

# Steroid treatment for prematurity – a remarkable follow up

#### A Lancet publication reports reassuring results



Babies whose mothers received steroid injections before giving birth have no higher risk of heart disease at age 30 than those whose mothers received a placebo treatment.

This result comes from a study, published in The Lancet on 28 May, of 30-year-olds whose mothers received either steroid or placebo injections when they went into premature labour.

The Lancet study did, however, discover indicators of possible mild insulin resistance in people whose mothers received the steroid.

Steroid treatment of women in premature labour became standard international practice after being discovered by Sir Graham (Mont) Liggins in the late 1960s. The treatment works by speeding up the maturation of babies' lungs.

The effectiveness of this new treatment was first demonstrated at National Women's Hospital in Auckland by Professors Sir Graham Liggins and Ross Howie in a landmark clinical trial published in 1972.

This publication rocked the medical world at a time when most very premature babies died of respiratory distress. The new treatment had a huge effect by halving the death rate.

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Bobbie and William Wilkins, pictured at one year, were born prematurely. Their survival is party due to the steroid injections their mother received. See page 6 for their story.

# Maurice & Nessie Paykel Clinical Research Unit opens

Governor-General presides at the official opening



Dame Silvia Cartwright and Mrs Nessie Paykel pose with (left to right) Christopher Condon, Holly Cutfield and Hanna Fairclough, who painted some of the artwork that adorns the Clinical Research Unit's walls

The Governor-General, Her Excellency The Honourable Dame Silvia Cartwright, officially opened the Liggins Institute's new Maurice and Nessie Paykel Clinical Research Unit (CRU) in March.

The CRU is a purpose-built facility that

will allow complex, cutting edge clinical research to be undertaken largely on children and young people.

It is the best-equipped unit in Australasia in which to perform metabolic studies on children, and will allow studies to be performed that are not possible at any other site in Auckland, explains CRU Director Associate Professor Wayne Cutfield.

The CRU is already the site of new, innovative and important research projects. Profiles of some of the studies can be found on page 4 and 5 of this newsletter.

Funds to renovate, equip, staff and operate the CRU were donated by the late Maurice Paykel and his widow Mrs Nessie Paykel. Before his death, Mr and Mrs Paykel and Liggins Institute Director Professor Peter Gluckman envisaged a clinical research unit as a world class facility.

"This very generous donation has created a facility that will attract clinical researchers to undertake cutting edge research," said Professor Gluckman. "It will encourage collaborative clinical research not only across Auckland, but nationally and internationally.

"The donation underpins Maurice Paykel's commitment to supporting high calibre clinical research in Auckland and reflects the influence he has had on the development of a research culture in Auckland over the years.

"Mr Paykel was arguably New Zealand's most generous and significant benefactor in the area of medical sciences, but sought no public recognition for his philanthropy."

Mr Paykel (1914-2002) and his late brotherin-law Sir Woolf Fisher founded Fisher and Paykel with their fathers in 1934.



# Walls of children's art



Kiwis, clowns and a hippopotamus are among the subjects of brightly coloured paintings and artwork that decorate the walls of the Maurice & Nessie Paykel Clinical Research Unit (CRU).

"Most of our subjects are young children, so we wanted the CRU to have a friendly, non-threatening atmosphere," says CRU Director Associate Professor Wayne Cutfield. "The artwork is bright and full of wonderful contrasts which helps the children feel welcome and comfortable."

The pieces were framed after being selected from two Auckland primary schools, Campbell's Bay School and Kristin School.

Two of the pieces played a special role in the opening of the CRU.

After the formal opening ceremony, the official party was taken on a tour of the facility. As the party entered the CRU,

pupils Hanna Fairclough and Holly Cutfield of Campbell's Bay School and Christopher Condon of Kristin School presented Dame Sylvia Cartwright and Mrs Nessie Paykel with framed photographs of their paintings.

Children who contributed art, along with their parents and teachers, visited the CRU in May to see their work on the walls and hear about the research carried out under its colourful countenance.

# **Boosting brains**

#### A donation has opened new doors



Jubilee Trust Chair Mr John Moody (left) and trustee Mr John Steer (right) have been shown stem cells in a system used by Dr Thorsten Gorba to measure their mobility as part of his research.

Brain function and repair research at the Liggins Institute has been further strengthened by a significant donation from the Jubilee Crippled Children Foundation Trust.

The money will go towards developing treatments for repairing the brains of infants with severe neurological or neuromotor dysfunction caused by disruption of brain development.

