., B.Med.Sc.<br>MARGARET SANDERS, M.B., B.S. |
| **Registrar** | D. M. ENGLER, M.B., B.S., F.R.A.C.P. (until Feb. 1977)<br>D. J. TOPLISS, M.B., B.S. (from Feb. 1977) |
| **Resident Medical Officers** | G. MORSTYN, M.B., B.S., B.Med.Sc.<br>B. A. KHALID, M.B., B.S., B.Med.Sc.<br>B. A. HARRISON, M.B., B.S.<br>R. J. S. HOWSAM, M.B., B.S. |
| **Biochemists** | MARION J. MARTIN, Ph.D. (London)<br>J. W. BARLOW, B.Sc. (from June 1977)<br>S. PETROU, B.Appl.Sc.<br>ELIZABETH L. WHITE, B.Sc. |
| **Nurse Technologist** | ELAINE BRENNAN (until July 1977)<br>MARGOT HEWETT (from June 1977) |
| **Ward Sister** | MARY ESPARON |
| **Technical Staff** | IDA EKKEL, A.A.I.M.T.<br>W. H. HUDSON (until June 1977)<br>FREDERICKE RABOLD<br>JULIE LLOYD |
| **Secretary** | BRENDA ROACH |

## GENERAL SUMMARY

This year has seen the continuation of the Unit's previous commitments in patient care, research and teaching, but a major reorganization of the Unit's Laboratory facilities has been begun. Remodelling of the Unit Laboratories, made possible by a bequest to the Ewen Downie Metabolic Unit from the estate of the late Mr. G. E. Gillet, will be undertaken early in 1978. With the opening of the main Ward block in November of 1977, space has been made available to the Unit in the adjacent special purposes Laboratory area so that our own Laboratory could be vacated for alteration. The Unit Ward has been moved from the Centre block to the adjacent area of the main Ward block on level five, thus preserving the close relationship between Ward and Laboratory.

Our major interests continue to be in Thyroid Hormone physiology and in Endocrine Hypertension. The request rate for radioimmunossays has continued to increase and during 1977 we have acquired adequate computer facilities for more rapid processing of routine assays. Additional isotope counting facilities, shared with the Monash University Department of Medicine, have contributed to the increased capacity of the Laboratory.

Dr. Dennis Engler, formerly Registrar in the Unit, whose work figures prominently in this report, commenced work with Dr. Albert Burger in the Laboratoire d'Investigation Clinique at the Hôpital Cantonal in Geneva in July 1977. He has continued studies of the peripheral metabolism of thyroid hormones which were initiated in the Unit, presenting some of our findings at the European Thyroid Association meeting in Lyon in September 1977. Dr. Engler's work in Geneva has been supported, in part, by an Alfred Hospital research grant. In mid 1978, he will take up a post at the New England Medical Centre Hospital in Boston where he has been appointed to the Endocrine Division headed by Dr. Seymour Reichlin. He has been succeeded as Registrar by Dr. Duncan Topliss who comes to us as our first advanced trainee undertaking a programme of supervised study of Endocrinology to qualify him for Fellowship of the Royal Australasian College of Physicians.

We look forward in 1978 to the initiation of a venture in partnership with the Medical Research Centre at Prince Henry's Hospital. Dr. Ken Wynne, formerly working at the Cancer Institute, has been appointed research fellow by the Medical Research Centre at Prince Henry's Hospital and the Ewen Downie Metabolic Unit. He will be based at Alfred Hospital and his chemical work with steroids will complement the molecular biologic and clinical interests of our two units in this group of hormones. This represents yet another facet of the close collaboration which has long existed between the Endocrine Units at the two hospitals.

Continued and valued collaboration with the Alfred Hospital Clinical Research Unit, the Baker Institute and the Howard Florey Institute, University of Melbourne, is again acknowledged, as is financial support from generous benefactors —

Alfred Hospital Wives Auxiliary
Estate of the late Vincenza Acton
Estate of the late G. E. Gillett
Mr Alan Pay
Rollason Trust
Sandoz Aust. Pty. Ltd.
Financial tributes offered by many in memory of Ewen Downie

### Overseas Visits

Dr. Breidahl was the recipient of an Alfred Hospital Travelling Fellowship and during 1977 visited centres in the U.S., Canada and the U.K. The purpose of his visit was to seek information on varied approaches to Diabetes Health-Care Delivery Systems and to observe developments in the education of the diabetic patient, instruction of the Nurse-Educator and Nurse-Physician-Assistant and in continuing education of Family Physicians. He also attended meetings of the British Diabetes Association, European Association for the Study of Diabetes and of the International Diabetes Federation. During his overseas visit, Dr. Breidahl spoke at clinical meetings in Singapore, Rochester, Minnesota and Vancouver on Diabetes in pregnancy and on Thyrotoxicosis in pregnancy.

In December 1976, Dr. Marion Martin attended the World Health Organization Seminar on Standardization and Quality Control of Radioimmunoassay of Hormones in Bangkok, Thailand.

Dr. Stockigt attended the Annual Meeting of the American Thyroid Association in Cleveland. During his brief stay in the U.S., he visited the Hypertension Research Centre at the Indiana University in Indianapolis, discussing problems of mutual interest with the Director, Dr. Myron Weinberger. At the University of California, Los Angeles, Dr. Stockigt reviewed progress

with Dr. Inder Chopra in the clinical investigation of peripheral thyroid hormone metabolism, which has been a major interest of the Unit. It was a resumption of discussions, as Dr. Chopra had visited us early in 1977.

**Lectures and Meetings**

Dr. Taft was an invited speaker at the Annual Meeting of the Phillipine College of Physicians in Manila where he addressed a plenary session on the subject of Recent Advances in Insulin Therapy in Diabetes.

The Unit was again well represented on the programme of the 20th Annual Meeting of the Australian Endocrine Society in Melbourne in August, Mss. A. Ekkel, E. J. Higgs, E. L. White, Mr. E. B. Donaldson, Mr. S. Petrou, Drs. M. J. Martin, J. R. Stockigt, P. Taft and D. J. Topliss contributing to various sessions of the Meetings.

At the Postgraduate course in Chemical Pathology given in March 1977 by the Royal College of Pathologists of Australia and the Australian Association of Clinical Biochemists, Dr. Martin lectured on Evaluation of Radioimmunossay Systems and Dr. Stockigt spoke on Renin and Aldosterone in Hypertension, and presented a segment on Clinical correlation of Thyroid function tests.

