

## Milestones

# Professor Graham Liggins, Dr Ross Howie and fetal lung maturity

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*“In the field of observation, chance favors only the prepared mind”*

Louis Pasteur

Corticosteroid enhanced pulmonary maturity was an unsought finding in an experiment on parturition physiology. Though unsought, it was the prepared mind of Sir Graham Liggins that gathered the chance finding into a hypothesis and later a fully elucidated theory. This theory of corticosteroids enhancing pulmonary maturity was put to the test with a randomized trial and years later became a part of routine clinical practice.

The story began with Sir Graham Liggins in the year 1959. He had returned to New Zealand after training in the UK and was appointed as a Senior Lecturer in Obstetrics and Gynecology at the National Women's Hospital. He set about to do academic work on the origins of parturition with a view that if the initiation point was known, one could prevent it in preterm mothers. At the time, there was a rudimentary idea that lambs without pituitary function (cyclopians) had prolonged pregnancies<sup>1</sup>. Having no resources and no animal laboratory, he called on friends at Ruakura Agricultural Research Station, 80 miles south of Auckland. They generously provided the lambs, and over the next sheep season, he worked out how to do fetal hypophysectomies and adrenalectomies. The following year he went for a sabbatical to the Vet School at the University of California at Davis, and put the techniques to the test. The results were dramatically successful. Pregnancies continued on and on after hypophysectomy.

Back in Auckland he needed a laboratory and money. The Hospital gave him an abandoned shed and the Wellcome Trust provided him with funds. His first experiments were to test the idea that the effects of the pituitary were mediated by the fetal adrenal. Infusion of cortisol or ACTH caused premature delivery at any gestational age. Professor Liggins was studying lambs at 115 days of gestation (the human equivalent of about 25 weeks). One morning, he noticed a lamb lying in a cage with its mother who had delivered in the night. What surprised him was that the lamb was still alive. The breathing was irregular and strained, but was present nevertheless. Keeping with his keen scientific nature, he conducted an autopsy and found inflated lungs. He postulated that cortisol had induced one or more enzymes responsible for surfactant synthesis and/or release, it seemed very likely that this was not a species-specific response since cortisol was well known to induce a variety of enzymes in a variety of species. He now needed to test this hypothesis in lambs and later in humans.

This brought about an unusual pairing: an experimental scientist who was also an obstetrician, with a highly specialized clinician and paediatrician, Dr Ross Howie (Figure 1). He was basically a clinician and not inclined towards academic work. His clinical work was highly specialized for the times and he was the only paediatrician in the whole of New Zealand who could



**Figure 1.** L to R: Professor Ross Howie and Sir Graham (Mont) Liggins

artificially respire premature babies. Together, they worked out a rigorous protocol. To simplify administration to the mothers in the trial a once daily dose was selected. The active agent was to be betamethasone 21 phosphate (Betnesol). As luck would have it, this random choice was best suited for the purpose. The placebo had to be identical in appearance. They chose cortisone acetate which is a suspension but one-seventieth of the potency of the active agent. The staff at the Hospital gave their full support, so that 287 mothers were recruited in 22 months. The trial ran within the clinical care of each mother and no funding was required. Two hundred and thirteen mothers were in spontaneous premature labor. When necessary, ethanol or salbutamol infusions were used to delay delivery while steroid or placebo therapy was given. Early neonatal mortality was 3.2% in the treated group and 15.0% in the controls ( $p < 0.01$ ). There were no deaths with hyaline membrane disease or intraventricular cerebral hemorrhage in infants of mothers who had received betamethasone for at least 24 hours before delivery<sup>2</sup>. The manuscript of the study was initially offered to *Nature* and then *Lancet*. It was rejected at both places. It was finally published in an American journal called *Paediatrics*<sup>3</sup>.

Interest in the subject was limited at first. There was very little acceptance of the idea. However, the matter was one of life and death of premature infants and the cause had its supporters. A number of trials followed and later, a metaanalysis proved the benefits of

corticosteroids for neonatal survival in prematurity<sup>4</sup>. Even this was not enough for it to be accepted in widespread clinical use. This occurred only after guidelines from various professional organizations including the Royal College and American College reinforced this intervention. The story reveals an interesting aspect of clinical research. This lamb trial was simply a sideline of the main work of both, Professor Liggins and Dr Howie. It's an interesting warning against the narrow and predetermined endpoints of some research programmes, and highlights the importance of serendipity in progress.

#### References

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