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The Liggins Institute
An Institute of The University of Auckland

Dialogue

A second chance for Cody PAGE 7

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Inaugural SMSP seminar with Lord Robert Winston PAGE 5

Professor Peter Gluckman FRS (left), Founding Director of the Liggins Institute, with his friend and mentor Sir Graham Liggins FRS, Emeritus Professor of The University of Auckland.

The knowledge dream

The establishment of the Liggins Institute is the culmination of a five-year dream for Founding Director Professor Peter Gluckman FRS who has stepped down as Dean of The University of Auckland's Faculty of Medical and Health Sciences to head the University's first research institute.

Professor Gluckman, who was recently elected to the fellowship of the prestigious Royal Society of London, says his aim is to establish a world-class centre for medical and health research which will not only carry out excellent basic research but will advance healthcare outcomes.

"It has long been my personal ambition that we build at least one centre of iconic value in New Zealand where research of the highest possible quality in any area of medical science can be undertaken.

"We are quite unabashed in our belief that in each of our four research areas we meet the criteria to be globally recognised," he says.

The Liggins will conduct research in key interrelated areas where the Institute's scientists have already established international reputations – pregnancy and labour, the fetus and newborn, growth, development and ageing, and the brain and behaviour.

Intellectual property arising from the research will be harnessed, to build knowledge-based industries in biotechnology which will benefit New Zealand, and to enhance prevention, diagnosis, treatment and management of a range of conditions and diseases.

Science, medicine and society

Parallel to the biomedical research themes, the Institute will develop a Science, Medicine and Society Programme which will have a broader academic and public role. (See story page 5.)

Research will be conducted into ethical, philosophical and economic perspectives on medical research and decision-making, and the public will be invited to become involved in the Institute's programme of dialogue, seminars and novel partnerships.

The Institute has been named in honour

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THE UNIVERSITY OF AUCKLAND
FACULTY OF MEDICAL AND HEALTH SCIENCES

Helping small babies to grow

Research at the Liggins Institute could lead to a first ever treatment for small babies while they are still in the womb.

Twins – one (left) undernourished in the womb and the other, normal birth weight at delivery.

A team led by Professor Jane Harding, Associate Director (Academic) of the Liggins Institute and Professor of Neonatology, Faculty of Medical and Health Sciences, The University of Auckland, is investigating whether providing supplements or hormones directly into the amniotic fluid before birth might improve the infant's growth.

Poor growth in the womb is more likely to result in a stillborn baby or one that is born prematurely. The infant who is born small is also more vulnerable to complications in the newborn period.

He or she may fail to thrive and may also suffer delayed development in childhood. Research is now showing that babies born small are also at greater risk of diseases in adulthood, particularly diabetes, high blood pressure and heart disease.

There are presently no treatments available for these infants before birth, so they are often delivered prematurely. This means they are exposed to the risks of prematurity as well as low birthweight.

Professor Harding says many babies who grow poorly before birth are literally starved in the womb and have a limited supply of amino acids – the building blocks of proteins.

Starved in the womb

"This is not usually because the mother is not eating sufficient protein. It is because the baby is not receiving enough. This may be because the placenta is not functioning properly or because of other factors such as maternal illness," she says.

Before birth, infants receive some nutrients by swallowing the amniotic fluid. Professor Harding's research aims to identify which amino acids the infant is short of and to determine whether injection of supplements or hormones into the amniotic fluid improves fetal growth.

A second study is investigating whether the growth of these babies can be improved following birth.

"Our work suggests that these babies have difficulties in processing the protein in their diet. This means that they cannot tolerate a diet containing extra protein that might otherwise improve their growth," says Professor Harding.

"We are investigating where the problem lies in the biochemical pathways involved in the processing of protein, and whether it is possible to get past that block, for example by giving the infant supplements of amino acids in their diet.

"This might allow children born small to catch up after birth and possibly avoid some of the later complications."