Dr. Taft was chairman of a joint session at the annual meetings of the Royal Australasian College of Physicians and of the Australian Diabetes Society in which various aspects of Diabetic Retinopathy were presented by a panel of speakers.

**Teaching**

Drs. Breidahl, Stockigt and Taft taught Endocrinology, Diabetes and General Medicine in all three clinical years of the Monash University undergraduate curriculum during 1977, and were each involved in bedside teaching, seminars and lectures.

A regular weekly clinical tutorial and lecture programme in Endocrinology was conducted as part of the postgraduate teaching undertaken at the Alfred in preparation of Basic Trainees in Medicine for Part I, F.R.A.C.P.

**Country Visits**

During 1977 the Unit has continued to run an Endocrine Consultative Clinic at Latrobe Valley Hospital, Moe and at the Central Gippsland Hospital, Traralgon. Members of the Unit have also participated in Postgraduate sessions at Ararat, Albury, Bendigo, Morwell, Traralgon and Wangaratta.

**Seminar Programme**

Monday lunchtime Seminars have been conducted in rotation with our colleagues at Prince Henry's Hospital. Topics presented at Alfred Hospital Seminars during 1977 were —

1. Autoimmune Endocrine Disease.
2. Problems of Employment for the Diabetic.
3. Non-surgical Treatment of Cushing's Syndrome.
4. A Longitudinal Clinical Study of Hyperprolactinaemia.
5. Lithium and the Thyroid.
6. Congenital Adrenal Hyperplasia in 3 sisters.
7. Addison's Disease — Mineralocorticoid Aspects.
8. Malignant Pituitary Tumour — A Problem in Management.
9. Diabetic Autonomic Neuropathy.
10. Varying Adrenal Responsiveness in Addison's Disease.
11. Primary Hyperparathyroidism with Renal Disease.
12. Gastrointestinal Manifestations of Diabetic Ketoacidosis.
13. The Natural History of Diabetic Retinopathy.
14. Pituitary Apoplexy in Nelson's Syndrome.
15. Electrophysiologic Studies in Diabetic Neuropathy.

The Unit acknowledges the contribution to these Seminars made by the following visitors to the hospital:

Dr. J. Nerup, Steno Memorial Hospital, Copenhagen.

Prof. R. Ardaillou, Hôpital Tenon, Paris.

Dr. E. Kohner, Hammersmith Hospital, London.

Prof. L. Waller, Department of Law, Monash University.

Prof. J. B. Brown, Department of Obstetrics and Gynaecology, University of Melbourne.

Mr. W. Shaw, Master Builders' Association.

Mr. H. Carslake, Builders' Labourers' Federation.

Dr. R. J. Pepperell, Royal Women's Hospital, Melbourne.

Numerous colleagues from Units within the hospital also contributed to these sessions.

## GENERAL PROJECTS

### 1. Premonitory Symptoms in Pituitary Apoplexy

P. Taft, H. A. Luke*, J. R. Stockigt, W. Elrick† and K. Siu.† * Department of Radiology, †Neurosurgery Unit.

The term pituitary apoplexy is used to describe the sudden severe headache and disturbance of consciousness, sometimes with visual loss and cranial nerve palsies, which results from acute haemorrhage into a pituitary tumour which may be previously unsuspected. Standard accounts of this syndrome suggest that it occurs without warning. In the past five years we have been involved in the care of 10 patients suffering from pituitary apoplexy in nine of whom the diagnosis was confirmed at operation undertaken for the relief of pressure symptoms. In seven patients there was a history of recurrent headaches before the presenting episode, in several extending over many years and involving more than 10 episodes. These intense headaches, often associated with vomiting, varied in location in different patients, but were similar in each individual from episode to episode. The headaches were commonly unilateral, supraorbital or temporal, and were frequently regarded as migraine. In two patients there was transient diplopia or visual impairment, associated with headache.

This group of 10 patients consisted of four with Nelson's Syndrome, one with acromegaly and five with chromophobe adenomas without clinical evidence of endocrine excess. It was of particular interest that in four patients, three of whom had Nelson's Syndrome, the pituitary fossa was radiologically of normal size.

We have thus come to recognize that premonitory symptoms and signs may precede a clear-cut episode of major pituitary apoplexy. Awareness of minor pituitary apoplexy may allow elective treatment before a life-threatening episode occurs, so as to avoid the need for emergency surgery in an unconscious patient with a major uncorrected endocrine deficiency. The occurrence of major pituitary apoplexy without radiological enlargement of the pituitary fossa highlights the difficulty of recognizing this condition.

### 2. Steroid Receptor Studies

J. W. Barlow, J. W. Funder* and J. R. Stockigt. *Medical Research Centre, Prince Henry's Hospital

Hormones may circulate in plasma in one of two forms, either bound to plasma proteins or in free form. Steroid hormones are extensively bound in plasma and only the free fraction is able to migrate across the plasma membrane into the cytoplasm of animal cells. Only certain target tissues are able to recognize a steroid within their cells and hence respond to the stimulus. The first step in this recognition is interaction of the steroid with a specific receptor. Binding of steroid to a receptor initiates a complex process within target tissue cells which results in production of a new protein which in turn initiates the tissue response. Steroid receptor proteins are of vital importance because they are the first step in steroid hormone action. While absence of specific receptors identifies a non-target tissue, the presence of a receptor does not necessarily indicate that a tissue is steroid-responsive.

We have recently been studying receptors for steroid hormones, in particular those for glucocorticoids. Receptors for glucocorticoid hormones were orginally described in cytoplasmic extracts prepared from kidney or liver of adrenalectomised rats. These receptors have a high affinity, i.e. they bind a significant amount of hormone at physiological concentrations, have a limited capacity, and exhibit a distinct order of displacement of radio-labelled hormone by unlabelled steroids.

Like kidney and liver, the adrenal medulla is a tissue with known sensitivity to glucocorticoids. The medulla responds to glucocorticoid administration by increasing production of phenethanolamine N-methyl transferase, an enzyme which converts noradrenaline to adrenaline. The present study has demonstrated the existence of a receptor for the synthetic glucocorticoid, dexamethasone, in bovine adrenal medulla. Like classical glucocorticoid receptors, this protein demonstrates appropriate high affinity and limited capacity, but the order of displacement of $^{3}$H-dexamethasone by unlabelled steroids differs from that found in other glucocorticoid-responsive tissues. Kinetic studies indicate that dexamethasone interacts with the receptor extremely quickly to form a very stable hormone-receptor complex. In this respect, and in the hierarchy of affinities for unlabelled steroids, these results suggest the possible existence of a novel steroid receptor. Studies are currently in progress to determine whether this receptor can be identified in adrenal glands of other

animals, and also to determine the physical characteristics of the receptor molecule.

