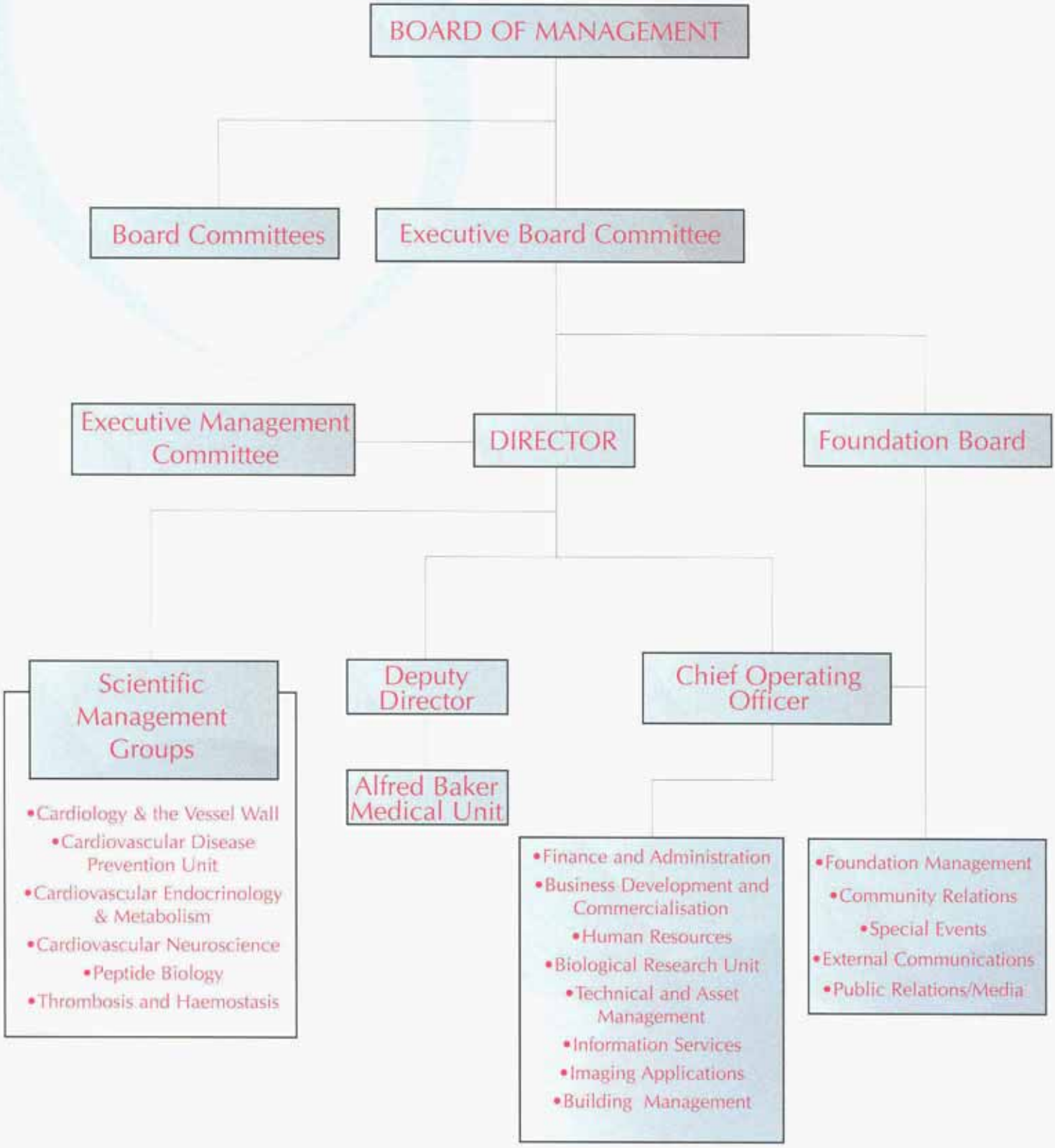
BAKER MEDICAL RESEARCH INSTITUTE

ANNUAL REPORT 2000

Organisational Chart



Whether you are a millenarian or not, the year 2000 was a very exciting one from the Baker's point of view.

First, the Federal Government adopted and confirmed the key recommendations of the Wills Committee (on which Professor John Funder served) which will see an effective doubling of the amount of money which the Federal Government devotes to medical research over the next five years. Whilst this will mean the end of block-funding to institutes in the NHMRC system, the Baker warmly welcomes the increased funding and expects that its world best research will attract an increased level of NHMRC funding, which is surely needed. There were many highlights in the past year. Here are a few of them.

Prestigious Prize To Professor Murray Esler

Adding to his impressive list of prizes for medical research, Murray Esler received the prestigious Merck Sharp and Dohme International Award given to a scientist who has made an important contribution to our knowledge of human hypertension, at the International Society of Hypertension conference in Chicago last August. In receiving his "big gold medal" and $US10,000 prize money, Murray joins the former director of the Baker Institute, Prof Paul Korner, as two of only four Australians who have won the award. Murray's research has shown that the most common non-drug treatments for hypertension, namely restriction of calories in the diet and exercise, work by inhibiting the sympathetic nervous system.

Stress Hormone Research Challenges Long-held Beliefs

The so-called 'impact factor' of a journal doesn't come much higher than that of *Immunity*, in which Tim Cole and his PhD student, Jared Purton recently published an important paper. With collaborators at the Monash Medical School, they used Tim's 'knockout mouse' (which is unable to respond to an important stress hormone) to show that immune cells from the thymus were normal. These findings challenged current thinking. But importantly they also showed that stress, which is known to affect the heart and blood vessels, does not interfere with the developing thymus, which is an important component of the immune system. Jared's work earned him the Institute's Rod Andrew Prize for the presentation of research by a 2nd or 3rd year PhD student.

Special Thanks

Bobbie Renard and members of the Community Relations department have had a very successful year in attracting bequests to the Institute, which itself originated from a private bequest 75 years ago. Community Relations is continuing the tradition of inviting supporters to bequeath a portion of their estates to the Baker in their wills. Income from bequests goes into the Baker Capital Fund which is invested to ensure the continuing strength of the Institute, unless donors direct their gift to a particular project. The Baker's bequest program has grown through increased personal contact with interested individuals. Bobbie stresses that all donations, whether by bequest or regular contribution, are greatly appreciated, both by her team and the Institute as a whole.

Support Therapy For The Failing Heart

You may wonder what a vet with a PhD is doing at the Baker. If the vet is John Power, the answer is "making an innovative contribution to the treatment of heart failure". John had the idea of providing physical support to the left ventricle of the heart to see if it would halt the chain of damaging events that ends in heart failure. His solution was to wrap the ventricles in a 'cardiac support device' made of special woven polyester, a bit like a support stocking. The results were dramatic. Within a month, the progress toward damage ceased and heart function improved. Feasibility of the treatment for use in humans has now been established and larger trials are about to begin in the USA and Germany.

The End Is In Sight

It's impossible to travel down Commercial Road without noticing our impressive new edifice rising opposite Fawkner Park. The group of buildings is the Alfred Medical Research and Education Precinct, or AMREP, and represent a unique partnership between the Baker Institute, the Macfarlane Burnet Centre for Medical Research, Monash University Medical Faculty and the Alfred Hospital Bayside Network.

When construction is completed in mid-2001, Baker scientists will finally escape their cramped and unsatisfactory conditions at the existing site, and even have the luxury of room for expansion. The Baker Tower, which is nearly finished, will be eight levels of mainly research space. A generous (anonymous) donation has meant that the East (MacFarlane Burnet) Tower is now also set for completion, offering the Baker two additional floors for future expansion.

News On Nerves And Heart Failure

David Kaye and his colleagues have shown for the first time that people with heart failure have lower levels than healthy people of a factor called NGF, which controls the growth of nerves. These findings

could explain why nerves to the failing heart are switched on all of the time, instead of responding only when needed to help pump more blood from the heart, such as during exercise. David's work appeared during 2000 as an 'ultra rapid publication' in *Circulation Research*, a leading journal in the field. NGF also helps to remove active chemicals released from nerve endings, so less NGF in heart failure means fewer nerve endings, but persistence of active chemicals.

The Baker's Singapore Connection

Jaye Chin-Dusting was the prime mover in establishing the Baker Singapore Medical Unit with the National Heart Centre at the Singapore General Hospital. She recently visited the new unit and is very pleased with progress since Ian Codreanu began setting up the laboratory in August. Patient recruitment is about to begin for two studies: the effect of omega-3 fatty acids in patients with heart failure and the effect of medications to treat high blood pressure on the elasticity of vessels. Jaye's colleagues will have the opportunity to study heart disease in a population from a gene pool different to that in Australia and will also contribute to the local Singaporean knowledge of cardiovascular research.

Leading Research Into How Thrombosis Occurs

Working with national and international colleagues, Michael Berndt and his team in The Hazel & Pip Appel Vascular Biology Laboratory published some important observations about how blood clots form. This process, called thrombosis, is an acute form of cardiovascular disease in which specialised blood particles called platelets aggregrate to form a mass which blocks the supply of blood to tissues. Amongst other causes, the high shear stresses experienced by cells in arteries with atherosclerosis can trigger thrombosis. The Berndt laboratory researchers have described in molecular detail the important features of the molecules which initiate the formation of a thrombus. In other collaborative studies, they have identified a receptor on platelets which enables the interaction between white blood cells which can promote inflammation of blood vessels in some disease states.

New Drugs On The Horizon.

Ian Smith was awarded an R & D START grant for his work on novel compounds to treat a source of damage to the brain, triggered by stroke. Now entering the third and final year of the grant, the Smith laboratory and its collaborators in the project are yielding some very strong and exciting science. Ian and his colleagues have described a compound which successfully inhibits the target enzyme in the 'test tube' situation. The next 12 months should see the development of modified compounds suitable for testing in animal models. Meanwhile, the research has led to a number of publications, invitations to write review articles and presentations overseas, at Leeds, Oxford, Montpellier and Copenhagen.

Thanks And Praise

Of course, none of these achievements could be made without the help and support of so many other people. My thanks go first and foremost to Professor John Funder who completed his 10th year as Director of the Institute at the end of 2000. John has been a tower of strength both within and outside the Institute as one of the iconic figures of Australian medical research and we are both proud and pleased that he continues to lead the Baker.

The Board of the Institute has also worked tirelessly in its interests throughout the year. I am very grateful for the work which all of the Board members voluntarily put into the Institute and know that they derive great pleasure from its productivity and achievements. Early in 2001 our longest serving Board member, Margaret Ross, was honoured by membership in the Order of Australia and her citation expressly referred to her marvellous efforts as a member of the Baker's Board of management over such a long period. Both Margaret and Peter Barnett announced their retirement from the Board early this year, but both have agreed to go on to the Board of the Baker Foundation, about which you will hear much more during the coming months. The Board eagerly anticipates the Foundation as a means to endow the Baker for the future and to ensure its continuing success and productivity.

The Baker also has a new Chief Operating Officer, Peter Hughes, who joined the Institute at the end of 2000 to lead an exciting process of change through all of the non-research areas of the Institute. The Baker family welcomes Peter and looks forward to his guidance and direction in the management of its affairs. Once again my thanks go to all of those donors, contributors and volunteers without whom the Baker simply could not continue in its current shape or form.

Thanks to you all for your sterling efforts and I look forward to greeting you personally in the new building at its opening later in 2001.

Norman O'Bryan

Norman O'Bryan

President
BMRI Board

Director's Report

For those of us who remember the monthly Y2K countdown procedures, reporting on readiness, sign off by one of the Big Six, the Year 2000 dawned with not even a whimper. We had been predicted utter confusion, and the worst we got was the telephones going out for a few hours in Uttar Pradesh. A year down the track and Y2K manuals already have the quaint iconic status of 1950's backyard bomb shelters in middle America, testaments to distressed mining engineers, distressed computer folk alike. Plus ça change, plus la même chose.

For the Baker, the Year 2000 was one of change in a number of ways. In January 2000 rebuilding had started, on a seven-storey Baker tower and a three-storey building for the Macfarlane Burnet Centre, both backing onto two floors of Monash laboratories over a basement library serving Alfred/Baker/MBC/Monash. By December 2000 we had a seven-storey Baker tower, and an MBC building also going up seven floors, shared between the four precinct partners.

This dramatic transformation came about largely thanks to Garry Jennings, the Deputy Director of the Institute and Director of the Alfred and Baker Medical Unit. Through his representations our anonymous donor, whose generosity had allowed us to take the Baker tower from five to seven floors, gave us another $20m towards completing the precinct. His generosity has substantially advantaged all those involved, and to Garry Jennings we all owe a substantial debt of thanks.

As the rebuilding project gathers pace, new and (for the Institute) very important questions come into focus, in terms of the nature of partnerships and joint ventures. The difference between engagement and commitment is sometimes illustrated by the classic English breakfast of bacon and eggs, a process in which the hen is engaged but to which the pig is committed. Monash and Alfred are engaged, in this sense; Baker and MBC are committed. Monash has a Council, and Bayside Health (Alfred), MBC and Baker have Boards of Management: how can they, and to what extent should they, devolve decision-making power to the joint venture? How can Baker and MBC preserve and if possible increase their particular identities, as part of a joint venture with institutionally much larger partners? There are no simple answers, and over the second half of the year in particular I spent hours and days in discussions with our precinct partners on these issues.

One of the things that has emerged (from the ground, rather than these discussions) over the course of the year was the seven-storey Baker tower. By December 2000 it was essentially externally complete, but with another six or seven months to fit out and commission. From the initial concept of how it would look through the architects' model it was going to be a love it or hate it building. In the flesh, so to speak, it looks terrific. You can see it across Fawkner Park from any south-facing window in a city high-rise building, a source of considerable satisfaction during 46th floor meetings, for example...

One of the other areas of change in 2000 was the way we are to be funded by NHMRC. In 1968 the Walter and Eliza Hall Institute was 'block-funded', given a bundle of money for the next five years' research, and told to get on with it. The Howard Florey followed in 1972, and the Baker under Paul Korner and Paul Nestel went into block funding mode a decade later. Starting in 2001, over a three-year period, the now six block-funded institutes will be unbundled, on balance to our great relief.

