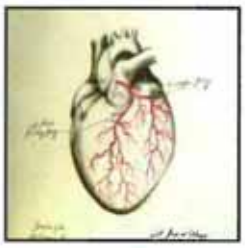
ANNUAL REPORT 1998

BAKER MEDICAL RESEARCH INSTITUTE



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AIMS OF OUR RESEARCH

In Australia, 43% of deaths and serious illness are due to diseases of the heart and circulation.

Most of these deaths follow high blood pressure and clogging of the arteries with fatty, cholesterol-laden plaques which cause strokes, heart attacks, heart failure and kidney failure.

Our research aims to increase the understanding of the underlying causes of hypertension and atherosclerosis, to use this knowledge to prevent heart and vascular disease in the community and to improve medical and surgical treatment.

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, with Baker staff holding appointments at both these institutions. In addition, the Baker is a World Health Organisation collaborating centre for research and training in cardiovascular diseases, the only one in Australia.

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The Baker has many reasons to celebrate its achievements in 1998 and to look forward to a bright and promising future ahead. When I say "its" achievements, you will know that I am talking about the achievements of the captain and all of the crew (paid and unpaid) who sail together in the Good Ship Baker. Let us consider just a few of those achievements in 1998:

- John Funder's contribution to medical and scientific research was recognised with the award of a well deserved Order of Australia. Despite the tragic loss of his beloved wife Kate (whose passing was mourned by all who knew her), John has managed to contribute throughout 1998 at his usual highest level.
- John was also invited to be involved in a number of extra-BMRI activities which are a testament to his leadership in Australian medical and scientific research. He was a member of the vitally important Wills Committee reviewing health and medical research in Australia and of the assessment panel for the Pharmaceutical Industry Investment Program. He also continued as Chairman of the Victorian Health Promotion Foundation.
- The Baker was able to recruit several key support staff and scientists in 1998 including Tony Hendy (technical manager), Brian Jones (digital imaging), Melissa Tobin (PC support) and Janine Krochmal (librarian). Ross and Kate Hannan joined the Molecular Physiology and Diabetes Cell Biology labs respectively.
- The Baker initiated an alliance with three other major Australasian institutes with a cardiovascular research focus: the Victor Chang Institute, Christchurch Cardioendocrine Group and Heart Research Institute of Sydney.
- The Baker won its first R&D START grant under Ian Smith.This heralds the beginning of an Institute-wide program to obtain greater commercial funding for Baker research. The grant is held in partnership with Monash University Departments of Chemistry and Biochemistry, The Biomolecular Research Institute and AMRAD.
- The Baker Institute initiated an exchange program with the National Heart, Lung and Blood Institute in the USA which involves 2 to 3 month exchanges between Baker and US scientists. In 1998 Michael Berndt visited Houston and later on his host, Jose Lopez, spent two months in Michael's laboratory. Dmitri Sviridov spent two months in San Francisco and Elizabeth Woodcock went to San Diego, returning in March 1999.
- The Baker received its first Anti-Cancer Council grant in more than 20 years, following the successful application by Jun-Ping Liu.
- Baker Honours and PhD students performed very well in gaining external scholarships (NHMRC, National Heart Foundation and Monash University) with a record number of six in one year.

These are only the highlights of a range of achievements which the Baker's scientists realised in 1998. On behalf of the Board I congratulate all of them on their excellent work.

In late 1997 the Baker welcomed the Hon. Michael MacKellar (formerly Federal Health Minister) who is dedicating himself to realising the long awaited new Baker building within the Alfred Medical Research & Education Precinct. The precinct is a joint venture between the Baker, the Inner & Eastern Health Care Network, Monash University and the Macfarlane Burnet Centre. With Michael leading the Baker team for the realisation of the precinct, we anticipate being in our new building early in the new millennium, a very exciting prospect for all those who have worked so hard for many years to realise the Baker's ambitions. Bill Gurry AO, Chairman of the Baker Foundation, is busily gathering financial support for the building, so be sure to welcome him generously when he calls.

Another exciting prospect on the horizon is the likely implementation of the recommendations of the Wills Committee, mentioned earlier. Having worked at close quarters with the NHMRC in recent years, it has become clearly apparent to me that new ideas and systems for the funding of Australian medical research are urgently required. It seems at last that the visionary developments

PRESIDENT'S REPORT

in funding medical research which have occurred in the USA in the last few years are to be replicated (although on a much smaller scale) in Australia. A renovation of the funding base for Australian medical research is long overdue and will ensure the development and maintenance of the intellectual capital which is essential to keep Australia competitive in an increasingly knowledge and information based global economy. It is possible that you will hear in the next year or two that the Baker (and the other five currently block funded Institutes) are no longer NHMRC block funded. This is actually an opportunity and not a threat; the Baker has no fear of competition for medical research funds against its peers in Australia (or indeed overseas) and will be a beneficiary of the abolition of block funding.

In closing, I congratulate our Director and the scientific and support staff of the Institute on another year of outstanding achievement. I also thank all of my fellow members of the Board and all of the other supporters of the Institute (many of whom are mentioned in this Annual Report) whose hard work makes possible everything which BMRI does and rewards all of those involved.

I look forward to seeing you at the Baker during 1999.

Norman O'Bryan

NORMAN O'BRYAN

President

As a lifelong optimist, there are good years and great years; and in the scheme of things 1998 was a good year rather than a great year. The Baker continued to be busy, productive and an exciting place to do research. The plans for the new building crystallised, and the funding contributions ($7.6m each) from the Commonwealth and State Governments approved and gazetted. The Capital Campaign started up afresh, and by the year's end had raised a further sum in excess of $1m, including a major gift of $450,000 from National Mutual: we still need ~$3m towards the building, and probably a similar amount to equip it appropriately. The Baker Foundation, major historic and current supporters of the Institute, notified the Board that for 1999-2001 they were raising their level of annual support of the Institute from $1.05m to $1.15m.

All of which sounds pretty good, and not a bad beginning: why not a great year? At a personal level, I had a very difficult twelve months (see below); more importantly from the Institute's point of view 1998 was the year when the mechanism of block funding of the Institute was operationally broken by the current Research Committee of NHMRC, in their recommendations to Council and to the Minister.

Approximately 35% of the Institute's budget comes as a 'block' of funds to the Director, for a five year period, notionally to allow flexibility and the ability to pursue medium to long term avenues of research. In fact, this core funding now represents a grant-in-aid rather than a realistic estimate of what NHMRC-supported research actually costs, for a number of reasons. First, there are no infrastructure allowances for research institutes or hospital based investigators (university based research attracts some infrastructure from DEETYA, by contrast).

Secondly, though the NHMRC has mandated enterprise bargaining in setting academic salaries, it provides funding at a level currently 10-12% below that obtaining in the universities - and university salaries are very much lower in Australia than in other first-world countries. Third, the current NHMRC has an explicit policy of spreading the funds available as widely as possible, so that in tough times one line budgets of $4m look invitingly simple to trim - unfortunately, in 1998 in the case of the Baker, to the bone.

In 1997 the Institute was reviewed by a committee of national and international experts who recommended a modest increase in funding, with a fall back position of continuation for 1998-2002 of the same number of positions. Even this latter represents a ~10% increase in funding, as NHMRC funding over the quinquennium progressively falls short of what the positions approved actually cost. At the end of 1997 we were informed that for 1998 funding would be frozen at the 1997 level, pending the rapid implementation of a review of block funding mechanisms, and that the level of funding for the remainder of the quinquennium would be at the fall back level - i.e., we would get the real costs of the fifty positions covered.

Not unexpectedly, the review of block funding took much longer than advertised, and the relevant committee did not circulate its draft document until the end of 1998. Also at the end of the year came the news that despite the written assurances given of the level of funding, the amount proposed had been lowered by 10% net of Research Fellows salaries, for 1999-2000. In setting our budgets for 1998 we took the prudent step of putting down NHMRC support at the 'fall back' level, on which basis we would have come in on budget, as opposed to the operating deficit noted later on in these pages.

For 1999 we set our budgets on the basis of written assurances of what would flow to the Institute: again, in mid November 1998, there comes this second blow to our bottom line, currently being very actively contested. We are thus facing a sizeable operational deficit reflecting not only this eleventh hour additional proposed cut, but also that we have raised staff salaries (save those of Director and Chief Operating Officer, Building and Fundraising) by 6%, roughly half of what academic and general staff at Monash and Melbourne Universities received over the past two years. We're still behind, but equity demands we catch up, and the sooner the better.

This is a pretty fine-grained analysis of the situation, and you might be pardoned for asking why. First up, as I never tire of saying at the Baker VIP tours, we have to give an account of ourselves: whether the money comes from Canberra or Spring Street, private or corporate sources, it's basically community money, and we are responsible to

tax payers and donors for how it is spent. The NHMRC has historically been the pacesetter in terms of funding, and for a variety of reasons is currently facing considerable difficulty in discharging this role. Some of these difficulties are policy-driven - like spreading the available funds very widely, rather than giving fewer, more realistically funded grants; others are procedural, like making policy about block-funding mechanisms on the run, comminuting five year commitments to stuttering one and two year funding periods. At base, however, there are two salient problems - resources and money, and in this instance they're not absolutely identical.

First, resources. The NHMRC is comprehensively undergunned and underresourced for the task it has to do, in terms of secretariat, personnel, IT, corporate memory. In 1998 the review of project grant applications - for which the Baker currently cannot compete - was a fiasco, reflecting underresourcing, lack of preparation and very poor IT support.

Secondly, money. Currently NHMRC recommends funding to 24% of project grant applications, and then probably on average covers only ~60% of the real costs of the research. Historically universities and hospitals have had ways to cover shortfalls, and even made resources available for setting up and supporting their new appointees, with technical assistance and research consumables. No longer is this the case; they realise that their impact will be much more if they focus and concentrate what resources they have on a few particular areas - leaving NHMRC the impossible task of trying to cover the field, and spreading itself thinner and thinner.

So if we're going to fund medical research in any way approaching adequately, how can we do it? First up, there has to be (and increasingly is) a higher level of industry funding of research in places like the Baker. Over the past decade pharmaceutical companies - the obvious partners for a medical research institute - have taken their levels of outsourcing basic 'discovery' research from five to over fifteen percent, and it's still growing. The Baker has historically been concerned with working out mechanisms and pathways, rather than seeking new chemical entities as potential pharmaceuticals. Notwithstanding this history, we are very much expanding our partnerships with pharmaceutical companies, under the guidance of Paul Nestel, as Chair of the Commercialisation Committee. Ian Smith, for example, won a R&D START grant with academic and commercial partners; and at the time of writing a series of propositions have been put to a variety of pharmaceutical companies, in Australia and overseas, by - for the first time - over half the laboratories in the Institute. In this regard it was both consoling and exciting to see the commitment to outsourced discovery by a number of the pharmaceutical companies applying for pricing relief as part of the Pharmaceutical Industry Investment Plan (PIIP), a committee on which I served from September to November, and which sat for fifteen days, alas only one in Melbourne.

Of major importance - to industry investment, and to the community's tax resources invested via NHMRC - will be the outcome of the Health and Medical Research Strategic Review, chaired by Peter Wills, who is also chairman of the Garvan Institute Board and deputy chair of the Committee for Sydney. I was privileged also to be a member of the Wills review, which met from

March to November, for around twenty five working days, alas only two in Melbourne. The report was delivered to Minister Wooldridge, who commissioned the review, in November and at the time of writing is out for comment and consultation. Its recommendations are simple, sweeping and interconnected into what, presumably in contrast to a vicious cycle, is termed a 'Virtuous Cycle'.

First, the Commonwealth Government needs to increase investment in biomedical research by 15% per annum for each of five years: compounded this represents a doubling. Secondly, the capital gains tax rules currently in operation make Australia 25-40% non-competitive in terms of attracting venture capital to high risk, high return investment: a tapered system, along the lines of the recently introduced UK model, plus reform of limited liability arrangements, are crucial for industry to be able to lever off our basic research, and to do it in Australia. Third, strategic, priority-driven research - in public health, health promotion, health economics - needs radical review and expansion: currently it is ad hoc, sometimes lacking rigour, and often poorly disseminated given the federal nature of our health system. At first approximation (and not from want of trying to ferret out the figures) we currently spend ~$50m - of a $43 billion health budget - on such research. In the UK the figure is 1.2% of a much bigger budget: currently, we are devoting around one dollar in every thousand to ask if the system is working, and to see how it might work better, or faster, or more cheaply, or with wider spread. Private companies in innovation-rich sectors like health spend up to 20% of turnover on R&D: you wouldn't run a lolly shop on 0.1%.....

For this to work requires considerable structural change, and the Wills report recommends appropriate empowering and restructuring of NHMRC and its roles and functions. Recommendations include appointment of an eminent scientist as CEO, with a group of similarly full-time high level scientific appointees to head the dependent committees; appointment of research management and capture teams, for a period of 2-3 years, to assist the laboratory researchers to commercialise their intellectual capital; salary conditions for researchers which are competitive across sectors and internationally; and emphasis on funding excellent applications adequately, rather than spreading resources thinly.

While the report was tabled in late 1998, much of the work in terms of its acceptance and implementation remains to be done in 1999. A doubling of community investment via NHMRC over five years still leaves us considerably short of the OECD average - we're not talking rule-the-world sort of levels, and in both the US (which accounts for 50% of the world's biomedical research) and the UK further major increases are foreshadowed. We've got a relatively brief period of time before the window of opportunity in terms of biotechnology closes. If we fail to implement the Wills report we will become users rather than producers, in the same way as we are in the area of I.T. I would hope that by the time this Annual Report is printed and available we have a firm commitment from Canberra - on doubling, on capital gains tax, on priority-driven research - that should enable us to compete internationally in the field most likely to provide the major intellectual currency of the next two decades.

