



**‘Gastric and intestinal function in diabetes and obesity: prevalence,  
pathophysiology, management and impact on glycaemic control’**

A thesis submitted for the Degree of

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**DOCTOR OF SCIENCE**

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in the  
**Faculty of Sciences**  
of  
**The University of Adelaide**  
by  
**Michael Horowitz MBBS, PhD, FRACP, FAAHMS**

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THE UNIVERSITY OF ADELAIDE

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Pages 2-93 are not available.

## Dedication

To my late mother, Edith, who imbued her passion for science and respect for intellectual rigour and my wife, Karen, a scientist and my partner on this journey.

*'Would you tell me, please, which way I ought to go from here?' said Alice.*

*'That depends a good deal on where you want to get to' said the cat.*

*'I don't much care where' said Alice.*

*'Then it doesn't matter which way you go', said the cat.*

*'As long as I get somewhere', added Alice as an explanation.*

*'Oh, you're sure to do that', said the cat, 'if you only walk long enough'.*

*from Alice in Wonderland (Lewis Carroll 1857), a conversation between Alice and the Chesire Cat.*

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The following previous and current collaborators made a substantial intellectual contribution to the reported work.

### **Australia**

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### Statement supporting applicant's claim for the award of Doctor of Science degree

The claim for the award of the degree of Doctor of Science is based on research publications in internationally reviewed journals, invited book chapters and one book since 1985. These publications are detailed below. In total, I am the author of 731 papers and 42 book chapters. My papers have been cited 52115 times (16440 times since 2015) and my h-index is 118 (Google Scholar - <https://scholar.google.com.au/citations?user=PJ62CYoAAAAJ&hl=en>). Based on h-index, I was ranked 1892 in the world (<https://www.webometrics.info/en/hlargerthan100>) and 42 in Australia in 2019. I am a pioneer in my research area and arguably the leading international authority in the area of gastrointestinal function in diabetes. The research programme has been driven intellectually by myself since its inception some 38 years ago and has been supported by continuous funding from the National Health and Medical Research Council (NHMRC) of Australia (25 project grants and, in 2019, an Investigator Grant).

I have been the recipient of a number of awards related to my research, including the Distinguished Research Prize of the Gastroenterological Society of Australia (1999), the Eric Susman Prize of the Royal Australasian College of Physicians (2000), the Kellion Award of the Australian Diabetes Society (2009), a Masters Award for Sustained Achievement in Digestive Sciences from the American Gastroenterological Association (2010), and the Royal Australasian College of Physicians 75th Anniversary Award (2014). I was an inaugural Fellow of the Australasian Academy of Health and Medical Sciences (2014).

### Statement detailing the applicant's affiliation with the University of Adelaide:

My undergraduate degree was pursued at the University of Adelaide (1971-1977). My PhD was awarded by the University of Adelaide in 1985. I have been employed by the University of Adelaide in the Faculty of Health and Medical Sciences since 1984, initially as Gwendolyn Michell Research Fellow.

### Statement declaring that none of the work has formed part or all of an award for another degree

I confirm that none of the work submitted in this application for the degree of Doctor of Science has formed part or all of an award for an earlier degree.

An introduction addressing the nature and significance of the work and a conclusion. The concluding passage should summarise how this work has contributed to knowledge.

### Outcomes of my research

My research represents a paradigm shift in knowledge in a long-neglected area, which has now been translated to substantial improvements in clinical practice. Of seminal importance is the recognition that gastric emptying is integral to the pathogenesis and management of type 1 and type 2 diabetes, as well as diabetes associated with pancreatic exocrine insufficiency. Furthermore, measurement of gastric emptying is of increasing relevance to the personalised management of diabetes. I have made a major contribution to the following observations:

- Scintigraphy (i.e. the use of radioisotopically labelled meals and a gamma camera) can be used to measure gastric emptying (GE) precisely for both clinical and research purposes.
- In health GE exhibits a wide inter-, but low, intra-individual variation, with major differences in emptying of solids, nutrient and non-nutrient liquids.