### 3. The Efficacy of Biguanide Therapy in Diabetes Mellitus

P. Taft, H. D. Breidahl, D. Lording, R. Dargaville, G. C. Ennis*, M. Baillie and P. Dennis*.
*Prince Henry's Hospital.

Early this year the Federal Department of Health elected to restrict the use of biguanides in the treatment of maturity onset diabetes because of their reported potential to induce lactic acidosis. In conjunction with the Diabetes Clinic at Prince Henry's Hospital, a prospective study in 67 patients of the effects of biguanide withdrawal on diabetes control and on serum lactate and pyruvate levels was initiated. All but three patients were initially taking combined sulphonylurea-biguanide therapy.

They were studied on entry into the trial and four weeks and three months after biguanide withdrawal. No change in sulphonylurea dosage was made before four weeks and, after that, only if indications existed. Arbitrary categories of control were delineated based on random two hour postprandial blood sugar — below 10 mmol/1 — good, 23 patients; 10-12 mmol/l — fair, 14 patients; more than 12 mmol/l — poor, 30 patients.

In the group as a whole, no significant blood glucose difference from initial levels was noted at four weeks and where the sulphonylurea dose remains unchanged, at three months. Where, however, comparisons were made within the different categories of control, it was noted that mean blood sugar rose significantly from 8.6 mmol/l to 10.5 mmol/l ($p < 0.05$) in the good control group.

No similar change was observed in the fair or poor control groups. Only four of those initially under good control required insulin up to five months after biguanide cessation. Not surprisingly, 15 of those under fair or poor control are now using insulin. Thus clinically significant deterioration in blood sugar levels followed biguanide withdrawal in fewer than 10% of the population studied.

In the 41 patients in whom the measurements were made, initial serum lactate levels were marginally elevated in eight, in only one of whom was serum creatinine elevated. Over the group as a whole, there was a significant ($p < 0.01$) fall in lactate following biguanide withdrawal, pyruvate remaining unchanged. These findings indicated some degree of lactate excess. In the 12 patients taking Phenformin, initial lactate levels were slightly, but not significantly, higher than in the 29 taking Metformin. The fall in lactate on drug cessation was significant only in those taking Phenformin, (Table 1).

**TABLE I**

**BIGUANIDE CESSATION: EFFECT ON BLOOD LACTATE**

| | PHENFORMIN (n = 12) | | METFORMIN (n = 29) | |
|---|---|---|---|---|
| ON | 1.86 ± 0.25 | NS. | 1.38 ± 0.10 | N.S. |
| | $p < 0.05$ | | | |
| OFF | 1.23 ± 0.14 | NS. | 1.21 ± 0.08 | |
| FALL | 0.63 ± 0.25 | | 0.15 ± 0.08 | |
| | | $p < 0.001$ | | |
| % FALL | 33.6 ± 9.1 | | 6.8 ± 7.1 | |

It was concluded that cessation of biguanide was followed by significant deterioration of diabetes control in only four patients, 6%, (the previously well controlled patients now requiring insulin) blood glucose levels in all other patients not changing significantly. Reversible, clinically insignificant lactate excess was observed in 20% of the group as a whole, but was not related to impaired renal function. This appeared to be more significant with the use of Phenformin and suggests that if a biguanide is to be used, Metformin is the drug of choice.

# Renin, Aldosterone and Hypertension

It is now almost a decade since reliable methods became clinically available for the measurement of renin and aldosterone. Although the use of these techniques is clearly established in a definite group of patients with suspected secondary hypertension, there is still controversy about the appropriate application of these techniques in the investigation of essential hypertension. We have so far held to the view that hormone measurements should be used mainly after screening tests have indicated the need for detailed investigation. However, the alternative view that "renin profiling" of younger untreated patients with moderate or severe hyptertension can give a useful guide to therapy or prognosis, is now gaining wide publicity, although this proposal still requires confirmation before it can be generally advocated. The techniques currently available in the Unit are ones which could be widely applied if the effectiveness of more extensive investigation can be demonstrated.

We have now had experience in selective renal vein renin sampling in 152 patients, and have used intravenous Diazoxide as an acute stimulus to renin release in 107 of these studies. The findings indicate that asymmetrical renin secretion, with persistent suppression of renin secretion from the non-involved kidney after an acute stimulus, can reliably identify correctable renal hypertension. In primary aldosteronism, diagnosis is now much simplified by demonstration of suppressed renin, associated with elevated plasma aldosterone which fails to suppress after intravenous saline infusion. However, the distinction between unilateral adenoma and bilateral hyperplasia continues to be difficult.

While it is clearly established that deficient renal blood supply and adrenal steroid excess may each cause hypertension which can, at times, be surgically cured, it is still not known *how* each of these abnormalities causes a rise in blood pressure. It is therefore not easy to assess whether similar mechanisms may be important in essential hypertension. Interpretation is complicated by the demonstration of different initiating and sustaining mechanisms in many types of hypertension. Studies at the onset of hypertension may therefore be of more fundamental importance than studies of established hypertension. It is obviously difficult to investigate essential hypertension at its onset, and in many cases of secondary hypertension the fundamental abnormality is removed or modified surgically. However, there is a small group of conditions in which hypertension can be corrected medically without alteration of the fundamental abnormality. This group includes the Dexamethasone-responsive hypertension which occurs in glucocorticoid-remediable mineralocorticoid hypertension and in 17$\alpha$hydroxylase deficiency, the Triamterene-responsive hypertension of Liddle's syndrome and Spironolactone-responsive hypertension in primary aldosteronism. In each of these conditions hypertension returns slowly after cessation of medical treatment, so that patients can be safely studied during the phase of mild recurrence. In the past several years we have, in collaboration with the Howard Florey Institute, University of Melbourne and the Department of Medicine, University of Hong Kong, begun studies of medically-correctable steroid hypertension in a group of patients with these conditions.

**Projects**

1. **Selective Renin Sampling in Transplant Renal Artery Stenosis**
   J. R. Stockigt, J. Sabto*, F. W. Gurr* and N. Sachariast. (*Renal Unit, †Department of Radiology)

Hypertension may be associated with a stenosis in the artery to a transplanted kidney. In this situation it is difficult to decide whether the hypertension is related to defective perfusion of the transplant, or to the patient's own abnormal kidneys. In an attempt to resolve this problem, selective renin sampling, which compares the renin content in the effluent from all three kidneys with the peripheral level, has been performed in five hypertensive transplant recipients in whom the transplant artery was narrowed.