If this sounds counterintuitive (...why not just take the bundle of money?) it needs to be set in context, and that context was noncompetitive even well before Alan Fels. Block-funded institutes were reviewed every five years, and normally awarded very small increments; most importantly, those who worked in such institutes – even when their support was not from block funding – were denied the chance to bid for NHMRC project or program grant funding. The Wills report, adopted by the Commonwealth, put in place a doubling in NHMRC funds over five years, 2001-2006. What is often

forgotten is that NHMRC funding in constant dollar terms doubled once before, but over ten years from 1983 to 1993 - and the block-funded institutes came nowhere near doubling their share. In the early 1980s the three block-funded institutes received just over 20% of the total NHMRC funding: 15 years later, with six institutes, the figure is 16%, hardly an incentive for critical mass or long-term scientific programs.

Over the course of the year the procedures and processes for unbundling took shape. The Institute has been coalescing our various laboratories into half a dozen programs, a very neat fit for unbundling. By year's end two Baker program grant applications had been written —one headed by Murray Esler, including Geoff Head, David Kaye and Gavin Lambert, and the other by Michael Berndt and Rob Andrews. The Berndt program is part of an alliance with groups in Sydney and Canberra, each bringing complementary skills and interests into a whole designed to be more than the sum of its parts, which I guess is not a bad institutional definition of synergy.

In the light of our new building to be ready mid-2001, we have also entered into discussions with a number of other investigators and groups about their possibly joining the Baker: the good part about unbundling is that this can now happen, and nobody is precluded from applying for NHMRC funds if they work at a previously block-funded institute. Some of these discussions are continuing: one, for part of the Christchurch Cardioendocrine Group to move to the Baker in 2002, was overtaken by the elegantly termed 'retention package' offered to our New Zealand colleagues for 2001-2003. Despite their being in Christchurch, relations have bloomed, and now we have five areas of collaboration across the Tasman, testimony to silver linings.

At the end of 1999 we farewelled Stella Clark, who for three years had been Scientific Executive Officer. Stella had made an outstanding contribution to the Baker over her time at the Institute, perhaps most notably in terms of doubling the number of students, and mentoring them over the course of their studies. In recognition of this capacity, Stella was head-hunted to the position of General Manager of the Graduate School at Melbourne University, but remains very much in touch with many of her former colleagues: only in a formal sense, then, Vale.

For every Vale there is an Ave, in the words of the gladiators addressed to the Emperor (Ave atque vale: morituri te salutant: Hail and farewell, we who are about to die salute you). Early in 2000 we welcomed Rob Stewart on board as a limited term, part-time Chief Operating Officer. Rob had recently 'retired' as Managing Partner at Minters, and become inter alia the Chair of Melbourne IT. His expertise, drive, and sense of humour have been a Godsend; more than anyone else, Rob has taken our hardworking but under-resourced administrative and support staff structures in hand, and transformed them. In December 2000 Peter Hughes was appointed as full time C.O.O., with the remit to continue the processes Rob set in train. We should move into the new building with a full head of steam, and with an efficient and properly-resourced administration to support and promote the work of our scientists.

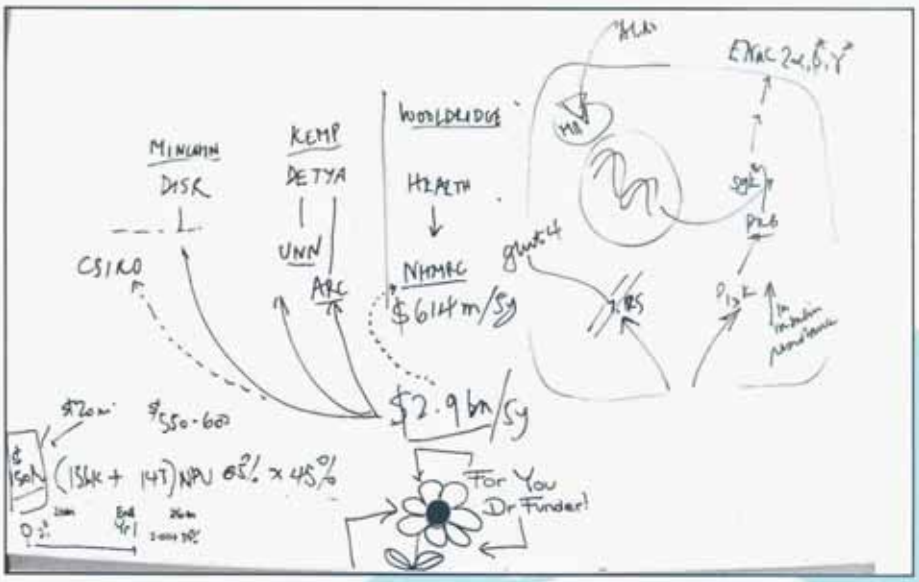
In terms of people, I would like to congratulate Jaye Chin-Dusting, appointed Senior Research Fellow, Dominic Autelitano and Ross Hannan, appointed Research Fellow, and Bronwyn Kingwell, promoted to Senior Research Fellow, all effective 1/1/2001. I would like to farewell Kathleen

Curnow, who has gone to Sydney to work for Pharmacia, to welcome Michael Hickey who arrived in December 99, and Craig Neylon in December 2000. Among a list of people to whom as a whole I have no hope of doing justice, I would like to thank George and Gita Smorgon, for their generosity in endowing the spectacular atrium in our new building; the students and staff of the Institute, for their dedication, their hard work, and their colleagiality; Garry Jennings, the Deputy Director, and the Associate Directors (Murray Esler, Michael Berndt and Ian Smith) for their scientific leadership and their unflagging commitment, and finally the Board of the Institute, led by Norman O'Bryan, for their guidance, advice, support and friendship.

John Funder

Director

John Funder, on a good day



The Director's whiteboard.
Garry Jennings, the Deputy Director, recently commented (approvingly) on the juxtaposition of a kidney tubule cell (top right) and a sketch of who's who at a Commonwealth level in research (top left). Since then two additions were made before this snap was taken: jottings by Peter Hughes (Chief Operating Officer) on fit out costs and rents to be paid by spin-offs and start-ups in the new Baker buildings (bottom left), and a message from Louise Smith (daughter of Sue Smith, John Funder's secretary) one late afternoon on her way to a Peter Garrett lecture with her mother.

The basic plan of decision-making and responsibility in Canberra was drawn for the recently arrived Scientific Attache to the Italian Embassy, brought to the Baker by Anna-Maria Arabia, one of our PhD students. The kidney cell shows a possible pathway whereby insulin (the sugar regulating hormone, important in diabetes) and aldosterone (the salt regulating hormone, important in heart failure) may act together within the cell in the so-called metabolic syndrome, or Syndrome X (high blood pressure, obesity, glucose intolerance and elevated blood lipids).

Publish or Perish

There's a lot of talk today about the IT revolution, and a knowledge-based economy. We've always had knowledge-based economies, from the domestication of wheat near Jericho to the Silk Road to the Industrial Revolution; what's new, I suppose, is the proportion of the (first-world) population no longer engaged in a basic subsistence economy. The IT revolution, however, is much more recent: in 1941 a transatlantic telephone call cost £10 per minute, and in 1981 it was still telegrams and telexes. Twenty years later our scientists average an hour and a half a day sending and responding to emails, a rather larger slab of time than even the most ardent telegram/telex user could possibly afford, but giving them a degree of connectedness undreamed of back then.

What's also changed immeasurably are the ways we can access information, which sometimes has been transformed into knowledge. Historically research was published in learned journals: in the library at the Baker, for example, are bound volumes of the *American Journal of Physiology* in neat rows back to 1926, the year the Institute was founded. Today the AJP publishes almost 40 times as much research as it did 75 years ago, and now there are more than 40 times as many journals as there were then. We've had the Indexus Medicus for decades, which catalogued by year publications as they appeared; now most journals are published on-line, as well as on paper, and Medline now has over 11 million articles available on-line. The implications for access, and the prospects for publication, are profound.

Historically and currently, a research scientist is judged by his or her output. Research findings are contexted, presented and discussed in 'journals of record', almost always after peer review by two or three referees. The process is measured: the average time from "Gee: that's how it works/what it means/the answer to my question" to seeing it in print is commonly between a year and eighteen months. It's not the only criterion, or for those that prefer it KPI, but it's crucial: research is a sequence of hypotheses, testing and publication, and until you've published it you haven't done the research.

It's a process that sits oddly with the pace of communication, and the pace of discovery: in your particular area of expertise, you'll usually know at least a year before publication of results from laboratories in USA and Europe: the surprises tend to come from Japan, or Chile, for example.

Janine Krochmal has been the librarian at the Baker for some years, and is in the process of morphing into the position of Information Services Manager. In the new precinct on Commercial Road, a total of four libraries (Alfred/Baker/Monash/Macfarlane Burnet) will be merged into one, on site and to be run by the Alfred on a cost sharing basis. We'd hoped that this would result in significant cost savings, but should have known better: what it will provide is an upgraded level of services, particularly for casual or infrequent users. Which, by and large, research staff and students are not.

For some of the older staff, the tradition of browsing through each issue of *Nature* or *The New England Journal of Medicine* as it arrives remains strong; for most people, browsing is now on the web. Printouts of abstracts (or even whole papers) not due to be published in the journal for six weeks fly round with little post-it notes ("Thought you might be interested in this"). Over the past three years there have been strenuous efforts to combine rapid on-line publishing with some measure of peer review - not an easy achievement, and not yet effectively resolved. Even the 'mainline' journals, with electronic submission and review, still take many months for papers to see the light of day.

The notion of a paperless journal is somehow counterintuitive, but that's what the *Journal of Biological Chemistry* plans for 2005. Printing is expensive, with the cost of paper spiralling up, as well as the cost of postage. Shelf space is an enormous problem: if it's available on-line, why devote expensive buildings to act as mausoleums for never-touched volumes? The classic 'gift' to a visiting academic is a selection of the department's reprints, for edification (? sleep induction) on the long plane ride home - and with paperless publishing, you can still download the relevant 'papers': what will be interesting to see is whether the popular language changes, so that 'publications' rather than 'papers' becomes the normal.

When the Baker library is merged into the campus-wide facility, Janine is staying on, to use her considerable technical and personal skills within the Institute in the expanding areas of information provision – from revamping our website to tracking Institute papers, oops publications, to being a linchpin in terms of publicity material and raising the Institute's profile. Librarians have an image of being neat, bespectacled and law abiding: *The Harvard Lampoon* once published a skit entitled 'Conan the Librarian'. Janine is all those things, and much more: and by her approachability, energy and versatility she has made an outstanding continuing contribution to the research and life of the Baker Institute.

Tanya Medley

Blood Vessels and Bagpipes

The word compliance has many meanings, even in medicine. When patients take their medication as suggested, they are said to be compliant. In cardiovascular medicine, compliance means something else as well, and it refers to arteries. It refers to the ability of a blood vessel to stretch, to accommodate the blood that is pumped into the aorta with each heartbeat. It also refers to the vessel's ability to assume its original dimensions, as the blood passes down the line into the smaller distributing arteries. Elasticity is an important component of compliance, but not the whole story: the healthy aorta and large arteries are not just rubber tubes.

It may be easier to think negatively, for once, by considering the things that make a large artery non-compliant. If there is calcification (deposition of bone) in the vessel wall, the artery understandably has difficulty ballooning out and snapping back seventy-two times a minute. If the aortic wall is full of atheroma, the porridge-like collections of lipids and cells, the vessel is also obviously not well placed to be properly compliant. But even without bits of bone and goop in the vessel wall, there can be marked differences in large vessel compliance – with age, and exercise and hormone status.

Compliance can also be affected by the genetic types of protein that are woven together to form the scaffolding of the vessel wall – the collagens, elastin and fibrillin molecules, which is what Tanya Medley's PhD is about. Tanya measures the compliance of the large arteries and takes a blood sample to examine the person's DNA for what individual genotypes of the protein fibrillin the person carries.

It's an attempt to establish guilt-by-association: we know that mutations in the fibrillin gene can lead to a condition called Marfan's syndrome, which used to be called arachnodactyly (spider fingers). Patients with this syndrome have long hyperextensible ('double-jointed') fingers, and are generally long and thin. Among other things, their defective fibrillin is responsible for their having a very high incidence of cardiovascular problems, perhaps most dramatically, aortic aneurysms. The aorta is the big artery into which the left ventricle of the heart pumps the blood, and from which the main distributor arteries run off. An aneurysm is a balloon, caused in this instance by blood getting into the aortic wall because it is weak, and then gradually forming a 'second channel' in the wall before bursting: bad news.

What Tanya is doing is what a lot of medicine over the next decade will be about - working out the extent to which minor genetic variants, commonly found in the population, make a protein more or less efficient. We've got the drama, the very bad news mutation of Marfan's; now we need to know the variation 'within the normal range'. If you have no growth hormone you become a dwarf, unless you're treated; if you have a tumour secreting growth hormone you can wind up seven foot something, and in all sorts of strife, again unless you're treated. That said, within the Australian population normal height varies from five feet, or a bit less, to closer to seven than six feet tall. This normal variation in height may determine your likelihood of playing Olympic netball or AFL football: but in the case of arterial compliance, we know that it is a very good predictor of cardiovascular health.

Tanya is an outstanding PhD student: hard working, smart, cheerful, bridging two areas (clinical physiology with Bronwyn Kingwell, genetics with Tim Cole). She'll do a great job, whether or not she and Bron and Tim can find particular phenotypes (how the patient appears on examination - i.e. high, mid or low artery compliance) that match particular genotypes (individual differences in genes, within the normal range). Even if she finds a significant association, and everybody cheers and whistles, it's likely that someone else will carry on from where she leaves off.

Tanya loves dealing with her patients, and ploughing through the genetic analyses, but there is something she loves even more: being an entrepreneur. Her St-Paul-falling-off-his-horse equivalent experience was going to a seminar on the commercialisation and capture of research, organised by the Australian Society for Medical Research each year. She's doing the three year Masters of Entrepreneur and Innovation at Swinburne, 6 pm - 9 pm classes, two nights a week, plus assignments and reading on top of her PhD work.

Looking back, it was almost inevitable: for the last decade Tanya has supported herself as a student by playing the bagpipes at weddings and funerals - and, incidentally, winning a string of national championships. Looking forward, the sky's the limit. We've had great scientists, and capture and commercialisation that's patchy at best. Let's make the science even better – and with people like Tanya, our prospects of making a contribution to the knowledge economy just got a lot brighter.

Alex Bobik and the Unstable Plaque

Alex Bobik heads the Cell Biology laboratory at the Baker, and has been contributing to the research of the Institute longer than anybody else on staff: as a young pharmacist/toxicologist he welcomed Professor Paul Korner to the Baker in 1976. He is the initiator and driver of the Australian-Russian scientific exchange, which on a very modest budget has provided extraordinary value, for short-term visits by Baker scientists to Russia, and longer term visits from our Russian colleagues here. Alex is also Associate Director (Laboratories) of the Alfred Baker Medical Unit, and has supervised, with Garry Jennings, a series of cardiology fellows enrolled for their PhD at the Institute.

