DEVELOPMENT OF NOVEL

THERAPIES FOR GUT DYSBIOSES

A Thesis Submitted For the Degree

Of Doctor of Science

By

Thomas Julius Borody

BSc (Med), MBBS, MD, PhD, FRACP,

FACG, FACP, AGAF

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DECLARATION

I certify that the work in this thesis has not previously been submitted as part of requirements for a higher degree except as fully acknowledged within the text.

I also certify that the thesis has been written by me.

Any help that I have received in my research work and the preparation of the thesis itself has been acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

Signature of Student: _____

Date: 11 July 2016

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The work that led to this Thesis was carried out over 30 years at the Centre for Digestive Diseases starting with the establishment of the clinic on 16th October, 1984 and was completed in early 2015. The work was carried out during routine clinical sessions, after hours, often on weekends, on international travel where writing was so much easier, but in particular during stimulating sessions with numerous staff members, Researchers, Research Managers of the clinic and in particular, Professor Robert Clancy – Professor of Pathology, Faculty of Health and Biomedical Sciences, University of Newcastle. I am indeed grateful to Professor Clancy for his invaluable support, guidance, ideas and help with the construction of the writing. I'd also like to thank Professor Ian Charles, the head of **i3** Institute for his help and support in progressing the work through discussion session.

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ABSTRACT

This thesis reports results of 30 years of systematic clinical investigations carried out by the author in the general area of "*infection-driven inflammation*". The Centre for Digestive Diseases (CDD) endoscopy clinic was founded by the author in 1984 closely coinciding with Drs Barry Marshall and Robin Warren reporting gastric spiral bacteria with pathogenic role in ulcer disease. CDD was able to source gastric biopsies with ***Helicobacter pylori***(HP) from numerous patients with ulcer disease creating the environment necessary for HP research. Hence, *Section 1* of the Thesis describes systematic studies which asked questions such as 'which is the best therapy', 'what is the role of acid suppression' and the 'role of cigarettes'? This culminated in the development of '*triple therapy*', the first clinically effective HP cure commercialised later as *Helidac*.

Success in HP research soon led to the treatment of the candidate infective cause of Crohn's disease called ***Mycobacterium avium subspecies paratuberculosis*** (MAP). This comprised of three antibiotics which were active intracellularly - another 'triple therapy' akin to HP treatment. However, curing HP could be achieved in 7 days and ulcer healing in 6 weeks whereas MAP – one of the slowest growing bacterial pathogens – required treatment for many months to heal the bowel. So in *Section 2* of the Thesis the effect of Anti-MAP therapy on healing Crohn's disease was studied. Funding from the Broad Foundation supported culture and PCR of MAP while an Israeli company, RedHill Biopharma has funded current pivotal trials with a view to an FDA approval.

Section 3 of the Thesis describes research in Faecal Microbiota Transplantation (FMT). FMT was first used at CDD in 1988 in a patient with indeterminate colitis - the first patient world-wide treated for colitis and cured. Generally ***Clostridium difficile*** infection (CDI) is treated with FMT at CDD with a cure rate exceeding 95%. Subsequently over 6,000 FMT treatments were carried out and new indications for FMT were discovered, both within and outside of the GI tract. These included ulcerative colitis, irritable bowel syndrome, constipation, MS, arthritis, acne, and others, reported in enclosed publications. CDD work in FMT contributed to the global growth of microbiome research and culminated in the creation of the lyophilised encapsulated FMT.

Each of the three Sections has addressed "*infection-driven inflammation*" in different body regions. It is hoped that reported findings in this Thesis will lead to new therapies that will result in significant clinical improvements.