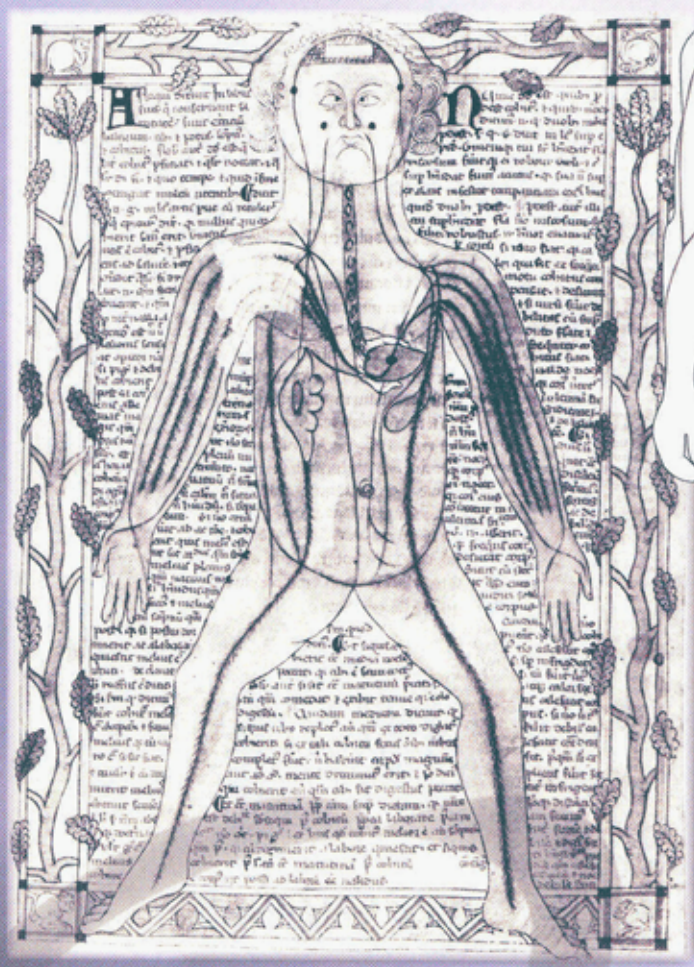
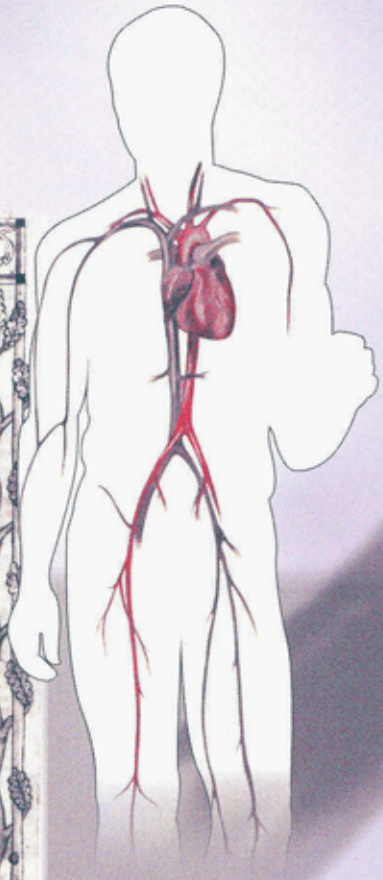
ANNUAL REPORT 1999

BAKER MEDICAL RESEARCH INSTITUTE





Aims of Our Research

In Australia, over 40% of deaths and serious illness are due to diseases of the heart and circulation.

Most of these deaths are the result of hypertension (high blood pressure) and atherosclerosis (clogging of the arteries with fatty, cholesterol-laden plaques) which cause strokes, heart attacks, heart failure and kidney failure.

Our research aims to understand what causes hypertension and atherosclerosis and to apply this knowledge both to prevention of heart and vascular disease in the community, and the improvement of treatments.

The Baker Institute is a Block Funded Institute of the National Health and Medical Research Council of Australia, and is also supported by the Victorian State Government and the Baker Benefaction. The Institute is affiliated with Monash University and the Alfred Hospital, with staff holding appointments at both of these institutions. In addition, the Baker Institute is a World Health Organisation collaborating centre for research and training in cardiovascular diseases, the only such centre in Australia.

Front cover: Page from a 13th- century manuscript with anatomical figure in typical medieval posture, showing the limited knowledge of the circulatory system. Ms. Ashmole 399, fols. 22, 19, Bodleian Library, Oxford. Modern Vascular system illustrated by Andrew N Plant

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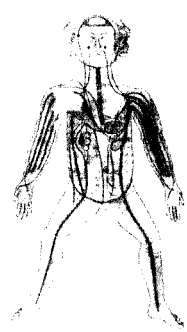
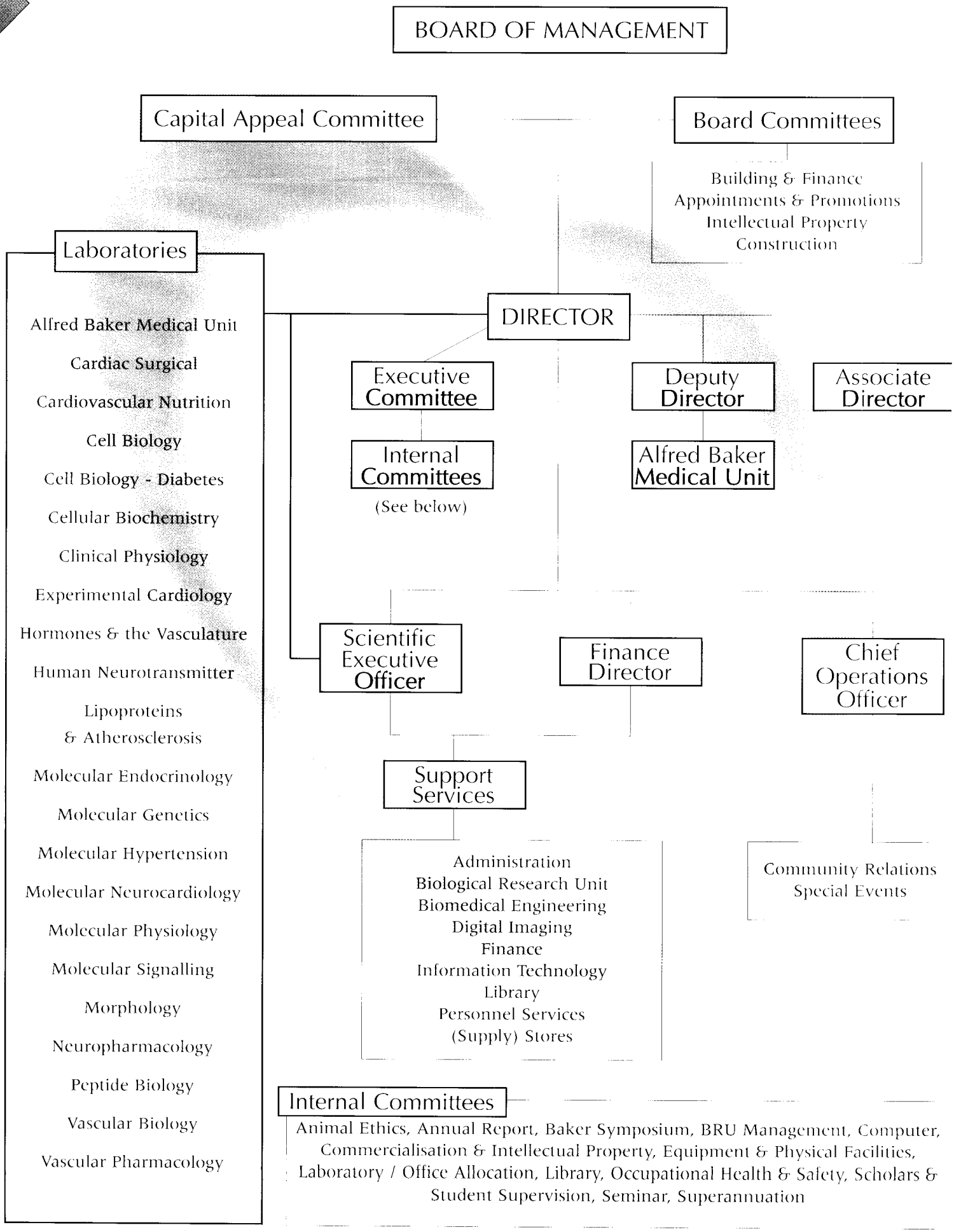


Organisational Chart



President's Report

As you will discover when reading this Annual Report, the Baker Medical Research Institute continued its productive and successful research activities in 1999. A few highlights of that year follow.

The Baker's New Home

At long last, in October 1999 the contract was let for the construction of the Alfred Medical Research and Education Precinct, which includes the new building for the Baker Institute. By the time you read this report, the foundations and lower storeys of the new Baker building will be clearly apparent, adjacent to the East Wing of the Alfred Hospital and rising out of the huge construction site on Commercial Road. Finally the Baker is well on the way to realising its long-held ambition to properly accommodate its scientific and other staff, operating state of the art research equipment and services. The Baker is confident that its new home will not only provide a perfect environment for excellent research but will also become a landmark building in Melbourne of outstanding architectural design and appearance.

A Few Scientific Highlights

Baker scientists continued to advance their research during 1999 in the many ways described under Laboratory Reports. For example, Murray Esler and his team have added an important chapter to the story of leptin, which plays an important part in regulating fat mass by decreasing food demand and increasing energy output. Murray and his team have found that the human brain adds leptin to the blood, more in women than in men and more in overweight than in lean people. Murray's team is now researching the possibility that the message sent by leptin to eat less may be blocked in some people because their brains are unable to recognise leptin.

Jun-Ping Liu and his team described for the first time a direct interaction between two key agents in the growth of human cancers. Jun-Ping's team has shown that these two cell proteins bind together in the test tube. If the same relationship can be proven in living cancer cells, increasing the level of one of these proteins may have a role in the future treatment of cancer.

Maro Williams, a Baker PhD student, made a major contribution to research on DHEA by showing for the first time that blood vessel cells respond to DHEA, even after they were prevented from responding to sex hormones.

Paul Nestel (our evergreen senior researcher) has been awarded a prestigious R&D START grant of $3.75 million from the Commonwealth Government, with funds matched by Novogen Ltd. Paul and his team will use the grant to study the potential therapeutic value in heart disease of certain molecules which are derived from soy and red clover isoflavones.

The Baker in the World

Many of the Baker's scientists travelled overseas in 1999. Wally Thomas and Ian Smith represented the Baker at Europe's major biotechnology fair, Biotechnica '99, in Germany. Ian and Wally had numerous enquiries from European students seeking post-doctoral opportunities in Australia. They also visited Roche in Switzerland, with which the Baker hopes to establish a strategic partnership shortly, following a more recent visit by John Funder and Garry Jennings. Peter Little took sabbatical leave in Seattle,

"...to study the potential therapeutic value in heart disease of certain molecules which are derived from soy and red clover isoflavones."

USA to concentrate on his diabetes research. His trip was part of the exchange program between the Baker and the National Heart Lung and Blood Institute of the USA.

The Baker's Benefactors

It is always gratifying to see the number and range of benefactions which the Baker receives each year. The inaugural function for the Baker benefactors club took place at the Institute in September 1999. A morning tea was held to thank those who have made a bequest to the Baker and to present them with a gold pin commemorating the occasion and their generosity.

> *"I am sure all of you who attended the 1999 Ball would agree that they do a fantastic job."*

The Wills Committee and the Federal Government's Response

Undoubtedly the most important thing to happen in Australian health and medical research during 1999 was the delivery of the report of the Wills Committee entitled "The Virtuous Cycle: Working together for health and medical research". The report is a general review of the whole Australian medical research effort.

From the Baker's perspective, perhaps the most urgent and important issue which needs to be addressed is the significant shortfall between the funding available from the NHMRC and the actual salaries, on-costs and overheads which are borne by Australian medical research institutes. Current NHMRC salary scales lag well behind comparable university salaries and most of the annual budget deficit which the Baker incurs goes on making up the difference.

My Thanks

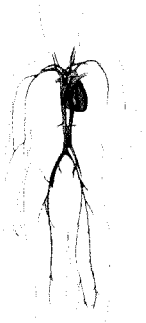
I thank all of the scientists and staff of the Institute for their excellent efforts in 1999. They work in crowded and far from ideal conditions but they still turn out an impressive corpus of highly valuable research, (nearly) always with a cheerful disposition. The Baker's non-scientific staff work tirelessly to provide the money and other resources needed to keep the Institute afloat and at full steam ahead. Special thanks must go to the Special Events Committee, ably chaired by Sue Calwell. This Committee is an enthusiastic group of people who give much of their time and energy in support of the Institute. I am sure all of you who attended the 1999 Ball would agree that they do a fantastic job. Last but not least, I thank my fellow members of the Board and its various committees. All of them work tirelessly for love and not money, in the knowledge that the Institute's efforts are worthy of their support, as they are also of yours. I look forward to catching up with you at the Baker during 2000.

Norman O'Bryan

NORMAN O'BRYAN

President
BMRI Board

Director's Report



As noted in last year's report, for lifelong optimists there are good years and great years. In the scheme of things 1998 was a good year, AND 1999 a great year. Last year I dealt with research funding difficulties, in extenso; the promise of things to come, in terms of the Health and Medical Research Strategic Review, culminating in the Wills Report; the beginnings of a cultural change, in terms of capture and commercialisation of our research efforts: and, finally, of our being within $3m of our target to erect (but not equip) Stage 1 of our new building on Commercial Road.

On all counts, there's been very substantial - and often, despite the gravitas of advancing years, very exciting - progress: this is what has made 1999 one of the great years.

Last shall be first, and the first last, as the Bible says: the new building. In February I was in Los Angeles for a week, as Visiting Professor at UCLA. "In Los Angeles" is short-hand for being ferried around the southern half of California to a total of nine hospital campuses, sixteen hour days with no time off for good behaviour. Very early one morning, before the 7 a.m. pick up, a call from Garry Jennings: "I think we've got the possibility of a major anonymous donor who might be interested in the Baker."

And so it came to pass: a proposal put in record time by Garry, a subsequent visit and cheerily informal meeting, with some of the younger scientists presenting, a cup of tea in the Boardroom, and a parting "I'll see what I can do". A long month later the news that our proposal - in fact, the first of three sequential levels of proposals - had been accepted as requested - and would we please prepare a cash flow chart indicating when, over the course of the building project, the tranches of money would need to be paid. Adrian O'Brien has never had a sweeter job, in stark contrast with his usual battling with our seemingly inevitable operating shortfalls.

What this extraordinary act of philanthropy has enabled us to do is to go from Stage 1 straight to Stage 2 for the Baker on Commercial Road. The architectural specifications for the new building included footings designed to take an additional two floors; a modest expenditure of money, covering what seemed to be somewhere between wishful thinking and cargo cult. Suddenly, we've got two additional floors of laboratories, plus a Clinical Trials Centre on the fourth floor of the East Block linking us to the Alfred, plus we're no longer $3m short to get to Stage 1.

By the end of 1999 the site of the new Baker building was an impressive hole in the ground. The Coles family had graciously agreed to the demolition of the old Margaret Coles wing on the site, a generosity of spirit we will commemorate in the foyer of our new building. There was inevitably more asbestos than originally diagnosed, so that the demolition took longer and cost more (surprise, surprise) than advertised. The large hole in the ground episodically filled with water, despite the dry summer, once when the diggers hit a spring, and on another occasion a water main, all of which has been fixed. Early in 2000 we have pillars and concrete and a variety of perhaps inevitable industrial skirmishes. The completion time has inched backwards, but is currently set at June 2001...

What Stage 2 gives us is two extra floors of laboratory modules, and the chance to leap frog the current constrictions (in terms of space) on commercialisation and capture. Where there's a will there's a way may be consolation in the face of uncertainty, but on occupational health and safety grounds we just cannot fit any more people into our existing laboratories/animals in the Biological Research Unit: parts of the Institute make down-

town Tokyo look truly rural. Over the past few years, thanks largely to the efforts of Paul Nestel and Ian Smith, and more recently Wally Thomas and Philip Munz, a Baker board member, the will has certainly been there; the way of the future lies in the additional laboratory space our anonymous donor has afforded us, at one fell swoop. Now that the Annual Report contains both individual laboratory profiles and research reports, the latter can cover a broader canvas than used to be the case: one of these reports, on the pages that follow, thus covers the burgeoning activities of the Commercialisation Committee at the Institute.

The second major piece of good news in 1999, for medical research as a whole, was the adoption by the Commonwealth Government of the Wills report, produced by the Health and Medical Research Strategic Review chaired by Peter Wills throughout 1998. What the Treasurer announced in May is a doubling of the NHMRC budget over five years, from July 2000, for an additional investment over that period of $614m 1999 dollars. Once before (1983-1992) NHMRC funding doubled, in constant dollar terms, but over a ten year rather than a five year term: over most of the rest of the decade the level of support has been more or less static, and with a considerable proportion of the allocation time-limited and thus not part of 'the funding base'.

