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**INVESTIGATIONS INTO
THE IMMUNOLOGY, PHYSIOLOGY AND EPIDEMIOLOGY
OF PERTUSSIS**

by

**MARK GREENSLADE THOMAS
MB ChB, FRACP**

**A collection of papers submitted for the degree of Doctor of
Medicine of the University of Auckland, 1994.**

INDEX OF CONTENTS

Acknowledgements	4
Abstract	5
Statutory Declaration	8
Research Aims	11
Introduction	12
Paper 1	52
Human serum antibody responses to <i>Bordetella pertussis</i> infection and pertussis vaccination. (J. Infect. Dis. 1989; 159 : 211 - 218)	
Paper 2	60
Serum IgG, IgA and IgM responses to pertussis toxin, filamentous hemagglutinin, and agglutinogens 2 and 3 after infection with <i>Bordetella pertussis</i> and immunization with whole - cell pertussis vaccine. (J. Infect. Dis. 1989; 160 : 838 - 845)	
Paper 3	68
Human serum antibody responses to acellular pertussis vaccine (unpublished)	

- Paper 4 **81**
Nasal immunoglobulin A responses to pertussis toxin,
filamentous hemagglutinin and agglutinogens 2 and 3
after infection with *Bordetella pertussis* and immunization
with whole - cell pertussis vaccine.
(pp330-333 In : Manclark CR. (Ed) 1990 Proceedings
of the Sixth International Symposium on Pertussis.
DHHS, USPHS, Bethesda, Maryland.)
- Paper 5 **85**
The contribution of breast feeding to immunity to pertussis.
(unpublished)
- Paper 6 **100**
Bordetella pertussis infection does not suppress
human serum immunoglobulin responses.
(unpublished)
- Paper 7 **108**
Human cellular immune responses to *Bordetella pertussis* infection.
(FEMS Microbiol. Immunol. 1989; 47 : 205 - 212)
- Paper 8 **115**
Severe hypoxaemia in pertussis.
(Arch. Dis. Child. 1988; 63 : 598 - 605)
- Paper 9 **123**
Effects of *Bordetella pertussis* infection on human respiratory
epithelium in vivo and in vitro.
(Infect. Immun. 1991; 59 : 337 - 345)
- Paper 10 **132**
Epidemiology of pertussis.
(Rev. Infect. Dis. 1989; 11 : 255 - 262)

Paper 11 . From whom do children catch pertussis? (Brit. Med. J. 1987; 295 : 751 - 752)	140
Paper 12 Antibiotics in whooping cough. (Drug Ther. Bull. 1986; 24 : 91 - 92)	141
Discussion	143

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ABSTRACT

This volume contains an introduction to the topic of pertussis followed by twelve papers on pertussis arising from research conducted while I was a research fellow at St. George's Hospital Medical School from 1985 to 1988.

Paper 1 provides a qualitative description of the serum antibody responses to several *Bordetella pertussis* antigens. It demonstrates that the serum antibody response to a specific *B. pertussis* antigen, following either natural infection or vaccination, is dependent both on the antigen and on the subject. Some *B. pertussis* antigens appear to consistently evoke strong serum antibody responses following either natural infection or vaccination, while other *B. pertussis* antigens appear to consistently fail to evoke any significant serum antibody response. Other *B. pertussis* antigens induce an antibody response in a variable proportion of subjects.

Paper 2 describes the serum IgG, IgA and IgM responses to *B. pertussis* antigens in patients with pertussis. These antibody responses are compared with those in the family contacts of patients with pertussis and with those in infants immunised with a whole cell pertussis vaccine. It demonstrates that both pertussis and pertussis vaccination produce marked serum antibody responses to three *B. pertussis* antigens. In contrast, family contacts who are exposed to a patient with pertussis, but who themselves fail to develop disease, have a minor antibody response to the same antigens. Immunity to disease in these family contacts is associated with high titres of antibody to *B. pertussis* antigens at the time of exposure to infection.

Paper 3 demonstrates the serum antibody responses to *B. pertussis* antigens in two subjects immunised with new acellular pertussis vaccines. The antibody responses are compared with those in subjects who had been immunised with a whole cell pertussis vaccine, and with those in subjects who had suffered natural infection. The new acellular pertussis vaccines are shown to induce antibody responses solely to two purified *B. pertussis* antigens, and not to other potential contaminating antigens.

