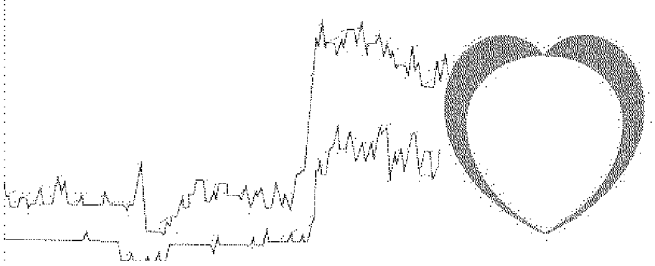
Research Annual Report 1979/80



Baker Institute
Alfred Hospital

Annual Report 1979/80 Baker Medical Research Institute

Affiliated with Monash University

This report provides audited accounts and details of scientific activity in the calendar year 1979. It reports on new people joining the Institute and planning during the first half of 1980.

Fifty-third Annual Report of

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

Thirty-first Annual Report of

THE ALFRED HOSPITAL CLINICAL RESEARCH UNIT

Twenty-third Annual Report of

THE EWEN DOWNIE METABOLIC UNIT

Report of

C. J. OFFICER BROWN CARDIOTHORACIC SURGICAL UNIT

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Laboratory Supervisor
C. LEWIS

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P. A. BLOMBERY, M.B., B.S., B.Sc.(Med.)(Syd.), Ph.D.(Mon.), F.R.A.C.P., Senior Research Officer, National Heart Foundation
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JUDITH R. OLIVER, B.Sc.(NSW), Senior Professional Officer

Visiting Scientists
MICHAEL C. ANDRESEN, B.S., M.S., Ph.D.(Texas) (from Jan. 1980)
M. FAHIM, Ph.D., Patel Chest Clinic, University of Delhi (till April 1980)
A. NAKASHIMA, M.D.,(Yamaguchi) (from Mar. 1980)
W. RIEDEL, M.D. (University of Vienna) (till August 1979)
R. WATSON, M.D.(Birm.) (till Mar. 1980)

Students
KATE DENTON, B.Sc.(Mon.) Honours Student
S. E. SELIG, B.Sc.(Hons.)(Mon.), Baker Institute Postgraduate Student

Technical Staff
M. CLARK (till April 1979)
K. HARE
A. HEAL
P. LEONARD
M. LE DUC
G. LOVE
V. LUKINS
K. ROUND

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ANDREA EVERITT, B.Sc., Research Assistant, National Heart Foundation
JANE MA, B.Sc.(Melb.), Research Assistant, National Health & Medical Research Council
MARGARET O'CONNOR, B.Sc.(Melb.), Research Assistant, Alfred Hospital Scholarship
KERIN O'DEA, B.Sc., Ph.D.(Melb.), Senior Research Officer, National Health & Medical Research Council

Visiting Scientists
M. HUFF, Ph.D.(UWO), Fellow Medical Research Council of Canada (from Mar. 1979)
N. TADA, M.D.(Tokyo) (till May 1980)

Students
B. WATSON, Postgraduate Research Fellow
J. BAZELMANS, B.Sc.(Mon.) Honours Student
G. COLLIER, B.Sc. (Hons.) (Mon.) Masters Student
ANN ROTMAN, B.Sc.(Mon.) Honours Student
ANGELA WARD, B.Sc.(Mon.) Honours Student

Technical Staff
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P. ASTWOOD
H. EDELSBACHER
D. FAULKNER
S. MENSEN
R. PAYNTER

Nursing Sister
JOAN LIST

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J. A. ANGUS, B.Sc., Ph.D. (Syd.), Senior Research Officer, National Health & Medical Research Council
E. R. ANDERSON, Research Assistant
R. M. BRAZENOR, B.Sc., Research Officer, National Heart Foundation (from Feb. 1980)

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A. J. McLEAN, B.Sc.(Med.), M.B., B.S., Ph.D.(Mon.), F.R.A.C.P., Research Fellow, National Health & Medical Research Council
P. CAHILL, Research Assistant
C. ISBISTER, Research Assistant
E. DELAFIELD-RAE, Technical Assistant

EXPERIMENTAL CARDIAC SURGERY LABORATORY

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M. ARNOLD, M.B., B.S., F.R.A.C.S., Windermere Fellow
A. FAMBIATOS, B.Sc.(Melb.), Research Assistant
C. BOYES, Technical Assistant

MORPHOLOGY AND CELL BIOLOGY LABORATORY

JULIE H. CAMPBELL, B.Sc.(NSW), Ph.D.(Melb.), Senior Research Officer, National Health & Medical Research Council
G. R. CAMPBELL, B.Sc., Ph.D.(Melb.), Senior Research Associate
L. POPADYNEC, B.Sc.(Mon.), Research Assistant, National Health & Medical Research Council
J. ROGERS, Senior Technician, Life Insurance Medical Research Fund
P. SHALLARD, Research Technician, National Heart Foundation

ELECTRONICS LABORATORY AND WORKSHOP

(Baker Institute and Clinical Research Unit)

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J. BAIRD
F. FORGIONE
R. VAUGHAN

Computer Services
S. JACKSON (till May 1979)
B. CHANDLER

Photography
A. LANGUSCH (till May 1979)
I. TRAVERS

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M. BEBBINGTON

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Librarian
M. DELAFIELD

Assistant
J. L. DELAFIELD-RAE

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(Alfred Hospital)

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N. J. WALDEN, B.V.Sc., M.R.C.V.S.

Officer-in-Charge
A. BONS

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A. GIULIANI
D. HARRISON
P. JONES
M. MOOR
A. MEDORO
K. O'CALLAGNAM
E. TURNBULL

SECRETARIES

AINA MARTIN (till Oct. 1979)
LYN CANNON (till Feb. 1980)
SEAH LIAN-KEE
KAREN KERR
CHERYL GRIFFITHS
HEATHER INGLIS (from Mar. 1980)
MARGIT SCOTT-MURPHY (from Jan. 1980)

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S. HART
J. PRITCHARD (from Oct. 1979)
S. DUMARU (till Oct. 1979)
D. SALAHORIS
D. THEODOROKOPOULOS

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Ms. J. R. OLIVER

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Rev. B. CAREY
Prof. I. DARIAN-SMITH
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Prof. B. G. FIRKIN
Dr. T. H. STEEL
Dr. R. P. STETTAFORD
Dr. N. WALDEN

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Dr. W. ANDERSON
Mr. M. DOWNES
Mr. F. FORGIONE
Mr. C. LEWIS
Dr. K. O'DEA
Ms. L. POPADYNEC
Mr. M. SANDERS
Dr. N. TADA

CONTENTS

Professor P. I. Korner

DIRECTOR'S REPORT

The end of 1979 marks the end of my first five years as director of the Baker Institute and this is an opportune moment for general stocktaking. Before doing this I want to review, as usual, the events of the last year.

The Last Twelve Months

At the beginning of 1979 we established a second Pharmacology Laboratory, in addition to the Clinical Phamacology Laboratory started by Dr. Allan McLean in 1978. Dr. James Angus, one of Australia's outstanding young pharmacologists, is in charge of the new laboratory. He is investigating fundamental mechanisms of the action of cardiovascular drugs. Much of the laboratory equipment was purchased through the generosity of the William A. Buckland Foundation. Staff salaries have come from grants from the National Health and Medical Research Council and the National Heart Foundation.

This is probably the last year in which the Institute will be managed by our Board of Trustees under its original constitution. Soon the Baker Medical Research Institute will be incorporated under its own Act of Parliament. This became desirable owing to the increase in the size of the Institute and the amount and range of its research. Alfred Hospital and Monash University have both supported the proposed changes. At the time of writing this report the Baker Medical Research Institute Act has had its First Reading in the Victorian Parliament and the Act became operative on 1st August, 1980.

In August 1979 building started on the extensions to the Alfred Hospital's Biology Research Unit. These will provide much needed additional facilities for laboratory animals and some additional offices. On current indications the building will be completed by August 1980. The cost of this project is approximately $450,000. It is a pleasure to acknowledge the help of the Victorian Government who gave a Special Grant of $240,000. The balance was provided by the Institute and by the Baker Benefactions.

The results of our research activities were demonstrated to the public during 'Open Day' on 7 August 1979. The Governor Sir Henry Winneke was present at this function and in his address stressed the great importance of medical research in producing fundamental changes in patient care. His Excellency and Lady Winneke showed a keen interest in the individual exhibits on their tour of the Institute. About 600 people came to our 'Open Day'.

In January 1980 we had the pleasure of welcoming to the Institute Dr. Gwyn Howells, the Commonwealth Director-General of Health. This was Dr. Howell's first visit and he met with many members of our senior scientific staff and several of our Trustees. Another visitor several days later was Dr. David de Souza, the new Secretary of the National Health and Medical Research Council. The last twelve months has been a vintage year for other distinguished visitors to the Institute and details of their visit are given elsewhere in the Annual Report.

It gives me particular pleasure to note that two of the Institute's staff members were

awarded the Australian and New Zealand's Cardiac Society prizes for distinguished cardiovascular research performed in Australia. Dr. Warwick Anderson won the R.T. Hall Prize for his work on experimental renovascular hypertension and Dr. Garry Jennings won the Young Investigator's Award for his work on how for prolonged control of blood pressure by anti-hypertensive medication, can reverse the narrowing of the small arteries in human essential hypertension.

Staff changes during the last year included the return of Dr. Peter Blombery to the Institute in December 1979 after an absence of three years. Dr. Blombery is a medical graduate who obtained his PhD at the Baker Institute and is our first trainee returning to a permanent position. He had been working in Dr. Irwin Kopin's laboratory at the National Institutes of Health in Bethesda, first under a National Heart Foundation Overseas Research Fellowship and then a Fogarty U.S. Public Health Fellowship. He is an expert in metabolism of catecholamines and is a welcome addition to the strength of the Hypertension and Circulatory Control Research Unit. Dr. Gordon Campbell accepted a position as Senior Lecturer in Anatomy at the University of Melbourne from the beginning of 1980 and we wish him well in his new position. He made a great contribution in establishing the Cell Biology Laboratory. He will continue to collaborate with different staff members and was appointed as Honorary Senior Associate of the Institute. In the same way we have appointed Dr. Barbara Evans of the Zoology Department of the University of Melbourne as Honorary Research Associate. She has worked on the neuro-anatomy of the circulatory control system in close collaboration with my laboratory.

The Last Five Years

When I took up my appointment at the beginning of 1975 the Trustees decided that the time was opportune to develop the Baker Institute and Clinical Research Unit of the Alfred Hospital as Australia's first research institute fully devoted to research into the problems of heart and vascular disorders. After five years we have a staff of 100 people and have become Australia's largest cardiovascular research institute. The accompanying Table shows that we have had a fourfold increase in our expenditure over the last five years.

ANNUAL EXPENDITURE OF THE BAKER INSTITUTE 1970 - 1979

YEAR	$
1970	217,445
1971	236,398
1972	295,503
1973	311,738
1974	363,371
1975	525,853
1976	731,984
1977	1,081,793
1978	1,227,375
1979	1,518,849

To finance these developments at a time of great stress in the national economy has been difficult. I sincerely hope that we can maintain some growth so that we can make additional contributions to those fields of cardiovascular research where we have been notably successful and also to some new areas.

Our present objectives are to discover the causes of high blood pressure and atherosclerosis. High blood pressure results in strokes, heart failure and kidney failure; atherosclerosis is associated with the development of fatty plaques projecting into the large arteries such as the coronary arteries supplying the heart. Deposits of blood clot on these plaques can result in their eventual obstruction and heart attacks.

These disorders account for about half of all deaths and serious illness in Australia and their ravages result in great economic losses. Our work concentrates on the analysis of the complex control systems in the body that regulate the blood pressure and maintain nutrition of the arterial wall. These regulating systems are critical to maintenance of good health and have to respond to a great range of requirements by the body. An understanding of the many factors important in their normal functioning forms the basis for identifying the multiple causes that can lead to chronic high blood pressure and to fatty damage of the large arteries.

What distinguishes the work of the Baker Institute from that of the other Australian centres active in cardiovascular research is that we have a greater range of disciplines, which allow us to tackle particular problems from numerous viewpoints. It is this multi-disciplinary approach that undoubtedly enlarges our perspective and provides us with new and often unexpected insights.

The most important determinant of the quality of the work of a research institute is the calibre of its scientists. We have been particularly fortunate that Dr. Paul Nestel, one of the world's leading authorities in the field of cholesterol and lipid metabolism joined our staff at the beginning of 1977 as Deputy Director of the Institute. The other scientists in charge of the different research laboratories also have an excellent record of research achievement. They include Dr. Warwick Anderson (Kidney and Hypertension), Dr. James Angus (Pharmacology), Dr. Peter Blombery (Autonomic Nervous System), Dr. Alex Bobik (Biochemical Pharmacology), Dr. Julie Campbell (Cell Biology), Dr. Pat Dorward (Neurophysiology), Dr. Murray Esler (Autonomic Nervous System and Hypertension), Dr. Noel Fidge (Lipid Biochemistry), Dr. Garry Jennings (Clinical Research Unit), Dr. Allan McLean (Clinical Pharmacology), Dr. Kerin O'Dea (Nutritional Biochemistry) and Mr. Frank Rosenfeldt (Cardiac Surgical Research). Our ability to attract them to the Baker Institute owes much to our good facilities and to the opportunity for interactions between basic and applied medical research, which is always attractive to both types of researchers. Some of the above laboratories because of their common interests join forces in the Hypertension and Circulatory Control Research Unit on the one hand, and the Cardiovascular Metabolism and Nutrition Research Unit on the other.

Our Hypertension Unit has been collaborating closely over the five years that I have been here with Professor Colin Johnston's group in the Monash University Department of Medicine at Prince Henry's Hospital. This has been mutually advantageous. It has allowed a most interesting collaboration on the role of various hormones on the blood vessels of the kidney and on the effects of altering dietary salt intake.

The scientific part of the Annual Report outlines in detail some of our research achievements. The work of our scientists at the Baker Institute has made a very significant contribution to Australia's overall effort in cardiovascular research.

The Next Five Years

I have no doubt that, given reasonable funding, we will go from strength to strength in the next five year period. We are planning modest staff increases in several of our present areas of research. In the field of hypertension research one of the most promising new areas relates to the interactions between central nervous and hormonal control mechanisms which probably will play a role in the 'resetting' the properties of the neural control system in its longterm operation. A most important area for further development by our Cardiovascular Metabolism and Nutrition Research Unit is in diabetes research particularly in relation to the development of vascular disease. These are some areas to which our current research programme will inevitably extend. I hope that we will also be able to increase our activity in neuropharmacology and in clinical pharmacology, where there are exciting opportunities for advances.

We would like to develop some basic research in electrocardiology at the Baker Institute. This involves the study of electrical activity of the heart and is relevant to the many types of rhythm disturbances affecting the heart beat. This has been a particularly rapidly developing field where our Cardiac Surgical Research laboratory is already active but where more basic studies are required.

The above may sound unreasonably optimistic and there is no doubt that there will be difficulties to maintain a modest rate of growth over the next five years. There are signs of increasing strains in sustaining sufficient income to maintain existing activities. As is evident from our current Balance Sheet we are doing what we can in the field of 'self-help'. We have received the maximum possible support from the Trustees of the Baker Benefactions, we are spending all income from our Endowment Fund and through the unremitting efforts of our Financial Director Mr. Michael Downes, our fund raising activities are the most successful of any medical research institute in Australia. We are receiving a relatively high proportion of funds available from non-government national medical research funds such as the National Heart Foundation and the Life Insurance Medical Research Fund of Australia and New Zealand. The Victorian State Government is now contributing about 9% of our running costs, similar to its rate of support of the other large Victorian research institutes.

The best hope that we have for obtaining a substantial increase in funding is through a National Health and Medical Research Council Institute Grant by the Federal

Government. We have recently applied for such an Institute Grant, similar to that supporting the two other major medical research institutes.

We believe that our performance over the last five years fully justifies that the Baker Institute be funded in this way and that the Institute and its research effort is a **national** asset. Although we are a relatively small group by international standards, we are making important contributions to medical knowledge which have gained increasing recognition throughout the world.

For our application for an Institute Grant to succeed it is important that the Federal Government should increase the overall funding for medical research and particularly for the support of 'centres of excellence' both in institutions such as ours an in universities. In 1979 the level of support to the National Health and Medical Research Council was $14.2 million for institutes, program and project grants. This is a derisory figure when related to the huge cost of the national health care bill of close to $8,000 million for the same year. Far too few research projects were funded in 1979 causing great consternation in the medical research community and likely to produce a 'brain drain' to overseas countries and above all leave the country without much needed personnel to bring about long term changes in health care.

There are several levels at which a vigorous national medical research programme repays the outlay made by the community. The minimum return is to provide personnel skilled in evaluating newly introduced treatment procedures in the delivery of health care. A more desirable additional return, given the calibre of Australian research workers, is that Australian researchers will make their contributions to new knowledge as valued members of the international research community.

The Baker Institute now has a substantial number of post-doctoral fellows and research students. Best of all has been the increasing number of visiting scientists from overseas who come and work here for periods of 1-2 years. This together with the number of our scientific staff members who are asked to participate in scientific meetings overseas and to contribute to various specialist books are perhaps the best indicators of the esteem in which our work is held.

A change in Federal Government policy would accord with the recommendations made by A.S.T.E.C., the Australian Science and Technology Council. ASTEC recently recommended that the Commonwealth Government give better support to 'centres of excellence' in all kinds of scientific research in Australia. We can fairly claim to be such a centre and deserve better and longer term funding through the National Health and Medical Research Council than we are currently receiving.

In 1979 the funds we received from N.H. & M.R.C. were $408,000. This is far smaller than the support given to the Walter and Eliza Hall and Howard Florey Institutes, the only institutions to receive Institute Grants. Moreover, in our funding only $225,000 came from a 5-year Program Grant, thus providing some security of employment for some of our senior staff members. The balance came through shorter term Project Grants of 1-3 years duration. The latter type of funding is unreasonable for supporting talented career scientists. It also makes long range planning in a complex institution such as ours exceedingly difficult.

I want to conclude by expressing the hope that our future will not be frustrated through lack of decisive leadership by the Government. The future of Australia depends on Research and Development in many areas of science including medicine. We will certainly do what we can to increase even further our own fund raising activity both in Australia and overseas. Cardiovascular medical research is one of the areas where there is good hope of increasing both the length and quality of life of our population. As it has had to do in many other areas this is a field where Australia must shoulder increasing international responsibility and give better support to institutions such as ours.

I should like to conclude on a personal note. I have never worked anywhere where the morale of the entire staff including scientists, technical, administrative and support staff has been so high. It has made our development as a cardiovascular research centre a particularly stimulating experience. I want to pay a particular tribute to the Chairman of our Board of Trustees, Mr. John Habersberger, who has toiled unceasingly on our behalf, and to the other Trustees, (now Board Members), who have given us so much support during the last five years.

People

Mr. J. D. Moir
Board Member

John Moir

John Moir is a member of the Board of the Baker Medical Research Institute. Prior to that he was a Trustee of the Institute and a member of the Business Management Advisory Committee.

Mr. Moir was educated at Scotch College and Melbourne University. He is a Senior Partner of Gillotts, Solicitors, where his specialty is commercial law.

Community Service interests have been at the YMCA where he was a Board member from 1965 to 1979 and President from 1972 to 1973. He serves on the Board of Ambulance Service, State Executive of the Scout Association and in the Rotary Club of Melbourne where he was President from 1975 to 1976.

A great deal of the work involved in the incorporation of the Institute by Act of Parliament was done by him and we are most grateful for his interest in us.

Mr. H. C. McConnell
Accountant

Hec McConnell

Hec McConnell, affectionately known as "MAC", has looked after the Baker Institute accounting since 1955. No-one knows the state of our finances better than he.

He is a Fellow of the Institute of Credit Management, Associate of the Australian Society of Accountants, licensed company auditor and registered tax agent.

He served in the Royal Australian Navy and was the Chief Accountant of Alfred Hospital from 1955-1980. His recreational activities include lawn bowls, fishing and gardening.

Mac is moving into retirement, and although we will still see him in the Institute it is opportune to thank him for all the years of service and wish him well in the future.

People

Miss J. Oliver
"Control of Circulation"

Judy Oliver

From an original interest in sugar chemistry, Judy Oliver followed a trend to the School of Physiology at the University of New South Wales. She spent many years doing science part-time in Zoology and Biochemistry studying Bandicoots and Anadara (Sydney cockle).

After a spell with electrophysiology of crays and sea hares, she moved to rabbits at the Hallstrom Institute, Sydney.

She supervised the general move of Professor Korner's Unit from Sydney to the Baker — still rabbits.

For relief, Judy follows feathered birds with binoculars and a camera. She has lots of "if only" slides.

Mr. C. Lewis
Laboratory Supervisor

Christopher Lewis

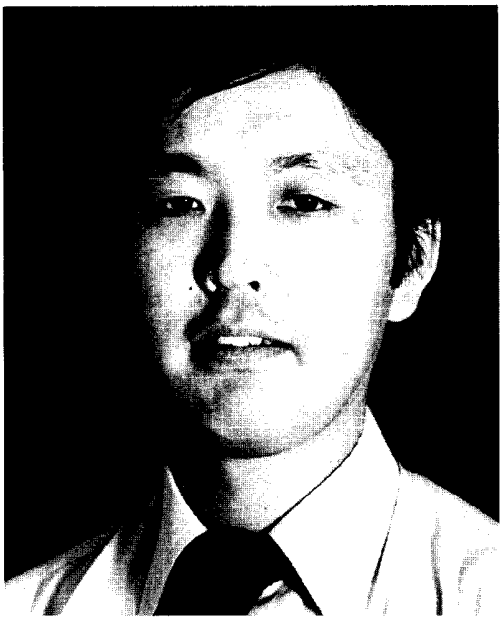
Chris joined the Institute in 1966 as a Technical Assistant. In those days the Institute was housed in the original 1926 buildings which were overcrowded and extremely dilapidated.

At the end of 1971, he was conscripted for 18 months military service in the Royal Australian Army Medical Corps returning to the Institute in 1973 to assist Dr. Gordon Hard, with his Cancer Research Programme. He was appointed Laboratory Supervisor in 1975.

His hobbies include amateur radio, electronics and motor cars.

His tireless efforts as our Laboratory Supervisor keep the place equipped and running smoothly.

People



Dr. N. Suzuki
Visiting Scientist

Naoki Suzuki

We are delighted to have Naoki with us as a visiting scientist.

He graduated MD at Jikei University of Medicine in Tokyo in 1976. During the last two years he has been studying human myocardial lipid metabolism and it is in this field that he is working with Dr. Nestel at our Institute. Two of our old friends, Dr. Ishikawa and Dr. Tada are at Jikei University now. Their laboratory is our sister laboratory in Japan.

Naoki and his wife are enjoying two day weekends. His hobbies are playing tennis and the guitar.

Mr. F. Hanneman
Electronics

Falk Hannemann

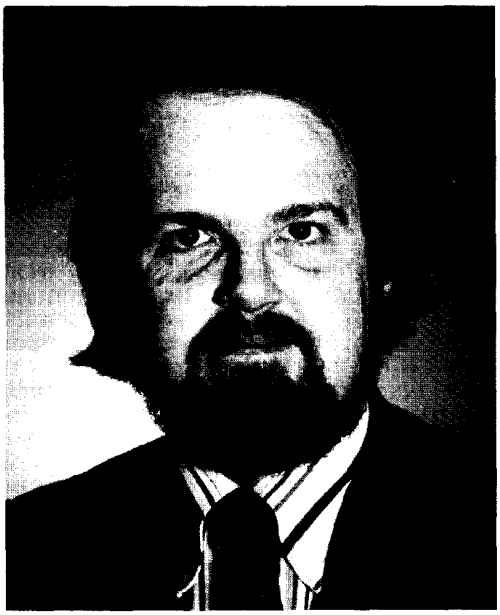
Falk joined the Institute in May 1980 to become the Head of our Electronics Laboratory. He obtained his Bachelor of Engineering (Electronics) in 1978 after ten years of part-time study.

His original training was as a radio and TV technician and then he worked for five years at the Institute for Plasmaphysics in Munich.

In Australia he worked in industry until he joined the Electrical and Electronic Engineering Department at Swinburne College.

Falk is married with 3 musical sons. His own outside interests includes music, hiking, building furniture and astronomy.

People



Dr. P. Blombery
"Neuro Transmitters in Cardiovascular Disease"

Peter Blombery

Peter graduated B.Sc. (Med.) Hons. I at the University of Sydney in 1967. He completed his medical degree with Honours in 1971 and his Ph.D. in 1979.

He was at the Prince Alfred Hospital 1971-74 then with Professor Korner 1974-77. For two years until 1979 he worked in the United States at the N.I.H. on a National Heart Foundation Research Fellowship.

He has been back at the Baker Medical Research Institute since the beginning of this year. His interests include music, camping, good food and wine.

Dr. G. Jennings
Staff Physician

Garry Jennings

Graduated M.B.B.S. from the Monash Medical School in 1969. He spent his resident years at the Alfred Hospital and later went to London to become Medical Registrar, Cardiology Registrar and eventually Lecturer in Cardiology at St. Mary's Hospital Medical School. He joined Professor Korner's group on his return to Melbourne in 1975 and since then has been Staff Physician in the Clinical Research Unit. He is interested in hypertension, exercise and cardiovascular pharmacology.

Garry is also the Master of Ceremonies at the end of year Baker Revue . . . a task that he tackles with wit and charm.

HYPERTENSION AND CIRCULATORY CONTROL RESEARCH UNIT

MAIN TOPICS

* HYPERTENSION IN MAN
* NERVOUS CONTROL OF THE CIRCULATION
* KIDNEY AND HYPERTENSION
* SALT, HYPERTENSION AND AUTONOMIC FUNCTION

GENERAL SUMMARY

HYPERTENSION IN MAN

We have studied:— (i) the effect of treatment of high blood pressure of the resistance to blood flow offered by the small blood vessels; (ii) the role of the autonomic nervous system in essential hypertension.

Effect of Treatment

Blood pressure can be high because the heart is pumping more blood than normal, or because the small arteries are abnormally narrow offering higher resistance to blood flow. In patients with so-called 'primary' (essential) hypertension we know that the blood pressure is higher because of the increased narrowing of the small arteries. We have found previously that even after drug-induced block of the activity of the sympathetic nerves the vessels of hypertensive patients are narrower than in subjects with normal blood pressure. Possible reasons for this non-sympathetic rise in resistance are structural changes in the blood vessels or an increase in the levels of circulating hormones or both factors. We and others have observed similar increases in resistance in many types of experimental hypertension where the underlying mechanisms can be more readily determined than in man. Under the higher pressure load there is enlargement of the muscle cells of the small arteries, leading to encroachment on the internal vascular diameter and an abnormally high resistance even when all smooth muscle tone has been removed by fully dilating the vessels. Moreover, any constrictor influence is 'amplified' by the enlarged arterial muscle coat of the hypertensive vessels resulting in greater narrowing and a greater rise in resistance than is found in the vessels of normal animals. A similar type of structural change probably occurs in the small arteries of human essential hypertension and constrictor influences become similarly 'amplified' through enlargement of the smooth muscle coat. As a result, any stimulus that causes blood pressure to rise will have greater effects in hypertensive patients than in subjects with normal blood pressure and will therefore place him at greater risk for developing complications.

We addressed the question to what extent good control of blood pressure by treatment could reverse the changes in the small arteries in hypertensive patients. After 12 months of standard drug treatment which produced excellent control of blood pressure we found that the initially high non-sympathetic component of vascular resistance became much lower, into the range of normal subjects. Good control of the blood pressure in hypertensive patients thus results in reversal of most of the structural changes due to enlargement of the muscle coat of the small arteries, thus removing the dangerous amplification effect of constrictor influences.

When treatment was stopped we obtained a dramatic illustration that despite the above beneficial effects of present-day drug therapy the basic underlying cause of the high blood pressure had not been removed. After stopping the drugs, blood pressure returned to its high initial value within 1-3 months, resulting again in enlargement of the arterial muscle coat, and suggesting that the structural changes were a consequence rather than a cause of the hypertension. The study emphasises that with presently available drugs the treatment of hypertension has to be a life long affair. Present drugs have vastly improved the outlook of hypertensive patients as far as their expectation of life and chances of developing serious illness are concerned. However, they still do not give the patient the same favourable expectation of life as possessed by subjects with initially normal blood pressures. The challenge is for more specific treatment that will really get to the fundamental cause of the raised blood pressure.

Autonomic Nervous System

There has been much speculation about the role of sympathetic over-activity as a trigger factor important in the causation of essential hypertension. One problem has

Standing (left to right): Dr. Archer Broughton, Anne Heal, Rosemary Smith, Paul Leonard, Geoff Head, Dr. Duncan Blake, David Melick, Steve Selig, Sandra Burke, Dr. Warwick Anderson, Dr. Pat Dorward, David Harrison, Margit Scott-Murphy. Seated: Judy Oliver, Professor Paul Korner, Dr. Michael Andresen, Dr. Murray Esler.

been to develop satisfactory methods for assessing autonomic function in man.

In recent years the concentration of the sympathetic transmitter noradrenaline in blood has been measured, to see whether patients with essential hypertension differ from normal subjects. It has become increasingly apparent that measurement of noradrenaline concentration in plasma is not sufficiently reliable as an index of autonomic function. Noradrenaline is released from the sympathetic nerve terminals and reaches a high concentration in the synaptic cleft between the terminal and the target organ (heart or blood vessels). Most of the transmitter is taken back into the nerve terminal by an efficient active transport system, so that very little of it spills over into the circulation. The level of plasma noradrenaline concentration depends on the balance between noradrenaline 'spillover' from sympathetic nerve terminals and clearance of noradrenaline from plasma into the tissues, urine etc. Obviously measurement of noradrenaline 'spillover' rate, clearance and reuptake rate back into the nerve terminal could provide more information about sympathetic function than measurement of noradrenaline concentration alone.

Dr. Murray Esler and associates have developed methods to measure all these variables in man. The tests involve tracer infusions of radio-labelled noradrenaline and mathematical analysis of the time-concentration curves. One group of patients illustrating the advantages of these somewhat complex methods over measurement of noradrenaline concentration alone are patients with peripheral autonomic insufficiency. In these patients there is truly gross impairment of sympathetic function and many of them are literally brought to their knees because of the disabling *falls* in blood pressure that occur when they assume the upright posture. Yet, in most of these patients plasma noradrenaline concentration is normal. This has been one of the important factors of casting doubts as to the reliability of noradrenaline concentration alone as an index of sympathetic function. However, when the rate of noradrenaline 'spillover' was determined it was found to be reduced to about half of that observed in normal subjects. These patients also

had a low clearance of noradrenaline explaining why plasma concentration remained normal.

In about 75% of patients with essential hypertension noradrenaline 'spillover' rate, clearance and re-uptake rate into the nerve terminal was the same as in normal subjects. However in about 25% of patients there was a slowing of the rate of noradrenaline re-uptake so that transmitter released by a nerve impulse tended to remain longer. These patients had, as would be expected, a higher noradrenaline 'spillover' rate than normal subjects.

The work has thus identified a subgroup of patients with essential hypertension with some evidence of sympathetic 'overactivity'. What was of particular interest was that the observed abnormality in sympathetic function was a defect in the *peripheral* sympathetic nerves rather than in the central nervous system. We still are not certain whether this abnormality is the cause of their hypertension but hope that current work will throw more light on this important question. At a more practical level, we would expect that the blood pressure of these patients will be more easily controlled with drugs that influence autonomic function than, for example, by diuretics. Our results to date emphasise that essential hypertension is probably not a single disorder and that the different subsets of patients reflect differences in the locus of disturbances of the blood pressure control system.

CENTRAL NERVOUS CONTROL OF THE CIRCULATION

Transmitters

During the year we have extended our studies of the role of noradrenergic neurons in the central nervous system, (i.e. nerve cells that release noradrenaline at their nerve endings) in different cardiovascular reflexes and control of blood pressure. We have also examined the role of another group of nerve cells, the serotonergic neurons, which release another transmitter, serotonin at their endings. Each transmitter can alter the excitability of the adjacent nerve cells on the other side of the synaptic cleft.

Both noradrenergic and serotonergic neurons have their cell bodies in the lower brain stem; some send axons (fibres) up to the *higher* brain centres whilst others send them down to spinal cord. We have used rabbits to study the role of noradrenergic and serotonergic neurons in the central nevous control of blood pressure. Two drugs have been used — 6-hydroxydopamine (6-OHDA) and 5,6-dihydoxytryptamine (5,6-DHT) that are each taken up fairly specifically by one group of neurons. Each drug when injected into the cerebrospinal fluid evokes acute circulatory changes and alterations in reflex properties which are of several hours duration. These acute changes are due to the effects on the central autonomic pathways of release of each transmitter from its specific terminals. These studies provide a model of what happens during excess release of a particular transmitter. Over the next few days or weeks chronic effects supervene after each drug which are generally opposite to those observed acutely. They occur owing to selective destruction of the particular group of nerve cells.

Our experiments have shown that the central noradrenergic and central serotonergic neuron systems participate in all reflexes that we have so far studied. Each neuron system can influence resting heart rate and blood pressure. Stimulation of the noradrenergic neurons which send fibres up to the higher brain regions will *increase* blood pressure, but stimulation of those noradrenergic neurons which send fibres to the spinal cord produce lowering of blood pressure. The pathways which mediate heart rate changes lie mainly in the lower brain stem:— excess stimulation of noradrenergic pathways causes slowing of heart rate and excess stimulation of serotonergic neurons causes a rise in heart rate. Thus, the two groups of neurons exert antagonistic effects on heart rate. However they both have similar effects on blood pressure:— a rise in blood pressure results from stimulation of noradrenergic and of serotonergic neurons that send fibres to higher brain regions. We have found that this is due to an arrangement whereby serotonergic and noradrenergic neurons form adjacent links in a chain controlling the centres involved in the rise in blood pressure.

Detailed analysis of the role of the transmitters involved in the different central autonomic pathways is a promising approach which may lead to development of drugs that produce very specific changes in autonomic function. We have found that the anti-hypertensive drug clonidine which affects both blood pressure and heart rate alters each variable through distinctive noradrenergic and serotonergic pathways. Our results

suggest that after injection into the cerebro-spinal fluid clonidine slows heart rate by acting on both serotonergic neurons and noradrenergic neurons. For lowering blood pressure the drug acts mainly on serotonergic neurons.