Finally, on a personal note, I owe an enormous debt of thanks to the staff, the Board and the wider Baker family for the enormous support they afforded me over 1998. In November 1997 my beloved wife Kate was found to have unsuspected secondaries from a tumour removed many years before, and she died on June 13 1998. For the first half of the year the Institute had a desperately distracted Director, and a grieving Director for the rest of the year. 1999 is a New Year, and on a personal level it would be almost inconceivable for it not to be a much better year than 1998. At the level of the Institute, there are also firm indications that 1999 will be a great year - in terms of a new building rising out of the cement dust on Commercial Road, in terms of successful commercial partnerships being established, in terms of the implementation of the Wills report. Vale 1998, and ave 1999: for a whole range of reasons it's got to be a better year.

John Funder
Director

David Kaye: Pontifex Maximus

Every year the Wellcome Trust in the UK puts more pounds sterling into medical research than the U.K. Medical Research Council does. In Australia, the Trust has sponsored Senior Research Fellowships for the past 15 years, primarily as a way to repatriate our best and brightest from the bright lights and big cities of the northern hemisphere. Each award is worth the best part of a million dollars over five years - salaries, technical assistance, consumables, on-costs. They're understandably hotly contested, and 'The Wellcome Fellows' are a superb group of young Australian investigators.

Young by the standards of the sector - this is not tennis or swimming - David Kaye started his medical course in 1979, and in 1998 began his Wellcome Fellowship at the Baker. It has taken him almost twenty years to step out as a fully-fledged investigator: why so long?

The answer is that David is a 'bridge person', in two ways. Firstly, he bridges clinical practice and clinical research in cardiology, and secondly he bridges clinical research on patients and basic research on genes and molecules. To do this you have to be good, you have to be dedicated, and it still takes a long time: it's a bit like qualifying as an actuary and a fully-fledged member of the SAS. The answer to why so long is that's how long it takes.

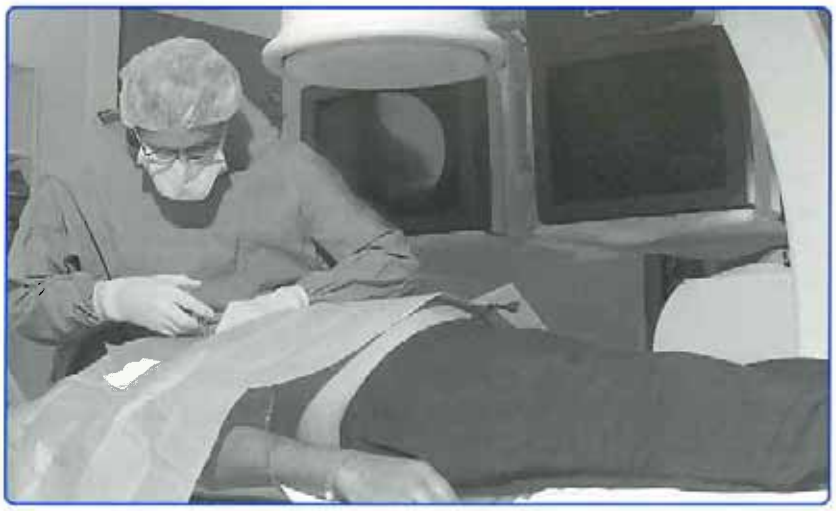
> "It's a bit like qualifying as an actuary and a fully-fledged member of the SAS."

After graduating in 1984, David did the three routine years of internship and residence, followed by four years specialist training in cardiology. In 1991 he became FRACP, testimony to his specialist status in terms of clinical practice. That year, he began his PhD in Murray Esler's Human Autonomic Function laboratory, on the way that nerves talk to the heart - not in rats or dogs, but in normal people and patients in heart failure.

In 1994 he gained his PhD, testimony to his status as a bonafide clinical researcher, and moved to Harvard as a National Heart Foundation Overseas Research Fellow. At the Brigham and Women's Hospital David immersed himself in molecular biology for two years, learning about genes and chromosomes, DNA and RNA. Back to Melbourne in 1996 with support from the NHF and the High Blood Pressure Research Council of Australia for a year each, and then he lands 'the Wellcome'.

The prevalence of heart failure has risen spectacularly over the past decade, with little indication to date of it peaking. In one way this is a success story, in that fewer

people die acutely of heart attacks - but it means we need to know a lot more about how to treat heart failure to maximise quality of life.



David has extended his thesis work on cardiac nerves in heart failure to ask questions at the molecular level. In human heart failure, in experimental heart failure in rats, or even in heart muscle cells in culture exposed to the neurotransmitter noradrenaline, the levels of a signalling molecular called nerve growth factor (NGF) fall. It looks as though the muscle cells turn down their synthesis of NGF to protect themselves: how can we use this information? Should we try to accentuate this biological response, or to block it? Is it best to try and intervene at the level of noradrenaline, or NGF itself?

In heart failure, the blood flow to your muscles doesn't increase properly with exercise. The consequences of such a situation are obvious, but how it happens is not so clear. One of the key molecules in dilating blood vessels is a gas called nitric oxide, made from the amino acid arginine in one layer of the blood vessel and diffusing through the vessel wall to relax the muscular coat. David has shown that the pump which transports arginine into the cells where nitric oxide is made works only at 20-50% capacity in heart failure. What's telling it to go slow? Is this the body's way of protecting the compromised heart against too much exertion? Can we target this system to make things better? How can we tell, using cells and rats and ultimately human volunteers, that we're not making things worse?

> "Sometimes the questions are straightforward, but always the context is complicated."

Sometimes the questions are straightforward, but always the context is complicated. Twenty years of training helps with choosing the right questions, but is absolutely crucial in putting the answers into context. That's why bridge people like David are worth their weight in gold, as the Wellcome Trust recognised - at least in the metaphorical sense. Come to think of it, at current gold prices, over five years it's close enough to literally true.

Hands Across the Water

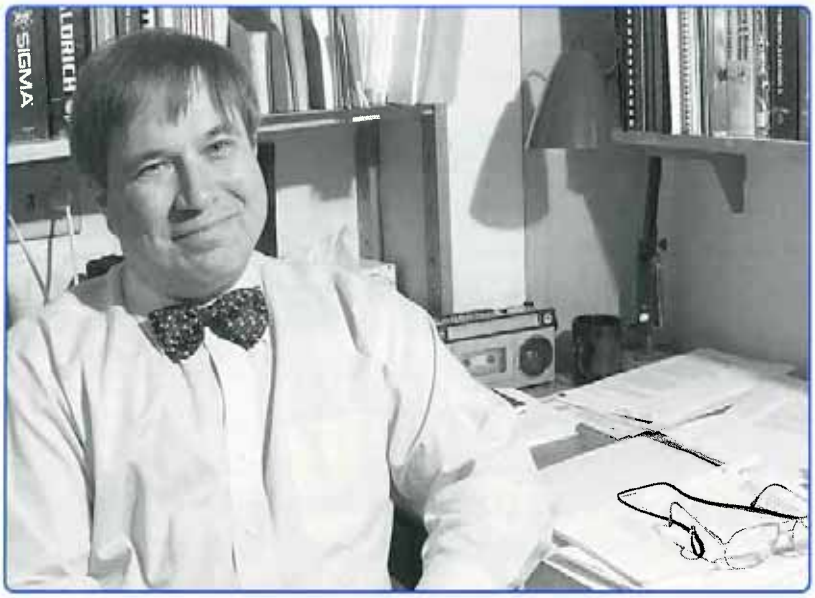
In 1970, before the dawn of time, two young men started working as postdoctoral fellows at the Cardiovascular Research Institute (CVRI) in San Francisco. Peter Spooner, originally from Providence, Rhode Island, had done his PhD in Urbana, Illinois, on how estrogen works in its target tissues. John Funder, from Melbourne, had done his PhD at the Howard Florey Institute on hormones and hypertension. Judith Jones, doing advanced physician training in clinical pharmacology, had started in the same laboratory at the CVRI the year before.

Time passes, and there are only six billion people on earth. Judith, now in Washington and in contact with the Spooners, comes to Melbourne to visit an American friend, who invites Funder to dinner. Next time Funder is in Washington, the Spooners host a dinner where all three of the class of 1970 are reunited, twenty five years down the track: what ever happened to Tom? Where's Vivian now? and other questions of high science.

Peter Spooner has forsaken hormone action for a more varied scientific career, and for the past fifteen years has been a top-level scientist-administrator in the National Heart, Lung and Blood Institute (NHLBI). Funder, now at the Baker, is still working in hormones and hypertension: the more you learn, the more you realise there is to know. At that dinner in Washington, or more precisely in Potomac, Maryland, the notion of the NHLBI-Baker exchange was conceived.

Elephants go up the mountain to mate, a process accompanied by horrendous footstamping and trumpeting, and followed if successful by a newborn eighteen months later. Government processes are often compared, some times unfavourably, with the mating of elephants. Male and female elephants are of comparable size, but the Baker annual budget is A$11m, to the NHLBI's US$1.7 billion, itself the equivalent of a mountain; footstamping and trumpeting were at a minimum, but the process still took eighteen months.

"Government processes are often compared, some times unfavourably, with the mating of elephants."



Dr Dmitri Sviridov

The deal is simple. If a Baker scientist wants to work in the United States in an NHLBI-supported lab, then we continue his/her salary and cover airfares, and the NHLBI covers local accommodation, medical insurance and a US$26/day meal allowance, for up to three months. If an NHLBI-supported scientist wants to come to the Baker, it's exactly the opposite, up to three months.

Drs José Lopez & Michael Berndt

Baker people have never been big on taking sabbaticals. Long periods of 'study leave' are often domestically difficult, and short periods are expensive, especially in terms of accommodation: nobody wants to rent your bijou bungalow in Balaclava for three months, particularly if the spouse and kids are still there. On the other hand, there's no question that working in the US, full steam ahead on a collaborative project, normal distractions suspended, is a terrific way not just to recharge your batteries but also to accomplish an enormous amount.

The first cabs off the rank were Michael Berndt and Dmitri Sviridov. Dmitri went to work with Chris and Phoebe Fielding, at the University of California San Francisco, on how cholesterol gets taken up into cells. The results of three months of hard work and high intellectual stimulation are a paper published, a joint grant application worked through and largely written, and the Fieldings applying to spend three months at the Baker in 1999.

> "The more you learn, the more you realise there is to know."

Michael spent November 1997-February 1998 (their winter, mercifully) at Baylor College of Medicine in Houston, Texas, with José Lopez. Together they made a range of human-dog chimeras - not the many-headed Cerberus, but part-canine, part human molecules of von Willebrand factor, to explore exactly how blood clots form. Michael allows that - apart from the two weeks when his family visited, and they drove 2000 miles to all the local holy places (Graceland, Disneyland etc) - he has never worked harder.

In July 1998 José Lopez forsook the 100% humidity of Houston for two months in Michael Berndt's laboratory, and in November Liz Woodcock from the Baker went off to San Diego for three months' intense focussing on a strain of transgenic mouse it would take a year to get through quarantine here. For 1999 there are three more applications from our lot to spend time over there, and five from NHLBI-supported folk to come here. In February 1999 Funder will be in Washington, and is scheduled (over lightly grilled fish and a glass of red wine) to discuss, with Peter Spooner and NHLBI Director Dr. Claude Lenfant, how to expand the current exchange to include graduate students and postdocs, as well as the current senior staff.

The moral of the story would appear to be two-fold. First, great oaks from little acorns grow; and secondly, never knock back an invitation to dinner.

Two and Two Sometimes Makes Six

There are a number of remarkable things about Alex Bobik. First, he speaks fluent Russian. Second, he has single handedly run the cardiovascular program of the Russian-Australian scientific exchange, pre- and post Glasnost, a program which has proven extraordinarily productive on both sides. Third, he is an outstanding vascular biologist, a long way from his roots in medicinal chemistry and toxicology. Finally, he is a very enterprising and enormously obliging collaborator.

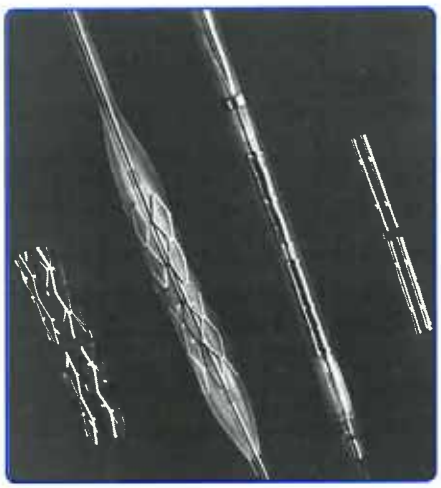
During 1997 John Funder had been doing a lot of work in the laboratory on a new aldosterone antagonist called eplerenone. Aldosterone is the steroid hormone that retains sodium, in the kidney and the colon, and thus recognised as important in blood pressure control. Recently, following work in the US, France and at the Baker, it has become clear that aldosterone and salt are also crucially involved in promoting cardiac fibrosis, which prevents the heart from contracting properly, with obvious consequences.

The same year also saw the publication, from one of the French laboratories, of a paper showing that the current aldosterone antagonist, (spironolactone) blocked narrowing in rabbit carotid but not femoral arteries after they had been damaged by having the lining rubbed off. The inference from these studies was that perhaps aldosterone was playing a role not only in cardiac fibrosis, but also in the injury response in at least some other tissues.

Take the above three paragraphs together, and the collaboration was born in a corridor conversation on the ground floor at the Baker. Alex had the pigs, a much closer model of the human heart than other species. Michael Ward in Alex's laboratory was a wizard at damaging arteries, by blowing up little balloons at the tip of a coronary catheter, the so-called 'balloon angioplasty'. Funder had the eplerenone, and convinced an initially uncertain pharmaceutical company that it was worth their while underwriting the studies. Michael was in a flurry of activity, writing up his PhD thesis before moving off to Stanford, but still managed to squeeze in 24 operating theatre sessions to balloon angioplasty four groups of pigs' coronary arteries, and equivalent size branches of their femoral arteries.