It's a terrific outcome, a tribute to the Minister of Health Michael Wooldridge, who initiated the Review and steered it through Cabinet and the Economic Review Committee; to the Prime Minister, who formally endorsed the proposals at a major speech in October in Melbourne, and to his Cabinet; to Peter Wills, whose vision and sheer hard work underpinned its reception and adoption; and to the research community in general, and the Australian Society for Medical Research in particular, for their enthusiastic support for the proposals the Review enshrined, however challenging some of these may be.

Even as a lifelong optimist, it's not all finished and done. Very properly, the additional funds have to be accounted for in terms of outcomes: I have every confidence that this will be the case. On the other hand, even with a doubling in funding we'll still be below the current OECD average figure for investment in medical research, and there's every indication that nobody is going to mark time for the next five years in the northern hemisphere. And finally, the speed of adoption of the recommendations of the Wills Report has not been matched by the take up process: the Implementation Committee was not constituted until November 1999, and the initial CEO appointment is not anticipated, all going well, until July/August 2000, with a start date then to be negotiated. Even with the gravitas of advancing age, as noted earlier, this appears to be an agonisingly extenuated process. Australia comprehensively missed out on the information technology revolution, in terms of being providers (we're great consumers), and the window of opportunity to take a seat at the biotechnology table is narrower than you might think.

So much for the big picture - enabling anonymous donations, doubling of NHMRC funding over the next five years. On the day to day level, the Institute faces an operating shortfall, essentially totally reflecting the difference between what the funding bodies pay towards salaries at the various scientific levels, and prevailing academic rates. We're not talking high salaries, on an individual basis: a newly appointed Senior Research Fellow at the Baker earns less than a builder's labourer on our Commercial Road building site. Add up the difference of 12-14% over 180 people and there's an inevitable shortfall - very hopefully, given Minister Wooldridge's response to the Prime Minister's October launch of the Wills Report, to be made good from 2001. Until that time, for our scientists to be paid at locally (forget internationally) competitive rates, we need to rely on our endowment - which, in reality, should be devoted to other, creative, lateral things.

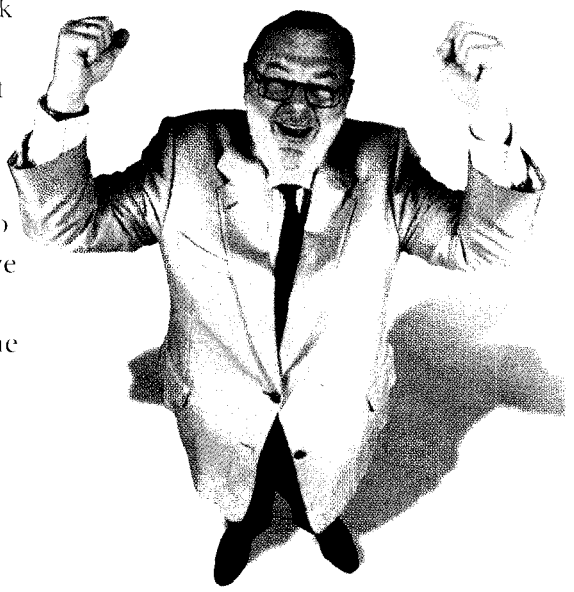
Enough of money and buildings, the perpetual concerns of an Institute Director, and to people. At the end of 1998 we welcomed Gavin and Elisabeth Lambert back to the Baker, from Sweden and France; and at the end of 1999 Michael Hickey, as a Howard Florey Fellow of the NHMRC, from the fastnesses of Calgary. At the end of 1999 we farewelled Stella Clark, for three all too brief years Scientific Executive officer at the Institute, and a tower of strength and inspiration to young and old. Stella has been appointed Associate Professor, and General Manager of the School of Graduate Studies at Melbourne University, her alma mater; she retains both formal and many informal links with the Baker, and takes the best wishes of all at the Institute to her new job.

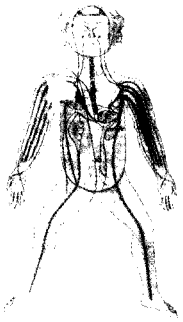
Congratulations are due to Paul Nestel who in 1999 successfully steered a START grant into fruition, with other academic and industrial partners, adding to Ian Smith's success in this regard in 1998. At the meeting of the Institute's Appointment and Promotions Committee Tony Dart was promoted to Senior Principal Research Fellow, equivalent to a personal chair, and Xiao-Jun Du to Senior Research Fellow; Wally Thomas was appointed Senior Research Fellow and Dominic Autelitano Research Fellow: congratulations all round are due.

1999 also saw the first National Heart Lung and Blood Institute (NHLBI)-Baker symposium in Atlanta, where each 'side' was represented by eight scientists, talking about their work and joint projects, and making plans for the future. That was November; in August thirty Baker folk went to Sydney, to the second Baker-Victor Chang-Christchurch Cardioendocrine-Heart Research Institute (BCCH) joint symposium: lots of science, lots of interactions, and Paul Korner (Director BMRI 1976-1990) giving a superb after-dinner speech, on the barbarians at the gates. At the end of 1999 Jaye Chin-Dusting has come forward with a Baker-Singapore joint venture, watch this space: and in 2000 we hope to launch a Baker-Japan effort in her wake. In all of this activity what should not be overlooked is the Russian-Australian exchange, run quietly and very effectively by Alex Bobik for the last decade from the Institute, to the enormous benefit of both Russian and Australian science.

Finally, some words of thanks - to the staff of the Institute, who have been passionate about their research, uncomplaining about the seemingly inevitable delays in building, and a delight to work with. I would also offer my appreciation to the members of the Institute Board - in particular to Norman O'Bryan for his infectious and sustaining enthusiasm; to Bill Gurry for his role as chair of the Capital Appeal to Gerry Johnston for his commitment to innovation; to Ross Barker for his efforts towards a tidier bottom line to Philip Munz for his drive and savvy, and to Margaret Ross for being the inspiration she is. And finally, to the supporters of the Baker in the wider community - private, corporate and philanthropic - who make it possible for the Institute to do the work we do, and to make the best possible return on investment we can, our very sincere thanks are due.

John Funder

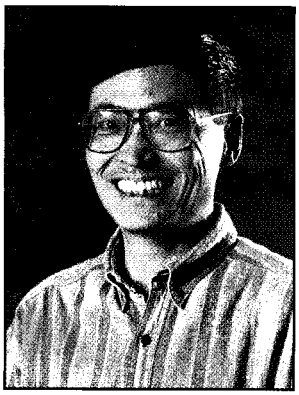




JUST DU IT

Genes and environment, environment and genes. We hear a lot - and rightly - about how smoking causes lung cancer, and how fish oil protects against cardiovascular disease. But only one in three heavy smokers dies of lung cancer, and not all the others have premature heart attacks: some people have protective genes, and we don't really have any clues as to what they are.

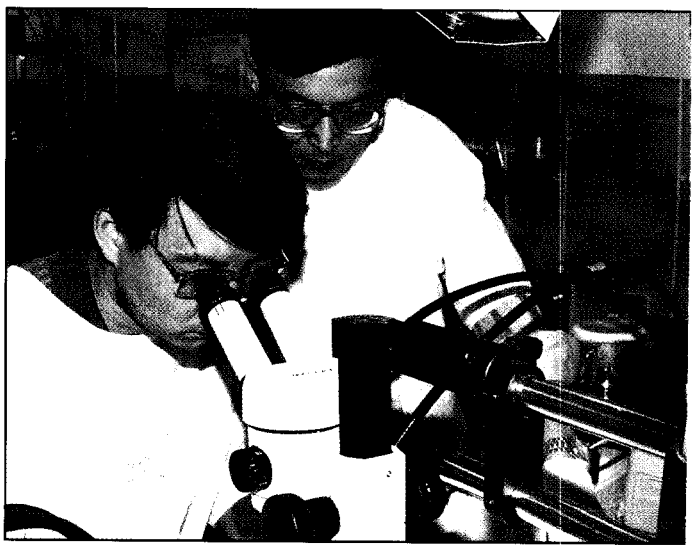
It's a lot more obvious when a particular gene is defective, and causes disease, rather than protects against it. Sometimes these genes are recessive - as in cystic fibrosis, or thalassaemia - which means that both copies of the gene need to be defective before the person is affected; people with one normal and one defective copy are "carriers" of the disease. Sometimes the inheritance is so-called "dominant", which means that a single defective gene leads to profound clinical consequences, despite the coexistence of a normal gene: an example of such a "dominant"condition is Huntington's disease.



Studying the role of mutations has given us considerable insights into human disease: but it's still very much a matter of family trees, of genetic analyses of increasing power, or recording post-hoc rather than asking a coherent set of questions. Enter the mouse: over the past decade the 'knock-out' mouse has emerged as a major tool in medical research, allowing questions to be asked of particular genes, rather than merely observing and analyzing experiments of nature.

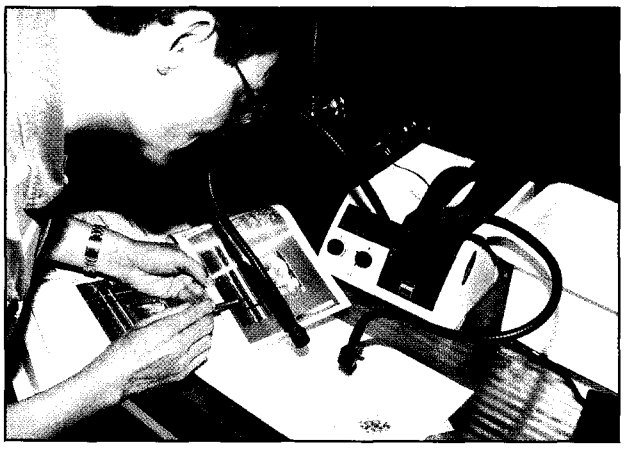
When mice, or fruit flies, or people are exposed to X-rays or a range of chemicals, their genetic material (DNA) can be damaged and not properly repaired, leading to mutations - in some cells more than others, certainly, but by and large in any cells anywhere. In contrast, in the knock out mouse a particular gene coding for the protein of interest can be disrupted in the laboratory, by putting a large lump of foreign DNA into it. Mice breed...well, like mice, and in relatively short order you can have definitive results or lots of affected animals to work with. There are very few people in the world who even try and do catheters and echoes on mice - they're fiddly enough for the human heart, about a thousand times bigger - but for

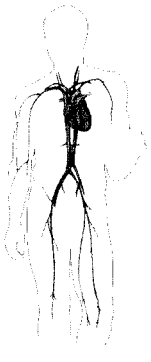
> *"But when all is said and done, what counts is the person"*



Du and his colleagues they've become routine procedures.

They use the human echocardiography set-up - in the evenings, and at weekends, with little regard for day or night: imagine if we were able to provide a dedicated facility. There's enormous demand from our fellow institutes for Du's expertise in collaborative studies, with Victor Chang, the Howard Florey, and the St. Vincent's Institute of Medical Research: big pharma is circling, and maybe we can lever a dedicated mouse facility from them. But when all is said and done, what counts is the person, Xiao-Jun Du - Chinese MD, Glasgow PhD, unassuming, enormously committed, and one of the major strengths for the Baker in the decade to come. ○





GAVIN and ELISABETH LAMBERT

Some years ago the Annual Report featured a picture of Gavin Lambert the student. The photograph caught him writing his thesis, with balls of crumpled paper in and around the waste paper basket. Sometimes photographs are posed, and sometimes they just happen: Gavin, wrestling with writing, was one of the latter. The thesis was duly finished, submitted, examined and passed with flying colours, and after almost a decade at the Baker, the boy from Geelong was off to Europe.

"The most common time for heart attacks is about 9 in the morning: Why? The frequency of suicide depends on the season: How?"

For the first half of that decade Gavin worked in Murray Esler's laboratory as a research assistant, after doing his science degree at Deakin. Murray is the clinical investigator par excellence; Gavin started as a backroom boy, measuring levels of adrenaline and nor-adrenaline in blood samples from patients with high blood pressure or heart failure. Murray is also a wise mentor, and recognised in Gavin much more than his undoubted technical ability. At the end of five years Gavin had a string of publications to his name, and was enrolled to do his PhD.

Now Murray is recognised internationally as top of the class; why should Gavin move on? The answer is that however good we are, we contribute only ~2% of the world's medical research; and just as Murray moved on to Ann Arbor, Michigan, after completing his PhD with Paul Nestel (then in Canberra) Gavin moved off to equally tropical Sweden. He went as a C.J. Martin scholar of the NHMRC, which meant two years working over there and two years support back home in 1999 and 2000. There were lots of places he might have gone, in Europe or North America: Sweden won for two reasons.

First, Peter Friberg and Gunnar Wallin, long-time collaborators with the Esler laboratory and frequent visitors to work on combined projects, acted as a conduit, introducing Gavin to his colleagues, and matching Gavin's emerging interest in what might be called 'psychocardiology' with things going on in Sweden. Secondly, another visitor to the Baker was Elisabeth Gaudet, a PhD student on exchange for a year in Geoff Head's laboratory. Elisabeth had returned to Paris, to write her thesis/crumple balls of paper, and France is a lot closer to Sweden than Michigan - or, for that matter, Melbourne.

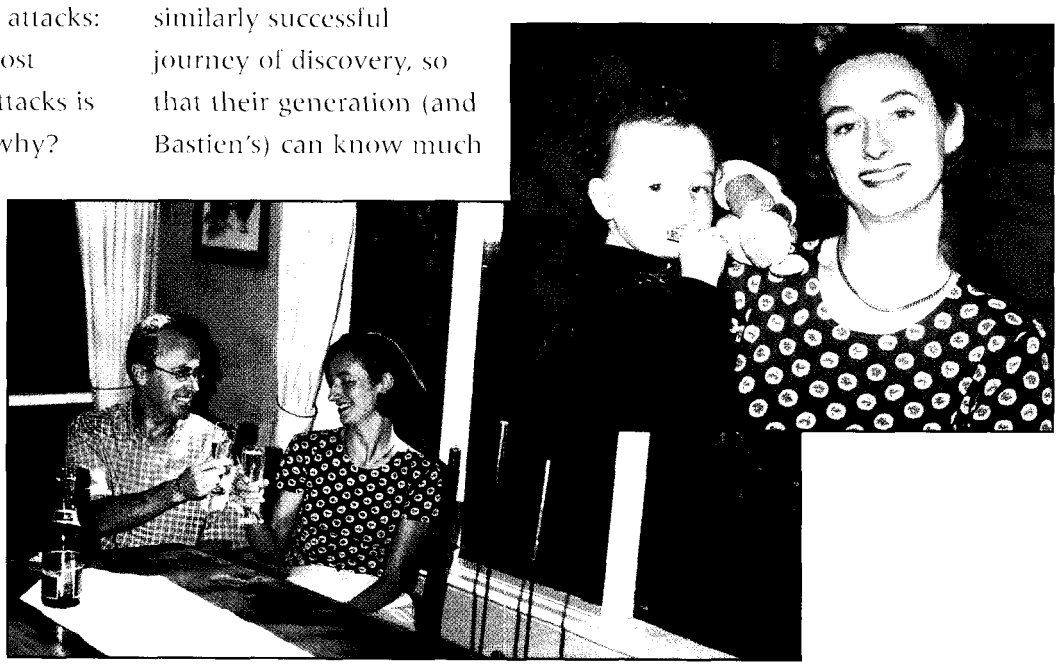
And so for two years Gavin worked in Sweden and Elisabeth in Paris,

with frequent emails and occasional trips. At the end of two years of engagement, a double move for Gavin, to a second postdoctoral position in Paris, and for both a trip down the aisle. Murray Esler had seen all this coming from a long way off and wrote both Elisabeth and Gavin into his laboratory profile when they finally returned to Melbourne - not à deux, but enlivened by the presence of the infant Bastien, complete in tiny Geelong football jumper.

Gavin works on psychocardiology (hearts and minds), or perhaps even more improbably psychochronobiology (it's time for hearts and minds). People who are depressed are between two and three times more likely to have heart attacks: why? People with panic disorder, in its various forms (the 'phobias') are even more likely to have heart attacks: why? - and how? The most common time for heart attacks is about 9 in the morning: why? The frequency of suicide depends on the season: how? The more such questions can be answered, the better we can intervene, to treat or even prevent mental illness and cardiovascular disease.

Elisabeth also works on the brain, but asking perhaps more conventional - if no more easily answered - questions. A major cause of cardiovascular mortality, and particularly of cardiovascular morbidity, is stroke: people rightly fear strokes – which can leave a patient disfigured, powerless and dependent – much more than they fear heart attacks. Some of the things that contribute to stroke, for instance, high blood pressure, are obvious, and can be treated; other things that culminate in a blood vessel blocking or breaking, denying an area of the brain nutrients and oxygen and spilling blood where it's not meant to be, are not nearly as well worked out, and thus not nearly as easily treated or prevented.