It follows the formal publication in January of an international trial showing that a head cooling device developed by Liggins scientists reduces brain damage in oxygendeprived newborns. This trial provided the first-ever evidence that birth asphyxia can be treated.

The Jubilee Trust donation has allowed the research programme to be advanced by the appointment of a developmental neuroscientist, Dr Thorsten Gorba. Thorsten specialises in the study of what makes the brain's stem cells differentiate into specialised cell types. The answers, he believes, hold the potential to repair a host of neurological problems.

"Usually neural stem cells are confined to a very specific region of the brain," he says. "If you have an injury or neurodegenerative disease, you'd like to have a factor which would attract the cells away from where they're generated to an area where they can cause regeneration of the damaged part of the brain."

Thorsten has been working on a gene family that produces peptides which direct the migration of stem cells in the brain. It was discovered by Dr Frank Sieg, an honorary member of the Liggins Institute, and has other useful properties, such as making brain cells proliferate and differentiate into functioning brain cells, and protecting them from dying.

"I was very excited to work on these genes," said Thorsten. "Not very often can you discover a whole new family of genes with such a profound impact on the central nervous system."

At the Liggins Institute, Thorsten will focus on applying this work to infant brain injury. Full-term babies who are deprived of oxygen during birth are susceptible to such injury, as are very premature babies. Little is known about the processes that lead to the injury in preterm babies. Dr Gorba believes that the developmental processes in their brains must be disturbed.

Thorsten's stem cell work does not use

embryonic stem cells, the use of which is controversial. Instead, he studies the stem cells that naturally occur in the brain throughout life.

Thorsten did his degrees at the Ruhr-University Bochum, Germany. His Masters degree was in plant physiology, after which he turned to developmental neurobiology for his PhD. He then became fascinated by the field of stem cell research, and after a postdoctoral year he headed to Edinburgh to the Centre for Genome Research, now called the Institute for Stem Cell Research. New Zealand became his home in 2002, when he joined biotechnology company NeuronZ.

The Jubilee Crippled Children Foundation Trust was established in 1985 by Lionel Brierly. Mr Brierly was a Rotorua electrical engineer who was helped by the Auckland Crippled Children Society when he had polio as a child. On his death in 2003 Mr Brierly left his Estate to the Jubilee Trust. The Jubilee Trust's objectives include supporting organisations actively serving the needs of physically disabled people in the Auckland region, including CCS Auckland (formerly called the Auckland Crippled Children Society), and funding research to alleviate physically disabling conditions.

# We need you!

#### Clinical research studies need volunteers to answer intriguing questions

Several exciting new studies that are the first of their kind in the world are being launched at the Liggins Institute's new Maurice and Nessie Paykel Clinical Research Unit (CRU).

"There are already a number of truly novel, innovative and important clinical research projects getting underway in the CRU," explains the CRU's Director, Associate Professor Wayne Cutfield.

Wayne and the CRU's other senior staff member, Dr Paul Hofman, are paediatric endocrinologists who spend a portion of their time working with young patients at Auckland's Starship Hospital, where Wayne is Clinical Director of Endocrinology. The pair are parents themselves and have put much thought into making the CRU childfriendly.

"We are very grateful to all the volunteers who help us, and we do our best to make their experience as enjoyable and rewarding as possible," says Wayne.

The only potentially uncomfortable test that volunteers undergo is blood sampling, and for this they are given a patch that numbs the skin, making the procedure virtually painless.

Participants are compensated for their travel and inconvenience, and given a reward as thanks. Travel can only be compensated for within the Auckland region.

Any Dialogue readers who are interested in learning more about taking part in the studies below can contact Dr Paul Hofman on 09 373 7599 ext 86453, or email p.hofman@auckland.ac.nz.



Dr Harriet Miles listens to the chest of Annika Siegers, aged 4

### Genes or environment: can you help?

Children who were born prematurely at less than 34 weeks of gestation can help researchers answer questions about how genes can be altered by the environment.

Humans have a clutch of about 50 genes that can change form in the early months of life – meaning that we don't necessarily grow up with the genes we are born with. Liggins researchers are testing whether early care in neonatal units can permanently alter some of those 50 genes.

The researchers already know that some aspects of premature babies' growth

hormones are different by the time they are aged six to ten. They don't yet know whether that difference is caused by genes that were altered early on.

A single blood sample is needed from 100 ex-premature babies and 100 children who were born at full term (38-42 weeks of gestation). The volunteers should be aged between 2 and 20 years.

If you can help, please contact Deborah Rowe on 09 373 7599 ext 87408, or email d.rowe@auckland.ac.nz.