The findings summarized in Table II demonstrate that selective sampling can identify the source of circulating renin and suggest that renin secretion is suppressed in normally-perfused renal tissue, as occurs in the usual forms of unilateral renal hypertension. This technique appears to be useful in defining the haemodynamic significance of a transplant stenosis and may avoid unnecessary surgical re-exploration. The technique may also define an indication for removal of the

TABLE II
SELECTIVE RENIN SAMPLING IN HYPERTENSIVE TRANSPLANT RECIPIENTS

| Case | Sampling | Renin Activity ng/ml/3hr* | | | | Treatment |
|---|---|---|---|---|---|---|
| | | RRV† | LRV† | Transplant Vein | Femoral Vein | |
| 1 | Basal | 12 | 18 | 5 | 7 | Medical |
| | Diazoxide Stimulus | 35 | 29 | 7 | 10 | |
| 2 | Basal | 12 | 10 | 33 | 9 | Revascularization |
| | After Revascularization | 5 | 5 | 5 | 3 | |
| 3 | Basal | 36 | 58 | 13 | 13 | Medical |
| 4 | Basal | 17 | 21 | 42 | 17 | Removal of Transplant for Rejection |
| 5 | Basal | — | 9 | 16 | 7 | Medical |

*Normal 2-8 ng/ml/3hr.
†RRV Right Renal Vein, LRV Left Renal Vein.

patient's own kidneys if control of hypertension is poor.

**2. Renin Responses to Acute Diuretic Administration in Hypertension**

J. R. Stockigt, E. J. Higgs and M. J. Hewett, in collaboration with the Clinical Research Unit.

It has been proposed that assessment of plasma renin may be worthwhile in the subclassification of patients with hypertension. Suppressed renin has been variously regarded as an index of abnormal steroid secretion, or of diminished sympathetic activity, and it has been suggested that knowledge of plasma renin may be helpful in slecting optimal treatment. The renin-stimulating techniques used to classify hypertensive patients have varied widely and we have evaluated a simple one: the renin response 20 and 30 minutes after intravenous Frusemide in ambulant, untreated hypertensives ingesting an ad libitum diet. Thirty eight patients have been studied using 40mg intravenous Frusemide.

The hypertensive subjects showed a wide range of ambulant renin values with a lower mean value than normal subjects. Twenty, (54%) of the hypertensive subjects responded to the diuretic with an increase in mean ambulant renin from $5.5 \pm 0.8$ to $11.1 \pm 1.4$ ng/ml/3hr, while nine had clearly suppressed renin which failed to respond to the stimulus. Three of this latter group had primary mineralocorticoid hypertension, but the remainder showed no evidence of an adrenal abnormality. Nine patients did not have suppression of ambulant renin, but failed to increase the plasma level after the diuretic. Patients with suppressed or unresponsive renin were significantly older than the responsive group ($p < 0.01$). These findings confirm that about 25% of a selected hypertensive population have suppressed renin which fails to respond to an acute stimulus. However, the fact that an additional 25% of hypertensives without renin suppression fail to increase renin acutely in response to Frusemide, introduces complexity into the classification. This group appears to respond normally to a more prolonged stimulus to renin secretion, such as sodium restriction or thiazide treatment.

Unless failure to respond acutely to Frusemide can be shown to have some unique significance, it seems unlikely that measurement of renin after this diuretic adds any useful information to the measurement of ambulant renin alone.

**3. Stability of Angiotensin I in Vitro**

J. R. Stockigt and M. J. Hewett

All current renin assays depend on measurement by radioimmunoassay of the amount of angiotensin I generated during incubation of plasma *in vitro*. Angiotensin I is normally unstable in plasma because of conversion to angiotensin II and degradation by angiotensinases. Both of these changes destroy its immunologic activity and will lead to falsely low assay results. The enzyme inhibitors EDTA, Dimercaprol and 8 hydroxy quinoline are added in order to retain angiotensin I as the stable end-product of the renin reaction. The effectiveness of these inhibitors can best be examined by measuring the recovery of added peptide. Studies with added synthetic material from three different sources have demonstrated that recovery is incomplete at pH 5.5 using standard concentrations of inhibitors. Mean recovery in 10 experiments was $68 \pm 5$ (S.D.) %.

In order to determine whether loss of naturally-generated angiotensin I was similar, we compared the recovery of the synthetic peptides with that of material formed by exhaustive incubation of human plasma with human renal renin in the presence of the same inhibitors. Recovery of naturally-generated immunoreactive angiotensin I was 94-108%, indicating that this material is more stable than the synthetic peptides, and that the currently-used inhibitors adequately inhibit the destruction of natural angiotensin I.

This finding indicates that natural and synthetic peptides may differ in their resistance to degradation by plasma enzymes and suggests that caution may be necessary in drawing conclusions about the metabolic fate of other peptides from studies using synthetic material.

**4. Amiloride in the treatment of Primary Mineralocorticoid Hypertension**

J. R. Stockigt, Ida Ekkel and E. J. Higgs

Medical treatment with aldosterone antagonists is used in primary aldosteronism both as preparation for surgery in patients with a unilateral adenoma, and as long-term treatment in those who fail to show a unilateral aldosterone source. Spironolactone, given in adequate doses, is effective in completely reversing the features of primary aldosteronism, but this drug frequently produces impotence and gynaecomastia. For this reason, we have evaluated the long-term efficacy of the potassium-sparing diuretic Amiloride which has previously been shown to be a satisfactory short-term alternative to Spironolactone.

The response to Amiloride 20-40mg daily for up to 12 months has been evaluated, during ad libitum sodium intake, in five patients with primary mineralocorticoid hypertension. Response was assessed by changes in blood pressure, plasma electrolytes, plasma aldosterone and plasma renin activity.

Comparison of changes in response to Spironolactone and Amiloride are shown in Table III. Despite favourable impressions of the short-term effect of Amiloride as an alternative to Spironolactone, the hypotensive response to Amiloride in doses up to 40mg daily was less satisfactory than that achieved with Spironolactone. This diminished hypotensive response is associated with less complete reversal of renin suppression. Preliminary findings suggest that this may be due to a progressive rise in plasma aldosterone during Amiloride treatment.