Destruction of both noradrenergic and serotonergic neurons also reduces food and water intake and our current work suggests that integrity of serotonergic neurons are critical for normal eating and drinking behaviour. The brain amine transmitter systems appear to play a role linking the central circulatory autonomic pathways and those regulating food and water intake.

Action of Anaesthetics

We have examined the sites of actions on the central autonomic pathways of three anaesthetics — althesin, ketamine and thiopentone. The last is a well established barbiturate anaesthetic and the others are new agents introduced relatively recently. In man althesin produces less depression of the higher autonomic pathways whilst ketamine raises blood pressure and has been recommended as an agent par excellence for patients requiring surgery when they are in shock, or other states with a low blood pressure. We have found that these anaesthetics produce similar circulatory changes in rabbits as in man. Each drug exerted distinctive effects on blood pressure, heart rate, cardiac output and vascular resistance. These were mostly due to differences in the sites of action of the different drugs on the central baroreflex pathways which processes information about changes in blood pressure. Ketamine disrupted this information more than the other drugs whilst althesin disrupted it least. In addition to these critical effects on the CNS ketamine also has a stronger direct depressive action on the heart and circulation. These results cast doubts whether ketamine is the anaesthetic of choice in shock-like states in patients with very low blood pressure. The study shows how the greater analytical potential of animal studies can complement clinical research.

KIDNEY AND HYPERTENSION

The role of the kidney in the regulation of blood pressure has been studied from a number of angles this year. We have continued work examining the consequences for the kidney of the highly complex nature of stenosis (narrowing) of the renal artery and the mechanisms that come into play within the kidney. We have also studied how the sympathetic transmitter noradrenaline constricts the vessels of the kidney, and the possible significance of two putative renal dilator systems — the prostaglandin and the kallikrein-kinin systems.

The studies of renal arterial stenosis are a continuation of previous work where we showed that the hydraulic properties of this narrowing produced unexpected results. We had observed that a stenosis of fixed diameter of the renal artery did not exert a constant resistance to blood flow. Surprisingly, its resistance varied in inverse relationship to the vascular tone of the kidney. After experimentally narrowing the renal artery to produce a gradient across the stenosis of as much as 50-70 mmHg, the subsequent constriction by the intrarenal action of the hormone angiotension II of the blood vessels of the kidney resulted in reduction of the resistance to blood flow offered by the stenosis so that there was no permanent elevation of blood pressure. We have extended this work to show quantitatively how relatively small changes in resting vascular tone of the kidney can influence the degree of narrowing required to establish a given pressure gradient. A greater reduction of the renal artery diameter is needed to produce pressure and flow reduction when the kidney is vasoconstricted than when it is dilated. This explains why development of hypertension and greater renin release occur more readily after establishing a given pressure gradient across an experimentally induced renal artery stenosis in dogs that have been anaesthetised compared with conscious dogs. The results also support our contention that sustained hypertension only results from severe renal artery stenosis; in mild to moderate stenosis renal vasoconstriction restores distal pressure making the stenosis less critical and preventing the development of hypertension.

It has been known since the 1920s that noradrenaline produces a rise in the fraction of plasma filtered at the glomerulus of the kidney. More recently it has become known that stimulation of the renal sympathetic nerves also produces renin release from the kidney. We have shown that the renal vasoconstrictor effect of noradrenaline is mediated partly through its action in releasing renin, causing increased formation of angiotensin II which in turn constricts the efferent arterioles which carry blood away from the renal glomerulus after the plasma has

been filtered. When angiotensin II formation is blocked by the converting enzyme inhibitor teprotide noradrenaline infusions into the renal artery cause a fall instead of a rise in the filtration fraction of the kidney.

There is considerable evidence that various stimuli, including renal ischaemia, cause prostaglandin production in the kidney. It has been postulated that the prostaglandins act to protect the kidney under these circumstances. Much of the above work has been done in *in vitro,* so that we have commenced a study in conscious dogs to test whether prostaglandins are formed in mild and severe renal ischaemia produced by renal artery stenosis.

The new anti-hypertensive drug captopril is an inhibitor of converting enzyme which catalyses not only angiotensin II formation but also the breakdown of bradykinin. It has been suggested that some of the anti-hypertensive effects of captopril can be ascribed to a subsequent increase level of the dilator substance bradykinin. However, no changes in the circulatory levels of this peptide have yet been demonstrated. Our results in anaesthetised dogs have suggested that captopril does prevent the normal degradation of bradykinin *locally* in the kidney and there is evidence suggesting that this may influence the way in which the kidney handles sodium. After giving captopril the amount of bradykinin excreted from the urine increased markedly whilst there was no change in concentration in either arterial or renal venous blood.

The Mechanism of Hypertension in Renal Artery Stenosis

Experiments still in progress suggest that in renal artery stenosis severe enough to cause hypertension a substantial component of the increased vascular resistance resides in the mechanical resistance to blood flow of the stenosis itself. This has been studied in a group of experiments where we have measured not only changes in renal blood flow and renal vascular resistance, but also the output of the heart and the body's total peripheral resistance to blood flow. We have found that the resistance offered by the stenosis itself accounts for half or more of the rise of the total peripheral resistance.

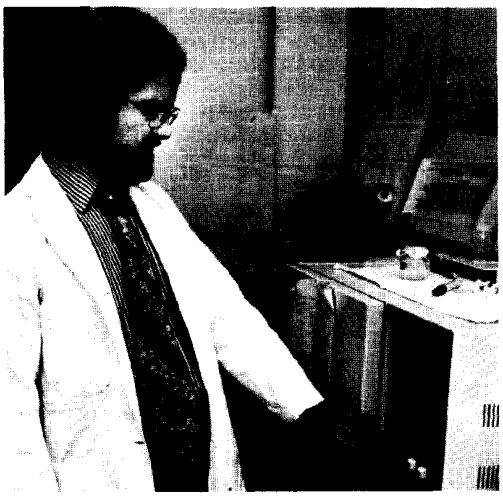
The question arises whether the increased renin release and angiotensin II formation constitutes an essential trigger factor in the pathogenesis of the hypertension of renal artery stenosis. Our present hypothesis is that it is not, and that hypertension will still occur with a tight stenosis even if increased activity of the renin-angiotensin system could be prevented. This view is at present based on the results of our experiments with cellophane wrap hypertension which normally develops very slowly without any increase in activity of the renin-angiotensin system. In this type of hypertension the kidney becomes gradually encased by a firm, fibrous capsul which exerts a relatively high pressure on the renal blood vessels within the kidney. At this stage there is a virtual pressure gradient between aorta and renal artery and the renal capsule pressure can be regarded as the source of the kidney's resistance to blood flow. The situation is closely similar to the renal artery stenosis model, with the exception that the latter has an increased activity of the renin-angiotensin system in the early stages whilst the cellophane-wrap model shows no such increase.

Our present hypothesis is that the critical 'constrictor' factor in renal artery stenosis and other types of renovascular hypertension is the mechanical resistance of the renal artery stenosis itself, or that offered by the renal compression forces. In our view any increased activity of the renin-angiotensin system serves a predominantly catalytic role in the development of the high blood pressure. This will hasten the structural changes in the smooth muscle coat of the body's resistance vessels, thus accelerating the development of this 'amplification' effect of further constrictor influences. In the absence of increased activity high blood pressure will still occur, but more slowly and with less danger of developing the complication of malignant hypertension.

The work provides an important new insight into the pathogenesis of renovascular hypertension. Our work has also emphasised that whilst the renin-angiotensin system has only a facilitatory action of the development of hypertension, it has a very important physiological role in maintaining the kidney's ability to filter plasma and form urine when blood pressure is low, or under conditions of increased sympathetic activity.

SALT: ITS ROLE IN HYPERTENSION AND ON AUTONOMIC FUNCTION

We studied the effects of varying salt intake on blood pressure, cardiac output



Dr. Peter Blombery

and vascular resistance in rabbits with fully established renal hypertension and in a sham-operated control group. We found that two weeks after lowering the salt intake to 1/9th of their normal intake the blood pressure of the hypertensive rabbits had fallen by about 12 mm, i.e. 25% of the original rise in their blood pressure.

The fall in blood pressure was entirely due to reduction in cardiac output, which was in turn due to a lowering of the blood volume in the hypertensive animals. Raising their salt intake to six times normal did not increase blood pressure or cardiac output but increased their blood volume significantly. The control animals with normal blood pressures were able to handle these variations in salt intake without any effects on blood pressure or other circulatory variables.

The results in the hypertensive animals are important in showing that changes in salt intake can alter blood pressure entirely through changes in cardiac output ('volume' factors) rather than through changes in vascular resistance. The chronically hypertensive rabbits had some changes in their kidney function so that they were less well able to handle a high salt intake than the control group of normal rabbits. Our results suggest that in hypertensive patients a modest reduction in salt intake would be well worthwhile in helping to maintain blood pressure at the lowest possible level.

We also studied the effects of changing salt intake on the properties of the baroreceptor-heart rate reflex in renal hypertensive rabbits and in the control animals. It has long been known that in hypertensive rabbits on a normal salt diet the reflex sensitivity (i.e. the changes in heart rate per unit change in blood pressure) is less than in animals with normal blood pressure. A similar reduction in reflex sensitivity has been observed in patients with hypertension. We found that the above range of dietary salt intake had no effect on the properties of the baroreceptor-heart rate reflex in the control group, but that it altered the reflex properties of hypertensive animals. Low salt diet tended to increase reflex sensitivity on low salt and high salt to depress it. These changes probably depended in part on the interactions in the central nervous system involving pathways carrying information from the arterial pressure baroreceptors and receptors carrying information from the heart chambers. When the latter are distended because of the high blood volume on the high salt diet the reflex sensitivity to changes in arterial pressure is depressed, whilst when chamber size is normal on the low salt diet it is restored to normal.

Low salt is also a strong stimulus to the activity of the renin-angiotensin system which is suppressed on high salt. We wished to examine whether these 'physiological' dietary stimuli modified the reflex responses through the renin-angiotensin system, at least in normal animals. This was done by studying the effects of saralasin a competitive angiotensin antagonist. We found that in normal rabbits on low salt the increase in angiotensin II tended to depress the sensitivity of the baroreflex and that sensitivity increased markedly after saralasin. These changes occurred in both control rabbits and hypertensive rabbits. However, in the hypertensive animals administration of saralasin brough the reflex sensitivity into the same range as in the control group with normal blood pressure. Probably both the reduction in the volumes of the heart chambers produced by the low salt diet and the removal of the effects of increased angiotensin II produced by saralasin contributed to this normalization of reflex properties.

It has always been thought that the depressed sensitivity of the baroreflex in hypertensive patients was fairly fixed as long as blood pressure remained high, but our study has shown that it can be altered very rapidly.

Dr. Robert Watson, who has been visiting us for the last 12 months from Birmingham, has studied in collaboration with Dr. Murray Esler the effects of low, normal and high salt diet on autonomic function of normal subjects. For this work the biochemical methods discussed earlier were used. In these normal subjects high salt diet produced little change in autonomic function. Low salt produced a modest increase in sympathetic activity though there was a much greater enhancement of the activity of the renin-angiotensin system. The low salt diet did not lower blood pressure of these normotensive subjects (which behaved similarly in this respect to the normal rabbits referred to above) and it will be a matter of great interest to extend this work to patients with hypertension.

DETAILS OF PROJECTS

1. **Effect of Long Term Treatment of Essential Hypertension**
   (G. L. Jennings, M.D. Esler, P. I. Korner)

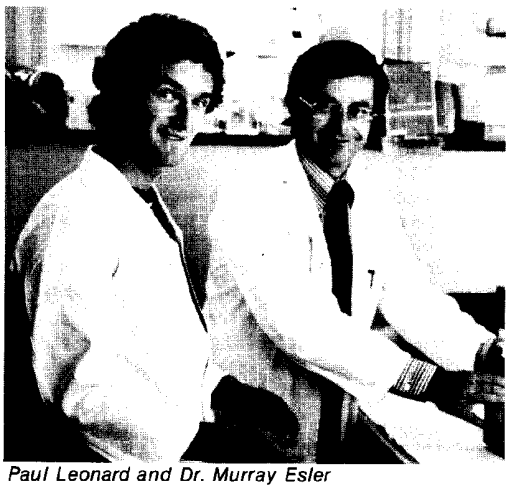
Systemic haemodynamics were studied in 13 patients with essential hypertension (i) before treatment and (ii) one year later, 4 weeks after stopping diuretics and 1 week after stopping the other drugs. On each occasion we measured mean arterial pressure (MAP), cardiac index (CI) and total peripheral resistance index (TPRI) both before and after autonomic effector blockade. Twelve months of treatment lowered mean arterial pressure by 15 mmHg, increased cardiac index by 25% and lowered TPRI by 31%. After autonomic blockade the differences between the first and second studies were almost identical indicating that the reduction in TPRI mainly involved the non-autonomic component of resistance. The latter was brought into the range we have previously observed in autonomically blocked normotensive subjects. The findings indicate that high vascular resistance of hypertension can be almost completely reversed by one year's good control of the patients blood pressure. After stopping treatment the blood pressure returned to initial values within 1-4 months in 12/13 patients.

2. **Noradrenaline Kinetics in Man**
   (M. D. Esler, G. Jackman, A. Bobik, P. Leonard, H. Skews, G. L. Jennings and P. I. Korner)

We have developed tracer techniques, using radio-labelled noradrenaline to measure noradrenaline kinetics in man including (i) noradrenaline 'spillover' rate, (ii) noradrenaline steady-state clearance, and (iii) the parameters of the disappearance curve of radioactive noradrenaline. In healthy subjects with normal blood pressure the noradrenaline 'spillover' rate into plasma is 0.3-0.9 μg/min and noradrenaline clearance is 1.5-4.0 l/min. Neuronal uptake of noradrenaline was assessed from the rapid component of the plasma noradrenaline disappearance curve. As expected, the half-time of the initial rapid removal phase was lengthened by drugs which block neuronal re-uptake (e.g. desipramine).

3. **Defective Neuronal Uptake of Noradrenaline in Some Patients with Essential Hypertension**
   (M. D. Esler, P. Leonard, G. Jackman, A. Bobik, D. Kelleher, H. Skews, G. L. Jennings and P. I. Korner)

The above methods were used to determine noradrenaline kinetics in 38 patients with essential hypertension and in 17 normal subjects. In 9 of 38 patients with essential hypertension (including 6 with mild hypertension) the initial component of the noradrenaline disappearance curve was abnormally slow suggesting a reduction of neuronal re-uptake of noradrenaline. In these patients the rate of noradrenaline 'spillover' into plasma was high. This defect in neuronal re-uptake of noradrenaline exposes the post-synaptic adrenergic receptors to high local noradrenaline concentrations and our work is now endeavouring to see whether in about 25% of patients with essential hypertension it is the underlying reason for their high blood pressure.



Paul Leonard and Dr. Murray Esler

4. **Noradrenaline Kinetics in Patients with Autonomic Insufficiency**
(M. D. Esler, G. Jackman, D. Kelleher, H. Skews, A. Bobik, G. L. Jennings and P. I. Korner)

Patients with failure of the autonomic nervous system fall into two groups:— (i) those with 'central' autonomic insufficiency where there is central nervous system disease and the peripheral sympathetic nerves are intact and (ii) those with 'peripheral' autonomic insufficiency where the function of the peripheral sympathetic nerves are abnormal but there is no sign of central nervous disease. In both groups the symptoms are similar and include dizziness on assuming the upright posture owing to poor reflex control of the circulation and blood pressure. Study of these patients has been helpful in validating the use of noradrenaline kinetics as indicators of sympathetic nervous function in man.

In patients with 'peripheral' autonomic insufficiency the noradrenaline 'spillover' rate was reduced to about 50% of that observed in normal subjects, noradrenaline clearance was slow and there was marked reduction in re-uptake rate of noradrenaline into sympathetic nerve terminals. In patients with 'central' autonomic insufficiency the noradrenaline 'spillover' rate was also low. However, clearance and noradrenaline re-uptake rate were both normal, since these patients have intact peripheral sympathetic nerves.

5. **Effect of 5,6-Dihydroxytryptamine on Blood Pressure, Heart Rate and Baroreceptor-Heart Rate Reflex Properties of the Rabbit**
(G. A. Head and P. I. Korner)

5,6-dihydroxytryptamine (5,6DHT) given intracisternally destroys serotonergic neurons. In this study 5,6-DHT or vehicle were given to conscious instrumented rabbits in which an indwelling catheter had been implanted in the cisterna magna. Aortic and vena caval perivascular balloons for altering blood pressure had also been inserted at a preliminary operation. Circulatory and reflex changes were studied before and over the first 5 hours after injection and again chronically at 7 and 14 days. The acute effects for the first few hours after injection consisted of a significant increase in mean arterial pressure (14.8 ± 2.1 mmHg). Both heart rate and blood pressure had returned to initial control values by day 14. The acute effects on the baroreceptor-heart rate reflex consisted of a significant reduction in heart period range (between upper and lower plateau levels of the sigmoid curve), a significant decrease in gain and an increase in median blood pressure. By day 14 the heart period range and gain had both increased, i.e. showed the opposite changes to the acute effects. Since the acute and chronic effects are in opposite directions this suggests that the acute changes result from increased release of transmitter whilst the chronic effects occur owing to destruction of specific neurons. Our results with 5,6-DHT and our previous findings with 6-OHDA on heart rate, heart period range and baroreflex gain suggest that noradrenergic and serotonergic neurons have antagonistic effects on these variables. However, stimulation of either neurons results in similar changes in resting blood pressure and median blood pressure (baroreflex) and preliminary findings of studying the acute effects of transmitter release from one group after destruction of the other suggests that the two groups are adjoining links in an important suprapontine pathway involved in the control of blood pressure. 5,6-DHT produced marked reduction in eating and drinking behaviour for 5-7 days after injection; by day 7 the animals had lost 14% of their body weight but by day 14 they had resumed normal eating and drinking began to gain weight. The effect of 5, 6-DHT was greater and more prolonged than that of 6-OHDA.

6. **Mechanism of Acute Hypertension and Bradycardia After Intracisternal 6-hydroxydopamine (6-OHDA)**
(G. A. Head and P. I. Korner)

Conscious rabbits were given intracisternal 6-OHDA; (600 μg/kg) through an indwelling cisterna magna catheter. This resulted in a rise in blood pressure averaging 31 mmHg and a fall in heart rate of 51 bpm. Pre-treatment with the alpha-receptor antagonist phentolamine given intracisternally 10 minutes before 6-OHDA abolished or greatly attenuated both the hypertension and the bradycardia. When phentolamine was given later, about 2.5 hours after 6-OHDA (i.e. at the height of the circulatory response), the fall in heart rate was again abolished but there was little change in blood pressure. The results after pre-treatment with phentolamine suggest that both the rise in blood pressure and bradycardia are mediated through 6-OHDA induced release of noradrenaline acting on central alpha-

adrenoceptors. The reason why only the bradycardia but not the rise in blood pressure is blocked by late intracisternal administration of phentolamine can best be explained by postulating that the two effects are mediated through distinctive noradrenergic pathways:— the terminals involved in the rise in blood pressure probably lie in the hypothalamus whilst those eliciting the slowing of the heart rate are probably located in the bulbo-spinal parts of the brain.

7. Role of Central Adrenoceptors on Thermoregulatory Autonomic Effector Activity
(W. Riedel, P. K. Dorward and P. I. Korner)

To investigate the involvement of central noradrenergic neuron systems in the control of response patterns in autonomic thermoregulation, rabbits were chronically implanted with hypothalamic thermodes, intracisternal cannulas and electrodes for recording renal (visceral) sympathetic activity. Ear skin temperature serving as an index for cutaneous vasoconstriction and core temperature were measured with thermistors. Respiratory rate was counted. Heart rate was obtained from the blood pressure recorded in an ear artery. Ambient temperature was controlled at 25°C. Injections at 20, 200 and 2000 ng noradrenaline intracisternally had no effect on blood pressure, produced a dose-dependent suppression of renal sympathetic nerve activity with peak depressions of 20, 26 and 32%, occurring at 8, 16 and 32 minutes after the injection. Respiratory rate, heart rate and ear skin temperature decreased with a similar time course. Core temperature rose maximally by 0.3°C within 30 minutes. 100 μl saline intracisternally produced no effect on any parameter. On the next day the hypothalamic thermode was randomly perfused for 10 minutes with water of 34, 36, 43 and 45°C (thermode temperature). Beginning with thermode temperature 34°C, respiratory rate, renal sympathetic activity and ear skin temperature increased with rising hypothalamic temperature, this exhibiting the typical autonomic thermoregulatory response pattern, and core temperature changed in the opposite direction. Injection of 200 ng noradrenaline interacisternally caused a parallel shift of the temperature-response curves of respiratory rate, renal sympathetic activity and ear skin temperature to lower values. In contrast, they were found to be shifted in a parallel manner to values above control 24 hours after injection of 600 μg/kg 6-hydroxydopamine. These shifts suggest that central noradrenergic neurons are involved in determining the thermoregulatory set-point in such a way that their activation increases and their abolition decreases body temperature.

8. Effect of Althesin, Ketamine and Thiopentone on Systemic Haemodynamics and Baroreceptor-Heart Rate Reflex Properties
(D. W. Blake and P. I. Korner)

The study was performed in rabbits with previously implanted Doppler flowmeters for measuring cardiac output and with balloons placed around the thoracic aorta and inferior vena cava for raising and lowering blood pressure. Resting circulatory changes and changes in baroreceptor-heart rate reflex properties were studied in each animal on four occasions, with 2-3 days between experiments. Each experiment consisted of control observations with the animal conscious, followed by a period with one of the following treatments:— thiopentone, althesin, ketamine or dextrose, the last serving to assess time-related effect. The anaesthetics were given by intravenous infusions for one hour to produce similar levels of light anaesthesia. With all anaesthetics there was a sustained rise in heart rate and cardiac output. With ketamine and thiopentone mean arterial pressure and total peripheral resistance increased but these did not alter with althesin.

The steady-state properties of the baroreceptor-heart rate reflex were studied by deriving sigmoid mean arterial pressure — heart period curves and determining the usual three parameters:— the heart period range between upper and lower plateau levels; median blood pressure and average gain. Ketamine and thiopentone lowered heart period range and gain by about 70% of control and increased median blood pressure significantly. After althesin given in a dose which produced the same depth of anaesthesia heart period range and gain fell significantly less and median blood pressure did not alter. None of the parameters of the sympathetic component of the baroreflex (estimated after giving methscopolamine) were significantly altered by althesin; with ketamine and thiopentone the threshold for eliciting bradycardia increased and in addition ketamine depressed the heart period range and gain. The differential effects of

the three anaesthetics suggested that they acted on different sites of the baroreflex arc. This would explain the different circulatory effects which each produces and we are currently testing this hypothesis.

9. Effects of Renal Vascular Tone on the Severity of Renal Artery Stenosis Including the Effects of Anaesthesia
(W. P. Anderson and P. I. Korner)

We had previously shown that the effective resistance to blood flow exerted by a fixed renal artery stenosis was not constant, but varied in inverse relation to the distal renal vascular resistance. Thus renal vasoconstriction (mediated by angiotensin II) sufficiently minimized the resistance of renal artery stenosis as to prevent development of chronic hypertension, even if the stenosis had initially produced a 50 mmHg or greater pressure gradient. Our work seemed at variance with other workers in the field, who have reported hypertension resulting from more modest stenosis pressure gradients. Unlike our experiments in trained, conscious, quietly recumbent dogs, most other workers have produced renal artery stenosis in anaesthetised animals in which renal vascular resistance may be high. We therefore undertook a series of experiments to determine the relationship between the state of distal vascular tone during production of a stenosis and the subsequent blood pressure, renal haemodynamic and renin angiotensin system responses.

In one group of conscious, chronically instrumented dogs, the vascular tone of the kidney was altered by brief (2-3 minutes) infusions of acetylcholine, methoxamine, angiotensin II or normal saline into the renal artery. During this period, the renal artery was narrowed to reduce distal pressure to 40 mmHg, the renal artery cuff or snare was then changed to maintain stenosis for 1 hour. The subsequent blood pressure and renin responses were markedly influenced by the vascular tone at the time of stenosis. Following stenosis in the dogs infused with acetylcholine, distal renal artery pressure was promptly restored towards pre-stenosis values and there were only small and transient rises in arterial pressure and plasma renin activity. In contrast, following renal artery stenosis in dogs infused with angiotensin or methoxamine, there were large, sustained rises in arterial blood pressure and renin, and well-maintained gradients across the stenosis.

The values of the effective stenosis resistance achieved occurring during initial production of the stenosis and at 1 hour after stenosis were also consistent with the hypothesis that greater reduction in vessel diameter was needed to reduce distal pressure to a given value in the vasoconstricted kidney compared to the vasodilated kidney.

In a second group of dogs a 50 mmHg pressure gradient across a renal artery stenosis was created on two occasions; with the animal conscious and with it anaesthetised with pentobarbitone and prepared for surgery. One day later, the conscious dogs had no hypertension and renin levels were normal; the dogs that had been anaesthetised for stenosis production all had significant elevations in arterial pressure and renin, and greatly reduced creatinine clearance.

Thus, the pressure gradient across a stenosis is not a reliable indicator of the severity of a renal artery stenosis. The severity depends critically on the vascular tone of the kidney.

10. Prostaglandins in Mild and Severe Renal Artery Stenosis
(W. P. Anderson)

It is claimed that prostaglandins have several roles in the kidney, including modulation of the renal vascular resistance response to ischaemia and vasoconstrictor agents and the stimulation of renin release from the kidney. However, almost all the experiments supporting these hypotheses have been performed *in vitro* or on anaesthetized animals. There are several reports showing that some effects attributed to prostaglandins in anaesthetised animals are absent in conscious animals. To resolve these conflicting findings the effects of renal artery stenosis have been studied in chronically instrumented conscious dogs, with and without pre-treatment with cyclo-oxygenase inhibitors indomethacin or aspirin. Two degrees of stenosis severity have been used: (1) 'mild' stenosis in which the renal artery is narrowed to reduce distal pressure to 60 mmHg and then pressure maintained at or about this level for the next 90 minutes (within the 'autoregulatory' range of the kidney); (2) 'severe' stenosis in which renal blood flow is reduced and maintained at less than 20% of resting, pre-stenosis values.

Preliminary results indicate very little difference in the haemodynamic responses

to normal and cyclo-oxygenase blocked dogs, at either level of stenosis. Plasma prostaglandin levels are currently being measured by Professor G. Thorburn, Universtity of Queensland.

11. Effects of Captopril on Urinary Kallikrein and Kinin Excretion
(B. H. Clappison, W. P. Anderson, C. I. Johnston and P. Bartley)

Converting enzyme inhibition prevents both the formation of angiotensin II and the destruction of bradykinin. Captopril, the new orally active converting inhibitor, causes a significant reduction in blood pressure in human hypertensives, but lack of correlation of the fall of blood pressure has led to suggestions that the fall may be due to increased bradykinin levels. Significant increases in circulating blood levels of bradykinin have not been demonstrated but it is still possible that bradykinin may be a local regulator of blood flow. We have therefore measured the urinary excretion rate of kinins, as a possible indication of change in local renal production after captopril administration.

The studies were carried out in pentobarbitone anaesthetised dogs in which a renal artery electromagnetic flowmeter was used to measure blood flow, a renal vein catheter and ureteric catheter, and an aortic cathetor were also inserted. Glomerular filtration rate was measured by tritiated inulin clearance. Urine and arterial and renal venous blood samples were collected into inhibitors of kinin degradation before and after captopril (1.5 mg/kg, a dose sufficient to produce a 20 fold shift to the right in the blood pressure response to angiotensin I).

We found that urinary kinin excretion increased significantly after captopril while kallikrein excretion did not change. This strongly suggests that the local degradation of kinins in the kidney was inhibited by captopril. There were no changes in either arterial or renal venous kinin concentrations. Captopril lowered blood pressure, and increased renal blood flow with no change in glomerular filtration rate. We are currently doing additional experiments to differentiate which renal effects after captopril are due to block of angiotensin II formation or to block of

Left to right: Steve Selig, Dr. Warwick Anderson, David Harrison, Peter Bartley and Matthew Le Duc.

bradykinin degradation. These results suggest that captopril inhibits kinin degradation in the kidney.

12. Role of the Autonomic Nervous System in the Acute Responses to Renal Artery Stenosis in Conscious Dogs
(W. P. Anderson and M. Le Duc)

It is known that direct or reflex stimulation of the renal nerves causes release of renin from the kidney, and there have also been claims that renal innervation is necessary for the release of renin by other stimuli. We have investigated the role of sympathetic nerves in renal stenosis stimulated renin release, comparing the responses in normal dogs with intact autonomic function to the responses in dogs with 'complete' surgical and pharmacological block of efferent autonomic effectors.

Renal artery pressure was reduced to 60 mmHg and 30 mmHg in conscious dogs and held at this level for 1 hour. Much greater rises in plasma renin activity were seen in autonomically blocked dogs than in normal dogs at 60 mmHg (mean values 3.28 vs 1.90 ng/ml/hr respectively) and at 30 mmHg (19.1 vs 3.65 ng/ml/hr respectively). Arterial blood pressure also rose more in the autonomically blocked dogs in accord with the greater rises in renin. The relationship between the increases in arterial pressure and plasma renin were closely similar in the two groups.

The results suggest that the release of renin and increase in arterial blood pressure in response to renal artery stenosis is normally inhibited by arterial baroreflexes.

13. Noradrenaline and the Kidney
(S. E. Selig and W. P. Anderson)

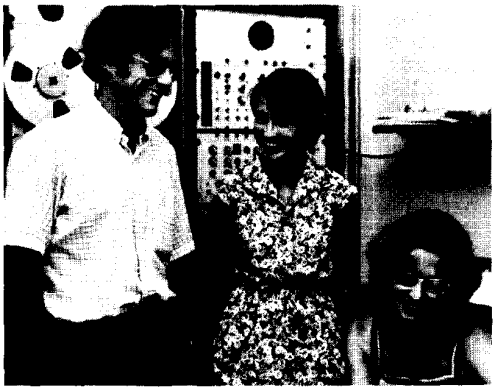
Many investigators over the last 50 years have shown that infusions of adrenaline and noradrenaline tend to increase the fraction of plasma filtered at the glomerulus of the kidney. This effect has usually been attributed to a direct vasoconstriction of the efferent arterioles of the kidney. More recently it has been shown that noradrenaline stimulates renin release from the kidney and thus angiotensin II formation. Since angiotensin II is known to act on the efferent arteriole, we hypothesised that the effect of noradrenaline on the kidney could be partially mediated by angiotensin II.

Noradrenaline was infused intrarenally and intravenously into conscious dogs with and without pre-treatment with teprotide, an inhibitor or converting enzyme to block the formation of angiotensin II. Infused into the renal artery, noradrenaline produced a dose-related rises in renin, angiotensin II and arterial blood pressure, which were all abolished by teprotide pre-treatment (Fig). Teprotide also abolished the rise in glomerular filtration rate. Surprisingly noradrenaline infused into the renal artery also resulted in a significant rise in renal blood flow which was still present after teprotide. Glomerular filtration rate was again elevated by noradrenaline, with the rise attenuated or abolished by teprotide (depending on the noradrenaline dose). Renal blood flow rose 30-40% following noradrenaline infusion intravenously. This vasodilation was not blocked by teprotide propranolol, or indomethacin. However after pentolinium pre-treatment, noradrenaline caused renal vasoconstriction at the same doses.

Thus, the effects of blood-borne noradrenaline on the kidney are the integrated result of direct effects and secondary effects through angiotensin II and through buffer reflex inhibition of renal sympathetic nerve activity.

14. Properties of Renal Baroreflex in Conscious Rabbits
(Patricia Dorward, Sandra Burke, M.C. Andresen, P. I. Korner)

Many of the technical problems associated with recording renal sympathetic nerve activity in the conscious animal have now been overcome and this can now be done reliably in most animals for periods of several days or longer. In the conscious animal the renal baroreflex gain is two to four times that previously observ-



Dr.Michael Andresen with Sandra Burke and Dr. Pat Dorward (seated).

ed in rabbit subjected to sodium pentobarbitone anaesthesia. Work currently in progress is examining the effect vasodilator agent on the properties of the renal baroreflex and the aortic baroreceptor discharge.

15. Effect of Vasodilator Agents on the Baroreceptor-Heart Rate Reflex
(P. I. Korner, Judith Oliver, Patricia Dorward, M. Andresen, and Sandra Burke)

Vasodilator drugs lower blood pressure but to our surprise produced a considerable amount of 'resetting' of the properties of the baroreceptor-heart rate reflex. The function curve which relates mean arterial pressure to heart period is normally sigmoid and is characterized by the heart period range, median blood pressure and average gain. We administered graded doses of nitroprusside intravenously and derived serial function curves after 30 minutes infusion at each dose. There was a significant dose-related shift to the left in the curve, so that the threshold for eliciting bradycardia became progressively reduced as dose of vasodilator increased. At the two lower doses (2.5 and 5 μg/kg/min) gain was little and variably affected but at the highest dose (10 μg/kg/min) it was significantly reduced by about 30-50% control, this reduction in gain was related to the nitroprusside mediated release of angiotensin II. Nitroprusside was not the only vasodilator drug that altered baroreflex properties. Similar shifts in the baroreflex curves were also obtained with intravenously administered glyceryl trinitrate and with hydralazine.

The question arises whether the shift in baroreflex curves is due to changes in the properties of the arterial baroreceptors themselves (e.g. due to drug induced dilatation of the large arteries) or whether it occurs owing to any central nervous effects of the drugs. Accordingly we are currently studying the changes in aortic arterial baroreceptor discharge in anaesthetised animals. Preliminary studies suggest that a large proportion of the shift in baroreflex curves may be due to effects of the drugs on the arterial baroreceptors themselves.

16. Assessment of Ventricular Performance by Means of Isovolumic Indices
(A. Broughton and P. I. Korner)

Work has continued in anaesthetised dogs to determine under what conditions isovolumic indices (dP/dt) max, (dP/dt) at developed pressure 40 mmHg and (dP/dt/TP) max could be used to assess changes in inotropic state. It turns out that the last index is extremely sensitive to changes in preload, whilst the other two become relatively independent of this variable at left arterial pressures > 12 mmHg. On the other hand even under resting conditions (dP/dt) max falls at aortic diastolic pressures below 70 mmHg due to premature opening of the aortic valve. These results suggest that in man or the intact animals the loading conditions are such that it will be extremely difficult to utilize the indices where changes in contractility can be validly expressed.