Paper 4 demonstrates that the IgA antibody response in nasal mucus in patients with pertussis is less pronounced than the serum antibody responses. It also demonstrates that titres of antibody in nasal mucus are not especially strongly correlated with immunity to pertussis in family contacts.

Paper 5 compares the serum antibody responses to *B. pertussis* antigens in breast fed infants with pertussis with those in bottle fed infants with pertussis. It also compares the levels of IgA to *B. pertussis* antigens in breast milk from mothers of infants with pertussis with the levels in breast milk from mothers of healthy infants. This paper provides further evidence that *B. pertussis* infection does not produce an especially strong secretory immune response.

Paper 6 provides evidence that *B. pertussis* infection does not produce a significant impairment of immunoglobulin synthesis.

Paper 7 compares the responses of peripheral blood lymphocytes, from patients with pertussis and two control groups, to *in vitro* stimulation with *B. pertussis* antigens. This study is the first to show that *B. pertussis* infection induces cell mediated immune responses.

Paper 8 describes the respiratory physiology of six infants with severe pertussis. It demonstrates that abrupt severe hypoxaemia may be due to prolonged apnoea or may occur despite continued breathing movements and respiratory airflow. It postulates that these findings are due to a ventilation perfusion mismatch secondary to alveolar atelectasis caused by a defect in lung surfactant synthesis, secretion or function.

Paper 9 describes the effects of *B. pertussis* infection on the ciliary function and electron microscopic appearances of human nasal epithelial cells. These findings are extended by similar investigations performed on human nasal epithelial cells exposed to *B. pertussis* toxins *in vitro*.

Paper 10 attempts to explain the large-scale epidemiology of pertussis by a simple mathematical formula. This formula is then used to derive an estimate of the proportion of the population susceptible to pertussis. Finally the relationship between the incidence of pertussis and the level of vaccine uptake is illustrated using data from several countries during the last century.

Paper 11 describes the small-scale epidemiology of pertussis and demonstrates that pertussis is usually transmitted by patients with clinical disease rather than by persons with either atypical disease or asymptomatic infection.

Paper 12 briefly discusses the use of erythromycin and other antimicrobial agents in the treatment and prophylaxis of pertussis.

STATUTORY DECLARATION

I, Mark Greenslade Thomas of Auckland, Candidate for the Degree of Doctor of Medicine of the University of Auckland hereby state and declare as follows:

1. THAT in the research described in the paper entitled "Human serum antibody responses to *Bordetella pertussis* infection and pertussis vaccination" the execution of the study, the interpretation of the results and the preparation of the manuscript were largely my own work. Prof. Harold Lambert initiated the collaboration with Dr. Keith Redhead and contributed advice on the final wording of the manuscript. Dr. Keith Redhead assisted with the design of the study and contributed advice on the final wording of the manuscript.
2. THAT in the research described in the paper entitled "Serum IgG, IgA and IgM responses to pertussis toxin, filamentous hemagglutinin, and agglutinogens 2 and 3 after infection with *Bordetella pertussis* and immunization with whole - cell pertussis vaccine" the design and execution of the study, the interpretation of the results, and the preparation of the manuscript were largely my own work. Prof. Harold Lambert initiated the collaboration with Dr. Ted Ashworth and Dr. Liz Miller and contributed advice on the the interpretation of results and the final wording of the manuscript. Dr. Ted Ashworth performed the antibody assays and contributed advice on the interpretation of the results and the final wording of the manuscript. Dr. Liz Miller provided the sera from healthy vaccinees and contributed advice on the interpretation of the results and the final wording of the manuscript.
3. THAT in the research described in the paper entitled "Human serum antibody responses to acellular pertussis vaccine" the design and execution of the study, the interpretation of the results, and the preparation of the manuscript were largely my own work. Prof. Harold Lambert suggested the topic and contributed to the final wording of the manuscript. Dr Patrick Olin provided the serum samples from two Swedish vaccinees. Dr. Keith Redhead contributed to the interpretation of the results and the final wording of the manuscript.