> "... and the collaboration was born in a corridor conversation on the ground floor of the Baker."

The first group of pigs received a twice-daily dose of eplerenone for four weeks after operation, and the



second group spironolactone. The third group got additional aldosterone, continuously by a minipump (the size of an AA battery) implanted under their skin. The fourth group had no treatment post-operatively, to serve as a control: you always have to have a control group, to give a baseline.

Four weeks later the pigs were killed and the vessels taken, blocked, sectioned, stained and their size and state determined. For the femoral arteries, which are not nearly as easily damaged as the coronary arteries, there was no difference between groups. For the coronary arteries, eplerenone was clearly and significantly protective: the diameter of the vessels was equivalent to that in a non-traumatised vessel, whereas that in control, untreated, vessels was reduced by 40%, not good news in terms of blood flow. Pigs getting spironolactone were in between eplerenone and control, and those getting aldosterone were marginally worse than control.

Now it's early days, and like all experiments it needs to be repeated; we are currently in discussion with colleagues at Emory University in Atlanta to do just that. We also need to repeat the studies with what are called 'stents' in the vessels, as almost 70% of human balloon angioplasties for narrowed coronary arteries include putting a stent in the area of constriction. A stent is a wire cage to hold the vessel walls apart, a rather elaborate version of the wire thingy holding champagne corks in place. The

"A stent is a wire cage to hold the vessel walls apart, a rather elaborate version of the wire thingy holding champagne corks in place."

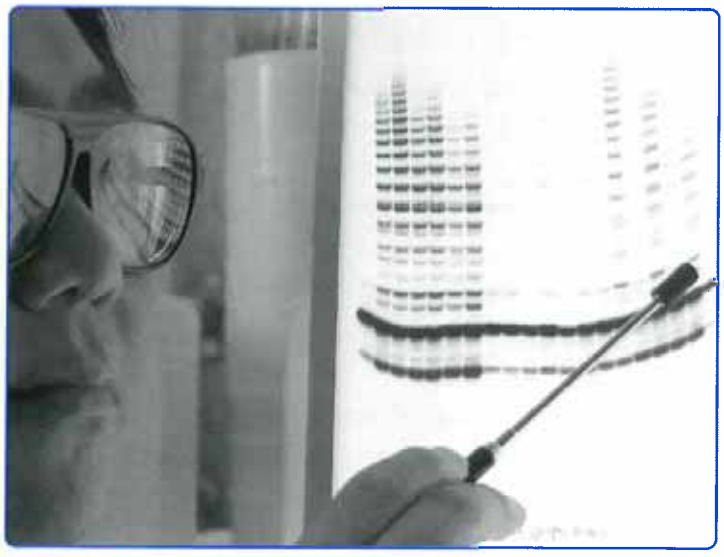
reason why 70% of balloon angioplasties include stents is that they slow the rate of reclosure from 30-40% to nearer 10%; vessel reclosure means such patients then either have a second angioplasty, or coronary artery graft surgery. Then again, it's a bit of wire in your coronary vessels, on first principles something you'd rather not have if at all possible.

Eplerenone might just be the answer, acting as a pharmacological stent for the crucial days and weeks after angioplasty, when the processes that determine reaction to injury and scarring and contracture are in full swing. It might also tell us something about the normal physiology of aldosterone, in its expanded role from salt-retaining to pro-fibrotic hormone. And it certainly tells us that while we work in laboratories and clinics, and operating theatres, and arm-wrestle with pharmaceutical companies by fax and email, some of the most illuminating studies are done as a result of corridor conversations, in a physical rather than virtual Institute.

Team China, Team Australia

Sixty years ago, medicine and medical research were a single field, relatively speaking: Howard Florey, for example, published most of his life in the area of blood vessels and lymphatics, and specialisation within medicine and surgery was in its infancy. Forty years ago the specialist system came in with a vengeance, and medical research became divided into specialist areas - cardiology, immunology, endocrinology and so on.

Twenty years ago, radiating out of San Francisco's Bay Area, came the molecular biology revolution, like a giant wave washing over the decks of all the individual ships. Today, molecular biology has become the lingua franca of medical research, from developmental biology to epidemiology: just like air-traffic controllers the world over communicate in English, over the last decade and into the foreseeable future the commonality binding medical research into a whole is cellular and molecular biology.



Most of the work that Jun-Ping Liu and his team have done over the three years they have been at the Baker has been on breast cancer cells, with some studies on

"Twenty years ago, radiating out of San Francisco's Bay Area, came the molecular biology revolution."

pituitary tumour cells. Jun-Ping studies how a protein called dynamin II is involved in the processes of secretion from cells, how an enzyme called PKC activates parts of the cell machinery while an enzyme called PP2 works in the opposite direction, and how a very interesting enzyme - part protein, part ribonucleic acid - called telomerase is regulated, and just exactly what it does in normal and cancer cells.

The laboratory, perhaps understandably, is called the Molecular Signalling laboratory; what, you might ask, have studies like this to do with heart disease? The heart either pumps or it doesn't, right? Blood vessels either work or get clogged up, don't they? Actually, it's never been as simple as that, since William Harvey: and in the last decade of the twentieth century we need to ask the same questions of cardiomyocytes (heart muscle cells) or vascular smooth muscle cells that we do of cancer cells. And we've started to do so - but for many studies cancer cells, which divide and replicate out of control, are much more convenient than cells laboriously grown from neonatal rat hearts or from the bovine aorta.

As cells divide, the ends of each chromosome, the telomeres, get shorter and shorter, and eventually the cells can divide no

longer: cells in culture can thus divide for so many generations. In normal mature cells the enzyme telomerase is not turned on; in most cancer cells it is,

and we know very little of how, let alone why. Jun-Ping and his team have established that a cycle of adding and subtracting phosphate groups serves to turn telomerase activity on and off in breast cancer cells. They have also shown that telomerase is surprisingly active in vascular smooth muscle cells from the blood vessels of some strains of rats, but not others, an absolutely unexpected observation. What it means, in terms of structure and function and responses to stimuli, are yet to be explored - but if you don't ask the questions nobody is likely to present you with the answers.

"This is exactly what Jun-Ping and his colleagues are doing - asking questions in an established system, and then following up the answers with further questions in the heart and blood vessels."

The pituitary is an endocrine gland, meaning it makes hormones for export into the blood stream. It's not known for its ability to contract rhythmically, and has never been observed to pump blood: how can it be relevant to the heart and blood vessels? Well, just over a decade ago the heart was shown to be an endocrine organ, secreting a hormone called Atrial Natriuretic Peptide (ANP) into the blood; since then, other "heart" hormones, most notably BNP, have been discovered, and their levels are currently the gold standard in establishing a patient's prognosis after a heart attack.

As we approach the end of the century, the wheel has come full circle, and biology increasingly becomes a seamless garment. Within five years the human genome project should be complete; with such a rich data base, every question answered will pose two or twenty more. Already the old divisions, for example between neurobiology and developmental biology or cancer biology and immunology, are breaking down; molecular biology has been relatively late coming to cardiology, which thus must borrow from a range of allied disciplines. This is exactly what Jun-Ping and his colleagues are doing - asking questions in an established system, and then following up the answers with further questions in the heart and blood vessels.

If I Can't Have a Horse, Can I Have a Bicycle...

Rod and Rosey sounds like the name of a rainbow trout farm, or maybe a pair of pop singers from Oregon. In the context of the Baker neither is quite the right, though image is everything for both Rosey and Rod. Together they constitute the Morphology Laboratory, and drive the various types of microscope in the Institute to capture the images of the tissues, cells, organelles and even molecules with which we work.

Rod Dilley has been at the Baker since 1989, after a decade as an undergraduate and postgraduate student at the University of Western Australia, and three postdoctoral years in Seattle. At the Institute Rod fills two roles. Very importantly, he is an integral part of a whole range of studies across the Institute, where looking at pictures of the heart muscle or blood vessels adds considerably to what the data can tell us. Secondly, and increasingly, Rod is steering his 'own' experiments, in which looking at the pictures is paramount.

> "...image is everything for both Rosey and Rod. Together they constitute the Morphology Laboratory...."

Of all Rod's collaborative studies the longest-standing have been with Alex Bobik and his colleagues in the Cell Biology laboratory, to do with blood vessel function, both normal and abnormal. There are a number of ways you can study blood vessels, from gauging their response to drugs or hormones in the intact human forearm to seeing how well they contract and relax in organ baths. Historically, such techniques are useful for studying acute responses, and then making inferences about longer term structural changes from the pattern of acute responses.

Taking a vessel and examining it under the microscope gives a different and more direct fix on its structure than inferences from organ bath studies; on the other hand, ordinary morphology tells you less about function. When, however, morphology is combined with either the use of antibodies or radioactive DNA strands complementary to messenger RNA in the tissues under examination, then very useful inferences can be made about function, and the cellular changes underlying the changes in structure.

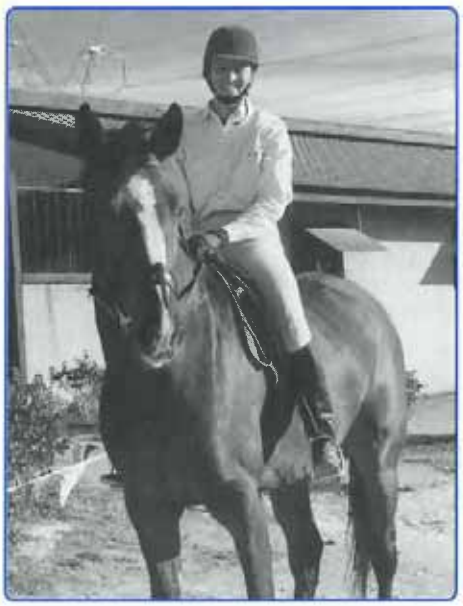
In addition to the Cell Biology laboratory, Rod collaborates with Zig Krozowski and his colleagues, to localise the enzymes 11ßHSD1 and 11ßHSD2 to interstitial cells in the kidney, to white blood cells, and subpopulations of cells in the heart, stomach and lung;

these are all 'unsuspected' sites, and prompt the question of what the enzyme is doing there. With Du, Rod is using heparin to lessen the extent of cardiac fibrosis after myocardial infarction in a rat model; similarly, Rod and Du are documenting the extent of cardiac fibrosis in transgenic mice making abnormally high levels of a particular sort of receptor for noradrenaline in their hearts.

> "With the naked eye you can see the tractor in the paddock; .. with the electron microscope you can see not only each blade of grass, but the ants in procession on the third blade from the left"

These are but two of a number of such collaborative studies; off his own bat Rod is currently involved in a series of experiments under contract from Johnson and Johnson. When blood vessels are injured they respond by making a number of new proteins, to direct and take part in the repair process. To do this various genes have to be turned on in sequence by signals called 'transcription factors'. Rod has used antisense molecules, which bind and inactivate the messenger RNA read off the genes, to see whether blocking a transcription factor called EGR, can affect the stenosis and scarring that characterise the repair process.

Rosey van Driel worked three days a week in 1998 at the Baker, and will be full-time from 1999. Rosey is an electron microscopist, driving an instrument that can magnify things by a factor of 100,000. With electron microscopy you can see not only cells and their larger constituent bits (like the nucleus); you can see down to the detail of individual large single molecules. With the naked eye you can see the tractor



in the paddock; with the ordinary (light) microscope you can see each grass tussock; and with the electron microscope you can see not only each blade of grass, but the ants in procession on the third blade from the left.

So Rosey's looking at the cardiovascular equivalent of grass seeds and insects with Noel Fidge, to see how lipoproteins are internalised using ultrasmall gold probes; with Tim Cole, at deficiencies in surfactant synthesis in the lungs of newborn mice in which the receptors for cortisone-like hormones have been 'knocked out' by genetic engineering; with Zig Krozowski, at 11ßHSD1 and 11ßHSD2; and with Rod Dilley, at how injured vessels regrow in response to the trauma of angioplasty.

There's a folk saying, from time immemorial, that seeing is believing. Sure, we have to believe evidence other than visual, but more recently the observation has been made that one picture is worth a thousand words. Rod and Rosey are in the business of pictures; they are the image-makers of the Institute, and their contribution is difficult to overestimate.

Fascinating Rhythms

We hear a lot about the rhythm of life: there's even a song about it. Some of these rhythms are externally dictated - ewes lamb at the end of winter for very good reason, and adult humans (but not teenagers, or rats) sleep at night. Some of these rhythms are internally generated - think of the menstrual cycle, or the beating of your heart. All of them can be altered - by moving sheep towards the equator, by jetlag, by stress or by pregnancy - and all of them are part of the normal way in which the body - sheep, rat and human - orchestrates the way it operates.

In biological as well as orchestral terms, Geoff Head works in the rhythm section. What he studies are patterns of nerve impulses, from the brain to the rest of the body. The way nerves work involves both electricity and chemistry. When you wriggle your toes, a nerve cell in your brain fires off, and a minute electrical impulse travels down your spinal cord to a way station, a synapse. At the synapse the burst of electrical activity causes the nerve ending to release little packets of chemicals, 'neurotransmitters', which activate neighbouring nerves and cause them to fire off an electrical signal, down to the muscles involved in toe-wriggling. Again the chemistry is repeated: at the nerve ending the electrical activity causes the nerve ending to release neurotransmitters, which hit the muscle cell membranes and tells them to contract. In a much shorter time than it has taken to write (or even read) this paragraph I could wriggle my toes dozens of times.

"In biological as well as orchestral terms, Geoff Head works in the rhythm section."

What I have described is pretty basic - a spike of electrical activity, a burst of neurotransmitter and then action. This is a very limited, on/off, yes/no information system, and not nearly as content rich as Morse code, let alone FM radio or fibre optics.