Continued from page 1

of Professor Gluckman's mentor, Sir Graham Liggins, Emeritus Professor at The University of Auckland, and the only other New Zealand-born doctor to have been elected a Fellow of the British Royal Society. Professor Gluckman is one of only 37 New Zealanders elected to Fellowship, and the second paediatrician ever.

Sir Graham, who discovered that giving steroids to women experiencing early labour could accelerate infant lung development sufficiently to enable premature newborn babies to breathe independently, says he is honoured that the Institute has been named after him.

Pioneering tradition

Professor Liggins' work has been a source of inspiration for the Institute's founding scientists, says Professor Gluckman, and they will continue the pioneering traditions he established for New Zealand science.

Research at the Liggins is at both ends of the lifespan, and covers the spectrum from "blue skies" to clinical or applied research.

"We are interested in what controls fetal growth and development of the brain, what happens at birth – the most dangerous day of your life – and the problems of premature birth," says Professor Gluckman.

"We have a very large interest in the consequences of being born small as a lot of work is showing that what happens in fetal life can have a major impact on the origins of adult disease." (See story page 3.)

One of the largest areas of research activity at the Liggins is exploring development of the brain and behaviour, with a focus on new treatments to reverse or reduce the death of brain cells caused by birth asphyxia, trauma or stroke, and neurodegenerative diseases such as Parkinson's, alzheimers and multiple sclerosis.

Exploring boundaries

"It is quite extraordinary that out of perinatal research, we have research which impacts on these adult diseases and increasingly this is becoming part of our activities," says Professor Gluckman.

The Liggins is also pioneering exploration of the boundaries between public good science and the private sector.

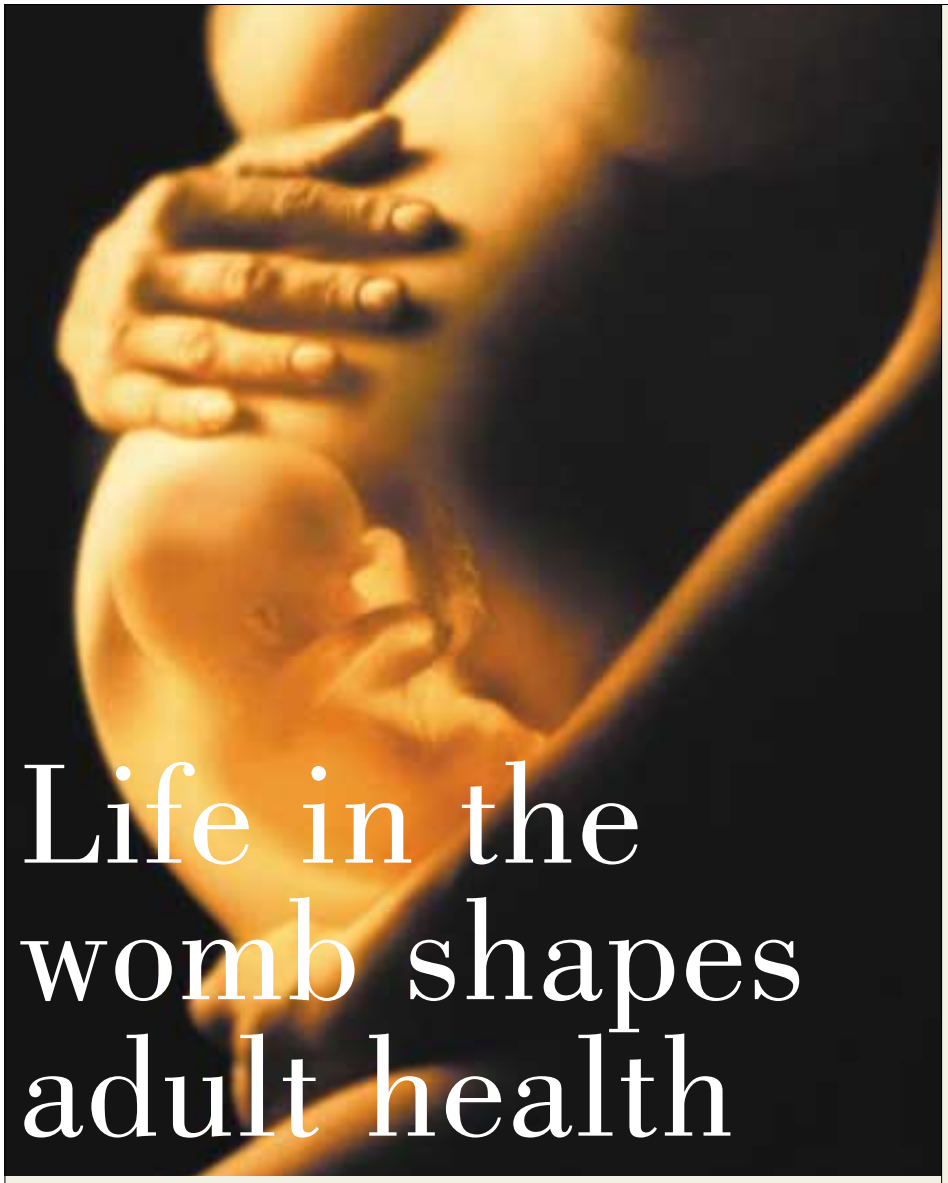
"Those who followed the knowledge wave dialogue will understand there is a growing belief that universities are the drivers of economic as well as social development. Part of that is how to translate knowledge from the public to the private sector.