There's a long way to go, and it's a long way from France and Sweden back to Melbourne, but Elisabeth and Gavin have made that journey. May they also make a similarly successful journey of discovery, so that their generation (and Bastien's) can know much more about the links between heart and mind, blood vessels and brain - the hows and whys of anxiety, depression, strokes and heart attacks. ○

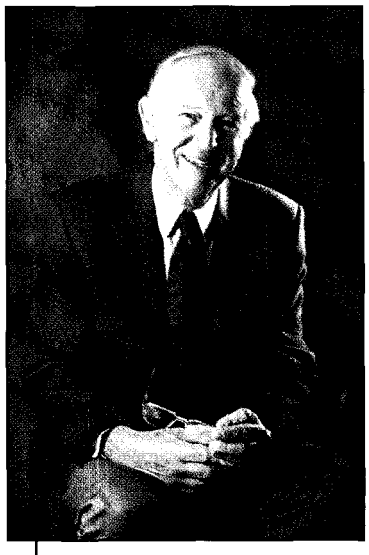


BLUE SUEDE OR PATENT LEATHER?

In the best of all possible worlds, funding of research would never be a problem: all pigs greased and ready to fly. Most of us working at the Baker are much more interested in science than where the next dollar is coming from, but fortunately some people are interested in both. Even with the doubling in Commonwealth (NHMRC) support committed for the next five years, the competition for such funds will remain fierce; the NHMRC covers only 40% of our budget, and the rest has to come from elsewhere.

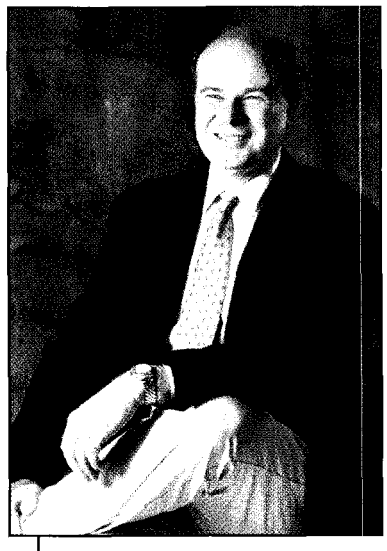
> *"Australia has historically been slack in 'capturing' the research done here, and the Baker has been no exception to the rule"*

Australia has historically been slack in 'capturing' the research done here, and the Baker has been no exception to the rule. A number of factors may be involved - an ivory tower tradition, little or no chemical/pharmaceutical industry, a venture capital sector accustomed to mining but not medicine. Fortunately it's changing, and fast: and among the changes is the evolution of the Commercialization Committee at the Baker.



Paul Nestel

Paul Nestel AO is a distinguished physician-scientist, who was Deputy Director of the Baker for a decade before being appointed Chief of the CSIRO Division of Human Nutrition in Adelaide in 1986. Three years ago Paul returned to the Baker, where he has made an outstanding contribution in many ways - and none more than in establishing and maintaining a culture of commercialization of Baker research. Part is probably a legacy of the CSIRO push for 'external earnings', and part native savvy: but carefully, gently and very effectively Paul has opened the shutters on the ivory tower, and encouraged the winds of change to blow through the place.



Ian Smith

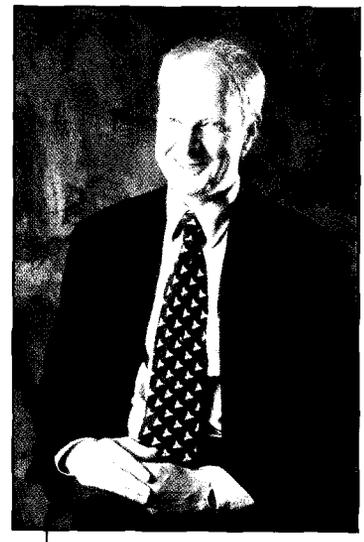
Ian Smith is a Geordie by birth, and an Australian for the last fifteen years. Since his arrival at the Baker in 1990, Ian has been an outstanding collaborator, both within the Institute as the resident protein and peptide chemist, and in a series of joint projects with other institutes and departments at Melbourne, Monash and La Trobe Universities. Many of these collaborations involve requests for multi-user, heavy (and often very expensive) equipment, and Ian and his colleagues have a very good record of successful applications for such infrastructure items. Nothing succeeds like success, and Ian has become a prominent and expert exponent of the importance of commercialization to this Institute.

Philip Munz is a lawyer, an industrialist and a long time Board

Philip Munz

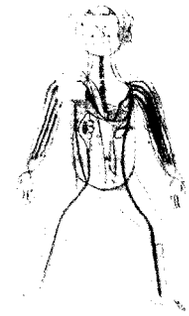
member at the Baker. Early in 1999 the Institute commissioned the consulting firm Foursight to review the structures and processes of commercialization at the Baker, at Paul Nestel's instance: one of the recommendations was that the Committee be expanded to include outside expertise, and importantly that it become a Board subcommittee, chaired by a Board member. Philip accepted the nomination to serve in this capacity, and is set fair to turn the committee - and, if he has his way, the Institute - into "a well-oiled fighting machine". His energy, enthusiasm and contacts should prove invaluable in this role.

A key cog in this machine is Alan Robertson, the newly appointed Director of Commercialization for the Baker, who, when excited, lapses into an impenetrable Glasgow accent. Alan has had a wealth of experience - a PhD in organic chemistry, drug development at Glaxo in the UK, experience with Fauldings and AMRAD here in Australia - and has already made his mark at the Institute, talking to the scientific staff, probing, questioning, formulating concepts, helping write 'business plans'. Currently Alan is based at the Baker, but also works for Rothschilds, supervising a couple of their biotechnology ventures elsewhere in Australia.



Alan Robertson

The structures are in place, and the climate within the Institute is changing: for the first time intellectual property and license fees and share prices are not dirty words, unworthy of the pure scientist. Paul and Ian have led by example in many ways, not the least by both obtaining R&D START grants from the Department of Industry, Science and Resources, in collaboration with commercial and academic partners. Philip and Alan are providing the governance and hands on expertise needed to complement the scientific leadership from within the research staff of the Baker. It's a new decade, a new century, and (equally arguably) a new millennium: and even with a vision limited to the first five years of the decade, we're on the way - to substantial commercial support of our research, and in the longer term, substantial return on our own intellectual property.



WHAT MAKES HEARTS GROW?

There are answers to this question at several levels. In the embryo, the heart forms from a tube doubled back on itself, forming the four chambers, the valves, the inflow and outflow vessels, growing all the time, part of a very delicate process of differentiation and development. A major glitch is usually incompatible with a continuing pregnancy, and results in death in utero; less severe defects lead to congenital heart disease, often able to be corrected medically or surgically in the newborn.

> *...it's the hypertrophy that accompanies cardiovascular disease...*

Over the first fifteen years or so of life the heart obviously grows with the rest of the body, in response to a similar set of growth stimuli: so far, so good. In athletes, the hearts get bigger with training, to help push more blood around to high-demand muscles.

This is physiological hypertrophy, which is medical for increase in size: and when an athlete is grounded by a broken leg, say, or stops intensive training, the heart muscle mass will decrease, just like muscles everywhere else.

Yet when people in the field talk about cardiac hypertrophy, it's usually neither developmental or exercise-induced: it's the hypertrophy that accompanies cardiovascular disease, from aortic stenosis to high blood pressure to heart failure. The hypertrophied heart is commonly pumping blood against increased resistance, or when some of the muscle itself is below par. In such circumstances hypertrophy may be a reasonable response to what the heart is facing - but it's a response that contains the seeds of its own destruction.

Ross Hannan is a molecular biologist, from the University of Tasmania followed by a five year postdoctoral stint in Pennsylvania, who probes and dissects how the heart gets bigger in response to agents like adrenaline and nor-adrenaline. The branch of the autonomic (subconscious) nervous system that goes to the heart uses these transmitters to flog the heart into action (faster! harder!), like one of those trim and tireless aerobics instructors. What Ross and his team do is to study the command system, and work out just how the heart operates to comply.

First, we need to know about the inside of a cell. The genes (DNA) are the blueprints, the messenger RNA the working drawings. DNA is very tough, like blueprints; mRNA is flimsy because often you need to trash one set of working drawings and copy another part of the blueprints. The sequences for proteins, long chains of amino acids, are read off the RNA. Proteins are the girders and joists of cells, and lots more: enzymes are proteins, as are hormones like insulin, and special-purpose oxygen carrying molecules like haemoglobin.

Working drawings are read off in little factories in the cell called ribosomes: if we need more proteins read off, we need more everything - working drawings, amino acids, ribosomes. As it happens, in most cells there's plenty of copies of the working drawings, and plenty of amino acids: what's rate-limiting is the factories, the ribosomes. If there is going to be a hypertrophic response to a particular stimulus, then the chances are more factories will have to be built.

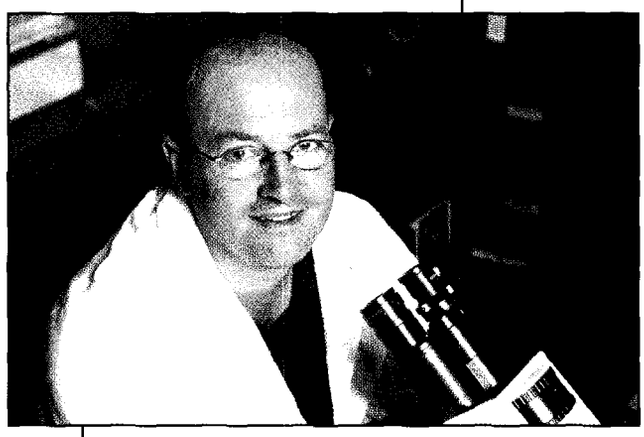
Ross works on cardiac myocytes (muscle cells) from newborn rats. The hearts are digested with enzymes, and the muscle cells separated from the others, and then plated out in little Petri dishes as a cell culture. They grow until there's a flat sheet of cells: if you stimulate them they'll contract, in ripples across the surface of the

dish; normally, however, they're quiescent - can't beat, can't pump.

So when Ross and his team want to look into the black box, they stimulate the cells with phenylephrine, a synthetic adrenaline-like drug. What they see is more ribosomes and essential ribosomal machinery: so far, so good. What turns it on seems to be a signal to the DNA called UBF - its levels certainly rise in response to phenylephrine, and it's a known 'transcription factor', stimulating read out or transcription of DNA to make working drawings.

To prove it, Ross and his colleagues trick the cells in a number of ways. First, they 'overexpress' VBF (i.e. have the cells make to much), and up go the levels of readout. Conversely, they have the cells make a mirror-image, 'antisense' working drawing for VBF, which binds with and blocks the real message - and hey presto, no hypertrophy. It's tighter and tighter evidence that CBF is a key molecule, both necessary ans sufficient for rybosomal proliferation in response to hypertrophic stimuli, and thus for the process of hypertrophy as a whole.

Well, you might ask, so what? The answer is that, as yet, we're not sure. Hearts may need to go harder and slower (like an athlete's heart), rather than harder and faster: how can we selectively tinker with the mechanisms involved, to keep the 'good' bits of the hypertrophic response, and minimise the downside? We don't know yet where that point of attack will be, but when Ross and his team are finished there's a good chance we might - and thus be in a much better position to provide much improved quality of life and protection against premature death for those with aging, failing or hypertrophied hearts. ○



Ross Hannon

OUT OF THE MOUTHS

The Baker is affiliated with the Alfred Hospital and Monash University. You might be excused for asking what this exactly means: dusty documents and long-forgotten handshakes, or something rather more lively. Fortunately, the latter is the case, in both instances.

In terms of the Alfred, the links are strong and obvious. First, both the current and new Baker buildings are on the Alfred site. Secondly, the Alfred and Baker Medical Unit provides the formal link between the Alfred Heart Centre and the Baker. Third, Garry Jennings is Director of Cardiovascular Services at the Alfred, and Deputy Director of the Baker. Finally, perhaps the most important functional linkage, what the Baker does as research the Alfred translates into practice.

For Monash, the links are strong but less obvious. The senior staff at the Baker have honorary appointments at Monash, and as such contribute to both under-graduate science and medical teaching, here and at Clayton. The Baker makes outstanding contributions to Monash in terms of ethics, through the Eleanor Shaw Centre, and has a growing involvement via the recently established umbrella Biocom International, to commercialise intellectual property.

But perhaps the most important ongoing linkage is via our post-graduate students. Each year a dozen or so students do their fourth year of science - their Honours year - at the Baker, enrolled through one of the Monash departments. Each year we have twenty something PhD students, post BSc Honours or MBBS, who work in various laboratories at the Baker and in the Alfred Baker Medical Unit, the majority enrolled via the Monash Department of Medicine.

Not all those who do a PhD will (or should) wind up in research. When Kim Webber, now of the Common-wealth Department of Health, was asked at a student retreat what she liked doing best, her response was clear: "I like doing the experiments, I like analysing the results, I like writing them up for publication, I don't even mind standing up at meetings talking about them - but what I <u>really</u> like is planning the experiments".

Uh huh - and have you ever thought about a career in research administration, doing policy and planning? In the middle of writing up all her pharmacology came the call from Canberra; now, two years later, Kim has graduated PhD and gained a wealth of experience across the health sector. Until 1976 only 10% of Commonwealth employees could be university graduates (Australia ? the clever country ?); Kim is part of a new wave of professionally qualified trainees, hopefully to make content-free administration a thing of the past.

Corie Shrimpton thought long and hard about what to do after finishing her PhD with Ian Smith, and is now at Baylor University in Houston, Texas. She works with Jose Lopez, a friend and collaborator of Michael Berndt: as part of the National Heart Lung and Blood Institute-Baker exchange program, Michael spent three months of study leave at Baylor, and last year Jose (rightly) July and August in Melbourne.

She's a remarkable young woman in many ways. To go to Texas, she's shifted her scientific focus: a challenge, but potentially more productive than staying in the same field forever. Corie spent a week during her time at the Baker on the Queen's Trust program - and on return set up, singlehanded, a series of monthly public interest lectures at the Institute. And when her father died of a heart attack, she endowed a travelling scholarship for a third year PhD student in his memory. All this, and here current email address begins "cowgirl...".

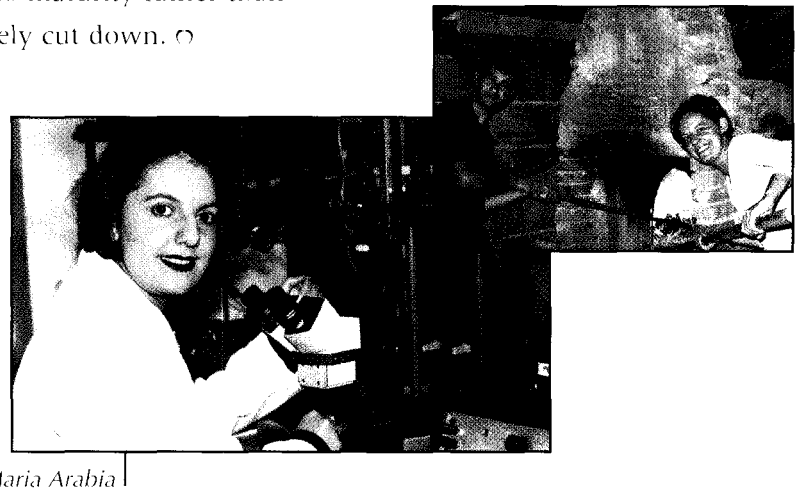
Anna-Maria Arabia has taken another route, that of spending

some of her time before graduation overseas: she's currently in Milan, learning new techniques and doing stuff on the brain she couldn't do here, and will return to write up in the second half of 2000. Like Corie, she has been President of the Baker Students' Society; she has also been very active in the Italian Cultural Institute, and in Australian -Italian scientific exchange programs.

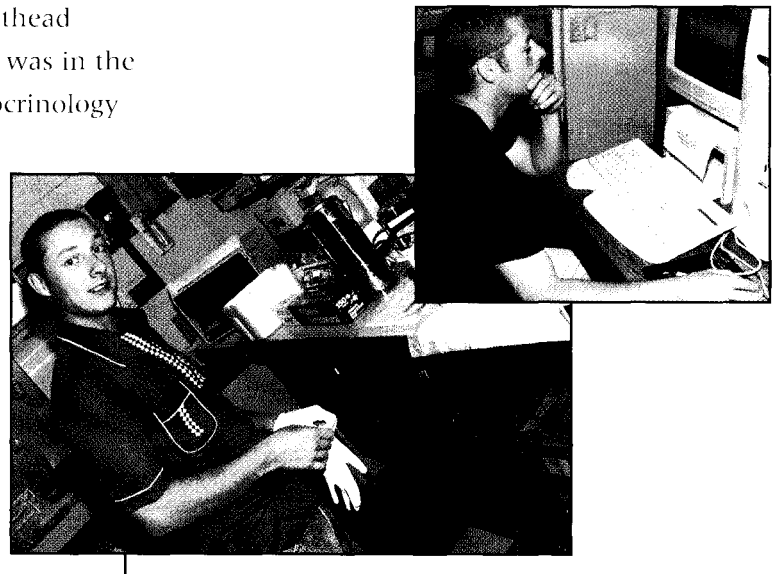
Glen Wiesner works with Murray Esler, on the hormone leptin. Leptin was discovered in the early 90s to be made by fat cells, and to act on the brain to regulate hunger and satiety, the feeling of 'I've had enough'. Most of the work has been done in rats; Glen and Murray looked at arterial and venous concentrations across the human brain, and found to their surprise that the human brain makes heaps of leptin, and that there's a marked gender difference: so who's a fathead now? Glen's first paper was in the Journal of Clinical Endocrinology and Metabolism - and had the rare honour of the editorial which opens each issue of the journal being devoted to it.