TABLE III

EFFECT OF SPIRONOLACTONE AND AMILORIDE IN MINERALOCORTICOID HYPERTENSION

| | Spironolactone | | Amiloride | |
|---|---|---|---|---|
| | Untreated | Treated | Untreated | Treated |
| Duration months | 5 | 5<br>3-12 | 5 | 5<br>3-21 |
| Mean BP mmHg | 138 ± 3 | 103 ± 3* | 145 ± 3 | 116 ± 4* |
| Plasma K mmol/l | 2.8 ± 0.1 | 4.2 ± 0.2 | 3.0 ± 0.1 | 4.1 ± 0.1 |
| Renin Activity ng/ml/3hr | <1 | 6.3 ± 1.7** | <1 | <1-3.4** |

*$p<0.1$, **$p<0.05$

**5. Polyarteritis Nodosa and Renin-Dependent Hypertension from Drug Abuse**

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

Drug abuse, an increasing problem in this community, presents a wide spectrum of unusual medical features of which physicians should be more aware. Hypertension has been described in the polyarteritis syndrome which is associated with arterial immune complex deposition and hepatitis B antigenaemia, but the mechanism of this hypertension has not so far been defined. We have recently had the opportunity to determine whether the renin-angiotensin system is crucial in the causation of this unusual type of hypertension.

The patient, a 24 year-old man, was hospitalized for investigation of severe resistent hypertension (180/130),

associated with hypokalaemia (2.6 mmol/1), proteinuria (3gram/day) and an increased erythrocyte sedimentation rate (40-80 mm/hr). He had casually used intravenous heroin and amphetamines over several years in addition to inhalation of propellant sprays. For several months before admission he had lost weight and complained of morning headache and nocturia. Physical examination was normal, and optic fundi showed no evidence of accelerated hypertension.

Plasma renin and urinary aldosterone were both greatly increased and infusion of the angiotensin antagonist Saralasin (8.6 ug/Kg/min) lowered blood pressure from 170/115 to 140/95 and from 160/110 to 125/95 on two occasions. Renal angiography showed bilateral coarse cortical scarring of normal-sized kidneys, with multiple 1-2mm beaded dilations of intrarenal arteries. Renal venous sampling indicated bilateral symmetrical oversecretion of renin. Hepatitis B antigenaemia at a titre of 1:64,000 was detected in serum. Cryoglobulinaemia was present, but serum complement was not depressed. High-dose corticosteroids were begun in an attempt to control the arteritis.

This example of renin-dependent hypertension with secondary hyperaldosteronism indicates that the renin-angiotensin system may be closely involved in the development of acute hypertension in drug abusers who develop arteritis. It is obviously necessary to remain alert for possible hepatitis-positive patients in unusual clinical situations.

# Thyroid Hormone Physiology and Thyroid Function

The Unit's involvement in the laboratory investigation of thyroid disease has continued during 1977. Over 4500 samples have been received from the Alfred Hospital and other centres during 1977, with an average of three measurements performed on each sample. Many of the patients investigated have other major medical problems and this has allowed us to further develop our interest in the thyroid hormone changes which occur as a result of illness, carbohydrate restriction, surgical stress or steroid therapy.

The laboratory has extended its development of "in house" assays for thyroid-related hormones and is now almost totally independent of commercial kits which must be imported at great expense. Appropriate isotopically-labelled hormones are obtained in bulk or labelled on site, and are used with locally-produced antisera in the radioimmunossays of thyroxine ($T_4$), triiodothyronine ($T_3$) and reverse $T_3$. While the routine assays require overnight incubation, we have developed a modification of the $T_4$ assay which can provide a result within three hours. This method is especially useful in situations such as suspected myxoedema coma or thyroid storm.

During 1977 we have extended our studies of the effect of illness, stress and glucocorticoids on the peripheral metabolism of thyroid hormones. While the fundamental mechanisms regulating the extra-thyroidal deiodination of $T_4$, $T_3$ and reverse $T_3$ remain unknown, it is now clear that the processes are enzymatic and that they occur in liver and kidney. The production and removal of these hormones varies more quickly than was previously thought and short-term changes can be diagnostically confusing. We have demonstrated that the stress-related change in serum $T_3$ may be sufficiently great to compromise the reliability of $T_3$ measurement as an index of hyperthyroidism in the face of severe non-thyroidal illness.

It now seems likely that stress and illness may also influence the pituitary secretion of TSH, as well as inducing peripheral changes in thyroid hormone metabolism. Transient neuroendocrine or pituitary changes of central origin, in either a hyper- and hypothyroid direction may occur during non-thyroidal illness, and could lead to inappropriate ablative treatment or unnecessary replacement therapy. The search for features which will distinguish these situations from true thyroid dysfunction remains an important objective.

In addition to our own studies, summarized below, the Unit has collaborated with the Departments of Endocrinology and Biochemistry, Royal Melbourne Hospital in studies of thyroxine deiodination by rat kidney tubules, with the Endocrinology Department, Austin Hospital in studies of acquired resistance to thyroid hormones and with the Medical Research Centre, Prince Henry's Hospital

in studying the effects of TRH infusion on thyroid hormones.

**Projects**

1. **Effect of Inhibitors of Serum Protein binding in Thyroxine Radioimmunoassay**
   M. J. Martin, E. L. White, S. Petrou and J. R. Stockigt.

After release from the thyroid gland, thyroid hormones circulate in association with high affinity binding proteins, so that only a small proportion of the total hormone is free and available for immediate tissue-uptake at its site of action. When *in vitro* assay methods are used to measure total serum levels of a hormone, binding proteins in the sample will interfere with the reaction between the hormone and its antiserum, the basis of the radioimmunoassay method. The problem is greatest for thyroxine ($T_4$), which shows very high affinity binding, but also occurs with other substances which bind to circulating proteins, including drugs and vitamins. Several compounds have been used to inhibit binding between $T_4$ and thyroxine binding globulin (TBG) without major interference with antibody binding, thus allowing assays to be performed without extraction.

If $T_4$ binding to TBG is not completely inhibited in assays using unextracted serum, radioimmunoassays which rely on second antibody separation will classify TBG-bound hormone as "free", while charcoal separation will classify it as "bound". If serum samples and reference standards have different TBG content, this effect produces false results in the presence of suboptimal concentrations of TBG blockers.