Dr. Archer Broughton and Anne Heal

We have also produced graded noradrenaline dose-response curves in this preparation using optimum loading conditions. It turns out that (dP/dt) max increased to 600-700% of resting, whilst the other two indices (which occur during earlier phases of systole) only increase to about 200% of systole. The dose-response curves for all indices was sigmoid with a maximum effect attained to doses of noradrenaline > 4 ug/kg/min when dose-response curves were pro-

duced with isoprenaline. (dP/dt) max increased to only about 300% of resting since isoprenaline also evoked a fall in blood pressure. When this was prevented the index was restored to its 'true' maximum. With very high inotropic stimuli premature opening of the aortic valve occurs at aortic diastolic pressure well above the 'physiological' range, i.e. at < 120 mmHg.

Our results suggest that (dP/dt) max can yield results similar to those obtained in isolated papillary muscle stips studied under isometric conditions. The other indices probably occur too early in systole for 'active contractile state' to have fully developed. However, the conditions obtainable in the controlled dog preparation for studying changes in inotropic effects using isovolumic indices are unobtainable in man under conditions such as maximum exercise. Despite all the work done in this area by many investigators our study has clearly shown that these indices can only be utilized under special conditions in animal experiments.

Work has proceeded well on evaluating the effects of myocardial hypertrophy on the catecholamine dose-response curve. This work has been performed by comparing initial weight matched hypertensive and normotensive dogs. Hypertension was induced using renal artery stenosis after removing the contralateral kidney, and maintaining hypertension for a period of 2 months. In these animals the slope of the stimulus-response was significantly steeper than in normotensive and the plateau reached about 30% higher. This effect is very similar to the increased senstivity and maximum constrictor effect obtained in vascular smooth muscle of hypertensive animals. It can be regarded as a direct structural 'amplification' effect of myocardial hypertrophy. It is important since a given level of, say, sympathoadrenal stimulation will produce greater contractile effects and make greater demands on the myocardial oxygen reserves of the hypertrophied compared with the normal heart.

17. Effect of Adrenergic Influences on the Properties of Cardiac Beta Receptors and the Adenylate Cyclase System
(A. Bobik, P. I. Korner, Valerie Carson and Julie Campbell)

During the development of congestive heart failure from long standing hypertension, the myocardium is exposed to large alterations (both increases and decreases) in cardiac sympathetic activity. Our experiments were designed to examine the properties of myocardial beta receptors and the adenylate cyclase system during alterations in sympathetic activity. We examined the effects of short and prolonged activation of beta-receptors by varying concentrations of isoprenaline on beta-receptor numbers, intracellular 3,5-cyclic AMP levels, adenylate cyclase and phosphodiesterase activity of chick embryo myocardial cells in primary tissue culture. We also extended these experiments *in vivo* by examining the effects of three levels of chronic sympathetic activity on left ventricular beta-receptor density and adenylate cyclase activity of normotensive and renal hypertensive rabbits.

Myocardial cells in primary tissue culture when exposed to isoprenaline (50 μM) increase intracellular 3,5-cyclic AMP levels by 310% within 5 minutes. During prolonged (16 hours) exposure of cells to varying concentrations of isoprenaline (10^{-7} M to 10^{-4} M) maximum beta-receptor responsiveness was inversely related to the concentration of agonist in the culture medium. On removal of the agonist the response returned to control by 24 hours. Beta-receptors in the 30,000 xg particulate fraction of these cells altered in parallel with the receptor response. Phosphodiesterase activity in homogenate preparations was unaltered. In order to more fully understand the mechanisms by which changes in beta-receptor responsiveness occurred we examined the time course of changes in 3, 5-cyclic AMP concentration during exposure to 50 μM isoprenaline. After 20 minutes exposure to isoprenaline the beta-receptor mediated increase in 3, 5-cyclic AMP levels was greatly impaired (< 10% control cells). Studies on beta-receptors and adenylate cyclase in 30,000 g. particulate fraction and phosphodiesterase activity of these cells suggest that this loss in beta-receptor mediated response was due to regulation of adenylate cyclase activation by beta-receptors at a site between the receptor and adenylate clyclase. Beta-receptor density, fluoride activiated adenylate clyclase and phosphodiesterase were unaltered at this time. These results suggest that cardiac beta-receptors and the beta-receptor related to the degree of receptor occupancy by beta-receptor agonists. The initial regulatory site appears to be at a coupling unit between the receptor and adenylate cyclase.

In another series of experiments we examined in the hearts of normotensive and renal hypertensive rabbits the effects of three levels of chronic sympathetic activity: (i) normal activity, (ii) reduced activity after 2 weeks treatment with guanethidine and (iii) 2 weeks increased activity following sino-aortic denervation (SAD) on beta-receptor density per mg left ventricular sarcolemmal protein and total beta-receptor number per left ventricle. Adenylate cyclase activity, including basal activity plus changes due to stimulation with isoprenaline and fluoride were also examined. In normotensive rabbits guanethidine treatment increased beta-receptor density and total left ventricular receptor number and caused an approximately parallel rise in basal and isoprenaline stimulated activity. After sino-aortic denervation all the above variables and left ventricular catecholamines were closely similar to those of autonomically intact rabbits. In renal hypertensive rabbits (autonomically intact and sino-aortic denervated subgroups) beta-receptor density was 36% lower than in normotensives, but receptor number per left ventricle was not different. After guanethidine neither receptor density or number increased in the hypertensive rabbits, contrasting with the response of normotensives. Autonomically intact hypertensive rabbits had an increased basal adenylate cyclase activity per left ventricular compared to normotensive whilst receptor number and response to isoprenaline were unaltered. This increase in basal enzyme activity could be a compensatory response to maintain adequate 3,5-cyclic AMP levels in the hypertrophied left ventricular. Chronic sympathetic stimulation in sino-aortic denervated hypertensive animals tended to lower left ventricular adenylate cyclase activity and reduced catecholamines to 38% of the value of autonomically intact hypertensive rabbits.

The results from this study suggest that the chronic hypertensive heart has lost the capacity of the normal heart to increase beta-receptors during low levels of sympathetic normal activity. Alterations in beta-receptor density occur in parallel with the degree of activation of adenylate cyclase by beta-receptor activation. During the increase in cardiac sympathetic activity from sino-aortic denervation, left ventricular sarcolemmal adenylate cyclase enzyme activity becomes impaired in hypertensive animals.

18. Effect of Anti-hypertensive Treatment on Baroreflex Properties
(D. W. Blake and P. I. Korner)

Rabbits were studied before and several times after bilateral renal cellophane wrapping (n = 12) or sham-operation. On each occasion we measured mean arterial pressure and studied the properties of the vagal component of the baroreceptor-heart rate reflex. All rabbits were studied before treatment, and 4-6 weeks after operation without treatment; at that point hypertension had become established at a stable level of blood pressure; then followed a 2 week period on treatment and a 2 week period off treatment using a cross-over experimental design, with reflex properties studied at the end of each period. Treatment consisted on timolol (8 $mgkg^{-1}$ twice daily) and frusemide (2 $mgkg^{-1}$/day) given intramuscularly. With this combination blood pressure fell from 140 mmHg before treatment to 105 mmHg.

Before treatment the heart period range and gain of the vagal component of the baroreceptor-heart rate reflex, was in agreement with previous studies. After treatment both parameters were partly, but not completely, restored. The incomplete restoration may have been due to the relatively short duration of treatment. The findings indicate that a substantial component of the reflex changes can be restored by reduction of blood pressure.

19. Salt and Haemodynamics of Hypertension
(P. I. Korner, Judith Oliver and D. Casley)

We studied the effects of altering the salt intake on the haemodynamics of established cellophane wrap hypertension and after sham-operation. The animals were maintained on normal salt for the first 6 weeks after renal wrapping or sham operation and they were then subjected to three experimental periods, each of 2 weeks duration. Haemodynamic observations were made with the animals on low, normal and high salt intake (about 1, 9, 50 mmol of sodium/100 g food). In the sham operated group this range of dietary salt produced no significant circulatory effects or alterations in blood volume. However, in the cellophane wrap hypertensive animals blood pressure was significantly reduced on low dietary salt intake compared with values under normal and high salt diet (122 v. 132 and 136 mmHg). Changing dietary salt from 1/9 to 6 times normal thus altered blood pressure through a range of about

25% of the original rise in blood pressure on normal dietary salt intake.

The reduction in blood pressure on low salt was entirely due to a lowering of cardiac output which was largely determined by a reduction in blood volume. On normal and high salt diets cardiac output of the rabbit was higher than in sham operated animals. In the wrapped animals total peripheral resistance was unaffected by dietary salt. Therefore lowering cardiac output through lowering 'volume' produced long term reduction of blood pressure for a 2 week period without altering TPR; raising blood volume with high salt was also without effect on vascular resistance. These results indicate that blood pressure can be altered over prolonged periods by changes in cardiac output. These results are important theoretically since they are not in accord with the currently popular 'autoregulation' theory of hypertension. These results taken with previous experimental observations we have made, suggest that disturbances in 'volume' and 'constrictor' mechanisms can each exert distinctive long term effects on blood pressure. Hence the search for different determinants of each haemodynamic abnormality is likely to prove of value in the search for the causes of hypertension.

20. Effects of Changes in Dietary Salt Intake on the Baroreceptor-Heart Rate Reflex in Normal and Hypertensive Rabbits

(P. I. Korner, Judith Oliver and M. Fahim)

The baroreceptor-heart rate reflex was studied in conscious, instrumented rabbits, in which perivascular balloons had been previously implanted to allow raising and lowering of blood pressure. Sigmoid mean arterial pressure-heart period curves were derived in each animal and characterised in the usual way by the heart period range, gain, median blood pressure. The protocol was the same as in the previous project with the animals 2 weeks each on low salt, normal salt and high salt diets. On each occasion the reflex properties in a given rabbit were studied before and after administration of either saralasin (a competitive angiotensin II antagonist) or captopril (converting enzyme inhibitor); both drugs exerted similar effects when tested in normotensive rabbits.

In the normal rabbits the baroreceptor-heart rate reflex properties were all the same on each level of salt before administration of either saralasin or captopril. However, after blocking the effects of angiotension II the heart period range and gain both increased and the median blood pressure fell on the low salt diet; none of the parameters altered on the other diets. Infusing angiotensin II produced the opposite changes, i.e. falls in heart period range and gain and an increase in median blood pressure. The effects of captopril and saralasin on the reflex sensitivity were entirely due to their role in removing the physiological effects of endogenous angiotensin II. The study shows that 'physiological' alterations in plasma angiotensin II can influence baroreceptor-heart rate reflex properties in normal animals. We have not yet analysed whether the above actions of angiotensin II affect the baroreceptor-heart rate reflex properties through its peripheral or through its central nervous action.

In the hypertensive rabbits the situation was more complicated because of the alterations in blood volume and heart chamber size which were induced by the different diets. In these rabbits the effect of low salt diet together with angiotensin II blockade increased the previously depressed gain of the baroreflex to almost the same levels observed in normal rabbits.

CARDIOVASCULAR METABOLISM AND NUTRITION RESEARCH UNIT

Major Research Interests

* LIPOPROTEIN METABOLISM
* CHOLESTEROL METABOLISM
* NUTRITIONAL CONTROL OF GLUCOSE HOMEOSTASIS
* OBESITY — METABOLIC DERANGEMENTS
* DIETARY AND DRUG MANAGEMENT OF HYPERLIPIDAEMIA AND OBESITY
* EPIDEMIOLOGY OF DIABETES IN ABORIGINES
* DETECTION OF CORONARY RISK FACTORS

General Summary

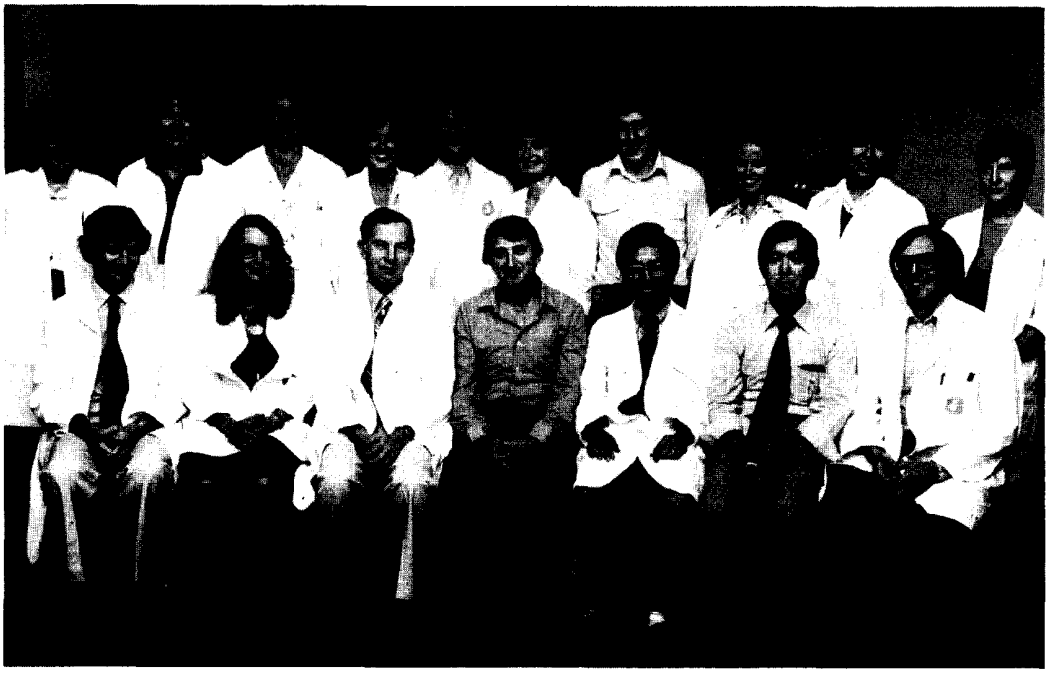
At the end of the year the Unit comprised three senior research scientists, Dr. Nestel, Dr. Fidge and Dr. O'Dea, three post-doctoral fellows, Dr. Billington, Dr. Huff (Canada) and Dr. Tada (Japan), three graduate research assistants (Mrs. Everitt, Miss O'Connor and Ms. Ma), a dietitian (Mrs. Promeroy), technical staff (Mr. Edelsbacher, Mrs. Paynter, Miss Mensen and Mr. Faulkiner) and a secretary (Mrs. Cannon). Two graduate scholars obtained their B.Sc. Honours (Mr. G. Harrison, 1st class and Miss P. Snow, 2A).

Andrea Everitt (formerly Poyser) left the Unit and will be missed after her long association with the group in Melbourne and Canberra.

Penny Snow who completed a successful year as a Biochemistry honours student working on factors influencing rates of starch hydrolysis in vitro and in vivo, will continue on in 1980 as a research assistant. Lynne Antonoff, who left in August, is greatly missed both for her excellent laboratory work and her friendly disposition.

A. Lipoprotein Metabolism

The major emphasis in our basic research is the study of the protein moieties of the lipoproteins. Each of the four major lipoprotein classes carries its specific complement of proteins, the functions of which relate to the secretion, trans-



Standing (left to right): Geoff Bazelmans, Sandra Mensen, Greg Collier, Angela Ward, Steven Rockman, Penny Snow, Hubert Edelsbacher, Margaret O'Connor, Jane Ma, Robyn Paynter. Seated: Dr. Timothy Billington, Dr. Kerin O'Dea, Dr. Paul Nestel, Dr. Noel Fidge, Dr. Norio Tada, Dr. Naoki Suzuki and Dr. Murray Huff.

port and catabolism of these large lipid-carrying macromolecules. As yet, only a few of these proteins have been shown to have unique functions and the absence or deficiency of several are known to result in abnormal lipoprotein transport. Of particular interest is the likelihood that some forms of hyperlipidaemia, and atherosclerosis itself, might be due to abnormal concentrations of one or more of these proteins or to an abnormal interaction of the proteins with components of the arterial wall. This may be related to the recognition of these proteins by specific receptor sites on cell membranes; the dysfunction of one such receptor is the cause of genetic hypercholesterolaemia.

We have approached the problem from several angles:

1. Quantification of several key proteins has been achieved by development of electroimmunoassays.
2. The metabolism of the proteins is being studied at the cellular level: in intestinal and liver cells and skin fibroblasts.
3. The transport kinetics (the rates of secretion and removal, and the pools of distribution) are being determined in humans and experimental animals, by reinjecting lipoproteins radiolabelled in the protein moiety.
4. The metabolism of the lipoprotein proteins is being compared in subjects with normal and abnormal lipids and the effects of intervening through diet and drugs are being assessed.
5. The interactions between the metabolism of the proteins and that of the lipoprotein lipids are being studied, especially in relation to the control of cholesterol production and removal.
6. Lipoprotein protein metabolism in obese subjects is being related to disturbances in glucose and insulin which may be responsible for the hyperlipidaemia of obesity.

B. The Heart Risk Evaluation Clinic

This service was set up in collaboration with the Victorian Division of the National Heart Foundation (plus support from I.C.I. Australia) to provide a simple and quick means for healthy individuals to have their blood lipids, blood pressure and weight checked. Two thousand subjects were seen during the year including large groups from special industries (such as the waterfront) and government clerical employees. The proportion of middle-aged individuals requiring treatment for hyperlipidaemia (25%) and for hypertension (15%) remains high.

Sylvia Pomeroy, Dietitian

It is important to know whether the high prevalence of risk factors reflects the true incidence in the community and furthermore, whether the incidence is changing. The steady decline in the mortality from coronary heart disease might partly stem from widespread reduction in risk factors. The clinic will therefore be utilized to answer this question by measuring risk factors and assessing dietary habits in randomly selected populations at 3-yearly intervals.

C. Studies on Obesity and Diabetes

General Summary

Obesity and maturity-onset diabetes (MOD) are among the first diseases to appear with economic development. For this reason they are often referred to as "diseases of affluence". In the case of diabetes, and to a lesser extent for obesity, genetic factors appear to be important in determining which individuals have the potential for developing the condition. However, it must be emphasized that environmental factors play a key role in actually precipitating obesity or diabetes.

In approaching these questions we have attempted to define, firstly, the metabolic characteristics which may identify people who are susceptible to diabetes and/or obesity, and secondly, the particular aspects of our western lifestyle (such as diet and lack of exercise) which could act as environmental triggers.

The incidence of diabetes among urban or fringe-dwelling Aborigines is much higher than in the Australian population as a whole. We have been fortunate to be able to collaborate with Dr. R. M. Spargo of Community Health Services in Derby, W.A. in carrying out a number of studies (detailed below) on Aborigines under a variety of environmental conditions. This work is helping us elucidate the reasons (genetic and/or environmental) for the high prevalence of diabetes among these people and to gain further insight into the underlying mechanisms of diabetes generally. Such knowledge is essential before soundly-based preventive procedures can be instituted.

Other studies carried out in this research program are concentrating on particular environmental factors which may act as triggers, precipitating diabetes and/or obesity in susceptible individuals. Two aspects of western lifestyle which are being studied in this context are exercise and refined carbohydrate (see below).

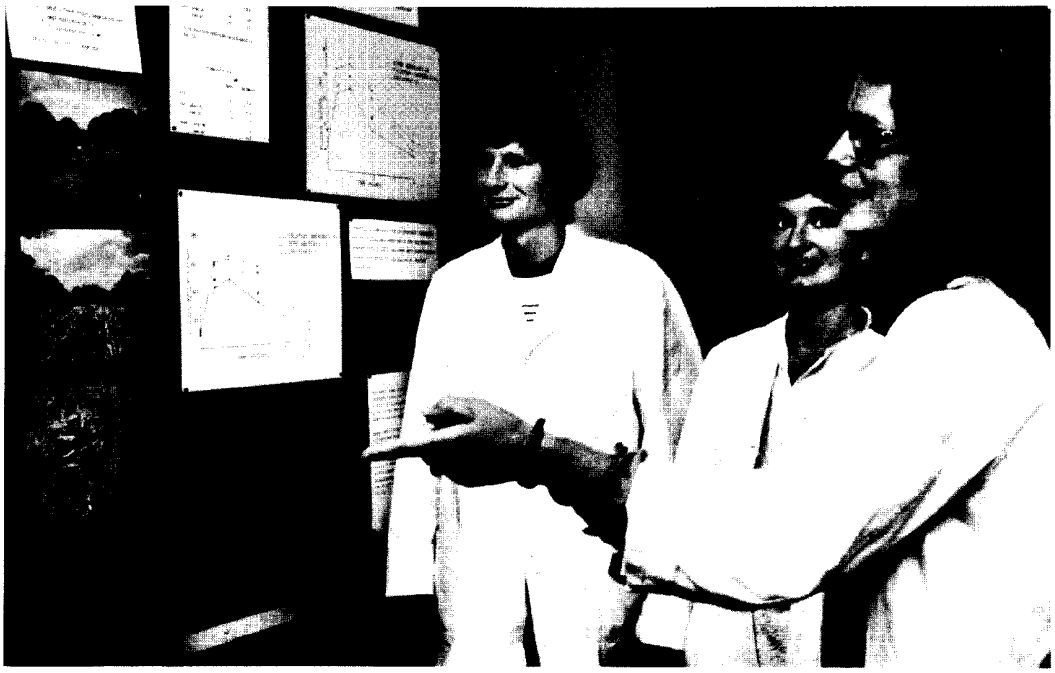
In addition we are beginning a study of the sympathetic nervous system activity in obesity in collaboration with Dr. Murray Esler. Is a person more prone to develop obesity because of a lower than normal sympathetic nervous system activity (SNA) in the presence of excess food intake? Are any differences in SNA between obese and lean groups the cause or the consequence of obesity?

Scientific Projects

A. Urbanisation and diabetes among Australian Aborigines

K. O'Dea and R. M. Spargo, CHS, Derby, W.A.

The incidence of diabetes in the Australian population is about 2%. Among urban or fringe dwelling Aborigines, however, diabetes is much more widespread. A recent survey in the West Kimberleys, for example, revealed that 15-20% of Aborigines over 20 years of age have diabetes. These people were drawn from communities with generally poor diet and nutritional status and high alcohol consumption. In 1979 we conducted a



Dr. Kerin O'Dea (right) explaining the Nutrition Education Programme for Aborigines to David Faulkner and Penny Snow.

diabetes survey on a small, isolated mission community in the same general geographical region. This latter community had no direct access to alcohol; fresh fruit, vegetables and meat were available on a daily basis. Seventy people over the age of 15 were surveyed. No-one under 54 had diabetes and the overall prevalence rate for the community was less than 6%. More detailed metabolic studies were conducted on two groups of men aged between 15 and 35 from these two quite different communities. Essentially identical insulin secretory responses to oral glucose were measured in the two Aboriginal groups. However, these insulin responses were significantly higher than those for age and weight matched caucasians. These results appear to support the suggestion that the metabolic abnormality ("initial lesion") preceding diabetes is an unusually high insulin response to glucose i.e. that this is the "genetic factor" which renders an individual susceptible to diabetes. Whether or not such people develop diabetes, however, will depend upon the environment (i.e. diet, physical activity etc.) of the particular community.

These results provide a strong rationale for preventive measures in the form of a nutrition education program. We are basing such a program on the positive aspects of traditional life — both from the point of view of diet and level of physical activity. Future studies will concentrate on the unusually high insulin secretion. Both insulin and GIP (gastric inhibitory polypeptide) responses to protein and fat (as well as glucose) will be measured to see if the high insulin response is mediated via this gastrointestinal factor. Without the cooperation, help and friendship of the people at Kalumburu Mission, W.A., Community Health Services, Derby, W.A. and the Mowanjum Community, Derby, W.A. these studies could never have been carried out.

B. Exercise and Obesity

K. O'Dea, G. Jennings, P. Nestel

(a) Acute heavy exercise

An exhausting bout of exercise (1 hour on a bicycle at 70% maximum work level) appeared to have different effects in obese and normal weight individuals as determined by the insulin secretory response to intravenous glucose one day before the exercise, compared with the response one day after. Insulin sensitivity tended to increase after exercise in normal weight individuals but was unchanged in obese people.

(b) Long term physical training

The effects of a long term exercise program lasting three months and resulting in a 50% increase in maximum oxygen consumption were quite different. Those people with an initially high insulin response to oral glucose showed consistent reductions in insulin secretion and improved glucose tolerance after the training program. However, those individuals who had low insulin secretion initially showed no change (or an increase) in insulin response to oral glucose after the training program and no change in glucose tolerance. The three month training program also resulted in consistent reductions in plasma triglycerides, but no change in total plasma cholesterol or HDL cholesterol. Body weights were maintained at a constant level throughout the study so that any effects of the exercise program could not be attributable to weight loss.

These studies are continuing.

C. Metabolic responses to refined and unrefined carbohydrate

K. O'Dea, P. Snow, P. Nestel

Previous studies have established that the glucose and insulin responses to orally ingested starches vary widely according to the source and form of the starch. For example, rice elicits much smaller glucose and insulin responses postprandially than does the same amount of starch given as potato. Ground rice results in much higher glucose and insulin responses postprandially than whole rice. Starch has to be broken down to its individual glucose units before it can be absorbed into the bloodstream. We have set up a simple in vitro method which can be used to predict the metabolic responses to complex carbohydrate in vivo. Those starches which are hydrolysed to glucose most rapidly in the test tube when incubated with pancreatic hydrolytic enzymes are those which elicit the highest glucose and insulin responses when they are eaten as a test meal. This suggests that the rate of hydrolysis of starch in the gut is a major factor in determining the metabolic responses to dietray carbohydrate. Refined carbohydrate tends to

be digested and absorbed much more rapidly than unrefined carbohydrate. One of the major signals for insulin secretion is the **rate of change** of blood glucose. Thus, rapidly absorbed carbohydrate (i.e. refined) stimulates a much greater insulin secretion than slowly absorbed (i.e. unrefined) carbohydrate. This principle should prove to be very useful in designing diets for the treatment of diabetes.

Future work in this are will include:

(i) Measurement of oxygen consumption during the starch tolerance test to see if the quite different postprandial insulin and glucose responses obtained, for example, between ground and unground rice are associated with changes in oxygen consumption.

(ii) Measurement of the gastrointestinal polypeptide GIP in response to rapidly and slowly absorbed starch loads.

(iii) GIP and insulin responses to carbohydrate alone, carbohydrate and fat, protein, and protein and fat. The inactive isomer of propranolol will be given with each meal and used to monitor changes in splanchnic and liver blood flow. These studies will be done in collaboration with Dr. A. McLean.

SCIENTIFIC PROJECTS

D. Lipoprotein and Cholesterol Research

(a) Apoprotein-C Metabolism in Man

M. Huff, N. Fidge, P. Nestel, B. Watson, T. Billington

This group of apoproteins, comprising at least five separate proteins, are related to the catabolism of triglyceride-rich lipoproteins, through their activation of one and possibly two key enzymes. We have developed techniques for their separation by isoelectric-focusing, allowing the measurement of the specific radioactivity of each protein, after the reinjection of radiolabelled lipoproteins. This has enabled us to define, for the first time, the amounts of these proteins that are synthesized and removed daily in normal and hyperlipidaemic subjects. We are extending the studies to hypertriclyceridaemic individuals because of the key role of these proteins in the dismantling of triglyceride-rich lipoproteins.

(b) Apoprotein-E Metabolism in Man

N. Fidge, P. Nestel, T. Billington, M. O'Connor

This group of apoproteins, separable into at least four proteins by isoelectric focusing is involved in the removal

Left to right: Dr. Murray Huff, Dr. Noel Fidge, Robyn Paynter, Hubert Edelsbacher, Margaret O'Connor, Dr. Norio Tada.

of remnant particles derived from catabolized triglyceride-rich lipoproteins. We have developed a technique similar to that for the C-apoproteins to measure E-apoprotein kinetics in man, especially in subjects who retain abnormally, remnant particles in the circulation.

(c) Lipoproteins in Alcoholic Hepatitis
N. Tada, N. Fidge, P. Nestel

The abnormal lipoproteins that appear in the plasma of subjects with alcoholic hepatitis have been characterized by us. Abnormal complexes of apoproteins, containing the E-apoprotein, have been found in high concentration; their origin is uncertain but the abnormal lipoproteins in which they occur can be transformed to normal species after in vitro addition of cofactors and enzyme which are deficient in these subjects. The accumulation of the abnormal proteins is directly related to the severity of the disease.

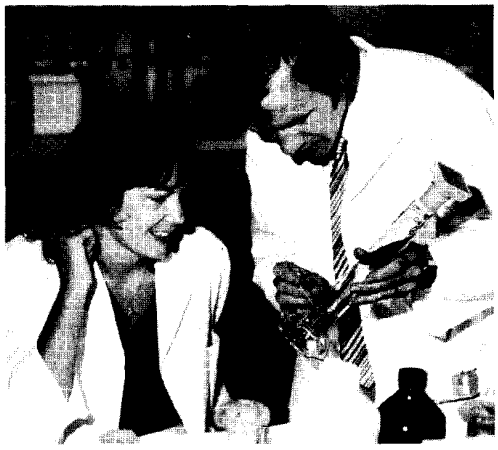
(d) Lipoproteins with Cholesterol Feeding
P. Nestel, N. Tada, N. Fidge

A new species of lipoprotein has recently been described that appears in the circulation after the addition of cholesterol to the diet. We have isolated this particle by heparin-affinity chromatography and are studying its metabolic characteristics: the relationship of this E-apoprotein-rich lipoprotein to the diet-induced changes in the concentrations of other lipoproteins and lipids and to the control of cholesterol production and excretion.

(e) Very Low-Density Lipoprotein Metabolism in Man
P. Nestel, T. Billington, N. Fidge

We are continuing studies of this triglyceride-rich lipoprotein in the direction of the fate of the smaller particles that remain after the VLDL have been partly depleted of triglyceride. The remnant particles may be highly atherogenic and are metabolized by more than one mechanism especially in hypertriglyceridaemic subjects. This latter aspect is being investigated by simultaneously measuring the kinetic parameters of the two major groups of particles, individually labelled prior to reinjection.

(f) Lipoprotein and Cholesterol Metabolism in Vegetarians
P. Nestel, T. Billington, A Everitt, S. Mensen



Sandra Mensen and Dr. Timothy Billington

Vegetarians, and vegans in particular, have low serum cholesterol levels. The main reduction is in the low density lipoprotein (LDL) fraction, which is a highly atherogenic particle. However, the concentration of high density lipoproteins (HDL) which appear to protect against atherosclerotic disease, are also lowered. We are therefore studying the kinetics of LDL-apoprotein B (the major LDL protein) and of HDL-AI and AII apoproteins (the major HDL proteins). These findings are being related to cholesterol synthesis and excretion and bile acid excretion (derived from cholesterol). Findings to date show that the low concentrations of circulating LDL and HDL are due to decreased production (LDL) and increased removal (HDL). Cholesterol production is in the low normal range.

(g) Lipoprotein and Cholesterol Metabolism with the Cholesterol-lowering Drug, Probucol
P. Nestel, T. Billington, S. Mensen, A. Everitt

We are studying the mode of action of this newly available cholesterol-lowering drug. Measurements include kinetics of LDL (in which the cholesterol concentration is predominantly lowered) and of HDL, and the production and excretion of cholesterol and bile acids. Results to date suggest that the main effects include enhanced LDL removal and increased bile acid

excretion, the two effects being probably related.

E. Rat Apoprotein Studies

There is a striking homology between many rat and human apolipoproteins. For this reason, the rat appears to be a suitable model for investigating the origin, fate and fuction of these important biological peptides. The main thrust of this work involves three projects.

(a) In vivo metabolism of apolipoproteins

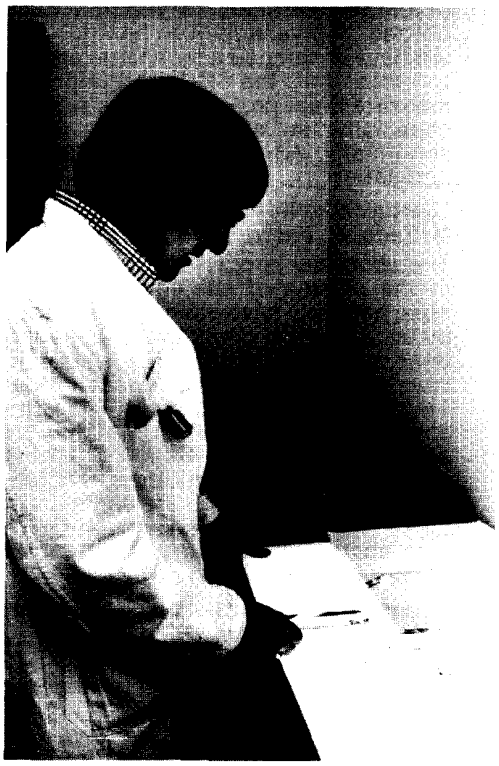
The rates of production and removal of AI and AIV apolipoproteins are being studied in the rat after injecting lipoproteins containing ^{125}I-labeled apoproteins. Evidence is accumulating to suggest that most of the apoproteins are synthesised in the gut, secreted into the lymph with chylomicrons which after entering the plasma are catabolised with a subsequent transfer of apoproteins into HDL and lipoprotein-free fractions.

(b) Biosynthesis of lipoproteins in cultured cells

We have been successful in producing monovalent antisera to several key rat apolipoproteins, including AI, AIV, E and B apoproteins. This will allow us to quantitate the production and secretion of these proteins from cultured cells, particularly hepatocytes and intestinal mucosal cells. Use of an immunofluorescent technique has enabled us to identify the presence of AI and AIV in intestinal cells and E apoprotein in hepatocyts.

(c) Search for receptors of apoproteins in cells

The recognition of LDL by some cells, e.g. skin fibroblasts has been shown to depend on the presence of the B apoprotein component. Other lipoproteins, which do not contain B apoprotein, are taken up and degraded by various tissues, a process which may also depend on the recognition of certain apoproteins. To examine this possibility, purified apoproteins (AI, AII, AIV, E and B apoprotein) are isolated and purified, and complexed with phospholipid micelles for lipoprotein recombinants. The characteristics and specificity of the binding, uptake and degradation of these apoproteins by cells such as skin fibroblasts, hepatocytes and intestinal cells is being carried out by tissue culture studies. Early experiments suggest specificity of uptake by cells for the E and AIV apoproteins.