Part of what Geoff and his team do is to study the patterns of nerve impulses from the brain to the kidney, to understand what messages are being conveyed beyond on/off, yes/no. Think of Morse code, and how even this very primitive signalling system has become more information rich by distinguishing dots (shorts blips) and dashes (long blips) by grouping dots and dashes in different orders to represent different letters of the alphabet, and so on. Nerves are the same: in addition to on/off, yes/no, the patterns of bursts of activity and the intervening lulls, the regularity (or otherwise) of these bursts and lulls, and so on - all these affect the way the kidney regulates blood pressure, alters heart rate, modifies sodium excretion and controls release from the kidney of renin, a powerful kidney hormone with a wide range of cardiovascular effects.

To start to make sense of this example of Morse code you need to do a number of things. First, you need to be able to measure the patterns of electrical activity in the nerve, in this case the sympathetic nerves to the kidney. You need to be able to measure the things that the nerves affect - blood pressure, heart rate, sodium excretion, renin release. And finally, you need to be able to perturb the system - a bit like thinking "I'm going to wriggle my toes" - to see how that alters patterns of nerve firing and with it patterns of kidney response.

Dmitri Maiorov in Geoff's lab has worked out how to microinject things into the brainstem, the seat of this sort of nerve activity (just as your motor cortex is for toe wriggling), in conscious, unstressed rabbits. When he does this the pattern of traffic down the nerves to the kidney can be modified, with some variety introduced by varying the concentration and nature of what is injected, probably a pale shadow of what is really the case, but a start. Only one other group (in Brazil) have managed to do this, in conscious rats, and for studies of this sort a rabbit is a much better bet. In most other experiments the microinjection had been upstream, and necessary more diffuse, and the animals anaesthetised, much more a pale shadow of what is really the case.

"With all this talk of pale shadows, it's perhaps apposite that the mathematical handling of the patterns generated is called spectral analysis...."

With all this talk of pale shadows, it's perhaps apposite that the mathematical handling of the patterns generated is called spectral analysis, although in this case the derivation is from spectrum rather than spectre. Elena Lukoshkova, from the Cardiology Institute in Moscow, spends three months a year at the Baker writing programs for spectral analysis, and then doing it: her next stint is in April 1999, just after defending her DSc. thesis.

All of which may be (and indeed is) very fascinating: but you might be pardoned for asking whether it yet has any relevance to the human heart and kidney, for example. The answer is probably yes, but to date we don't know very much about exactly how. Rhythms are important for human heart disease: our blood pressure and heart rate, as well as sodium handling, have clear day/night differences, and on a statistical basis the danger time for heart attacks is very much around 9 am. We don't do microinjections into people, or record bursts and lulls from their renal sympathetic nerves - but we can record 24 hour blood pressure and heart rate in 800 patients, and do a lot of human/rabbit comparisons.

If, for example, we can get a handle on the early morning rise in blood pressure, then possibly the rate at which the pressure rises, unfettered by normal damping mechanisms, may represent a risk factor for heart attacks. Which, basically, is what the Baker is about; taking the fruits of curiosity driven, investigator initiated basic research - on rabbits, microinjected and instrumented, conscious and feeling no pain, measuring everything we can - and applying it to the human situation, in this instance with the goal of lowering the incidence of preventable heart attack in the human population.

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The Hon Mr Michael MACKELLAR BSc.Agr.,M.A. M.A.I.A.S.

BAKER MEDICAL RESEARCH INSTITUTE LABORATORY REPORTS

Alfred and Baker Medical Unit

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Murray Esler BMedSc, MBBS Melb, PhD ANU, FRACP

Associate Director (Atherosclerosis)
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Secretarial
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James Shaw MBBS FRACP Mel

The Alfred and Baker Medical Unit (ABMU) has developed into a group of laboratories within the Baker whose common feature is the conduct of clinical research on human subjects and/or a particular link to The Alfred. Our broad interests are in prevention of cardiovascular disease by lifestyle measures, clinical cardiovascular research and treatment.

ABMU research activities appear throughout the Laboratory Reports under Clinical Physiology, Experimental Cardiology, Human Neurotransmitter Research, Cardiovascular Nutrition, Molecular Neurocardiology, and Vascular Pharmacology.

In sharing the Heart Centre with Cardiovascular Medicine, ABMU has unique access to patients and the opportunity to apply our research results to clinical practice.

We have found that a disease management program for heart failure patients reduced their admissions to hospital by over 50%. Similar programs are being examined for primary and secondary prevention. The excellent patient databases in ABMU will soon be available for research into the genetic basis of cardiovascular disease through establishment of a gene bank.

Work this year has supported our view that elasticity of the large arteries is important in determining risk of cardiovascular disease. Interventions including exercise, nutritional modification and hormones improved the elasticity of arteries. ANBP2, a large national trial in general practice coordinated by ABMU passed the milestone of recruiting 6000 patients by mid-1998.

Cardiac Surgical Research Unit

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Salvatore Pepe BscHons Flinders, PhD Adel
Julian Smith MBBS, MS Melb, FRACS

Technical & Professional:
Heather Gallichio BSc Melb,

Phyllis Halliday (from July)
Dip Immunol Mon
Freya Thompson BA, BSc Mon
Michelle Wowk BAppScHons Swinburne

Research Students:

Silvana Marasco MBBS Mon
Francis Miller MBBS Mon
Olivier Van den Brink

Our laboratory aims to improve the efficacy of heart surgery and transplantation, with research covering cellular organelles, large animals and human trials.

Coenzyme Q_{10} (CoQ_{10}) protects particularly aging rat hearts and human cardiac tissue against stresses such as electrical stimulation, ischaemia or hypoxia. Preliminary results of a human trial of CoQ_{10} treatment before cardiac surgery suggest it is beneficial in decreasing myocardial damage. We are also trialing in healthy human volunteers the efficacy in raising blood levels of a new lipid gel formulation of CoQ_{10}.

Early clinical results from the evaluation of a new technique for harvesting and dilating the radial artery for use as a bypass graft suggest it is faster, simpler and cheaper than the standard technique.

Good preservation of the donor heart is a constant issue in heart transplantation. Variables we are testing to improve survival of donor hearts are K^+ concentration, temperature, continuous perfusion and removal of leukocytes during the reperfusion phase.

We have shown that during aging, mitochondrial DNA in the human heart progressively undergoes mutation. We are now developing techniques to quantify the extent of mutation and assess whether it correlates with contractile dysfunction and susceptibility to ischaemic stress.

Cardiovascular Nutrition

Head:

Paul Nestel AO, MD, FTSE FRACP

Professional & Technical:

Robyn Kaye RN, BEd, RM
Phillip Mottram MD
Sylvia Pomeroy BSc, RDtGradDipEd MPH

Our main objective is to identify nutrients and foods likely to prevent heart disease in Australia. To achieve this we add various nutrients to the diet of study participants, chosen because of their particular risk of heart disease, and regularly assess outcomes relevant to cardiovascular health. These include measurements of arterial compliance as an indicator of the elasticity of large arteries, and levels of the blood lipids, cholesterol and triglyceride.

We found that arterial elasticity was beneficially increased by Vitamin E supplements, and by including phyto-estrogens from soybeans or red clover in the management of menopausal complications. However, in very fat people, even a diet low in fat but high in complex carbohydrate and fibre failed to improve metabolic abnormalities unless weight loss was also a key feature.

Two studies are in progress on the effects on arterial compliance and blood lipids of two fatty acids from fish oil, and of the cholesterol-lowering drug, Simvastatin. The fatty acids are thought to be responsible for the cardioprotective properties of a diet rich in fish. A third study examines arterial function six hours after a fatty meal, the time when such meals can trigger anginal chest pains.

Cell Biology

Head:

Alex Bobik BPharm Melb MSc, PhD Syd

Scientific:

Alex Agrotis BScHons, PhD Mon

Professional & Technical:

Melanie Condron BScHons Latrobe
Peter Kanellakis BSc Mon
Gina Kostolias BScHons Latrobe

We study growth factors which control the structure of blood vessels and the changes in them due to heart disease. We aim to develop novel therapies that prevent or cure blood vessel disorders.

We have measured high expression of transforming growth factor-beta (TGF-ß), and its signaling receptors in smooth muscle cells, monocyte/macrophages and foam cells from human atherosclerotic lesions, but not in normal human arteries, indicating that TGF-ß contributes to the accumulation of cholesterol in the lesions.

We have also shown TGF-ß to be important in vessel inflammation and proliferation after intralumenal stenting. When activation of the TGF-ß system is inhibited (by tranilast) in stented porcine coronary arteries the size of the occluding neointima is greatly reduced.

The growth factors for intimal smooth muscle cells are largely unknown but we have shown that fibroblast growth factor-9 is a potent stimulator of intimal smooth muscle replication in blood vessels of experimental animals.

We have advanced our understanding

of how blood flow mediates different types of vessel remodeling during hypertension and after angioplasty and have demonstrated that epleronone, an aldosterone antagonist, can attenuate the remodeling that led to smaller vessels and restenosis after angioplasty, without affecting the size of the neointima or the injured media.

Cell Biology of Diabetes

Head:
Peter Little BPharm Vic, MSc, PhD Syd

Scientific:
Kate Hannan BSc Tas, PhD Penn State, USA

Professional & Technical:
Luke Robinson BApp Sc Mon

We study vascular smooth muscle cells (VSMC) and endothelial cells (EC) from the major blood vessels. We examine migration, proliferation and apoptosis of these cell types, which contribute to the development of atherosclerosis, particularly in relation to hyperglycaemia and the actions of anti-diabetic agents.

We have shown that one such drug, troglitazone, inhibits the proliferation of EC. At high concentrations, it activated apoptosis, or programmed cell death. We are confirming the biochemical nature of the cells classified as "apoptotic" and have initiated an in vivo study to examine the effect of troglitazone treatment on EC re-growth in rat aorta.

Sodium/hydrogen exchange (NHE) is necessary for VSMC growth, so targeting NHE may prevent the unregulated growth of VSMC, which contributes to atherosclerosis and restenosis. We are applying molecular techniques to measure mRNA for NHE and an activating protein, calcineurin homologous protein (CHP), and to express NHE and CHP for the preparation of antibodies.

A separate field of research relates to sleep apnoea and the activity of the sympathetic nervous system. We have established that the measure of urinary neurotransmitter levels is suitable for estimating sympathetic activity, and have shown a stepwise increase in activity for patients with sleep apnoea and heart failure.

Cellular Biochemistry

Head:
Liz Woodcock PhD Macquarie

Scientific:
Jane Arthur PhD Melbourne
Bing Hui Wang PhD LaTrobe

Professional & Technical:
Nancy Reyes Assoc Dip AppSc

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

Our studies aim to delineate the functional importance of inositol phosphate signalling pathways in heart muscle.

We have found evidence that the role of Gq, a coupling protein involved in the α_{1A} adrenergic receptor response, differs in mature heart cells from other cell types. Whereas Gq does not mediate inositol phosphate signalling in the heart, such signalling in other tissues is mediated by Gq and phospholipase C-ß.

In heart, activation of Gq caused inhibition of inositol phosphate metabolism, due to direct interaction between Gqα and inositol polyphosphate 1'phosphatase, indicating that both the generation of inositol phosphate signalling, and metabolism of intermediates is controlled by G proteins.

We have also investigated the involvement of α_1 adrenergic receptors in cardiac hypertrophy in vivo. The model used was transgenic mice expressing constitutively active mutant α_{1B} adrenergic receptors in heart. When subjected to thoracic aortic banding, transgenic mice showed an enhanced hypertrophic response and accelerated progression to heart failure compared to control mice. With the onset of hypertrophy, hearts from the transgenic mice had less mRNA encoding α_{1A} receptors. These findings show that α_{1B} adrenergic receptors increase hypertrophic responses in mice and that α_{1A} receptors do not appear to be involved.

Clinical Physiology

Head:
Bronwyn Kingwell BScHons, PhD Melb

Professional & Technical:
Tanya Medley BScHons VUT

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

A major aim is to evaluate the measurement of large artery

compliance, or elasticity, as a basis for stratification of cardiovascular risk. Preliminary data indicate a strong correlation between the properties of the aorta and the time to onset of coronary ischemia during a standard exercise test in patients with coronary artery disease.

We are examining the basis of arterial stiffening in people with Marfan syndrome, caused by mutations in the gene for the connective tissue protein,

fibrillin, and studying cells cultured from skin biopsies to learn whether minor variations in fibrillin contribute to arterial stiffening.

Aerobic exercise training, strength training and hormonal therapy have all been shown to modulate arterial compliance. In young, healthy individuals, aerobic training reduced arterial stiffening, but it had no effect in older patients with isolated systolic hypertension. Strength-trained athletes had stiffer arteries than sedentary controls, possibly putting them at a higher risk of cardiovascular disease. Hormonal therapy for as little as one month reduced arterial stiffening in healthy, post-menopausal women.

Continuing studies aim to elucidate the role of nitric oxide in controlling the uptake of blood glucose at rest and during exercise, particularly in patients with type II diabeties.

The Emily Stewart Molecular Endocrinology Laboratory

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

Scientific:
Hongwei Qian (from July 1998)

Professional & Technical:
Thao Pham
Luisa Pipolo AssocDipAppSc Swin

Research Students:
Felicity Chalmers BAppScHons RMIT
Natalie Job BSc Deakin
Maro Williams BScHons Mon

We study the mechanisms for hormonal control of blood pressure, including regulation of receptors for angiotensin

II, and biosynthesis of the salt-retaining hormone, aldosterone.

We showed that multiple sites of agonist-induced phosphorylation of the rat AT_{1A} receptor occur within the carboxyl-terminus, in a region previously associated with receptor internalisation. Several lines of experimental evidence confirmed a correlation between receptor internalisation and phosphorylation.