That's five, out of thirty odd. When we look at today's students, they're bright, they're science graduates rather than medical doctors, and they're overwhelmingly female. They will work eventually in a variety of positions - in research, in industry, in policy, in start-ups, as lecturers, wherever; and, hopefully, a goodly proportion will live in and contribute to Australia, after their time overseas. Today's students are tomorrow's leaders: we're not very good at acknowledging leadership, but hopefully the next generation of tall poppies can flower into maturity rather than be routinely cut down. ○

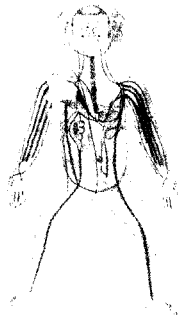
Corie Shrimpton



Anna-Maria Arabia



Glen Wiesner



FROM BENCHTOP TO BEDSIDE - AND BEYOND

The Latin word fasces means a bundle of sticks. Mussolini used a bundle of sticks as the badge of fascism: to this extent unbundling is something to be desired. The other, more current sense of unbundling is not so clear cut. Health departments have unbundled hospitals, on the basis that their remit is health care, and that education is the province of the universities, and research of the NHMRC.

On the surface it sounds reasonable, but first impressions are sometimes deceptive. The rationale for unbundling has been that it was difficult to account for the cost of teaching and research in teaching hospital budgets in the 1970s and 1980s. Hospitals are now paid per patient, per diagnostic category, per procedure - with upper limits fixed. Welcome to warehouse medicine, Billy Guyatt comes to health care.

What has happened is that in Victoria teaching and research have become divorced from patient care. This might make some sort of short-term economic sense, but is not good news for today's patients, and potentially a disaster for tomorrow's. It's not just in Victoria: to some extent it's happening all over Australia, and in a different context in the USA.

Which makes the remit of the Baker, cardiovascular research from benchtop to bedside, doubly important: over half the senior staff of the Baker are clinically qualified, and the majority of them are clinically active. It also makes it important to go beyond the bedside, into areas of public health, of health promotion and of evaluation.

Over the past decade, for instance, the Institute has grown into this role in a number of ways. Laboratories, headed by Garry Jennings, Paul Komesaroff, Chris Reid and Bronwyn Kingwell have had projects and projects funded by the Victorian Health Promotion Foundation. These have covered areas like diet and heart disease, exercise, and menopause in the community at large, and in various sections of the community in particular.

In Chris Reid's case, these studies have been an add-on to his 'day job', that of running a major drug trial (The Australian National Blood Pressure Trial, or ANBP2) for the High Blood Pressure Research Council of Australia. This is an enormous trial, involving 6000 patients and more than 10% of the general practices in Australia. It is novel in that the pharmaceutical company Merck, and the Common-wealth Government, have joined forces to support the trial and get the results: good medicine not only saves lives, it saves money.

ANBP2

The follow up - actually, it overlaps with ANBP2 - is a trial called OPERA (all trials have an inner logic of an easily remembered abbreviation, the catchier the better). OPERA is taking a drug called Omipatrilat out into the field, in what is the biggest (at least in terms of expense) clinical trial ever attempted. What is particularly relevant about the OPERA trial is that a large component, of the order of a quarter of the patients, is to be run by Colin Johnston. Colin recently retired to the Baker from his previous position as Professor of Medicine. He has a wealth of research experience and wide international recognition: what he contributes to OPERA is not merely hundreds of patients from Australia, but also expertise in study design and analysis.

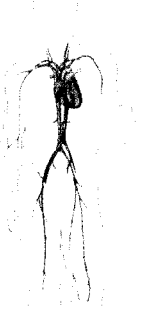
Too often, to date, Australia has been a sort of research equivalent of Costa Rica in the fruit

business: it may grow great bananas, but nobody mistakes United Fruit for a Costa Rican company. We've provided well-managed patients, clean data, interested and intelligent commentary - but the value adding bits, of design and monitoring and analysis have been squarely Northern Hemisphere. Nobody's suggesting that Merck or Bristol Myers Squibb are rushing to relocate to Melbourne, or list on the Australian Stock Exchange - but the sort of input Colin's having is a very good start.

People have by and large heard of ACE inhibitors, widely used in the treatment of hypertension and heart failure. ACE is short for angiotensin converting enzyme, which converts an inactive precursor protein into the active peptide angiotensin. Angiotensin does a bunch of things, including constricting blood vessels, stimulating the hormone aldosterone to retain salt, and causing blood vessel walls and the heart muscle to thicken up. These are great if you're salt deficient or have lost a lot of blood - but by and large in today's circumstances they're counterproductive, as the management gurus say.

ACE inhibitors are relatively (but not absolutely: nothing is absolute ...well, almost nothing) specific, that is they block ACE much better than they block other enzymes. Omapatrilat is different: in addition to being a good ACE inhibitor it is also a very good peptidase blocker - that is, it stops the breakdown of particular peptides thought to wear the white hats in terms of blood pressure control and cardioprotection.

So for the next five years Colin will be part of the team exploring whether this added action makes Omipatrilat an even better drug than the current generation of straight ACE inhibitors. In addition, he will have quite particular responsibilities for the major Australian component of the trial. Five years seems a long time - but the OPERA isn't over until the fat lady sings, Brunnhilde comes to Bristol Myers Squibb. ○



ROLLING AND STICKING AND MORPHING

When we think of heart attacks and strokes, we think heart and brain, when we ought to be thinking about heart, brain and blood. Obviously a heart can't do much with nothing to pump, and the brain tolerates oxygen deprivation very poorly - but the red cells and serum are only half the story. Michael Berndt and his team work on the other constituents of blood - white cells, platelets - which at first sight might appear counterintuitive for a cardio-vascular research institute - aren't they about infectious diseases, and haemophilia, and things like that?

Well, sure - but they're also mainstream cardiovascular medicine. Other names for a heart attack are coronary thrombosis or myocardial infarct, which describe in turn the process and the results of blocking one of the arteries supplying the heart muscle. A thrombosis is a clot, formed by platelets and stuck together with fibrin; a coronary thrombosis is a clot in one of the coronary (heart) arteries. An infarct is an area of dead tissue beyond a blocked blood vessel: a myocardial infarct is dead heart muscle, and diffuse small infarcts in the brain with aging are a more common cause of dementia than Alzheimer's disease.

So in the context of heart attacks and strokes, platelets are important, and so are the white blood cells. White blood cells are the panzer divisions of the immune system, protecting us from invasion by foreign organisms (e.g. bacteria), and mounting the inflammatory response; it takes a little time to organise the antibodies, soluble proteins circulating in blood, foot soldiers bringing up the rear. When our blood cholesterol is higher than it should be, cells in the blood vessel wall (which includes white cells) get filled with cholesterol, the process of atherosclerosis, a cardiovascular accident waiting to happen.

What Michael has done throughout his twenty year career in cardio-vascular research is to work out how platelets, and more recently white cells, interact with the cells lining the blood vessels. This is no mean feat, both for a scientist and for a blood cell. Whereas in the capillaries things are pretty slow and meandering, this isn't where the action is in terms of athero-sclerosis and coronary thrombosis: it's in the main distributing vessels. Here the pressure is much higher, and the flow is fast. It's easy to see how a willow wand might get caught up on the banks of a gently flowing stream; it's much harder seeing how it might strike in the bank of a torrent.

In the bloodstream, platelets and white blood cells are normally borne along in the current: we have 5-6 litres of blood, and we circulate it every minute - it's a pretty dynamic system. When there's inflammation, however, the call goes out (it's a chemical call, rather than a trumpet) for the calvalry, and the lining of the blood vessel in the immediate area of the inflammation subtly changes, to allow the white cells to stick to and then migrate through the wall to the trouble spot.

What Michael and his team have worked out is that white cells are always rolling on the endothelial cells, the lining of blood vessels. When you see them under a microscope, they touch, slow up, roll for a bit, and then get swept on, back into the mainstream, in a healthy vessel. When the signals from an area of inflammation are there, however, they're like a tennis ball on Velcro - roll for a bit, and then stop despite all the buffeting. They then morph, as the young would say, and migrate between overlapping cells to go out of the bloodstream to do their job in the surrounding tissue.

And when the blood vessel itself is damaged - when we cut ourselves, or when a bulging atherosclerotic plaque ruptures through the wall

into the interior of the coronary artery - then the platelets come into play. We can make platelets less sticky : for people on aspirin shaving nicks take forever to stop bleeding. At a cellular and molecular level, its important to know how white cells roll, how platelets stick, for several reasons. First, the more we know about how a system works physiologically, in health, the less likely we are to do mischief out of ignorance. Secondly, the more we know about how it works (or fails to work) in disease, the more likely we are to come up with useful medication for the treatment, or even the prevention, of coronary thrombosis and stroke.

Over the past decade Michael has built an internationally recognised team around him at the Baker. Rob Andrews, a Senior Research Fellow, has for instance exploited particular pit viper (snake) venoms in his research, among other things: these venoms are toxic because they wreck the clotting system, delicately balanced between bleeding forever and totally clogging up. Like Michael, Rob is originally a Queenslander, and returned to Australia in the early 1990s after a postdoctoral period in the USA.

Liz Gardiner is a Senior Research Officer, and an accomplished cellular biologist, again joining the Berndt laboratory straight from her time overseas in the US.

Yang Shen, also a Senior Research Officer, is a Chinese medical graduate who did a PhD in molecular biology in Adelaide, and has brought a range of superb skills to the group. Finally, Michael Hickey returned in December 1999, from an extended postdoctoral stint in Canada, to begin his studies on vasculitis, inflammation of the blood vessels, on a Florey fellowship from NHMRC.

How white cells and platelets interact, with each other and with blood vessel walls, is of crucial importance not only in whether or not we get coronary thromboses or stuttering strokes (transient ischaemic attacks: TIAs): it's also crucial in how we respond, for example, to angioplasty after we've had the procedure for angina, or for an almost blocked coronary artery. When we know the cellular and molecular machinery involved, we'll know where and how to interrupt the process when appropriate, without having the whole system crashing down. That's the way to apply cutting-edge basic research - and that's what Michael and his team are doing. ○

THE WILLS COMMITTEE REPORT

There are big questions in medical research, and middle-sized questions, and small questions: science as Goldilocks. One of the middle-sized questions is who reads Annual Reports. By and large, scientists don't: they look at the publication list, check who is still in which laboratory, note that the picture of so-and-so is at least ten years old. Donors may check who else is supporting the Institute, and perhaps read the President's report.

So even though there's no clear answer as to whose eyes will actually ever scan this page, we have to proceed on certain assumptions. First of these is that the eyes are pretty sharp, but do not necessarily have an MD and PhD. Second, and probably very importantly, the people who read the Annual Report are interested in medical research in general, and perhaps the Baker in particular. For this group, the outcome of the Health and Medical Research Strategic Review is probably the single most important event of 1999.

The HMRSR was launched in February 1998 by the Minister for Health, the Hon. Michael Wooldridge, with Mr. Peter Wills, AM, in the chair. Michael Wooldridge practised as a doctor before entering politics, including a brief time in the laboratory, and has a very firm commitment to medical research in this country. Peter Wills is, among other things, Chairman of the Board of the Garvan Institute of Medical Research in Sydney, similarly evidence of commitment to medical research.

The committee met monthly in the first half of 1998, then fortnightly, then it seemed weekly. There were four members from Melbourne, four from NSW, one Queenslander and three overseas members linked in by teleconference and occasionally in person. Midway through the process Peter Wills and Peter Conde, the head of the secretariat sustaining the committee, set off on a three week trip, interviewing scores of people in half a dozen countries around the world, making the contacts, picking their brains: we're a big country in physical terms, but only 2% of the global effort in this sector.

The draft report went to Cabinet in December 1998, and then out for comment. Almost 2000 responses were received in a couple of months, over 99% totally supportive, an extraordinary outcome in a sector where 'refining' statements is almost a stock in trade, and right across the broad spectrum of constituencies - the public, the research workers, industry, the government, venture capital.

So where was the magic? First, the report proclaimed a 'Virtuous Cycle', in which research, government funding and industry fed off one another and fed into one another: all for one and one for all. It proclaimed the importance of the discovery dimension of research – investigator-initiated, curiosity driven – as the prime mover in the sector: research is not dial-a-pizza, or something that you can order by the metre.

It acknowledged the financial constraints under which Australian

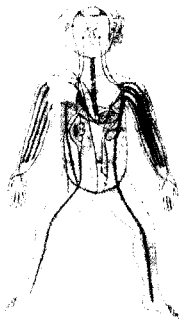
Peter Wills and Michael Wooldridge

science generally operates; poor salaries, a historically non-competitive capital gains tax, the practice of spreading resources very thinly, and our reliance on improvisation, the great Australian fallback: two bits of string and a broken razor blade, and she'll be right.

It pointed out that in a $50 billion health sector we spend about 0.1% on 'priority driven' research, finding out where needs really are, how best to address them, how to make the system more efficient. The much reviled UK NHS spends over 1% in such research, demonstrably a wise investment: as has been said in another context, you wouldn't run a lolly shop spending only one dollar in a thousand to make sure it's working properly. And finally, it called for a major investment in biotechnology, so that Australia can be a producer as well as a consumer in what seems set fair to be the major economic driver of the early decades of the 21st century.

In the May Budget the Treasurer announced an additional $614 million for medical research, to double the level of NHMRC funding over the next five years. It's a triumph for Michael Wooldridge and Peter Wills, and an enormous shot in the arm for the sector as a whole. It means we can pay reasonable salaries, promote the formation of critical masses, encourage flexibility between academia and industry, start asking (and answering) the hard questions about health care delivery.

It may be a triumph, and a shot in the arm, but it's only the start. The biotechnology revolution is moving apace, and "she'll be right" is no justification for standing still. Secondly, even with a doubled NHMRC budget in 2005, our spending will still be below the OECD average in 1999 - and its member countries are certainly not standing still. It's only the start, and it's no iron clad guarantee of success - but it's arguably the news of the century for medical research in Australia. Watch this space. ○



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Dr Jean-Phillippe BAGUET	Grenoble
Dr Yves BRANDENBURGER	Geneva
Dr. Hanspeter BRUNNER	Zurich
Dr. Ying CAO	Shenyang
Dr Osamu EBISUI	Kyoto
Dr Genro FUJISAWA	Oyama City
Dr. Yoshiaki FUKUHIRO	Okayama
Dr Gabrielle GALLON-BEAUMIER	Marseilles
Dr. Xiaoming GAO	Xinjiang
Dr Kazuhiko HASHIMURA	Osaka
Dr Matsuhiko KIMURA	Hamamatsu
Dr Natalia KALININA	Moscow
Dr Kaori KOYAMA	Sendai
Dr Atsushi KUBO	Tokyo
Dr Elena LUKOSHKOVA	Moscow
Dr Michael MENCHEKOV	Moscow
Dr Michael NAVAKATIKYAN	Auckland
Ms Magdalena RUMANTIR	Jakarta
Prof Desmond SHERIDAN	London
Dr. Hideki SHIGE	Tokyo
Dr. Satoshi SUZUKI	Sendai
Dr Hitoshi UENO	Toyama
Dr Olivier VAN DEN BRINK	Amsterdam

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Assistant Surgeon General, Australian Defence Forces - Navy

Prof. Stephen R. Holdsworth
MD, PhD, FRACP
Professor and Chairperson of Dept of Medicine, Monash Medical Centre
Clinical Dean of Monash Medical Centre Medical School
Director, Clinical Immunology, Southern Healthcare Network

Mr Philip Munz
LLB (Hons)
Group Executive Chairman, GSA Group Pty Ltd

Mrs Margaret S. Ross
Member, Board of Australian War Memorial Foundation

PAST PRESIDENTS

J.F. Mackeddie
BA, MD, BS
1929 - 1944

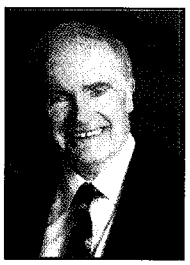
E. Rouse
CBE, FRACR (Hon)
1944 - 1971

J.C. Habersberger AO
B. Comm 1972 - 1983

Sir Laurence Muir
VRD, LLB, FSIA FAIM
1984 - 1986

J.D. Moir AM
1987 - 1992

D.F Hogarth OAM
BSc
1992 - 1994



Professor Richard Smallwood AO,
MD, FRACP, FRCP, FACP (Hon)
NHMRC Representative

PATRON

Sir Laurence Muir
VRD, LLB, FSIA, FIAM
Company Director
Patron of the Institute and former President of the Board of Management

FOR THE YEAR ENDED 31 DECEMBER 1999

The Board of Management present their report together with the financial statements of the Institute for the year ended 31 December, 1999 and the auditors' report thereon.

