Top of the pile: the institutes

Richard Smith

Critical mass seems to be essential for internationally competitive research. But large research institutions may easily become bureaucratic, atherosclerotic, and unproductive. Another dilemma is that most researchers insist that scientists work best when free to do whatever research they want, but those funding research want value for money and answers to problems with clinical and social importance. Everywhere, those organising research efforts must battle with these dilemmas, and often they fail. The medical research institutes of Australia are organisations that seem well designed to find a middle way, and generally they are, I judge, succeeding.

The institutes have their roots not, however, in any clever plan to solve semiphilosophical dilemmas but rather in a need to provide practical answers to pressing problems. They have mostly grown organically around productive scientists to establish high quality medical research in Australia and to attract back bright researchers from overseas. In the early days the institutes were funded by a mix of private, Commonwealth, state, and foreign funding, but a crunch came in the mid-1960s when the United States National Institutes of Health were forced to cut back drastically on their overseas funding. The two oldest institutes—the Walter and Eliza Hall and the Florey, both in Melbourne—depended heavily on money from the National Institutes of Health and hurriedly had to find an alternative source of funds.

Intense personal lobbying of politicians led the Commonwealth government to put up money for the institutes through the National Health and Medical Research Council (NHMRC). But NHMRC's "murky legal status" meant that it couldn't employ people directly. Thus was invented the block grant that is made to institutes and reviewed five yearly. The researchers in the institutes, even the directors, exist on five yearly support: there is no tenure.

For many years the Hall and the Florey were the only institutes receiving block grants from the NHMRC, although there were others receiving project and programme grants. In the late '70s a politician in New South Wales became upset that the only institutes receiving block grants were in Melbourne and generated pressure for block funding of more institutes. The result was that in 1983 another institute received a grant—the Baker Medical Research Institute in, yet again, Melbourne. (The open conflict between the two universities in Sydney was one stumbling block: the Melbourne universities, I was told, fight behind closed doors.) Later, further institutes were invited to apply for block grants, and the two that were successful were the Garvan Institute in Sydney and the Murdoch Institute for Research into Birth Defects in Melbourne.

A sketch of the institutes

WALTER AND ELIZA HALL

At the end of last year I visited all the institutes that receive block grants from the NHMRC and some of those that don't. The oldest, biggest, richest, and most famous of the institutes is the Walter and Eliza Hall, which began in 1915 and was directed for 21 years by the Nobel laureate Sir Macfarlane Burnet. Connected

Medical research institutes in Australia that receive block funds from the NHMRC

by a bridge to the Royal Melbourne Hospital, it is now directed by Sir Gustav Nossal (known to some of his friends as "Gus Muscle"), a scientist of unrivalled influence in Australia who achieves his ends with a powerful mix of intellect, enthusiasm, and charm.

All of the institutes have (or are at least supposed to have) a theme, and that of the Hall is immunology, which Sir Gus says is an "orienting thing and should be a window not a prison." One comparatively recent highlight in the Hall's history was the discovery of colony stimulating factor, and the institute includes one of the groups in the world closest to developing a malaria vaccine.

The institute, which has six fellows of the Australian Academy of Science (three of whom are also fellows of the Royal Society) among its 320 staff, was recently reviewed by an international committee including two Americans and two Europeans, one of whom was Sir David Weatherall, Nuffield professor of clinical medicine at Oxford. The committee recommended increased funding, and three of the eight groups were reckoned to be outstanding by any international standards.

FLOREY

Just across the road from the Hall institute—on the campus of the University of Melbourne—is the Florey Institute, which since the beginning of this year has been directed by Professor John Coghlan, who has also been chairman of the Australian Medical Research Committee for the past three years. The work of the institute, which now has a staff of just over 100, began in 1947 when the previous director, Professor Derek Denton, cooperated with Professor Sir Douglas Wright, professor of physiology, in studying a patient with a duodenal fistula who had severe fluid balance problems. They later introduced flame photometry into medicine in Australia and laid some of the important groundwork for intensive care. A more recent important achievement has been the cloning and

synthesising of the genes for relaxin, and the institute is now contributing to research on an annual immunisation against pregnancy. The theme of the institute may be described as regulatory processes right through from the gene to physiological regulation.