The role of protein kinase C (PKC) in the phosphorylation of AT_{1A} receptors has been studied by mutating the three putative PKC phosphorylation sites in the carboxyl-terminus of the AT_{1A} receptor and investigating its phosphorylation by AngII and TPA. All three consensus PKC sites were phosphorylated in response to AngII and TPA. We found, unexpectedly, that a 'constitutively active' AT_{1A} receptor mutant was poorly phosphorylated in the presence or absence of AngII stimulation.

We have increased by 40-fold the poorly expressed human AT_1 receptor cDNA in transfected cells by including the 5' leader sequence in the encoded mRNA, and are currently studying how this leader sequence augments receptor synthesis.

Polymorphism of the aldosterone synthase gene was found not to be associated with human hypertension, but mutations resulting in loss or gain of aldosterone synthase activity were identified.

Experimental Cardiology

Head:
Anthony Dart BA, BMBCh, DPhil Oxon FRACP

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

Professional & Technical:
Elodie Percy BScHons Melb

Research Students:
Deepak Haikerwal MBBS Mon
Xiaoming Gao MBBS Xinjiang

Our research is focused on understanding both the factors contributing to heart failure and those

which lessen its severity, using various models of the disease in test situations.

In perfused rat hearts, we have shown that the norepinephrine (NE) released under conditions of ischemia and anoxia causes arrhythmia unless inhibitors of the NE transporter are present. In reperfused hearts, the burst of NE release was accompanied by increased production of Ins(1,4,5)P_3 in the heart tissue.

Stimulation of sympathetic nerves in induced myocardial infarction and heart failure triggers ventricular tachyarrhythmias which we could prevent with ß-blockers. Similar studies in transgenic mice expressing constitutively active α_{1B} -adrenoceptors, and with low activity of the α_{1A} receptor, showed that compared with control mice, there was less Ins(1,4,5)P_3 production and less severe tachyarrhythmias, suggesting a role for the α_{1A}-adrenoceptor in mediating reperfusion arrhythmias.

To learn how NE is released under ischemic conditions, we have developed a model of CHO cells expressing the NE transporter. Under conditions where catecho-O-methyl-transferase activity, which metabolises NE, is inhibited, the transporter behaves similarly to that of neuronal preparations.

With the availability of several transgenic mouse lines overexpressing adrenergic receptors, we have developed microsurgical and cardiophysiological techniques to allow better study of the murine heart failure model.

H & L Hecht Hormones and the Vasculature Laboratory

Heads:
Paul Komesaroff BScHons, MBBS Melb, PhD Latrobe, FRACP
Krishnankutty Sudhir MBBS, PhD, FRACP, FACC

Professional & Technical:
Meryl Fullerton BSc Melb
Shanhong Ling MD China
Lisa McLennan

Research Students:
Ben Pang
Maro Williams BScHons Mon

Our major research emphasis is on defining the role of sex hormones on vascular function, both in vitro and in vivo.

We have shown that in elderly, hypogonadal men, estrogen supplementation for six weeks improved several markers of vascular health. Studies on aromatase, the enzyme that converts androgen to estrogen, include the search for activity in vascular smooth muscle cells and use of the aromatase knockout mouse model to examine the role of aromatase on the cardiovascular system.

We tested whether medroxyprogesterone acetate counteracted the protective effect of estrogen on endothelial function in post-menopausal women on HRT and found no effect, although arterial elasticity was improved.

Young diabetic women are at high risk of vascular disease and seem to lack the protective effect of estrogen. To

begin to understand why, we have studied vascular smooth muscle cell proliferation in vitro and shown that estradiol is inhibitory in normoglycemic media, but not in high glucose media.

We have developed a non-invasive technique to assess vascular reactivity with widespread applications in cardiovascular risk assessment and other areas, eg. to demonstrate variations in vascular function during the menstrual cycle in young women, and for the first time, a non-genomic response to estrogen in young men.

Human Neurotransmitter Research

Head:
Murray Esler BMedSc, MBBS Melb, PhD ANU, FRACP

Scientific:
Jacqui Hastings PhD Deakin (from August 1998)

Professional & Technical:
Janice Fulton BSc (to August 1998)
Flora Socratous BSc Latrobe
Andrea Turner (to August 1998)

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The Jo Giuliano Molecular Neurocardiology Laboratory

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The focus of the laboratory is cardiovascular neuroscience, in all its guises. The idea of stress causing heart disease, once banished to the realm of mythology, now has strong supporting evidence. To better understand the nature of the stress-heart link and to develop preventive strategies in panic disorder sufferers, we are exploring the mechanisms of cardiac risk in patients who suffer panic attacks.

Our studies on obesity-related hypertension have centred on two questions - is low activity of the sympathetic nervous system the metabolic basis for obesity? and does chronic over-eating activate the sympathetic nervous system, causing high blood pressure?

We found that in normotensive obese subjects, the noradrenaline spillover rate for whole body was normal, while that for the kidney was twice normal and spillover from the heart was 50% of normal. The main discriminating feature of obesity-related hypertension was the lack of suppressed cardiac sympathetic outflow.

Sympathetic nerves to the heart are maintained by nerve growth factor (NGF), secreted by cardiac myocytes. Based on our finding that NGF normally overflows into the coronary sinus, we initiated a study of patients with pure autonomic failure and demonstrated an absence of NGF, so providing a possible explanation for the cause of this poorly understood disease.

Our major research interest centres on the study of congestive heart failure (CHF) and the factors contributing to the pathophysiology of the condition.

We have previously shown that activity of the sympathetic nervous system is one such factor and have further explored this observation by examining the regulation of nerve growth factor (NGF), a protein responsible for the survival and function of sympathetic nerves. This year we showed that NGF is down-regulated in the failing human and rat heart, providing an explanation for a number of previously unexplained findings in CHF.

Control of the sympathetic nervous system relies on the termination of neurotransmitter action by specific transport proteins and we recently identified a novel amino acid target in the norepinephrine transporter which is regulated by nitric oxide. We also showed that the anti-arrhythmic drug amiodarone has an anti-adrenergic action, similar to that of reserpine.

The L-arginine:nitric oxide pathway is implicated as having a role in human heart failure. For the first time, we have found that, compared with healthy controls, subjects with CHF have reduced uptake of radiolabeled L-arginine in the forearm circulation.

Finally, we have studied the relationship between sleep apnoea and heart failure and identified elevated intra-cardiac pressure as being of potential importance.

Lipoprotein & Atherosclerosis

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Our research focuses on the protective function of plasma high density lipoprotein (HDL) against heart disease.

Applying molecular techniques to our cloned HDL receptor, HB_2, we have shown that its binding domain resides within 112 amino acids, proximal to the membrane spanning domain.

We have analysed the structure/function relationships of apolipoproteinA-I (apoA-I), the main ligand of HDL, by in vitro mutagenesis of the cDNA and expression of peptides in a baculovirus/insect cell system. The region found to be of most importance in the movement of cholesterol from cells lies between amino acids 140 and 150, which we are now studying in detail.

ApoA-I is formed as a prepro-peptide, for which the function of the pro segment is unknown. While pro-apoA-I and mature apoA-I have

similar activity in most biological assays, such as lipid binding or cholesterol efflux from cells, the synthesis and secretion of pro-apoA-I in the expression system was much greater. We are developing an assay for the plasma activity of the pro-apoA-I cleavage enzyme.

ApoA-I was found to markedly enhance intracellular trafficking of cholesterol to caveolae, compared with a non specific stimulator of cholesterol efflux. Also, apoA-I treatment increased the levels of caveolin mRNA by 40% and protein by 60%.

Molecular Genetics

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We have extended our studies on the role of mineralocorticoids (aldosterone) and glucocorticoids (cortisol), particularly with respect to cardiovascular function, using gene-targeting of the receptors for mineralocorticoid (MR) and glucocorticoid (GR). We are also interested in a possible role for these pathways in hypertension in humans.

In GR-deficient mice, we found no evidence of elevated blood pressure despite elevated cortisol. Levels of plasma corticosteriod binding globulin increased and the analysis of hepatic cytochrome P450 enzymes showed a different requirement for glucocorticoid activation via GR.

MR-deficient mice show normal prenatal development but die 1-2 weeks after birth due to symptoms of pseudohypoaldosteronism, unless maintained on saline. We plan to study the effects of MR deficiency on cardiac function, particularly the suggested role of aldosterone in the pathology of cardiac fibrosis.

The enzyme 11ß-hyroxysteroid dehydrogenase 2 (HSD2) is an important regulator of aldosterone and cortisol. We are developing HSD2-deficient mice to study the specific role of HSD in vivo and in 1998 introduced the CRE-recombinase/loxP targeting system to direct gene-targeting of the HSD2 gene to specific tissues. We are currently analysing 2.5 kilobases of upstream HSD2 gene sequence for the presence of enhancer elements.

Molecular Hypertension

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We study hydroxysteroid dehydrogenases enzymes, and their role in cardiovascular disease. Continuing work on the cortisol metabolising enzymes, 11ßHSD1 and 11ßHSD2, has led to the detection of cell types in the rat not previously known to express these enzymes. In particular, 11ßHSD1 was expressed in restricted cellular populations of heart, stomach, adrenal gland and blood which we are now trying to identify.

Although there is no link between the 11ßHSD2 gene and the broad population exhibiting essential hypertension, we have commenced clinical studies in a subgroup of patients with essential hypertension and abnormal mineralocorticoid activity to determine the role of 11ßHSD2.

Reports that 11ßHSD2 is present in breast cancers and may modulate the growth of some cancer cells in culture prompted our study of 11ßHSD2 protein in a tumour cell line. We found that the protein differs between the cell line and normal cells. Further

work may identify new therapeutic targets for the treatment of cancers expressing 11ßHSD2.

Last year, we identified a new enzyme, Pan2, which is highly expressed in the human heart. Studies underway on the protein and its gene should reveal whether Pan2 is associated with cardiovascular disease and is involved in other physiological processes.

Molecular Physiology

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Our research focuses on the roles of hormones and neurotransmitters in the cardiovascular system.

The molecular mechanisms of cardiac hypertrophy in response to adrenergic stimulation are under investigation in neonatal rat cardiomyocytes. We recently showed that the alpha$_{1A}$ adrenergic receptor agonist, A-61603, is sufficient to mediate the morphological, biochemical and molecular alterations in cardiomyocyte hypertrophy. The rate-limiting step in the hypertrophic response to phenylephrine is ribosomal gene transcription, which is influenced by transcription factor UBF. We have begun studies on the regulation by UBF of RNA Polymerase I activity. We are also investigating the role of the novel cardiac hormone, adrenomedullin, in regulating cardiomyocyte hypertrophy by examining its effects on various biochemical and molecular markers.

In researching mineralocorticoid and glucocorticoid action in various tissues, we have recently described a novel nuclear receptor with high affinity for 11-dehydrocorticosterone in rat colon. This area includes investigations of the accessory factors that modify intracellular mineralocorticoid and glucocorticoid receptors, and the multi-drug resistance pumps that differentially regulate steroid movement across cell membranes.

Other major interests are the effect of novel mineralocorticoid receptor antagonists on experimental hypertension, cardiac hypertrophy and cardiac fibrosis; the proteins induced by aldosterone action on its target tissues and the relationship between aldosterone, angiotensin and endothelin in cardiac fibrosis.

Molecular Signalling

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Research Students:
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We study diverse aspects of signalling, including the GTP-binding protein dynamin II, control of telomerase activity; and the roles of stress-sensitive MAP kinases in the actions of hormones and growth factors.

The function of dynamin II remains unknown. However, we have shown that dynamin II is localised to the trans-Golgi network. Lowering the dynamin II levels in mouse pituitary cells impairs the formation of secretory vesicles and the release of hormones from the cells, without affecting receptor endocytosis.

While prolonging the lifespan of cells, telomerase may, if inappropriately activated, cause tumour formation. We have described two forms of telomerase - one is phosphorylated and highly active, the other is dephosphorylated with low activity. In human breast cancer cells, protein phosphatase 2A and protein kinase Cα were found to regulate telomerase activity.

ERK, one of the MAP kinase family, is activated by TGFß and EGF in vascular smooth muscle cells of normal and spontaneously hypertensive rats (SHR). However, the activation of ERK by EGF is faster in SHR cells and is potentiated by TGFß, suggesting a possible role for ERK in the development of

hypertension. We have shown rapid, selective activation of ERK by androgen in human breast cancer cells, suggesting that the hormone regulates cell growth by a non-genetic mechanism.

Morphology and Sir Thomas Ramsey Electron Microscope Suite

Head:
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Professional & Technical:
Natalie Corlett BSc
Rosemary van Driel BSc

Our research looks at the processes regulating cardiovascular growth, particularly those which might interfere with undesirable aspects of that growth.

Novel drugs called DNAzymes targeted at specific growth factors for smooth muscle cells were found to be effective in inhibiting proliferation of these cells in culture. However, our first tests of DNAzymes on a rat model of arterial injury showed no effect on neointima formation in vivo.

With our continuing interest in how cardiac collagen synthesis is regulated, we examined the effects of heparin in a myocardial infarction model. Heparin had no influence on the size of the experimental infarct but it reduced fibroblast proliferation at the injury site and in the surrounding myocardium, suggesting that heparin may improve cardiac function long term and reduce the heart failure caused by excessive fibrosis.

Although there were no effects of receptor overexpression on cardiac function, mice that overexpress ß2 adrenergic receptors were found to have increased collagen in the left ventricle and were susceptible to substantial scarring when a constricting band was placed on the aorta to increase blood pressure.

To study cholesterol movement in cells, we have labeled apolipoprotein A-I particles with gold, and followed the time course of their entry into cells using electron microscopy.

Neuropharmacology

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We study how the central nervous system (CNS) controls the heart and circulation. Our interests include the cardiovascular actions of noradrenaline, serotonin and dopamine, the renin-angiotensin system and endothelin. A central question is how new imidazoline compounds, acting on the brain, lower blood pressure.