"One of the things we have done at the Liggins is to create NeuronZ which has been formed specifically to further develop Liggins' intellectual property in the neurological area. It is an independent company with the University as a shareholder but has entirely separate management. Much of its research is done by contract back to the Liggins."

Knowledged-based industries

Life sciences research, says Professor Gluckman, will be a major driver in the development of New Zealand's knowledge-based industries, providing opportunities for the private sector to leverage off ideas, and to create jobs and economic growth.

"At the Liggins, we aim to attract the brightest young minds, capable of research and innovative thinking, and to encourage talent to stay or return. To do this, we will need to ensure an environment of high intellect and critical thinking, with leading-edge technologies."



Life in the womb shapes adult health

Researchers at the Liggins Institute are aiming to unravel the mystery of what happens in the womb to make some people overeat, become overweight and suffer from a range of diseases traditionally believed to result from a Western lifestyle.

Eating too much saturated fat, combined with smoking, a lack of exercise and being overweight, are acknowledged major contributors to diabetes, heart disease and stroke – the constellation of conditions known as syndrome X. What is less well known is that life in the womb shapes health in adulthood.

Scientists at the Liggins Institute and elsewhere have now established that the environment in the womb – from the cascade of hormones which flow from the mother, to how well the placenta delivers nutrients to the tiny developing fetus – determines whether or not children in later life are destined to enjoy good health or suffer problems. There is growing evidence that certain conditions during gestation affect fetal physiology in such a way that metabolism in the child and adult is set for life.

The teams, led by Professor Jane Harding, Associate Director (Academic) at the Institute, and Associate Professor Bernhard Breier, are examining the complex mechanism of 'fetal programming' to see if it can be treated in the womb or its effects reversed soon after birth.

Research at the Liggins has established that undernutrition or stress in the womb triggers adaptive responses in the fetus to ensure survival. This biological phenomenon, which can have significant, long-term health consequences, is called 'fetal programming'.

Killer gene

If nutrients are scarce in the womb, adaptive responses are aimed at helping the fetus to make the most of what's available. But in an environment of plenty after birth, those physiological changes may be critical in the development of overeating, obesity and hypertension.

"Our research suggests that an adverse environment in the womb leads to irreversible changes in the mechanisms that regulate growth and metabolism, and heart and blood vessel development," says Dr Breier.

"It's a mismatch between what the fetus is prepared for in the womb and what it actually experiences after birth."

This aspect of fetal programming can be compared with the so-called 'thrifty genes' in Polynesians. The thrifty genes, which lower metabolism and promote the storage of nutrients, were lifesavers for Polynesians living on coral atolls, or surviving the rigours of long canoe voyages. But in an environment of abundance, they become killers.