Currently, Andrew Taylor fills that role. Andrew graduated in medicine from Monash, and has his specialist qualification in cardiology: for three years he will continue to keep his hand in clinically, while being busy in the lab doing experiments on the formation and rupture of atherosclerotic plaques. Nobody thinks that atherosclerotic plaques per se are benign; globs of goop in your arterial walls don't help the biomechanical properties of your blood vessels. However, if a plaque is just sitting there, a so-called 'stable plaque', its capacity for catastrophic mischief is circumscribed.

An unstable plaque, on the other hand, is a bomb with the fuse lit. The atherosclerotic goop, if it gets through the cell layer lining the blood vessel, is fiercely thrombogenic (clot-forming), causing platelets to adhere and release their suicide packages, which in turn causes the build up of a scaffolding of fibrin on which the clot forms. If this happens in one of the arteries supplying the heart, you get a coronary thrombosis leading to myocardial infarct (death of heart muscle). If it happens in the wall of the carotid artery, you may get a TIA, or transient ischemic attack, with signs and symptoms of the blood supply to part of the brain being temporarily interrupted.

Alex and Andrew and Garry have devised an animal model of unstable plaque rupture which uses cholesterol-fed rabbits. Rats are very atherosclerosis resistant; feed them a high cholesterol diet and they send out for hot buttered crumpets, with no effects on their arteries. Rabbits are like us, in that a high cholesterol diet predisposes to the build up of atherosclerosis in blood vessel walls. Normally this would take years to accumulate: to speed the process up in the rabbit model Andrew and Alex resort to a trick. The trick is to remove the lining cells in a segment of iliac artery, which runs off the aorta on each side to supply the pelvis and the legs. After a month, on a high cholesterol diet, they are rewarded by a fine atherosclerotic plaque at the site of so-called endothelial denudation, which is jargon for having blown up a tiny balloon in the iliac artery, under anaesthesia, to break up the pavement of cells that normally lines the artery.

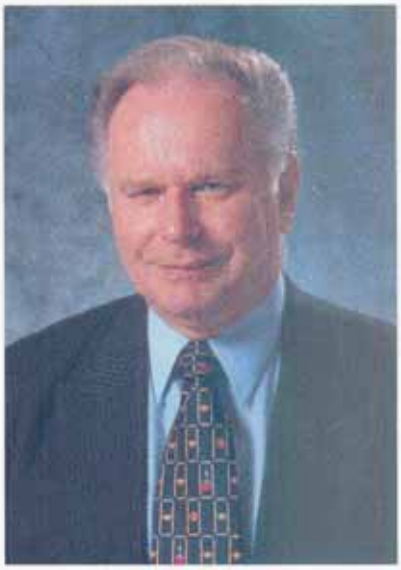
So here we are with a fine stable atherosclerotic plaque in an otherwise relatively normal rabbit; where to now? The second trick is to convert the stable plaque model into an unstable plaque, under controlled circumstances, rather than it just happening, as is the case with a human coronary thrombosis or TIA. It's fairly straightforward: after four weeks the plaque is manually disrupted, by passing a stiff-ended wire under X-ray guidance via the carotid artery and the aorta to the site of the iliac artery lesion, and scraping the surface of the plaque – lighting the fuse in the time bomb.

What happens is both expected and unexpected. The stable plaque after four weeks blocks the artery by about two thirds; when the plaques are ruptured, the cap of thrombus forms as predicted, and the blood flow falls to a quarter, with the resistance beyond the ruptured plaque more than doubling. What everyone expected was that this increase in

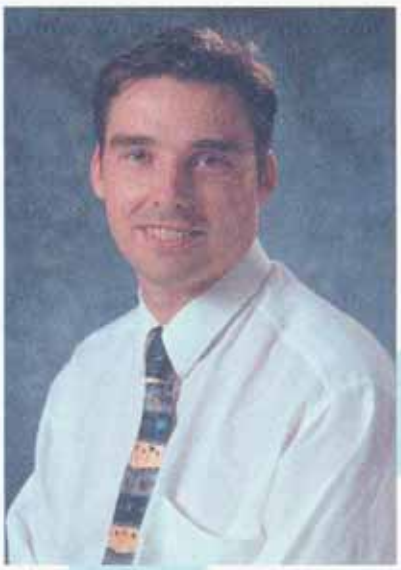
resistance, and decrease in flow, would be the result of little bits of clot breaking off, travelling downstream, lodging in the smallest arterioles or capillaries, and blocking them. Sometimes hunches pay off, and sometimes you have to think again.

In over 700 tissue sections of leg muscle from 15 different rabbits there were no differences between the 'good' leg and the 'bad' leg in the rabbits with a unilateral plaque rupture in terms of capillary number or patency: there's really no evidence for 'embolization', breaking off of little fragments of clot that clog up small vessels downstream, raise resistance and reduce flow.

So how does it happen? The answer is that we don't know, but that it looks like being a consequence of potent vasoconstrictor substances released from the disrupted plaques and aggregating platelets. The endothelium, normally the source of relaxant factors, is disrupted, so that the system is biased towards contraction. The next thing is to find out what substances – endothelin, urotensin, whatever – are involved in the shut down after plaque rupture. When we know the agents involved, it may be relatively easy to give antagonists that block their action, and thus spare the tissue downstream the effects of precipitous falls in blood flow: and that would be a big bonus for folk with atherosclerosis and a past history of coronary thrombosis. One day, using models such as that developed by Alex and Andrew and Garry, we might even be able to snuff out the wick, to stop the time bomb from exploding, rather than just minimising the consequences; only time, and more experiments, will tell.



Alex Bobik



Andrew Taylor

Peptides and Proteins

Over the last few years we've heard a lot about genes, the blueprints made of DNA, in each cell of the body. Then there's RNA, which are the relatively flimsy working drawings read off the really quite stable DNA. These RNA working drawings are used in specialised factories in the cell called ribosomes, and the information that they contain specifies the particular protein read off them. Hemoglobin, which carries oxygen in red blood cells, is a protein (or rather, the globin bits are proteins, arranged around an iron molecule to form hemoglobin).

When a baby is in the womb, the globin produced is specified by messenger RNA for fetal hemoglobin, which works well at the relatively low oxygen levels available from the mother's blood. As birth approaches, a different gene is switched on, which codes for adult hemoglobin, and works much better when we are directly breathing air. In the wake of the successful sequencing of the human genome, one of the most important questions is just how do we turn one gene on, and another one off, as part of development, or in response to the environment.

Proteins are long chains of amino acids, from around fifty to thousands. They are produced as a long string, but rapidly fold and self-associate to form particular structures. Collagen, for example, the protein which forms the scaffolding of bone and tendon and cartilage, arranges itself as a long, triple-stranded spiral, and then associates with other collagen molecules to form very strong sheets or cords, or even lattices. Boil up the calf's foot, and what you get is collagen, reassociating as jelly rather than what the anatomists call 'connective tissue'.

Peptides are bits of proteins, from two amino acids up, and in nature are clipped off one end or the other of proteins, or on some occasions out of the middle. An example of a dipeptide (two amino acids) is the artificial sweetener aspartame, found in diet drinks, which consists of an aspartic acid molecule linked to a phenylalanine molecule. Proteins do a whole range of jobs in the body – structural like collagen, functional like hemoglobin or the enzymes that are responsible for the cutting and shaping of all the other molecules in a cell – including the production of peptides from precursor proteins.

Peptides have a narrower focus, largely that of messengers. Many hormones are peptides; thyroid hormones, for example, are dipeptides of two tyrosines decorated with three or four iodine atoms. Angiotensin is a peptide of eight amino acids, formed by the action of renin and converting enzyme on the protein angiotensinogen; the so-called converting enzyme or ACE inhibitors, widely used in hypertension and heart failure, block the generation of angiotensin and thus its effects on blood vessel walls and the heart. Angiotensin, like other peptides, doesn't last forever, but is broken down by enzymes called peptidases, to fragments which are then recycled.

Much of Ian Smith's time is spent looking at peptidases, and how to fool them. Enzymes recognise a small stretch of amino acids – usually up to about five – which are referred to as a 'motif'. When the motif is present, the enzyme binds to the peptide, cleaves it, and the bits fall out. What Ian does is to build unnatural peptides, by using so-called beta-amino acids, a sort of left-handed and extended version of the usual form. If you use your right hand to shake someone's left hand, it doesn't work: and judicious use of beta-amino acids in peptidase recognition motifs can produce a peptide that sits nicely in the recognition site, but that prevents the cleavage process from proceeding.

This is the classic definition of an inhibitor: the flu drug Relenza, while not a peptide, acts in

exactly this way, by sitting in the jaws of the enzyme neuraminidase, which the virus needs to attack cell walls. The cells lining blood vessels, the so-called endothelial cells, have enzymes on their surface which can inactivate peptides that relax blood vessels, and activate other peptides which constrict blood vessels. The finding that beta-amino acids in synthetic peptides can act as inhibitors of enzymes has enormous potential, on the design of specific and targeted therapies in blood pressure control, the treatment of heart failure - and, as a platform technology, in a host of other areas.

One last word. Ian trained as a protein chemist, separating proteins in blood and cell extracts by a process known as chromatography. If you make a column of talc powder in a glass tube, kept in with a cotton wool tip, put a drop of ink onto the top, and then gently drip water through, the ink will separate into different colours as it proceeds down the column – black, green, red etc – depending on the size of the various colouring agents. We still use chromatography, but now the same principles are used to separate proteins on the basis of their size and electrical charge, in two dimensions, by running them into a sheet of porous gel, and then staining the gel to show up the proteins.

Where this is relevant is beyond the genome, to what is called the proteome. One of the totally unexpected findings of the Human Genome project is that we have 'only' about 30,000 genes, rather than the 70,000-150,000 which had been predicted: the old adage 'one gene, one protein' is clearly not the case. All cells (except sperm and ova) have the same set of blueprints, but they make very selective working drawings, and very different sets of proteins. Ian is tooling up to establish proteomics at the Baker, so that we can take a short cut looking at the protein responses of different cells – say endothelial cells, or cardiac muscle cells – to different stimuli. Ian has done the groundwork in 2000, and by the end of next year we should have a working proteomics analysis facility in place, to the enormous benefit of every single laboratory at the Institute.

Ian Smith

High Pressure Liquid Chromatography

Maro Williams

As a rule, women live longer than men: for a child born in Australia in 2001, there's a difference of seven years in terms of life expectancy. In all sorts of ways the male sex is more fragile: for every 100 female conceptions there are 120 males, and for every 100 female live births there are 106 males. In all age groups men are more likely to die than women, but the big difference is in old age. Look in the Probus Clubs, the elderly citizens groups, the aged care facilities, and it's the same story: for every man there are two, or three, or more elderly women. The big difference is cardiovascular disease, where female sex hormones (estrogens) are protective. Before puberty and after the menopause women have relatively low estrogen levels, as do men; over the past few years we have learnt just how important these low levels are, in both sexes. Over the course of their reproductive years, however, women secrete high levels of estrogen from their ovaries, as part of the process of ovulation, or releasing an egg. These episodically high levels are clearly protective of the heart and blood vessels, so that heart attacks and atherosclerosis are relatively rare in women before the menopause. After the menopause, the incidence of heart attacks parallels that in men – but from a much later starting point.

We don't know how estrogen produces its protective effects. Decades ago, on the basis that if estrogens protected women they might also protect vulnerable men, male heart attack survivors were treated with high doses of estrogen, with no beneficial effect. Very little in human biology and medicine is as simple as it at first seems; right now we're just scratching the surface in terms of how sex hormones affect the heart and blood vessels, and how we can mimic those effects without increasing the risk of breast cancer in women, or turning men into Priscilla Queen of the Desert. Enter Maro Williams, and DHEA. DHEA is merciful shorthand for dehydroepiandrosterone, and is in some countries available off prescription as an 'anti-aging' agent. DHEA is normally made in the adrenal gland, and together with a derivative (DHEA-sulphate) is the most abundant steroid hormone made in the body, though levels fall 20-fold with age (thus its use as a possible anti-aging agent). We know that it can be converted by enzymes present in various tissues into testosterone, the male hormone; we also know that testosterone can in turn be converted into estrogen. In fact, in girls before puberty and postmenopausal women, DHEA is the major source of circulating estrogen. How DHEA might work to do whatever it does is therefore very complicated, given that it can be converted into testosterone and estrogen. We know that the male hormones act, on blood vessels and elsewhere, by activating so-called androgen receptors (AR) within the cell, keyholes into which the male hormone fits like a key in a lock. Estrogens work similarly, by fitting like a different key into different locks (ER). DHEA could act through one or both of these receptors, with the overall effect being a balance between how much was converted into androgen, and how much androgen was converted into estrogen.

Or DHEA could act on blood vessels through its 'own' receptor, its own keyhole into which it fits like a key. This is what Maro has found, in both the contractile cells of blood vessel walls (vascular smooth muscle cells), and in the specialised cells which line blood vessels (endothelial cells). He's done it by using specific blockers ('antagonists') of AR and ER, and showing that DHEA still exerts its effect. He's done it in cultured cells, and in patients: and in cultured cells, by using tritiated (lightly radioactive) DHEA he's been able to show that it goes into receptors which don't recognise androgens or estrogens.

It's still early days, and while we can measure DHEA effects, we're a long way from knowing exactly what it's doing, and how, like estrogen, it might be protective. Maro has presented his findings to the American Heart Association, at their annual meeting, and is currently writing up his PhD thesis. Under the supervision of Paul Komesaroff and Krishna Sudhir, he's struck the first blow, and it's up to those who succeed him in the laboratory to exploit these very exciting findings. Maybe the health food stores have got it right, and DHEA may lower the rate of progression of cardiovascular disease. If this proves to be the case, an important early piece of the mosaic will be the work Maro Williams did for his PhD at the Baker.

The Biological Research Unit: of mice and minipigs

The BRU, as it is widely abbreviated, is the noncommital name for the Baker Animal House. In an Annual Report – or in fact anywhere – to write about animals in research is not conventional wisdom: why do something that may range from upsetting to the height of folly?