Dr. Murray Huff

Overseas Visits:

Dr. Nestel gave an invited lecture on "Cholesterol metabolism in diabetes mellitus" at the International Diabetes Federation Congress in Vienna.

Dr. N. Fidge and Dr. P. Nestel were invited to present review lectures at the Vth International Symposium on Atherosclerosis in Houston, Dr. Fidge on "Quantitation of apoproteins in metabolic studies in human subjects", and Dr. Nestel on "Very low density lipoprotein protein catabolism in man". Dr. Fidge and Dr. Nestel presented additional papers in Houston and at the American Heart Association meeting in Los Angeles; titles were "Cholesterol kinetics in hyperalphalipoproteinaemia" (PN), "Apoprotein AI and AII turnover in alcoholic hepatitis" (PN) and "Turnover and metabolism of C-apoproteins in human subjects" (NF).

Local Lectures

P Nestel:

1. National Heart Foundation Fifth Triennial Conference: "Receptors Involved in Lipoprotein Transport".
2. Australian Postgraduate Federation in Medicine, Annual Forum: "Diet and Coronary Heart Disease".
3. Cardiac Society of Australia and New Zealand: "How could high density lipoproteins protect against coronary heart disease?"
4. Australian Atherosclerosis Group: "Cholesterol transport in hyperalphalipoproteinaemia".
5. Australian Medical Association Annual Meeting: "Diet and Coronary Heart Disease".

K. O'Dea:

1. Some studies on the relationship between urbanisation and obesity and diabetes in a group of Australian Aborigines.
   K. O'Dea, R. M. Spargo, K. Akerman
   49th ANZAAS Congress, Auckland, Jan 22-26.
2. Changes in insulin receptor binding and glucokinase activity in rat liver in response to fasting and refeeding.
   K. O'Dea and J. Field
   Endocrinology Society of Australia, Perth, Aug 29-31.
3. Physical factors influencing postprandial glucose and insulin responses to starch.
   K. O'Dea, P. Nestel, L. Antonoff
   Australian Diabetes Society, Perth, Aug 31-Sept 1.

N. Fidge:

1. Biochemical and clinical relevance of lipoprotein metabolism. Seminar presented to Department of Medicine, St. Vincent's Hospital, Melbourne.

MORPHOLOGY AND CELL BIOLOGY LABORATORY

Major Research Interests

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

GENERAL SUMMARY

An understanding of the biology of the muscle cell is of fundamental importance to research into both atherosclerosis and hypertension as the arterial wall is not a static conduit but a complex, integrated functional unit capable of remodeling its structure and matrix composition to fulfill functional demands. This adaptive capability is centred about the only cell type present within the media of the artery, the smooth muscle cell. This cell, described by some as multifunctional mesenchyme is capable not only of contraction but of synthesis of extracellular matrix and repair. A greater understanding of smooth muscle cell biology will enable us to distinguish "normal" adaptive processes (such as hyperplasia and migration, leading to the formation of a neointima in response to an injury, and hypertrophy and laying down of connective tissue as the cell adapts to excessive medial tension such as occurs in hypertension) from pathological ones leading to the disease state.

It has been suggested that atherosclerotic plaques form after injury to the normally tight barrier of endothelium (which separates the vessel from the blood stream) allows cholesterol-rich lipoproteins and a platelet-derived growth factor in the blood to come into contact with mature smooth muscle cells in the intima and media, causing them to migrate, divide and lay down connective tissue. However, this is an oversimplification since our studies have shown that smooth muscle cells in the "contractile" state (as they exist in the mature blood vessel) do **not** respond to these substances from the blood, but that under certain conditions they can undergo a reversible physical and functional change, called 'phenotype modulation', to a 'synthetic' state where they can no

Left to right: Janet Rogers, Lucy Popadynec, Dr. Barbara Evans, Dr. Julie Campbell, Dr. Gordon Campbell, Paul Shallard, Kim Round.

longer contract but can divide, migrate and lay down connective tissue when challenged with whole blood serum.

Atherosclerotic plaques contain smooth muscle cells, connective tissue elements, some non-muscle cells, and varying amounts of fatty material both inside and outside the cells. Studies with the electron microscope and myosin immunofluorescence have shown that the smooth muscle cells in atherosclerotic plaques are in the 'synthetic' state. Thus, if the smooth muscle of plaques is derived from normal, mature smooth muscle, then change from the 'contractile' non-dividing state to the 'synthetic' state is an important initial step in atherogenesis.

Using the technique of cell culture we have been studying factors that determine the phenotypic state of arterial smooth muscle cells and have found that a chemical substance released from large numbers of 'contractile' state smooth muscle cells acts on other 'contractile' state smooth muscle cells to prevent them from changing into the 'synthetic', and thus dividing, phenotype. We have also found that the same substance in larger amounts, or a similar, more potent substance, is present in endothelial cells, and that the active material is not produced by either 'synthetic' state smooth muscle cells or by fibroblasts which are present in the outer arterial layer (adventitia). The active substance does not appear to be a prostaglandin as the presence of postraglandin synthesis inhibitors has no effect on its production. Preliminary studies using column chromatography of aortic extracts suggests that the substance may be a low molecular weight protein.

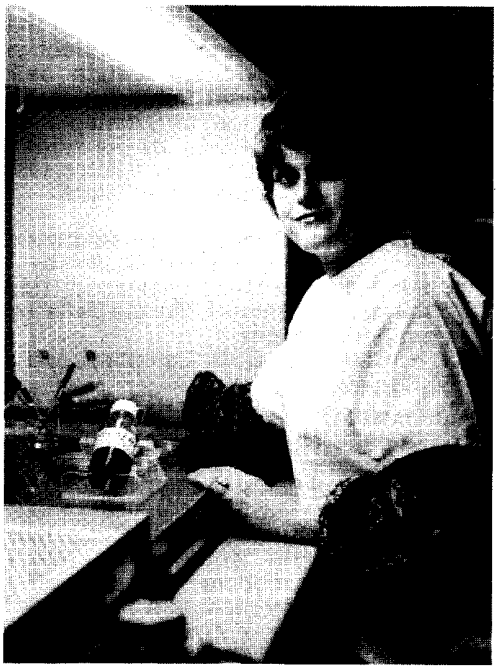
The major function of the elastic lamellae is to distribute tensile stresses uniformly throughout the artery wall. Therefore any dramatic changes, such as their fragmentation or loss of structural integrity severely weakens the wall at that site. The sudden increased pressure encountered should then initiate a repair response from those medial smooth muscle cells remaining causing them to migrate, proliferate and synthesize extracellular matrix. There is currently a considerable body of both chemical and morphological evidence indicating that changes occur in elastin and elastic lamellae of arteries both with age and atherosclerosis. For instance a recent report suggests that degradation of elastin observed in the human aorta between the ages of 20-60 years is due to increased elastolytic protease activity. If the elastolytic protease activity lies in smooth muscle cells and platelets as well as in other blood borne elements as suggested, one might expect changes in elastica to occur with age in other vessels apart from the aorta. Our studies on both large and small arteries in rats and rabbits indicate changes do indeed occur in elastic lamellae with age and this process is exacerbated by hypertension. Whether this is due to increased elastolytic protease activity is as yet unresolved, however our studies on neo-intima formation in the rabbit renal artery indicate that other factors, such as hemodynamic forces are also capable of inducing elastic lamellae breakdown.

DETAILS OF PROJECTS

1) Influence of Prostaglandins and Prostaglandin Synthesis Inhibitors on Smooth Muscle Phenotypic Modulation and Proliferation

J. H. Campbell and G. R. Campbell

Prostaglandins (PG) are local hormones acting at or near their site of origin and are synthesized by virtually every tissue in the body with the exact products formed



Dr. Julie Campbell changing medium of a culture.

dependent on the specific enzymes present in that tissue. Smooth muscle produces a mixture of PG E_2, $F_{2\alpha}$ and I_2 (prostacyclin). The active half life of PGI_2 at 37°C is less than 10 minutes forming 6-keto $PGF_{1\alpha}$.

Prostaglandins have, in several ways, been implicated in atherogenesis. To determine whether they have any influence on the modulation from the "contractile" (non-dividing) phenotype to the "synthetic" (dividing) phenotype or on the subsequent proliferation of "synthetic" state cells, we incubated "contractile" state cells in the presence of each of the three prostaglandins E_2, $F_{2\alpha}$ and 6-keto $F_{1\alpha}$ at several doses for 15 days at 37°C adding fresh medium and drug at 2 day intervals. It was found that none of the prostaglandins had any effect on phenotypic modulation, but that PGE_2 completely inhibited proliferation of "synthetic" state cells at 20 μm (but not 2 μm), $PGF_{2\alpha}$ slightly stimulated growth at 20 μm, and 6-keto $PGF_{1\alpha}$ to 20 μm had no effect.

To determine whether endogenously produced prostaglandins could control proliferation, the "contractile" state cells were incubated with several doses of the prostaglandin synthesis inhibitors indomethacin, betamethasone and aspirin for 15 days at 37°C, adding fresh medium and drug every second day. It was found that there was a potent stimulatory effect on proliferation of "synthetic" state cells with all prostaglandin inhibitors, suggesting that inhibition of prostaglandin synthesis (probably PGE_2), by the smooth muscle cells themselves stimulates their proliferation in the "synthetic" state.

2) Inhibition of Phenotypic Modulation of Arterial Smooth Muscle Cells by a Chemical Substance Released from "Contractile" Smooth Muscle Cells and from Endothelium

J. H. Campbell, G. R. Campbell, and J. D. Rogers

When isolated "contractile" state smooth muscle cells are seeded very densely in culture (greater than 10^6 cells/ml) so that they form a confluent monolayer from day 1, the cells do not phenotypically modulate to the "synthetic" state but remain indefinitely in the "contractile" state. If they are seeded moderately densely (5×10^4 — 10^5/ml) they modulate to the "synthetic" state after 7 days, proliferate to confluency within 5 days, then rapidly regain the "contractile" phenotype. However, if they are seeded very sparsely (10^3/ml), they modulate on day 7, proliferate, and achieve confluency after about 3 weeks. Under these circumstances the smooth muscle cells do not regain the "contractile" phenotype, but appear permanently in the "synthetic" state. This latter phenomenon appears to be analogous to the forming atherosclerotic plaque.

To determine whether the inhibition of modulation by the large numbers of "contractile" smooth muscle cells back on themselves is due to a released chemical or to cell contact, two experiments were carried out. Firstly, we grew the same number of aortic smooth muscle cells in the same volume of medium in two different sized culture dishes with one threefold the surface area of the other, so that in one the cells were very close together and in the other, further apart. We did this using five different total numbers of cells in the same volume of medium and found that with the highest number of cells in both sized dishes there was no modulation after 8 days, but with all the lower cell numbers in both sized dishes modulation occurred. This suggests that the concentration of a chemical substance produced by the cells, rather than cell closeness, is important in inhibiting modulation.

In confirmation, it was found that a confluent monolayer of "contractile" state smooth muscle cells seeded onto one coverslip of a Rose Chamber with a sparse seeding of the same cells on the opposite coverslip such that the two layers were not in contact but continually bathed by the same medium, inhibits the modulation of the sparsely seeded cells. Similarly, a confluent monolayer of endothelial cells inhibits the modulation, and thus proliferation, of sparsely seeded smooth muscle cells. However, a confluent monolayer of "synthetic" state smooth muscle cells or of adventitial fibroblasts does not inhibit modulation of the sparsely seeded "contractile" smooth muscle cells, indicating that the active substance(s) is not present in these cells. Transfer of 2 day old conditioned medium from "contractile" state smooth muscle cells or from endothelial cells to chambers containing sparsely-seeded "contractile" state smooth muscle cells does not inhibit their modulation and proliferation, showing that the factors involved are relatively short-lived.

Addition of the prostaglandin synthesis inhibitors indomethacin, betamethasone

or aspirin to the joint cultures containing sparsely-seeded "contractile" smooth muscle cells and a confluent monolayer of either "contractile" smooth muscle or endothelium on the opposite coverslip does not prevent the inhibition of modulation and proliferation of the sparsely-seeded smooth muscle cells, indicating that the active substance released by the cells is not a prostaglandin.

3) Influence of Aortic Extract on Smooth Muscle Modulation and Proliferation

J. H. Campbell, G. R. Campbell, N. Fidge, N. Tada and L. Popadynec

In 1973, Martin and Sprague postulated that atherogenesis may be a function of an age-related decline in smooth muscle stem cell activity with a subsequent decrease in the concentration of replication-inhibiting chalones normally secreted by the stem cells. They suggested that the effect was negligible in the media because of the large number of cells there, but in the intima, where smooth muscle cells are few, it had a potent influence. Chalones are tissue-specific, species non-specific mitotic inhibitors which have been found in every tissue examined. Biochemical studies reveal that chalones are proteins of two distinct molecular weight classes: less than 10,000 daltons and around 50,000 daltons. Chalones act at the G_2 phase of the cell cycle inhibiting entry into mitosis, and also at a different point in the cycle serving as a switch between cell division and maturation.

We prepared alcohol precipitable aqueous extracts from rabbit and pig aortic intima and media. With polyacrylamide gel electrophoresis the rabbit aortic extract showed a broad band which when scanned gave an estimate of 13,000 dalton molecular weight. When this was added to the culture medium at a concentration of 500μg/ml, both phenotypic modulation of "contractile" state cells and proliferation of "synthetic" state cells was inhibited.

The pig aortic extract gave a number of bands, one group in the low molecular weight range around 12,000 daltons and the other in the high molecular weight range around 60,000 daltons. Attempts to separate the two groups by column chromatography were unsuccessful with one broad band resulting. When this was split into five arbitrary fractions of increasing molecular weight and the fractions tested in culture with fresh medium and extract added each day, it was found that the second lowest fraction inhibited modulation and proliferation, the two highest fractions had no effect on modulation but stimulated proliferation of "synthetic" state cells, and the lowest and middle fractions had no effect. The unfractionated sample of pig aortic intima and media extract had an overall proliferative effect on the "synthetic" state cells and no influence on modulation of "contractile" state cells.

In conclusion, a substance can be extracted from aortic intima and media which acts back on aortic smooth muscle to control its phenotype and thus capacity for responding to proliferation-stimulating agents.

4) Effect of Hyperlipidemic Serum on Smooth Muscle Cells in Culture and Changes in Low Density Lipoprotein (LDL) Binding and Degradation After Phenotypic Modulation

J. H. Campbell, A. Everitt, G. R. Campbell and P. Nestel

Rabbits were made hyperlipidemic (2,000 mg%) by feeding 2% cholesterol and peanut oil in normal chow. Serum from these animals was added to culture medium to a final concentration of 5%, and incubated at 37°C with isolated "contractile" state smooth muscle cells. Serum (5%) from normolipemic (200mg%) was used as control. It was found that hyperlipemic serum had no influence on the modulation of the "contractile" smooth muscle cells, but that "synthetic" state smooth muscle was stimulated to proliferate far in excess than with normolipemic serum.

When binding and degradation of I^{125}-labelled LDL before, during and after phenotypic modulation of smooth muscle was examined, it was found that binding did not alter, but that beginning day 7 (when modulation is first evident) the degradation of LDL/cell decreased significantly and continued to decrease for several days afterwards. This suggests that smooth muscle in the "synthetic" state metabolises LDL in a different manner from "contractile" state cells, and may account for the fact that in atherosclerotic arteries the "synthetic" state cells of the lesion are often filled with fat droplets, while most "contractile" state cells in the adjacent media are not.

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

5) "Spontaneous" Internal Elastic Lamina Loss in Small Arteries of Rats and Rabbits. Effect of Age and Hypertension

G. R. Campbell and J. H. Campbell

The vessels examined in this study were the caudal, mesenteric and renal arteries.

In the 12-32 week virgin male rats (both normotensive and the Kyoto-Wistar spontaneously hypertensive) there were numerous regions where the internal elastic lamina (IEL) was absent over all or a part of the above vessel circumference for distances of up to 1,000μ. In the majority of cases, there was no sign of degeneration or fragmentation of the IEL and the site of rupture appeared as a clean abrupt break. Areas where recent breaks in the IEL had occurred (as determined by endothelial cell mitosis) could also be distinguished. Here the underlying media contained necrotic cells, "synthetic" state smooth muscle cells and cells with a fibroblastic appearance (presumably derived from the blood or adventitia). Particularly noticable in the spontaneously hypertensive rats were areas of intense smooth muscle cell proliferation, adjacent to the lesions. Here the smooth muscle cells were smaller than those of the media and were longitudinally placed with respect to the length of the vessel. Due to new elastin formation and a process of elastosis these areas of smooth muscle might be either intimal or medial in location. Although there appeared to be a greater frequency of IEL loss in hypertensive than in normotensive rats this was difficult to quantify.

The 4 month old cellophane perinephritic hypertensive rabbit was then examined to determine the effect of hypertension upon IEL loss, as similar lesions had not been observed in a large number of control animals. Spontaneous rupture of the IEL in the caudal and renal arteries of four of ten hypertensive rabbits was observed after one to two months hypertension. This is at least suggestive (but not conclusive) that high blood pressure can play a role in the development of this type of lesion.

What are the consequences of a "spontaneous" break in the IEL? As discussed above the immediate effect is damage of the artery wall with a subsequent response of the smooth muscle cells to this injury and eventual remodelling of the wall with new elastic laminae formation. However, one feature of the aging arteries is a loss of smooth muscle cells from within the media. This also occurs in hypertension by medionecrosis and is one of the reasons why hypertension has been described as accelerating the aging process. This loss of cells from the media means a severe weakening of the wall making it susceptible to rupture should the elastic component fail. Three aneurisms to date have been observed in renal arteries of spontaneously hypertensive rats.

6) Experimental Loss of Internal Elastic Lamina (IEL) and Formation of Neo-Intima in the Renal Artery of the Rabbit

G. R. Campbell and J. H. Campbell

The left renal arteries of six, 2-5 month rabbits were looped around a piece of 0.05 inch polyethylene tubing in such a way as to avoid occlusion of blood flow. These vessels were then examined after a period of 2 weeks. Proximal and distal areas immediately adjacent to the loop contained a neo-intima composed of longitudinally orientated smooth muscle cells. This neo-intima was in some instances of equal or greater thickness than the media. The IEL in these regions was continuous at two weeks. Within the loop a neo-intima of longitudinally orientated smooth muscle cells had also formed. However, here the IEL was ruptured over lengths of up to 800μ making it difficult to distinguish intima from media. The majority of cells in close proximity to the endothelium within

these areas were smooth muscle cells in the "synthetic" phenotype. However, a number of fibroblast-like cells (probably blood-derived monocytes) were also found in close contact with fragmented areas of IEL.

This model will provide further information on factors involved in rupture of the IEL and also why "contractile" smooth muscle cells modulate to the "synthetic" state and migrate to the intima. The presence of modulated smooth muscle cells within the intima also provides an ideal opportunity to study the influence of hyperlipidemic serum upon these cells **in vivo.** To this end rabbits have been fed a high cholesterol-diet to determine the effect of high serum cholesterol levels on "synthetic" state smooth muscle cells within the intima.

Another question relevant to this model is the etiology of fibromuscular hyperplasia (FMH), a disease usually confined to the renal arteries causing stenosis and subsequent systemic hypertension. Arteries demonstrating FMH have areas of medial thickening secondary to hypertrophy of smooth muscle and fibrous elements. Areas adjacent to such regions consist of thinned intima, disruption of IEL and a markedly thinned media composed predominantly of fibrous tissue. It has been suggested that disruption of the arterial elastica is the primary defect of FMH and area of medial thickening reflect compensatory muscular hypertrophy.

7) Arterial Changes in Human Female Renal Arteries
G. R. Campbell and J. H. Campbell

Of all types of fibromuscular stenosis medial fibromuscular dysplasia is the most common comprising 60-70% of cases. It is usually found in women between the ages of 25-50 years and characteristically affects the distal two-thirds of the renal artery. The angiographic appearance is much like a "string of beads" which under the light microscope can be seen to be due to thickened fibromuscular ridges alternating with mural aneurisms which result from thinning or complete loss of smooth muscle and a deficient internal elastic lamina (IEL).

To determine the changes which occur in human renal arteries and to compare these with experimental animals (see previous projects) the renal arteries of 30-40 year old women were examined at the time of kidney removal.

A characteristic feature of all vessels examined (although the frequency varied considerably) were areas in which rupture of the IEL had occurred. In some cases this involved almost the whole diameter of the renal artery. Often beneath these large areas or adjacent to them were abnormal accumulations of connective tissue. The cells present here were predominantly of a fibroblastic appearance being narrow spindle-shaped with long cytoplasmic processes and a definitive diminution in cytoplasmic volume and cellular organelles. They did however contain small bundles of myofilaments and were surrounded by a basal lamina indicating they were of smooth muscle origin. The continuum of cellular appearances ranging from normal media smooth muscle cells to ones with a fibroblastoid appearance could also be determined, suggesting a smooth muscle origin.

Although no gross pathological changes indicative of arterial dysplasia were observed in this study the changes in the smooth muscle cells indicate a reaction to an abnormal functional state and/or an altered tissue response. Certainly a predominance of myofibroblastic cells, as well as fragmentation of the IEL has been described as characteristic features of human arterial dysplasia.

8) The Effect of Hypertension on Dietary Induced Atherosclerosis in the Rabbit — a Morphological Examination
G. R. Campbell and J. H. Campbell

Ten, approximately 2 Kg rabbits from the colony within the Baker Institute (developed by the Commonwealth Serum Laboratories, Melbourne from several multicoloured English strains, and closed since 1961) were examined for spontaneous occuring lesions within the aorta. Nodular medial sclerotic lesions visible to the eye were the most common and could be detected in 30% of the animals. These were usually confined to the ascending thoracic aorta and in the area of the arch. Microscopically these lesions were confined to the inner one-third of the vessel and consisted of dense accumulations of connective tissue, disrupted elastic lamellae with a few smooth muscle or fibroblastoid cells present. Occasionally these areas were calcified.

Ten rabbits were then made hypertensive by wrapping their kidneys in cellophane, their blood pressure reaching a stable 130-150 mmHg within six weeks. After 2-3 months hypertension the aortas of these

animals were again examined for evidence of nodular sclerotic lesions. Lesions were found in 90% of animals examined and were not just confined to the ascending thoracic aorta and the arch but extended further down the vessel. In two cases lesions were observed in the abdominal aorta. Lesions in the upper segments of the aorta were usually more extensive than those found in normotensive animals, often with marked calcification. Microscopically, they appeared similar to the spontaneous lesions of the normotensive animals. Examination of presumably newly formed lesions within the descending thoracic aorta suggested a sequence of formation: Smooth muscle cells are affected by the increased blood pressure and become foveated (moth-eaten) in appearance; many of these cells then die stimulating the remaining smooth muscle cells to hypertrophy (up to 2-3 times normal medial cell volume) and lay down large amounts of connective tissue; the majority of these cells then die and fragmentation of the elastic lamellae occurs, forming the lesion.

There is now a large body of evidence in favour of the hypothesis that hypertension promotes (accelerates) atherogenesis. To examine this process, perinephritic hypertensive (kidneys cellophane wrapped) rabbits were fed a 2% cholesterol diet for 1-2 months and their aortae examined to determine whether there was any predilection of atheroma formation at sites of spontaneously occuring or hypertension — induced nodular medial sclerotic lesions. This is particularly relevant in view of recent publications indicating that entry of low density lipoprotein into the aorta of rabbits fed a 1% cholesterol diet is significantly greater in the aortic arch of hypertensive than normotensive animals. After 1-2 months on a 2% cholesterol diet typical atheromatous plaques characterized by an intimal accumulation of lipid-filled foam cells were prominent, making identification of nodular medial sclerotic lesions difficult from a gross morphological standpoint. Microscopically the two types of lesion could be easily distinguished with the atheromatous plaque often superimposed upon the sclerotic lesion. Plaques were indistinguishable from one area to another. However, although the medial lesions themselves did not play a direct role in plaque formation they appeared to provide a site of predilection to atheroma formation as almost all medial lesions observed were surrounded by large atheromatous plaques. This suggests some of the pathogenic phenomena involved in the formation of medial sclerotic lesions within the aorta eg. hemodynamic factors, may also be involved in atherogenesis.

CARDIAC SURGICAL RESEARCH LABORATORY

The second year of the Cardiac Surgical Research Unit has brought recognition of the unit's work by the National Health and Medical Research Council, in the form of a Project Grant, the first of its kind in this field in Australia. Important financial support came from the Windermere Hospital Foundation of Victoria. This enabled Dr. Malcolm Arnold, a trained cardiac surgeon, to join the unit for a year as the Windermere Fellow. During 1979 the unit moved to new laboratory space in the basement of the Institute. This large area made possible the performance of complex experiments using the isolated supported heart preparation. A pleasing feature of 1979 was the visit to the Baker Institute of Dr. David Sabiston, Professor and Chairman of the Department of Surgery at Duke University in North Carolina. Dr. Sabiston's advice and encouragement and his interest in the work of the unit were most welcome.

MAIN TOPICS

- MYOCARDIAL PRESERVATION DURING HEART SURGERY
- HEART-LUNG BYPASS
- CORONARY ARTERY SURGERY
- SURGICAL TREATMENT OF DISTURBANCES OF HEART RHYTHMN
- TREATMENT OF INFECTION IN THE CHEST CAVITY

GENERAL SUMMARY

Myocardial Preservation

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

The pump oxygenator can take over the function of the heart and lungs during surgery but to provide the surgeon with a

Dr. Frank Rosenfeldt (centre) with John Grepiglia (left), Andrew Fambiatos and Christine Boyes examining recordings of tissue pH.

quiescent heart in a bloodless field, the coronary blood flow to the heart muscle must be interrupted. The muscle is placed in a state of "suspended animation" (cardioplegia) by perfusing it with an iced cardioplegic solution containing potassium and other ions. The ions produce immediate cardiac standstill, while cooling the heart reduces its oxygen requirements so that under optimal conditions the heart can remain in this protected state for two hours or more while the surgical procedure is carried out and subsequently return to normal function.

Cooling the heart exerts the major protective action and hence we have devoted considerable effort in measuring heart temperature in the laboratory and the operating theatre and in devising techniques to improve cardiac cooling. The frequent use of a miniature heart temperature probe in patients during cardiac surgery showed the patchy and unpredictable nature of cooling produced by the standard methods. We therefore developed a recirculating cooling circuit to produce lower cardiac temperatures. Comparison with previously used standard cooling methods during coronary surgery showed the superiority of this new technique.

During the arrest period necessary for heart surgery, acid accumulates in the heart muscle and may injure the muscle cells. Many surgeons try to counteract this by adding alkaline substances to the cardioplegic solutions infused into the heart. We believe a useful end-point for evaluating the effect of such infusions is the measured value of cardiac acidity (pH). During 1979 we have been measuring cardiac pH with miniature electrodes and testing the ability of various cardioplegic solutions to maintain pH within normal limits during simulated surgical procedures.

During heart-lung bypass, the circulation of blood to the heart muscle itself is maintained by the pump oxygenator. If the pressure and flow generated by the machine is low, the supply of blood to the heart muscle may be insufficient, particularly in the reperfusion phase following induced cardiac arrest and damage may result. It is difficult to measure continuously the supply of blood to individual areas of the heart muscle. With the help of Professor Lampard of the Department of Electrical Engineering at Monash University we have set up an electrical technique to make these measurements of regional blood flow to heart muscle and to detect abnormalities under surgical conditions.

Arrhythmia Surgery

The regular beat of the heart is generated by the cardiac pacemaker and the system of conducting fibres throughout the heart. In certain disease states this regular beat becomes disordered and bursts of rapid beating may cause the patient suddenly to collapse and even die. Most of these rhythm irregularities can be satisfactorily controlled by drugs but there are a group of patients who continue to suffer disabling symptoms in spite of maximal drug treatment. In recent years some of these refractory cases have been successfully treated by operations to modify or interrupt the conducting system and in some instances to replace it by an implanted artificial pacemaker. Alternatively the area of the heart giving rise to abnormal impluses can be completely removed or electrically isolated from the rest of the heart. This new branch of cardiac surgery was introduced to the Alfred Hospital in late 1978 with help from the Baker Institute. After preliminary tests in dogs, ten patients were operated upon in the hospital using these new techniques with good results.

Treatment of Intrapleural Infection

An empyema is an abscess in the pleural space between the lung and the chest wall and occasionally follows surgery for removal of lung tissue or operations on the oesophagus. The conventional method of treating this condition is to administer antibiotics and insert a drainage tube through the chest wall to allow the pus to escape until the abscess heals. This process usually takes 2-3 months. We have developed an alternative method of treatment in which the infected area is irrigated cyclically with dilute antiseptic solution through our specially designed double lumen tube. Once the infection is eradicated the tube is removed and the wound sealed. Three patients at the Alfred Hospital have now been treated using this new method and the infections have been eradicated in less than two weeks.

SCIENTIFIC PROJECTS

1. Development of Miniature Myocardial Temperature Probe

As a result of continued collaboration with the Royal Melbourne Institute of Technology the initial design of this probe has been improved and a new display unit produced. These probes have now been

used in over 300 patients having heart surgery at the Alfred Hospital. Probes and displays have been supplied by R.M.I.T. to cardiac surgical units in Sydney and Brisbane.

2. Recirculating Cooler

The usual source of cold fluid to irrigate the heart during surgery is a bottle of sterile intravenous fluid taken from a refrigerator. Prolonged operations may require 20 or more bottles of fluid which is often inadequately cooled before use. A British cardiac team have developed a recirculating cooling system in which the cold fluid is sucked from around the heart, recooled by a heat exchanger and refrigeration unit and returned to the heart. We have simplified this system and made it disposable (See. Fig. 1). In 20 patients having coronary bypass surgery, we carried out a trial to compare the recirculating cooler with the conventional technique using a bottle and intravenous drip set. The recirculating system produced more profound cooling and was judged by the surgeons to be more convient. This cooling system is now produced commercially in Melbourne and is used routinely in patients having open heart surgery at the Alfred Hospital. Sample curcuits have been shipped on request to the U.S.A. and England.

3. Hypothermic Damage

Some investigators have suggested that if the rat heart is cooled to below 10°C, permanent damage may result. Efficient cooling techniques in the human during surgery may result in at least the outer layers of the heart being as cold at 4°C and therefore susceptible to this form of damage if it exists. Thus, it is important to determine the optimal temperature for cardioplegia. This information has great importance in the field of human heart transplantation. When the donor heart is transported to a distant recipient it is usually stored in fluid at 1-4°C and could thus be damaged.

We studied this problem in dog hearts removed from the body and supported by the circulation of another dog. The hearts were deprived of their blood supply, cooled to various temperatures, then reperfused and allowed to recover. This function, composition and microscopic structure of the heart muscle was compared before and after cooling.

Hearts arrested at 30°C and −3°C showed 60% and 0% recovery of prearrest function respectively; on the other hand, hearts arrested at 4°C and 15°C showed full recovery of function. Biochemical and structural examination revealed a similar pattern to the function measurements. We

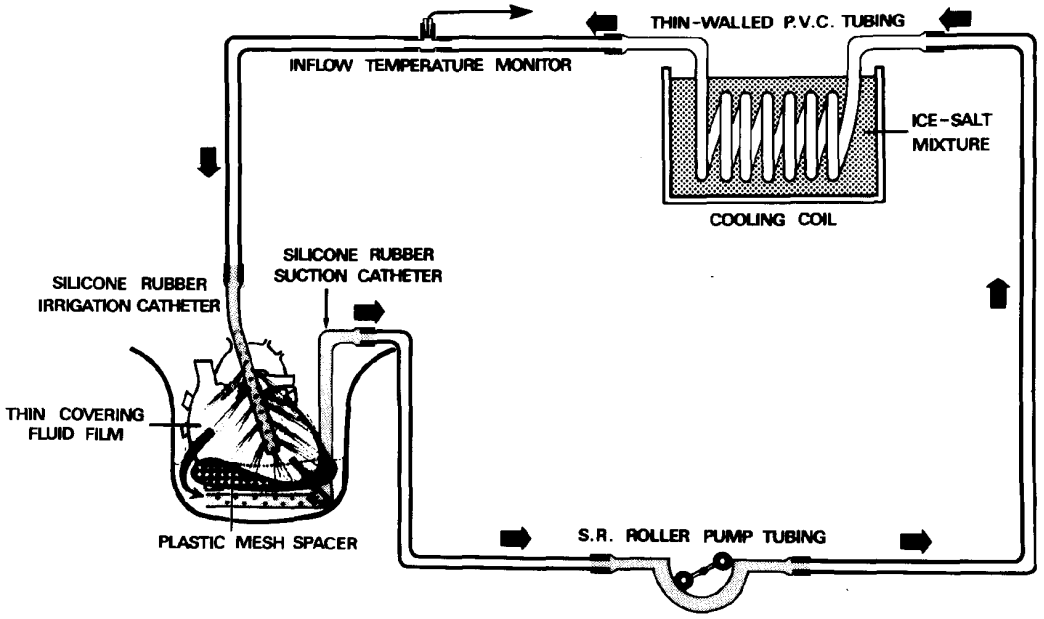


Fig. 1. Recirculating cooling current for use during heart surgery.

concluded that provided freezing is avoided, cooling does not damage the heart and that profound cooling of the surface of the heart is desirable to ensure optimal preservation of the innermost muscle layers.

4. Cardiac Spacer

The heart is kept cold during surgery by irrigating its surface with cold fluid. Occasionally, the cold fluid fails to circulate freely between the back of the heart and the chest wall, particularly if the heart is enlarged, and the inadequately cooled region of the heart may be damaged. We have designed a plastic mesh pad (spacer) to lift the heart forwards and allow free flow of cooling fluid on all surfaces of the heart. A trial of the spacer in patients having valve replacement showed some improvement in cooling but revealed the need for improved mechanical design. We are currently investigating a spacer made from urethane foam.

5. Myocardial pH

In 1978 we carried out a survey of cardioplegic solutions used in all cardiac surgical units in Australia. The results showed that half the solutions contained no buffer and some were pH 5 to pH 6. The other half contained various amounts of sodium bicarbonate buffer.

In view of the unknown effect of the buffering capacity of the intracellular and extracellular protein and tissue fluid already in the heart we felt it desirable to measure myocardial tissue pH during cardioplegic arrest. We have tested a number of commercial tissue pH electrodes and have found none of them particularly suitable for use in the heart. A new pH-sensitive polymer has recently been invented and we have been using this with some success to make robust miniature pH needle electrodes for use in the myocardium.