Syndrome X

A number of studies in Britain and the United States have shown striking correlations between birth size and high blood pressure, diabetes, and heart disease.

The evidence did not appear to make sense. The incidence of low birth weight and neonatal deaths is generally higher in lower socio-economic areas. Heart disease has, until recently, been considered a disease of affluence.

However, work by several Liggins scientists including Professor Harding, Associate Professor Breier, Associate Professor Wayne Cutfield, Dr Paul Hofman and others confirmed the theory that low birth weight is linked to a higher incidence of syndrome X conditions.

Growth retardation in the womb – and low birth weight babies – can be caused by a range of factors including under-nutrition of the mother, an inadequately functioning placenta, and maternal stress. These conditions trigger physiological changes which can lead to leptin resistance.

Leptin is a hormone, produced by fatty tissue in the body, which regulates appetite. When it is functioning properly, it signals to the brain that a person is no longer hungry. People with leptin resistance, however, continue to feel hungry.

Prevention

Research at the Liggins has already established that leptin resistance is a central mechanism in the development of syndrome X, and that the physiological changes which cause it occur some time between conception and birth. The latter finding came out of research by Dr Mark Vickers for his PhD.

While postnatal environmental factors are important in the incidence of disease in adulthood, the Liggins' findings reinforce the evidence that the environment within the womb can affect long-term, health outcomes.

"This suggests that health care funding may be better spent on preventing health problems during pregnancy rather than waiting until metabolic and cardiovascular disorders manifest, years or even decades later," says Dr Breier.

Predicting early birth

Babies born before their due date cost New Zealand an estimated $40 million a year in perinatal care alone, yet there is no reliable way of determining which mothers will have their babies early.

A team of researchers, headed by Liggins Institute Associate Director (Research) Professor Murray Mitchell, is investigating the mechanisms involved in preterm birth, in particular the role of infection in the womb and factors which trigger an inflammatory response.

Their aim is to develop a reliable way to identify and predict which mothers are likely to give birth before their due date so that steps can be taken to try to prevent this or to prepare for it.

Despite decades of research, preterm birth remains a major obstetric problem worldwide with evidence that rates may actually be increasing.

In New Zealand, the figures from National Women's Hospital show that almost five percent of babies are born spontaneously before 37 weeks gestation. Add to this premature deliveries for medical reasons and the figure jumps to just over 11 percent.

The risk for Maori mothers is even higher with some eight percent delivering spontaneously before the due date. Indeed, their risk of delivering before 32 weeks is three times higher than for other women, including Pacific Island mothers.

Delivery before 32 weeks gestation poses significant risks of an infant developing a number of serious, life-threatening complications, which can carry long-term health effects.

Complications

Because the baby's lungs are immature, it is unlikely to be able to breathe properly and its brain may be deprived of oxygen. Other complications include cerebral palsy, lung and heart problems, neonatal infection and necrotising enterocolitis - a serious condition affecting the baby's digestive system. Long-term effects include hearing and visual impairment, and intellectual deficit requiring life-long educational assistance.

Dr Jeff Keelan, Senior Lecturer in Pharmacology and Chair of the Liggins Pregnancy and Labour Research Group, says the chances for a baby born this early are "not good" without access to sophisticated neonatal care.

"There are plenty of sound economic and health care reasons why a test to determine whether a woman experiencing contractions is in true early labour or not.

Major causes

"Obviously, we are keen to be able to identify women who are at risk of going into preterm labour so that we can try to prevent it, or at least make sure that access to appropriate neonatal intensive care facilities is available."

Dr Keelan says more than half the women who present to their doctor or clinic with apparent preterm contractions do not actually deliver early. The contractions stop, they go home and deliver at term (40 weeks).

"If this happens in a remote area, the caregiver has to decide whether to call in an emergency helicopter and admit the woman to hospital, or wait and see. A reliable test would be extremely helpful in this situation."