The answer is simple. At the Baker we use animals in our research, where studies on cells in vitro or computer simulation cannot address the questions posed, and posing those particular questions in humans without prior animal studies is precluded on a variety of grounds. Where we can, we use cells and computers and human volunteers; where we can't, after an exhaustive process of vetting by the Animal Ethics Committee, we use rats and mice and rabbits and sheep and mini pigs. These studies, and the BRU staff who enable them to be done, are a core activity of the Institute. The Annual Report exists to give an account of the activities of the Baker – scientific, financial, operational. The BRU is central to the science of over half the laboratories in the Institute; if to write about it is the height of folly, then here I stand.

The BRU is unthinkable without Debra Ramsey. From an office the size of an outback, outdoor toilet, in a building that is in part a World War II bomb shelter, Deb with the assistance of Susan Mooney organises the animal husbandry and care; directs and mentors her staff of seven assistants; runs the operating theatres and acts as more than occasional animal surgeon; ensures that applications to the ethics committee are complete, and contributes enormously to the workings of the committee; and has designed the very much expanded, up to the minute animal house under the new Baker building on Commercial Road, which the Institute (i.e. Deb) will run on behalf of all the precinct partners.

In her spare (?) time Deb has computerised the business of the BRU, acted as an advisor to other research groups regarding their animal facilities, bought, revamped and sold a series of bayside houses, learned basic Japanese and taken courses on successful sharemarket investment. Even without the Japanese (for the series of exchange students in her house), or the stockmarket, it's a far cry from most animal facilities in the past, corner store to Deb's Coles-Myer.

Why the change? At least in part, it's a question both of numbers and of specialisation. Over the past decade the patterns of animal usage at the Baker have changed, in a number of ways. A decade ago there were no mice, and now there are thousands. Then there were dogs; now there are sheep and minipigs. Rats are up, in the language of the Bourse, and rabbits are a bit down: guinea-pigs a forgotten memory.

What's driven the mouse situation (which sounds a bit like what a diplomatic Wimmera politician would call a mouse plague) is the advent of transgenic and knockout mice. You can get a lot of mice in a relatively small space, and they breed relatively quickly, so that on those grounds alone they're a good bet for studies in which their genetic material is permanently manipulated. For some reason, it's also been a lot easier to do technically than in rats. Knockout mice have a particular gene inactivated, and on the principle of what goes wrong under such circumstances we can get a handle on what that particular gene product (i.e. protein) normally does. Transgenic mice have genes added: one early TG mouse had additional copies of the growth hormone gene added, and weighed in at twice the normal size.

So mice are small, easy to breed: where's the drama? Well, for obvious reasons of safety and containment, such mice have to be in quarantine for a period, which is space-demanding and extra work. Not nearly as much work as testing the genetic make-

up of litters born, with thudding regularity, by snipping a millimetre or so off the end of the tail and preparing it for genetic analysis. Plain old mice are easy: transgenic and knockout mice are high complexity, high maintenance, and on occasion high drama.

In theatrical terms, the minipigs provide occasional moments of high comedy. We use pigs because their coronary vessels (the arteries supplying the heart muscle) are very like human coronary arteries; studies on angioplasties (blowing up tiny balloons inside narrowed arteries, to widen them) and stents (the little metal gizmos inserted to keep angioplastied arteries open) are really best studied experimentally in such pigs. The pigs weigh about 60 kg, are boisterous and occasionally not well behaved, like an average teenager. No system is perfect, and pigs are very intelligent: they open latches with their snouts, quick as a flash. One memorable Monday Deb arrived at 6.30 a.m. to find that whoever had been on the previous day had not firmly locked the pigs' door: she found them guilty, slightly green, 12 kg (on average) heavier and asleep in a very diminished bin of pig pellets.

The professionalism of Deb and her staff, the leadership of Warwick Anderson (Baker 1978-1996) in establishing the Code of Practice, now accepted Australia-wide, and the devotion of our Animal Ethics Committees mean that when animal studies are required they can be done humanely, efficiently and productively. Those who work in the BRU make a special, and crucial, contribution to the work of the Baker - and their contribution should be saluted like any other part of the Institute.

Debra Ramsey

Board of Management

PATRON

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

Mr Norman O'Bryan SC
BA, LLB, BCL
President, Baker Board of Management
Barrister-at-Law

Dr Gerard P Johnston
BSc, PhD
Vice President, Baker Board
of Management
Trustee Baker Foundation

Professor John Funder AO
MD, PhD, FRACP
Director, Baker Medical
Research Institute

Mr Ross Barker
BSc (Hons) MBA ASIA
Hon Treasurer, Baker Board
of Management

Mr Peter C Barnett FCPA
Director, Ericsson Australia Pty Ltd
Director, Mayne Nickless Limited
Director, Santos Limited

Professor Peter LePoer Darvall
BCE (Hons) Melb, MS Ohio State MSE
MA PhD Prin. DipEd, FIE Aust, FTSE
Deputy Vice Chancellor (Research &
Development), Monash University

Mr William P Gurry AO,
LLB
Chairman, Baker Capital Campaign
Executive Chairman, Warburg Dillon Read
Australia Ltd

Dr Peter G Habersberger AM
RFD, MB, BS, FRACP
Visiting Cardiologist, Alfred Hospital
Assistant Surgeon General, Australian
Defence Forces - Navy

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

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

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

PAST PRESIDENTS

J.F. Mackeddie BA, MD, BS 1929 - 1944	E. Rouse CBE, FRACR (Hon) 1944 - 1971	J.C. Habersberger AO B. Comm 1972 - 1983
Sir Laurence Muir VRD, LLB, FSIA FAIM 1984 - 1986	J.D. Moir AM 1987 - 1992	D.F Hogarth OAM BSc 1992 - 1994

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

FOR THE YEAR ENDED 31 DECEMBER 2000

The Board of Management present their report together with the financial statements of the Institute for the year ended 31 December, 2000 and the auditors' report thereon.

Board Members

The following persons were Board Members of the Institute during the whole of the financial year up to the date of this report:

Mr N O'Bryan SC, President
Dr G P Johnston, Vice-President
Mr R E Barker, Hon. Treasurer
Professor J W Funder AO, Director
Mr P C Barnett (resigned 26 February 2001)
Professor P Darvall (resigned 28 March 2001)
Mr W P Gurry AO
Dr P G Habersberger AM
Prof. S R Holdsworth (resigned 16 Feb 2001)
Mr P Munz
Mrs M Ross AM (resigned 28 March 2001)
Professor R Smallwood AO

Professor G Ryan AC was a Board Member from the beginning of the financial year up to his resignation on 30 June 2000.

The following Board Members were appointed during the period after financial year end, up to the date of this report:

Professor D Alcorn (appointed 5 February 2001)
Professor N Saunders (appointed 28 March 2001)
Mr R Stewart (appointed 17 February 2001)
Dr M Walsh (appointed 24 April 2001)

Principal Activities

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

Operating Result

The financial result from research activities was a deficit of $1,507,828 (1999: deficit $470,084). After allowing for the surplus arising from the Capital Fund which incorporates grants and contributions received towards the cost of the new Institute the consolidated result for the year was a surplus of $13,389,846 (1999: surplus $3,793,098). It is expected that excess funds of $11,038,050 received for capital works during the year will be spent in the following year. 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.

Likely Developments

The Institute does not expect any significant changes to its operations in the coming year.

Environmental Regulations

The Institute complies with the Environmental Protection Act in respect of its operations.

Insurance of Officers

During the financial year, the Baker Medical Research Institute paid a premium of $3,700 to insure certain officers and board members of the Institute.

The liabilities insured include costs and expenses that may be incurred in defending civil or criminal proceedings that may be brought against the officers in their capacity as officers of the Institute.

State of Affairs

The new Baker Medical Research Institute with its colourful facade, now makes an imposing sight from Commercial Road, Prahran. Although delays due to extremely hot weather and rain have occurred, final external work and internal fit-out continues apace.

During the year another substantial donation was made which, together with additional contributions from the State Government and from AMREP partners will see the full AMREP site completed by early 2002.

The project is now being constructed in two phases. The original AMREP together with the Baker extensions is now due for completion in mid 2001, with the Baker planning its move for August / September 2001.

AMREP-2, essentially the extension of the MBC building to its full potential of 7 floors, is provisionally due for occupation in early 2002. The Baker will have the rights to lease floors 6 and 7 in this extension, with some 2,000 sq metres available on each floor. The other floors are assigned to MBC, Monash University and the Alfred.

Government grants and private/corporate contributions totalling $34m have been and are due to be received towards the cost of the new Baker Tower.

Events Subsequent to Balance Date

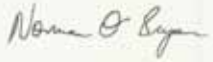
There has not arisen in the interval between the end of the financial year and the date of this report any item, transaction or event of a material and unusual nature likely, in the opinion of the Board of Management of the Institute, to affect significantly the operations of the Institute, the results 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 a shareholder and was an employee and Director 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.

Dated at Melbourne this 1st day of May 2001

Signed in accordance with a resolution of the Board of Management



Norman O'Bryan SC
President

John W Funder AO
Director

BAKER MEDICAL RESEARCH INSTITUTE
STATEMENT OF FINANCIAL PERFORMANCE
YEAR ENDED 31 DECEMBER 2000

	Note	2000 $	1999 $
Consolidated Income	3	**47,792,705**	19,222,691
Consolidated Surplus for the year		**13,389,846**	3,793,098
Represented by:			
Deficit from Operations		**(1,507,828)**	(470,084)
Surplus from Capital Fund		**14,924,417**	4,343,938
Deficit from Specific Purpose Fund		**(26,743)**	(80,756)
Consolidated Surplus before income tax	4	**13,389,846**	3,793,098
Income tax attributable to surplus	2(k)	**0**	0
Consolidated Surplus after income tax		**13,389,846**	3,793,098
Accumulated funds at the beginning of the financial year		**11,425,370**	7,632,272
Accumulated funds at the end of the financial year		**24,815,216**	11,425,370

The accompanying notes form an integral part of these financial statements

BAKER MEDICAL RESEARCH INSTITUTE
STATEMENT OF FINANCIAL POSITION AS AT 31 DECEMBER 2000

		2000	1999
ASSETS	Note	$	$
Current Assets			
Cash	16	**0**	786,626
Receivables		**2,536,996**	938,172
Inventories		**55,143**	77,161
Prepayments		**277,022**	137,778
Accrued Interest		**30,451**	95,389
Investments (at cost)	9(a), 16	**15,604,598**	6,163,533
Total Current Assets		**18,504,210**	8,198,659
Non - Current Assets			
Plant & Equipment	10	**2,913,234**	2,428,981
Investments (at cost)	9(b)	**8,330,634**	7,190,033
Total Non - Current Assets		**11,243,868**	9,619,014
TOTAL ASSETS		**29,748,078**	17,817,673
LIABILITIES			
Current Liabilities			
Bank Overdraft	16	**3,021,281**	0
Creditors		**390,811**	2,521,847
Lease Liability	2(f)	**60,206**	62,323
Prepaid Grants	11	**0**	2,562,109
Provisions	12(a)	**1,043,629**	754,100
Total Current Liabilities		**4,515,927**	5,900,379
Non - Current Liabilities			
Lease Liability	2(f)	**136,790**	204,419
Provisions	12(b)	**280,145**	287,505
Total Non - Current Liabilities		**416,935**	491,924
TOTAL LIABILITIES		**4,932,862**	6,392,303
NET ASSETS		**24,815,216**	11,425,370
FUNDS			
Accumulated Funds			
Operating Fund	5	**(5,889,547)**	(4,381,719)
Capital Fund	6	**28,528,987**	13,604,570
Specific Purpose Fund	7	**174,288**	201,031
Asset Revaluation Reserve - 1/1/93		**2,001,488**	2,001,488
TOTAL FUNDS	8	**24,815,216**	11,425,370

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 2000

	Note	2000 $	1999 $
Cash Flows from Consolidated Activities			
Receipts from Granting Bodies		**3,651,958**	4,739,532
Donations and Bequests		**7,037,473**	5,648,823
Receipts for Building Works		**28,917,049**	8,402,888
Payments to Suppliers & Employees		**(34,532,583)**	(14,598,355)
Dividends Received		**402,947**	305,542
Interest Received		**736,274**	235,019
General Income		**244,987**	319,060
Net Cash Inflow from Consolidated Activities	17	**6,458,105**	5,052,509
Cash Flows from Investing Activities			
Payment for Investment Securities		**(3,048,330)**	(2,914,375)
Proceeds from sale of Investment Securities		**3,346,401**	2,154,648
Payment for Property, Plant & Equipment		**(1,077,851)**	(755,807)
Net Cash Outflow from Investing Activities		**(779,780)**	(1,515,534)
Cash Flows from financing activities			
Principal Repayments under finance leases		**(47,593)**	(49,640)
Net Cash Outflow from financing activities		**(47,593)**	(49,640)
Net Cash Increase in cash held		**5,630,732**	3,487,335
Cash at beginning of the financial year		**6,950,159**	3,462,098
Effects of exchange rate changes on cash held in foreign currencies		**2,426**	726
Cash at the end of the financial year	16	**12,583,317**	6,950,159

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

This general purpose financial report has been prepared in accordance with Accounting Standards, other authoritative pronouncements of the Australian Accounting Standards, Urgent Issues Group Consensus Views and the Corporations Law.

Set out here under are the significant accounting policies adopted by the Institute in the preparation of its accounts for the year ended 31 December 2000. 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 Institutes 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

A distinction is made between finance leases, which effectively transfer from the lessor to the lessee substantially all the risks and benefits incident to ownership of leased non-current assets, and operating leases under which the lessor effectively retains substantially all such risks and benefits.

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.

Operating lease payments are charged to the profit and loss statement in periods in which they are incurred, as this represents the pattern of benefits derived from the leased assets.

(g) Land and building

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

(h) Inventories

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

(i) Cash

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

(j) Investments

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

(k) Tax status

The income of the Institute is exempt from income tax pursuant to the provisions of section 50-5 of the Income Tax Assessment Act 1997. The Institute is also exempt from other government levies such as payroll tax, but not exempt from fringe benefits tax or goods and services 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 a bank account in the USA for the purpose of receiving donations and for the purchase of equipment and supplies. Foreign currency transactions are initially translated into Australian currency at the rate of exchange at date of the transaction. Amounts receivable or payable in foreign currency at balance date are translated to Australian currency at exchange rates at balance date. Exchange gains and losses are brought to account in determining the operating surplus or deficit for the year.

(n) Trade and Other Creditors

These amounts represent liabilities for goods and services provided to the Institute prior to the end of the financial year and which are unpaid. The amounts are unsecured and are usually paid within 30 days of recognition.