- GE is abnormally delayed (i.e. gastroparesis) in 30-50% of individuals with longstanding, complicated type 1 and type 2 diabetes – the rate of solid GE is not strongly predictive of that of liquid.
- In well-controlled, uncomplicated, type 2 diabetes and adolescents with type 1 diabetes GE is normal, or slightly accelerated.
- Upper gastrointestinal symptoms occur very frequently in type 1 and type 2 diabetes and affect quality of life adversely, but only correlate weakly with the rate of GE.
- The motor/sensory dysfunctions in diabetic gastroparesis are heterogeneous and correlate poorly with cardiovascular autonomic dysfunction.
- Novel pharmacotherapy (cisapride, domperidone, erythromycin), which accelerates GE, can reduce symptoms in diabetic gastroparesis.
- GE is slowed during acute hyperglycaemia and accelerated by insulin-induced hypoglycaemia – the latter is likely to be an important counter-regulatory mechanism.
- GE, even when normal, is a major determinant of postprandial blood glucose excursions and the release of the incretin hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1), in health and type 2 diabetes.
- The magnitude of the incretin effect in health and type 2 diabetes is dependent on small intestinal glucose exposure.
- Exogenous (iv) and endogenous GLP-1 slow GE and this is the major mechanism underlying postprandial glucose lowering, rather than the stimulation of insulin.
- The effect of exogenous GLP-1 to slow GE is attenuated, but not abolished, with sustained stimulation of the GLP-1 receptor i.e. ‘tachyphylaxis’
- Exogenous (iv) GLP-1 normalises elevated blood glucose levels in critically ill patients with ‘stress’ hyperglycaemia.
- ‘Short-acting’ GLP-1 receptor agonists (exenatide BID, lixisenatide) used in the management of type 2 diabetes slow GE markedly, an effect which is dependent on the baseline rate of GE and predictive of the reduction in postprandial glucose.
- ‘Long-acting’ GLP-1 receptor agonists (e.g. liraglutide, exenatide QW) probably slow GE less than ‘short-acting’ drugs, but still significantly.
- In insulin-treated diabetes gastroparesis probably increases the propensity for postprandial hypoglycaemia.
- Nutrient ‘preloads’ diminish postprandial glucose excursions in type 2 diabetes by slowing GE and stimulating GLP-1 and may prove useful in management.
- Antral distension is a major determinant of postprandial satiation.

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- Gastric emptying is modulated by acute changes in patterns of nutrient intake.
- Gastric emptying is a major determinant of alcohol absorption.
- Upper gastrointestinal symptoms are increased in obesity.
- Rapid gastric and small intestinal transit are major determinants of changes in blood glucose, incretin hormones and symptoms after Roux-En Y gastric bypass for obesity.
- Dietary and pharmacological strategies which slow gastric emptying attenuate the postprandial fall in blood pressure.

### Publications

See attached CV for a full list of publications. Also attached is a list of publications specifically relevant to this application.

### Bibliometric Analysis

#### Metrics relating to this Bibliography

\*University of Adelaide credited as institution on all publications

1 Book

69 Reviews and editorials

220 Articles

#### Authorship

- 2 authors = 11
- 3 authors = 12
- 4 authors = 49
- More than 4 authors = 218

Most of the manuscripts in the Curriculum Vitae and presented for the DSc resulted from collaborative efforts.

As a general principle:

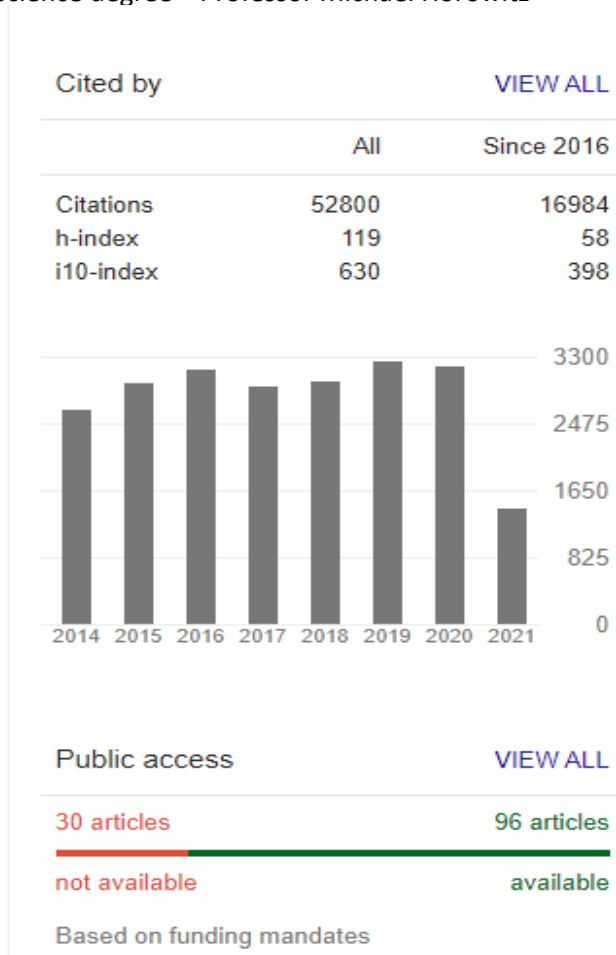
I had a critical role in all publications on which I am listed as an author.

I had a major contribution to the research presented in any manuscript on which I am listed as either first or last author.

The contribution is progressively less from second author to second last. In the majority of last-named publications, my postgraduate student is the first-named author.

- First or sole author = 34
- Last author = 104





***'Gastric and intestinal function in diabetes and obesity: prevalence, pathophysiology, management and impact on glycaemic control'***

**Original Papers**

1. **Horowitz M**, Harding PE, Chatterton BE, Collins PJ, Shearman DJC. Acute and chronic effects of domperidone on gastric emptying in diabetic autonomic neuropathy. *Dig Dis Sci* 1985;30:1-9.
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emptying in Type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 1990;33:675-80.

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