Board Members

The Board Members in office at the date of this report are:

Mr N O'Bryan	President
Dr G P Johnston	Vice-President
Mr R E Barker, Hon.	Treasurer
Professor J W Funder AO	Director
Mr P C Barnett	
Mr S Blair (resigned January 2000)	
Professor P Darvall	
Mr W P Gurry AO	
Dr P G Habersberger AM	
Professor S R Holdsworth	
Mr P Munz	
Mrs M Ross	
Professor G Ryan AC (appointed January 2000)	
Professor R Smallwood AO	

Principal Activities

The principal activities of the Institute are medical research into the basic causes of cardiovascular disease, to use this knowledge to help prevent heart and vascular disease in the community, and to improve medical and surgical treatment. No significant change in the nature of these activities occurred during the year.

Operating Result

The financial result from research activities was a deficit of $470,084 (1998:deficit $374,869). After allowing for the surplus arising from the Capital Fund which incorporates grants and contributions received towards the cost of the new Institute the consolidated result for the year was a surplus of $3,793,098. Income is not applicable.

Review of Operations

A review of the operations of the Institute during the year has been included in the President's and Director's report. The Institute's activities continued to be dedicated to medical research into the basic causes of cardiovascular disease. The Institute is a body corporate under an Act of Parliament and has no share capital.

Year 2000

The Institute's transition into the Year 2000 was completed successfully. Over the New Year weekend a review of all critical items of equipment was undertaken. Computer systems' hardware and software continued to operate as normal.

There are no outstanding issues that will affect the operations of the Institute.

State of Affairs

Thanks to a substantial donation, it has been made possible the two additional floors in the initial building project and increase the size of the Animal House, together with a replanning of the 3rd floor of the Alfred East Block and the staff amenities area. This necessitated a major review and redrafting exercise together with the commensurate changed requirements in the tender documents. Worked commenced on site in mid 1999 and demolition proceeded smoothly.

Multiplex was the successful tenderer for construction. Due to issues arising from the period of interim government, following the State elections, building did not commence on site until late in the year. Major industrial action within the construction industry has hindered progress and it is now likely that the date of completion will be mid 2001.

Government grants and private/corporate contributions totalling $33.121m are due to be received towards the cost of the Baker's new Medical Research Institute. Of the $10,575,881 received as at 31 December 1999 $3,126,972 has been spent on the project to date.

Events Subsequent to Balance Date

There has not arisen in the interval between the end of the financial year and the date of this report any item, transaction or event of a material and unusual nature likely, in the opinion of the Board of Management of the Institute, to affect significantly the operations of the Institute, the results of those operations or the state of affairs of the Institute in subsequent financial years.

Board Members Benefits

Since the end of the previous financial year, other than Mr R E Barker who is an employee, Director and shareholder of a firm of Stockbrokers which has received, or become entitled to receive, fees for services rendered to the Institute on normal commercial terms, no Board member has received or has become entitled to receive any benefit, by reason of a contract made by the Institute or a related corporation with any Board Member or with a firm of which a Board Member is a member or with an entity in which any Board Member has a substantial financial interest other than the Director of the Institute, Professor J W Funder, who receives a salary.

Dated at Melbourne this 17th day of April 2000

Signed in accordance with a resolution of the Board of Management.

Norman O'Bryan
President

John W Funder AO
Director

BAKER MEDICAL RESEARCH INSTITUTE
CONSOLIDATED PROFIT AND LOSS ACCOUNT
YEAR ENDED 31 DECEMBER 1999

	Note	1999 $	1998 $
Consolidated Income	3	19,222,691	12,026,768
Consolidated Surplus for the year		3,793,098	37,421
Represented by:			
Deficit from Operations		(470,084)	(374,869)
Surplus from Capital Fund		4,343,938	631,649
Deficit from Specific Purpose Fund		(80,756)	(219,359)
Consolidated Surplus before income tax	4	3,793,098	37,421
Income tax attributable to surplus	2(k)	0	0
Consolidated Surplus after income tax		3,793,098	37,421
Accumulated funds at the beginning of the financial year		7,632,272	7,594,851
Accumulated funds at the end of the financial year		11,425,370	7,632,272

The accompanying notes form an integral part of these financial statements

BAKER MEDICAL RESEARCH INSTITUTE
CONSOLIDATED BALANCE SHEET AS AT 31 DECEMBER 1999

	Note	1999 $	1998 $
ASSETS			
Current Assets			
Cash		786,626	92,927
Receivables		938,172	1,101,787
Inventories		77,161	104,574
Prepayments		137,778	189,930
Accrued Interest		95,389	69,926
Investments (at cost)	9(a)	6,163,533	3,369,171
Total Current Assets		8,198,659	4,928,315
Non - Current Assets			
Plant & Equipment	10	2,428,981	2,045,237
Investments (at cost)	9(b)	7,190,033	6,240,613
Total Non - Current Assets		9,619,014	8,285,850
TOTAL ASSETS		17,817,673	13,214,165
LIABILITIES			
Current Liabilities			
Creditors		2,521,847	522,622
Lease Liability	2(f)	62,323	59,532
Prepaid Grants	11	2,562,109	3,926,270
Provisions	12(a)	754,100	635,145
Total Current Liabilities		5,900,379	5,143,569
Non - Current Liabilities			
Lease Liability	2(f)	204,419	135,712
Provisions	12(b)	287,505	302,612
Total Non - Current Liabilities		491,924	438,324
TOTAL LIABILITIES		6,392,303	5,581,893
NET ASSETS		11,425,370	7,632,272
FUNDS			
Accumulated Funds			
Operating Fund	5	(4,381,719)	(3,911,635)
Capital Fund	6	13,604,570	9,260,632
Specific Purpose Fund	7	201,031	281,787
Asset Revaluation Reserve - 1/1/93		2,001,488	2,001,488
TOTAL FUNDS	8	11,425,370	7,632,272

The accompanying notes form an integral part of these financial statements

BAKER MEDICAL RESEARCH INSTITUTE
STATEMENT OF CASH FLOWS FOR THE YEAR ENDED 31 DECEMBER 1999

	Note	1999 $	1998 $
Cash Flows from Consolidated Activities			
Receipts from Granting Bodies		4,739,532	5,934,397
Donations and Bequests		5,648,823	4,375,136
Receipts for Building Work		8,402,888	0
Payments to Suppliers & Employees		(14,598,355)	(11,499,780)
Dividends Received		305,542	350,183
Interest Received		235,019	193,832
General Income		319,060	299,274
Net Cash from Consolidated Activities	17	5,052,509	(346,958)
Cash Flows from Investing Activities			
Payment for Investment Securities		(2,914,375)	(1,139,973)
Proceeds from sale of Investment Securities		2,154,648	1,391,085
Payment for Property, Plant & Equipment		(755,807)	(798,923)
Net Cash used in Investing Activities		(1,515,534)	(547,811)
Cash Flows from financing activities			
Principal Repayments under finance leases		(49,640)	(33,760)
Net Cash used in financing activities		(49,640)	(33,760)
Net Cash Increase / (Decrease) in cash held		3,487,335	(928,529)
Cash at beginning of the financial year		3,462,098	4,382,671
Effects of exchange rate changes on cash held in foreign currencies		726	7,956
Cash at the end of the financial year	16	6,950,159	3,462,098

The accompanying notes form an integral part of these financial statements

BAKER MEDICAL RESEARCH INSTITUTE
NOTES TO AND FORMING PART OF THE ACCOUNTS

1. Incorporation
The Thomas Baker, Alice Baker and Eleanor Shaw Medical Research Institute was incorporated as the "Baker Medical Research Institute" ("the Institute") under the Baker Medical Research Act 1980.

2. Summary of Significant Accounting Policies
Set out hereunder are the significant accounting policies adopted by the Institute in the preparation of its accounts for the year ended 31 December 1999. These policies have been consistently applied unless otherwise indicated.

(a) Accrual basis
The accrual basis of accounting has been used with revenues and expenses being recognised as they are incurred, and brought to account in the period to which they relate.

(b) Historical cost
The financial statements have been prepared on a historical cost basis and except where stated do not take into account current valuations of non-current assets.

(c) Fund accounting
The Institute operates on a fund accounting basis and maintains three funds; Operating, Specific Purpose and Capital Funds. The work of the Institute is financed from grants, investment income and donations of both general and specific natures. Income of a specific nature is used in accordance with the terms of any relevant convenants. The amount of grants received for specific purposes during the year but unspent at year end, will be generally expended in the next financial year. The Institute's capital fund comprises the capital donations, bequests and receipts from fundraising activities carried forward.

(d) Principles of consolidation
The Institute's accounts have been prepared on a consolidated basis. All inter-fund transactionshave been eliminated on consolidation.

(e) Plant and equipment
Items of plant and equipment are recorded at cost or Board's valuation and are depreciated over their useful lives using the straight line method. The expected useful lives for plant and equipment is 5-20 years. Profits and losses on the disposal of plant and equipment are taken into account in determining the result for the year.

(f) Leased Assets
Assets acquired under finance leases are included as property, plant and equipment in the balance sheet. Finance leases effectively transfer from the lessor to the lessee substantially all the risks and benefits incidental to ownership of the leased property. Where assets are aquired by means of finance leases, the present value of the minimum lease payments is recognised as an asset at the beginning of the lease term and amortised on a straight line basis over the expected useful life of the asset. A corresponding liability is also established and each lease payment is allocated between the liability and finance charge.

(g) Land and building
The Institute has adopted the policy that capital expenditure incurred in respect of the planned new building is written off against income during the year. The building currently occupied by the Institute and the Baker's new Medical Research Institute are not included as assets in the accounts as in neither case does the Institute have title to the property.

(h) Inventories
Stocks of consumable scientific and administrative items are stated in the Balance Sheet at the lower of cost and net realisable value. Cost is determined by the average cost method from computerised stock records.

(i) Cash
For purposes of the statement of cash flows, cash includes deposits at call which are readily convertible to cash on hand and are subject to an insignificant risk of changes in value, net of outstanding bank overdrafts.

(j) Investments
Interests in listed and unlisted securities are brought to account at cost and dividend income is recognised in the profit and loss account when receivable.

(k) Tax status
The income of the Institute is exempt from income tax pursuant to the provisions of section 50-5 of the Income Tax Assessment Act 1997. The Institute is also exempt from other government levies such as payroll tax and sales tax but not fringe benefits tax.

(l) Employee entitlements

Annual Leave
The Institute has fully provided for accrued annual leave entitlements for all employees as at balance date.

Long Service Leave
The liability to employee entitlements to long service leave represents the present value of the estimated future cash outflows to be made by the Institute resulting from employees' services up to the balance date. Liabilities for employee entitlements which are not expected to be settledwithin twelve months are discounted using rates based on government guaranteed securities, which most closely match the terms of maturity of the related liabilities. In determining the liability for employee entitlements, consideration has been given to future increases in salary rates, and the Institute's experience with staff departures. Related on-costs have also been included in the liability. It is Institute policy that employees with ten or more years of service qualify for long service leave entitlements.

(m) Foreign exchange transactions
The Institute maintains a bank account in the USA for the purpose of receiving donations and for the purchase of equipment and supplies. Foreign currency at balance date is translated to Australian currency at exchange rates at balance date. Exchange gains and losses are brought to account in determining the operating surplus or deficit for the year.

(n) Trade and Other Creditors
These amounts represent liabilities for goods and services provided to the Institute prior to the end of the financial year and which are unpaid. The amounts are unsecured and are usually paid within 30 days of recognition. This amount includes $1,866,602 payable in respect of the new building.

(o) Comparative figures
Where necessary comparative figures have been adjusted to conform with changes in presentation in the current year.

3. Consolidated Income

	1999	1998
	$	$
Grants:		
Government and Statutory Bodies	6,157,889	5,938,270
Baker Foundation	1,150,000	1,050,000
Other Income:		
Fundraising, Corporate & Private Support	4,242,315	3,195,115
Capital Works Campaign	6,536,286	730,850
Dividends Received / Receivable	321,509	320,973
Interest Received / Receivable	259,700	194,792
Foreign exchange gain	726	7,956
Proceeds from sale of non-current assets	204,425	276,039
General Income	349,841	312,773
	19,222,691	12,026,768

4. Consolidated Surplus

The consolidated surplus before income tax is arrived at after crediting and charging the following specific items:

Credits		
Dividend revenue	321,509	320,973
Interest revenue	259,700	194,792
Net gain on disposal of non-current assets	204,425	276,039
Foreign exchange gain	726	7,956
Charges		
Borrowing costs		
Finance charges relating to finance leases	72,822	50,410
Less: Amount capitalised	(49,639)	(33,760)
Borrowing costs expensed	23,183	16,650
Depreciation - Plant and Equipment	437,489	441,928
Amortisation - Motor Vehicles under finance lease	70,444	47,493
Write down of inventories to net realisable value	27,413	45732
Employee Entitlements	103,828	19,407
Rental expense relating to operating leases	330,679	259,241

5. Operating Fund

Balance at beginning of year	(3,911,635)	(3,536,766)
Deficit for year	(470,084)	(374,869)
Balance at end of year	(4,381,719)	(3,911,635)

6. Capital Fund

The Institute's Capital fund comprises donations, bequests and receipts from fundraising activities. Each year the Board allocates a proportion of these funds to supplement the research operations of the Institute. The Fund also incorporates grants and contributions received towards the cost of the new Institute building and the associated interest earned thereon. Funds received in respect of the new Medical Research Institute, but not outlaid at 31 December 1999, are carried forward.
The current balance is:

Balance at beginning of year	9,260,632	8,628,983
Surplus for year	4,343,938	631,649
Balance at end of year	13,604,570	9,260,632

7. Specific Purpose Fund

Specific purpose funds comprise funds provided to the Institute for special purposes other than through normal fund raising activities. The funds are used in accordance with the wishes of donors. Institute accounting records are kept so as to identify expenditure charged against income of these funds. All such income and expenditure is incorporated in the consolidated Profit and Loss Account.
The current fund balance is:

	1999	1998
	$	$
Balance at beginning of year	281,787	501,146
Deficit for year	(80,756)	(219,359)
Balance at end of year	201,031	281,787

8. Fund Balances

Balance at 1 January 1999	7,632,272	7,594,851
Surplus / (Deficit) for year -		
Operating Fund	(470,084)	(374,869)
Capital Fund	4,343,938	631,649
Specific Purpose Fund	(80,756)	(219,359)
	3,793,098	37,421
Balance at 31 December 1999	11,425,370	7,632,272

9. Investments (at cost)

(a) Current		
Short term deposits	6,163,533	3,369,171
Total Current Investments	6,163,533	3,369,171
(b) Non - Current		
Shares and Debentures	7,190,033	6,175,580
Trust Units	0	65,033
Total Non - Current Investments	7,190,033	6,240,613
Total Investments	13,353,566	9,609,784

The Institute's investments are shown at cost. As at the 31 December 1999 the market value of the Institute's non-current investments was $10,338,214 (1998: $8,677,565)

10. Plant and Equipment

	1999	1998
	$	$
Plant and Equipment (at cost or Board's valuation)	5,581,616	4,825,809
Less: Accumulated Depreciation	3,378,063	2,940,575
	2,203,553	1,885,234
Motor Vehicles under finance leases	364,314	277,561
Less: Accumulated Amortisation	138,886	117,558
	225,428	160,003
Total Plant and Equipment	2,428,981	2,045,237

11. Prepaid Grants

Prepaid Grants include capital works grants of $2.224m received from the Federal Government for the redevelopment of the Institute.