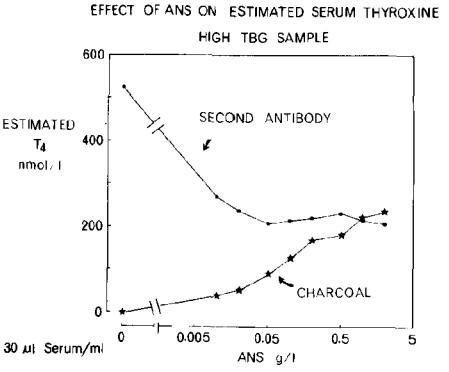



FIG 1
Effect of increasing concentrations of ANS (see text) on apparent serum thyroxine, when a high TBG serum sample is compared with standards prepared in charcoal-treated hormone-free plasma. Below the optimum concentration of inhibitor, charcoal separation gives an underestimate and second antibody an overestimate of serum thyroxine.

Figure 1 shows the effect of altering the concentration of the binding inhibitor 8-anilino 1-naphthalene sulphonic acid (ANS) when 30*u*l serum samples are assayed against standards prepared in charcoal-treated hormone-free plasma. Charcoal-treatment removes a substantial proportion of TBG from the hormone-free plasma, so that the unknown samples are assayed in the presence of higher TBG concentration than the standards. Therefore, below a critical concentration of inhibitor, the charcoal separation will give an underestimate of serum $T_4$ while second antibody separation gives an overestimate. The two separation methods should correspond under optimal conditions. A similar effect has been demonstrated with the alternative TBG-inhibitor Merthiolate. This important artefact is more easily controlled with second antibody than with charcoal separation, because additional error is caused by charcoal-adsorption of the binding inhibitor, which may allow reassociation between hormone and TBG. In routine application, the second antibody method gives accurate estimates of iodothyronines over a wide range of inhibitor and TBG concentrations.

This type of evaluation may be necessary for other radioimmunoassays of hormones, drugs or vitamins which show extensive binding to serum proteins, especially where the concentration of the binding protein shows physiologic variation or where preparation of "blank" plasma may remove or damage the binding protein.

2. **Effects of Glucocorticoids on Thyroid Hormone Deiodination in Man**
   E. B. Donaldson, D. Engler, S. Petrou and J. R. Stockigt

Circulating 3,3',5-triiodothyronine ($T_3$) and 3.3',5'-triiodothyronine (reverse $T_3$) are both derived predominantly from peripheral deiodination of thyroxine ($T_4$). Malnutrition, severe illness and surgical stress cause an alteration in the balance between these two pathways of deiodination so as to increase reverse $T_3$ and decrease $T_3$. Dexamethasone has been shown to produce similar changes, but the factors normally regulating the two alternative pathways of $T_4$ deiodination remain to be defined.

**TABLE IV**
**EFFECT OF DEXAMETHASONE ON $T_3$ AND REVERSE $T_3$**

| Dex. Dose | Reverse $T_3$ nmol/l Control | Reverse $T_3$ nmol/l Peak | $T_3$ nmol/l Control | $T_3$ nmol/l Nadir |
|---|---|---|---|---|
| 2mg | 0.29 ± .04 | 0.44 ± 0.7 | 1.77 ± .11 | 1.61 ± .08 |
| 4mg | 0.25 ± .05 | 0.40 ± .07 | 1.82 ± .12 | 1.55 ± .03 |
| 8mg | 0.23 ± .02 | 0.35 ± 0.6 | 1.49 ± .06 | 1.25 ± .09 |
| All doses | 0.25 ± .02 | 0.39 ± .04** | 1.69 ± .08 | 1.48 ± .06** |

**$p < 0.0025$

To determine whether the reported effect of high dose Dexamethasone on $T_4$ deiodination could be reproduced by glucocorticoids in physiologic doses, normal subjects were treated with (i) oral Cortisone Acetate 25mg, 50mg and 100mg 12 hourly for periods of three days at each dose level (n = 3); (ii) a single intramuscular injection of Hydrocortisone hemisuccinate 200mg (n = 4) and (iii) single oral doses of Dexamethasone 2mg, 4mg or 8mg (n = 9). All three doses of Dexamethasone increased reverse $T_3$ and decreased $T_3$ with maximal changes after 24 hours, without evidence of a dose-response relationship. (Table IV). Serial increments of oral Cortisone Acetate, up to 100mg 12 hourly, failed to influence the concentration of either hormone. Injected hydrocortisone, 200mg, increased reverse $T_3$ by 22% four hours after injection ($p < 0.05$), and decreased $T_3$ by 16% 24 hours after injection ($p < 0.1$).

These acute steroid-induced effects are smaller than those which occur with malnutrition, stress or illness. Disproportionately large doses of natural glucocorticoid were required to reproduce the effect of Dexamethasone, suggesting that natural glucocorticoids are not major regulators of peripheral thyroid hormone metabolism. Measurements of $T_3$ and reverse $T_3$ before and after treatment in Addison's disease also suggest that physiologic levels of glucocorticoids do not have a major influence on the pathways of $T_4$ deiodination.

### 3. Reversible Thyroid Dysfunction in Primary Adrenal Insufficiency

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

Thyroid function is usually assessed in patients presenting with idiopathic Addison's disease, because of the known association with primary subthyroidism. Because some reports suggest that apparent primary thyroid failure may be reversible with steroid replacement, we have assessed serial changes in thyroid function during corticosteroid replacement in eight consecutive cases of untreated Addison's disease. Serum $T_4$, $T_3$, reverse $T_3$ and TSH, and the TSH response to thyrotropin releasing hormone (TRH) were assessed by radioimmunoassay. Changes were observed for 4-12 months in patients with a biochemical thyroid abnormality. No patient showed clinical features of thyroid dysfunction at any stage.

Four of these eight patients showed normal thyroid function before corticosteroid treatment. Three patients without thyroid hormone deficiency had increased TSH secretion before treatment, which reverted to normal during steroid replacement. In one 33 year-old woman with positive thyroid antibodies, the changes of definite biochemical primary subthyroidism were present before treatment, with gradual improvement during steroid replacement. After eight months treatment there is still evidence of diminished thyroid reserve. (Fig 2).