BAKER

This theme is similar to that being worked out on the other side of Melbourne for the Baker Institute by its new director, Professor John Funder. This institute began in 1926 but had no particular theme until the arrival of Professor Paul Korner as director in 1975. He concentrated the institute on studying cardiovascular disease, particularly hypertension. One of its strengths is its "bench to bedside" studies (it has 15 beds in the adjacent Alfred Hospital), and it has made crucial contributions to the understanding of hypertension. Professor Funder is a neuroendocrinologist with an interest in hypertension and molecular biology, and he is crafting a theme for the institute that will allow the study of cardiovascular disease at the levels of the gene, the cell, the organ, and the whole animal or patient. The arrival of a new director obviously leads to the redirecting of an institute, a process that requires considerable finesse if there is not to be a large fallout.

MURDOCH INSTITUTE FOR RESEARCH INTO BIRTH DEFECTS

Back across Melbourne—on the top floor of the Royal Children's Hospital—is the Murdoch Institute for Research into Birth Defects, which has grown up around Professor David Danks, a clinical geneticist who did his postgraduate training in London. The institute developed within the Royal Children's Hospital Research Foundation with a programme grant from the NHMRC, but in 1982 it spawned itself as the birth defects institute in order to be able to find more money. The Murdoch family, particularly Dame Elisabeth (mother of the well known Rupert), gave it \$A5m in 1986, and in 1987 it got its block grant from the NHMRC. The theme of the institute, which has some 75 staff, is understanding the genetic causes of birth defects with emphasis on what has been called "physiological" genetics. The clinical contacts of the institute are strong: it provides a clinical genetics service for the whole of Victoria and has trained almost all the clinical geneticists in Australia. Its most pressing

problem is lack of space, but this should be solved soon.

GARVAN

Up in Sydney—adjacent to St Vincent's Hospital—the Garvan Institute is also hoping to get a new building. It too has a new director, Professor John Shine, who took over from Professor Leslie Lazarus, who had directed it since 1963. It began as an offshoot of the hospital's endocrinology department and became a true institute in 1975. It absorbed groups interested in breast cancer and bone disease, and its theme now is the molecular biology of multifactorial disease; studies of diabetes are the "remnant" of the endocrinological interests. The institute, which has some 120 staff, has been through some painful transitions but now seems well set for the future.

INSTITUTE OF MEDICAL AND VETERINARY SCIENCE

I also visited two institutes that haven't yet made it to receiving block grants—the Institute of Medical and Veterinary Science in Adelaide and the Queensland Institute of Medical Research in Brisbane. The Adelaide institute was founded in 1938 and now has 750 staff—500 who do pathological service work, 150 who do full time research, and 100 who do both. Dr Brendon Kearney, who as well as directing the institute is chief executive officer of the Royal Adelaide Hospital, believes that this mixture works well—not least because some of the profits from the service work fund the research.

The institute has considerable external funding—including from the National Institutes of Health—and was, when I visited, about to open the Hanson Centre for Cancer Research on the site. Dr Kearney says that the whole institute doesn't want an NHMRC block grant because the South Australian government doesn't provide grants for the infrastructure funding that would be needed. The institute is cooperating in developing a research strategy for the whole campus of the institute, the hospital, and the University of Adelaide, and it is possible that the institute might attempt to develop a theme that would be eligible for a block grant. Whether the institute should develop a theme and oblige researchers to "fit in" or conduct a competition for space within the building was unresolved when I left Adelaide.