(o) Recoverable Amount of Non Current Assets

The recoverable amount of an asset is the net amount expected to be recovered through the net cash inflows arising from its continued use and subsequent disposal. Where the carrying amount of a non current asset is greater than its recoverable amount, the asset is revalued to its recoverable amount.

(p) Comparative figures

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

3. Consolidated Income

	2000 $	1999 $
Grants:		
Government and Statutory Bodies	**6,202,009**	6,157,889
Baker Foundation	**1,150,000**	1,150,000
Other Income:		
Fundraising, Corporate & Private Support	**6,787,503**	4,242,315
Capital Works Campaign	**30,783,651**	6,536,286
Dividends Received / Receivable	**389,923**	321,509
Interest Received / Receivable	**670,868**	259,700
Foreign exchange gain	**2,426**	726
Proceeds from sale of non-current assets	**1,466,398**	204,425
General Income	**339,927**	349,841
Total Income	**47,792,705**	19,222,691

4. Consolidated Surplus

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

Credits		
Dividend revenue	**389,923**	321,509
Interest revenue	**670,868**	259,700
Net gain on disposal of non-current assets	**1,466,398**	204,425
Foreign exchange gain	**2,426**	726
Charges		
Borrowing costs		
Finance charges relating to finance leases	**67,963**	72,822
Less: Amount capitalised	**(47,593)**	(49,639)
Borrowing costs expensed	**20,370**	23,183
Depreciation - Plant and Equipment	**531,481**	437,489
Amortisation - Motor Vehicles under finance lease	**67,690**	70,444
Write down of inventories to net realisable value	**22,018**	27,413
Employee Entitlements	**282,169**	103,828
Rental expense relating to operating leases	**429,501**	330,679

5. Operating Fund

	2000	1999
	$	$
Balance at beginning of year	**(4,381,719)**	(3,911,635)
Deficit for year	**(1,507,828)**	(470,084)
Balance at end of year	**(5,889,547)**	(4,381,719)

6. Capital Fund

The Institutes Capital fund comprises donations, bequests and receipts from fundraising activities. Each year the Board allocates a proportion of these funds to supplement the research operations of the Institute. The Fund also incorporates grants and contributions received towards the cost of the new Institute building and the associated interest earned thereon. Funds received in respect of the new Medical Research Institute, but not outlaid at 31 December 2000, are carried forward.

The current balance is:

Balance at beginning of year	**13,604,570**	9,260,632
Surplus for year	**14,924,417**	4,343,938
Balance at end of year	**28,528,987**	13,604,570

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 Income and Expenditure Statement.
The current fund balance is:

Balance at beginning of year	**201,031**	281,787
Deficit for year	**(26,743)**	(80,756)
Balance at end of year	**174,288**	201,031

8. Fund Balances

Balance at 1 January 2000	**11,425,370**	7,632,272
Surplus / (Deficit) for year -		
Operating Fund	**(1,507,828)**	(470,084)
Capital Fund	**14,924,417**	4,343,938
Specific Purpose Fund	**(26,743)**	(80,756)
	13,389,846	3,793,098
Balance at 31 December 2000	**24,815,216**	11,425,370

9. Investments (at cost)	2000 $	1999 $
(a) Current		
Short term deposits	**15,604,598**	6,163,533
Total Current Investments	**15,604,598**	6,163,533
(b) Non - Current		
Shares and Debentures	**8,330,634**	7,190,033
Total Non - Current Investments	**8,330,634**	7,190,033
Total Investments	**23,935,232**	13,353,566

The Institute's investments are shown at cost. As at the 31 December 2000 the market value of the Institute's non-current investments was $11,206,292 (1999: $10,338,214).

10. Plant and Equipment		
Plant and Equipment (at cost or Board's valuation)	**6,659,467**	5,581,616
Less: Accumulated Depreciation	**3,909,544**	3,378,063
	2,749,923	2,203,553
Motor Vehicles under finance leases	**275,213**	364,314
Less: Accumulated Amortisation	**111,902**	138,886
	163,311	225,428
Total Plant and Equipment	**2,913,234**	2,428,981

11. Prepaid Grants

The 1999 Prepaid Grants include capital works grants of $2.224m received from the Federal Government for the redevelopment of the Institute.

Prepaid Grants	**0**	2,562,109

12. Provisions

(a) Current		
Annual Leave	**528,355**	460,080
Long Service Leave	**515,274**	294,020
Total Current Provisions	**1,043,629**	754,100
(b) Non - Current		
Long Service Leave	**208,092**	215,452
Deferred Maintenance	**72,053**	72,053
Total Non - Current Provisions	**280,145**	287,505
Total Provisions	**1,323,774**	1,041,605

13. Lease Commitments

	2000 $	1999 $
Finance Lease Commitments		
Finance Lease Commitments are payable as follows:		
Not later than 1 year	**76,292**	80,877
Later than 1 year and not later than 5 years	**162,927**	241,169
Minimum lease payments	**239,219**	322,046
Less: Future lease charges	**(42,223)**	(55,304)
Provided for in accounts	**196,996**	266,742
Representing lease liabilities:		
Current lease liability	**60,206**	62,323
Non-current liability	**136,790**	204,419
	196,996	266,742
Operating Lease Commitments		
Commitments for minimum lease payments in relation to non-cancellable operating leases are payable as follows:		
Not later than 1 year	**143,167**	110,226
Later than 1 year and not later than 5 years	**286,334**	220,453
	429,501	330,679

14. Capital Commitments

As at 31 December 2000, capital expenditure contracted for, in respect of completion of the building, at balance date but not provided for in the accounts of the Institute, is payable:

Not later than 1 year	**31,669,961**	19,696,509
Later than 1 year and not later than 2 years	**0**	6,981,026
Total Capital Commitments	**31,669,961**	26,677,535

15. Related Parties

(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 2000 are:

Mr N O'Bryan SC	Professor P Darvall	Mrs M Ross AM
Dr G P Johnston	Mr W P Gurry AO	Professor G Ryan AC (resigned June 2000)
Mr R E Barker	Dr P G Habersberger AM	Professor R SmallwoodAO
Professor J W Funder AO	Professor S Holdsworth	
Mr P C Barnett	Mr P Munz	

(b) Other than Mr R E Barker who is a shareholder and was an employee and Director 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.

16. Cash

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

	2000	1999
	$	$
(Overdraft) / Cash	**(3,021,281)**	786,626
Deposits at call	**15,604,598**	6,163,533
Total	**12,583,317**	6,950,159

Deposits at Call

The deposits are bearing fixed interest rates between 6.19% and 6.35% as at 31 December 2000.

17. Reconciliation of Surplus to Net Cash from Consolidated Activities

Operating Surplus from Consolidated Activities	**13,389,846**	3,793,098
Effects of exchange rate changes on cash held in foreign currencies	**(2,426)**	(726)
Depreciation and Amortisation	**599,171**	507,933
(Profit) on sale of non-current assets	**(1,466,398)**	(204,425)
Changes in net assets and liabilities		
(Increase) / Decrease in debtors	**(1,598,824)**	163,615
Decrease in inventories	**22,018**	27,413
(Increase) / Decrease in prepayments	**(139,244)**	52,152
Decrease / (Increase) in accrued interest	**64,938**	(25,463)
(Decrease) / Increase in creditors	**(2,131,036)**	1,999,225
(Decrease) in prepaid grants	**(2,562,109)**	(1,364,161)
Increase in provisions	**282,169**	103,848
Net cash from consolidated activities	**6,458,105**	5,052,509

18. Non-cash Financing Activities

Motor Vehicles

During the year the Institute purchased motor vehicles for staff under salary sacrifice arrangements with a value of $64,391 by means of finance leases. These acquisitions are not reflected in the statement of cash flows.

19. Financial Instruments

(a) Significant Accounting Policies
Details of the significant accounting policies and methods adopted, including the criteria for recognition, the basis of measurement and the basis on which revenues and expenses are recognised, in respect of each class of financial asset, financial liability and equity instruments are disclosed in note 1 to the accounts.

(b) Significant Terms, Conditions and Objectives of Derivative Financial Instruments
The Institute does not enter into or trade complex derivative financial instruments.

(c) Credit Risk
The Institute does not have any significant credit risk exposure to any single counterparty or any group of counterparties having similar characteristics. The carrying amount of financial assets recorded in the consolidated balance sheet, net of any provision for losses, represents the Institute's maximum exposure to credit risk.

(d) Net Fair Value
The net fair value of the Institute's financial assets and financial liabilities is not materially different to their carrying amount in the financial statements, other than non-current investments. The net fair value of non-current investments is disclosed in note 9 to the accounts.

(e) Interest Rate Risk
The following table details the Institute's exposure to interest rate risk and the effective weighted average interest rates by maturity on financial instruments at balance date.

31 December 2000	Variable Interest Rate	Less than 1 Year $	1 to 5 Years $	More than 5 Years $	Non - Interest Bearing	Total
Financial Assets						
Receivables					2,536,996	**2,536,996**
Fixed Interest Securities		15,604,598				**15,604,598**
Investments	8,330,634					**8,330,634**
Total Financial Assets	8,330,634	15,604,598			2,536,996	**26,472,228**
Average interest rate	3.44%	6.26%				
Financial Liabilities						
Bank Overdraft	3,021,281					**3,021,281**
Trade and other Creditors					390,811	**390,811**
Lease liabilities			60,206	136,790		**196,996**
Total Financial Liabilities	3,021,281		60,206	136,790	390,811	**3,609,088**
Average interest rate	8.86%		21.08%	16.04%		
Net Financial Assets / (Liabilities)	5,309,353	15,604,598	(60,206)	(136,790)	2,146,185	**22,863,140**
31 December 1999						
Financial Assets						
Cash	786,626					**786,626**
Receivables					938,172	**938,172**
Fixed Interest Securities		6,163,533				**6,163,533**
Investments	7,190,033					**7,190,033**
Total Financial Assets	7,976,659	6,163,533			938,172	**15,078,364**
Average interest rate	3.59%	5.42%				
Financial Liabilities						
Trade and other Creditors					2,521,847	**2,521,847**
Lease liabilities			62,323	204,419		**266,742**
Total Financial Liabilities			62,323	204,419	2,521,847	**2,788,589**
Average interest rate			22.94%	15.24%		
Net Financial Assets / (Liabilities)	7,976,659	6,163,533	(62,323)	(204,419)	(1,583,675)	**12,289,775**

20. 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.

21. Auditors Remuneration

	2000 $	1999 $
Amounts received or due and receivable by the auditors of the Institute for:		
- audit of the financial report	**17,000**	16,500

22. Segment Information

The Institute operates in the medical research industry in the geographical area of Australia.

23. Reconciliation of Net Assets / (Liabilities) to Net Assets

	Note	2000 $	1999 $
Net financial assets as above	19	**22,863,14**	12,289,775
Non-financial assets and liabilities:			
Other assets		**362,616**	310,328
Property, plant and equipment	10	**2,913,234**	2,428,981
Other liabilities	11	**0**	(2,562,109)
Provisions	12	**(1,323,774)**	(1,041,605)
Net Assets per Balance Sheet		**24,815,216**	11,425,370

BAKER MEDICAL RESEARCH INSTITUTE
BOARD MEMBERS DECLARATION

The Board Members declare that the financial statements and notes set out on pages 23 to 34:

(a) comply with Accounting Standards, the Corporations Regulations and other mandatory professional reporting requirements; and

(b) give a true and fair view of the Institutes financial position as at 31 December 2000 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 Member's 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 SC
President

John W Funder AO
Director

Melbourne
1st May 2001

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 2000 as set out on pages 23 to 34. 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 in Australia so as to present a view which is consistent with our understanding of the Institute's financial position, and performance as represented by the results of its operations and its cash flows.

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

Qualification

As stated in note 2(g) to the accounts, the Institute has written off to expense certain capital expenditures incurred on a planned new building, currently under construction, which we understand is going to be subject to a long term sub-lease to the Institute and other parties. This is a departure from Accounting Standard AASB 1021 'Depreciation' which requires recognition of an asset with physical substance which is expected to be used during more than one financial year.

In our opinion, costs amounting to $19,745,601 (1999 - $1,399,490) should have been recognised as capital works in progress. Had this been done, non-current assets would be $30,989,469 (1999 - $11,018,504), total assets would be $49,493,679 (1999 - $19,217,163), consolidated surplus after income tax would be $33,135,447 (1999 - $5,192,588), capital funds would be $34,670,018 (1999 - $5,743,428) and accumulated funds would be $44,560,817 (1999 - $12,824,860).