A number of factors are associated with preterm labour, including extremes in the size and age of mothers, smoking, the level of physical activity and socioeconomic factors. Medical factors include multiple pregnancies, fetal malformations, low weight gain, too much or too little amniotic fluid, and intrauterine infection. This latter factor is of particular interest to the Liggins Institute researchers.

Professor Mitchell, an international expert on the biology of preterm labour, was director of the original research team which discovered in the 1980s that the inflammatory response to infection in the womb is a major cause of early birth, triggering the release of prostaglandins – substances which trigger contractions.

"Once contractions start, this produces more inflammation and more prostaglandins, and it becomes a very difficult process to stop. Unfortunately, antibiotics seem to be ineffective in these circumstances, possibly because they cannot be administered early enough in the course of the infection," says Dr Keelan.

Test needed

"In addition, it is often hard to diagnose infection in the womb before delivery and many preterm births don't have any clinical signs of infection but are associated with inflammation. Plans are underway to see if women without infection in the womb, who deliver their babies early, are especially sensitive to factors that trigger the inflammatory response. This could explain a significant proportion of these births."

A study using gene chip technology, conducted by the team's Head of Molecular Biology, Dr Keith Marvin, has identified a range of novel genes which are expressed in the membranes of the wombs of mothers who have their babies early.

Says Dr Keelan: "One of the genes in particular looks extremely promising, and in collaboration with an overseas group we will be following this up to see if we could use it as an indicator of preterm labour and infection in the womb."

Inaugural SMSP Seminar

The relationship between science and society has never been more important, and scientists must improve their ability to communicate if further advances are to be made without difficulties, says Professor Lord Robert Winston.

Speaking at the Liggins Institute Inaugural Science, Medicine, Society Programme seminar, Lord Winston said most scientists had failed miserably in their efforts to express themselves in ways which were understandable to the public.

Often when controversial issues arose, such as genetic modification and stem cell research, scientists were not available to explain the "colossal benefits" to human society in a positive way.

"Scientists should see themselves not as the masters of society but as slaves of society. That's important. It is a key component in how we see our accountability," he said.

Lord Winston said it was a great privilege to be present at the inception of an institution that had made a serious commitment to the philosophy of science and its social context, and to understanding where research should be making an impact.

"It is not just a matter of making television programmes or giving the right buzz words to journalists, it's about trying to do something of academic importance."

Liggins Institute Director Professor Peter Gluckman said the Science, Medicine and Society Programme aimed to bridge the gap between medical science and the community.

"We've seen evidence lately that if science doesn't manage its pace of development and societal understanding of it, gulfs develop which create societal discontent about what scientists are trying to do."

Professor Gluckman said the Science, Medicine and Society Programme will develop novel cross-disciplinary partnerships to explore a number of topical issues such as the economic role of medical research and decision-making on the allocation of resources.

The Institute will look at how the public and private sectors should work together, and the relationship between science and the media. It will also research and debate ethical, philosophical and social issues related to medicine and health care.

Understanding what makes us tick

The secret life of cells may hold some of the answers to a range of medical disorders and conditions. Research at the Liggins Institute aims to untangle the complex mechanisms controlling cell growth and differentiation, and to determine the role of hormones.

The work by a team of researchers, headed by the Deputy Director of the Liggins Institute, Professor Stewart Gilmour, could lead to better understanding of many diseases, from metabolic disorders such as diabetes and obesity, to more serious conditions such as leukaemia and breast cancer.

The research could also lead to the development of a new generation of drugs to help reduce the incidence of these diseases and disorders.

Cell changes

Professor Gilmour says in disease the transmission of molecular information that forms the cell's control circuitry becomes disturbed leading to permanent changes in cell behaviour.

"The challenge for us is to understand what these controls are and what can be done to reverse abnormalities or stop them developing.

"It's a bit like mending a clock. You can't just look at its face and ascertain what the problem is. You have to look deeper inside to find out what's causing it. Our approach is no different - just a little more complicated.