## Bonus for late bloomers?

Do you know any children who look particularly young for their age? Liggins researchers are looking for late bloomers – a condition also called 'constitutional delay'. Such children tend to be small and enter puberty late, and often have parents who entered puberty late.

The researchers want to test whether such children are particularly sensitive to insulin. If that's true, it means they're likely to live longer, because insulin sensitivity is the physiological trait that distinguishes healthy 100 year olds.

Insulin resistance, on the other hand, is less desirable: it's associated with adultonset diabetes and the health problems that go with it. People who are insulin resistant while they are young need to live really healthy lifestyles to counteract their risk.

The researchers also want to test children who are of average height and physical development in order to compare them to the late bloomers.

Children will be given a hand x-ray to confirm whether their development is delayed.

Children need to be aged 11 or under. Their parents should contact Dy Wilson, tel 09 373 7599 ext 82769, email da.wilson@auckland.ac.nz.

### Exercising in pregnancy



Pregnant women who are interested in the health effects of rest or exercise during pregnancy can help Liggins researchers find more answers about this topic.

The study is expected to provide vital information for pregnant women wishing to do the best for their babies. It is likely that exercise during pregnancy has beneficial effects for mothers and their babies – perhaps even preventing later obesity in the babies as they grow up. However, there is a prevailing belief that a fetus will take what nutrients it needs, leaving the mother lacking if there is a deficit. This is not true.

Women who volunteer will be randomly allocated to either doing their normal amount of activity or a supervised, moderately intense exercise programme from 20 weeks onwards. The women will have a blood test at 20 and 36 weeks of pregnancy. The body composition of mothers and their babies after birth will be assessed using sophisticated and very safe scanning techniques.

Interested women who are less than 20 weeks pregnant should contact Dr Paul Hofman on 09 373 7599 ext 86453, or email p.hofman@auckland.ac.nz.

Liggins PhD student Sarah Hopkins supervises Vicki Poole, 20 weeks pregnant.



### Continued from front page...

Subsequent studies showed that the treated babies performed at least as well at school as those who survived without treatment. Until now, however, there has been almost no information about how these babies do as adults.

Researchers from the Liggins Institute and other parts of The University of Auckland's Faculty of Medical and Health Sciences (FMHS) launched the Lancet study in the face of mounting concern from around the world that fetuses exposed to steroids may grow up with an increased risk of disease. However, this concern is based largely on animal studies that have exposed fetuses to repeated doses of steroids or much larger doses than are used clinically.

For the Lancet study, 534 of the "babies" who were born while their mothers took part

in the original Liggins and Howie trial were tracked down and tested in 2002 and 2003, at age 30. Their body size, blood pressure, blood lipids and response to glucose were measured, and aspects such as lifestyle factors and socioeconomic status were also recorded.

Professor Jane Harding, an author of the Lancet study, neonatologist and Liggins Deputy Director, says that the advantages of the treatment vastly outweigh any possible disadvantages. "This is a treatment that dramatically reduces the chances that a premature baby will have lung disease, bleed into its brain, or even die. We can now be confident that this very effective treatment is also very safe. It results in more babies surviving to become adults with no increased health risk up to 30 years of age." "The findings of possible insulin resistance are scientifically interesting," says lead author Dr Stuart Dalziel. "They provide the first proof in humans that exposure to steroids before birth might permanently alter metabolism."

Dr Dalziel undertook the study as his PhD project, based jointly at the Liggins Institute and the FMHS's Clinical Trials Research Unit. The other authors of the paper are Natalie Walker, Varsha Parag, Colin Mantell, Harold Rea and Anthony Rodgers. The study was supported by the Health Research Council of New Zealand, the Auckland Medical Research Foundation and the New Zealand Lottery Grants Board.



## The gift of a family

#### Judie Wilkins is an eternally grateful mum

Judie Wilkins wrote to the Liggins Institute from Brisbane last year seeking to thank Sir Graham Liggins. "He has given us the gift of a family," she wrote.

Judie knew she would only be able to have one pregnancy due to injuries she'd suffered in a car accident – and she knew the birth would have to happen prematurely.

She and her husband Robbie visited the Royal Brisbane & Women's Hospital and were told about the steroid injections discovered by Professor Liggins.

"Knowing that the steroids were available

to be given to me to help lung development was a big factor in our decision to have a family," wrote Judie.

Judie conceived twin boys.

Their birth happened at 32 weeks' gestation in January 2004 after Judie had 10 weeks of hospital bed rest. She was given steroid injections during this time.