4. THAT in the research described in the paper entitled "Nasal immunoglobulin A responses to pertussis toxin, filamentous hemagglutinin, and agglutinogens 2 and 3 after infection with *Bordetella pertussis* and immunization with whole - cell pertussis vaccine" the design and execution of the study, the interpretation of the results, and the preparation of the manuscript were largely my own work. Prof. Harold Lambert initiated the collaboration with Dr. Ted Ashworth and Dr. Liz Miller and contributed advice on the the interpretation of results and the final wording of the manuscript. Dr. Ted Ashworth performed the antibody assays and contributed advice on the interpretation of the results and the final wording of the manuscript. Dr. Liz Miller provided the nasal swabs from healthy vaccinees and contributed advice on the interpretation of the results and the final wording of the manuscript.

5. THAT in the research described in the paper entitled "The contribution of breast feeding to immunity to pertussis" the design and execution of the study, the interpretation of the results, and the preparation of the manuscript were largely my own work. Prof. Harold Lambert initiated the collaboration with Dr. Ted Ashworth and Dr. Liz Miller. Dr. Ted Ashworth performed the antibody assays and Dr. Liz Miller provided the serum samples and nasal swabs from healthy vaccinees and also the breast milk samples from the mothers of healthy vaccinees.

6. THAT in the research described in the paper entitled "*Bordetella pertussis* infection does not suppress human serum immunoglobulin responses" the design of the study, the interpretation of the results, and the preparation of the manuscript were my own work. Prof. Harold Lambert initiated the collaboration with Dr. Pamela Riches. Dr. Pamela Riches performed the antibody assays and contributed to the final wording of the manuscript.

7. THAT in the research described in the paper entitled "Human cellular immune responses to *Bordetella pertussis* infection" I made a major contribution to the design of the study, provided the blood samples from patients with pertussis, and contributed to the interpretation of the results and the final wording of the manuscript.

8. THAT in the research described in the paper "Severe hypoxaemia in pertussis" the execution of the study, the interpretation of results, and the preparation of the manuscript were largely my own work. Prof. Harold Lambert initiated the collaboration with Dr. David Southall and contributed advice on the final wording of the manuscript. Dr. David Southall designed the study, and assisted with the interpretation of results and the preparation of the manuscript.

9. THAT in the research described in the paper entitled "Effects of *Bordetella pertussis* infection on human respiratory epithelium in vivo and in vitro" I made a major contribution to the design of the study, provided the nasal epithelial samples from patients with pertussis, and contributed to the interpretation of the results and the final wording of the manuscript.

10. THAT in the research described in the paper entitled "Epidemiology of pertussis" the conception, and execution of the study were my own work. Dr Norman Noah and Prof. Harold Lambert contributed advice on the final wording of the manuscript.

11. THAT in the research described in the paper entitled "From whom do children catch pertussis?" the execution of the study, its interpretation and the preparation of the manuscript were my own work. Prof. Harold Lambert suggested the topic and contributed advice on the interpretation of results and on the final wording of the manuscript.

12. THAT the paper entitled "Antibiotics in whooping cough" was the result of my own research into this topic. Prof. Harold Lambert and the editors of the Drug and Therapeutics Bulletin contributed to the final wording of the manuscript.

I further state and declare THAT none of the work identified as being my own in (1) to (12) above has previously been accepted for a degree or diploma awarded to me by any University.

Signed by me MARK G. THOMAS

this 11 th day of JULY 1994.

MG Thomas.

Witnessed by P. Huggard. J.P.

PETER HUGGARD MANAGER AUCKLAND, NEW ZEALAND JUSTICE OF THE PEACE

RESEARCH AIMS

1. To investigate the immune responses to purified components of *B. pertussis* following natural infection and to compare these responses with those produced by immunisation with the killed whole - cell pertussis vaccine. The *B. pertussis* antigens selected for study were those regarded as most important in conferring immunity to pertussis and were those included in new acellular pertussis vaccines manufactured by a variety of pharmaceutical companies.
2. To compare the immune responses to *B. pertussis* antigens found in patients with pertussis with those found in family contacts of patients with pertussis in an attempt to identify determinants of immunity to disease.
3. To investigate the value of immune responses to component antigens as a diagnostic test for *B. pertussis* infection.
4. To investigate the clinical and pathophysiological features of pertussis particularly with regard to the mechanisms responsible for apnoea and hypoxaemia.
5. To investigate the epidemiology of pertussis particularly with regard to the frequency with which persons with asymptomatic infection or atypical illness transmit the infection to susceptible children.