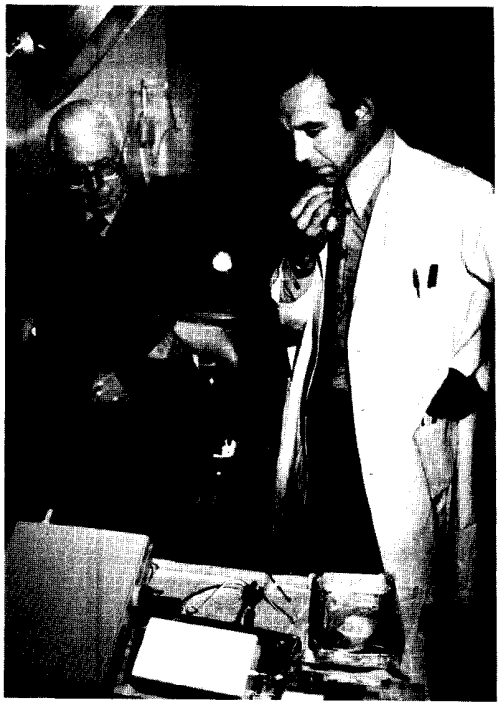
Initially we have recorded the time course of pH change during occlusion of a single coronary artery in the beating heart and also during ischaemia of the whole heart. We have now begun to test the effect of buffered solutions on this pH change.

A problem with current methods of myocardial preservation during cardiac surgery is that there is no indication of impending myocardial damage until after the arrest period when the myocardium is sometimes found to be irreversibly damaged. A continuous monitor of myocardial metabolism would be desirable during ischaemic arrest. We believe an intramyocardial pH electrode could fulfill this need. While monitoring intramyocardial pH in dogs during ischaemic arrest, we found a relationship between ischaemic arrest time and intramyocardial acidosis. If a suitable clinical probe could be provided to the surgeon, a safe level of pH could perhaps be set at which remedial action should be taken to prevent serious myocardial damage. We have found myocardial lactate concentration in biopsies is a good predictor of myocardial viability and believe that myocardial pH might be of similar value.

6. Reperfusion Phase following Cardioplegic Arrest

Following cardioplegic arrest, the heart must be reperfused with warm blood at an adequate pressure to restore mechanical and electrical function to the myocardium before the patient can be weaned from the heart lung machine.

The problem with the reperfusion phase of coronary bypass surgery is that during initial reperfusion the coronary grafts are not functioning and often, due to systemic vasodilation, there is a perfusion pressure



Dr. Gwyn Howells, Commonwealth Director-General of Health examining temperature monitoring equipment with Dr. Frank Rosenfeldt.

of only 40-60 mmHg from the heart-lung machine. Thus the stage is set for subendocardial ischaemia which may progress to infarction.

A problem also occurs in valve replacement cases because the inner layers of the thickened left ventricle are poorly perfused at low pressure from the heart-lung machine. These low pressure situations commonly occur in the reperfusion phase and there is a real possibility that they produce or exacerbate myocardial damage. Thus there is a need to study the uniformity and adequacy of myocardial perfusion under a variety of conditions following ischaemic arrest.

Myocardial perfusion can be measured very readily using the hydrogen desaturation technique. We have used this technique in dogs in our laboratory and have found it a sensitive indicator of changes and absolute levels of myocardial perfusion. We propose to use hydrogen electrodes to study myocardial perfusion in dogs during the recovery phase following cardioplegic arrest to help delineate the best arterial pressure for myocardial recovery.

Ultimately we envisage an extension of hydrogen desaturation into the clinical area to study myocardial reperfusion in man after heart surgery. The usual concentration of hydrogen used in the technique is 5%. This is explosive and hence too hazardous to use in an operating theatre. We have obtained satisfactory measurements of myocardial blood flow with a 1.6% mixture of hydrogen in air. The concentration is non-explosive and could safely be used in an operating theatre to study reperfusion in patients.

7. Surgical Treatment of Disturbances of Heart Rhythm

In collaboration with the Cardiac Diagnostic Service and the Electronics Departments of the Alfred Hospital and Baker Institute, equipment was assembled to map out precisely the conducting system of the heart at operation. In the Institute, tests were done in dogs of a technique new to Australia in which parts of cardiac conducting system are blocked by a cryosurgical (freezing) probe. Following these tests, sufficient confidence was gained to begin mapping out and operating on the conducting system in man.

During 1978 and 1979 four patients had cryosurgery performed with cure of their rhythm problems and a further 6 patients have had a electrophysiological mapping perfomed during removal of left ventricular aneurysms associated with life-threatening arrhythmias. One patient died, one patient was improved and four were cured of their rhythmn disturbances.

We are proposing to continue this surgery in 1980 and beyond, but before operating on more complex arrhythmia problems, a precise method of timing intramyocardial activation is necessry. A monitor and timing system for this purpose is currently under construction in the Electronic Workshop at the Alfred Hospital. This should be available early in 1980 and this will enable us to study arrhythmias in the animal laboratory. We propose to evaluate various methods used during surgery for detecting the arrhythomengic zone around left ventricular aneurysms. Methods we have used to date are not completely successful and we wish to determine which is the best method to identify these zones.

Dr. Allan McLean (left) with Peter Cahill and Cheryl Isbister.

CLINICAL PHARMACOLOGY

* LIVER BLOOD FLOW AND DRUG METABOLISM
* LIVER DISEASE AND DRUG METABOLISM
* AUDIT OF THERAPEUTIC DRUG USAGE

GENERAL SUMMARY

Clinical pharmacology is concerned with the action and fate of drugs in man and the institute's laboratory under Dr. Allan McLean has been in operation since 1978. The work has been concerned with determining how the body handles different drugs and how this handling is affected in variety of disease processes. Much of the work involves determining drug concentrations in body fluids and a detailed analysis of drug disposition. The latter involves both mathematical modelling and animal experiments. A pleasing feature of our research is that it now involves active collaboration with other members of the Baker Institute, Clinical Research Unit, Cardiology Service and particularly with Dr. Frank Dudley and his team in the Gastro-enterology Unit.

An interesting result of one of our studies has indicated an important role of liver and gastrointestinal blood flow on the blood concentrations reached by certain classes of drugs. We have found that so called 'high clearance' drugs such as the anti-hypertensive agent propranolol reach much greater concentrations in the blood when liver blood flow increases after oral administration than under control conditions. Such an increase in liver blood flow occurs usually secondarily to a rise in gastrointestinal blood flow. In our study the 'bioavailability' of propranolol was greatly increased by simultaneous administration of another anti-hypertensive drug, hydrallazine, which is a vasodilator agent. Hydrallazine presumably facilitates availability of propranolol by increasing gastrointestinal tract blood flow. The increased blood flow due to digestion after a meal has a similar effect to hydrallazine on the absorption and bioavailability of propranolol.

We have also studied how different drugs are handled by patients with liver disease, including those that have had vascular surgery. The latter is done to reduce the high pressure that patients with cirrhosis

of the liver have in the veins draining their gastrointestinal tract. One byproduct of this work has been the development of a non-invasive technique which utilises the clearance of propranolol by the liver for assessing the amount of blood flow that passes through the liver and the amount that is shunted past the liver directly into the systemic cirulation.

We have also begun to monitor how well drugs commonly prescribed are utilised by different units in the hospital. At present we have only performed preliminary studies looking at the drugs prescribed in a small number of medical units. One surprising finding has been that a high proportion of drugs are given in therapeutically ineffective amounts. There is clearly much scope for careful clinical pharmacology audits and improvements in medical staff education about the optimum use of drugs.

Left to right: Dr. Allan McLean, Professor Sir Gustav Nossal, Professor P. I. Korner.

DETAILS OF PROJECTS

Hepatic Drug Metabolism and Hepatic Blood Flow

A. J. McLean, A. Bobik, G. Jennings and F. J. Dudley

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

Initial studies with hydrallazine confirmed theoretical predictions that oral vasodilators should increase systemic availability of high clearance drugs. These studies have been extended to an analysis of the effects of various types of food on drug availability. It is planned to extend these studies to include other high clearance materials originating in the splanchnic circulation (insulin etc.) in collaboration with the Nutrition Laboratory.

Influence of Liver Disease and Surgically-Induced Portacaval Shunts on Systemic Availability of Propranolol in Dogs and Man

A. J. McLean, I. E. McInnes, D. North and F. J. Dudley

Theoretical analysis has allowed the development of a non-invasive method for estimation of hepatic perfusion and hepatic shunt flow in man. This has led to the development of a method of assessing surgical porta-caval shunts detailed below.

We have explored the changes in both first-pass clearance and systemic clearance and systemic clearance resulting in the creation of Eck (porta-caval) shunts in dogs. We have confirmed observations in the literature that post-operatively dogs develop classical neurological sequelae normally observed in subjects with cirrhosis — changes in mood and conscious state, ataxia and hindlimb weakness if meat-feeding is continued even in minor amounts. Measurements of availability indicate that these procedures cause almost complete shunting in dogs without major change in systemic clearance.

Similar types of observations have been made in man, indicating that both mesocaval (central) and lieno-renal (distal) shunts have quantitatively similar effects on the shunting of drugs past the liver.

Studies of Acetylation Markers in Man

A. J. McLean and K. Guest

The genetically determined capacity of subjects to N-acetylate substrates (acetylator phenotype) is the single most important determinant of dosing regimens with major therapeutic substances (eg. isoniazid, procainamide, hydrallazine). In clinical practice, metabolic clearance is rarely determined, rather a patient is dosed with a model substrate and measurements are made in plasma samples or defined urine collections.

A series of pharmacokinetic studies have been performed in normal volunteers which confirmed that the range of variaton of non-metabolic pharmacokinetic parameters in normal subjects is very wide. These findings together with recent evidence of non-linear pharmacokinetics in animals and man has led to the prediction that delay in absorption or decreased renal clearance will lead to errors in assignment of phenotype. Preliminary results in patients with mild to moderate degrees of renal impairment confirm predictions related to renal disease.

Preliminary studies on a single subject with coeliac disease indicates that predictions regarding absorption parameters may also be clinically significant.

Systematic studies on patients with clinically significant renal disease and patients with malabsorption syndromes will be undertaken.

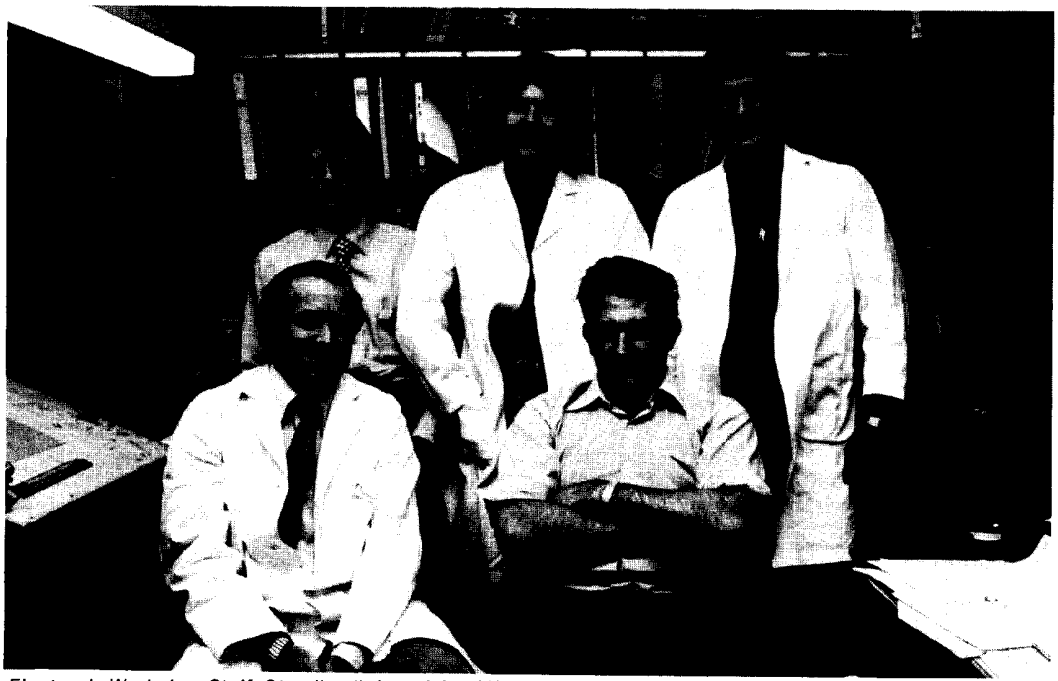
Study of Patterns and Utility of Drug Administered to Hospital In-Patients
K. Guest, A. J. McLean and C. V. Wellington

A preliminary study has been completed of drug assay levels and patterns of utilisation of drug assay information in routine patient care.

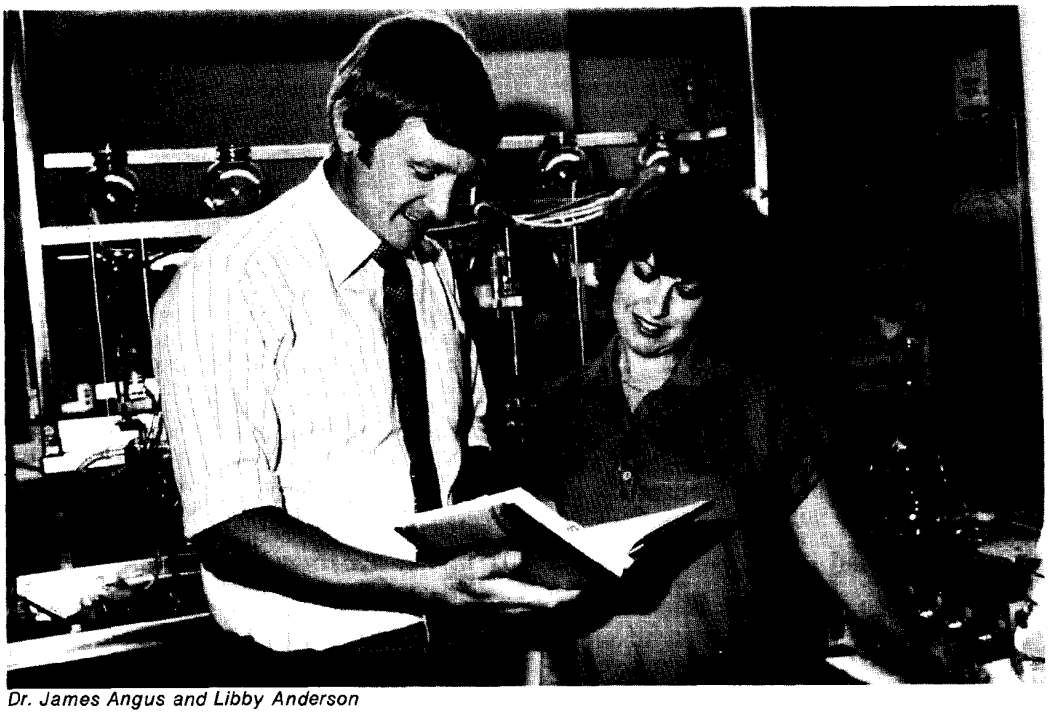
Results indicate significant inefficiency in drug delivery and in the utilisation of drug assay results. Prospective studies are being undertaken to evaluate requirements for pharmacokinetic evaluation of drug assay data and the provision of pharmacokinetically based consultation services.

ACKNOWLEDGEMENTS

In addition to the collaboration of individuals detailed above in the project section, the progress achieved has depended on the help of a number of people: veterinary support of Dr. Neville Walden, Adrian Bons and staff of the Alfred Hospital Biological Research Unit; the help of Sister Jan Dixon and theatre staff; the help of Sisters Sue Scealy, Helen Hall and Sue Ellett; the assistance of the Alfred resident staff; the secretarial assistance of Clare Harwood; the assistance of Mary Delafield with library research and reference retrieval; the help of Dr. Meg Breidahl and staff of Biochemistry. All help is gratefully acknowledged.



Electronic Workshop Staff: Standing (left to right): Michael Percy, Rohan Vaughan, Frank Forgione. Seated: Kevin Harvey, John Baird.



Dr. James Angus and Libby Anderson

PHARMACOLOGY LABORATORY

* RECEPTORS AND DRUG ACTIONS
* DRUGS AND SYMPATHETIC TRANSMISSION
* HISTAMINE
* CORONARY ARTERY SPASM

GENERAL SUMMARY

An important event in 1979 was the establishment of a laboratory to investigate the fundamental mechanisms of drug actions on the heart and circulation. Dr. Jim Angus, who returned to the Institute at the beginning of 1979 is in charge of the laboratory. Other graduate staff members of the team are Dr. Robert Brazenor (Post-doctoral Research Fellow) and Dr. Akio Nakashima (Visiting Scientist from Shimonoseki, Japan). A wide range of techniques and preparation are employed to analyse the actions of drugs including isolated tissue systems where the experimental conditions can be rigidly controlled. At the other end we are studying the effects of drugs in the intact animal which simulates the clinical use of the drugs in man. In between the use of isolated organ preparations and special animal preparations (for example, with impaired circulatory reflexes) all help in the overall analysis of how drugs act on the circulation.

Receptors

It is generally accepted that a given drug reacts with a specific 'receptor' site on the cell membrane. As a result there is a 'change' which sets in train a series of actions within the cell which are responsible for the pharmacological and therapeutic effects of the drug. In this regard drugs behave in a manner that is very similar to the way that the body's own hormones or the transmitters released at the nerve endings exert their physiological effects. The difference from these 'natural' substances are that drugs are often 'foreign' compounds to the body and that a given drug often has many other effects than the specific action of therapeutic interest. Some of these side-effects are of course, troublesome in the clinical use of drugs. However, quite apart from this many of these side-effects greatly complicate the analysis of how the drugs work. This is one reason why one must use such a number of different preparations in pharmacology.

Quantitive study of the responses of a given tissue to known concentrations of drugs permits inferences about the reaction that have taken place at the receptor and about the transformation of the drug-receptor linkage into a biological response. During the year we have studied how the anti-hypertensive drug clonidine influences sympathetic transmission at the sympathetic nerve endings going to the heart and blood vessels. A by-product of this work has been an increase in our understanding of some of the factors that are important in the control of the release of noradrenaline at the sympathetic nerve endings. Noradrenaline is of course, the 'natural' transmitter released at the sympathetic nerve endings. The above studies have been performed in isolated small pieces of heart tissue maintained alive in a warmed organ bath. This preparation can be maintained in good condition for many hours, with very reproducible responses to sympathetic nerve stimulation or to different drugs.

We have re-examined a widely accepted hypothesis that the noradrenaline released from sympathetic nerve terminals acts not only on post-synaptic receptors on the cells of the heart muscle or of the cardiac pacemaker but also on so-called presynaptic receptors which are situated on the sympathetic nerve terminal itself. The hypothesis is that after release of noradrenaline from the nerve terminals some of the transmitter will stimulate the presynaptic alpha-receptors and that this will act as a negative feedback system which inhibits further release of noradrenaline by a given sympathetic nerve impulse. This attractive idea has received support from measurements of radioactively labelled noradrenaline where repeated stimulation of the sympathetic nerves has been associated with reduction of transmitter release per unit nerve impulse. By contrast administration of alpha-adrenergic blocking drugs, which block the presynaptic alpha receptors were shown by this technique to increase the transmitter overflow. The drawback of the radioactive overflow method is that very strong stimulation of the sympathetic is necessary in view of the signal-noise ratio of the method to obtain clear cut experimental results. The stimulation parameters in these studies have been well above what occurs under physiological conditions. There has been a great deal of interest in the idea of presynaptic modulation of sympathetic transmission and a very large number of different receptor types have been postulated. These include beta-adrenoceptors, dopamine receptors, histamine receptors, prostaglandin receptors and many others. It has been difficult to envisage how sympathetic transmission could occur as an orderly process in the presence of such a large number of modulators.

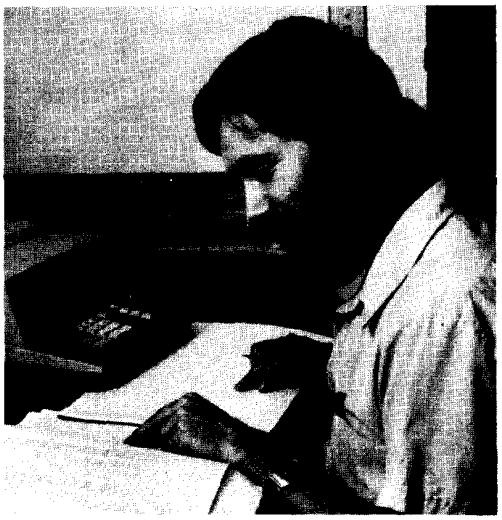
Accordingly we re-examined the presynaptic modulation hypothesis using a more physiological range of stimuli of the sympathetic nerves to the heart. Our work has indicated that under these conditions there is probably no important modulatory function that can be ascribed to the presynaptic alpha-receptors in the heart. Under physiological conditions the nerve stimulation frequency seems to be the only important determinant of transmitter release.

The anti-hypertensive drug clonidine has always been considered to simulate the actions of noradrenaline on alpha-adrenergic receptors. However, our studies have shown that in contrast to the 'natural' transmitter the drug **does** modulate release of noradrenaline per unit sympathetic nerve impulse to the heart even in quite low concentrations. Our studies to date suggest that the effect is at a presynaptic site. It does not appear to be mediated through a presynaptic alpha-adrenoceptor but through a receptor specifically responsive to clonidine and related imidazoline compounds.

Histamine

Histamine is found in most of the tissues of the body. It plays an important role as a stimulus to gastric acid secretion. It is present in very large amounts in the heart, in the lungs and in cells called mast cells in many body tissues. However, its function in relation to the heart and circulation are still poorly understood and indeed its only physiological role relates to gastric acid secretion and to responses of the skin circulation to injury.

Our work on histamine started from an investigation of one of the side effects of the anti-hypertensive drug guanethidine. We had observed that guanethidine caused a marked vasodilatation, particularly in hindlimb skin and muscle vessels. Repeated injections of guanethidine always produced identical large vasodilator responses even when the auto-



Matthew Le Duc

nomic reflexes were fully blocked by the drug. We found that guanethidine releases histamine primarily in the smaller arteries of the skeletal muscle bed to cause a marked selective vasodilatation in this bed and virtually no other. By contrast when histamine is infused intravenously to the animal it affects a much greater range of vascular beds. This year we compared the blood flow distribution changes of guanethidine with those of histamine in different vascular beds using radioactive microspheres. By far the greatest increase in tissue blood flow that has occurred as a result of histamine infusions has been in the mucous membrane lining the stomach, but dilatation also occurred in many other beds. The effect on the stomach is probably secondary to the action of histamine as a stimulus to gastric acid secretion. Our present conclusion about the endogenous release of histamine produced by guanethidine is that the histamine released probably acts on a histamine receptor located at a different site than those on which histamine acts when given intravenously.

Coronary Spasm

Angina pectoris or cardiac pain mostly occurs during exercise and signals an inadequacy of blood flow to the heart muscle. There is also another type of pain arising from the heart. This is the so-called variant angina which occurs at rest. Clinical observations make during examination of the coronary arteries by angiography; when contrast medium is injected into the coronary arteries, have shown that variant angina is often associated with transient and **reversible** coronary spasm and not with large atherosclerotic plaques in the main arteries that are usually found in patients with angina during exercise. It is a matter of great interest to determine what factors contribute to the development of spasm of the coronary arteries. Patients suspected of having variant angina respond to an ergot derivative, ergometrine, with marked contriction of a local segment of a coronary artery, when small quantities of the drug are injected into the artery in the course of angiographic examination.

We are currently determining how ergometrine produces spasm in animal experiments. Preliminary work suggests that ergometrine causes spasm not as has been thought by stimulating alpha-adrenergic receptors but by its effect on serotonin receptors in the dog's coronary artery. However, many factors are likely to contribute to the development of spasm and we are currently examining the role of sympathetic nerve stimulation and changes in the wall/lumen ratio occurring in experimental hypertension. This is an important field of great topical interest.

DETAILS OF PROJECTS

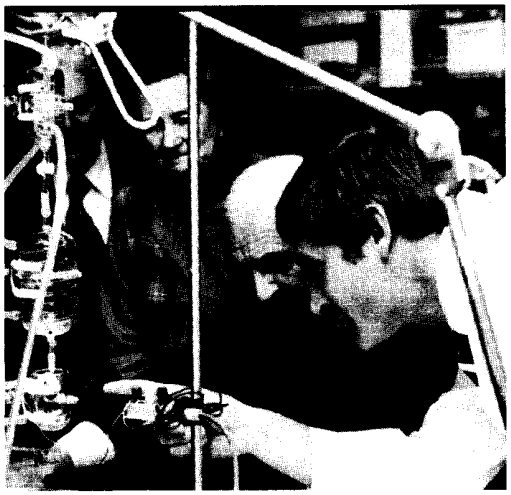
1. **Evidence against the hypothesis of presynaptic** *a*-adrenoceptor modulation of cardiac sympathetic transmission
(J. A. Angus and P. I. Korner)

Spontaneous electrocardigram signals were measured by surface platinum electrodes on isolated guinea pig right atrium. The interval (period) between succeeding signals were continuously monitored by a microprocessor controlled period meter. In the presence of atropine sympathetic nerve fibres were stimulated by applying field pulses (2 ms duration, 100 mA) programmed to occur just after the onset of the spontaneous electrogram signal in the so-called refractory period of the atrial muscle. In this way we avoided difficulties of arrhythmia which commonly occurs. The heart rate increased during random application of the stimulus following a single field pulse of 20-40 ms and returned to control after some 20 seconds. This rise in heart rate was directly related to the number of field pulses delivered. Phenoxybenzamine (10^{-6} to 10^{-5} M) markedly protentiated the rise in heart rate and its dura-

tion following a single pulse or after multiple pulses. This finding is in contrast to work by others measuring noradrenaline overflow following a single field pulse. Our results could be entirely accounted for by the well know 'side effect' of phenoxybenzamine in blocking the noradrenaline removal processes, so-called neuronal reuptake. By contrast the drug phentolamine, a potent alpha blocking drug, was completely without effect on the tachycardia response to one or more pulses. Similarly yohimbine another alpha receptor antagonist was also without effect. Therefore we conclude that under physiological frequencies of sympathetic stimulation, we can find no evidence to support the concept of presynaptic alpha-receptor inhibition of sympathetic transmission in the heart.

These findings challenge not only the concept of a modulatory role of noradrenaline on the nerve terminal, but also the accepted mode of action of clonidine on sympathetic nerves. This drug is considered to stimulate presynaptic alpha receptors located on the nerve terminal to inhibit noradrenaline release. Having failed to show the existence of presynaptic alpha receptors for noradrenaline, consideration as to the mode of action of clonidine must be revised. Using the same preparation as outlined above we have shown that clonidine (10^{-9} to 10^{-6} M) will block the rise in heart rate to one, two or four pulses in a dose-related way. By increasing the number of field pulses delivered to maintain the same rise in heart rate we have determined the degree of interference with noradrenaline release produced by a given clonidine concentration.

Concentrations of both phentolamine and yohimbine (10^{-7} to 10^{-5} M) that were completely ineffective on responses to one, two or four pusles did antagonise the clonidine induced sympathetic nerve block. Therefore it appears that these receptors located presynaptically are not activated by the transmitter noradrenaline but by highly reactive imidazolines such as clonidine. At the present time we conclude that these receptors probably should not be classified as alpha receptors at all. This work may lead to a better understanding of sympathetic nerve transmission, the mode of action of clonidine on peripheral and on autonomic nerve cells in the central nervous system and on its mode of action in hypertension.



Dr. Jim Angus (right) showing His Excellency The Governor Sir Henry Winneke and Lady Winneke an experiment to test cardiac stimulant drugs in the pharmacology laboratory.

2. Effect of Clonidine on the inotropic response to sympathetic stimulation in left atria

(J. A. Angus and E. Anderson)

Clonidine has been reported to reduce noradrenaline release from cardiac sympathetic nerves during low frequency of stimulation but increases the release during high frequency stimulation. If this increased release occurs in the vicinity of *B*-receptors there should be an elevated contractility during high frequency stimulation. We have investigated the effects of clonidine over a wide range of frequencies using the contractile response of guinea pig left atria contracting at a fixed rate from puncuate electrode stimulation. Immediately following muscle depolarisation a field pulse was delivered via a pair of platinum electrodes during the muscle refractory period to depolarise the sympathetic nerve endings and release noradrenaline. Subsequent contractions were substantially increased following the field stimulation. We found that clonidine (10^{-9} to 10^{-5} M) almost abolished the responses to low frequency of stimulation. In contrast the inotropic response to high frequency stimulation was unchanged by clonidine. Clonidine did not significantly alter either the max-

imal response nor the location parameter of noradrenaline dose-response curves suggesting that the site of action of clonidine was confined to the sympathetic nerve terminal. Therefore clonidine reduces the inotropic response to low but not high frequencies a sympathetic stimulation. We found no evidence for a partial agonist action of clonidine in this response. Further experiments showed that the clonidine block of low frequency stimulation could be abolished by drugs classified as alpha adrenoceptor antagonists such as phentolamine and yohimbine. However we have recently found two compounds that block this clonidine effect that have **no** alpha antagonist activity. These results and the data from the right atria experiments lend further support to the hypothesis that the mode of action of clonidine may not be mediated by presynaptic alpha receptors.

3. Vascular histamine receptors

(J. A. Angus and P. I. Korner)

Previously we have shown that guanethidne released histamine in the rabbit causing marked vasodilation in skeletal muscle. The histamine receptor subtypes have been characterised as H_2- and H_2-receptors and it was of interest whether the histamine released within tissue by guanethidine caused a similar change to blood flow distribution as did histamine receptors stimulated by exogenous histamine.

Chronic left atrial catheters were implanted in rabbits 2 weeks prior to the experiments for microsphere injections. Ear artery pressure and heartrate were monitored and autonomic reflexes were abolished by pharmacological blockade. Two microsphere injections of different label (strontium or cerium) were given to each rabbit, the first as a control measurement of blood flow and the second during histamine H_1-or H_2-receptor stimulation.

We found that H_2-receptor stimulation evoked by impromidine infusion or by histamine infusion in the presence of mepyamine caused a marked (700%) increase in gastric mucosal blood flow probably as a secondary consequence of the stimulated metabolic requirement of gastric acid secretion. Adrenal blood flow also increased markedly but not skeletal muscle flow. Guanethidine was without significant effect on gastric mucosa but elevated adrenal blood flow and flow to skeletal muscle. Therefore it appears that endogenous release of histamine by guanethidine may occur only in specific tissues such as skeletal muscle and that H_2-vasodilator receptors stimulated by exogenous agonists may not be reached as readily by endogenous histamine.

4. Pharmacological and Physiological Analysis of Coronary Artery Spasm

(J. A. Angus)

Angina pain at rest or variant angina has recently been documented under some circumstances as being due to coronary spasm. These episodes of severe major coronary artery constriction are not necessarily associated with severe atherosclerotic lesions but often occur at the site of a minimal lesion. Patients suspected of having variant angina respond to the ergot derivative ergometrine with marked local coronary constriction. The mode of action of ergometrine is not known but we have preliminary data to suggest that ergometrine causes spasm by stimulating serotonin receptors in dog coronary arteries as distinct from activating alpha receptors. Our investigations are directed along two lines: one, a pharmacological receptor analysis of coronary artery ring segments in vitro where a range of spasmogenic substances and specific receptor antagonists can be investigated. Secondly, a Doppler sonomicrometer technique has been developed for quantifying changes in the major coronary artery diameter in anaesthetised dogs. We also monitor coronary blood flow, coronary resistance, coronary artery pressure and myocardial oxygen consumption during physiological stimuli such as stellate ganglion stimulation. Reactivity of the coronary vasculature to constrictor substances will be assessed in control dogs and in animals where small local lesions have been produced in the large coronary vessels in an attempt to produce a model of coronary spasm.

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CARDIOVASCULAR METABOLISM AND NUTRITION RESEARCH UNIT

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1. Rosenfeldt, F. L., Cobb, F. R., Bache, R. J. and Sabiston, D. C. Effect of increases in afterload before and after coronary occulusion in awake dogs. Cardiovascular Research. **13:** 392-400, 1979.
2. Rosenfeldt, F. L., Hearse, D. J., Cankovic-Darracott, S., Braimbridge, M. V.: The Additive protective effects of hypothermia and chemcial cardioplegia during ischemic cardiac arrest in the dog. Journal of Thoracic and Cardiovascular Surgery, **79:** 29-38, 1980.
3. Rosenfeldt, F. L., McGibney, D., Braimbridge, M. V., and Watson, D. A.: Comparison between irrigation and conventional treatment for empyema and pneumonectomy space infection. Thorax, accepted for publication.

CLINICAL PHARMACOLOGY

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A. T. ELVIN, D. LALKA, K. D. STOECKEL, P. DU SOUICH, J. E. AXELSON, L. H. GOLDEN and A. J. McLEAN Tocainide pharmacokinetics in man: effects of coadministration of an enzyme-inducing agent or substrate for glucuornyl transferase. Clin. Pharmacol. Therap. (submitted).