"Without those steroids I might not have my boys or they might have been in intensive care for longer. I wanted to find out who did the research. Thanks to medical staff here I have been told about Professor Liggins. I would really like to thank Professor Liggins for what he did," she wrote.

Judie already had a passion for the plight of premature babies because one of her uncles died at one day of age after being born prematurely in 1936.

"He died because they could not help him to breathe," she wrote. "I was very close to my grandmother and she endured a lot of heartache over losing her 'Billy boy'".

Judie and Robbie named one of their twins William after her uncle.

## The extinction of eugenics

The fascinating yet terrifying topic of eugenics came under scrutiny by Associate Professor Hamish Spencer during his Science, Medicine and Society talk at the Liggins Institute in March.

The eugenics movement was strong in many parts of the world in the early part of last century. Eugenicists sterilised what they considered to be the 'wrong' sort of people, including sixty thousand Americans. 'Feeblemindedness' was their main target, blamed for social problems including drunkenness, poverty, immorality and criminality.

Eugenic practices were dealt a heavy blow when the Nazi atrocities were revealed, said Dr Spencer, who is from the Allan Wilson Centre for Molecular Ecology and Evolution at Otago University's Department of Zoology. The rise of medical and reproductive rights for patients was also very important in the societal rejection of eugenics.

"Today we have a number of problems with eugenics and they are all political, social or ethical," he said. University students are taught a rather different story, however. According to textbooks, the eugenics movement was extinguished by a biological hitch – one that has been ironed out by modern scientific discoveries.

Eugenicists, including many respected scientists, strongly believed in a study – ridiculous in hindsight – that apparently proved that feeblemindedness was inherited via a recessive single gene defect.

Sterilising individuals affected by this type of gene defect would therefore be wildly inefficient. It could only wipe out a minority of offending genes, because most recessive genes exist 'silently' in people with only one copy. (In recessive single gene defect diseases, a copy of the defective gene must be inherited from both parents in order to affect its carrier.)

University students are taught that this inefficiency was the reason that eugenics failed and, by implication, that the early eugenicists were rather dim not to understand this basic genetic knowledge.

But the eugenicists were aware of the inefficiency of the sterilisation process. One of the world's greatest statisticians, R.A. Fisher, had applied himself to the problem, and calculated that even if sterilisation couldn't wipe out feeblemindedness, it provided worthwhile gain.

This all matters today, because we have the genetic tools to circumvent the inefficiency problem. "If the inefficiency of the eugenics argument is the only objection that you have to eugenics, then what you're saying is that eugenics is OK in principle," said Dr Spencer. "Modern genetic testing is very good at picking up carriers of genes that cause a large number of diseases [but not feeblemindedness]. We could target the carriers that contain most of the undesirable genes."

In the end, our current attitudes towards human rights are what hold eugenics at bay.

The Liggins Institute is committed to maximising the benefit of its research for New Zealand and, where appropriate, seeing its research translated into effective therapies. Accordingly, in some areas it has licensed its intellectual property to the pharmaceutical industry or to start-up companies associated with the Institute. The terms of these arrangements provide funds which can be committed to public good (ie non-commercial and cutting-edge) research within the University. In accordance with University policy and international practice in developing start-up companies, some staff will, or could, personally benefit from interest in these start-up initiatives. The University and, therefore, the Institute have taken this approach with the aim over time of increasing the capacity of the University and the Institute to undertake novel and leading-edge fundamental research. Most of the research within the Institute is, and will always be, of this nature and can never attract commercial investment. The University and Institute are mindful of the need to ensure that donated funds are applied only to the public good research components of the Institute's activities and cannot be applied (unless requested by the donor) to projects where commercial arrangements have been entered into. Specific procedures have been developed to ensure this, and potential donors are invited to contact the Institute's Chief Operating Officer or the University Registrar for further information.

#### Become Part of Our Vision

If you are committed to advancing healthcare and improving quality of life, and want to see New Zealand take greater strides in the knowledge society, then you may wish to consider supporting the Institute. Please contact us at:

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# From sleeping astronauts to fighting AIDS

Fascinating scientist to visit the Liggins



Professor Short advised on the breeding of the world's first cama, a camel-llama cross, pictured here with Sheikh Mohammed Bin Rashid Al Maktoum, who funded the project.

Whether it be jetlag cures, primate mating systems or wildlife conservation, Professsor Roger Short's name keeps popping up.

One of his many claims to fame is the discovery that popping a melatonin pill can induce a fake 'night' in the body – a treatment that has been enthusiastically taken up by long haul travellers and NASA astronauts.