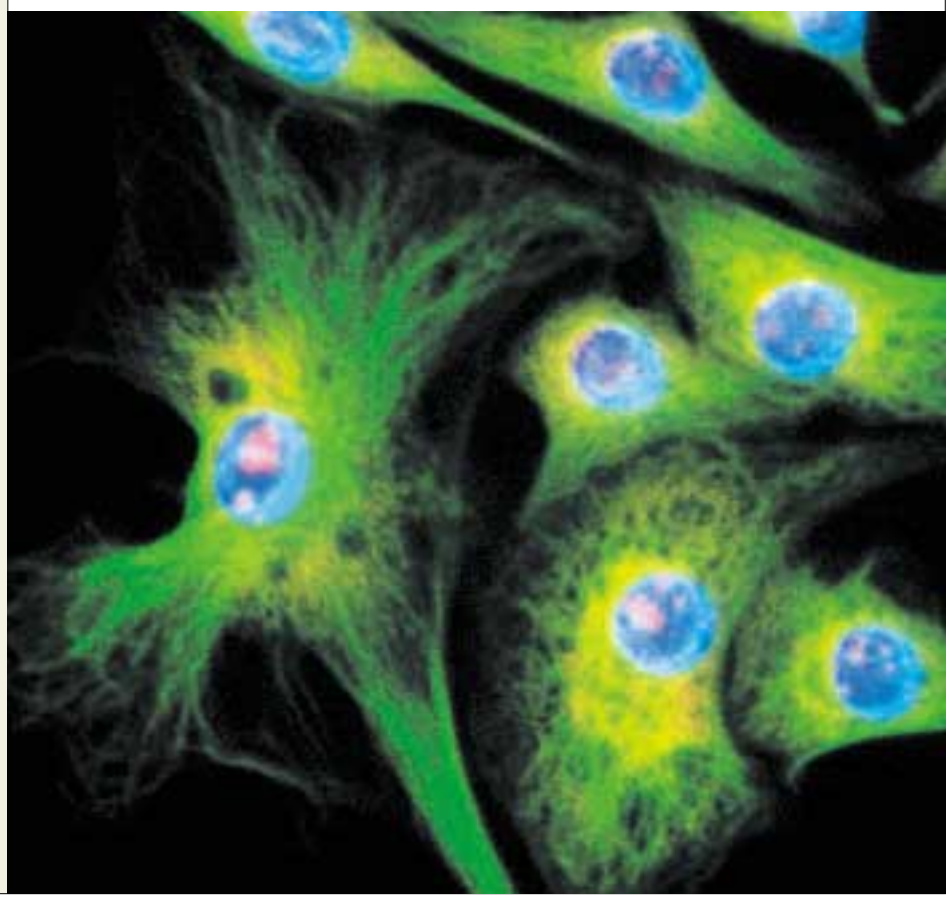
"In the case of cancer for example, the cells in our body do their own thing - they don't follow the rules. Key regulatory steps are subverted and the growth of the cells becomes uncontrollable."

Obesity is another increasing problem and is widespread in the Western world. It is often the observable endpoint of a disturbed metabolism, bringing with it a host of other disorders such as diabetes and heart disease.

Key steps

"In cases of obesity, the hormonal communication system in our body that sends messages to tell us to stop eating is not functioning. The challenge is to determine whether targeting drugs at key steps in the growth process can circumvent this disorder."

Professor Gilmour's research, with its emphasis on how the cell's clockwork is altered by disease, has relevance to a wide range of medical problems including the range of conditions of specific interest to the Liggins Institute.



Cooling the infant's brain allows the body's natural repair mechanisms to work.

Giving babies 'a fighting chance'

Ground-breaking discoveries in perinatal medicine by Liggins Institute researchers are giving hope to parents of newborn babies at risk of brain damage.

The perinatal period is the time immediately before or after birth. It is critical to a child's growth and development, and carries specific risks. About one to two in 1,000 newborn babies are at risk of brain damage during the birth process – often despite normal, healthy pregnancies. Cerebral palsy or intellectual impairment can be the heartbreaking result.