We have used "environmental" stress to study responses in rabbits, and the CNS pathways involved. Two such stresses are a continuous, fine jet of air to the face, or white noise, like that heard when the radio is not tuned to a station. Both caused heart rate and blood pressure to increase, but the drug rilmenidine only ameliorated changes caused by air jet stress, suggesting different central processing for different stimuli.

To model psychological stress, rats were placed in an open field. Blood pressure and heart rate recorded by an advanced telemetric method revealed increases in heart rate and blood pressure, though not if the rats were first treated with the anti-anxiety drug, diazepam.

With a new method for injection into specific sites of the brain in conscious rabbits, (to avoid interference from anaesthetics), we identified a brain region that applies a brake to increased sympathetic activity to the kidney while apparently not contributing to the resting activity.

Peptide Biology

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Our research aim is to better understand how information is transferred between the brain, endocrine and cardiovascular systems, with emphasis on the role of peptide hormones. We examine the structure

and function of peptides with cardiovascular actions and the activities of the peptidases which regulate peptide signals. One ultimate goal of our work is the design of specific peptidase inhibitors which may prove to have therapeutic value.

The enzymes expressed on the surface of vascular endothelium are of interest because they inactivate vasodilator peptides such as atrial natriuretic peptide and bradykinin. In addition, the endothelium secretes vasoconstrictor peptides and can convert angiotensin I into the active angiotensin II, another powerful vasoconstrictor.

Our research over the last year has yielded many interesting discoveries. We have developed a stable and specific inhibitor, effective both in vitro and in vivo, of the endothelial cell metalloproteases EC 3 4 24.15 and EC 3 4 24.16. We have shown by in vivo experimentation that one or both of these enzymes is crucial in bradykinin degradation and that both are secreted by endothelial cells in a calcium-dependent process.

In other studies, we have determined the 3-D structure of the peptide urocortin and elucidated the mechanism of its potent vasodilator action.

Hazel and Pip Appel Vascular Biology Laboratory

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Our research involves 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 initiate a sequence of events that results in occlusive thrombus. Both these events are mediated by the platelet adhesion receptor, the GP Ib-IX-V complex that binds von Willebrand factor (vWf).

On human GP Ib-IX-V, binding sites for vWf reside within the N-terminal 275 amino acids of the α-chain of GP Ib. Since this region differs functionally between dogs and humans, we used canine-human chimaeras of structural domains of GP Ibα stably co-expressed with human GP Ibß and GP IX in CHO cells, to show that the N-terminal 81 amino acids of the α-chain of GP Ib are important for vWf binding.

Due to its similar properties to PSGL-1, a neutrophil receptor for endothelial and platelet P-selectin, we queried whether the GP Ib-IX-V complex could also bind this ligand and so mediate platelet rolling on vascular endothelium. Cells expressing GP Ib-IX-V, but not control cells, rolled on immobilized P-selectin, and CHO cells expressing P-selectin adhered to GP Ibα suggesting that GP Ib-IX-V may serve a dual role in thrombosis by promoting platelet adhesion through both vWf and P-selectin.

Vascular Pharmacology

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Research Students:
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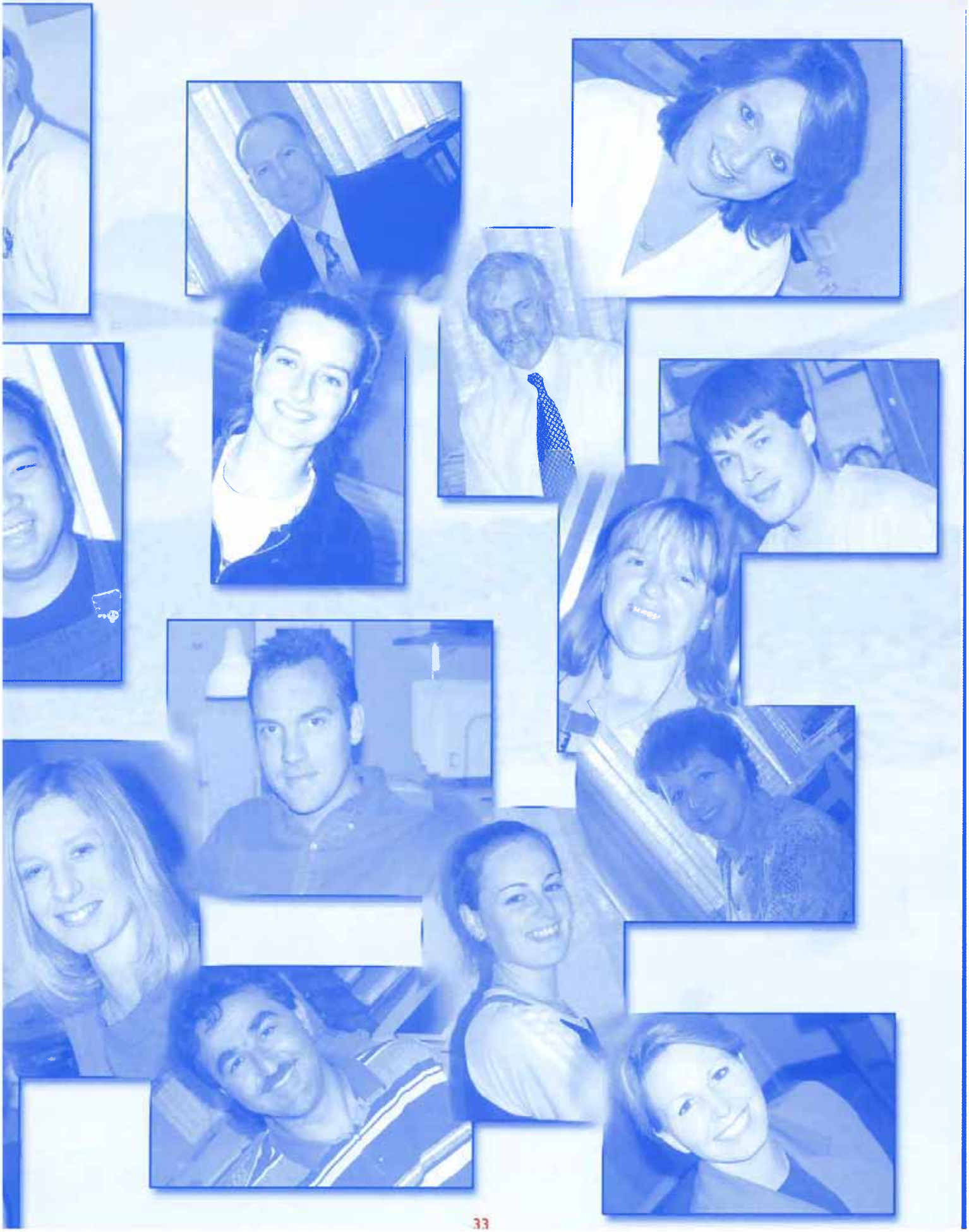
Our major research interest is endothelium-dependent relaxation. In 1998 we have extended our findings that LDL inhibits endothelial-dependent relaxation in people with high cholesterol levels, to show that VLDL, a major component in hypertriglyceridaemia, causes similar inhibition.

Heart failure in humans and experimental animals is often accompanied by abnormalities of nitric oxide (NO) signalling, although the mechanism is unknown. We believe the L-arginine transporter, y+, may play a role in the pathology and have initiated studies of the transporter. These have included measurement of L-arginine uptake in vivo in human forearm arteries and in vitro assay of [^{3}H] L-arginine uptake by isolated human mononucleocytes.

To assess whether perturbation of the L-Arg/NO pathway yields clinical outcomes, we have begun to recruit patients with congestive heart failure to a study of the effect of dietary fish

ADMINISTRATIVE & SUPPORT STAFF

ADMINISTRATIVE & SUPPORT STAFF



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(Those publications numbered in red indicate collaborations between one or more Baker laboratories)

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BAKER PUBLICATIONS (IN PRESS)

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149. **Brunner-La Rocca HP, Vaddadi G, Esler MD.** Recent insight into therapy of congestive heart failure: focus on ACE inhibition and angiotensin II antagonism. J Am Coll Cardiol (in press).

150. **Fidge NH.** High density lipoprotein receptors, binding proteins and ligands. J Lipid Res (in press).

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152. **Haikerwal D, Little P, Dart AM, Kaye DM.** Identification of a novel, inhibitory action of amiodarone on vesicular monoamine transport. J Pharmacol Exp Ther (in press).

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158. **Komesaroff PA, Murray R, Rajkumar C, Esler MD, Jennings GL, Dart AM, Funder JW, Sudhir K.** Aromatase inhibition alters vascular reactivity and arterial compliance in men: a possible vascular role for endogenous sex hormones in males. Aust N Z J Med (in press).

159. **Komesaroff PA.** Ethical implications of competition policy in health care. Med J Aust (in press).

160. **Komesaroff PA.** Ethical affairs. Fellowship Affairs (in press).

161. **Komesaroff PA.** The faces of the clinic. In: Proceedings of the sixth national conference of the Australian Bioethics Association, Hobart, Tasmania, Nov 1998 (in press).

162. **Komesaroff PA.** Complementary medicines: the case for research. Australian Doctor (in press).

163. **Lewis TV, Dart AM, Chin-Dusting JPF.** Endothelium dependent relaxation by acetylcholine is impaired in hypertriglyceridaemic humans with normal LDL cholesterol. J Am Coll Cardiol (in press).

164. **Lu L, Gatzka CD, Du X, Cameron JD, Kingwell BA, Dart AM.** Effects of heart rate on arterial compliance in men. Clin Exp Pharmacol Physiol (in press). 165. **Maiorov DM, Wilton ER, Badoer E, Petrie D, Head GA, Malpas SC.** Sympathetic response to stimulation of the A5 cell group in conscious rabbits. Brain Res (in press).

166. **Marasco S, Pepe S, Rosenfeldt FL.** Clinical application of coenzyme Q10 therapy for heart disease. Antioxidants (in press).

167. **McNally T, Berndt MC.** Antiphospholipid antibodies & thrombosis. In: Platelets, thrombosis and the vessel wall, Series: Advances in vascular biology, London: Gordon & Breach (in press).

168. **Mottram P, Shige H, Nestel P.** Vitamin E improves arterial compliance in middle-aged men and women. Atherosclerosis (in press).

169. **Nestel P.** Fish oil and cardiovascular disease: lipids and arterial function. Am J Clin Nutr (in press).

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174. **Poon J, Van den Buuse M.** Autonomic mechanisms in the acute cardiovascular effects of cocaine. Eur J Pharmacol (in press).

175. **Reid CM, Maher T, Jennings GL.** Substituting lifestyle management for pharmacological control of blood pressure in general practice: results from the HEART project. HEART Project Steering Committee (in press).

176. **Rosenfeldt FL, He GW, Buxton BB, Angus JA.** The pharmacology of coronary bypass grafts. Ann Thorac Surg (in press).

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180. **Solin P, Bergin P, Richardson M, Kaye DM, Walters EH, Naughton MT.** Raised pulmonary capillary wedge pressure is associated with central sleep apnoea in heart failure. Circulation (in press).

181. **Speed CJ, Neylon CB, Little PJ, Mitchell CA.** Regulation of inositol 1,4,5-trisphosphate-mediated calcium oscillations by the 43 kDa inositol polyphosphate 5-phosphatase. J Cell Sci (in press).

182. **Sviridov D.** Intracellular cholesterol trafficking. Histol Histopathol (in press).

183. **Thomas WG.** Regulation of angiotensin II type 1 (AT1) receptor function. Regul Pept (in press).

184. **Thomas WG.** Control of angiotensin II action through receptor regulation. In: Drugs, enzymes and receptors of the renin-angiotensin system: a century of discovery, A Husain and RM Graham eds (in press).

185. **Vranes D, Cooper ME, Dilley RJ.** Cellular mechanisms of diabetic vascular hypertrophy. Microvasc Res (in press).

186. **Waddell TK, Rajkumar C, Cameron JD, Jennings GL, Dart AM, Kingwell BA.** Withdrawal of hormonal therapy for 4 weeks decreases arterial compliance in post menopausal women. J Hypertens (in press).

187. **Ward CM, Berndt MC.** Von Willebrand factor. In: Platelets, thrombosis and the vessel wall, Series: Advances in vascular biology, London: Gordon & Breach (in press).

188. **Woodcock EA, Reyes N, Jacobsen AN, Du XJ.** Inhibition of Ins(1, 4, 5)P3 generation by endothelin-1 during post-ischaemic reperfusion: a novel anti-arrhythmic mechanism. Circulation (in press).

189. **Zhang C, Lee A, Liu VWS, Pepe S, Rosenfeldt F, Nagley P.** Mitochondrial DNA deletions in human cardiac tissue show a gross mosaic distribution. Biochem Biophys Res Commun (in press).

190. **Zhu X, Li H, Liu JP, Funder JW.** Androgen stimulates mitogen-activated protein kinase in human breast cancer cells. Mol Cell Endocrinol (in press).