SEMINAR PROGRAMME — 1979

Date	Title	Lecturer
16 March	An antihypertensive action for Angiotensin II.	Dr. Warwick Anderson Baker Institute
23 March	Dietary protein, hypercholesterolemia and atherosclerosis.	Dr. Murray Huff, Visiting Scientist, Department Biochemistry, University of Ontario, Canada
30 March	Rate of disappearance of glyceryl trinitrate tablets once they are in the patient's possession.	Dr. John Shaw, Department Clinical Pharmacology Royal Melbourne Hospital
6April	Generation of the cardiac action potential: chemical and electrical.	Dr. Brian Chapman Physiology Department, Monash University
20 April	Clinical Pharmacology of autonomic insufficiency — D.H.E. results.	Dr. G. Jennings, Dr. M. Esler, Baker Institute
27 April	Regulation of adenylate cyclase.	Professor Jack Martin, Department of Medicine, University of Melbourne
11 May	Application of engineering to biological systems.	Professor D. Lampard, Department of Electrical Engineering, Monash University
18 May	Fetal and neonatal pancreatic B-cell function and adipose tissue development after maternal ingestion of glucose and caffeine (Coca-Cola) during pregnancy in rats.	Mrs. Marjory Dunlop, Department of Developmental Paediatrics, University of Melbourne
25 May	Androgen receptor defects in disorders of sexual differentiation.	Dr. Garry Warne, Endocrine clinic, Royal Children's Hospital
1June	The significance of isolated thyroxine excess.	Dr. Duncan Topliss, Downie Metabolic Unit, Alfred Hospital
8 June	Basal metabolism of the arrested dog heart on cardiac bypass.	Dr. Colin Gibbs, Physiology Department, Monash University
15 June	Neuromuscular transmission in arterioles.	Dr. David Hirst, Physiology Department, Monash University
22 June	The price of civilization: diabetes, hypertension and gout in developing Pacific populations.	Professor Paul Zimmet, Department of Metabolic Medicine & Epidemiology, Southern Memorial Hospital
29 June	*B*-Blockers and the prevention of myocardial ischemia.	Dr. Barry McGarth, Department of Medicine, Prince Henry's Hospital
6 July	Hypertension in rabbits and rats: morphological examination and implications of Atherogenesis.	Dr. Gordon Campbell, Baker Institute
13 July	Acetylation phenotype screens as metabolic guidelines for dosing with procainamide, hydralazine and related drugs — influence of altered renal and absorption mechanisms.	Dr. Allan McLean, Baker Institute
20 July	Plasticity of cardiac *B*-receptors.	Dr. Alex Bobik, Baker Insitute
27 July	Non-uniformity of vasomotor outflow in response to changes of the inner millieu.	Dr. W. Riedel, Max Max Planck Institute, Bad Nauheim, West Germany
21 September	What causes smooth muscle to proliferate?	Dr. J. Campbell, Baker Institute
28 September	The autoregulation theory of hypertension — Should it be interred?	Professor P. Korner, Baker Institute
5 October	Pharmacology of cardiac sympathetic innervation.	Dr. J. Angus, Baker Institute

12 October	Cardiac hypothermia. Bane or boon.	Mr. Frank Rosenfeldt, Baker Institute
19 October	Blood pressure regulation in non-mammalian vertebrates.	Dr. David Smith, Zoology Department, Melbourne University
26 October	Platelet specific release proteins.	Dr. Frank Morgan, Melbourne University, Department of Medicine, St. Vincents Hospital
2 November	Multiple sclerosis as a possible autoimmune disease.	Professor P. Carnegie, Latrobe University
9 November	Vasopressin and hypertension.	Professor C. I. Johnston, Prince Henry's Hospital
16 November	Aspects of zinc nutrition in Australia.	Professor M. Wahlquist, Deakin University
23 November	"What you always wanted to know about lipoproteins but . . ."	Dr. P. Nestel, Baker Institute
30 November	Synthesis of matrix components by neonatal rat aortic smooth muscle cells in culture.	Dr. Barry Oakes, Anatomy Department, Monash University
7 December	Refined carbohydrate and the aetiology of obesity and diabetes.	Dr. K. O'Dea, Baker Institute

SEMINARS GIVEN BY DISTINGUISHED VISITORS

Date	Title	Lecturer
6 March	Pharmacology of N-allyl-clonidine, a specific bradycardiac agent.	Prof. W. Kobinger, Director Boehringer Institute Vienna
7 March	Adrenal chromaffin cells in culture.	Prof. K. Unsicker, Center of Anatomy & Cell Biology Philipps University West Germany
April 19	The mystery of the obese mouse — research findings in the genetically obese mouse. and The myth of diet in the management of obesity: — critical evaluation of methods of treatment.	Prof. G. Bray, Professor of Medicine University of California
April 26	Is the incidence of coronary artery disease really declining.	Dr. R. I. Levy, Director National Heart Lung and Blood Institute N.I.H. Bethesda, USA
August 21	Changing concepts in ischaemic heart disease. and Clinical aspects of rest angina.	Prof. A. Maseri, Professor of Cardiology Royal Postgraduate Medical School Hammersmith, London
September 11	The clinical spectrum of hyponatraemia.	Dr. R. Schrier, Professor of Medicine University of Colorado Denver, Colorado
October 1	The physiological and clinical aspects of the coronary circulation.	Dr. D. Sabiston Jr., Professor & Chairman Department of Surgery Duke University, N. Carolina, USA
November 23	Protein synthesis in hypertension.	Dr. W. Lovenberg, Chief of Section of Biochemical Pharmacology Experimental Therapeutics Branch, National Heart and Lung Institute, Bethesda, USA
November 26	Clinical pharmacology of beta adrenoceptor blockers.	Prof. D. Shand, Professor of Pharmacology, Duke University N. Carolina, USA

ANSETT SEMINAR SERIES

The special Ansett Seminar Series for 1979 again covered a wide range of topics. The five Australians and one American who gave lectures are all internationally renowned in their particular fields.
Flights for Professor Barger, Professor Ada, Dr. Uther and Mr. Williams were generously donated by Ansett Airlines of Australia. We are most grateful to Ansett for making the series possible.

Date	Title	Lecturer
February 21	Regulation of blood pressure by the renin-angiotensin and autonomic nervous system.	Professor A. C. Barger, Department of Physiology Harvard Medical School
April 18	Charlatens, ratbags and wise virgins.	Mr. Robyn Williams, ABC Science Unit
June 20	The cell-mediated immune response to viral infections.	Professor G. L. Ada, Microbiology Department Kohn Curtin School of Medical Research
September 27	Chemical and hormonal genesis of instinctive behaviour.	Dr. Derek Denton Howard Florey Institute for Expermental Physiology & Medicine
October 23	Mechanisms of supraventricular and ventricular tachycardia.	Dr. John Uther, Cardiology Department Westmead Hospital Sydney
November 29	Lithium nephrotoxicity.	Professor P. Kincaid-Smith Royal Melbourne Hospital

Dr. A. C. Barger, Professor of Physiology, Harvard Medical School with Professor Korner. Dr. Barger was a speaker in the Ansett Seminar Series during the first half of 1979. We are pleased to have him return in August, 1980.

PRESENTATIONS AT INTERNATIONAL MEETINGS DURING 1979

STAFF MEMBER	INSTITUTION/MEETING
Professor P. I. Korner	Australian Physiological & Pharmacological Society and New Zealand Physiological Society, Invited Speaker (Auckland, January).
	Department of Pharmacology, University of Vienna (Vienna, June).
	International Society of Hypertension Round Table (Goteborg, June).
	American Physiological Society, Invited Speaker (Dallas, April).
	University of Washington (Seattle, April).
	University of Michigan (East Lansing, April).
	National Institute of Health (Bethesda, April).
	John Hopkins Medical School (Baltimore, April).
	New York Downstate Medical School (Brooklyn, April).
	Emory University (Atlanta, Georgia, April).
	Department of Physiology and Biophysics (Jackson, Mississippi, April).
Dr. P. J. Nestel	International Diabetes Federation Congress (Vienna, September).
	Vth International Symposium on Atherosclerosis (Houston, November).
	American Heart Association (Los Angeles, November).
Dr. W. P. Anderson	Joint meeting of Australian Physiological & Pharmacological Society and Physiological Society of New Zealand (Auckland, January).
Dr. G. R. Campbell	Vth International Symposium on Atherosclerosis (Houston, November).
Dr. J. H. Campbell	Vth International Symposium on Ahterosclerosis (Houston, November).
Dr. M. Esler	University of Southern California Medical Centre, (Los Angeles, October).
	University of Michigan Medical Centre, Department Cardiology and Division of Hypertension (Ann Arbor, October).
	Cleveland Clinic, Cardiovascular Research Division (Cleveland, November).
Dr. N. Fidge	Vth International Symposium on Atherosclerosis. (Houston, November).
	American Heart Association (Los Angeles, November).
Dr. G. L. Jennings	International Society of Hypertension (Goteburg, June).
Dr. K. O'Dea	Australian & New Zealand Association for the Advancement of Science (ANZAAS, Auckland, February).

VISITORS TO THE INSTITUTE

A delegation from the People's Republic of China visited the Institute on September 14 as part of their visit to Victoria from September 11-15. The visitors expressed a keen interest in the work of the Institute and a desire to exchange further information in the future. Members of the Chinese delegation who toured the Institute were:

Professor Gao Yu, Professor of Internal Medicine, Wuhan Medical College.

Mr. Chen Xiu, Associate Professor of Pharmacology, Hunan Medical College.

Mr. She Mingpeng, Deputy Chief of Pathological Division, Institute of Basic Medical Science.

In November, Members of the Asian Scientific Study Group sponsored by the World Health Organisation through the National Health & Medical Research Council visisted the Institute. Members of the group comprising scientists from Japan, Korea and the Philippines are as follows:

Dr. Yasuzo Tsukada — Professor of Physiology, School of Medicine Keio University.

Vice-Chairman, Medical Panel, Science Council of Japan.

Dr. Toru Takahashi — Medical Officer and Deputy Director, Medical Economics Division, Health Insurance Bureau, Ministry of Health, Japan.

Dr. Paulo Campos — President, National Academy of Science and Technology.

Chairman, Medical Division, National Research Council of the Philippines.

Dr. Basaca Sevilla — Acting Director, Research and Laboratories Bureau.

Dr. Ryu Younghat — President, Korea Health Development Institute.

Dr. Min Chang Hong — Director, Department of Microbiology, National Institute of Health.

On 24 January 1980, Dr. Gwyn Howells, Commonwealth Director-General of Health visited the Institute for the first time. Dr. Howells has been Commonwealth Director-General during the period of unprecedented demand on the Australian health care system. A strong supporter of medical research, he spent a whole day at the Institute and met many of our scientists and members of the Board of Trustees.

Dr. David de Souza visited us in his capacity as Secretary of the National Health & Medical Research Council. He was previously First Assistant Director, General Therapeutics Department of the Health Department.

Sir Gustav Nossal, Director of the Walter and Eliza Hall Institute visited us on 5 February 1980. Sir Gustav is one of Australia's best known scientists for his research on immunology.

Judy Oliver showing flowmeter to members of the Chinese delegation.

STUDENT VACATION COURSE

During the May vacation period, seventy Medical and Science students from Melbourne and Monash Universities attended a course on "The Cardiovascular System in Hypertension and Atherosclerosis". The course lasted for two days (May 16 and 17) and was designed to introduce the students to current research into these two cardiovascular diseases and to emphasise the diversity of that research. The course consisted of both lectures and laboratory demonstrations of the investigatory techniques used at the Institute.

Wednesday, 16 May

Welcome to the Institute and Introduction — Prof. P. Korner.

Clinical aspects of hypertension, atherosclerosis and pharmacology — Dr. G. Jennings, Dr. A. McLean, Dr. M. Esler.

Morphogenesis of hypertension & atherosclerosis — Dr. G. Campbell.

Cell biology of hypertension & atherosclerosis — Dr. J. Campbell.

Time-lapse microcinematography of cardiac and smooth muscle cells in culture — Dr. J. Campbell.

Summary of research in the cardiovascular metabolism and nutrition research unit — Dr. N. Fidge.

Microquantitation of lipids by two different methods — TLC scanner and GLC — Dr. T. Billington & Ms. A. Everitt.

Lipoproteins — prime suspects in the cause of vascular disease — Dr. N. Fidge.

Genetic and environmental factors in the etiology of diabetes and obesity — Dr. K. O'Dea.

Dietary protein and atherosclerosis — Dr. M. Huff.

Thursday, 17 May

Control of the circulation by the central nervous system — Prof. P. Korner.

The kidney and blood pressure control — Dr. W. Anderson.

Laboratory demonstrations

- Cardiovascular reflexes in conscious rabbits — Prof. P. Korner, Ms. J. Oliver, Mr. G. Head, Dr. D. Blake. Blake.
- Electrophysiological techniques in cardiovascular investigation — Dr. P. Dorward.
- How to measure the contractile force of the heart — Dr. A. Broughton.
- The kidney and the circulation — Dr. W. Anderson, Mr. S. Selig, Miss J. Wilson.
- Heart-lung bypass machine — Sister J. Dixon.

Receptor taxonomy: Pharmacological, biochemical and clinical implications — Dr. J. Angus.

Clinical pharmacokinetics — Dr. A. McLean.

How to assess sympathomimetic activity in man — Dr. M. Esler.

Molecular pharmacology of beta-receptors — Dr. A. Bobik.

Laboratory demonstrations

- Methods in analytical pharmacology — Dr. A. Bobik, Dr. A. McLean.
- Quantifying drug-receptor interaction in isolated tissues — Dr. J. Angus.

Closing Remarks — Dr. J. Campbell.

LIBRARY REPORT 1979/1980

The Library houses a very selective collection of specialized monographs with a few general texts and handbooks for background reference.

The periodical collection follows the same selective pattern, but also includes some general medical and scientific titles.

The Library is considered to be very much a working rather than a reference library and subscriptions are begun and cancelled as the need arises to coincide with current research directions.

The Librarian works in co-operation with other medical librarians in Melbourne through the Medical Librarians Group — a special interest group of the Library Association of Australia. Such co-operation ensures easy inter-library loan and photocopy request transactions. The great reference resources of the Monash Biomedical and Melbourne Brownless Medical Libraries are gratefully acknowledged.

During 1979 the Institute Library was reviewed and many out of date and irrelevant books were withdrawn. A small historical collection was established from some of these, others were sold to staff members and the rest were discarded. The periodical collection underwent the same revision and many early volumes, no longer considered useful, were either discarded or sent to a central store at Melbourne University for later distribution to libraries wanting them to complete broken sets or to help establish reference collections. Many feet of much needed shelf space were thus released.

In early 1980 the librarian is to undertake a Medline course offered by the Australian National Library. This course is for one week and will enable research workers, through the librarian, to have "on-line" access to the MEDLARS resources at the National Library in Canberra.

Mrs. Mary Delafield, Librarian

Secretarial Staff: Standing (left to right): Karen Kerr, Margit Scott-Murphy, Clare Harwood (CRU). Seated: Seah Lian-Kee, Cheryl Griffiths, Heather Inglis.

OPEN DAY

The Institute held an Open Day on August 7, 1979. His Excellency The Governor Sir Henry Winneke and Lady Winneke were guests of honour and officially opened the Day. The Governor praised the work of the Institute over the last 50 years and expressed particular interest in the current research into cardiovascular diseases.

Over 600 people attended and included scientists, doctors, hospital staff, donors and friends. Visitors were taken on a tour of the Institute to look at the various displays which were explained to them by members of the Institute's scientific staff.

The Clinical Research Unit, organised by Drs. M. Esler, G. Jennings and A. McLean demonstrated exercise testing and discussed clinical pharmacology.

Dr. J. Angus displayed several aspects of cardiac pharmacology and Miss J. Oliver discussed the control of the circulation. Dr. P. Dorward had a display on electrophysiological techniques used to investigate circulatory control and Drs. G. & J. Campbell's displays included morphology of smooth muscle and tissue culture techniques.

Dr. F. Rosenfeldt provided demonstrations on his experiments into several practical problems in cardiac surgery and Dr. W. Anderson explained about renal hypertension.

His Excellency The Governor Sir Henry Winneke, Professor Paul Korner (left), Mr. John Habersberger (right).

Professor Paul Korner explaining displays to His Excellency The Governor Sir Henry Winneke and Lady Winneke.

Dr. T. Billington discussed the problems of altered cholesterol metabolism and Dr. N. Fidge gave a display on lipids and lipoprotein metabolism. Dr. Bobik's laboratory demonstrated biochemcial techniques used in pharmacology.

A display was also organised at the Electronics Workshop. The visitors were introduced to the function of the Heart Risk Evaluation Service which formed an interesting part of the day's programme.

The Open Day was designed to allow our many friends the opportunity to know more about us and it was a great success.

OVERSEAS VISITORS 1979

February 19-27
Professor A. C. Barger
Robert Henry Pfeiffer Professor, Harvard Medical School. Professor Barger is known for his research on the role of the kidney and renin-angiotensin system in hypertension. He has been a pioneer in the use of conscious animals. A former President of the American Physiological Society; he did his best to train Professor Korner and Dr. Anderson in the formative years. He was recently appointed 'official adviser' on future developments of the Baker Institute.

Seminar topic: "Regulation of blood pressure by the renin-angiotensin and autonomic nervous system".

March 6
Professor Walter Kobinger
Head of Pharmacological Research at the Ernest Boehringer Institute, Vienna and Professor of Pharmacology at the University of Vienna. Professor Kobinger is well known for his contribution on the mechanism of action of clonidine and other anti-hypertensive drugs. This is his second visit to the Institute.

Seminar topic: "Pharmacology of N-allyl-clonidine, a specific bradycardiac".

March 7
Dr. Klaus Unsicker
Professor of Medicine at the Center of Anatomy and Cell Biology, Philipps University, West Germany. His research interests include development of the adrenal medulla and sympathetic innervation of autonomic effector organs. He was Guest Speaker at the Neurosciences Symposium in Adelaide in 1979.

Seminar topic: "Adrenal chromaffin cells in culture".

April 19
Dr. George Bray
Professor of Medicine at the University of California, Los Angeles. He is also consultant on nutrition to the U.S. Government. He has carried out distinguished research in the field of obesity, both at the basic and clinical levels. Dr. Bray was the National Heart Foundation Distinguished Visitor for 1979.

Seminar topics: "The mystery of the obese mouse — research findings in the genetically obese mouse" and "The myth of diet in the management of obesity — critical evaluation of methods of treatment".

April 26
Dr. Robert I. Levy
Director of the National Heart Lung and Blood Institute of the National Institutes of Health, Bethesda, United States. His major research interests is in lipoprotein metabolism. He was the R. T. Hall Lecturer of the Cardiac Society of Australia and New Zealand in 1979.

Seminar topic: "Is the incidence of coronary artery disease really declining".

August 21
Professor Atilio Maseri
Formerly Professor of Medicine from the University of Pisa and recently appointed Professor of Cardiology, Royal Postgraduate Medical School, Hammersmith Hospital London. He is distinguished for his research work on the role of spasm of the coronary arteries in certain types of angina pectoris.

Seminar topics: "Changing concepts in ischaemic heart disease" and "Clinical aspects of rest angina".

September 11
Dr. Robert Schrier
Professor of Medicine, University of Colorado School of Medicine, Denver, Colorado. He is a distinguished nephrologist who has made many important contributions to our knowledge of the renin-angiotensin system, anti-diuretic hormone and renal prostaglandins are of the clinical syndrome of acute renal failure.

Seminar topic: "The clinical spectrum of hyponatraemia".

October 1
Dr. David Sabiston Jr.
Professor of Surgery, Duke Univeristy and a well known cardiac surgeon who has made major contributions to his field.
Seminar topics: "The pathophysiology, diagnosis and management of pulmonary embolism" and "The physiological and clinical aspects of the coronary circulation".

November 14

Dr. Walter Somerville

Dr. Somerville has been an influential figure of British cardiology, both in his capacity as Head of Cardiology Department at the Middlesex Hospital, and also as Editor of the British Heart Journal.

November 26

Professor David Shand

Formerly Professor of Pharmacology at Vanderbilt University, Dr. Shand has made important contributions to clinical pharmacology, particularly of beta adrenoceptor blockers. He was Roche Visiting Lecturer in 1979.

Seminar topic: "Clinical pharmacology of beta adrenoceptor blockers".

November 23

Dr. Walter Lovenberg

Head of the Department of Biochemical Pharmacology, National Heart Lung and Blood Institute, National Institutes of Health, Bethesda. He visited the Institute after spending a sabbatical few months at the Flinders Medical School and generously donated a colony of spontaneously hypertensive rats to the Institute. He is well known for his research on the role of brain amine transmitters in the central nervous system.

Seminar topic: "Protein synthesis in hypertension".

February 12, 1980

Professor Jacques Genest

R. T. Hall Lecturer 1980. Chief of the Nephrology Hypertension Service, Hotel-Dieu Hospital of Montreal and Scientific Director, Clinical Research Institute of Montreal. Professor Genest is well known for his clinical and research work on hypertension.

Seminar topic: "Management of renovascular hypertension".

VIP TOURS

During 1979 we were privileged to welcome the following visitors:

Mrs. D. Alley, President, National Council of Women of Victoria

Mr. B. Baker, Baker, Suttie & Co. Pty. Ltd., Estate Agents

Mr. K. Barnes, Director — Finance, Alfred Hospital

Mr. P. T. Bartels, Group General Manager, Henry Jones Ltd.

Mr. L. E. Beck, Managing Director, Nissan Motor Manufacturing Co. Ltd.

Mr. W. Beckett, Account Executive, CBA Insurance Services Ltd.

Mr. J. Beggs, President, Waterside Workers Federation

Ms. O. Bell, Representative, Hedges & Bell Pty. Ltd.

Mr. L. L. Blyth, Industrial & Training Officer, Trustee Companies Association

Mr. R. Brett, Parliamentary Counsel, Parliamentary Counsel Chambers

Mr. J. Briglia, Senior Trust Officer, National Trustees Executors & Agency Co. of Australasia

Mr. T. A. E. Bull, Secretary, Waterside Workers Federation

Mr. W. A. Butterss, Managing Director, Hardie Trading Limited

Mrs. C. Campbell, Women's Coordinator, Shop Distributive & Allied Employees Association

Mr. N. R. Campbell, Branch Manager, Bank of New South Wales

Mr. N. M. Carlyon, Managing Director, Carlyon Group

Mr. J. Carroll, Business Manager, Howard Florey Institute

Mr. A. E. Chegwin, Treasurer, Royal Victorian Bowls Association

Mr. D. L. Chisholm, Maddock Lonie & Chisholm, Solicitors

Mr. J. Cobb, Group Travel Supervisor, CBA Travel Services Limited

Mr. P. Cole-Adams, Associate Editor, The Age

Sir Norman Coles, Chairman, G. J. Coles & Co. Ltd.

Mrs. E. Connor, Chief Executive Officer, State Film Centre

Mr. T. B. Cook, Registar, Collingwood Technical College

Mr. D. J. Cornish, Manager, The Trustees Executors & Agency Co. Ltd.

Mr. D. Dawson, Solicitor-General, Victoria

Mr. K. Dawson, Manager, Perpetual Executors & Trustees Association of Australia

Mr. K. Devine, Staff Training & Development Officer, Alfred Hospital

Mr. D. L. Elsum, Chief General Manager, Capel Court Corporation

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

Ms. N. J. Findley, Principal, Emily McPherson College

Mr. J. Foley, Executive Director, Multiple Sclerosis Society

Mr. J. E. Gamble, Director, Collie & Co. Pty. Ltd.

Mr. A. G. Gibbs, A.O., Chairman, Victorian Railways Board

Mr. K. Gifford, Q.C. c/- H. D. Muir, Barristers

Mr. I. A. Gittus, General Manager, Nabisco Pty. Ltd.

Mr. P. Grey, State Manager, CBA Insurance Services Ltd.

Dr. M. Halford, Technical Secretary, Australian Associated Brewers

Dr. H. Halse, Senior Medical Officer, Public Service Medical Centre

Mrs. H. Handbury, Director, Southdown Press

Mr. G. Hay, Secretary, Walter & Eliza Hall Institute

Mr. & Mrs. G. F. Hicks

Dr. G. Hodgson, Chairman — Laboratory Research Division, Cancer Institute

Mr. J. Holland, Medical Correspondent, The Age

Mr. D. Holt, Corporate Trusts Officer, Trustees Executors & Agency Co.

Mr. B. Hoy, Assistant Manager, National Trustees Executors & Agency Co. of Australasia

Ms. S. Humphrey, Compere, Nationwide, ABV-2

Mr. M. Johnson, Senior Trust Officer, Equity Trustees Executors & Agency Co. Ltd.

Professor C. I. Johnson, Department of Medicine, Prince Henry's Hospital

Mr. R. Jubb, Assistant State Manager, ANZ Banking Group Ltd.

Mr. J. Kennedy, Yarwood Vane & Co., Accountants

Mrs. Y. Klempfner, Co-ordinator, Women's Affairs, Premier's Department

Mr. G. S. Lang, Managing Director, K. Gardner & Lang

Mrs. J. Leckie, President, The Royal Women's Hospital

Mrs. W. L. Lord, Director — Board of Australian American Association

Mr. B. T. Loton, Chief General Manager, The Broken Hill Pty. Ltd.

The Hon. Mrs. Justice Lusink, Family Court of Australia

Dame Patricia Mackinnon, D.B.E., President, Royal Children's Hospital

Dr. N. J. McCarthy, Director, Commonwealth Serum Laboratories

Mr. J. I. McCoy, General Manager — Administration, Petersville Ltd.

Mr. L. McGrath, Assistant Property Manager, Equity Trustees Executors & Agency Co. Ltd.

Mr. P. McIntosh, Medical Journalist, The Age

Mr. L. McKenzie, General Manager, Trans Australia Airlines

Cr. L. R. McMahon, Councillor, City of Springvale

Ms. D. Manning, Promotions Officer, Epworth Hospital

Lady Matheson, Chairman, Equal Opportunity Advisory Council

Mr. S. Meese, Medical Journalist, Sun News-Pictorial

Mr. K. A. Mitchell, Managing Director, Puma Australia Pty. Ltd.

Mr. J. Montes, Programme Officer, Ethnic Radio 3EA

Mr. W. Morton, Manager, Union Fidelity Trustee Co. Australia Ltd.

Mr. N. E. Mutton, Deputy General Manager, Royal Insurance Australia Ltd.

Mr. K. Baillieu Myer, Chairman, Myer Emporium Limited

Mr. B. Naylor, GTV-9 News

Mr. B. Noseda, Director — Engineering & Building Services, Alfred Hospital

Councillor Hanna Pan, Chairman, Health & Social Services Committee, Melbourne City Council

Mr. M. Pawsey, Controller (Buildings), University of Melbourne

Mr. T. Peden, Agency & Interline Supervisor, Ansett Airlines of Australia

Mr. D. Phelps, GTV-9 News

Mr. P. M. Popple, Consul-General, American Consulate General

Mr. S. C. Price, Sales Director, Georges Australia Ltd.

Ms. R. Pryor, Organiser, Federated Municipal & Shire Council Employees Union

Mr. J. Quine, Manager, Caulfield Hospital

Ms. J. Rigg, Producer — ABC Science Bookshop, Australian Broadcasting Commission

Mr. R. D. Roberts, Director — Personnel Services, Alfred Hospital

Mr. R. Scholes-Robertson, Assistant Manager, Perpetual Executors and Trustees Association of Australia Ltd.

Ms. R. Rodie, Assistant Director — Personnel Services, Alfred Hospital

Ms. C. Ross, Journalist, Sun-News Pictorial

Mr. H. Sakai, Consul Representative, Consulate General of Japan

Ms. S. Sampson, Lecturer, Faculty of Education, Monash University

Mrs. D. Sargeant, Director, Social Biology Resource Centre

Mr. G. G. Saunders, Charitable Trust Officer, Trustees Executors & Agency Co. Ltd.

Mr. M. Simpson, Director, United Shoe Machinery Group

Mr. A. F. Smith, Gillotts, Solicitors

Mr. K. L. Smyth, Director, R. L. Polk & Co. (Aust.) Pty. Ltd.

Mr. C. R. Taylor, Taxation Officer, Union Fidelity Trustees Co. of Australia

Mr. J. Taylor, Taylor & Roberts, Insurance Representatives

Mr. B. Tobin, State Manager, CBA Travel Services Pty. Ltd.

Mr. F. R. Townsend, Chief Chemist, Arnott Brockhoff-Guest Pty. Ltd.

Mr. J. C. Trethowan, Chairman, State Electricity Commission

Dr. G. Trevaks, Chairman, Health Commission of Victoria

Dr. F. Trinker, Medical Director, Peter MacCallum Hospital

Mr. P. C. Trumble, Mallesons, Solicitors & Notaries

Mr. G. W. D. Tyler, Executive Director, St. Georges Hospital

Mr. A. E. Watkin, Consultant, H. Byron Moore, Day & Journeaux

Ms. L. Wells, Victorian Bureau Chief, Women's Weekly

Matron M. A. West, Windermere Hospital

Mr. G. McK. Wilson, Consultant, H. Byron Moore, Day & Journeaux

Mr. P. J. Wiltshire, Administration Manager, Royal Victorian Bowls Association

Mr. D. Wittner, President, Rotary Club of Melbourne.

Mr. J. P. Young, O.B.E., Chairman, J. P. Young & Associates (Aust.) Pty. Ltd.

Merck, Sharpe & Dohme (Aust.) Pty. Ltd.	17,000.00
Windermere Hospital Foundation	15,500.00
The William Buckland Foundation	15,000.00
H. & L. Hecht Trust	14,000.00
Sandoz Research Fund	13,000.00
The Percy Baxter Charitable Trust	11,100.00
Alan Williams Trust	10,300.00
The Felton Bequest	6,500.00
Dow Chemical (Aust.) Ltd.	6,000.00
The James & Elsie Borrowman Research Trust	5,950.00
Broken Hill Co. Pty. Ltd.	5,000.00
The Collier Charitable Trust	5,000.00
The American Sugar Association Incorporated	4,705.00
The George Thomas Lockyer Potter Charitable Trust	4,125.00
The William Anglis (Victoria) Charitable Trust	4,000.00
Estate Edward Wilson	4,000.00
Ciba-Geigy (Aust.) Ltd.	3,350.00
Jack Brockhoff Foundation	2,500.00
The Appel Family Trust	2,000.00
Kodak (A'Asia) Pty. Ltd.	2,000.00
Sidney Myer Charitable Trust	2,000.00
E. R. Squibb & Sons Pty. Ltd.	2,000.00
I.C.I. Australia Ltd.	1,900.00
Truby & Florence Williams Charitable Trust	1,750.00
C.F.W. Taylor Public Charitable Bequest	
H. G. Turner Estate, Helen G. Turner Samaritan Fund	
T. J. Sumner Trust Charity Fund	
Alfred Edments Trust	
Waterside Workers Federation of Australia	1,521.00
Bank of N.S.W. Ltd.	1,400.00
The Marian & E. H. Flack Charitable Trust	1,310.00
The Bell Charitable Trust	1,250.00
Boehringer Ingleheim Pty. Ltd.	1,000.00
G. J. Coles & Coy Limited	1,000.00
Estate R. V. Hall	1,000.00
David Syme & Co. Ltd.	1,000.00
J. B. Were & Son	1,000.00
Estate Barbara Collie	900.00
Truby & Florence Williams Charitable Trust	900.00
Estate Alfred Edments	850.00
C.B.A. Travel Service	750.00
Estate Catherine M. Collie	600.00
E. Armanious	500.00
Werge Batters Trust	500.00
Estate P. Brennan	500.00
Capel Court Corporation Ltd.	500.00
Carlton & United Breweries Ltd.	500.00
Barry Dunbar	500.00
R. W. Ennis	500.00
Laurie Fitzgerald	500.00
N. H. Gallagher	500.00
General Motors Holden's Ltd.	500.00
J. C. Habersberger	500.00
The George Frederick Little Trust	450.00
Baker Medical Research Institute Social Club	418.00
Mrs. E. E. B. Hewgill	300.00
Kraft Foods Limited	300.00
W. A. Deutscher	250.00
F. Murphy	250.00
Nabisco Pty. Limited	250.00
Pethard Charitable Trust	250.00
The Shell Company of Australia Limited	250.00
H. B. Blaich	200.00
Bly's Industries Pty. Ltd.	200.00
Greig Bros.	200.00
M. & E. Helmer	200.00
A. Janetzki	200.00
Prof. P. I. Korner	200.00
J. L. Purves	200.00
Repco Ltd.	200.00
H. Schrieber	200.00
Ms. M. A. Simpson	200.00
G. Stirling	200.00
Smith Kline & French Laboratories (Aust.) Ltd.	200.00
Alan Watkin	200.00
Roger David London Stores Social Club	155.00
Royal Insurance Australia Ltd.	150.00
F. K. Alfredson	100.00
Alls Souls Opportunity Shop	100.00
Gillian Ansell	100.00
N. H. Ansell	100.00
A.N.Z. Banking Group Ltd.	100.00
H. & I. Arnold	100.00
Clarendon Finance Pty. Ltd.	100.00
Commonwealth Industrial Gases Ltd.	100.00
Construction Engineering (Aust.) Pty. Ltd.	100.00
N. F. Cruickshank	100.00
C.T.M. Nominees Pty. Ltd.	100.00
Cypress & Sons Pty. Ltd.	100.00
Mrs. M. A. Dobson	100.00
Drummond Air	100.00
L. M. Francome	100.00
Kenneth G. Gifford	100.00
Mrs. B. L. Glascodine	100.00
Miss H. D. Glascodine	100.00
Ben Halpen	100.00
H. R. Holdenson	100.00
R. W. Lister	100.00
Mrs. Lois Lowe	100.00
Alice B. & B. J. Marks	100.00
Mrs. D. M. Martin	100.00
Anonymous	100.00
E. M. Monotti & Son	100.00
G. Montesalua	100.00
L. M. Muir	100.00
Miss G. B. Murray	100.00
J. R. McDonnell	100.00
Mrs. Shirley McKenry	100.00
R. E. Nelson	100.00
Mrs. A. O. Officer	100.00
C. N. Pitt	100.00
V. Reeves	100.00
B. N. Richardson	100.00
Roger David Stores Pty. Ltd.	100.00
Mr. & Mrs. C. & J. Roxburgh	100.00
Sister of Mercy — Mercy Maternity Hospital	100.00
Mrs. M. Slater	100.00
Mrs. A. K. Stewart	100.00
H. D. Stewart	100.00
R. J. Stewart	100.00
A. Stickland	100.00
Taylor & Roberts	100.00
The Southsiders	100.00
Mrs. M. C. Volum	100.00

Wenzel Distributors Pty. Ltd.	100.00
I. M. Willis	100.00
A. & V. Wilkison	100.00
G. McK. Wilson	100.00
Wiretainers Pty. Ltd.	100.00
F. Yencken	100.00
John F. Malesa	80.00
Seigfried Meyer	75.00
Norlane Bowling Club Associates	73.00
Mrs. J. Farrarin	60.00
Ms. A. B. Williams	60.00
Anonymous	50.00
Australian Institute of Management	50.00
A. Barouh	50.00
T. W. Canly	50.00
Mrs. M. Cottrell	50.00
A. G. Coulthard	50.00
Country Women's Association of Victoria	50.00
W. B. Crothers	50.00
Miss I. Davidson	50.00
F. Davis	50.00
Mrs. D. Dobney	50.00
Mrs. D. Doons	50.00
J. W. Duggan	50.00
J. Dunham	50.00
Mr. & Mrs. A. S. Edwards	50.00
J. J. Farish	50.00
L. K. Farmer	50.00
Mrs. M. Fetter	50.00
Ms. S. Fink	50.00
A. E. Foers	50.00
Miss E. Gaylard	50.00
Mr. & Mrs. J. G. Gaylard	50.00
Rix. A. Geeves	50.00
C. N. George	50.00
G. Gibson	50.00
Miss M. Greig	50.00
Mrs. R. B. Hallows	50.00
T. Holden	50.00
Mrs. N. Horton	50.00
F. K. Hough	50.00
Mrs. F. Hunter	50.00
Jenglass Products	50.00
R.G.A. Johnston	50.00
F. Karpenkow	50.00
Mrs. E. F. Lamburd	50.00
J. C. Lloyd	50.00
Mrs. G. Marks	50.00
Martyniuk Family	50.00
Mercantile Mutual Insurance Co. Ltd.	50.00
D. Messenger	50.00
G. F. Mitchell	50.00
Morris Ross Enterprises Pty. Ltd.	50.00
E. W. Muntz	50.00
A. W. McDonald	50.00
H. L. McDonald	50.00
B. M. McKay	50.00
I. D. MacKinnon	50.00
Mrs. J. F. McNab	50.00
Sir James McNeill	50.00
Ms. McNicoll	50.00
Mrs. D. Newton	50.00
Nissan Motor Manufacturing Co. (Aust.) Ltd.	50.00
P. L. Norris	50.00
S. J. Oakes	50.00
Dr. K. Oppenheimer	50.00
Packard Instrument Co.	50.00
Pen Dragon Nominees	50.00
H. I. Phillips	50.00
Pilkington A.C.I. Ltd.	50.00
R. G. Pitcher	50.00
Planex Pty. Ltd.	50.00
D. Porter	50.00
Mr. & Mrs. L. Read	50.00
A. L. Renshaw	50.00
Ken Richards	50.00
N. Rockman	50.00
C. Rutledge	50.00
A. E. Stansen & Co. Pty. Ltd.	50.00
Selbys Scientific Ltd.	50.00
D. W. Scott	50.00
K. A. Skinner	50.00
James Smith	50.00
J. Smith	50.00
F. Szappanos	50.00
Mrs. F. Taylor	50.00
Mrs. D. Teasdale	50.00
I. Turriff	50.00
R. Vickers	50.00
N. Walden	50.00
Miss F. Walsh	50.00
B. J. Walter	50.00
Thos. Warburton Pty. Ltd.	50.00
Mrs. J. Winter	50.00
L. A. Young	50.00
	$324382.00

Other donations under $50.00 from Friends of the Heart People $14,390.00

Further contributions were received from —
Australian Eagle Insurance Co. Ltd., Associated Broadcasting Services Ltd., 2/14 Australian Field Regiment Association, R.M.V. Blakemore, Mrs. E. Cooper, Miss N. E. Cameron, Mrs. K. Coffey, Mr. & Mrs. M. A. Cuming, Ms. Ivy Dickie, Miss E. Denham, Mr. J. C. Habersberger, Cynthia-Shina-Caroline & Paul Holder, Elinor Hancock, Misses D. & J. Jeffrey, Mary & Chris McPherson, Miss M. McPherson, J. & H. McConnell, Mrs. M. Murphy, Mrs. Zaglio, Noel Gwen Monteith, Mrs. M. E. Rumble, E. S. Scrutin, J. Scott, Mrs. T. Shelley, Arthur Turner, N. T. Veal, West Brighton Club.