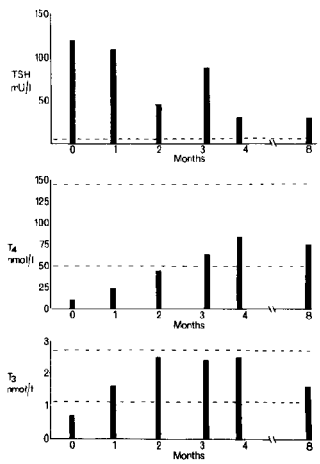



*Fig. 2.*
*Changes in thyroid hormone levels during steroid replacement in a 33 year-old woman with Addison's disease.*

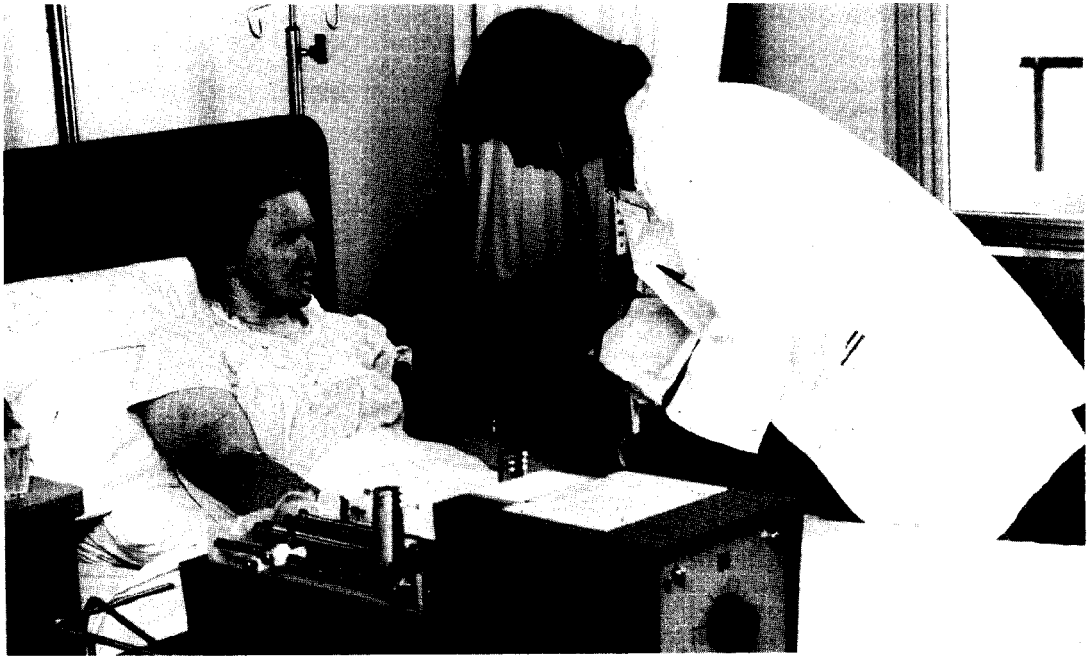
These findings indicate that biochemical abnormalities of the pituitary-thyroid axis are common in untreated Addison's disease and suggest an important interaction between corticosteroids and the pituitary-thyroid axis. The knowledge that apparent thyroid dysfunction may be temporary in primary adrenal insufficiency may avoid unnecessary lifelong thyroid replacement. Glucocorticoids are known to have a negative influence on pituitary TSH secretion and TSH excess might therefore occur because of steroid deficiency. However, the subnormal thyroid hormone levels in association with increased plasma TSH suggest that steroid deficiency may temporarily impair the thyroid response to TSH.

**4. The Natural History of Untreated $T_3$ Hyperthyroidism**

D. Engler, M. J. Martin, E. L. White, P. Taft and J. R. Stockigt

The variant of hyperthyroidism in which serum triiodothyronine ($T_3$) is increased without thyroxine ($T_4$) excess has been described as a premonitory stage of classical hyperthyroidism. In order to determine whether isolated $T_3$ excess is a brief phase in the evolution of classical hyperthyroidism, or whether persistence of isolated $T_3$ excess is more usual, 12 patients with $T_3$ hyperthyroidism have been followed without treatment for 6 to 31 months (mean interval 18 months). In 11 cases treatment was withheld because the disease was mild, without evidence of progressive weight loss, myopathy, arrhythmia or cardiac failure, or because of initial diagnostic uncertainty. One patient presented with cardiac failure and isolated $T_3$ excess in November 1973, but the $T_3$ excess was not appreciated until July 1975, when features of classical hyperthyroidism had developed.

Criteria for inclusion in this study were: (i) clinical features suggestive of hyperthyroidism; (ii) serum $T_3$ values more than 2 S.D. above the age-related mean in at least two separate samples and (iii) a normal initial serum $T_4$ and free thyroxine index (FTI) in at least two samples. The thyrotropin (TSH) response to thyrotropin-releasing hormone (TRH) was undetectable in all nine patients in whom the test was performed. No patient had received any thyroid-related treatment for at least four years before initial assessment. Ten patients had never been treated for thyroid disease, but two patients had recurrent hyperthyroidism, one after a partial thyroidectomy five years previously, the other after $^{131}$I therapy four years previously.



*Constant Infusion study of Angiotensin antagonist in the investigation of renal hypertension in area 5A of the Main Ward Block.*

In the group as a whole, neither the mean serum $T_3$ nor $T_4$ changed significantly, but two patients showed definite progression to classical hyperthyroidism, while in two additional patients *either* the FTI or serum total $T_4$ increased to values just above normal. In the remaining eight, isolated $T_3$ excess persisted without alteration in mean serum $T_4$. Clinical features showed no progression apart from the single patient in whom treatment was unintentionally delayed.

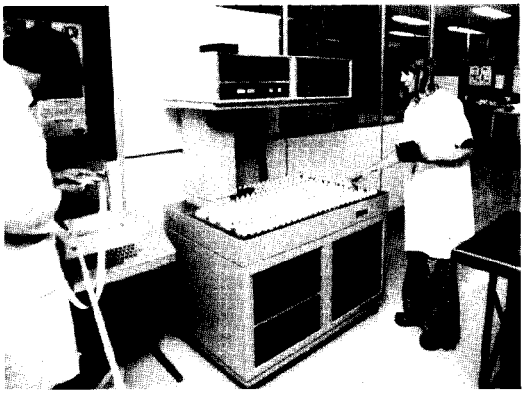
Thus, in this small number of patients with mild $T_3$ hyperthyroidism, the predominant natural history has been one of persistently raised $T_3$ without development of $T_4$ excess. The pattern of change with longer follow-up is so far unknown, but there are some reports of prolonged persistence of isolated $T_3$ excess. It is therefore appropriate to treat patients on the basis of $T_3$ excess alone if clinical features warrant this, but the adverse effects of antithyroid drugs or $^{131}I$ justify a delay in treatment if the disease is mild.