In New Zealand, the average cost of a prolonged stay in neonatal intensive care is about $172,000 per infant.

But thanks to the dedication and commitment of a team of Liggins scientists and neonatal specialists at National Women's Hospital, 28 hospitals around the world are now assessing a new therapy for preventing the damage caused by oxygen deprivation at birth.

More than a hundred babies worldwide have been treated with the Liggins specially designed, water-cooled skull cap, after complications at birth put them at risk of brain damage.

Cell 'suicide'

The cap works by lowering the temperature of the baby's brain, preventing the death of oxygen-deprived cells. Liggins research has shown that many brain-injured babies appear to recover in the first few hours after birth, but the cells that initially survive may still swell up and die many hours afterwards. Studies show that these brain cells commit what is known as apoptosis, or 'cell suicide'. Cooling the brain appears to halt this process, allowing time for the body's natural repair mechanisms to work.

Paediatrician and Liggins medical researcher Dr Alistair Gunn is one of the original team who, with his late mother Professor Tania Gunn, pioneered the research. He is now building on the work they started together.

"Similar approaches involving cold water baths were used by Scandinavian and Soviet groups back in the 1950s but there were never any controlled trials," says Dr Gunn.

"We knew that lowering a baby's body temperature slows their metabolism and could act as a protection against brain damage. With that background, we set out to do something more systematic and logical to assess whether it was effective and, if so, under what conditions."

Pilot studies began in 1994. Results illustrated the importance of very early application of the cooling cap treatment, and continuing cooling, until all the damaging processes started by injury had resolved. It was this work that enabled the clinical trial to go ahead.

"Data about brain swelling in babies and how fast brain injury evolves in newborns is extremely limited," says Dr Gunn. "What we do know is that ideally the cooling treatment should be applied within ninety minutes of when the original brain injury happened, and that cooling becomes rapidly less effective after that time, so there is an extremely small window of opportunity to make a difference.

"The clinical trials are in their infancy and there is still a large number of unanswered questions," says Dr Gunn. "But this is the most likely treatment to become available for asphyxiated babies. At the moment, there is no other alternative.

"It will be difficult getting it right, but if we can define the proper parameters for using this treatment it could be widely used by medical practitioners to give premature babies a fighting chance of a normal, healthy life."

Vulnerable brain tissue

Until recently, the cooling treatment was only thought to have protective effects on brain grey matter. The question Dr Gunn and his team are now asking is whether the treatment also provides protection for white matter tissue, which is particularly vulnerable in the brains of premature babies.

United States figures from the early nineties show that 50,000 infants a year were born with a birth weight of less than 1500 grams - of which 85 percent survived. Of those, five-15 percent had major spastic motor defects and 25-50 percent significant developmental disabilities.

Damage to white matter is the major cause of these disabilities and no specific treatment exists. If cooling could reduce this type of damage it would help reduce the single most important cause of disability in childhood.

'Miracle' baby

Two-year-old Cody is a miracle baby who survived at birth against unbelievable odds, says his mother Shelley Crump.

Staff at North Shore Hospital believed he was dead until a nurse detected slight movement from the 4240 gram infant.

During delivery, Cody's head came out easily but his shoulders were stuck and there was a delay before his body was delivered. As a result, he was born in an extremely poor condition with no heart rate, and not breathing.

Cody was given prolonged resuscitation with drugs and cardiac massage. After 20 minutes the team at the hospital was considering whether to stop resuscitation - until movement was detected.

After further successful resuscitation, Cody was transferred to National Women's Hospital and underwent head cooling for three days to help minimise the risk of him developing brain damage. If left untreated, it is likely that Cody may have been intellectually impaired or developed cerebral palsy.

"The whole experience was awful and I wouldn't wish it on anyone," says Shelley. "But now we have a delightful little boy who appears to have no problems developmentally. In fact, tests indicate that he is above average intelligence and has normal physical ability for a child of his age.

"We are eternally grateful to the staff at the hospital who cared for Cody and to the team that developed the cooling cap. Without them Cody might not have been here today."