In Memory of —
John William Archer, Percy Howard Boden, Mr. Burdett, Alan Berhault, Dr. A. Cooper, Mrs. Ethel Campbell, George Harvey Crammond, John Harold Collier, Alan Dowdall, W. Davis, Cyril W. Edwards, James Robert Eager, Martin Egan, Ernie Fraser, Lily A. Hosking, Mr. N. W. Hepples, Mr. B. E. Coombes, Mr. R. D. Birdsey, G. W. U. Jewell, A. Joel, George E. Knox, Sister Kerry Kocovski, Mr. L. E. Lesser, Louis Francis Lette, Elva Maitland, Mrs. Connie Pugsley, S. Pecumia, Ivan Stedman, Mrs. Edwin Spry, Mrs. Nell Scrivens, Mrs. Rosie Seefeld, William Thornton, Mrs. Mary Alice Turner, L. Williams.

Total $617.00.

Auditors' Report to the Trustees of The Thomas Baker, Alice Baker and Eleanor Shaw Medical Research Institute.
In our opinion the balance sheet and statements of movement in accumulated funds, as set out on schedules 78 to 81 are properly drawn up to show a true and fair view of the state of the Institute's affairs at 31 December 1979.

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

Melbourne
15 April 1980

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

Balance Sheet at 31 December 1979

ACCUMULATED FUNDS AND LIABILITIES			
Operating Fund			
Accumulated (deficit)			(73,985)
Bank overdraft			115,759
Sundry creditors and accured expenses			50,338
			92,112
Endowment Fund			
Accumulated fund			1,498,617
			1,498,617
Research, Scholarship and other funds			
Restricted fund			37,323
Edgar Rouse Memorial Fellowship Fund			58,302
Laura Nyulasy Scholarship Fund			2,873
William Buckland Research Fund			30,757
Lang Research Scholarship Fund			4,852
			134,107
			$1,724,836
ASSETS			
Operating Fund Assets			
Cash on hand			300
Sundry debtors			5,568
Short term deposits (at cost) held by Trustees of the Institute			86,244
			92,112
Endowment Fund Assets			
Investments (at cost) —			
Held by Trustees of the Institute:			
Freehold properties	40,000		
Government and semi-government stock	86,124		
Shares and debentures in companies	130,817		
Short term deposits	263,552		
Mortgage loans	348,000	868,493	
Held by the Trustees, Executors & Agency Co. Ltd			
Shares in companies	64,322		
Trust units	548,719		
Short term deposits	7,200	620,241	
Cash at bank		9,883	1,498,617
Research and Scholarship Fund Assets			
Investments (at cost):			
Held by Trustees of the Institute:			
Shares in companies		4,852	
Short term deposits		53,000	
		57,852	
Held by the Trustees, Executors & Agency Co. Ltd			
Shares in companies	8,698		
Trust units	22,059		
Short term deposits	5,673	36,430	
Cash at bank		39,825	134,107
			$1,724,836

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

Year Ended 31 December 1979

Statement of Movement in Accumulated Funds

Operating Fund		
Salaries and wages		908,803
Laboratory supplies and isotopes		172,696
Additional equipment and building costs		178,287
Library maintenance		20,685
Postage and telephone		14,104
Printing and stationery		21,439
Light and power		42,124
Insurance		15,065
Repairs and renewals		34,255
Animal house contribution		9,000
Collaborative Grant — NH & MRC Programme		50,000
Travelling expenses		26,076
Public relations		6,010
Stanhope Court		1,541
Sundries		11,466
		$1,511,551
Deficit for year		23,719
Accumulated deficit as at 1 January 1979		50,266
Accumulated deficit as at 31 December 1979		$73,985
Donations from Baker Benefactions		
Statutory amount	11,569	
Transfers from Endowment Fund	311,291	
		322,860
Donations other		190,117
Grants-in-Aid of Research Projects		
Life Insurance Medical Research Fund of Australia and and New Zealand	55,879	
National Health and Medical Research Council	408,459	
National Heart Foundation of Australia	50,063	
		514,401
Other Grants		
The James and Elsie Borrowman Research Trust	5,950	
The William Buckland Research Fund	2,000	
Victorian State Government	130,000	
Laura Nyulasy Research Scholarship Fund	660	
		138,610
Interest from Investments		
Held by Trustees of the Baker Institute Grant Trust	3,161	
Other investment income	163,544	
		166,705
Other Income		
Rentals	49,357	
Sundry sales, recoveries and refunds	105,782	
		155,139
Deficit for the year		23,719
		$1,511,551

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

Year Ended 31 December 1979

State of Movement in Accumulated Funds Research, Scholarship and Other Funds

Restricted Fund		
Balance at 31 December 1978		73,083
Patients' Fees	55	
Baker Benefactions Statutory Amount 1980	11,569	
Donations	25,705	
Investment income and bank interest	390	
NIH (USA) (Dr. J. Maloney)	17,329	
Dow Chemicals Clinical Trial	3,000	
		58,048
		131,131
Transfer to Operating Fund		
— Baker Benefactions Statutory Amount 1979	11,569	
—Donations, Grants and Other Income	64,887	
Transfer to Monash University (Dr. J. Maloney)	17,329	
Other	23	
		93,808
Balance at 31 December 1979		$ 37,323
Edgar Rouse Memorial Scholarship Fund		
Balance at 31 December 1978		54,145
Donations (includes $296 transfer from Endowment Fund)	617	
Investment income and bank interest	6,181	
		6,798
		60,943
Transfer to Operating Fund — Other Income		2,641
Balance at 31 December 1979		$ 58,302

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

Year Ended 31 December 1979

Statement of Movement in Accumulated Funds

Endowment Fund		
Balance at 31 December 1978		1,446,707
Donations	356,652	
Interest	795	
Profit on sale of shares	6,050	
		363,497
		1,810,204
Transfer to Operating Fund	311,291	
Transfer to Edgar Rouse Memorial Scholarship Fund	296	
		311,587
Balance at 31 December 1979		$1,498,617

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

Year Ended 31 December 1979

Statement of Movement in Accumulated Funds Research, Scholarship and Other Funds

Laura Nyulasy Scholarship Fund	
Balance at 31 December 1978	2,864
Investment income	669
	3,533
Transfer to Operating Fund	660
Balance at 31 December 1979	$2,873
William Buckland Research Fund	
Balance at 31 December 1978	29,218
Investment income	3,539
	32,757
Transfer to Operating Fund	2,000
Balance at 31 December 1979	$30,757

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

Notes To and Forming Part of the Accounts for the Year Ended 31 December 1979

1. STATEMENT OF ACCOUNTING POLICIES

The following accounting policies were also adopted in the preceding year of the Institute's operation, unless otherwise stated:

(a) Historical Cost

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

(b) Institute Funds, Income and Expenditure

The work of the Institute is financed from grants, endowments, donations and bequests of both general and specific natures. Income is taken to the Operating Fund within the terms of any relevant covenants applicable to that income.

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

(c) Capital Expenditure and Depreciation

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

The insurable value of such accumulated capital expenditure, including buildings, to 31 December 1979 was approximately $5,700,000 (1978 $5,700,000).

(d) Investments

The market value of shares in companies listed on the Australian Stock Exchange at 31 December 1979 was $355,578 (1978 $243,010).

The Trustees, Executors & Agency Co. Ltd., is the custodian and manager of certain investments of the Institute. These investments are included in the balance sheet of the Institute in accordance with statements provided by the custodian company, giving details of the Institute's entitlements in securities held by the custodian company in its own name.

Biology Research Unit Extensions in progress.

BIOLOGY RESEARCH UNIT

Increased requirements for dogs and rats and guinea pigs were fully satisfied, despite difficulties of space and facilities. No serious disease problems were evident and all experimental animals were maintained in excellent health. Good staff, Husbandry and Preventative Health Programmes contributed largely to this satisfactory result.

The 'New Building' was commenced in September 1979 to cater for increased Research needs for animals and is scheduled for completion in August 1980. This building extension links the Baker Institute to the old animal house. The new structure is of two stories and has direct access from the ground and first floor of the 'Old' Baker building. The building provides for greatly needed space, convenience and comfort for both animals and Research workers.

In August '79, Mr. Paul Dewsnap Second-in-Charge of the Department left to take charge of the animal facilities at the John Turnbull Research Laboratories at Frankston (State Dept. of Vermin and Noxious Weeds). Paul worked in the unit for over 4 years successfully completing the course for Animal Technicians (Applied Science Course Dept. of Education). His contribution to Husbandry generally and in particular the rabbit breeding colony was a valuable contribution to the units efficiency. Two other Animal Technicians, Mr. David Harrison and Mr. Paul Jones completed the 1st year of the Animal Technicians Course of 4 years duration (part-time studies) Mr. Richard Hackett started work in the unit Dec '79 as an animal assistant.

LIST OF STAFF MEMBERS

Name	Designation
	1979
Dr. N. Walden, B.V.Sc., M.R.C.V.S.	Veterinary Consultant
Mr. A. Bons	Technical Officer in Charge
Mr. P. Dewsnap	Technical Officer (Resigned Aug '79)
Mr. D. Harrison	Technical Assistant
Mr. P. Jones	Technical Assistant
Mr. A. Medoro	Technical Assistant
Mr. E. Turnbull	Animal Assistant
Mr. C. Wiley	Animal Assistant
Mr. R. Hackett	Animal Assistant (Dec '79)
	1980
Mr. D. Harrison	Resigned and Transferred to Baker Jan '80
Mr. K. O'Callaghan	Started Jan '80 to replace above
Mr. C. Wiley	Resigned to live in Queens. Jan '80
Mr. W. Grant	Started Jan '80 to replace above

Michael G. Downes

THE NEED FOR SELF HELP

(by M. G. Downes, Financial Director, Baker Institute)

The importance of medical research in Australia is probably well appreciated by most of the recipients of this Annual Report. However, there are attitudes in our community that research activities could well be left to other nations.

Australians have contributed a great deal to worldwide knowledge in the field and we will continue to do so. A sound and enthusiastic Australian medical research programme, which is adequately funded is important not just for new knowledge but to improve the standards of high quality medical care. It aids the evaluation of new procedures in Hospitals, plays an important role in teaching medical students and transferring knowledge to medical pratitioners.

Those who provide finance for such activities help not only an Institute like ours, but in the long term help themselves and Australia.

When one considers the lack of funds for medical research in this country, there are really only two avenues ahead. The first is ably covered by the Director in his report when he stresses the need for a substantial increase in Federal funding through the National Health and Medical Research Council.

The second avenue, in addition to further Government funding is that we can help ourselves by raising other income through an effective fundraising programme.

A not-for-profit organisation can attract finance from trusts, companies and people sympathetic to their cause. To do this however requires a careful and considered approach.

Fundraisers in Australia don't do this well enough. Most of them sit down and write their appeals quite subjectively without any appreciation of what the recipient knows, believes or feels about the cause. The correct procedure is as logical as planning a scientific experiment. It involves understanding the community and their philanthropic attitudes, understanding what we at the Baker Institute offer the community, being able to identify those people likely to be sympathetic towards our work and then presenting our story properly. We must effectively position our cause in the minds of the right people as a unique service worth supporting.

Based on the best information we have in Australia, (which is not nearly accurate enough) we have made a guess that philanthropic giving in this country in 1979 was about $200 million or $13.30 per head.

In the United States, a very comprehensive document published each year gives the 1979 figure as $39,560 million or $184 per head. That's 14 times as much as Australians give.

Whilst we realise that there are some very large Foundations giving substantial amounts which disproportionately lift this per capita figure, the simple fact remains that Americans are more receptive to supporting their favourite charities out of their own pockets. To them, fundraising requests are an opportunity to give, and not seen as "begging" as seems to be the case in Australia.

The other significant factor in raising funds from the private sector is that these are not affected by national economic difficulties. Personal giving is geared to per-

sonal income, and today the opportunity to increase private donations is very real with regular increases in salaries.

Here at the Baker Medical Research Institute we are actively doing more to help increase private donations. During 1979 our mailing piece "The Silent Killer" was extremely successful. This mailing alone gathered 1500 new donors contributing in excess of $24,000. The Australian Direct Marketing Association presented the Institute with an award in recognition of the outstanding presentation of the mailing piece.

Our approach to Business and Industry is as yet in the early stages, but results so far have been encouraging. Broken Hill Proprietary Limited have in 1978 and 1979 contributed $5,000 each year.

Patients from the Alfred Hospital and our Heart Risk Evaluation Clinic have also helped us.

Our regular VIP tours bring support in financial terms and in kind.

Donations from appeals are steadily increasing — from $77,000 in 1977 to $128,000 in 1978 and and now 1979, $197,000.

In 1980 we have several special efforts under way and we aim to increase the general level of donations still further.

The secret of our success is that we have opened our doors to the public. Regular visits, regular press coverage and contact with Trusts, business and industry, and private individuals mean that we are better known.

The Institute now has a personality — "The Heart People" — we are not a sterile, uninteresting laboratory tucked away out of sight. We are people working to prevent heart disease and provide better treatment for people in our community.

Giving, is preceded by attitudes which are preceded by awareness. The question we constantly address ourselves to is this:

> "Who would we prefer to ask to donate —somebody who knows our work or somebody who has never heard of us?"

The answer is obvious and so we will continue to be visible to our community and hope that their increasing support will contribute to our further successes.

If you would like to help us with a donation, bequest, gift of property or shares, or legacies, remember we use this income for medical research only. All gifts are tax deductible and the writer would be happy to discuss with you how you might help.

Please contact: Michael G. Downes
Financial Director
Baker Medical Research Institute
Commercial Road
Prahran 3181
Melbourne, Victoria.

BAKER REVUE

The theme of our 1979 revue was "Keep the Beat" — the Institute's unofficial slogan. The cast of twenty-five entertained the audience of almost 200 in the Prahran Town Hall on December 8. The after dinner show consisted of sketches, song and dance. Amongst the many highlights were Norio Tada as a Japanese Elvis Presley, Kerin O'Dea as her idol Flo Bjelke-Petersen, Arch Broughton as the Ayatollah, Mike Downes in his ever-popular portrayal of Joh Bjelke-Petersen, Warwick Anderson as Bob Hawke, Peter Ashley and Mark Sanders as the Two Ronnies and Libby Anderson and Andrea Everitt singing Edna Everage's Hymn.

Many other members of the Institute helped with the production and special mention should be made of the Workshop (and in particular Kevin Harvey), Mike Downes (for scripts), Cheryl Griffiths, Karen Kerr and Lian Kee and Noel Fidge for his brilliant piano playing. And the most memorable sight of the evening — Paul, Peter, Frank, David, Geoff and Billy as victims of the Baker's contagious disease (i.e. pregnancy!).

Cast: Kerrie Anne Hare, Billy Jones, Cheryl Isbister, David Harrison, Lucy Popadynec, Frank Forgione, Gillian Love, Gordon Campbell, Libby Anderson, Arch Broughton, Andrea Everitt, Frank Rosenfeldt, Jan Dixon, Geoff Head, Mike Downes, Garry Jennings, Warwick Anderson, Paul Leonard, Julie Campbell, Peter Cahill, Norio Tada, Kerin O'Dea, Peter Ashley, Mark Sanders, Noel Fidge, Arthur Knights, Peter Anderson.

The Revue was produced by Warwick Anderson.

Mike Downes (left) as Dismal Downes and Frank Rosenfeldt as Frowning Frank in "More Misery".

CLINICAL RESEARCH UNIT

STAFF

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

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

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

Assistant Physician
M. ESLER, M.B., B.S., B.Med.Sci., F.R.A.C.P., Ph.D.(ANU)

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

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

Dietitian
SYLVIA POMEROY, M.Sc.

Scientific and Technical Staff
P. ASHLEY, B.Sc.
M. BANGAH, B.Sc.
JANET BROWN
A. IOANNOU
SUE ELLETT
M. SANDERS
HELEN SKEWS, B.Sc.

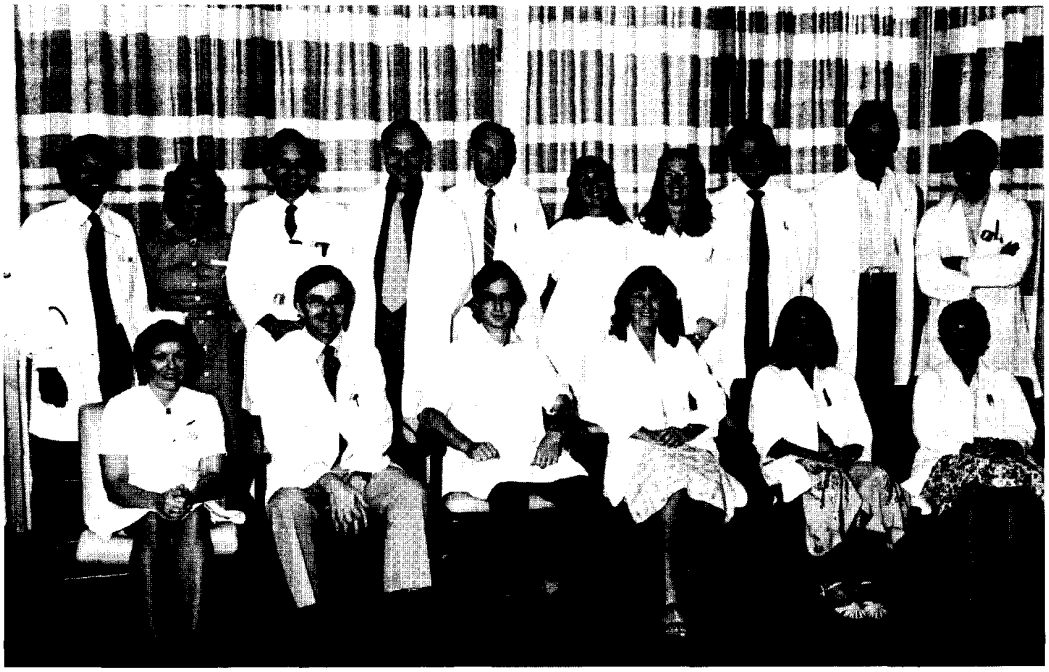
Registrars
R. NEWMAN, M.B.B.S., F.R.A.C.P.
D. ROSE, M.B.B.S., F.R.A.C.P.

Residents
H. HUNT, M.B.B.S., F.R.A.C.P. Part I
V. WAYNE, M.B.B.S., F.R.A.C.P. Part I
K. ROONEY, M.B.B.S., F.R.A.C.P. Part I
I. OLVER, M.B.B.S.

Laboratory and Ward Sister
SUE SCEALY

Hypertension Clinic
SR. HELEN HALL (Baker Institute)

Secretary
CLARE HARWOOD



Standing (left to right): Dr. John Gelman, Sr. Sue Scealy, Dr. Garry Jennings, Professor Paul Korner, Dr. Paul Nestel, Sue Ellett, Helen Skews, Dr. Alex Bobik, Mark Sanders, Dr. Graham Jackman. Seated: Sr. Judith Stewart, Dr. Murray Esler, Peter Ashley, Janet Brown, Anne Ioannou, Pam Scott.

CLINICAL RESEARCH UNIT

MAIN RESEARCH INTERESTS

Pathophysiology and treatment of hypertension
Clinical pharmacology of cardiovascular drugs
Exercise
Postural hypotension — pathophysiology and treatment
Role of the sympathetic nervous system in various diseases
Lipoprotein metabolism
Role of diet in the aetiology and treatment of diabetes and obesity

Both patient care and research activities of the Clinical Research Unit continued to expand during 1979. The unit provides a range of clinical and laboratory services in cardiovascular diseases, especially lipid abnormalities, hypertension, postural hypotension and clinical pharmacology. The units 12 beds have been fully occupied and we look forward to expanding the number of beds to the full complement of 18 in the future.

The Alfred Hospital Lipid Clinic (Dr. Paul Nestel) and Hypertension Evaluation Clinic (Dr. Garry Jennings) are provided by the Clinical Research Unit. The clinical laboratory area continues to be busy both with research activities and providing an exercise testing service. Details of our studies on lipoprotein metabolism, diet, obesity and diabetes performed by Dr. Nestel and Dr. O'Dea have been described in the Baker Institute report, as well as those on noradrenaline turnover performed by Dr. Murray Esler and on clinical pharmacology by Dr. Allan McLean.

The final phase of the study mentioned in last year's report, which investigates the effectiveness of standard drug therapy in essential hypertension in reversing the haemodynamic abnormalities of the disease, has been completed.

Patients with hypertension were studied before any treatment and one week after stopping one years therapy with standard antihypertensive drugs which had lowered blood pressure to the levels found in normal subjects. After one year the elevation of resistance found in these patients had completely reversed, particularly the com-

ponent which remains after blocking the nervous system with autonomic blocking drugs and is thought to reflect structural changes in the blood vessel walls. Cardiac output was also higher and there was other evidence of improvement in cardiac size. The drugs used for treatment in this study generally cause cardiac output to fall so the haemodynamic changes observed appear to be a consequence of the lower pressure rather than being due to direct effects of the drugs used. When treatment was stopped for longer than one week after the one years therapy blood pressure returned to pretreatment levels over the ensuing 1-3 months suggesting that the benefits of antihypertensive therapy depend on continuing administration of the drug.

Methods recently developed in our laboratory have increased our capability to investigate the role of the sympathetic nervous system in hypertension and other diseases. Dr. Murray Esler's methods of analysing noradrenaline secretion and reuptake by sympathetic nerves and methods of quantitating beta-adrenoceptor number and sensitivity in vivo and in vitro used by Dr. A. Bobik and Dr. G. Jennings allow the peripheral sympathetic nervous system to be investigated in more detail than standard methods allow and are providing interesting new information on this important problem.

We are particularly grateful for the continuing support given to us by other units in the hospital, such as Dr. J. Stockigt, visiting endocrinologists and other members of the D.M.U. who are collaborating with us in a study on sympathetic nervous system function in patients with thyroid disease, Dr. Frank Dudley and Mr. Ian McInnes who are collaborating with Dr. McLean on his studies on drug metabolism in liver disease, and many other members of staff of the Alfred Hospital and Monash University.

PROJECTS

(1) Influence of Intrinsic Sympathomimetic Activity (ISA) and Beta-1 selectivity on the Effects of Beta Adrenoceptor Blockers on Heart Rate and Blood Pressure During Graded Exercise

G. L. Jennings, A. Bobik, R. Newman, S. Ellett, P. Korner

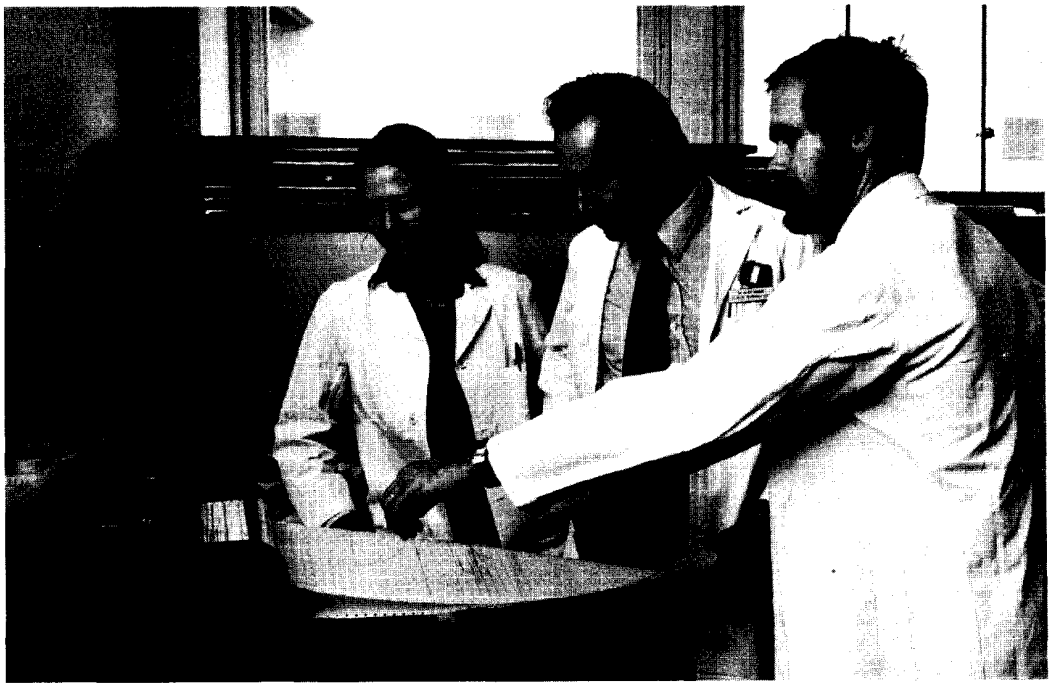
Of the wide range of beta-blocking drugs used in the treatment of hypertension and angina, various advantages are claimed for one or other of these drugs on the basis of their particular properties. Intrinsic sympathomimetic activity (ISA) refers to the ability of some beta-blocking drugs to stimulate beta receptors slightly at the same time as the receptor is competitively blocked to other stimuli. Drugs with ISA are said not to reduce resting heart rate (HR) as much as drugs without ISA. However, it has been suggested that this property reduces the maximum amount of beta blockade caused by the drug. Beta-1 selectivity refers to the propensity to block β_1 receptors (in the heart) at lower doses than are required to block β_2 receptors in the lungs and peripheral blood vessels. This property is said to be of advantage in patients with asthma and has also been claimed to cause greater reduction of blood pressure by drugs which are 'selective' during 'stress' than occurs with non-selective drugs. The effects of these properties on resting and exercise heart rate and blood pressure were examined in this study.

Heart rate and blood pressure during graded exercise after four doses each of pindolol (with ISA), oxprenolol (some ISA), metoprolol (beta-1 selective) and timolol (no ISA, non-selective) were studied in six normal subjects. Effects were measured on resting HR, slope of the work-HR relationship, HR at 0.5 Wmax (HR_{50}) and corresponding BP parameters. For each drug, an upper plateau of the relationship between plasma concentration and each exercise HR and BP parameter was obtained. Although reduction of resting HR was slightly less after pindolol and oxprenolol there was no significant difference between drugs with and without ISA in maximum reduction of slope (19, 22, 21, and 23% for pindolol, oxprenolol, metoprolol and timolol respectively). Slope of the work-BP relationship was similar at each dose tested after the beta-1 selective drug, metoprolol, and the other drugs. The results suggest that the relationship between dose and HR or BP effects are unaffected by ISA or beta-1 selectivity during exercise.

(2) Dihydroergotamine in the Treatment of Postural Hypotension

G. Jennings, M. Esler, H. Skews, A. Bobik

Postural hypotension (low blood pressure during exercise) is an uncommon, but debilitating aspect of diseases which affect the autonomic nervous system. In our previous report we have described suc-



Dr. Alex Bobik (centre) with Helen Skews and Graham Jackman examining HPLC Chromatograms of catecholamines isolated from plasma.

cess in the treatment of this condition using an ergot compound, dihydroergotamine (DHE). Further studies with this drug have confirmed our earlier suggestion that a limiting factor in the successful use of dihydroergotamine is poor bioavailability due either to inefficient absorption from the gut or extensive metabolism by the liver before the drug reaches the systemic circulation. Thus while administration of the drug intravenously to 12 patients with severe postural hypotension in a dose of 10 μg/kg has virtually abolished the fall in blood pressure on standing in 11/12 patients, oral doses of 20-60 mg/day have been required for satisfactory control in most patients and in three patients 60 mg/day has been insufficient. Measurement of blood concentration of DHE has confirmed low levels in these patients even at the highest doses. Further studies are underway to determine the pharmacokinetics of DHE and to investigate whether this problem can be avoided using other routes of administration.

(3) Quantitation of Beta-Adrenoceptor Number and Affinity in Man

G. Jennings, A. Bobik, M. Bangah

It has been suggested that beta-adrenoceptor numbers and affinity are altered by a large number of diseases, and drugs. However, to date no direct methods have been available to study beta-adrenoceptors in vivo in man. The beta-adrenoceptor consists of a binding site attached to the enzyme adenylate cyclase which causes conversion of ATP to cyclic AMP with subsequent cellular effects (e.g. increase in heart rate).

We have used the increase in heart rate caused by bolus doses of isoprenaline and analysis of the iroprenaline dose-heart rate response curve to indicate beta receptor number and affinity. The maximum change in heart period caused by bolus doses of isoproterenol was measured in 10 normal subjects. This was linearly related to the amount of cyclic adenosine monophosphate generated from lymphocytes in the

same subjects in vitro after incubation with isoprenaline. This high correlation between cardiac and lymphocyte β-adrenoceptor stimulation suggests that maximum response does not depend on innervation. Other factors, such as cell membrane properties or levels of circulating catecholamines, may be of greater importance.

In four patients with autonomic insufficiency a curious finding has been that the heart rate response to isoprenaline, and the cylic AMP production by incubation of lymphocytes with isoprenaline, suggest higher affinity of the beta receptors than in normal subjects in **all** tissues in this condition. The influence of plasma catecholamines on responsiveness to isoprenaline is also being investigated in these patients. No differences have been found between normal subjects and patients with established hypertension using these methods, but further studies are underway in patients with borderline hypertension.

(4) Beta-Adrenoceptors in Thyroid Disease
G. Jennings, M. Esler, J. Stockigt, M. Bangah, A. Bobik

Although patients with thyrotoxicosis have tachycardia and other features of excessive sympathetic nervous system activity and respond to adrenoceptor blockade, the relationship between thyroid disease and sympathetic nervous system is not clear as plasma catecholamines are not usually elevated in this condition. The methods described above for assessing beta receptor numbers are used in this study in patients with untreated thyrotoxicosis and hypothyroidism. So far three patients with each condition have been studied. Each patient has also had noradrenaline turnover studies. The results of this study are expected to provide information on the inter-relationship between thyroid hormone and sympathetic function when more patients have been studied.

(5) Reversibility of the Abnormal Haemodynamics by One Years Standard Drug Treatment of Essential Hypertension
G. Jennings, M. Esler, S. Ellett, P. Korner

Systemic haemodynamics before and after 'total' autonomic block were studied twice in thirteen patients with essential hypertension, before treatment, and again one week after cessation of antihypertensive drugs which had normalised blood pressure for one year. Measurements after autonomic block were used to assess the reversibility by treatment of non-autonomic (humoral or structural) factors influencing haemodynamics. After 12 months treatment mean arterial blood pressure (MAP) was 15.5 mmHg lower ($P < 0.05$), cardiac index (CI) 25% higher ($P < 0.05$) and total peripheral resistance (TPRI) 31% lower ($P < 0.01$) before 'autonomic' block than the corresponding pretreatment values. After block MAP was 14 mmHg lower ($P < 0.01$), CI 24% higher ($0.1 > P > 0.05$) and TPRI post-treatment had fallen by 37% ($P < 0.01$), to levels found in normotensives. Patients remained off therapy after the second study and blood pressure returned to pretreatment levels by 1-4 months in 12/13 patients. The findings suggest that one years successful treatment of mild essential hypertension almost completely reverses haemodynamics to normal, including 'non-autonomic' TPRI.