Qualified Audit Opinion

In our opinion, except for the effects on the financial report of the matter referred to in the qualification paragraph, the financial report of the Institute is in accordance with:

(a) the Corporations Law, including:

  (i) giving a true and fair view of the Institute's financial position as at 31 December 2000 and of its performance for the 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

Elizabeth Alexander — Melbourne

Partner — 1st May 2001

Directorate, Operational, Administrative and Support Staff

SENIOR MANAGEMENT

Director:
Prof John Funder AO, BA, MDBS PhD, *Melb*, FRACP

Deputy Director:
Prof Garry Jennings MD, MBBS, (Mon), FRCP, FRACP

Associate Directors
Prof Murray Esler BMedSc, MBBS *Melb*, PhD (ANU), FRACP
Dr Michael Berndt BSc(Hons), PhD *Qld*
Dr Ian Smith PhD *Mon*

Senior Principal Research Fellow:
Prof Colin I. Johnston AO MBBS *Syd*, MD (Hon) *Melb*, MRACP, FRACP

Chief Operating Officer:
Dr Peter Hughes B'Arch, MBA, DBA, FRAIA, AIMM (from Dec)

Finance Director:
Adrian O'Brien BEc, ACPA

BIOLOGICAL RESEARCH UNIT

Head:
Debra Ramsey AppSc (Animal Tech) *BHIT*

Deputy Manager:
Susan Mooney AppSc (Animal Tech) *BHIT*

Technical Staff:
Corina Backhouse AppSc (Animal Tech) *BHIT*
Jade Barbuto AppSc (Animal Tech) *VUT*
Samantha Hulme AppSc (Animal Tech) *VUT*
Elizabeth Langskaill AppSc (Animal Tech) *BHIT*
Sandra Miljavec AppSc (Animal Tech) *BHIT*
Fiona Share AppSc (Animal Tech) *FIT*
Wilfred Villareal AppSc (Animal Tech) *VUT*

Weekend and Casual Staff:
Kylie Aquilina AppSc (Animal Tech) *VUT*
Christine Egan AppSc (Animal Tech) *BHIT* (to June)
Kim Hauser AppSc (Animal Tech) *FIT*
Philip Littler
Marrit Postema

TECHNICAL SERVICES AND ASSET MANAGEMENT

Head:
Anthony Hendy BAgrSc (Hons) *Melb*

Biomedical Engineering Staff:
Jim Kirkas
Colin Lawson
John Mizzi

Supply Services Staff:
Sabine Gazic
Craig McIndoe
Perla Garces

BUILDING AND SPECIAL PROJECTS

Building:
The Hon Michael MacKellar BScAgr, MA, MAIAS MAICD

Special Projects:
Jan Strauss

INFORMATION SERVICES

Head:
Garth Stewart BSc (Hons) *UNSW* GradDipComp *UCAN* (from Dec)

Technical Support Staff:
Wayne Holden CNE
Chris Anderson BSc (Hons) *Mon* (from Aug)
Damian Lee

The Rouse Family Library:
Janine Krochmal BA (Mon), Grad DipInfServ *RMIT*

COMMUNITY RELATIONS AND FUNDRAISING

Foundation Executive Manager:
Vacant

Head:
Bobbie Renard

Donor Liason and Planned Giving Officers:
Gweny Mueller (to June)
Andrew Whiteley
Yvonne Williams
Myra De La Rue
Ian Misson (from June)

HUMAN RESOURCES

Manager:
Bryan Quinn MNIA, MAHRI

IMAGING APPLICATIONS

Manager:
Brian Jones BSc *Rochester*

SPECIAL EVENTS COMMITTEE

Sue Calwell (Chair)
Elizabeth Boydell (Manager)
Amanda Lachmund (Secretary)
Robyn Aylward-Austin
Annetta Conlan
Judith Evans
Gerard Johnston
Claude Lombard
Michael MacKellar
Tricia Neilson
Heather Rolls
Caroline Scott
Ruth Speedy
Paul Sumner

FINANCE AND ADMINISTRATION

Accountant:
Gary Loetsch BEcAcc *La Trobe* DipOD, ASA

Accounts Officer:
Montse Becker

Executive Assistant To Director:
Sue Smith

Executive Assistant To Chief Operating Officer & Finance Director:
Annetta Conlan

Scientific Secretary:
Donna Chandler

Reception:
Tracie Beck

Archivist:
Geoffrey Tolson

BUSINESS DEVELOPMENT AND COMMERCIALIZATION

Manager:
Dr Alan Robertson BSc (Hons), PhD *Glasgow*

VISITED IN 2000

AUSTRALIA
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BRISBANE
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GOLD COAST
LORNE
MARYSVILLE
MELBOURNE
PORT DOUGLAS
SYDNEY

CANADA
ALBERTA
TORONTO

CHINA
BEIJING
HONG KONG
NANJING

CZECH REPUBLIC
PRAGUE

DENMARK
AARKS

FINLAND
HELSINKI

FRANCE
MARSEILLE
MONTPELLIER
NICE
PARIS

GERMANY
BERLIN
ERLANGEN
FRANKFURT
MUNICH
NURRENBERG

HOLLAND
AMSTERDAM

ITALY
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TSIEKITA
TOKYO

MALAYSIA
PENANG

NEW ZEALAND
CHRISTCHURCH
WELLINGTON

NORWAY
BERGEN

SINGAPORE
SINGAPORE

SPAIN
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REDMOND
SAN DIEGO
SAN FRANCISCO
SEATTLE
STH CAROLINA
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ST. PAUL
WASHINGTON

VISITING SCIENTISTS

Dr. Yves Brandenburger - Geneva
Dr. Ying Cao - Shenyang
Dr. Genevieve Escher - Switzerland
Ms. Celine Fassot - Paris
Dr. Genro Fujisawa - Oyama City
Dr. Gabrielle Gallon-Beaumier - Marseilles
Dr. Xiaoming Gao - Xinjiang
Dr. Kazuhiko Hashimura - Osaka
Dr. Pieter Janssen - Nijmegen
Ms. Loes Kaarsgaren - Utrecht
Dr. Nathalia Kalinina - Moscow
Dr. Matsahiku Kimura - Hamamatsu
Dr. Atsushi Kubo - Tokyo
Dr. Osamu Miyazaki - Tokyo
Ms. Magdalena Rumantir - Jakarta
Dr. Markus Schlaich - Nurnberg
Dr. Simon Slight - Columbia
Dr. Nobuyo Tsunoda - Tokyo
Ms. Helena van der Hoeven - Utrecht
Dr. Cheng Wei - Wuhan

From 2001 onwards the Institute will group the various laboratories described below into six programs (Cardiovascular Neuroscience, Hemostasis and Thrombosis, Cardiology and the Vessel Wall, Cardiovascular Endocrinology and Metabolism, Peptides and Processing and Clinical Trials). This process of consolidation has been in train over the past couple of years, and coalesced early in 2000 in preparation for the 'unbundling' of the Institute Block Funding. Next year the scientific reports will be from each laboratory within each program - i.e. with an overview by the program leader, followed by laboratory reports.

John Funder

ALFRED AND BAKER MEDICAL UNIT

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

Associate Directors:

Hypertension:
Murray Esler BMedSc, MBBS Mel, PhD ANU, FRACP

Atherosclerosis:
Anthony Dart BA , BMBCh, DPhil Oxon, MRCP

Laboratories:
Alex Bobik BPharm Vic, MSc, PhD Syd

Medical:
Jane Thompson MD, MBBS Mon,
James Cameron BEElecHons, MEngSc, MBBS Melb, CPEBiomed,
Christoph Gatzka MD

Nursing:
Virginia Cable SRN (Menopause Clinic)
Elizabeth Jenkins SEN
Janis Jennings SRN
Leonie Johnston SRN, CCN, SCM
Sally Kay SRN, BBM Mon
Louise Noonan SRN, BApplSc Deakin
Marijke Tress SEN
Di Wilson SRN

Laboratory Manager:
Elizabeth Dewar BSc Mon

Technical & Professional:
Lesley Delcourt
Cleo Martin
Marcus Somerville

Administration:
Amanda Coates BA Mon
Viccy Wootton

Research Students:
Karen Murchie BScHons Mon
Andrew Taylor MBBS Mel, FRACP
James Shaw MBBS FRACP Mel

The ABMU is the primary interface between basic and clinical research at the Baker. An NHMRC Centre of Clinical Excellence in Hospital-based Research Grant to the ABMU has fostered clinical research amongst a number of science graduates and instructed cardiology trainees in research methodology.

The ethical framework, collection methodology and databases for a Cardiovascular Gene Bank have been established. We will collect 10,000 samples over the next two to three years, making this one of the most comprehensive cardiovascular genetic databases in the world. Gene Bank samples will be used to identify new genetic markers for cardiovascular diseases, and will provide a resource for pharmacogenetic research.

We have introduced clinical databases in all report-generating areas of cardiovascular medicine and linked them to a common demographics database. This process will ensure that patients are uniquely and reliably identified and that data from different sources is compatible.

Projects aimed at improving physician and patient compliance with published, evidence-based medicine have shown that computer-generated, personalised, evidence-based recommendations considerably improved adherence to best practice. Our findings from basic research projects on the effects of exercise in heart failure have been widely-adopted across Australia.

Other specific research findings are reported elsewhere in individual laboratory reports from Cardiovascular Nutrition, Cell Biology, Clinical Physiology, Experimental Cardiology, Human Neurotransmitter Research, Molecular Neurocardiology and Vascular Pharmacology.

CARDIAC SURGICAL RESEARCH UNIT

Heads:
Unit - Franklin Rosenfeldt MBBS, MD Adel, FRCSE, FRACS
Laboratory - Salvatore Pepe BScHons Flin, PhD Adel, GradDipHealthCouns Sth Aust

Scientific:
Ruchong Ou MBBS Kunming
Michelle Wowk BAppScHons Swinburne
Freya Sheeran BA, BScHons Mon

Research Nurse:
Robbie Brown RN

Research Students:
Sophie Gohl BSc Biomed Mon
William Lyon MBBS Flin
Silvana Marasco MBBS Mon
Ross McNeil BSc LaTrobe
Francis Miller MBBS Mon

Administrative:
Christine Ditterich

As the heart ages, there are numerous changes in anatomy and biochemistry which in turn alter cellular structure, function and the response to pathological stress. We completed a three-year clinical trial in which patients awaiting coronary artery bypass surgery were treated with coenzyme Q10, a natural agent involved in the provision of energy. The treatment produced major myocardial benefits which reduced the times patients spent in intensive care and in hospital overall.

We have shown that in human heart tissue, a 4977 kb deletion of mitochondrial DNA is associated with impaired cardiac protein synthesis and heart function, and is more abundant with age. In patients, this deletion was also associated with rapid irregular heartbeat post-operatively.

To improve the preservation solutions used in cardiac surgery and heart transplantation, we have begun to study the synthesis and role of opioid peptides in heart tissue. We have also examined the protective role of specific opioids on mitochondrial metabolism and contractile function of human heart in vitro during ischemia and recovery.

Our studies on artificial heart pumps to improve the quality of life for patients awaiting heart transplantation have continued. When transplanted into sheep, they have gradually extended planned survival from 48 hours to 4 weeks. A six-month trial is planned for 2001.

CARDIOVASCULAR NUTRITION LABORATORY

Head:
Paul Nestel AO, MD, FTSE FRACP

Professional & Technical:
Marja Cehun BEd
Sylvia Pomeroy BSc, RdtGrad DipEd, MPH

Our main objective is to identify dietary components likely to prevent heart disease by adding various nutrients to the diets of study participants, and regularly assessing outcomes relevant to cardiovascular health. These outcomes include arterial function, blood pressure and levels of cholesterol and triglyceride.

We continued our studies into fish oil and found that the improvement in arterial elasticity was due to two beneficial effects on the circulation - falls in both blood pressure and the resistance in smaller arteries.

Due to their cholesterol-lowering properties, plant sterol esters are now widely eaten in margarines. To extend the range of foods containing plant sterols, we tested their incorporation into cereal, bread and even a butter spread. For each of these foods, cholesterol was lowered substantially, without the potential, but unwanted, effect of impaired absorption of fat-soluble vitamins.

We have commenced a large trial, including men and women, to test the effects of various mixes of red clover isoflavones (phytoestrogens) on elasticity of the aorta, blood flow in the smaller arteries of the leg and arm and 24-hour blood pressure. To determine which manufactured food is best for providing isoflavones, we are also comparing how effectively isoflavones are absorbed when added to whole foods such as soybeans, and breakfast cereal.

CELL BIOLOGY LABORATORY

Head:
Alex Bobik BPharm V.I.C., MSc Syd, PhD Syd

Scientific:
Alex Agrotis BScHons, PhD Mon

Professional:
Peter Kanellakis BSc Mon
Melanie Condron BScHons LaTrobe (to April, 2000)
Giovanna Di Vitto BScHons Melb (from May, 2000)
Gina Kostolias BScHons LaTrobe

Postdoctoral Fellow:
Atsushi Kubo MD Tokyo

Research Students:
Andrew Taylor MBBS Mon, FRACP
Dassad Mulijono MBBS Mon, FRACP

Growth factors control processes in the blood vessel wall during normal development and in many vascular disorders.

We have proposed that transforming growth factor-beta (TGF-ß plays a key role in the development of fibrofatty atherosclerotic lesions, which are unstable regions within blood vessels, likely to rupture and cause strokes and heart attacks.

We have shown that TGF-ß contributes to the build up of reactive oxygen that can cause abnormal gene expression and even cell death in these lesions. TGF-ß activates the enzyme NADPH oxidase in monocyte/macrophages, but not in smooth muscle cells. Similar effects are also induced by another growth factor, interferon-gamma.

Our studies have indicated that TGF-ß protects monocyte/macrophages from death by reactive oxygen at high concentrations. These cells can then promote the premature death of smooth muscle cells in fibrofatty lesions, making the lesion more susceptible to rupture.

We have shown that the survival and proliferative ability of vascular smooth muscle cells after invasive procedures on blood vessels, such as angioplasty, are dependent on the cells' response to different fibroblast growth factors and that the morphology of the smooth muscle cells determines their ability to proliferate.

CELL BIOLOGY OF DIABETES

Head:
Peter Little B Pharm Melb MSc, PhD (Syd)

Professional & Technical:
Natalie Kvalheim BAppSc RMIT
Luke Robinson B AppSc Mon

Research Students:
Stephanie De Dios BScHons Mon
Julie Nigro

We study the properties of smooth muscle and endothelial cells from blood vessels and how they are affected by the high blood glucose concentrations which occur in diabetes, and by drugs used to treat cardiovascular risk factors in people with diabetes. These drugs are known to lower glucose and lipid levels, but our interest lies in whether they also have direct actions on blood vessels which reduce cardiovascular disease.

We found that gemfibrozil, used to lower blood lipids, inhibited the growth of vascular smooth muscle cells at normal, but not high, glucose concentrations. At both low and high glucose levels, gemfibrozil also inhibited the production and reduced the size of the proteoglycans made by these cells. We are now planning to measure the interaction between these modified proteoglycans and human lipoproteins which transport cholesterol and triglycerides.


Peter Little

We have commenced studies on three of the glitazone family of anti-diabetic drugs. Their varied actions on vascular smooth muscle cells suggest that they may have differing abilities to prevent vascular disease.

To fill the gaps in our knowledge of glucose metabolism in vascular smooth muscle cells, we have begun a systematic study of the factors controlling glucose utilization. This information will underpin the design of future experiments.

CELLULAR BIOCHEMISTRY

Head:
Elizabeth Woodcock PhD Macquarie

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Bing Hui Wang PhD LaTrobe

Technical:
Bronwyn Rees DipApplSci Swin

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

Our research explores the functional importance of inositol phosphate signalling pathways in heart muscle, with a view to understanding how cardiac arrhythmias arise and how hypertrophic growth is initiated and progresses to heart failure.

During 2000 we identified a novel anti-hypertrophic mechanism. Transgenic mice expressing a 50-amino acid peptide from the C-terminus of Gqα did not develop the hypertrophy and heart failure in response to pressure overload that was seen in non-transgenic mice.

To investigate how this peptide inhibits hypertrophic signalling, we used the neonatal rat cardiomyocyte model. The Gq peptide inhibited the signalling from α1-adrenergic receptors to two hypertrophic reporter genes by pathways which we have now largely characterised.