QUEENSLAND INSTITUTE OF MEDICAL RESEARCH

The Queensland Institute of Medical Research was founded in 1945 as part of the Queensland department of health to conduct research into the "fevers of Queensland." It was state funded for the next 30 years and still gets 40% of its funds from the state government. It does a wide range of research—into, for example, cancer (particularly melanoma), genetics, epidemiology, Aboriginal health, parasitology, and malaria—and some of its orientation comes from the previous director, Professor Chev Kidson, who believes passionately that Australia is "part of Asia." The institute has grown rapidly in recent years and will have some 350 people working in it when it moves into a brand new building in July 1991. It also has a new director—Lawrie Powell—who is professor of medicine in the University of Queensland and a leading expert on the liver.

The institute has bid for an NHMRC block grant but has failed to get one—ostensibly because it has too diverse a range of research to allow a coherent theme but at least partly because of internal dissension. It is still interested in winning a block grant, and various researchers told me that they didn't think the research in the institute was any more diverse than that in the Hall institute.

Mrs Margaret Thatcher, then British prime minister, and Sir Gustav Nossal, director of the Walter and Eliza Hall Institute of Medical Research, during Mrs Thatcher's visit to the institute in 1988

Organising for maximum effect

There is no point in having an institute unless the sum of the parts is greater than the whole. The basic philosophy of the Medical Research Committee in Australia—like that of many other research funding bodies—is that research initiated by the investigator is best: thus most of its money is spent on project grants awarded through intense competition. When it makes a block grant to an institute the committee loses the ability to peer review individual research projects. It must be sure in return that it gets a bigger bang for the bucks it gives to the institutes.

The institutes have obvious economies of scale with reagents, animals, computer resources, and the like, but they must also offer something more. It is essential that the groups within the institutes interact with each other. The existence of a theme is one way to increase the likelihood that researchers will interact, and the institutes think a lot about their themes: they must be specific enough to be meaningful but broad enough not to restrict constantly the ideas of the researchers. Researchers are encouraged to fit within the themes—mostly by gentle persuasion—but sometimes scientists pursue exciting paths that lead them away from the themes. These people are likely to be encouraged to go elsewhere and usually this happens amicably. One problem is, however, that you cannot take part of a block grant with you in the way that you can take a project or even programme grant.

The directors are active in shaping the work in their institutes, a task that is not easy. Some work with strategy teams but others do it more by themselves. The trick seems to be to inspire and guide without being too dictatorial, and not everybody succeeds all the time. It is because of this hands on crafting that the directors believe that it is vital to have an active researcher rather than a professional manager as director. The professional managers are there in all the institutes, but they are on tap rather than on top. The directors, for instance, seem to use budgets to only a small extent in exercising control.

The organisational structure of the institute is obviously important in trying to amplify the productivity of the groups. The Hall institute, being the largest, has a more definite structure than some of the smaller institutes. Its eight units are grouped into four major themes—basic immunology, cancer research, clinical research, and immunoparasitology—and then there are specialist laboratories and services that all can use. The biggest difficulty in such an organisation is to get cross links, and Sir Gus Nossal is anxious that these should happen. There are regular meetings between groups and constant nudges from Sir Gus. In addition, he has forbidden people to drink coffee and tea in individual laboratories—they are encouraged to ascend to the seventh floor twice a day for tea and coffee, and they also lunch together. All the seminar rooms are also on the top floor so that groups must go up there even for their internal meetings.

The Florey has a more fluid structure than the Hall. It puts together teams round programmes that change, and Professor Coghlan says that the structure is best envisaged as a Venn diagram. People may be working

on one particular programme but then they may shift or be shifted to another. Thus when a programme was begun to study atrial natriuretic factor a team was put together that ranged from molecular biologists to physiologists. "Intellectual interest is the motivating factor," says Professor Coghlan. All the institutes have regular internal and intergroup meetings.

Professor Funder at the Baker institute has opted for a flat structure and wants "no pyramids." He talks about crafting the institute and waves his hands like a potter. He uses phrases and words like "directing subliminally" and "energising," and he imagines that constructing the institute's quinquennial grant proposal will be an excellent opportunity to shape the work of the institute and get everybody on board.