Cody is now a happy and healthy little boy thanks to a dedicated medical team, his will to live and – Cody's parents believe – the availability of the cooling cap treatment.

Cody – now a happy, healthy two-year-old.

Associate Professor Chris Williams with the brain rescue monitor which is able to pinpoint 'sick' brain cells.

Liggins invention - a world first

A machine, capable of monitoring minute changes in the electrical activity of the brain in premature infants, has been developed by researchers at the Liggins Institute.

The so-called 'Dream Machine' - the first of its kind in the world - is able to detect and assess the extent of brain injuries in premature infants soon after birth.

Unlike conventional ultrasound technology or magnetic resonance imaging, the brain rescue monitor is able to pinpoint 'sick' brain cells before they die, giving a window of opportunity for rescue treatment.

Dr Chris Williams, Associate Professor of Neuroscience at the Liggins and Deputy Chief Scientific Officer, NeuronZ, says medicine is now very good at keeping premature babies alive, but has yet to "come to grips" with managing and treating brain injury.

Birth defects

About 500 premature babies weighing less than 1500 grams are born in New Zealand each year. Of the 450 who survive, between a quarter and a half of those suffer developmental difficulties.

These range from less severe disturbances of movement and thinking to major spastic motor defects, often accompanied by intellectual damage.

Dr Williams says until now, there has been no way to monitor and detect brain damage in premature infants early enough to treat it.

"Effective early detection of brain damage is needed to reduce health care costs and to improve an infant's quality of care and future wellbeing. Prevention relies on an early reliable diagnosis and a way to determine the timing of the injuries."

The characteristic patterns of brain injury in the premature infant differ from those seen in the full-term baby because the white matter of the brain is particularly vulnerable in premature infants.

The white matter is the brain's 'wiring' or 'circuitry', connecting different parts of the brain which co-ordinate movement, vision, hearing and thinking.

Areas of damaged tissue in the pre-term infant's brain show up as holes with conventional ultrasound scanning or MRI imaging. But this is too late, and of little help, in managing the infant, as the damaged brain cells are already dead.

The brain rescue monitor is now being further developed by NeuronZ with the intention of manufacturing it in New Zealand. It is about to be trialled in newborn, intensive care units at the Hammersmith Hospital in London and in the United States.

Pilot study

A small pilot study of 86 pre-term infants, ranging from 23 to 30 weeks of gestational age and a larger trial at the neonatal intensive care unit in Christchurch, have been completed. The latter, which involved 100 very low birth weight babies – under 1500 grams – showed promising results.

The electrophysiological information, gathered from brain rescue monitoring, was correlated with data from conventional imaging and with the infant's development in the period immediately after birth.

Meanwhile, Liggins researchers are also working on a number of new treatments to rescue the 'sick' brain cells before they die.

DIRECTORS

Professor Peter Gluckman FRS
Director

Professor Peter Gluckman is a world renowned Professor of Paediatric and Perinatal Biology. He is one of only two New Zealand doctors, and one of two paediatricians worldwide, to be elected Fellows of the British Royal Society. His work has focused on understanding the basic mechanisms of two major obstetric and perinatal problems – infant brain injury resulting from oxygen deprivation and intrauterine growth retardation.

Professor Stewart Gilmour
Deputy Director

Professor Stewart Gilmour has been Professor of Molecular Medicine and Pharmacology at The University of Auckland since 1995. He has led developments in biotechnology at the Faculty of Medical and Health Sciences.

Professor Murray Mitchell
Associate Director (Research)

Professor Murray Mitchell is Professor of Pharmacology and Clinical Pharmacology, and Deputy Dean of the Faculty of Medical and Health Sciences. Professor Mitchell has a worldwide reputation for his research into the biology of premature labour and the biochemistry of hormones related to this.

Professor Jane Harding
Associate Director (Academic)

Professor Jane Harding is internationally recognised as an academic neonatologist. Her research spans both clinical and biomedical studies. She is an authority on placental function, the regulation of fetal growth and the consequences of poor fetal growth.

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