We extended our studies on the control of inositol phosphate responses in heart by adrenergic receptors to show that stimulation of α1-receptors activated the ß1- isoform of phospholipase C (PLC), whereas responses to ATP were mediated by a different isoform. These results suggested that the PLC isoform determined specificity, since both receptor populations couple through the same G protein.

We found that the influx of Ca^{2+} rather than of Na^{+} was essential for the reperfusion-induced, increased production of Ins(1,4,5)P3 in isolated rat hearts, since the response required activation of the Na^{+}/Ca^{2+} exchanger in addition to activation of the Na^{+}/H^{+} exchanger.

CLINICAL PHYSIOLOGY

Head:
Bronwyn Kingwell BScHons, PhD Melb

Professional & Technical:
Melissa Formosa BSc VUT
Tamara Waddell BScHons Mon

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

A major aim of our studies is to evaluate whether the stiffness in large arteries can be used as a marker of cardiovascular risk.

Recently we have shown that large artery stiffness is a major contributor to chest pain during exercise in patients with coronary artery disease (CAD) and have begun to look for genes associated with arterial stiffening.

Our investigations have focussed on two genes. We have shown that variations in the gene coding for stromelysin-(an enzyme that regulates proteins in the arterial wall) affect how arteries stiffen with age. Furthermore, genetic variation in fibrillin-1 (an extracellular matrix protein linked to stiffening in Marfan syndrome) is also associated with stiffening in the large arteries of patients with CAD. These genetic investigations could help to identify patients at particular risk who could then be targeted for therapy.

From a therapeutic perspective, we have shown that aggressive treatment of elevated cholesterol leads to a decrease in large artery stiffness in patients with isolated systolic hypertension.

Finally, we have shown that nitric oxide appears to be important for the uptake of blood glucose into muscle in people with type 2 diabetes. This work highlights the potential of the nitric oxide system as a therapeutic target in these patients.

EXPERIMENTAL CARDIOLOGY LABORATORY

Head:
Anthony M. Dart BA, BMBCh, DPhil Oxon, FRCP

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Professional & Technical:
Elodei Percy BScHons Melb

Research Students:
Deepak Haikerwal MBBS Mon, FRACP
Xiaoming Gao MBBS Xinjiang
Mark Krawczyszyn MBBS Mel, FRACP

Our research focuses on the adrenergic mechanisms underlying the pathogenesis of cardiomyopathy, myocardial hypertrophy and heart failure. Much of our research involves the study of transgenic mice which overexpress $\alpha 2$-adrenergic receptors in the heart.

We have extended earlier studies by testing whether various drugs were effective in treating age-related fibrotic cardiomyopathy and heart failure in this mouse model.

We have shown that male mice are more susceptible than females to the development of cardiac hypertrophy, fibrosis and ventricular dysfunction, making this strain of mice useful in the study of how sex hormones affect the onset of heart disease.

Our transgenic mouse model has also provided evidence that higher levels of collagen in the heart, as occurs in the young animals, provide protection against the damage caused by experimentally-induced heart attack.

We showed that sympathetic neurons grown in culture had different functional properties if they were grown together with cardiac muscle cells, under both normal conditions and simulated conditions of low blood flow. We are studying how the muscle cells, which are a target for the neurons, are able to modulate neuronal function.

During 2000, seven scientists visited our laboratory to learn the techniques which we have developed specifically for research on mice.

H and L HECHT HORMONES AND THE VASCULATURE LABORATORY

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

Professional & Technical:
Meryl Fullerton BSc
Virginia Cable RN
Betty Kafanelis BSc, MA
Kazuhiko Hashimura MD
Aozhi Ling MD China

Research Students:
Shanhong Ling MD China
Maro Williams BScHons
Robert Lew MBBS, FRACP
Tye Dawood BSc
Anna Calkin BSc
Suzie Honisett BScHons
Martin Elmes

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

Dehydroepiandrosterone (DHEA) beneficially affects blood vessel cells in culture. We have now shown in clinical studies that DHEA improves endothelial function.

Aspirin is effective in reducing heart attacks but can have unpleasant side effects. It acts by blocking cyclo-oxygenase enzymes, or COX. The drug Celebrex is an example of a new type of COX inhibitor, designed to overcome the side effects of aspirin, which we have studied in a group of postmenopausal women. COX 2 inhibition appeared to improve endothelial function in small blood vessels, possibly acting in a similar way to estrogen.

Stress is an important risk factor for heart disease. We examined the effects of testosterone treatment on stress responses in hypogonadal male sheep. Our findings support the view that testosterone replacement in hypogonadal men is likely to improve cardiovascular health.

Programmed cell death, or apoptosis, may contribute to cardiovascular damage. In studying the effects of testosterone and DHEA on apoptosis in vascular endothelial cells in culture, we found that

testosterone, but not DHEA, enhanced apoptotic damage.

HUMAN NEUROTRANSMITTER RESEARCH LABORATORY

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

Scientific Staff:
Jacquiline Hastings BSc, PhD Deakin
Gavin Lambert PhD Mon
Elisabeth Lambert PhD Paris, France
John Power BVSc UQ PhD Mon
Markus Schlaich MD Freiburg, Germany

Professional & Technical:
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Flora Socratous BSc LaTrobe

Research Students:
David Barton MBBS NSW
Melissa Byrne BScHons RMIT
Nina Eikelis BScHons Mon
Magdalena Rumantir DM BMedSci Jakarta, Indonesia
Glen Weisner BScHons Melb

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

We have investigated the mechanisms of the known link between stress and heart disease by studying brain neurotransmitter changes and the responses in the sympathetic nervous system. Patients with depression had a lower turnover of noradrenaline, dopamine and probably also serotonin, in the brain. In healthy subjects, serotonin turnover was related to levels of bright sunlight.

High blood pressure is mediated by nerves, through a variety of processes, in about 25% of patients. Our findings could provide a theoretical base for the development of new drugs to treat hypertension.

After a heart attack, remodelling of the heart is at first a beneficial response, but it can progress to harmful dilation of the left ventricle, a condition for which the favoured treatment is high-risk surgery. We have found that encasing the ventricle in a supporting mesh is a promising alternative treatment. It is under evaluation in human trials.

We have shown leptin gene expression and leptin release in the rat and human brains, a finding that has lead to a paradigm shift in the understanding of the biology of leptin.

LIPOPROTEIN - ATHEROSCLEROSIS LABORATORY

Head:
Noel Fidge BScHons, PhD Adel

Scientific:
Dimitri Sviridov PhD Moscow
Gabrielle Gallon PhD, France
Anh Luong BScHons Melb

Technical & Professional:
Sarah Siggins BScHons Melb (to May)
Brian Drew BSc Deakin (from May)
Kally Theodore BSc LaTrobe (from September)
Fu Ying MSc LaTrobe

The focus of our research effort has been on understanding the role of the protein apoA-I in determining the function and metabolism of HDL. We have assigned specific functions to regions of the apoA-I molecule. Amino acids 140-150 are responsible for activation of the enzyme LCAT which is important in cholesterol transport. The region 63-73 was recognized as a second lipid-binding domain.

The presence of the pro-peptide, which is normally attached to newly-synthesized apoA-I and later removed, was found to increase the secretion of apoA-I, but to decrease the conversion of pre ß-HDL to α-HDL, a process which may be linked to reverse cholesterol transport.

Little is known about the reaction that cleaves the pro-peptide from the N-terminus to give the mature apoA-I protein. We found that deleting large segments from the C-terminus had little effect, whereas changing the amino acids surrounding the pro-peptide blocked the removal. The enzyme activity for cleavage was dependent on Ca^{++} and appeared to be a metalloproteinase.

Cross-linking studies have produced a number of cell signalling proteins that respond to apoA-I, and may trigger cellular events that are potentially antiatherogenic. Apart from forming cross-links with its known receptors, HB2 and SR-B1, apoA-I interacted closely with three other intracellular proteins. These are currently being identified by sequencing.

THE EMILY STEWART MOLECULAR ENDOCRINOLOGY LABORATORY

Head:
Walter Thomas BScHons, PhD UQ

Scientific:
Hongwei Qian PhD, WVU (USA)
Thao Pham

Technical & Professional:
Luisa Pipolo AssocDipAppSc Swin

Research Students:
Felicity Chalmers BAppScHons RMIT
Döne Onan BAppScHons RMIT
Alice Holloway BSc Melb

We study the hormonal control of blood pressure, including regulation of the receptors for the vasoconstrictor, angiotensin II, and

biosynthesis of the salt-retaining hormone, aldosterone.

In what is thought to be a fixed sequence, the signal produced by stimulation of the angiotensin II receptor, AT_1, is terminated by receptor phosphorylation, arrestin binding and internalisation. However, we have continued to investigate the alternative possibility that the AT_{1A} receptor can switch between different shapes which determine receptor coupling to different downstream events (e.g., signalling, internalisation or phosphorylation).

We have used angiotensin II and analogues to further define which specific contacts between angiotensin and the receptor promote these different receptor states. We have also developed an enhanced green fluorescent protein-tagged AT_{1A} receptor that allows direct visualisation of the receptor in the cell by confocal microscopy.

We have investigated the controversial role of arrestins in the deactivation of AT_{1A} receptors, using co-immunoprecipitation of normal and mutated AT_{1A} receptors with ß1- and ß2-arrestins. This interaction, which requires angiotensin II stimulation, depended on specific phosphorylation within the carboxyl-terminus of the receptor.

Mutations in the gene for aldosterone synthase that may relate to low activity of this enzyme and observed clinical features have been identified in a child patient.

MOLECULAR GENETICS LABORATORY

Head:
Timothy Cole BScHons, PhD Melb

Professional:
Morag Young BScHons Mon, PhD Mon

Research Students:
Isabelle Hoong BScHons Mon
Jared Purton BScHons Mon
Tanya Medley BScHons Mon
Louise Williams BSc Melb (from Nov)

During 2000, we extended our studies on two key steroid hormones - the mineralocorticoid, aldosterone, and the glucocorticoid, cortisol.

We had shown that the cardiac fibrosis appearing in rats after 4 to 8 weeks of treatment with high mineralocorticoid levels plus salt

was prevented by agents that neutralized the mineralocorticoid receptor. Follow-up studies have commenced to look at the early cellular changes arising from this treatment, and the mediators of inflammation that precede fibrosis.

Steroid hormones are known to promote fibrosis. We examined whether steroid hormones, produced mainly in the adrenal gland, might also be produced in the heart. Tissue from failing human hearts produced very low levels of the enzymes that make steroid hormones, suggesting that any contribution from the heart was unlikely to affect the levels of these hormones in blood. Aldosterone activates a growing list of genes in target tissues such as the kidney. We have added a kinase enzyme gene, SGK1, to the list and are investigating two other similar genes, SGK2 and SGK3.

With the ABMU, we are identifying variant genes that predict susceptibility of patients to coronary artery disease. Two genes of importance in the structure of arteries, fibrillin-1 (the Marfan's gene) and stromelysin-1 have been associated with a higher risk of developing stiffer arteries.

MOLECULAR HYPERTENSION LABORATORY

Head:
Dr. Zygmunt Krozowski BScHons WA, PhD Syd

Scientific:
Dr. Phillip Brereton PhD Melb (until October 2000)

Professional & Technical:
Varuni Obeyesekere BScHons Mon
Carla Duarte BScHons LaTrobe
Michelle Cinel CertVetNursing, AssocDipAppSci(AnimalTech)

Our primary interest is the role of steroid dehydrogenases in hypertension and heart disease. The enzyme 11ß-hydroxysteroid dehydrogenase type II (11ßHSD2) converts active glucocorticoids to inactive metabolites. In vivo, 11ßHSD2 protects the mineralocorticoid receptor (MR) from inappropriate activation by glucocorticoids in target tissues for mineralocorticoids, such as kidney.

We have shown colocalisation of 11ßHSD2 and MR in the human placenta and eye, suggesting the enzyme's possible role in fluid homeostasis. In the aromatase deficient mouse, 11ßHSD2 expression in the kidney is stimulated by estrogens. In complementary studies, we showed that 11ßHSD1 was localised in rat heart fibroblasts and interstitial cells of the lung and kidney.

Much effort has gone into characterising the enzyme, Pan1b, which exhibits 17ßHSD activity (and has therefore been renamed 17ßHSDXI) and, unlike all other members of this family, is found in peroxisomes.

In the foetus, staining for this enzyme was found in ciliated epithelia of the lung throughout gestation and appeared stronger later in pregnancy.

It was also found in the non-pigmented epithelium of the ciliary body of the eye, and in adrenocortical tumor cells. From its location, 17ßHSDXI may be involved in steroidogenic pathways and activity studies suggest that it may also be important in androgen metabolism.

MOLECULAR PHYSIOLOGY LABORATORY

Head:
John Funder BA, MDBS, PhD Melb, FRACP

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Dominic Autelitano BScHon, PhDs Mon
Ross Hannan BscHons, PhD Tas
Karen Sheppard BSc Hons PhD Mon

Professional & Technical:
Meryl Fullerton MSc Melb (to May)
Anna Jenkins DipApplSCiBiolSci Swin
Kathy Myles DipAppSCi RMIT, BSc Hons Melb
Rebecca Ridings DipLab Tech Penin TAFE

Research Students:
Lydia Labib BscHons Mon

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

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

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

We have investigated steroid-metabolizing enzymes that control the concentration of

steroid in cells, characterized two novel nuclear steroid receptors that bind a metabolite of glucocorticoids, and studied the effect of differential steroid receptor dimerization on transcription of genes responsive to corticosteroids.

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

THE JO GUILIANO MOLECULAR NEUROCARDIOLOGY LABORATORY

Head:
David M Kaye MBBSHons Mon, PhD Mon FRACP FACC

Professional & Technical:
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Samara Cairns BScHons Melb

Research Students:
Ann Aggarwal MBBS Melb, FRACP
Melinda Parnell BAppSci Deakin
Magda Rumanitir MD Indonesia
Glenn Wiesner BScHons SmGds Melb
Belinda Ahlers BScHons James Cook

The work of the laboratory continues to focus on the neurobiology of the sympathetic nervous system in the context of the failing heart and the role of the L-arginine/nitric oxide system, particularly in heart failure.

We have extended our previous finding of fewer sympathetic nerves in the failing heart, thought to be caused by decreased synthesis of nerve growth factor (NGF). We have commenced studies on how heart muscle cells make and release NGF, and on the potential of NGF as a treatment for heart failure.

We are currently examining the effects of NGF administration on heart function, and will look at the hearts of mice genetically engineered to produce large amounts of NGF in their hearts. In clinical studies, we have examined the relationship between blood pressure within the heart and the activity of sympathetic nerves, and how various novel treatments may beneficially influence this relationship in heart failure patients.