Professor Danks sits down with all of his groups "two weeks out of three" and discusses where they are going. He thinks that it is often difficult for scientists to work within institutes where they are not free to do whatever they want—but in exchange they have good facilities and the chance of exciting cross fertilisation. He frets that exchanges between groups are not always as good as they might be and encourages them wherever he can. One trick that the Murdoch institute has used is to circulate "technical biographies." This makes it less likely that somebody will spend months mastering a technique that somebody down the corridor has already mastered.

The Garvan institute has recently been reorganised into four divisions—neurobiology, metabolism, bone and mineral, and cancer biology—and the heads of the four divisions and the business manager make up the research strategy committee. Professor Shine works hard to encourage synergy among the groups but also among basic and clinical researchers. The Garvan—in the style of American corporations—has a mission statement, objectives, and aims, and this has something to do with Professor Shine having been the president of a Californian biotechnology company that grew rapidly to be a \$500m company. Professor Shine says that there is some professionalisation of research management in Australia but nothing on the scale of that in the United States.

One way that institutes can achieve the results they want is through their cultures—the values of the organisation. All seem to have cultures that emphasise excellence and the pre-eminence of science, but one problem is to create an atmosphere in which scientists can, at presentations, share their failures, difficulties, and anxieties as well as their successes. Also important is a culture that allows people to criticise each other's work without its being seen as a personal attack.

It's never easy to make the whole greater than the sum of the parts, and it becomes more difficult the larger the institute. But the institutes that receive block grants seem to be doing so to the satisfaction of the Medical Research Committee, and no institute has yet had its grant knocked back.

"Going round with the begging bowl"

None of the institutes funded by the NHMRC receives more than 65% of its money from the council, and most receive much less (table). It is the council's policy that the institutes should find much of their funding elsewhere. The council thus gets tremendous value for money, and another benefit is that the institutes must convince their communities of the value of medical research in order to stay alive. Some of the directors grumbled at having to spend time raising money, but most saw the value of the exercise. Some quite clearly enjoyed it.

A major source of funds is the state governments, and much of this load clearly falls on the Victorian state government. It seems willing to bear the load for the

Source of funds of five institutes supported with block grants by NHMRC (\$A000s)

Institute	Financial reserves	Total income	Source of income				
			Commonwealth	State	Interest	Private	Other
Hall	23 156	16 314	6 582	1 500	2 651	320	5 261
Florey	3 662	6 200	4 763	490	469	560	
Baker	1 858	5 446	2 191	300	593	828	1 534
Garvan	200	5 331	1 300	749	121	321	2 840
Murdoch	8 899	2 971	840	105	1 047	790	189

These figures are taken from the institutes' annual reports and are approximate because the institutes present their data in different ways.

Not the sun coming up over the Queensland bush, but a picture of a malarial oocyst on the stomach of a mosquito caught in Papua New Guinea. The picture comes from the Queensland Institute of Medical Research, which has a joint project with the Walter and Eliza Hall to produce a malaria vaccine. (Picture reproduced by permission of the institute and Patricia Graves.)

honour of having so much high quality research in the state. The state's finances are, however, fragile at the moment. Another important source of funds for some of the institutes is income from investments, but the Garvan and Florey have almost no pot of money whereas the Hall has a large pot.

The other major source of income is donations from corporations and individual people, and the boards of the institutes have an important part to play in this. Each institute has a board, and it comprises a judicious mix of the good, the great, the rich, and the well connected. The boards contribute to fund raising, but many of the institutes also have fund raising committees. Much of the fund raising, however, falls to the director because he is the person best able to convince potential donors of the value of the work—and the donors want a chance to look over the person who will be in charge of spending their money.

A particular problem for the institutes is finding capital for new buildings. The Hall has a new and splendid building and the Florey has a newish building, but all three of the other institutes are in search of more space. Raising money for buildings over and above the money needed for operations is difficult, and the Commonwealth government, recognising this, has created a budget of \$A45m for capital expenditure. The institutes needing more space are competing for the funds.