Prepaid Grants	2,562,109	3,926,270

12. Provisions

(a) Current		
Annual Leave	460,080	341,701
Long Service Leave	294,020	293,444
Total Current Provisions	754,100	635,145
(b) Non - Current		
Long Service Leave	215,452	230,559
Deferred Maintenance	72,053	72,053
Total Non - Current Provisions	287,505	302,612
Total Provisions	1,041,605	937,757

13. Lease Commitments

Finance Lease Commitments

Finance Lease Commitments are payable as follows:

Not later than 1 year	80,877	77,034
Later than 1 year and not later than 2 years	77,086	57,406
Later than 2 years and not later than 5 years	164,083	100,884
Minimum lease payments	322,046	235,324
Less: Future lease charges	(55,304)	(40,080)
Provided for in accounts	266,742	195,244
Representing lease liabilities:		
Current lease liability	62,323	59,532
Non-current liability	204,419	135,712
	266,742	195,244

14. Capital Commitments

As at 31 December 1999, capital expenditure contracted for, in respect of completion of the building, at balance date but not provided for in the accounts of the Institute, is payable:

	1999	1998
	$	$
Not later than 1 year	19,696,509	0
Later than 1 year and not later than 2 years	6,981,026	0
Total Capital Commitments	26,677,535	0

15. Remuneration of Board Members

(a) The names of each person who held office as a Board Member of the Baker Medical Research Institute during the financial year ended 31 December 1999 are:

Mr N O'Bryan	Mr S Blair	Professor S Holdsworth
Dr G P Johnston	Professor P Darvall	Mr. P. Munz
Mr R E Barker	Mr W P Gurry AO	Mrs M Ross
Professor J W Funder AO	Dr P G Habersberger AM	Professor R Smallwood AO
Mr P C Barnett		

(b) Other than Mr R E Barker who is an employee, Director and shareholder of a firm of Stockbrokers which has received, or become entitled to receive, fees for services rendered to the Institute on normal commercial terms, no Board Member has received or has become entitled to receive any benefit, by reason of a contract made by the Institute or a related corporation with any Board Member or with a firm of which a Board Member is a member or with an entity in which any Board Member has a substantial financial interest other than the Director of the Institute, Professor J W Funder, who receives a salary.

16. Cash

For the purpose of the statement of cash flows, cash includes cash on hand and in the bank and investments in the money market instruments, net of outstanding bank overdrafts. Cash at the end of the financial year as shown in the statement of cash flows is reconciled to the related items in the balance sheet as follows:

Cash	786,626	92,927
Deposits at call	6,163,533	3,369,171
Total	6,950,159	3,462,098

17. Reconciliation of Surplus to Net Cash from Consolidated Activities

Operating Surplus from Consolidated Activities	3,793,098	37,421
Effects of exchange rate changes on cash held in foreign currencies	(726)	(7,956)
Depreciation and Amortisation	507,933	489,421
(Profit) on sale of non-current assets	(204,425)	(276,039)
Changes in net assets and liabilities		
Decrease / (Increase) in debtors	163,615	(595,627)
Decrease in inventories	27,413	45,732
Decrease / (Increase) in prepayments	52,152	(59,412)
(Increase) in accrued interest	(25,463)	(9,959)
Increase in creditors	1,999,225	37,159
(Decrease) / Increase in prepaid grants	(1,364,161)	(22,009)
Increase in provisions	103,848	14,311
Net cash from consolidated activities	5,052,509	(346,958)

18. Non-cash Financing Activities

Motor Vehicles

During the year the Institute provided motor vehicles for staff under salary sacrifice arrangements with a value of $364,314 by means of finance leases. These acquisitions are not reflected in the statement of cash flows.

19. Superannuation

The Institute operates an accumulation type superannuation plan under which all employees are entitled to benefits on retirement, disability or death. Employees contribute to the plan at various percentages of their salaries. The Institute also contributes to the plan at rates related to employee contributions and pursuant to an award set down under a national wage case. Funds are available to satisfy all benefits that have been vested under the plan in the event of termination of the plan or voluntary or compulsory termination of employment of each employee.

BOARD MEMBERS' DECLARATION

The Board Members declare that the financial statements and notes set out on pages 28 to 37:

(a) comply with Accounting Standards except in relation to the treatment of the new building as set out in Note 2(g) to the accounts and referred to in the report of the Auditor, the Corporations Regulations and other mandatory professional reporting requirements; and

(b) give a true and fair view of the Institute's financial position as at 31 December 1999 and of its performance, as represented by the results of its operations and its cash flows, for the financial year ended on that date.

In the Board Members' opinion:

(a) the financial statements and notes are in accordance with the Corporations Law; and

(b) there are reasonable grounds to believe that the Institute will be able to pay its debts as and when they become due and payable.

This declaration is made in accordance with a resolution of the Board of Management.

For and on behalf of the Board.

Norman O'Bryan
President

John W Funder AO
Director

Melbourne
17 April 2000

Independent Audit Report to the Members of Baker Medical Research Institute

Scope

We have audited the financial report of the Baker Medical Research Institute (the Institute) for the financial year ended 31 December 1999 as set out on pages 28 to 36. The Institute's Board Members are responsible for the financial report. We have conducted an independent audit of the financial report in order to express an opinion on it to the members of the Institute.

Our audit has been conducted in accordance with Australian Auditing Standards to provide reasonable assurance as to whether the financial report is free of material misstatement. Our procedures included examination, on a test basis, of evidence supporting the amounts and other disclosures in the financial report, and the evaluation of accounting policies and significant accounting estimates. These procedures have been undertaken to form an opinion as to whether, in all material respects, the financial report is presented fairly in accordance with Accounting Standards, other mandatory professional reporting requirements and the Corporations Law so as to present a view which is consistent with our understanding of the Institute's financial position, and performance as represented by the results of its operations and its cash flows.

The audit opinion expressed in this report has been formed on the above basis.

Qualification

As stated in note 1(g) to the accounts, the Institute has written off to expense certain capital expenditures incurred on a planned new building, currently under construction, which we understand is going to be subject to a long term sub-lease to the Institute and other parties. This is a departure from Accounting Standard AASB 1021 'Depreciation' which requires recognition of an asset with physical substance which is expected to be used during more than one financial year.

In our opinion, costs amounting to $1,399,490 should have been recognised as capital works in progress. Had this been done, non-current assets would be $11,018,504 total assets would be $19,217,163, consolidated surplus after income tax would be $5,192,588, capital funds would be $5,743,428 and accumulated funds would be $12,824,860.

Qualified Audit Opinion

In our opinion, the financial report of the Institute is in accordance with:

(a) the Corporations Law, including:

(i) giving a true and fair view of the Insitute's financial position as at 31 December 1999 and of its performance for the financial year ended on that date; and

(ii) complying with Accounting Standards and the Corporations Regulations; and

(b) other mandatory professional reporting requirements.

PricewaterhouseCoopers

Chartered Accountants

E A Alexander
Partner

Melborne
17 April 2000

Alfred and Baker Medical Unit

Head:
Garry Jennings MD, MBBS Mon, FRCP, FRACP

Associate Directors:
Hypertension - Murray Esler, BMedSc, MBBS Mel, PhD ANU, FRACP

Atherosclerosis - Anthony Dart BA BMBCh, DPhil Oxon, MRCP

Laboratories - Alex Bobik BPharm Vic, MSc, PhD Syd

Medical:
Jane Thompson MD, MBBS Mon

James Cameron BEElecHons, MEngSc, MBBS Melb, CPEBiomed

Christoph Gatzka MD

Nursing:
Virginia Cable SRN (Menopause Clinic)

Elizabeth Jenkins

Janis Jennings SRN

Leonie Johnston SRN, CCN, SCM

Sally Kay SRN, BBM Mon

Louise Noonan SRN, BAppSc Deakin

Marijke Tress

Di Wilson SRN

Laboratory Manager:
Elizabeth Dewar BSc Mon

Technical & Professional:
Lesley Delcourt

Administration:
Amanda Coats BA Mon (Menopause Clinic)

Viccy Wootton

Research Students:
Karen Murchie BScHons Mon

Andrew Taylor MBBS Mel, FRACP

James Shaw MBBS FRACP Mel

The ABMU is a cohesive collection of laboratories, the research activities of which appear under the individual laboratory reports, including Cardiovascular Nutrition, Cell Biology, Clinical Physiology, Experimental Cardiology, Human Neurotransmitter Research, Molecular Neurocardiology and Vascular Pharmacology. All ABMU research is directed to the human cardiovascular system in health and disease, with an emphasis on prevention. It encompasses heart failure, hypertension, lipid disorders, diabetes, coronary heart disease, liver cirrhosis, arrhythmia, and panic disorder.

An important achievement has been our success in performing large clinical trials (e.g. Australian National Blood Pressure Study) in general practice. We are poised to begin the Australian arm of the OPERA Study, a large international trial of a novel blood pressure lowering drug. The trial will assess the benefits in treating borderline systolic hypertension, a prevalent condition in Australians over sixty.

In other research, we have demonstrated that adrenaline is released from the heart of patients with hypertension and clarified the different mechanisms of hypertension in obese and lean subjects. We have found that

arginine transport into cell in patients with heart failure is abnormal, which may explain their impaired nitric oxide release and we have shown arterial compliance to be a determinant of exercise capacity and ischaemia threshold in angina patients. ○

Cardiac Surgical Research Unit

Heads:
Unit - Franklin L. Rosenfeldt MBBS, MD Adel, FRCSE, FRACS

Laboratory - Salvatore Pepe BScHons Flin, PhD Adel, Grad Dip Health Counsell Sth.Aust

Scientific:
Ruchong Ou MBBS Kunming

Michelle Wowk BAppScHons Swinburne

Ming-Jie Zhang MD, MS Beijing

Robert F. Salamonsen MBChB, MD Otago, FFICANZCA

Research Students:
Paul Burton MBBS Mon

Thanae Georgakopolous BSc Mon

William J. Lyon, MBBS Flin

Silvana Marasco MBBS Mon
Francis J. Miller MBBS Mon
Freya Sheeran BA, BScHons Mon
Emma Zumpe BSc Melb

Administrative:
Christine Ditterich

Ageing impedes recovery from cardiac surgery because of increased sensitivity to metabolic and physiological stresses. We have shown that treatment of heart muscle with the antioxidant coenzyme Q10, which functions in cellular energy production, improved both the efficiency of oxygen use in biopsies of aged heart muscle and recovery of contractile function after oxygen and nutrient deprivation.

We have shown that in heart tissue, mutation of mitochondrial DNA increases with age, possibly altering cardiac protein synthesis and heart function. We have developed new techniques to show an association between a higher incidence of specific mutation of mitochondrial DNA and poor recovery of contractile function after ischemia.

In a rat heart model of surgical cardiac arrest, as occurs in transplant surgery, we have found that the drug cariporide protected against ischemic injury and improved the recovery of heart pump function.

New techniques using the radial artery as a coronary by-pass graft have proven faster, simpler and cheaper than the standard techniques.

We have worked with a manufacturer of temporary artificial hearts to design and test in sheep a compact centrifugal heart pump which, when fitted to patients awaiting heart transplant-ation, should give them greater mobility, better function and fewer complications.

Cardiovascular Nutrition

Head:
Paul Nestel AO, MD, FTSE FRACP

Professional & Technical:
Robyn Kaye RN, BEd, RM
Marja Cehun
Sylvia Pomeroy BSc, RDtGradDipEd MPH

Our main objective is to identify dietary components likely to prevent heart disease by adding various nutrients to the diet of study participants, and regularly assessing outcomes relevant to cardiovascular health. These include arterial compliance (or elasticity), and levels of cholesterol and triglyceride.

We found that fatty acids from fish oil beneficially increased arterial elasticity and also improved the blood fat profile by raising HDL and lowering triglycerides.

We also tested the cholesterol-lowering properties of three plant materials - sterol esters, beta-glucan and red clover isoflavones. The sterol esters, now present in some margarines, lowered LDL by 10%, by reducing the absorption of cholesterol in the gut. Beta-glucan from oats also lowered LDL cholesterol when eaten in bread and cereal. Although the isollavones lowered LDL substantially the effect took 12 weeks to appear.

We found that three and six hours after a fatty breakfast, when blood fats reached their peak, the large arteries became stiffer, which can reduce the flow of blood through the heart vessels and may explain why some people with coronary disease get angina following fatty meals. Elasticity of leg arteries was improved in subjects treated with the drug simvastatin to lower their cholesterol level.

Cell Biology

Head:
Alex Bobik BPharm Melb, MSc PhD Syd

Scientific:
Alex Agrotis, BScHons, PhD Mon
Atsu Kubo, MD Tokyo (from Mar)

Professional:
Peter Kanellakis BSc Mon
Melanie Condron BScHons La Trobe
Gina Kostolias BScHons La Trobe

Research Students:
Andrew Taylor MBBS Mon, FRACP

We continued to study growth factors and their role in regulating the structure of blood vessels in atherosclerosis, hypertension and during healing after angioplasty.

We have shown that the cytokine, transforming growth factor-β ((TGF-β)), induces the expression in macrophages and foam cells of components of the NAD(P)H oxidase system which generates the atherogenic reactive oxygen molecules, hydrogen peroxide and superoxide. The pattern of induction was related to the differentiation of monocytes to macrophages.

Studies on the function of different types of smooth muscle cells in blood vessels and their roles in vessel healing have revealed two cell types with different fibroblast growth factor (FGF) receptors, related to methylation patterns of the promoter regions of the receptor genes. Epithelial-like smooth muscle cells largely accounted for the early replication of cells in arteries after damage by angioplasty, possibly due to stimulation by FGF-9 and -16.

We have also shown that relatively small reductions in blood flow decrease the expression of the enzyme nitric oxide synthase (NOS) in the endothelial cells lining large arteries. When NOS levels were low, the concentration of nitric oxide was insufficient to inhibit the stimulation of cell proliferation by growth factors, causing changes to the structure of large arteries which predisposed them to atherosclerosis.

Cell Biology of Diabetes

Head:
Peter Little BPharm Melb, MSc, PhD Syd

Scientific:
Kate Hannan BSc Tas, PhD Penn State USA (till Aug)

Professional & Technical:
Natalie Kvalheim BAppSc RMIT (from Aug)
Luke Robinson BAppSc Mon

Research Students:
Stephanie De Dios

We study the properties of smooth muscle and endothelial cells from blood vessels and how they are affected by the high blood glucose concentrations which occur in diabetes, and by anti-diabetic drugs. The newest of these drugs, troglitazone, had multiple effects on endothelial cells grown in culture but interestingly, no effects on their growth in intact rat blood vessels.

We have introduced a new area of study to the laboratory - that of the proteoglycans produced by vascular cells. Proteoglycans are thought to bind lipoproteins in the blood as an early stage in the development of atherosclerosis. We have shown that the pro-atherosclerotic growth factor, transforming growth factor beta, stimulated production of proteoglycans from vascular smooth muscle and enhanced binding to lipoproteins. Troglitazone treatment of the cells inhibited production of proteoglycans and also had the effect of stimulating binding, a result which we are further exploring.

We have progressed with studies on the Na/H exchanger in vascular smooth muscle. Having shown that the exchanger was activated in parallel with enlargement of blood vessels in a rat model of diabetes, we have now confirmed its role in vessel enlargement by showing that inhibition of the exchanger prevented these vascular changes.

Cellular Biochemistry

Head:
Elizabeth Woodcock PhD Macquarie

Scientific:
Jane Arthur PhD Melb
Bing Hui Wang PhD LaTrobe

Technical:
Bronwyn Rees DipApplSci Swin

Research Students:
Sharon Harrison BSc Mon, BScHons Melb
Scott Matkovich BScHons Melb

Our research explores the functional importance of inositol phosphate signalling pathways in heart muscle with a view to understanding how cardiac arrhythmias are generated, and

how hypertrophic growth is initiated and subsequently progresses to heart failure.

During 1999 we identified a novel anti-hypertrophic mechanism. Transfection of neonatal myocytes with the gene for inositol polyphosphate 1-phosphatase caused a decrease in hypertrophic signalling. Furthermore, under in vivo conditions as well as in cell models, hypertrophy was associated with increased levels of inositol(1,4)bisphosphate, the substrate of polyphosphate 1-phosphatase. These findings are consistent with there being an inverse relationship between hypertrophy and polyphosphate 1-phosphatase enzyme activity. We showed in the cardiomyocyte that the enzyme was primarily cytoplasmic, whereas in some cell types, it is nuclear.

In other studies we obtained direct evidence that responses in cardiomyocytes to elevated Ca^{2+} caused substantial generation of inositol(1,4,5)trisphosphate, [Ins(1,4,5)P_3,] while those to G protein-activated inositol phosphate did not. As Ins(1,4,5)P_3 itself causes rises in Ca^{2+}, our results could mean that a positive feed forward mechanism is important in the development of arrhythmias.

The role of Ins(1,4,5)P_3 in reperfusion arrhythmias was further substantiated by showing that activation of Na^+/H^+ exchange was necessary for increased production of Ins(1,4,5)P_3 during reperfusion after ischaemia.

Clinical Physiology

Head:
Bronwyn Kingwell BScHons, PhD Melb

Professional & Technical:
Melissa Formosa BSc VUT

Research Students:
Tamara Waddell BScHons Mon
Karen Berry BScHons Mon
Karen Murchie BScHons Mon
Scott Bradley BScHons Mon
James Shaw MBBS Mon
Kathryn North BSc Mon
Tanya Medley BSc VUT

Broadly, our research covers disease states which involve the cardiovascular system. A major aim is to evaluate large artery compliance, or elasticity, as a basis for grading cardiovascular risk. So far, the indications are that for patients with coronary artery disease, compliance of the aorta and the time to coronary ischemia during an exercise test are correlated. Our investigations of the basis of arterial stiffening, focus on the extracellular matrix protein fibrillin-1 which has been linked to stiffening in Marfan syndrome and other conditions. We are examining genetic variation of fibrillin-1 in relation to arterial elasticity and measuring levels in skin biopsies from patients with stiff arteries.