In blood samples and tissues from patients with heart failure, we have identified for the first time a difference in the way the cells use L-arginine. This finding may lead to new approaches to the treatment of heart failure.

MOLECULAR SIGNALLING

Head:
Jun-Ping Liu MD Beijing, PhD Mon

Scientific:
He Li MD Beijing, PhD Mon
Fi-Tjen Mu MD Taiwan, PhD Mon

Research Students:
Ying Cao BMed, MMedSc China
Ling Guo BMed Shanghai

We study aspects of cell signalling – or how information is transferred within cells – including the regulation of telomerase activity, characteristics of the GTP-binding protein dynamin II, and how stress-sensitive MAP kinase enzymes influence the actions of hormones and growth factors.

Telomerase is an enzyme complex

with a key role in the control of a cell's replicative lifespan. We have found that in genetically hypertensive rats, selective activation of telomerase in vascular smooth muscle cells accounts for excessive production of the cells.

In cultures of vascular smooth muscle cells, down-regulation of telomerase led rapidly to programmed cell death, unless the tumour suppressor protein p53 was added to the cells. Telomerase also prevented programmed cell death in cardiomyocytes from neonatal rats. Our data suggest that telomerase protects the integrity and stability of the genome, which are also regulated by other signalling molecules, including p53.

We have cloned two new proteins. One is an ATP-binding protein found only in the Golgi apparatus

of nerve cells. The other is a novel heart protein, potentially involved in mitosis. We propose to further characterise these newly-identified molecules.

MORPHOLOGY LABORATORY

Head:
Rodney Dilley PhD WA

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

Our research examines how the growth of cardiovascular tissues is regulated under normal conditions and in disease states.

We have used genetically modified mice to test whether breakdown of fibrin is important in the remodelling of blood vessels. In an experimental model of hypertension, we found that remodelling of the cardiovascular system was stimulated and that fibrin breakdown was decreased. Follow-up studies suggested that fibrin may be important in providing support to the vessel wall during remodelling.

We have found that heparin, which prevents blood from clotting, inhibited up to 70% of the growth of human vascular smooth muscle cells in culture. Smaller fragments of heparin, some of which are used clinically, also inhibited cell proliferation.

Repair of the endothelial cells lining blood vessels strongly inhibits the growth responses that occur when vessels are injured. In examining the detailed structure of interactions between endothelial and smooth muscle cells, we have found numerous close junctions, the function of which is currently unknown.

An enzyme that is thought to influence local glucocorticoid levels, 11ßHSD1, is produced at high levels in the interstitial cells of the kidney and lung. Using electron microscopy, we have found the enzyme in the endoplasmic reticulum and nuclear membrane of these cells.

NEUROPHARMACOLOGY LABORATORY

Head:
Geoffrey Head BScHons Melb, PhD Mon

Scientific:
Dmitry Mayorov BScHons, PhD Moscow

Professional & Technical:
Sandra Burke BScHons Syd, MSc Mon
Shirley Godwin BAppSc RMIT

Research Students:
Candy Chan BPharm VCP, BScHons Mon
Anna-Maria Arabia BScHons Melb

We study how the central nervous system (CNS) controls the heart and circulation in normal conditions as well as during hypertension, environmental stress and heart failure. Our main interest lies in how neurotransmitters in the CNS influence the sympathetic nervous system and blood pressure.

We have shown that the kidney hormone, angiotensin, may act in the brain of rabbits to mediate stress responses that are greater if the animal has high blood pressure. We recently discovered that metabolites of dietary isoflavones lower blood pressure in hypertensive rats.

From a collaborative study, we found that in rats with heart failure, noradrenaline levels are elevated in a brain region important in cardiovascular control, and control of the heart by the CNS is impaired.

Strokes and heart attacks are more likely to occur in the morning, when blood pressure increases from the overnight low level. We showed that the rate of increase in blood pressure on awakening is higher in hypertensive rats than in normal rats. We have now patented the method that we developed to record changes in blood pressure over 24 hours and have found that in human subjects, the rate of increase in blood pressure on waking is highest in patients with hypertension.

PEPTIDE BIOLOGY LABORATORY

Head:
Ian Smith PhD Mon

Scientific:
Rebecca Lew PhD Virginia
Kelly Maxwell PhD Melb (until July 2000)
Mark Lanigan PhD Melb (from May 2000)
Mike Yarski PhD Calif (from Oct 2000)

Professional & Technical:
Shane Reeve AssocDipAppSci Lab Tech
Cath Hamilton

Research Students:
Nathalie Tochon-Danguy BScHons LaTrobe
Ursula Norman BScHons Mon

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

The enzymes on the surface of vascular endothelium, which lines blood vessels, have a number of activities that affect blood pressure. They can inactivate vasodilator peptides such as atrial natriuretic peptide and bradykinin, generate vasoconstrictor peptides such as endothelin and also convert angiotensin I into the active vasoconstrictor, angiotensin II. Thus, by manipulating the activities of these peptidases, we may be able to control cardiovascular function.

We have developed and validated a novel platform technology to generate specific peptidase inhibitors. It involves the incorporation of beta-amino acids into substrates for peptidase enzymes. Compared with the normally incorporated alpha amino acids, the beta form stabilises peptide bonds.

We are now in the process of using these inhibitors to learn more about how membrane-bound and secreted metallopeptidases regulate blood pressure. In addition, our finding that these modified peptide substrates can act as potent, specific inhibitors has enormous promise for the design of specific inhibitors with therapeutic potential.

HAZEL AND PIP APPEL VASCULAR BIOLOGY LABORATORY

Head:
Michael Berndt BScHons, PhD Qld

Scientific:
Robert Andrews BScHons, PhD Qld
Michael Hickey BScHons, PhD Melb
Yang Shen MMedScHons China, PhD Adel
Elizabeth Gardiner BScHons, PhD Mon

Professional & Technical:
Cheryl Berndt Cert Lab Tech Syd
Carmen Llerena AssocDip
Lab Tech Pens TAFE
Andrea Aprico BScHons Mon
Catherine Upton BScHon Mon

Our research looks at the role of blood platelets in arterial thrombosis. Adhesion of platelets where an atherosclerotic plaque has ruptured, or their activation by high shear stresses found at sites of arterial constriction, may result in a clot which blocks the artery. Both of these events are mediated by the platelet adhesion receptor, the GP Ib-IX-V complex, which binds a protein on vessel walls called von Willebrand factor.


Catherine Upton

We have defined regions of von Willebrand factor and GP Ib-IX-V important for shear- dependent interaction and identified a number of antibodies to von Willebrand factor which may inhibit shear-dependent platelet aggregation without stopping blood flow.

We have shown that two subunits of GP Ib-IX-V bind the intracellular calcium sensor, calmodulin, an interaction which is lost when platelets are activated. This finding suggests that calmodulin binding may mediate

one or more aspects of GP Ib-IX-V signaling.

We have recently set up an Intravital Microscopy Suite for analysing the interaction of blood cells within the vessel wall, in real time and in living animals. Studies have commenced which examine the role of white cells in a mouse model of systemic lupus.

VASCULAR PHARMACOLOGY LABORATORY

Head:
Jaye Chin-Dusting BScHons, PhD Mon

Professional & Technical:
Ann-Maree Jefferies BScHons Melb
Jennifer Starr

Research Students:
Brindi Rasaratnam MBBS Mon, FRACP
Belinda Ahlers BScHons James Cook
Ross Anderson

A major study was commenced this year at University College London to examine how high levels of cytokines, present in cardiovascular disease states such as heart failure and liver cirrhosis, influence the pathway for the production of nitric oxide. The research involved injecting cytokines, which are secreted proteins involved in inflammatory responses, into the veins of human volunteers and assessing L-arginine transporter activity. Plans are currently under way to complete these studies in Melbourne.

We completed a long-term clinical trial examining the effects of the antibiotic, norfloxacin, on hyperdynamic features of patients with liver cirrhosis. Such features included decreased total peripheral resistance and increased cardiac output. A major clinical sequelae of liver cirrhosis is high blood pressure in the portal circulation (vessels supplying the liver).

Previous studies from our laboratory had shown that the excessive vasodilation seen in patients with cirrhosis may result from stimulation of nitric oxide production in the vessel wall, caused by bacterial endotoxins arising from the gut. We performed a clinical trial which showed for the first time that decontamination of the gut with norfloxacin successfully reversed the hyperdynamic syndrome in these patients.

We have also shown that endothelium function in healthy people, but not in patients with coronary artery disease, followed a 24-hour rhythm.

CARDIOVASCULAR DISEASE PREVENTION UNIT

Head:
Christopher Reid BA, DipEd Qld, MSc WVU, PhD Mon

Administration:
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Research Staff:
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Suzanne Corcoran SRN
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Fiona Harper SRN
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Debra Hynd SRN
Suzanne Lipshut SRN
Anne Lyons SRN
Jan McCormick SRN
Tui Muir SRN (to Dec)
Kathryn Murphy SRN
Heather Norris SRN (from Sep)
Jan Peake SRN (from Nov)
Nolene Perry SRN (from Aug)
Alain Psyche (to Apr)
Fran Stewart
Christine Tauschke SRN
Liz Thomas SRN
Dianne Vincent SRN (from Aug)
Frances Walker SRN
Suzanne Warren SRN (from Sep)

Scientific:
Elisa Donaldson (from Dec)
Debbie Hilton BPhty, MPH
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Yu Lu Liang MBBS, PhD
Mark Nelson MBBS Mon, MFM, FRACGP
Leone Piggford MBBS
Melinda Rockell BScHons
Louise Shiel BSc Qld, GradDipAppSci Swin

The Australian National Blood Pressure Study, ANBP2, is a joint venture between the Commonwealth Government, the pharmaceutical industry and the High Blood Pressure Research Council of Australia, which is comparing two types of treatment for high blood pressure - ACE inhibitors versus diuretics. More than half of the hypertensive patients enrolled in ANBP2 have also taken part in sub-studies, including the importance of left ventricular hypertrophy and ambulatory blood pressure monitoring in the management of hypertension. ANBP2 will conclude in December, 2001.

The OPERA study is an international placebo-controlled trial of the treatment of borderline isolated systolic hypertension in older people using omapatrilat, a drug to treat high blood pressure that may have particular benefits in managing high systolic pressure. The trial, in which we will enrol 1500 patients and monitor their progress once a year for five years, is important because as yet there are no outcome data to support the current recommendations to treat borderline isolated systolic hypertension.

We have been appointed by the Australian Society of Cardiothoracic Surgeons as a Data Management and Analysis Centre for a project to identify key performance indicators for cardiac surgical outcomes. The project will initially involve developing a standard database for use in each of Victoria's public hospitals and models to measure surgical performance. Results from the Victorian study will form the basis for extending the project nationally and internationally.

ELEANOR SHAW CENTRE FOR THE STUDY OF MEDICINE, SOCIETY AND LAW

Director:
Paul Komesaroff BScHons, MBBS, PhD, FRACP

Research Students:
Bella Brushin MD Russia
Katrina Bramstedt BEng, MBioethics Loma Linda, USA
Rhian Parker MA UK
Kelvin Lam BSc Mon

Research Staff:
Deborah Zion PhD Mon
Kylie O'Brien MPH Mon

Administrative Assistant:
Victoria Baldwin BA, DipEd

The Eleanor Shaw Centre for the Study of Medicine, Society and Law provides a forum for the discussion of the relationship between medicine and the biological sciences and society. The Centre hosts lectures and symposia and, in conjunction with the Science Unit of the ABC, the annual Eleanor Shaw Lecture. The seventh Eleanor Shaw Lecture, "Bioethics - the first fifty years: was it worth it?", was delivered by Emeritus Professor Max Charlesworth AO, with a commentary and panel discussion by Professors Fiona Stanley AC, John Funder AO and Alex Cohen AO.

Staff, students and associates of the centre are involved in various research projects including investigation of the microethics of the medical consultation process; ethical aspects of aging and the quality use of medicines in non-English speaking communities.

Other projects examine the ethical implications of information technologies in medicine, ethical issues at the end of life and the use of complementary medicines among patients with HIV/AIDS.

We have established a Health Ethics Archive-an interactive, electronic archive of the experiences of ethics committees and researchers which will help bring consistency to decision-making related to ethics. Our clinical ethics service, established at the Alfred Hospital, offers assistance for patients, relatives and staff on ethical issues.

RISK REDUCTION CLINIC

Head:
Jan Jennings SRN

Nurses:
Virginia Cable SRN
Elizabeth Jenkins SEN
Marijke Tress SEN
Di Wilson SRN

Administration:
Amanda Coates BA Mon
(Menopause Clinic)

The Risk Reduction Clinic performs free screening to members of the community for risk factors related to diseases of the heart and circulation. The approach to screening is to apply simple and cost-effective tests, linked to lifestyle, that are of proven usefulness. We measure cholesterol and triglycerides and obtain information from a lifestyle questionnaire. Where necessary, the initial contact with the Risk Clinic may be followed up by medical intervention.

A close link exists between the Risk Clinic and the ABMU research interests in prevention of cardiovascular disease, nutrition and exercise. Staff at the Risk Clinic are involved in acquiring samples for the Gene Bank and a broad range of research studies in addition to their critical role of recruiting subjects for ABMU studies.

Research continues into finding better methods of defining risk in healthy subjects. In collaboration with Dr David Torpie of the University of Queensland a study of the genetic basis of chronic fatigue syndrome was recently completed.

The clinic provides a base for the Menopause Clinic and also for nutrition studies performed by the Cardiovascular Nutrition Laboratory.

MENOPAUSE CLINIC

Medical Staff:
Paul Komesaroff BScHons, MBBS, PhD, FRACP
Eleanor McDonald MBBS, FRACGP
Gisela Wilcox FRACP
Krishna Sudhir FRACP
Euhana Varigos MBBS, FACA
Sam Hargreaves MBBS, FRACOG

Nurses and Research staff:
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Research Students:
Anna Calkin BScHons
Suzy Honisett BScHons
Maro Williams BScHons

Administrative officer:
Mandy Coats BA Mon

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

Other projects range from the effects of estrogens on bone to cultural aspects of menopause, the experience of menopause and aging among women with physical disabilities, and the role of complementary therapies in the management of menopausal symptoms in healthy women. The research undertaken by the Menopause Clinic is closely integrated with that of the H and L Hecht Hormones and the Vasculature Laboratory. It also involves collaborations with other Baker Institute laboratories and with researchers from other institutions.

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