He's a scientist with a huge breadth of knowledge and skill, whose name appears in the world's most eminent scientific journals. He has advised the World Health Organisation's global programme on AIDS and population control; he's helped to cross a camel with a llama; he works on evolutionary conundrums such as the aquatic snorkelling ancestors of elephants. The list goes on.

To top it off, he's convivial company and a superbly entertaining speaker.

This August Professor Short FRS will visit the Liggins Institute as part of Mazda Artworks at the Hilton, a charity art event of which the Institute will be a beneficiary. He will be giving a free public lecture and will entertain diners at a charity auction dinner at The Hilton Hotel on 25th August. The remainder of his itinerary is still being planned – check www.liggins. auckland.ac.nz/events, contact Pandora Carlyon (09) 373 7599 ext 82305 or email p.carlyon@auckland.ac.nz for updates and booking details.

Professor Short's links with the Liggins Institute are based on his research on hormonal control of embryo development and his friendship with Sir Graham (Mont) Liggins.

He is an adjunct Professor of Zoology at the University of Melbourne, and the Wexler Professorial Fellow in the Department of Obstetrics and Gynaecology at Melbourne's Royal Women's Hospital. His official specialities are reproduction in mammals, fertility and infertility, and HIV and AIDS.

He co-edited and was the primary contributor to the highly successful textbook series 'Reproduction in Mammals' (Cambridge University Press). His most recent book is the acclaimed 'Ever Since Adam and Eve: the Evolution of Human Sexuality' (Cambridge University Press), coauthored with Dr Malcolm Potts.

His other research interests include contraception for humans and animals, the benefits of breastfeeding for health and population control, methods for reducing the sexual transmission of HIV, and sex determination and differentiation.

### Deputy Director joins list of prestigious speakers

Liggins Deputy Director Professor Jane Harding delivered the 2005 Arthur E Mills oration at the annual scientific meeting of the Royal Australasian College of Physicians in May.

Previous orators at the meeting include Sir Michael Hardie Boys during his time as Governor General of New Zealand, Bill Haydon as Governor General of Australia and Sir Guy Green as Governor of Tasmania. Professor John Funder, Professor of Medicine at Melbourne's Monash University and Chair of the Liggins Institute's scientific advisory board, was last year's orator.

The Royal Australasian College of Physicians is responsible for the education, training and continuing professional development of consultant physicians and paediatricians in many specialty areas.

Jane's oration was delivered at the College ceremony during which the new Fellows were presented and welcomed into the Fellowship. It was entitled 'Science and serendipity in the art of medicine'. In it she reminded the new Fellows of how, although science provides the fundamental underpinnings of medicine, breakthroughs are very often the result of serendipitous observations, and the art of good medical practice involves much more than just science alone.

Liggins scientist Dr Susan Morton received an award at the same meeting. She was presented with the Ken Newell Award for Excellence in the final examinations for the Australasian Faculty of Public Health Medicine, which is part of the College.

#### DIRECTORS

Professor Peter Gluckman FRS Director

Professor Gluckman is a world renowned Professor of Paediatric and Perinatal Biology. His research has focussed on the basic mechanisms of infant brain injury resulting from oxygen deprivation and intrauterine growth restriction.

Professor Jane Harding

Professor Harding is internationally recognised as an academic neonatologist. She is an authority on placental function, the regulation of fetal growth and the consequences of poor fetal growth.

Professor Murray Mitchell Research Director

Professor Mitchell is Professor of Pharmacology and Clinical Pharmacology at The University of Auckland. He has a worldwide reputation for his research into the biochemistry of hormones related to premature labour.

#### Assoc. Prof. Bernhard H. Breier Associate Director

Associate Professor Breier is an international authority on the endocrinology and physiology of fetal programming and the regulation of growth and metabolism by the somatotropic axis.

Assoc. Prof. Wayne Cutfield Associate Director

Associate Professor Cutfield is an expert on insulin sensitivity and action in children. He is Director of Endocrinology at Auckland's Starship Hospital.

Assoc. Prof. Peter Lobie Associate Director

Associate Professor Lobie has an international reputation for his research into the production of human growth hormone in the mammary gland and its role in the development of breast cancer.

#### Assoc. Prof. Chris Williams

Associate Director Associate Professor Williams is an innovative neuroscientist who pioneered world-first monitoring technologies and rescue treatments for brain injury.

#### Mr Mark Shepherd

Associate Director

Mr Shepherd is the Institute's Chief Operating Officer. He has made a career in change management consultancy, and has worked for some of the world's largest companies.



1 Series after another

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