We have found that before meno-pause, women's arteries are more elastic than men's, but as a result of menopause, the age-related decline in elasticity is faster in women. We have shown positive effects of post-menopausal HRT on compliance and are now determining whether this effect can lead to increased ischemic threshold in women with coronary disease. We are also testing the efficacy in improving larger artery elasticity of markedly lowering cholesterol in patients with isolated systolic hypertension.

Finally, we are assessing the role of nitric oxide in the uptake of blood-glucose in people with type II diabetes.

Experimental Cardiology Laboratory

Head: Anthony Dart BA, BMBCh, DPhil Oxon FRACP

Scientific:
Xiao-Jun Du MBBS Chingqing, MMed Xian PhD Edinburgh

Professional & Technical:
Elodei Percy BScHons Melb

Research Students:
Deepack Haikerwal MBBS Mon
Xiaoming Gao MBBS Xinjiang

Our research is focused on understanding the adrenergic mechanisms contributing to heart failure and myocardial ischaemia, using various models of the disease.

Having successfully adapted various techniques to the small scale required for experiments in mice, we have completed several studies on a transgenic mouse that

overexpresses β2-adrenergic receptors (β2,AR) in the heart.

Using a transonic flowmetry technique, we measured higher than normal cardiac output under resting and stressed conditions in these mice.

Transgenic mice had more severe heart failure than controls when subjected to aortic constriction, although heart function was stronger under the conditions of myocardial infarction. The impact of β adrenergic activation, via β2AR overexpression, on the development of heart failure may therefore depend on the aetiology. At nine months or older, the transgenic mice developed cardiomyopathy and heart failure.

Other studies using serial echo-cardiography, have provided the first-documented basic description of the mouse model of myocardial infarct.

We have developed a model of noradrenaline release under ischaemic conditions using cell culture of peripheral sympathetic neurons. We are now ready to use the model for studying the mechanism of noradrenaline release and to look for ways of inhibiting such release.

H and L Hecht Hormones and the Vasculature Laboratory

Heads:

Paul Komesaroff BScHons, MBBS, PhD, FRACP

Krishnankutty Sudhir MBBS, PhD, FRACP, FACC

Professional & Technical:

Meryl Fullerton BSc

Virginia Cable RN

Betty Kafanelis BSc, MA

Kazuhiko Hashimura MD

Catherine Black, BCh, FRACGP

Research Students:

Shanhong Ling MD China

Maro Williams BScHons

Robert Lew MBBS, FRACP

Tye Dawood BSc

Anna Calkin BSc

Our research aims to define the role of sex hormones on vascular function, using both in vitro and in vivo systems.

We have shown oestrogen supplementation in older, hypogonadal men improved their vascular health, whereas in cultured vascular endothelial cells, testosterone induced programmed cell death and in vascular smooth muscle cells, the androgen precursor DHEA inhibited growth.

Medroxyprogesterone acetate had no influence on the protective effect of oestrogen on endothelial function in postmenopausal women taking hormonal therapy, although arterial elasticity was improved with medroxyprog-esterone.

To begin to understand why young women with diabetes are at high risk of heart disease, we studied vascular smooth muscle cells in culture and found oestradiol to be inhibitory in normoglycaemic media, but not at high glucose. Women with diabetes lacked the increase in the vasodilator effect of acetylcholine normally produced by oestrogen.

In studying responses to stress, we showed that oestrogen reduced the hormonal responses in men and women, while testosterone lowered the responses to metabolic, but not emotional, stressors.

Applying non-invasive techniques in vivo, we have demonstrated changes in vascular function during the menstrual cycle; a non-genomic response to oestrogen in young men; the effect of androgens on vascular function in post-menopausal women and the effect of prostaglandins on vascular function.

Human Neurotransmitter Research Laboratory

Head:
Murray Esler BMedSci, MBBS Melb; PhD ANA; FRACP

Scientific:
Gavin Lambert BScHons Deakin; PhD Mon
Elisabeth Lambert PhD Paris
Jacqui Hastings BSc, PhD Deakin
Hanspeter Brunner MD
John Power BVSc Qld

Professional & Technical:
Flora Socratous BSc La Trobe

Research Students:
Glen Weisner BScHons Melb
Magdalena Rumantir DM, BMedSci Jakarta
Melissa Byrne BSc RMIT

The focus of the laboratory is cardiovascular neuroscience, with projects on the neural aspects of psychosomatic heart disease, high blood pressure, cardiac failure and subarachnoid haemorrhage.

Acute mental stress responses, panic disorder and depressive illness have recently been unequivocally linked to heart disease. We are investigating the mediating neural mechanisms of this stress-heart link, by studying the characteristic brain neurotransmitter changes and the responses in the sympathetic nervous system.

High blood pressure is neurally mediated in about 25% of patients via several processes; increased sympathetic nervous system outflow from the brain, release of adrenaline as a cotransmitter of noradrenaline in sympathetic nerves, and faulty reuptake of the noradrenaline by nerves. Our findings could provide a theoretical base for the development of new anti-adrenergic drugs to treat hypertension.

We have shown that chronic activation of the sympathetic nervous system, now treated by β adrenergic blocking drugs, leads to failure of the heart as a pump and is a major cause of death. Our novel approach is to study how neural growth factors in the heart influence the density of sympathetic innervation.

Finally, we are investigating in an animal model of subarachnoid haemorrhage and in the clinical condition, the mechanisms of potentially fatal cerebral spasm and how to prevent it pharmacologically.

Lipoprotein & Atherosclerosis Laboratory

Head:
Noel Fidge BScHons, PhD Adel

Scientific:
Dimitri Sviridov PhD Moscow
Gabrielle Gallon PhD Aix-Marseille (from Sept)

Professional & Technical:
Anh Luong BScHons Melb
Louise Pyle BScHons, MSc Melb (Until Aug)
Sarah Siggins BScHons Melb
Fu Ying MSc LaTrobe

We have extended our knowledge of the physiological function of HDL by tracking the movement inHepG2 cells of either apoA-I or the complete HDL particle labeled with gold.

Using electron microscopy, we found that apoA-I-gold first appeared in early endosomes, then moved to late endosomes before finally accumulating in lysosomes. A similar endocytic route was observed for HDL-gold, suggesting that it is the apoA-I component which specifically binds to cells and initiates the endocytic pathway that we saw.

A central region of apoA-I appears to achieve activation of the enzyme LCAT which is important in reverse cholesterol transport, although it is uncertain whether primary or secondary protein structures are involved.

Specific mutants of apoA-I were prepared, targeting primary sequences or key secondary domains which might function in LCAT activation. Four proteins with mutations affecting amino acids 140 to 150 were all significantly less effective in activating LCAT than the normal protein.

Experiments with the extracellular portion of the HDL receptor, HB2,

have identified an HDL binding site near the membrane domain. The precise sequence involved is under investigation.

We have established an assay for the human HDL receptor using blood derived monocytes which suggests a strong correlation between circulating HDL cholesterol and HB2 levels.

The Emily Stewart Molecular Endocrinology Laboratory

Heads:
Walter Thomas BScHons, PhD UQ
and Kathleen Curnow BScHons, PhD Melb

Scientific:
Hongwei Qian, PhD, WVU (USA)

Professional &Technical:
Thao Pham
Luisa Pipolo AssocDipAppSc Swin

Research Students:
Felicity Chalmers BAppScHons RMIT
Maro Williams BScHons Mon

We study the hormonal control of blood pressure, including regulation of angiotensin II receptors and biosynthesis of the salt-retaining hormone, aldosterone.

The signal produced by stimulation of the angiotensin II receptor, AT1, is terminated by receptor phosphorylation, arrestin binding and internalisation,in what is thought to be a fixed sequence. However, we have observed, using wild type and mutant $AT1_A$ receptors stimulated with angiotensin II or its analogues, that receptor phosphorylation does not require signalling and vice versa and that internalisation can occur without phosphorylation.

We investigated the controversial role of arrestins in the deactivation of $AT1_A$ receptors using co-immunoprecipitation of wild-type and mutated $AT1_A$ receptors with β1- and β2-arrestins. This interaction, requiring angiotensin II stimulation, depended on phosphorylation of the carboxyl-terminus of the receptor.

In studying the human gene for AT1 we have shown the level of synthesis of this receptor to be dependent on a short stretch of DNA sequence in exon 1.

We are currently investigating whether people with a type of hypertension characterised by increased angiotensin II receptor activity have variations in this DNA sequence.

We have produced large quantities of the enzyme aldosterone synthase in bacteria as a first step towards studying its structure.

Molecular Genetics Laboratory

Head:
Timothy Cole BScHons, PhD Melb

Professional & Technical:
Morag Young BScHons Mon, PhD Mon (from Sept)
Nicola Solomon BScHons Mon (until Oct)

Research Students:
Shirley Moore MD Shanghi, GradDipMedTech RMIT
Isabelle Hoong BScHons Mon
Jared Purton BScHons Mon

Our studies on two key steroid hormones - the mineralocorticoid aldosterone and the glucocorticoid cortisol - have examined the effect on late embryonic development and cardiovascular function of gene targeting steroid homone receptors.

In mice lacking the glucocorticoid receptor (GR) we found that differentiation of type 1 alveolar cells from the lung is aberrant. Normal T-cell development and selection in the thymus was not dependent on a functional GR. Mice lacking the mineralocorticoid receptor (MR) showed normal prenatal development but died one to two weeks after birth due to symptoms of pseudohypoaldosteronism, unless given saline. We will use the MR-deficient mice to examine normal cardiac function, and also the suggested role of aldosterone in the pathology of cardiac fibrosis.

The enzyme 11β-hyroxysteroid dehydrogenase 2 (HSD2) appears from in vitro research to be an important regulator of aldosterone and cortisol. To study its specific role in vivo we are developing HSD2-deficient mice. By using the CRE-recombinase/loxP system we will be able to direct

gene- targeting of HSD2 to specific tissues. In preparation, we have shown by analysis and testing of 2.5 kilobases of upstream HSD2 gene sequence that a region spanning the proximal 263 nucleotides directs proper gene transcription.

Molecular Hypertension Laboratory

Head:

Zygmunt Krozowski BScHons WA, PhD Syd

Scientists:

Phillip Brereton PhD Melb

Kaori Koyama MBBS PhD Sendai

Professional & Technical:

Lisa Berlingeri BScHons Melb (from Mar)

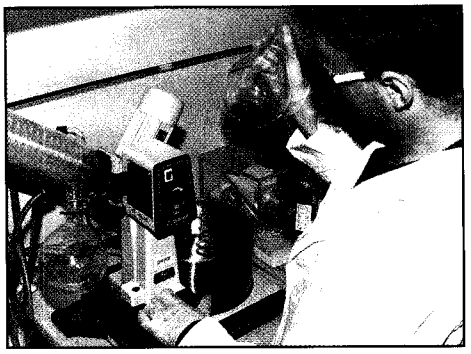
Michelle Cinel CertVetNursing, AssocDipAppSci. (Animal Tech)

Varuni Obeyesekere BScHons Mon (to Feb)

Robin Smith BSc La Trobe, DipEd Melb, MSc prelim Mon (to Mar)

We have continued our work on two enzymes, 11βHSD1 and 2, that metabolise glucocorticoids. The former converts inactive cortisol metabolites to biologically active compounds, mainly in the liver but also in other locations such as the outer nuclear envelope of rat kidney interstitial cells, parietal cells of the stomach and as yet unidentified cells isolated from the heart.

We have investigated the role of the glucocorticoid inactivating enzyme 11βHSD2 in cell lines from breast and endometrial cancer. In both cell types, we observed inhibition of growth in the presence of 11βHSD2 inhibitors and cortisol. We have also continued our studies on markers in the 11βHSD2 gene in a population of hypertensive patients with abnormal mineralocorticoid activity.



Considerable effort has gone into characterising Pan1b, a dehydrogenase with activity toward 17β-hydroxysteroid and retinol, which was cloned in our laboratory. We have raised antibodies to Pan1b and shown it to be present in human adrenal cells which make aldosterone and cortisol as well as in the primary follicle of the ovary, the placenta, liver, sebaceous glands and epithelia of the small intestine, lung and endometrium.

With a gene marker used in chromosomal localisation studies, we were able to pinpoint Pan1b to chromosome 4q21.2.

Molecular Physiology

Head:

John Funder BA, MDBS, PhD Melb, FRACP

Scientific:

Dominic Autelitano BScHons, PhD Mon

Ross Hannan BScHons, PhD Tas

Karen Sheppard BScHons, PhD Mon

Professional & Technical:

Meryl Fullerton MSc Melb

Anna Jenkins DipApplSciBiolSci Swin

Kathy Myles DipAppSC RMIT, BScHons Melb

Rebecca Ridings DipLabTech Penin TAFE

Research Students:

Lydia Labib BScHons Mon

Our research focuses on how hormones and neurotransmitters influence the cardiovascular system.

We are investigating the regulation of cardiomyocyte hypertrophy by the hormone, adrenomedullin, by examining its effects on various biochemical and molecular markers and by assessing the role of Receptor Activity Modifying Proteins in modulating the sensitivity of the adrenomedullin receptor.

The cardiac hypertrophic response depends on ribosomal gene transcription, which is influenced by transcription factor UBF. Based on adenovirus expression, we are studying the molecular signaling pathways that regulate UBF, both in rat cardiomyocytes in vivo and in culture. We are also determining whether increased UBF activity is required for the enlargement of these cells in cardiovascular diseases and whether UBF contributes to the hyperplastic growth of fibroblasts.

We have investigated steroid-metabolizing enzymes that control the concentration of steroid in cells, characterized two novel nuclear steroid receptors that bind a metabolite of glucocorticoids, and studied the effect of differential steroid receptor dimerization on transcription of genes responsive to corticosteroids.

Other major interests are the mechanism of action of mineralocorticoid hormones and salts in experimental hypertension, cardiac hypertrophy and cardiac fibrosis; the proteins induced by aldosterone action in its target tissues; and the mechanism of steroid action on the prevention of cerebral oedema.

The Jo Giuliano Molecular Neurocardiology Laboratory

Head:

David M Kaye MBBSHons, PhD Mon FRACP FACC

Professional & Technical:

Sara Gruskin BAppSci WA

Samara Cairns BScHon Melb

Research Students:

Ann Aggarwal MBBS Melb FRACP

Melinda Parnell BAppSci Deakin

Magda Rumanitir DM, BMedSci Jakarta

Glenn Wiesner BSc Hons Melb

Belinda Ahlers BScHons James Cook

Our major research interest is congestive heart failure (CHF) and the factors contributing to the pathophysiology of the condition. Our studies cover the range from humans down to sub-cellular systems.

We have shown that overactivity of the sympathetic nervous system (SNS) is a key adverse factor in CHF. An overactive SNS means that neuronal integrity is disturbed, which led us to examine the role of nerve growth factor (NGF) in heart failure. We found that the production of NGF was decreased in heart failure compared with a healthy heart, and will now assess whether production of NGF could be a therapeutic target in heart failure.

In a clinical trial, we are investigating how β-blockers improve heart function for patients with heart failure. Part of our study will directly measure catecholamine overflow in the heart, while another component will assess aspects of cardiac metabolism. Further, we have commenced molecular research on how β-blockers affect β-receptor function.

Abnormalities of the endothelial L-arginine:nitric oxide pathway have been implicated in human heart failure. We have been the first to show that subjects with CHF have reduced uptake of L-arginine in the forearm circulation compared with healthy controls, and are currently studying the mechanisms responsible for this observation.

Molecular Signalling

Head:

Jun-Ping Liu MD Beijing, PhD Mon

Scientific:

He Li MD Beijing, PhD Mon

Fi-Tjen Mu MD Taiwan, PhD Mon

Osamu Ebisui MD, PhD Kyoto (until June)

Frank Zhu MD Shanghai (until Feb)

Research Students:

Ying Cao BMed, MMedSc China

Visiting Scientists:

Ling Guo BMed Shanghai (from April)

We study aspects of signalling, including the control of telomerase activity, the GTP-binding protein dynamin II, and how stress-sensitive MAP kinases influence

the actions of hormones and growth factors.

Telomerase is a key enzyme complex in controlling cell replicative lifespan.

We have observed that the tumour suppressor protein p53 interacts with telomerase-associated protein 1 causing telomerase inhibition. Thus, loss of p53 may be involved in telomerase activation, thereby leading to cell immortalisation. In addition, we have shown that dynamin II, a protein of unknown cellular function, is localised to the trans-Golgi network of neuro endocrine AtT20 cells and perinuclear regions of PC12 cells, suggesting its involvement in exocytotic pathways. Lowering the dynamin II levels in mouse pituitary cells impaired the release of hormones from the cells without effecting receptor endocytosis.

A member of the MAP kinase family, ERK, is activated by EGF in vascular smooth muscle cells of normal and spontaneously hypertensive rats.