CITIES VISITED BY BAKER SCIENTIFIC STAFF IN 1998

In Australia:

Adelaide, Alice Springs, Brisbane, Cairns, Canberra, Heron Island, Hobart, Laguna Keys, Lorne, Melbourne, Perth, Sydney, Surfers Paradise

In Asia and the Pacific:

Auckland, Beijing, Hong Kong, Jakarta, Manila, Shanghai, Singapore, Taipei, Kitakyushi, Osaka, Tokyo

In Europe:

Amsterdam, Athens, Barcelona, Basel, Birmingham, Bonn, Bristol, Cannes, Florence, Frankfurt, Glasgow, Heidelberg, Helsinki, Istanbul, Leeds, Leiden, London, Lubeck, Maastricht, Monte Carlo, Montpellier, Moscow, Munich, Newcastle, Nice, Nottingham, Nuremberg, Oslo, Oxford, Padova, Paris, Rhodes, Rome, Sandwich, Sunderland, Versailles, Vienna

In the Middle East:

Haifa, Jerusalem

In North America:

Atlanta, Boston, Chicago, Dallas, Durham, Houston, Lake Tahoe, Los Angeles, Miami Beach, Milwaukee, Montreal, Nashville, New Orleans, New York, Orlando, Philadelphia, Phoenix, Quebec, San Diego, San Francisco, Seattle, Toronto, Washington

Visiting Scientists at the Baker:

ABMU

Dr Jean-Phillipe Baguet (Centre Hospitalier, Universitaire De Grenoble, France (from October)
Professor Desmond Sheridan, Head, Cardiology, St Mary 's Hospital, London, UK (October - March '99)

Cell Biology

Professor Seva Tkachuk, Cardiology Research Center, Moscow (September - October)

Human Neurotransmitter

Dr Guido Grassi, Centro di Fisiologia Clinica e Research Ipertensione, Universita di Milano, Milan, Italy (July/August)

Molecular Physiology

Dr Osamu Ebisui, Kyoto University, Japan
Dr Genro Fujisawa, Jichi Medical School, Japan (from August)
Dr Yves Brandenburger, University of Geneva (from November)

Molecular Signalling

Prof. Weigang Fang, Department of Pathology, Beijing Medical University, China (January / February)
Dr. Lisa Yu, Department of Microbiology, Zengzhuo Medical School, China (May - July)

Morphology

Dr Farihah Suhaimi, (MBBS), visiting PhD student Universiti Kebangsaan Malaysia (August - December)

Vascular Biology

Assoc. Prof. Jose Lopez (MD,PhD), Baylor College of Medicine, Houston, Texas, USA (July/August)

Vascular Pharmacology

Dr Masahiko Kimura Visiting Research Fellow. Hamamatsu University School of Medicine, Japan

Board Members' Report

FOR THE YEAR ENDED 31 DECEMBER 1998

The Board of Management present their report together with the financial statements of the Institute for the year ended 31 December, 1998 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 (appointed January 1998)
Professor P Darvall
Mr W P Gurry AO
Dr P G Habersberger AM
Professor S R Holdsworth
Mr P Munz
Mrs M Ross
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 consolidated surplus of the Institute for the year amounted to $37,421 (1997:surplus $1,224,207). Income tax 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 Compliance

The Institute has established a formal Year 2000 Project Management Plan. During 1998, the Institute completed an inventory of all the scientific equipment, computer systems and infrastructure that may potentially be affected by the Year 2000 problem.

Appropriate remedies to avoid any significant Year 2000 disruption to our research activities are currently scheduled for completion prior to June 1999. Assurances of compliance are being sought from our materials suppliers and service providers in an effort to prevent disruption to our operations.

State of Affairs

Plans for the rebuilding of the Institute have been agreed and are being documented prior to the letting of contracts. It is anticipated that work should commence on the site in May 1999 with construction to commence in mid year. The projected completion date is in the fourth quarter of the year 2000.

The Capital Campaign has been progressed with the State and Commonwealth Governments each contributing $7.6m, towards a total requirement of $22.8m. Corporate and individual contributions are continuing to be received and total some $4.6m.

Events Subsequent to Balance Date

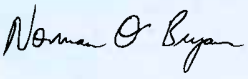
There has not arisen in the interval between the end of the financial year and the date of this report any item, transaction or event of a material and unusual nature likely, in the opinion of the Board of Management of the Institute, to affect significantly the operations of the Institute, the results 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 12th day of April 1999

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 1998

	Note	1998 $	1997 $
Consolidated Income	3	**12,026,768**	11,606,340
Consolidated Surplus for the year		**37,421**	1,224,207
Represented by:			
Deficit from Operations		**(374,869)**	(91,289)
Surplus from Capital Fund		**631,649**	1,548,673
Deficit from Specific Purpose Fund		**(219,359)**	(233,177)
Consolidated Surplus before income tax	4	**37,421**	1,224,207
Income tax attributable to surplus	2(k)	**0**	0
Consolidated Surplus after income tax		**37,421**	1,224,207
Accumulated funds at the beginning of the financial year		**7,594,851**	6,370,644
Accumulated funds at the end of the financial year		**7,632,272**	7,594,851

The accompanying notes form an integral part of these financial statements

BAKER MEDICAL RESEARCH INSTITUTE
CONSOLIDATED BALANCE SHEET AS AT 31 DECEMBER 1998

	Note	1998 $	1997 $
ASSETS			
Current Assets			
Cash		**92,927**	694,546
Receivables		**1,101,787**	506,160
Inventories		**104,574**	150,306
Prepayments		**189,930**	130,518
Accrued Interest		**69,926**	59,967
Investments (at cost)	9(a)	**3,369,171**	3,688,125
Total Current Assets		**4,928,315**	5,229,622
Non - Current Assets			
Plant & Equipment	10	**2,045,237**	1,628,816
Investments (at cost)	9(b)	**6,240,613**	6,222,931
Total Non - Current Assets		**8,285,850**	7,851,747
TOTAL ASSETS		**13,214,165**	13,081,369
LIABILITIES			
Current Liabilities			
Creditors		**522,622**	485,463
Lease Liability	2(f)	**59,532**	26,459
Prepaid Grants	11	**3,926,270**	3,948,279
Provisions	12(a)	**635,145**	619,976
Total Current Liabilities		**5,143,569**	5,080,176
Non - Current Liabilities			
Lease Liability	2(f)	**135,712**	102,872
Provisions	12(b)	**302,612**	303,470
Total Non - Current Liabilities		**438,324**	406,342
TOTAL LIABILITIES		**5,581,893**	5,486,518
NET ASSETS		**7,632,272**	7,594,851
FUNDS			
Accumulated Funds			
Operating Fund	5	**(3,911,635)**	(3,536,766)
Capital Fund	6	**9,260,632**	8,628,983
Specific Purpose Fund	7	**281,787**	501,146
Asset Revaluation Reserve - 1/1/93		**2,001,488**	2,001,488
TOTAL FUNDS	8	**7,632,272**	7,594,851

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 1998

	Note	1998 $	1997 $
Cash Flows from Consolidated Activities			
Receipts from Granting Bodies		**5,934,397**	5,408,093
Donations and Bequests		**4,375,136**	4,051,915
Payments to Suppliers & Employees		**(11,499,780)**	(10,025,934)
Dividends Received		**350,183**	312,278
Interest Received		**193,832**	304,997
General Income		**299,274**	398,607
Net Cash from Consolidated Activities	16	**(346,958)**	449,956
Cash Flows from Investing Activities			
Payment for Investment Securities		**(1,139,973)**	(4,439,058)
Proceeds from sale of Investment Securities		**1,391,085**	3,340,273
Payment for Plant & Equipment		**(798,923)**	(309,345)
Net Cash used in Investing Activities		**(547,811)**	(1,408,130)
Cash Flows from financing activities			
Principal Repayments under finance leases		**(33,760)**	(34,697)
Net Cash used in financing activities		**(33,760)**	(34,697)
Net Cash (Decrease) / Increase in cash held		**(928,529)**	(992,871)
Cash at beginning of the financial year		**4,382,671**	5,362,367
Effects of exchange rate changes on cash held in foreign currencies		**7,956**	13,175
Cash at the end of the financial year	15	**3,462,098**	4,382,671

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 1998. 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 transactions have 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 land and building occupied by the Institute is not included as an asset as the Institute does not have title to the property. The estimated replacement cost of this building is $13m.

(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 settled within 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 bank accounts in the USA and UK 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) Year 2000 software modification costs

Costs relating to the modification of computer software for year 2000 compatibility are charged as expenses when incurred.

(o) 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.

(p) Comparative figures

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

3. Consolidated Income

	1998 $	1997 $
Grants:		
Government and Statutory Bodies	**5,938,270**	5,609,440
Baker Foundation	**1,050,000**	1,050,000
Other Income:		
Fundraising, Corporate & Private Support	**3,925,965**	3,080,263
Dividends Received / Receivable	**320,973**	322,723
Interest Received / Receivable	**194,792**	277,242
Foreign exchange gain	**7,956**	13,175
Proceeds from sale of non-current assets	**276,039**	908,149
General Income	**312,773**	345,348
	12,026,768	11,606,340

4. Consolidated Surplus

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

Credits		
Dividend revenue	**320,973**	322,723
Interest revenue	**194,792**	277,242
Net gain on disposal of non-current assets	**276,039**	908,149
Foreign exchange gain	**7,956**	13,175
Charges		
Borrowing costs		
Finance charges relating to finance leases	**50,410**	55,278
Less: Amount capitalised	**(33,760)**	(34,697)
Borrowing costs expensed	**16,650**	20,581
Depreciation - Plant and Equipment	**441,928**	461,980
Amortisation - Motor Vehicles under finance lease	**47,493**	50,260
Write down of inventories to net realisable value	**45,732**	0
Employee Entitlements	**19,407**	(76,434)
Rental expense relating to operating leases	**259,241**	183,698

5. Operating Fund

Balance at beginning of year	**(3,536,766)**	(3,445,477)
Deficit for year	**(374,869)**	(91,289)
Balance at end of year	**(3,911,635)**	(3,536,766)

6. Capital Fund

The Institute's Capital fund comprises the capital 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. From time to time the Institute is the beneficiary under various wills and trust agreements. Such bequests and legacies are an unpredictable source of income each year. The current balance is:

Balance at beginning of year	**8,628,983**	7,080,310
Surplus for year	**631,649**	1,548,673
Balance at end of year	**9,260,632**	8,628,983

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:

	1998 $	1997 $
Balance at beginning of year	**501,146**	734,323
Deficit for year	**(219,359)**	(233,177)
Balance at end of year	**281,787**	501,146

8. Fund Balances

Balance at 1 January 1998	**7,594,851**	6,370,644
Surplus / (Deficit) for year -		
Operating Fund	**(374,869)**	(91,289)
Capital Fund	**631,649**	1,548,673
Specific Purpose Fund	**(219,359)**	(233,177)
	37,421	1,224,207
Balance at 31 December 1998	**7,632,272**	7,594,851

9. Investments (at cost)

(a) Current		
Short term deposits	**3,369,171**	3,688,125
Total Current Investments	**3,369,171**	3,688,125
(b) Non - Current		
Shares and Debentures	**6,175,580**	6,157,898
Trust Units	**65,033**	65,033
Total Non - Current Investments	**6,240,613**	6,222,931
Total Investments	**9,609,784**	9,911,056

The Institute's investments are shown at cost. As at the 31 December 1998 the market value of the Institute's non-current investments was $8,677,565 (1997: $7,894,465)

10. Plant and Equipment

Plant and Equipment (at cost or Board's valuation)	**4,825,809**	4,026,886
Less: Accumulated Depreciation	**2,940,575**	2,498,647
	1,885,234	1,528,239
Motor Vehicles under finance leases	**277,561**	194,814
Less: Accumulated Amortisation	**117,558**	94,237
	160,003	100,577
Total Plant and Equipment	**2,045,237**	1,628,816

11. Prepaid Grants

Prepaid Grants include capital works grants of $3.6m received from the Federal Government for the redevelopment of the Institute. In accordance with our accounting practices, income and expenditure associated with the redevelopment project will be brought to account in the period to which they relate.

	1998 $	1997 $
Prepaid Grants	**3,926,270**	3,948,279

12. Provisions

(a) Current		
Annual Leave	**341,701**	397,295
Long Service Leave	**293,444**	222,681
Total Current Provisions	**635,145**	619,976
(b) Non - Current		
Long Service Leave	**230,559**	226,321
Deferred Maintenance	**72,053**	77,149
Total Non - Current Provisions	**302,612**	303,470
Total Provisions	**937,757**	923,446

13. Commitments

Finance Lease Commitments		
Finance Lease Commitments are payable as follows:		
Not later than 1 year	**77,034**	41,798
Later than 1 year and not later than 2 years	**57,406**	61,150
Later than 2 years and not later than 5 years	**100,884**	62,455
Minimum lease payments	**235,324**	165,403
Less: Future lease charges	**(40,080)**	(36,072)
Provided for in accounts	**195,244**	129,331
Representing lease liabilities:		
Current lease liability	**59,532**	26,459
Non-current liability	**135,712**	102,872
	195,244	129,331

14. 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 1998 are:

Mr N O'Bryan	Mr S Blair (from Jan '98)	Professor S Holdsworth
Dr G P Johnston	Mr K Courtney (until Jan '98)	Mr P Munz
Mr R E Barker	Professor P Darvall	Mrs M Ross
Professor J W Funder AO	Mr W P Gurry AO	Professor R Smallwood AO
Mr P C Barnett	Dr P G Habersberger AM	

(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.

15. 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:

	1998	1997
	$	$
Cash	**92,927**	694,546
Deposits at call	**3,369,171**	3,688,125
Total	**3,462,098**	4,382,671

16. Reconciliation of Surplus to Net Cash from Consolidated Activities

Operating Surplus from Consolidated Activities	**37,421**	1,224,207
Effects of exchange rate changes on cash held in foreign currencies	**(7,956)**	(13,175)
Depreciation and Amortisation	**489,421**	512,240
Net assets disposed of	**0**	0
(Profit) on sale of non-current assets	**(276,039)**	(908,149)
Changes in net assets and liabilities		
(Increase) in debtors	**(595,627)**	(291,387)
Decrease in inventories	**45,732**	9,225
(Increase) in prepayments	**(59,412)**	(11,476)
(Increase) / Decrease in accrued interest	**(9,959)**	21,652
Increase / (Decrease) in creditors	**37,159**	(1,197)
(Decrease) / Increase in prepaid grants	**(22,009)**	46,345
Increase / (Decrease) in provisions	**14,311**	(138,329)
Net cash from consolidated activities	**(346,958)**	449,956

17. Non-cash Financing Activities

Motor Vehicles

During the year the Institute provided motor vehicles for staff under salary sacrifice arrangements with a value of $277,561 by means of finance leases. These acquisitions are not reflected in the statement of cash flows.