Left to right: Peter Ashley, Mark Sanders and Mohan Bangah.

(6) Non-Invasive Measurement of Cardiac Output using the indirect Fick Method
G. Jennings, K. Harvey, J. Baird, P. Korner

The value of an accurate non-invasive method of measuring cardiac output at rest and during exercise is obvious in studies in which haemodynamic measurements are made repeatedly over a long period of time. We have used the indirect Fick method to this end. This method involves a rebreathing technique to determine mixed venous carbon dioxide. Previous workers have found this method most accurate when measurements of cardiac output are made during exercise, but results have been more variable at rest.

With the help of the staff of our electronics workshop the method has been refined so that many of the complex series of tasks required to perform the measurements are controlled by microprocessors which provide a direct output of the results. It is hoped that the system will be sufficiently accurate to provide reliable measurements at rest as well as during exercise. During the year the same equipment has also been used to measure maximum oxygen consumption, a reliable measure of physical fitness in sedentary subjects undergoing fitness programs such as in the studies described by Dr. Kerin O'Dea in the Baker Institute report.

(7) Radionuclide Measurement of Left Ventricular Function at Rest and Graded Exercise in Normal Males

V. Kalff, G. Jennings, P. Korner, M. Kelly, S. Anderson, R. Harper, A. Pitt

During his term as CRU registrar, Dr. Kalff performed a study on left ventricular function during exercise with the Cardiovascular Diagnostic Service.

Equilibrium gated blood pool scanning (EQ) was used to assess left ventricular function in a group of 18 normal male volunteers at rest and graded exercise. Their mean age was 44; range 28 to 63 years.

A standard vertical sprint test was performed on a bicycle ergometer. The maximum work capacity (Wmax) was used to derive three steady state work-loads (0.25 Wmax, 0.5 Wmax and 0.85 Wmax) used subsequently.

Following an intravenous injection of Tc99m labelled to red blood cells, imaging using the equilibration technique was performed in the modified left anterior oblique projection. The subjects then exercised in the supine position for our minutes at each of the preselected work-loads with counts being collected for the final two minutes of each work-load.

An E.C.G. gate and computer were used to construct a composite 20 frame cardiac cycle. The ejection fraction (EF) was derived from separately defined end-systolic and end-diastolic left ventricular regions of interest after background subtraction.

The mean heart rate X systolic BP achieved at maximum supine exercise was 0.9 that achieved during maximum vertical exercise.

The EF values (mean ± SD) were 0.65 ± 5 at rest; 0.75 ± 6 at 0.25 Wmax; 0.78 ± 6 at 0.50 Wmax and 0.80 ± 6 at 0.85 Wmax. The changes between rest and 0.25 Wmax and 0.5 Wmax were statistically significant. In 16 of the 18 patients the major rise in EF occurred by the first work level.

It is concluded that in normal volunteers the EF rises progressively with increasing exercise, but the major rise occurs in the early phase of exercise.

Use of Captopril in the Management of Essential Hypertension Resistant to Standard Treatment

G. Jennings

Capropril is a new drug for the treatment of hypertension which appears to lower blood pressure through inhibition of the enzyme which causes formation of the vasoconstrictor angiotensin II from the inactive angiotensin I in the lungs. The same enzyme is involved in the degradation of the vasodilator bradykinin. We have used captopril in six patients in whom the maximum doses tolerated of standard antihypertensive drugs (including minoxidil in four patients) had failed to lower blood pressure to satisfactory levels. The protocol used requires cessation of other antihypertensive drugs while single doses of captopril are given, titrated against the blood pressure. In two patients no significant reduction of blood pressure occurred with single doses of captopril. In the remaining four patients diastolic blood pressure, which had been above 110 mmHg in all patients, fell below 90 mmHg. Blood pressure has remained under good control in these patients with chronic administration of the drug, but in each case the addition of a thiazide diuretic and propranolol, has been required to maintain ideal blood pressure control as maximum dose of captopril used in the study has not provided sufficient long term lowering of blood pressure. The reason for the disparity between doses required for acute and chronic therapy are not known, but the drug appears to be a major advance in the management of severe hypertension.

The Effects of Digoxin and Beta Blockade on Work-Related ST Changes

F. Panetta and G. Jennings

The well known appearance of ST depression at rest and during exercise in normal subjects after digoxin has led most cardiologists to consider that the results of any exercise tests performed on patients taking digoxin are inconclusive. Recently,

Dr. Garry Jennings with Sister Helen Hall measuring blood pressure.

however, some investigators have suggested that digoxin does not interfere with evaluation of exercise tests if the criteria for a 'positive' test are appropriately modified (eg. Nasrullah et al, American Journal of Cardiology 35: 160, 1975 Bartel et al, Circulation 48: 141-148, 1973). No previous studies have investigated exercise induced ST changes before and after digoxin in relation to resting abnormalities, or workload. Although digoxin induced ST changes are known to be unchanged by atropine, nitroglycerin or oxygen, the effect of beta blockers is not known. The present study is intended to investigate the nature of the change in ST segment with exercise in patients with ischaemic heart disease before and after digitalisation, and the influence of beta blockers on these changes.

The effect of digoxin on exercise performance of patients with ischaemic heart disease without obvious cardiac failure will also be investigated as this is of particular interest in view of recent studies (eg. Kotter et al American Journal of Cardiology 42: 563-569, 1978) showing no increase in myocardial oxygen consumption, despite increase in contractility in patients with ischaemic heart disease without clinical evidence of congestive heart failure. Any beneficial effect on myocardial oxygen consumption after digoxin in such patients would most likely be due to reduction in cardiac dimensions and should be even more obvious after beta blockade.

In five patients with ischaemic heart disease studied so far the ST changes in the exercise test after digoxin have shown little relation to those before digoxin. However, further studies are required before definite conclusions can be drawn.

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EWEN DOWNIE METABOLIC UNIT

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Ewen Downie Metabolic Unit January 1980. (L to R) Pincus Taft, Ann McClelland, Margot Hewett, Mary Blundy, Christopher Burke, Mary Esparon, Elizabeth White, Fredericke Rabold, Hal Breidahl (partly hidden), Linda Fielding, Ida Ekkel, Douglas Lording, Jim Stockigt, Marilyn Young, Margaret Sanders, John Barlow, Richard Dargaville, David Hurley, Anthony Hunter.

GENERAL SUMMARY

In 1979 the Unit spent its first complete year working in the newly-remodelled laboratory and office area of the fifth floor of the Centre Block. This allowed us to consolidate the numerous changes which occurred in 1978. There were only minor changes in the staff of the Unit in 1979, but we were pleased to welcome Dr. Christopher Burke, of the Department of Endocrinology, Radcliffe Infirmary, Oxford, England, who visited as Locum Specialist Endocrinologist from June 1979 to January 1980 during Dr. Stockigt's absence in Berlin. His interests and those of the Unit are complementary, so that he was able to bring expertise to improve some of the assays in the Unit, notably that for ACTH. He continued the Director's clinical commitments including undergraduate and postgraduate teaching. The current research projects on thyroid function and synthesis of novel steroids continued during this time, but Dr. Burke instigated a new project on steroid replacement therapy in hypoadrenal patients. He lectured in Melbourne, Canberra and Perth, and visited medical centres in Sydney and Hobart. He has expressed the wish that this report state that he much enjoyed meeting new colleagues at the Alfred Hospital and Baker Institute, and felt his time and effort worthwhile in terms of new ideas and different approaches, both scientific and clinical.

The service role of the Unit remains large, despite its relatively small number of inpatients. During 1979 there were 242 inpatients of the Unit and 305 other hospitalized patients were seen in consultation. In addition, we were responsible for 120 patients with less acute problems at Caulfield Hospital. The Diabetes Outpatient Clinic remains the largest associated with the Hospital, and attendance at Thyroid and General Endocrinology Clinics increased during 1979 to over 35 patients per week. The monthly consultative clinics at Moe and Traralgon also continue to be well attended. The routine laboratory received 3200 requests for thyroid function assessment and samples for renin and aldosterone came from a wide range of hospitals in Australia and South-East Asia.

As summarized below, our research interests continue to be in the fields of thyroid-

hormone changes in systemic illness, new abnormalities of thyroid hormone binding, structure-function relationships of steroids and the role of the renin-angiotensin-aldosterone system in blood pressure regulation. In addition, a collaborative project with the Baker Institute and Clinical Research Unit on autonomic function in thyroid disease has begun.

In late 1979 Dr. Pincus Taft, formerly Physician-in-Charge, now a Senior Visiting Staff Specialist to the Unit, was absent for several months because of illness. His excellent recovery augers well for a continuing active role with us in the future.

Dr. Jim Stockigt spent the period between July 1979 and January 1980 on study leave at Klinikum Steglitz of the Freie Universitat, Berlin, in association with Professors Horst Schleusener and Wolfgang Oelkers in the Thyroid and Adrenal Research Groups. During this time he also worked as Secretary to the Program Organizing Committee of the VIII International Thyroid Congress (Sydney, February 1980). This Committee met in London in September 1979 and, in addition, he participated in Thyroid and Hypertension meetings in Homborg (Saar) and Wurzburg and gave lectures and seminars in Heidelberg and Brussels. His work in Berlin was concerned principally with further characterization of the binding protein in a new familial abnormality of thyroid hormone binding (see below).

Dr. Hal Breidahl attended the 11th Congress of the International Diabetes Federation in Vienna in September 1979 where he delivered the address: "What has happened with Diabetes since the last Congress?" He also attended the South-East Asian Congress of Clinical Biochemistry in Singapore in October 1979 and participated in numerous seminars and clinical meetings in Victorian country centres.

The Annual Meeting of the U.S. Endocrine Society in Los Angeles in June 1979 was attended by Drs. Ken Wynne, David Hurley and Jim Stockigt, where two papers were presented (see Abstracts below). At that meeting it was interesting for three registrars of the Unit to meet together: Dennis Engler (currently working in Boston), Duncan Topliss (then en route to Toronto) and David Hurley. John Barlow attended the meetings of the Australian Endocrine Society and the Australian Society for Medical Research in December where he presented a paper on a new binding abnormality leading to thyroxine excess without hyperthyroidism.

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

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

Estate of the late Vincenza Acton
Estate of the late H. Vistaline
G. M. Rollason Trust
Vivian Hill Trust
Alfred Hospital Whole-Time Medical Specialists' Private Practice Fund.

Seminar Programme

In the programme of Monday lunchtime Seminars, held in rotation with Prince Henry's Hospital, the following topics were presented at the Alfred:

1. Conservative management of Cushing's Syndrome.
2. Interaction of Glucocorticoids and Thyroid Hormone.
3. Diabetes and Hyperlipaemia.
4. Fertility problems in treated Acromegaly.
5. Infection in Diabetics.
6. Hypothyroidism and Ischaemic Heart Disease.
7. Pancreatic Pseudocysts: Medical and Surgical Problems.
8. Hyperparathyroidism and Osteomalacia.
9. Renal Hypertension: Medical and Surgical Management.
10. Insulin Resistance.
11. Idiopathic Oedema.
12. Invasive Pituitary Tumours.
13. Oral Hypoglycaemic Drugs.
14. Traumatic Hypopituitarism.
15. Chlorpropamide-induced Flushing.

THYROID HORMONE PATHOPHYSIOLOGY

In the past year our attention has been directed back to abnormalities of thyroid hormone binding in plasma, a field which appeared to be almost fully understood at the time of our last report. This revival of interest has occurred for two reasons. Firstly, our chance involvement since 1976 with a new familial binding abnormality, which was initially regarded as a possible

variation in thyroxine deiodination. Secondly, the discrepancy in severe non-thyroidal illness, between standard abbreviated methods of assessing thyroxine binding (e.g. resin uptake) and more laborious methods such as equilibrium dialysis. The former methods suggest that free T_4 is low, while the latter often indicated a high free level in severe non-thyroidal illness. This discrepancy is in need of urgent solution to resolve the dilemma between inappropriate replacement therapy and unwarranted therapeutic conservatism in many seriously ill patients.

When thyroid hormones are released into the blood they circulate bound to serum proteins. In routine laboratory tests of thyroid function we measure the total serum thyroxine concentration and use an indirect test such as resin uptake to estimate the binding of hormone in serum. The total T_4 and resin uptake tests together give the free thyroxine index (FTI) which is usually proportional to the concentration of circulating free hormone. In states such as pregnancy, where TBG is increased, a high total T_4 is corrected by the low resin uptake to give a normal FTI. However, three proteins contribute to serum binding of T_4: thyroxine binding globulin (TBG) has the highest affinity and carries approximately 70% of T_4; prealbumin (PA) is the next most effective binding site and carries 20%; albumin which has a low affinity but very high capacity, carries only about 10%. We are at present investigating in a possible fourth binding protein which leads to familial euthyroid T_4 excess and also in a possible circulating inhibitor of binding which is responsible for a discrepancy between free T_4 and FTI in severe illness. Our findings to date suggest that, while the resin uptake and related tests give a valid index of alterations in TBG binding, they misclassify several other types of abnormal binding.

Familial Euthyroid Thyroxine Excess

J. R. Stockigt, J. W. Barlow, D. J. Topliss, E. L. White, D. M. Hurley, J. W. Funder and C. W. Burke

A discrepancy between total and free thyroxine is well recognised when levels of thyroxine binding globulin are abnormal. The free thyroxine index (FTI), derived from indirect binding corrections such as the T_3 resin uptake, or directly from the TBG level, usually compensates for these variations and prevents a false impression of thyroid disease. Recently a number of apparently euthyroid individuals have shown persistently high total T_4 levels, but normal resin uptake, giving an FTI suggestive of hyperthyroidism. However, these subjects have no symptoms and, when measured more directly, their free hormone levels are normal. The high total hormone levels with normal free concentrations suggest an increase in serum binding. We have now studied eleven subjects from three unrelated families who show this type of abnormality. Those affected are euthyroid, as shown by a normal TSH response to TRH and normal suppressibility of the pituitary-thyroid axis with exogenous T_4 or T_3. The condition shows autosomal-dominant inheritance, as demonstrated by male to male transmission and an affected to unaffected ratio of unity or greater in first-degree relatives. The initial subjects studied were usually referred for re-evaluation of abnormal thyroid function tests which were inconsistent with clinical findings. However, one was assessed after short-term treatment with anti-thyroid drugs and one after sub-total thyroidectomy elsewhere for presumed hyperthyroidism.

Our studies of this syndrome can be summarised as follows:

(i) Measurements of the major binding proteins indicate normal levels of TBG, prealbumin and albumin.

(ii) Studies of binding in vitro indicate that abnormal serum has a much increased capacity for T_4. The effect of increments of added unlabelled hormone on the free fraction of ^{125}I T_4 has been studied in diluted serum (Fig. 1). Compared with both normal and high-TBG serum, affected subjects show much less increase in free fraction, suggesting abnormal high-capacity binding sites. The abnormality cannot be demonstrated with ^{125}I T_3 or in barbitone buffer, features which resemble prealbumin binding.

(iii) Scatchard analysis of intermediate-affinity binding sites after equilibrium dialysis indicates a 5-10 fold excess of sites with affinity ($\sim 10^{-8}$M) comparable to prealbumin.

(iv) Polyacrylamide gel electrophoresis, in the presence and absence of excess unlabelled hormone, indicates that the abnormal high-capacity site migrates with albumin. However, it is clearly distinct from albumin on isoelectric focussing, where it shows an isoelectric point identical to prealbumin.

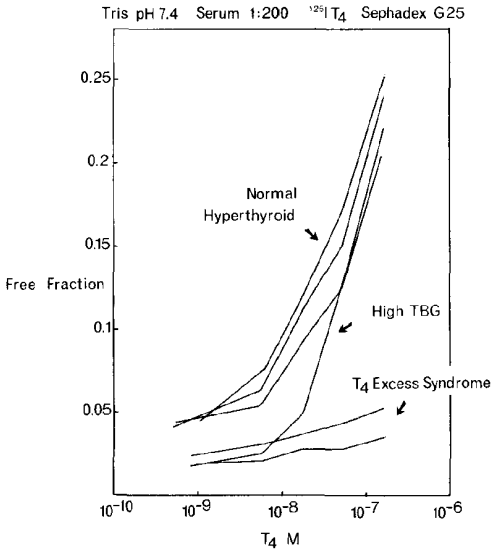

Fig. 1. In vitro determination of the free fraction for ^{125}I T_4, showing the effect of excess unlabelled hormone with normal binding proteins, high TBG and familial euthyroid T_4 excess.

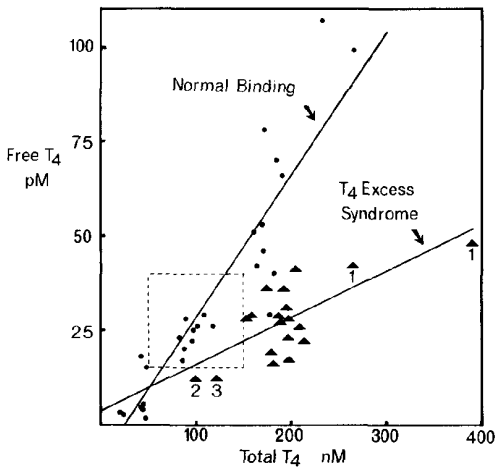

Fig. 2. Comparison of the relationship between total T_4 and free T_4 in subjects with normal binding and those with familial T_4-excess. Sample 1 taken after T_4 treatment, sample 2 after T_3 treatment and sample 3 after potassium iodide.

(v) Affected subjects, when compared to normal, show a lower level of free T_4 for the same level of total T_4 (Fig. 2).

We conclude that this syndrome, characterized by a persistently high total T_4 and free thyroxine index, with normal levels of free T_4, is due to increased intermediate affinity ($K_D \sim 10^{-8}$M) binding in plasma. At the same level of total T_4, those affected have lower levels of free T_4 than normal subjects ($p < .001$), suggesting that the increase in total hormone is an appropriate response to increased binding. The abnormal binding protein resembles prealbumin in several respects, although it migrates with albumin in conventional polyacrylamide electrophoresis and prealbumin levels are normal. Standard methods for T_3 resin uptake and free thyroxine index have an inherent defect because they do not recognise this type of abnormal, barbitone-sensitive T_4 binding and can lead to misdiagnosis of hyperthyroidism.

We have attempted to develop a modified simple adsorption binding test in order to improve detection of this condition. Provided ^{125}I T_4 is used in non-barbitone buffer, the abnormality can be detected by methods such as resin or charcoal uptake if proportional carriage on the abnormal site is increased by addition of unlabelled T_4 in 50-fold excess.

To summarize the value of various diagnostic procedures, total T_4 is high and standard adsorption techniques using T_3 in barbitone-buffer fail to make the appropriate correction, leading to a falsely-high FTI value. In contrast, free T_4 measured by a variety of methods gives a correct assessment, as does measurement of T_3, although the values for total T_3 are usually in the upper-normal range. The euthyroid state is clear if a TRH test is done, and the correct diagnosis can be made using a modified T_4-loaded uptake system to demonstrate abnormal, high-capacity intermediate-affinity binding.

Effect of Corticosteriods on the Pituitary-Thyroid Axis in Primary Adrenal Failure

D. J. Topliss*, E. L. White and J. R. Stockigt

Coincident thyroid disease and idiopathic adrenal failure, an association first described over 50 years ago, is now known to occur more frequently than can be attributed to chance, probably because of associated autoimmune disease of the two organs. It is therefore appropriate to assess thyroid function in adrenal insufficiency, but interpretation is complicated by several other interactions between adrenocortical hormones and the thyroid. For example, glucocorticoid excess can suppress TSH secretion and there is evidence that TSH may increase as a

direct result of glucocorticoid deficiency in the absence of thyroid disease.

An increase in plasma TSH in the face of normal or low-normal circulating thyroid hormone levels is usually regarded as evidence of diminished thyroid reserve. However, if plasma TSH can increase as a direct consequence of glucocorticoid deficiency without intrinsic thyroid disease, TSH becomes unreliable as an index of impending or potential thyroid failure. Furthermore, initial assessment of thyroid function may be unreliable because correction of corticosteroid deficiency has been reported to reverse thyroid failure in some patients with Addison's disease. To further define the relationships between corticosteroid deficiency and thyroid function, interactions between corticosteroids and the pituitary-thyroid axis were studied in ten consecutive patients with newly discovered Addison's disease, before and after steroid replacement. None had clinical features of thyroid disease or goitre, but the initial level of plasma TSH was high in six patients before corticosteroid treatment (mean 40 mU/l, range 14-120 mU/l, normal: < 5 mU/l). One patient with positive thyroid autoantibodies had severe biochemical features of thyroid failure before treatment (TSH 120 mU/l, T_4 < 10 nmol/l, T_3 0.5 nmol/l), but after steroid substitution thyroid hormones have become normal, although TSH excess (~30 mU/l) persists after 2½ years. In two, TSH was initially increased (30, 17 mU/l) in the face of low-normal T_4 and normal T_3 levels. After steroid treatment for 1-3 months all parameters became normal. This sequence resembles previous reports of improvement in autoimmune thyroiditis after steroid substitution.

In three patients, initial TSH excess (14, 19, 38 mU/l) was associated with mid-normal T_3 and T_4 levels. After steroid replacement TSH became normal with negligible change in T_3 or T_4, consistent with a direct steroid effect on pituitary TSH release. Autoantibodies were negative in this group, two of whom had adrenal failure due to disseminated malignancy.

Steroid treatment did not cause inverse changes in T_3 and rT_3 and the capacity of TBG showed no significant change, suggesting that physiologic levels of adrenal steroids are not major determinants of T_4 deiodination or of circulating levels of TBG.

These findings suggest that TSH excess in untreated adrenal insufficiency can occur for several reasons. In addition to the known association with autoimmune thyroid disease which may be reversible, absence of the normal suppressive effect of glucocorticoids on TSH release can result in transient TSH excess without thyroid malfunction. Hence, evaluation of thyroid function in untreated adrenal insufficiency is unreliable. A distinction should be made between findings before and after steroid replacement to avoid possible unwarranted lifelong treatment with thyroid hormone.

STEROIDS, RENIN AND ACTH

Receptor Binding of 19-Nor Steroids

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

Medical Research Centre, Prince Henry's Hospital

Minute changes in a steroid molecule may have a profound effect on its biological activity; in general the relationship between structure and function is poorly understood. In studies aimed at increasing this understanding, we have investigated the effect of 19-nor modification, i.e. absence of C-19 methyl group, from biologically-active steroids. So far, absence of the 19-methyl group has been shown to have different effects for different parent steroids. These investigations are complicated by the fact that there is no simple procedure to remove the 19-methyl group in vitro. Rather, these steroids must be synthesized by complex multi-stage methods (see 1978 report).

The synthesis of 19-norcorticosterone and 19-noraldosterone and studies of their receptor binding have now been completed. Briefly, it has been found that in mineralocorticoid radioreceptor assays, 19-nordeoxycorticosterone (x3-fold), 19-norprogesterone (x3) and 19-norcortisol (x1.5) show higher affinity than their respective parent steroids. In contrast, corticosterone and 19-norcorticosterone show equal affinity and 19-noraldosterone <1% the activity of aldosterone. In glucocorticoid receptor assays, 19-norprogesterone (x3) and 19-nordeoxycorticosterone (x1.5) show increased affinity, but 19-norcorticosterone (x0.3), 19-norcortisol (x0.1) and 19-noraldosterone (x<0.01) show decreased affinity compared with their natural parent compounds.

These findings suggest that while the 19-nor analogues of 11-deoxy steroids are consistently more active than their parent steroid, the 19-nor, 11-oxygenated adrenal

steroids show no predictable pattern of binding to either receptor.

These results should be viewed in relation to knowledge of the natural occurrence of 19-nor steroids. 19-Nordeoxycorticosterone has been found in the urine of rats with regenerating adrenals and may be a cause of hypertension in such rats. Further, the report of 19-norandrostenedione in equine follicular fluid and a report that 19-norprogesterone causes ovarian tumours in mice suggest that further understanding of the biological significance of this structural change will be important.

Simplified Renin Sampling using Heparin as Anticoagulant

M. J. Hewitt and J. R. Stockigt

In an attempt to simplify routine procedures for renin estimation we have evaluated samples processed at ambient temperature, using heparin as anticoagulant. In established techniques, samples are collected in EDTA, cooled rapidly, centrifuged at 4°C and the plasma frozen immediately. Simpler methods may create problems:

(i) prolonged storage at low temperature may increase the apparent renin value after activation of prorenin.

(ii) because EDTA inhibits angiotensinases and converting enzyme, storage of samples at room temperature allows accumulation of a pre-incubation angiotensin I blank before incubation, especially in high-renin samples. To evaluate these potential problems we have studied the effect of delay at ambient temperature, using either heparin (15 U/ml) or EDTA (pH 7.4, 15mM) as anticoagulant.

Contrary to a previous report using dialysed plasma, heparin in concentrations up to 40 U/ml did not inhibit the rate of angiotensin I formation, even when renin substrate was low. Storage of heparin plasma for up to 48 hours at room temperature had no effect on the subsequent assay of renin activity or renin substrate. Samples taken in EDTA and kept at 20-23°C gradually accumulated a preincubation angiotensin I blank at 5-10% of the generation rate at 37°C. In contrast, heparin samples did not develop a detectable preincubation blank even after 48 hours.

High, normal and low-renin samples were taken from patients with a variety of diseases. Heparin samples kept for 4 hours at ambient temperature, either as whole blood or plasma, gave values which

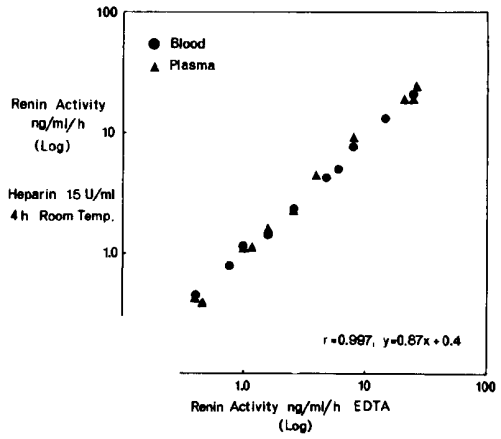

Fig. 3. Renin activity, determined by the standard EDTA technique (immediate cooling and centrifugation), compared with results obtained when samples taken with heparin (15 U/ml) were kept at room temperature for 4 hours, either as plasma or as whole blood.

were 99 ± 2.3(SE)% (n = 21) of the results obtained using a conventional EDTA collection procedure, in which samples were immediately cooled and separated (Fig. 3).

In summary, renin samples taken in heparin (15 U/ml) or EDTA can be kept at room temperature for up to 4 hours. For more prolonged storage or transit at ambient temperature, heparin is the anticoagulant of choice because no immunoreactive blank accumulates. Substrate depletion is not a limiting factor even in high-renin samples kept at room temperature for up to 48 hours.

In addition to its established role in the investigation of renal and adrenal hypertension, plasma renin measurement is being requested in the investigation, diagnosis and management of essential hypertension. Availability of the assay has been limited by the widely held view that specialized collection and immediate processing of samples is necessary. Our findings indicate that this can be simplified, but a more casual approach to sample collection does not diminish the importance of sodium status, blood pressure, posture and drug therapy in the evaluation of results. For direct measurement of the circulating peptides angiotensin I and II, samples must still be collected at low temperature using inhibitors of plasma angiotensinase and converting enzyme.

Steroid Replacement in Addisonian and Adrenalectomised Subjects: Comparison of Several Glucocorticoids

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*Medical Research Centre, Prince Henry's Hospital.

Since the introduction of cortisone acetate in 1948, most patients who would have died of hypoadrenalism remain in good health, but some never regain perfect health. There are scattered reports that failure of intestinal absorption of steroid acetates, or unusual dosage requirements may lead to partial failure of steroid replacement therapy. Other glucocorticoids with greater potency and better absorption are available, but systematic comparison between them does not appear to have been made.

We therefore compared the effects of cortisone acetate, hydrocortisone or cortisol (the natural glucocorticoid), prednisolone (a commonly-used synthetic glucocorticoid), and dexamethasone (a highly-potent synthetic fluorinated steroid). The subjects chosen were 8 patients with Addison's disease, and 4 previously adrenalectomised for Cushing's disease.

In all patients higher levels of plasma cortisol were found after cortisol than after cortisone acetate at equivalent dosage. Morning doses of both steroids given with breakfast produced lower cortisol levels, dose for dose, than evening doses given 2 hours after eating. However, the behaviour of plasma ACTH (measured by a sensitive radioimmunoassay on unextracted plasma) was similar after cortisone and cortisol. Neither method of replacement therapy prevented a rise in plasma ACTH in the afternoon in most patients. ACTH levels were generally lower after cortisol and suppression of ACTH was faster after cortisol.

Because comparison of prednisolone and dexamethasone with cortisol cannot be made by cortisol measurement, we measured 'glucocorticoid activity' in plasma by the ability of plasma to displace ^{3}H dexamethasone from glucocorticoid receptors in rat thymocytes. With cortisone and cortisol, glucocorticoid activity generally corresponded to plasma cortisol concentration, but with 2.5-5 mg doses of prednisolone (usually supposed to be equivalent to 25 and 12.5 mgs of cortisol), the sum of glucocorticoid activities during the 4 hours after the dose was 1½ times that after cortisol. With dexamethasone 0.5 mg (usually supposed to be equivalent to 12.5 mg of cortisol) the glucocorticoid activities were about equal to those after cortisol. This suggests that widely-used estimates of the potency ratios of prednisolone and cortisol may need revision.

Plasma ACTH showed no significant difference after prednisolone or cortisol, an afternoon ACTH rise being seen with both, but not with dexamethasone.

In adrenalectomised patients with abnormal ACTH secretion from the pituitary, where a major therapeutic objective is control of the plasma ACTH level, there may be advantage in using dexamethasone. However, in Addison's disease, dexamethasone has little advantage over cortisol or prednisolone replacement. Both of these, however, may be superior to cortisone acetate in terms of measurable parameters of control in plasma.

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C. J. OFFICER BROWN CARDIAC SURGERY UNIT

STAFF

Director:	George R. Stirling, M.B., B.S., F.R.A.C.S., F.A.C.S.
Surgeons:	Eric Cooper, M.B., B.S., F.R.A.C.S.
	Bruce B. Davis, M.B., B.S., F.R.A.C.S.
	Gil Shardey, M.B., B.S., F.R.A.C.S.
Assistant Surgeon:	Dame Joyce Daws, O.B.E., M.B., C.H.B., F.R.C.S., F.R.A.C.S.
Visiting Assistant Surgeon:	Franklin L. Rosenfeldt, M.D., B.S., F.R.C.S.E.

A major advance in early 1979 was the occupation of the new operating theatre facilities. The constant availability of two operating rooms, in the latter part of the year was of particular help. However, the increased operating load has thrown a heavy burden on the wards where the limited availability of beds and nursing staff is now the main bottleneck in further growth of the Unit's activities.

Although it is hoped that the Centre block Development for a new 10 bed post-operative intensive care ward and an 18 bed post-operative ward will commence soon, no definite commitment on this matter has yet been had from the Hospitals Commission.

A major effort has been made to improve the follow-up of patients after cardiac surgery, a secretary dedicated solely to that function has been employed and the systems necessary for data collection and retrieval have been improved. Plans for computerisation of follow-up data have been completed and it is hoped that the availability of a suitable computer facility will be a reality in 1980.

During 1979, 669 cardiac operations were carried out in the unit. Of these, 497 were open heart procedures which represents an increase of 28% over 1978. The bulk of the increase was due to increased numbers of coronary artery procedures as can be seen in the Table.

CASE TYPE	1975	1976	1977	1978	1979
Coronary Disease	115	166	177	211	308
Valve Disease	160	141	150	139	167
Congenital Disease	50	62	44	16	12
Miscellaneous	13	4	8	13	10
Total Open Heart	289	336	361	379	497
Open Heart Mortality	4.8%	3.6%	5.8%	3.7%	4.2%
Pacemakers	90	101	122	148	147
Closed Operations	30	33	30	17	25
Total Operations	409	470	513	544	669

CORONARY BYPASS SURGERY

There has been a continued increase in the number of referrals for coronary artery surgery — an increase of 48% compared with 1979. It is doubtful if there has been a real change in the accepted indications for referral so it is presumed that the increased numbers indicate more widespread appreciation in the medical community of the role of surgery in the treatment of coronary heart disease.

The concept of complete revascularisation whenever possible has been accepted. It is interesting that, in this year there has been an apparent inverse relationship between mortality and the number of grafts applied, suggesting that where there is potential for complete revasuclarisation, albeit with multiple grafts, the mortality is lower than the case where many vessels are diseased but few are graftable.

The overall mortality for coronary surgery was 3%. Although the mortality for operation for chronic stable angina remains less than 2%, there is a considerably increased risk in patients with unstable angina, particularly in those who have recently suffered or are evolving an acute myocardial infarction.

VALVE SURGERY

There has been a marked increase in referral of patients with aortic valve disease but no other significant change in numbers or indications for operation in patients with valve disease.

In 1979 the mortality for isolated aortic valve replacement was 1.3% and, for mitral valve replacement 3%.

SURGERY FOR ARRHYTHMIAS

Ten patients have now undergone surgical procedures for arrhythmic problems with the aid of intraoperative electrophysiological mapping. Four patients have had cryosurgical ablation of the bundle of His performed for supraventricular or tach- patient died, one patient was improved but still requires drug therapy and four were cured.

COMPLICATIONS

The re-operation rate for haemorrhage has been reduced from 5.5% in 1978 to 2.4% in 1979. We consider this to be largely due to the use of the monitoring of heparin dosage and reversal by the "Haemochron" technique. Blood usage has been further reduced and averages less than 2 units per case. One third of the cases have required no blood transfusion during their entire hospital stay.

Myocardial infarction during coronary bypass surgery continued to be a problem and one which caused several peri-operative deaths. The exact incidence of major or minor peri-operative infarction was hard to estimate but was probably in the region of 10%. Transient central ner-

336 procedures were carried out in 1979 compared with 305 in 1978. The low number of patients with operable bronchial carcinoma dontinues to be a source of major concern. There seems little doubt that this reduction is a direct consequence of the cessation of the mass miniature chest radiography programme three years ago.

RESEARCH PROGRAMME

Our research programme carried out under the direction of Mr. F. Rosenfeldt is described elsewhere in this report.

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F. L. ROSENFELDT: Hypothermic Damage: Fact of Fiction?

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

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

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