Activation of ERK by EGF is faster in cells from hypertensive rats than normals, suggesting that ERK may participate in the development of hypertension. In human breast cancer cells, ERK was also activated by androgen in a rapid and selective way that is therefore unlikely to be gene-based.

Morphology Laboratory

Head:

Rodney Dilley PhD WA

Professional & Technical:

Natalie Corlett BSc RMIT

Rosemary van Driel BSc

Research Students:

Bishoy Rizkalla

Maria Nataatmadja DDS AirLangga, MDSc Melb

Our research examines the mechanisms which regulate the growth of cardiovascular tissues under normal conditions and in disease states.

Migration, proliferation and matrix synthesis by smooth muscle cells, initiated in response to endothelial injury in arteries, are all inhibited by early regrowth of an intact endothelium. We have found that like early repair, delayed repair of the endothelium was also capable of reducing these neointimal growth mechanisms.

We have acquired evidence that inhibition by heparin of arterial smooth muscle cells in rats made hypertensive by angiotensin II infusion is due to exposure to angiotensin II, rather than the resulting hypertension per se.

We have followed cholesterol movement in cells by labeling with gold the apolipoprotein AI in cholesterol-containing particles and using electron microscopy to detect the gold. Particles first attached to the cell membrane where they were internalized by endocytosis before finishing up in cytoplasmic lysosomes.

In mice lacking the glucocorticoid receptor, we found that there is a delayed maturation of epithelial cells lining the air spaces of the developing lung. The resulting thicker walls may interfere with oxygen transport across the lung wall to account for the respiratory defects observed in newborn receptor-deficient mice.

Neuropharmacology Laboratory

Head:

Geoffrey Head BScHons Melb, PhD Mon

Scientific:

Maarten van den Buuse BScHons, PhD Utrecht (Until July)

Dmitry Mayorov BScHons, PhD Moscow

Professional & Technical:

Sandra Burke BScHons Syd, MSc Mon

Shirley Godwin BAppSc RMIT

Alison Learmonth (Until Jan)

Research Students:

Candy Chan BPharm VCP, BScHons Mon

Kim Webber BScHons Mon

Anna-Maria Arabia BScHons Melb

Nina Ross

We study how the central nervous

system (CNS) controls the heart and circulation in normal conditions as well as during hypertension, environmental stress and heart failure. Our main interest is how specific neurotransmitters in the CNS influence the regulation of the sympathetic nervous system and blood pressure.

This year we have shown that the sympathetic responses to "environmental" stress in rabbits is much greater if they have high blood pressure and that centrally acting antihypertensive drugs normalise both the blood pressure and the response to stress.

By microinjecting a blocker of the angiotensin receptor into the brainstem region which is the source of the sympathetic drive, we found that the sympathetic response to stress is blocked, but the normal level of activity remains unaffected. Central angiotensin may therefore be an important mediator of the central stress response. We are now investigating the influence of a high salt diet.

Using a radio-telemetry system, we found that androgens such as testosterone significantly increase the blood pressure response to "open field" stress in male and female rats. In contrast, estrogen and progesterone had only a small attenuating effect on the blood pressure response. The brain noradrenaline system had no major role in these stress responses.

Peptide Biology Laboratory

Head:
Ian Smith PhD Mon

Scientific:
Rebecca Lew PhD Virginia
Kelly Maxwell PhD Melb.

Professional & Technical:
Mary Mathew BAppSci RMIT
Shane Gerreyn
Cath Hamilton

Research Students:
Corie Shrimpton PhD Mon. (to Aug)
Nathalie Tochon-Danguy BScHons La Trobe
Ursula Norman BScHons Mon

The major aim of our research program is to better understand the role played by vasoactive peptides in the regulation of cardiovascular function. We are especially interested in the peptidases that generate and metabolise peptide signals, with a view to designing and characterising specific peptidase inhibitors, which may be of therapeutic value.

The enzymes on the surface of vascular endothelium can inactivate vasodilator peptides such as atrial natriuretic peptide and bradykinin, generate vasoconstrictor peptides such as endothelin and also convert circulating angiotensin I into the active vasoconstrictor, angiotensin II. Thus by manipulating the activities of these peptidases, we may be able to regulate/control cardiovascular function.

Over the past year we have shown that a peptidase which inactivates bradykinin is secreted from endothelial cells in a process involving calcium ions and we have used our novel peptidase inhibitors to learn more about how such secreted soluble enzymes regulate blood pressure. Our finding that the incorporation of β-amino acids into peptidase substrates converts them to inhibitors by stabilising peptide bonds has enormous promise as a platform technology for the design of specific inhibitors with therapeutic potential.

The Hazel & Pip Appel Vascular Biology Laboratory

Head:

Michael Berndt BScHons, PhD Qld

Scientific:

Robert Andrews BScHons, PhD Qld

Yang Shen MMedScHons China, PhD Adel

Elizabeth Gardiner BScHons, PhD Mon

Professional & Technical:

Cheryl Berndt CertLabTech Syd

Carmen Llerena AssocDipLabTech Pens TAFE

Andrea Aprico BScHons Mon

Leisel Fitzgerald BScHons Qld

Our research looks at the role of platelets in arterial thrombosis. Adhesion of platelets after atherosclerotic plaque rupture or activation by high shear stresses at sites of arterial stenosis may result in occlusive thrombus. In either scenario, the events are mediated by the platelet adhesion receptor the GP Ib-IX-V complex, that binds von Willebrand factor.

We have defined regions of von Willebrand factor important for its adhesive activation and binding to platelets. Complementary studies with human-canine receptor chimeras have helped define residues 60-128 of the α-chain of GP Ib as a critical binding site for von Willebrand factor.

Our studies identifying two novel adhesive ligands for the GP Ib-IX-V complex – P-selectin and the leukocyte integrin, Mac-1 – have suggested that the GP Ib-IX-V complex is not only critical for platelet adhesion to damaged vessels, but also mediates platelet interactions with inflamed vessels and is involved in vessel restenosis after angioplasty.

Other studies have focused on how the GP Ib-IX-V receptor complex initiates the signals which lead to thrombosis. We have localised sequences within its cytoplasmic domain that interact with the signaling protein, 14-3-3 zeta, and shown in transfected cells that this interaction is critical for cell activation.

Vascular Pharmacology Laboratory

Head:

Jaye Chin-Dusting BScHons, PhD Mon

Scientific:

Lisa Fisher BScHons PhD Monash (to Dec)

Professional & Technical:

Ann-Maree Jefferies BScHons Melb (from Oct)

Jennifer Starr

Research Students:

Brindi Rasaratnam MBBS Mon, FRACP

Belinda Ahlers BScHons James Cook

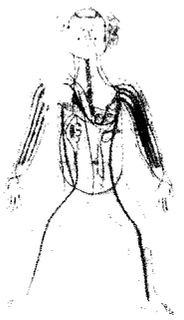
Lakmini DeSilva

Our research on the L-arginine transporter and its relationship to abnormalities of nitric oxide (NO) signalling continued through 1999, the highlight being our finding that the transporter is up-regulated in patients with liver cirrhosis which may provide a novel basis for therapy.

The up-regulation was positively associated with endotoxin levels and peripheral blood flow and may well contribute to the hyperdynamic circulatory state of these patients.

Another major program this year has been the study of vascular reactivity in genetically altered mice including a strain which lacks the aromatase gene and one which over-expresses the myocardial β2-adrenoceptor. In the latter model we detected an increase in the basal release of NO, a finding consistent with the hypothesis that the increased heart rate and LV dP/dt in these mice increases pulsatile flow and therefore NO levels.

In examining the second messenger systems of different vasodilators using rat isolated aortic rings, we have found that the vasodilatory effect of acetylcholine, but not that of isoprenaline, A23187 and sodium nitroprusside, appears to be sensitive to pertussis toxin. Finally, we have defined the vasoctivity of several isoflavone metabolites.



Cardiovascular Disease Prevention Unit

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Anne Jenes
Zoe Parsons
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Melinda Rockell BScHons Qld
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Nadine Blackman
Ann Bruce SRN
Marja Cehun SRN (until Mar)
Shauna Cotter
Noelene Frazer SRN
Irene Gale SRN
Fiona Harper SRN
Anne Hennessy SRN
Yu Lu Liang
Tui Muir SRN
Christine Tauschke SRN

ANBP2 is a large clinical trial being coordinated by the Baker Institute to compare two types of treatment for high blood pressure, ACE inhibition versus diuretic-based regimens. The outcome - the total number of fatal and non-fatal cardiovascular events for each treatment - will be assessed over five years, in men and women aged 65 to 84 years, with hypertension.

Secondary aims are to identify genetic markers linking hypertension and outcome, to seek an association between left ventricular hypertrophy (LVH) and 24-hour ambulatory blood pressure monitoring (ABPM) with outcome and to evaluate the effects of the treatments on LVH and ABPM as well as on quality of life.

The study is under way in over 1000 general medical practices across Australia. At the close of recruitment on 30 June 1998, 6083 of more than 54,000 patients attending the screening program had been assigned to a treatment group. Thirty eight percent of these were newly-diagnosed hyper-tensives and 62% had received treatment for hypertension. The average blood pressure at the start of the trial was 167/91 mm Hg.

Three months after the trial began, 70% of participants had blood pressures of less than 140/90 mmHg. To date, the rate of major cardiovascular events is 37 per1000 patient-years.

Eleanor Shaw Centre for the Study of Medicine, Society and Law

Director:

Paul Komesaroff BScHons, MBBS, PhD, FRACP

Research Students:

Bella Brushin MD
Katrina Bramstedt BEng, MBioethics
Rhian Parker MA

Research Officer:

Marj Milburn MBioethics

Administrative Assistant:

Victoria Baldwin BA, DipEd

The Eleanor Shaw Centre for the Study of Medicine, Society and Law provides a forum for the discussion of the relationship between medicine and the biological sciences and society. The Centre hosts lectures and symposia and, in conjunction with the Science Unit of the ABC, the annual Eleanor Shaw Lecture. The Sixth Eleanor Shaw Lecture, "Listening to the Earthbeat: the Challenge of Aboriginal Health in Australia" was delivered by Pat Anderson, director of the Danila Dilba Aboriginal Health Service in Darwin.

Staff, students and associates of the centre are involved in various research projects. They include qualitative investigation of the microethics of the medical

consultation process, experiences of menopause and ageing among women with physical disabilities, ethical aspects of ageing and the distribution of health care resources, philosophical and cultural aspects of cosmetic surgery and the quality use of medicines in non-English speaking communities.

There is also a project to establish an interactive, electronic archive of the experience of ethics committees which will help bring consistency to decision-making related to ethics across Australia.

Two books, *Sexuality and medicine: Bodies, Practices, Knowledges* and *Ethical Issues in Medical Research: An Operations Manual for Ethics Committees in Australia*, edited by staff from the Eleanor Shaw Centre and collaborators, have been prepared for publication.

Menopause Clinic

Medical Staff:

Paul Komesaroff BScHons, MBBS, PhD, FRACP
Catherine Black (until Dec) MBBS, FRACGP
Eleanor McDonald (from Dec) MBBS, FRACGP
Gisela Wilcox FRACP
Krishna Sudhir FRACP
Euhana Varigos MBBS, FACA

Nurses and Research staff:

Virginia Cable SRN
Jan Jennings SRN
Betty Kafanelis BScHons, MA

Research Students:

Anna Calkin BScHons
Suzy Honisett BScHons

The Menopause Clinic undertakes research into menopause and provides a general clinic, a clinic for women from a Greek-speaking background and a hysteroscopy service as well as participating in public education relating to menopause. The main area of research is how sex hormones influence the cardiovascular system, especially vascular reactivity and the stress response, in women and men.

Other projects range from the effects of oestrogen on bone to cultural aspects of menopause and the role of acupuncture in the management of menopausal symptoms in healthy women. Much of the research done by the Menopause Clinic involves collaborations, both with other Baker Institute laboratories and with researchers from neighbouring institutions.

We have demonstrated a novel, non-genomic action of oestrogen on the microvessels of healthy men which is absent from healthy women with diabetes. We have established that creams derived from wild yam have no effect on menopausal symptoms, and shown in menopausal women that micronised progesterone is safe and has no adverse effects on endothelial function and arterial compliance.

The Risk Reduction Clinic

Head:

Jan Jennings SRN

Nurses:

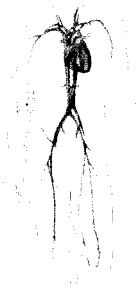
Virginia Cable SRN
Liz Jenkins
Marijke Tress
Di Wilson SRN

Administration:

Mandy Coats

The Risk Reduction Clinic performs free screening to members of the community for risk factors related to diseases of the heart and circulation. The approach to screening is to apply simple and cost effective tests, linked to lifestyle, that are of proven usefulness. We measure cholesterol and triglycerides and obtain information from a lifestyle questionnaire. This year we were able to extend the range of metabolic measurements with the introduction of new equipment. Where necessary, the initial contact with the Risk Clinic may be followed up by medical intervention. A close link exists between the Risk Clinic and the ABMU research interests in prevention of cardiovascular disease, nutrition and exercise. Staff at the Risk Clinic are involved in a broad range of research studies in addition to the critical role of recruiting subjects for ABMU studies. The clinic performed a study looking for genetic causes of hypertension and an audit of the secondary prevention measures used on patients recently discharged from hospital after heart attack and cardiac surgery. Research continues into better methods of defining risk in healthy subjects. The clinic provides a base for the Menopause Clinic and also for nutrition studies performed by the Cardiovascular Nutrition laboratory.

DIRECTORATE, ADMINISTRATIVE & SUPPORT STAFF



SENIOR MANAGEMENT

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Deputy Director:
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Associate Directors:
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Scientific Executive Officer:
Dr Stella Clark BAppSci RMIT, MAppSci VIC, PhD Melb

Chief Operating Officer - Building & Fundraising:
The Hon Michael MacKellar BScAgr, MA, MAIAS MAICD

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Elizabeth Langskaill
Fiona Share
Sandra Miljavec
Kirsty Stewart (to May)
Susan Mooney
Wilfred Villareal
Jade Barbuto
Samantha Hulme

Weekend & Casual Staff:
Kim Hauser
Karen Walls
Jeanette Leonard (to Apr)
Jennifer Atherton (to Nov)
Christine Egan (from Jun)
Kylie Aquilina (from Jun)

SCIENTIFIC SERVICES & BUILDING MANAGEMENT

Anthony Hendy BAgrScHons Melb

BIOMEDICAL ENGINEERING

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Colin Lawson
John Mizzi (from Oct)

COMPUTER SERVICES

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Melissa Tobin (to Jun)
Wayne Holden (from Jun)
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Amanda Lachmund (Secretary)
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Sue Smith

Assistant to Finance Director & Scientific Executive Officer
Annetta Conlan

Scientific Secretary
Donna Chandler

RECEPTION

Grace Pennisi (to Jun)
Tracie Beck (from Sept)

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Bryan Quinn MNIA, MAHRI

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Jan Strauss

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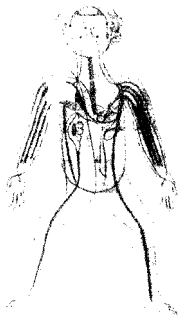
Alan Robertson BScHons, PhD Glasgow

ARCHIVIST

Geoffrey Tolson

PUBLICATIONS



(Those publications numbered in bold format indicate collaborations between one or more Institute laboratories)

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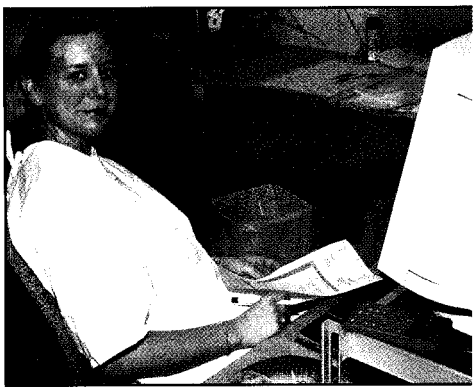

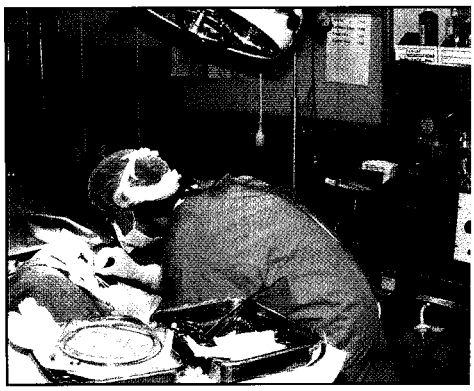

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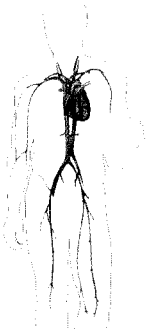

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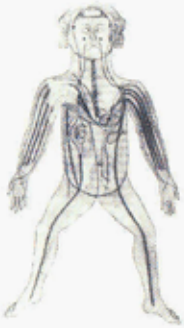

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