People

An important feature of the institutes is that nobody has tenure. Research fellows are on five year contracts, and other staff are on rolling one year appointments. The directors and the people funding the research like this system because it guards against the loss of productivity that may accompany tenure. (Australian researchers told me that they thought that the British Medical Research Council had made a bad mistake in having so many researchers on salaries.) Junior researchers accept it because the NHMRC and the institutes provide some career structure (20 April, p 946) and because there is trust that people will usually have their grants renewed if they perform reasonably. If a researcher is going off the rails then he or she will be helped considerably.

Training the next generation of researchers is important in all the institutes: the Garvan, for instance,

lists training as one of its four objectives. All of the institutes are linked with universities and offer PhD programmes. Some also provide some undergraduate teaching, but this is always secondary. The institutes also encourage young researchers to work overseas and offer places to overseas researchers in their laboratories. Indeed, one of their *raison d'être* is to provide high quality centres to attract back Australian researchers who have gone overseas. All of those working in the institutes believe very much that research is a global activity, and some admitted to being seen more often at international meetings than at meetings in their own cities.

Links with doctors and the community

All of the institutes are linked with hospitals and contain medically qualified researchers, and in most of them many of the staff teach medical undergraduates or postgraduates. All are intended to exploit the research opportunities presented by the proximity of patients. Yet in some places it seemed that the institutes were not an integral part of the hospital community and ordinary doctors were often only dimly aware of what went on in the institutes.

The Hall has beds in the Royal Melbourne Hospital, and until recently its link with doctors in the hospital was mostly through its clinical research group. Now direct links are being made with other groups, strengthening the contact with the hospital. The Florey does not have a clinical unit, but the Baker puts much emphasis on clinical links and has 15 beds in the hospital. The Garvan used to supply endocrine assays for local hospitals but has now moved that service component back to the hospital, wishing to concentrate on research. Yet it puts great emphasis on linking basic and clinical research. The Murdoch is probably the institute with the closest clinical links as it provides a clinical genetics service for Victoria; yet even here Professor Danks thought that many of the doctors in the hospital would know little about the research the institute was doing.

The links between the institutes and doctors are there but could probably be strengthened. The institutes also have to make links with the other health professions and with their broader communities, and the more they have to "take round the begging bowl" the more they are in touch.

Linking up with industry

The Australian government—just like the British and most others—is keen that researchers should make links with industry and allow commercial exploitation of their discoveries. The institutes have done this, recognising that industry is yet another source of much needed income. At least two of the institutes—the Hall and the Garvan—have applied for grants from the new cooperative research centre programme, which is designed to link scientists with "end users" and encourage exploitation of research (see article of 6 April). (It has just been announced (see this week's News) that the Hall was successful with its bid.) In addition, three of the institutes have associations with AMRAD (Australian Medical Research and Development), a company started with money from the Victorian government, venture capitalists, and the drug company Merck Sharp and Dohme to develop and market products arising from Australian medical research. The company has rapidly increased in size, and the Hall institute received over \$A1.3m income from the corporation in 1990. One of the projects that the Hall has conducted with AMRAD has been to clone leukaemia inhibitory factor.

There are many other links between the institutes

and industry. The Florey has a project with the Californian company Genentech to produce relaxin; the Baker has a deal with Glaxo (the director, Professor Funder, says that the rules in making links with industry should be "no promises, no equity"); the Garvan has joint projects with Pacific Biotechnology Limited; and the Murdoch has entered an alliance to market a database it has produced on birth defects.

These are just some of a myriad of links with industry, which occur at all levels of the institutes. For instance, Dr Tom Mandel, the head of the transplantation unit at the Hall, has joint projects going with three different companies, and a good proportion of the work in his unit is funded in this way. "Grants from the NHMRC are good for starting projects," he said, "but you've got to get money from elsewhere to build them."