**5. The Significance of Isolated Thyroxine Excess**

J. R. Stockigt, D. Engler, M. J. Martin, D. J. Topliss and P. Taft

An increased serum level of both thyroxine ($T_4$) and triiodothyronine ($T_3$) is characteristic of typical hyperthyroidism. While an increased level of $T_3$ with normal $T_4$ suggests $T_3$ toxicosis, the significance of increased $T_4$ with normal $T_3$ has so far been hard to define. A transient decrease of $T_3$ to normal has been described in hyperthyroid patients during severe non-thyroidal illness, due to diminished peripheral formation of $T_3$ from $T_4$. However, some euthyroid subjects appear to develop isolated transient illness-related $T_4$ excess without evidence of a persistent thyroid abnormality.

*The Endocrine Ward until November 1977. This area is being refurbished to provide office space for the Unit.*



*Laboratory work in the Special Purposes Area, Level 5, Main Ward Block.*

Twenty patients with confirmed $T_4$ excess, not due to increased protein binding, in whom age-related $T_3$ levels were normal, have been studied. On the basis of antecedent history, TSH responsiveness to TRH, evolution of laboratory findings after recovery from non-thyroidal illness and eventual clinical course, these patients showed the following diverse pattern:

a. True hyperthyroidism with normal $T_3$ during illness, but elevated $T_3$ after recovery from the non-thyroidal illness ($n = 5$). Absent TSH response to TRH.

b. Transient $T_4$ excess during non-thyroidal illness, with normal $T_4$ after recovery ($n = 6$). Normal TSH response to TRH.

c. Persistent isolated $T_4$ excess with features of hyperthyroidism, absent TSH response to TRH, but normal age-related $T_3$ ($n = 3$).

d. Isolated $T_4$ excess in terminal illness ($n = 4$). Thyroid status uncertain.

e. Persistent $T_4$ excess with normal $T_3$ and normal TSH response to TRH, without features of hyperthyroidism ($n = 2$).? Possible hormone resistance.

This study suggests that isolated $T_4$ excess is an ambiguous finding which should not be used as the sole basis for treatment of hyperthyroidism. Proper evaluation may only be possible by clinical and biochemical reassessment after recovery from non-thyroidal illness. In true hyperthyroidism the inverse changes in $T_3$ and reverse $T_3$ during illness indicate that temporary normalization of $T_3$ is the result of altered peripheral deiodination of thyroxine. The cause of the transient stress-induced increase in $T_4$ in the absence of a persistent thyroid abnormality, remains unknown.

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# C. J. OFFICER BROWN CARDIAC SURGERY UNIT

Director: George R. Stirling
Cardiac Surgeons: Eric Cooper
Bruce B. Davis
E. A. Shanahan
Gil Shardey

During 1977, over 380 open heart procedures were carried out by the Unit and the total number of cases operated on for heart disease approximated 500.

Mr Gil Shardey joined the Unit after continuing overseas experience in New Zealand and Toronto.

During the year, 2 major collaborative studies have been continued and, as neither is yet complete, final results are not available.

**1. Effect of Coronary Artery by-pass surgery on Peri-operative Infarction and Left Ventricular Wall Motion**
A. Pitt, L. Dugdale, D. Rose.

During 1976, Panetta, Pitt and Dugdale, carried out a study on patients undergoing openheart surgery correlating electrocardiographic and enzymatic changes with post-operative technetium pyrophosphate myocardial image scanning. Despite apparently satisfactory results as judged by crude clinical criteria, it was notable that a very high incidence of technetium pyrophosphate images was seen. The incidence of positive technetium pyrophosphate myocardial indicators of myocardial images exceeded that of the incidence of the other indicators of myocardial infarction and it was suggested that, although a positive image on scanning certainly suggested damage, the interpretation of the positive scan was a matter of some dispute. At worst, the myocardial image scan was interpreted as a very sensitive indicator of myocardial damage and, as such, seemed a useful tool for refinement of surgical techniques.

Rose, Pitt and Dugdale have continued the studies in 1977 with elaboration of the techniques to include pre-operative myocardial image scanning and also post-operative coronary angiography and studies of ventricular wall motion by ventriculography.

Whilst the results of these studies will form the basis of a separate report, the constant monitoring of surgical operations by refined techniques has clearly fed back directly into operative practice as there has been a considerable reduction in the incidence of positive myocardial image scans with improved surgical techniques.

**2. Hypothermic Cardioplegia**

Since the earliest days of open heart surgery, a major preoccupation of this Unit has been with the optimal preservation of myocardial integrity during the operative period. Whilst it has for long been known that profound perfusion hypothermia followed by aortic cross clamping and topical hypothermia, have been highly protective, our experience in recent years indicates an unacceptable degree of damage by modern criteria.

The notion originally postulated by Melrose of producing complete electromechanical arrest of the heart has again emerged as an important component of protecting myocardium during procedures where aortic cross clamping is inevitable. It is highly probable that the basic precept is that it is not possible to optimally perfuse the myocardium during cardiopulmonary by-pass if either severe hypertrophy of the ventricle exists or if, separately or additively, there are stenoses in the coronary arterial tree.

After some preliminary laboratory work, we have adopted a technique of rapid cooling and induction of complete mechanical arrest of the heart using an infusion of ice cold Ringer's solution with added Potassium, Magnesium and Procaine. This technique is now under clinical trial and the early results seem promising. We are looking forward to much more extensive animal and clinical research in this area in 1978 when Dr Frank Rosenfeldt joins our group.

### 3. Psycho-Social correlations of open heart surgery

R. Buckle, J. Crawshaw, R. Harper, P. Ryan, G. R. Stirling.

This study, commenced in 1976, is nearing completion. A selected group of 50 patients undergoing myocardial revascularisation for coronary artery disease have been intensively studied before surgery, in the immediate post-operative period and at a period of not less than 6 months following open heart surgery. On each occasion of assessment, a total physical evaluation has been made together with a detailed and structured psycho-social assessment. At the time of completion of this report, the data base is just complete and the correlative studies have not been completed. It is clear, however, that there is a moderate mis-match between "success" of an operation as judged by purely organic criteria and "success" as judged by return to satisfactory psycho-social function. Detailed study of individual cases has raised important questions as to the merit of current techniques of selection for coronary artery surgery and have spotlighted the necessity for more elaborate rehabilitation arrangements to be available for certain cases.

# HOW TO SUPPORT MEDICAL RESEARCH INTO HEART AND VASCULAR DISORDERS

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- LEGACIES

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- BEQUESTS

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