18. 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.

BAKER MEDICAL RESEARCH INSTITUTE
BOARD MEMBERS' DECLARATION

The Board Members declare that the financial statements and notes set out on pages 45 to 53:

(a) comply with Accounting Standards, 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 1998 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
12th April 1999

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 1998 as set out on pages 45 to 53.
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 presented by the results of its operations and its cash flows.

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

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 1998 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

Melbourne
12 April 1999

Major Donors 1998

The Institute is grateful for major contributions to its research from:

National Health & Medical Research Council of Australia
Baker Foundation
Victorian Government
National Heart Foundation
Victorian Health Promotion Foundation
Australian Research Council
High Blood Pressure Research Council Inc.
Foundation for High Blood Pressure Research
National Institutes of Health (USA)

Corporate

AMRAD
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Project Support

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Capital Appeal (since inception)

Alfred Healthcare Group
Amcor Limited
Arthur Robinson & Hedderwicks
Baker Foundation
Baker Medical Research Staff
Barker, Mr R
Beaurepaire, Dame Beryl
Burke MLA, Ms L T
Commonwealth Bank of Australia
Commonwealth Government
Crennan QC, Ms Susan
Dickson, Mrs L C
Funder AO, Professor J W
GSA Group Pty Ltd
Gurry AO, Mr W P
Habersberger AO, Mr J
Habersberger AM, Dr P G
Hogarth OAM, Mr D F & Mrs M
J B Were & Son Charitable Fund
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Johnston, Dr & Mrs G P
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Murdoch AC, DBE, Dame Elisabeth
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National Foods Limited
National Mutual Life Assn. of Australasia Ltd
O'Bryan, Mr N J
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Philip AM, Mr W G
Roche Bros Pty Ltd
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TAC Insurance
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Bakers Dozen (Capital Campaign)

Greenfield, Mr Henry
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Sydney Myer Fund
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Baker Institute Research Foundation (Founding Members)

GSA Group Pty Ltd
Gurry AO, Mr W P
Kodak (Australasia) Pty Ltd
O'Bryan, Mr N J
Ross, Mrs M S

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Ruby Wallace Travelling Fellowship
Joe White Bequest

Bequests

Estate Lindsay J Baldy
Estate Joan Henderson
Estate Barbara Roche
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Estate Anna Maria White
Estate Morris G White
Estate Philip F Woods

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Ray Shrimpton Memorial Travel Scholarship
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Miller Foundation
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Mornington Vineyards Estate
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Phillip Murphy Wines & Spirits
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Radio 3LO - John Faine Program
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Red Hill Estate
Rosemount Estate Pty Ltd
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Sally Browne's Life Shop
Schiaparelli
Scusa Mi Restaurant
Simply Sensational Catering & Events
Smorgon Steel Group
SPHC Group - Park Royal Surfers Paradise
Tattersall's
Temenos
T'Gallant Winemakers
The Australian Open
The Big Duck & Fish Company
The Colonial Tramcar Restaurant
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Thinking Partners
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Wilderness Wear Australia
Warburg Dillon Read Aust. Pty Ltd
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Bertalli, Mr N
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Westfold, Prof K C
Whatmough, Mrs P
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Williams, Mrs G E
Woolfe, Mr K

Certificates of Appreciation

In addition to the various Charitable Trusts, Foundations and Estates listed in the 1997 annual report a Certificate of Appreciation was also presented to the following at the 1998 Annual General Meeting.

Percy Baxter Charitable Trust
H & L Hecht Trust
Garnett Passe & Rodney Williams Memorial Foundation
William Buckland Research Fund
Grosvenor Settlement
Harbig Charitable Foundation
Berkowitz, Mr L
Burgesson, Mr & Mrs J E & B C
Davidovski, Mr Tony
Dawson, Miss N
Duffield, Miss J D
Drummond, Mrs N
Garner AM, Mr E L
Golden, Mrs A J
Haylock, Mr R
Hicks, Mrs I L
Hornung, Mrs R
Jones, Dr & Mrs F C
Lipscombe, Mr G J
McDonald, Mrs M
Maggs, Mrs P L
Miller, Mr G F
Monotti, Mr I
Nash, Mr G D
Newton, Dr D B
Niven, Mr J
Potter, Miss L M
Rofe, Mr & Mrs R L & J C
Rowland, Mrs V
Sablyak, Mrs P
Shaw, Miss J M
Templeman, Mrs E C
Teskey, Mr B D
Tumney, Mr S B
Wellington, Mrs P

In Memory of :	From:
Archer, Dorothy	Mrs H D Raw
Ashworth, Phyllis G	Mrs N W Prentice
Austin, Keith	Mrs S Scott
Baker, Powell	Mr & Mrs O & H Gara
Baker, Powell	Mrs I Dixon
Bank-Smith, Valda	Mr & Mrs G & S Lowe
Beck, William	Miss R A Middleton
Bentley, Isobel A	Mr & Mrs T J & E E Williams
Bentley, Isobel Ann	Anonymous
Bentley, Isobel Ann	Mr & Mrs J R & Y M Hull
Bentley, Isobel Ann	Mr & Mrs R & F Bentley
Bentley, Isobel Ann	Mr A Barrow
Bentley, Isobel Ann	Mrs A Kahrau
Bentley, Isobel Ann	Mrs P M Saville
Bentley, Isobel	Mr & Mrs G F Anderseon
Bentley, Isobel	Mr & Mrs R & G Grimshaw
Bentley, Isobel	Mrs J Cream
Blair, Lorna	Mr D S Blair
Brewer, Dorothy	Mrs A Collins
Brewer, Dorothy	Mrs J James
Buck, Margaret	Miss G M Collins
Burnham, Myrtle	Mrs I L Hicks
Butler, John	Dr & Mrs H C Barnes
Cameron, June Beryl	Mrs J A Dyke
Carmen, Mr T	2/14th Field Regt Association
Chambers, David	Mrs W C Chambers
Davies, Reggie	Mrs J Duncan
Di Rago, Mario	Mrs Y L Camera
Drane, Margaret	Mr J Drane & Family
Duncan, Ian	Mrs J Duncan
Dunlop, Leslie R	Mrs E & Miss B Knight
Dunstan, Noel	Mr & Mrs A & C Holper
Erlandsen, Elaine	Mr H C Trinick
Evans, Alan Rae	Mrs F J Evans
Finger, Arthur	2/14th Field Regt Association
Fozard, Ernie	Mrs L Herrmann
Funder, Kathleen (Kate)	Prof B Chertow
Funder, Kathleen	Mr J Schwartz
Gavin, John	2/14th Field Regt Association
Hawkes, Verna Forrest	Mrs J Hawkes
Hewat, Mr D	2/14th Field Regt Assoc
Hocking, Phyllis	Mr N Hamilton
Jackson, Mr R	2/14th Field Regt Association
Kemp, Phyllis & Sidney	Mrs C H Holper
Kidd, Jean	Mr & Mrs G & J Davenport
Knight, Emily Millicent	Miss H M Amies
Knight, Emily Millicent	Mr & Mrs K & M Blue
Knight, Emily Millicent	Mr & Mrs W J & M Hughes
Knight, Emily Millicent	Mrs M J Tabuteau
Ladd, Clarence J (Clarrie)	Mrs B S Gardiner
Ladd, Clarence J	Mrs E S Thomas
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Nash, John William	Miss E I S McKellar
Newton, Molly (Mary)	Mrs E E Anderson
Orde, Alison	Miss J A Macdonald
Portwine, Mr R	2/14th Field Regt Association
Richardson, Elizabeth Joan	Mr & Mrs D & A Doig
Rossi, Mrs N	2/14th Field Regt Association
Satcunan, Mr	Mrs M P Satcunan
Saunders, Mr R	2/14th Field Regt Association

In Memory of :	From:
Scott, Max	Mr S Scott
Scott, Max	Mrs E Easy
Scott, Max	Mrs M E Cox
Scott, Maxwell	Ms G Stringer
Scott, R M (Max)	Mr J Holzer
Scott, Richard Max	Mr & Mrs R Martell
Short, Danielle	Mr & Mrs D & A Doig
Skinner, Clive	Miss J A Macdonald
Sorrell, John Grantley	Mr & Mrs D & A Doig
Spicer, Ern	Mrs W Chambers
Stevens, Mr T N D	Mr & Mrs J & D Habersberger
Stone, Frank	Mrs P Sablyak
Strong, Neville	Mr & Mrs H & M Loewe
Sutcliffe, Dorothy	Mrs E J Meier
Theodore, Mr A	2/14th Field Regt Assoc
Thiele, Mrs M	Mrs P L Maggs
Treadwell, Gwen	Mr & Mrs M D & M R Treadwell
Tripodi, John	Catholic Regional College Traralgon
Tripodi, John	Peel Street Friends
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Tubbs, Keith John (Butch)	Mr & Mrs D & L Baker
Tubbs, Keith John (Butch)	Mrs J Leslie
Tubbs, Keith John (Butch)	Ms A Bennett
Tubbs, Keith John	Mr & Mrs F & B Parish
Tubbs, Keith John	Mr & Mrs R & R Parish
Waters, Mary Huntly	Mr & Mrs J & M Netherway
Waters, Mary Huntly	Mr & Mrs K & J Baird
Waters, Mary Huntly	Mr & Mrs K & R Balmaks
Waters, Mary Huntly	Mr & Mrs P & S Lovell
Waters, Mary Huntly	Mr D Walker
Waters, Mary Huntly	Mr/Ms D Jung
Waters, Mary Huntly	Mrs E Waters
Waters, Mary Huntly	Mrs P M Tuxen, Ms P Neville, Ms M Mansell
Waters, Mary Huntly	Mrs V Murphy
Waters, Mary Huntly	Ms L Baker
Waters, Mary Huntly	Ms M W Petherick
Waters, Mary Huntly	St George's Uniting Church
Waters, Mary	Mrs J Speirs
Webb, Mr M J	2/14th Field Regt Association
Wheat, Mr R	2/14th Field Regt Assoc
Wighton, Cecilia May	Mr & Mrs J G & G M Dawe
Wrigley, Mrs S	Mr & Mrs K W Joyce

Donations in lieu of gifts

To celebrate the following occasions:

50th Wedding Anniversary of Ivan & Maisie Dudakov from Aviva & Harry Stillman.

80th birthday of Mrs Alice Meyer from Alan Barrow

Birthday of John Eisner from Ivan & Maisie Dudakov

We gratefully acknowledge the very considerable support of many donors who have made smaller but equally valuable contributions to our work, some over a period of many years.

How You Can Support Medical Research at the Baker Institute

The Baker Medical Research Institute relies on non-government sources - including donations from members of the public - for a substantial part of its operating income.

The Institute enjoys an international reputation for the high quality of its basic and applied research into the causes of cardiovascular disease (in particular hypertension and atherosclerosis). It is an established centre for training in medical research, providing post-graduate education, and on-the-job training in specialised laboratory techniques.

Use of Donated Funds

All donations are used to support the Institute's medical research program, and in particular to assist with the purchase of equipment and laboratory supplies. Donations are not directed towards administrative costs, nor are they used to support our fund-raising activities.

Tax Deductibility

All donations over $2 to this Institute are tax deductible.

Specific Purpose Donations

We will be pleased to honour a request that your donation be applied to a particular area of research, a specialist piece of equipment, or used for a purpose which is consistent with our objectives as a research and teaching institute (for example, to establish a student scholarship, post-graduate scholarship).

Acknowledgement

All donations are acknowledged by letter, and those of $1,000 and over are listed in the pages of this Report. There may be other suitable ways to acknowledge your generosity - we will be pleased to discuss the options with you.

How to support the Baker Institute

There are a number of ways in which you can support our research effort. Some of these are listed below. Depending on the size and nature of your donation, it may be in your interest to obtain professional advice concerning taxation, probate and other financial matters. In these circumstances, we suggest that you discuss your situation with your solicitor, accountant or financial advisor.

Types of support

Donation

Remember that all amounts over $2 are tax-deductible.

Bequest

We prefer to invest amounts in excess of $10,000, and use the income. Your directions are welcome. See below for a suggested form of words for a bequest.

Gift of Assets or Property

Some donors elect to transfer property to the Institute, while retaining its use during their lifetime.

Trust or Named Fund

This option may be of interest to Trustees of existing Trusts, as well as to individual donors. A donor may elect to establish a fund by instalments.

We appreciate all donations - small or large, and we value our association with donors throughout Australia and overseas.

Should you have any enquiries, please do not hesitate to contact Bobbie Renard in our Community Relations Department: Telephone: (03) 9522 4333.

Mailing Address for all Donations:

The Baker Medical Research Institute
PO Box 6492 St Kilda Road Central
Melbourne 8008 Vic. Australia

All cheques should be made payable to the Baker Institute.

Wording of a conventional bequest:

"I give and bequeath (free of all duties) to the Baker Medical Research Institute, Commercial Road Prahran, in the State of Victoria, the sum of $..... or, ...% of my residuary Estate or, the whole of my residuary Estate to be applied for the general purposes of the said Institute and I declare that the receipt of the proper Officer for the time being of the Institute shall be full and sufficient release and discharge to my Trustee for the same".

ORGANISATIONAL CHART

DIRECTORY

Auditor

PricewaterhouseCoopers
333 Collins Street, Melbourne, Vic. 3000

Solicitors

Blake Dawson Waldron
101 Collins Street, Melbourne, Vic. 3001

Annual General Meeting

Monday 10th May
Baker Medical Research Institute
5.00pm

Baker Medical Research Institute

P.O. Box 6492 St Kilda Road Central
Melbourne 8008 Australia
Telephone: (03) 9522 4333