Some of the researchers in the institutes resent the time that they have to spend making links with industry, but most think it time well spent. Not only do the links produce resources for the institutes and potentially Australia but they also provide a route for ensuring that the fruits of research are used. One worry is that the need to make industrial links may distort research agendas, possibly into the trivial and short term. I found little evidence that this was the case.

Conclusions

None of the institutes with block grants has yet been knocked back by the NHMRC, and the council hopes

eventually to fund more. This is a measure of success. The success of the strategy also seems to be supported by a recent proposal to convert the John Curtin school of the Australian National University in Canberra to an NHMRC institute. The council and its international review teams must be convinced that they get value for money from institutes. My impression as well is that they are cost effective, have enough critical mass to allow internationally competitive research, and do well with the difficult business of guiding research without stifling it.

The fact that the institutes get only a proportion of their money from the NHMRC means that the council gets great value for its investment. The institutes' need to raise money also obliges them to make important contacts with their communities and with industry. The need for a theme for each institute's research is an important mechanism for producing synergy, but the institutes have to work hard to keep groups cross fertilising each other and to make sure that the total is greater than the sum of the parts. Having a director who is a researcher supported by professional managers also seems to be important. A final important feature of the institutes seems to be that nobody has tenure.

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Everyday Aids and Appliances

Ocular prostheses and contact lenses. I—Cosmetic devices

© Steven Bailey, Roger J Buckley

Among people presenting to ophthalmology departments, the commonest requirements for cosmetic purposes are for whole eye prostheses that will disguise the absence of an eye and for various types of contact lens that will sit on the surface of a disfigured globe and act as a façade.

Whole eye prostheses

Indications for removing an eye include irreparable traumatic damage, malignancy, intractable suppuration, intractable pain in a blind eye, cosmetic reasons, and the prevention of sympathetic ophthalmitis. Removal may be by enucleation (when the whole eye is taken) or evisceration (when the contents of the scleral envelope are scooped out). Enucleation is always used for intraocular tumours and, usually, for pain. Evisceration is used when there may be a danger of intraocular infection spreading back along a cut optic nerve sheath. In other circumstances either operation can be used, although there is controversy over the advantages and disadvantages of each.

At the end of the operation a simple conformer shell of clear perspex must be inserted into the eye socket (fig 1) to prevent postoperative shrinkage of the orbital tissues, which would make it difficult to fit an artificial eye. Care must be exercised over cleanliness at this and all other stages. As with all whole eye prostheses conformer shells should be removed for cleaning at least once every 24 hours.

Patients who have lost an eye are psychologically scarred, and the cosmetic deficit should be corrected at

the earliest opportunity by fitting a temporary coloured prosthesis that has been modified from a stock shape. This can be done in a hospital eye department that operates a prosthetic eye service or by the Artificial Eye Service. A final artificial eye can then be manufactured as soon as the postoperative inflammation has settled, usually within six to 12 weeks. The device will usually be made in clinical quality perspex, although glass may be used in selected cases.

To ensure that the eye sits in a natural position and does not fall back into the socket and to minimise any space in which infected debris could collect, the device should be shaped to match the contours of the orbital tissues. An impression of the socket is therefore taken using a quick setting material such as dental alginate. Once set, the alginate is removed and a plaster of Paris mould is made from it. The mould is used to cast a wax shape, which is then trimmed to fit the socket. A further mould is made from the modified wax shape, and the perspex prosthesis is cast in this mould. A hand painted iris button is placed on the front of the eye, scleral features are painted on, and clear plastic is laminated over the top (fig 2).

Whole eye prostheses should be worn overnight during periods of orbital growth. They may continue to be worn overnight later, perhaps for the sake of a partner or else to prevent eyelashes turning in and irritating the conjunctival surface, but if conjunctival inflammation develops secondary to the device it is probably best not worn during sleep. To remove an artificial eye the edge of the lower eyelid is first manipulated under the inferior edge of the device. The

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