# Pentose Phosphate Pathway Metabolism and Glutathione in the Host Mucosal Response to *Helicobacter pylori* Infection.

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By

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## ABSTRACT

### PENTOSE PHOSPHATE PATHWAY METABOLISM AND GLUTATHIONE IN THE HOST MUCOSAL RESPONSE TO *HELICOBACTER PYLORI* INFECTION.

*Helicobacter pylori* is the primary cause of gastritis and peptic ulcer disease. Recent studies have suggested a major role of reactive oxygen species (ROS) in the mediation of *H. pylori* associated disease. Hence, the severity of mucosal damage during *H. pylori* infection is likely to be dependent on the ability of mucosal cells to counteract the ROS load. It was the aim of this thesis to investigate both the activity of the oxidative pentose pathway (OPP) of glucose metabolism, and glutathione levels in the host response to *H. pylori* infection in both a mouse model and in adult symptomatic patients. Novel agents (N-acetylcysteine and oxythiamine) were assessed for their effects on the activity of the OPP and the levels of intracellular glutathione in host mucosa in the mouse. Concomitantly, measures of neutrophil infiltration, myeloperoxidase activity (MPO) were also carried out. Studies in *H. pylori* (SS1) infected mice were carried out to assess host mucosal responses at different times after infection. Studies in *H. pylori* infected adult humans assessed gastric mucosal G6PDH activity, GSH levels and MPO activity. The ability of the $^{13}$C-urea breath test to non-invasively determine the level of *H. pylori* infection was also investigated. G6PDH activity and GSH levels were both significantly increased in the gastric mucosa of *H. pylori* infected mice after one month of infection. A small increase in MPO activity was also observed but this returned to normal levels by six months. Oxythiamine treatment inhibited the up-regulation of G6PDH activity and

decreased GSH levels, while NAC administration significantly decreased OPP activity and GSH levels in *H. pylori* infected mice. No difference in G6PDH activity or GSH levels were observed between *H. pylori* infected and non-infected patients. However, MPO activity was significantly increased in *H. pylori* infected patients. Results of the $^{13}$C-urea breath test significantly reflected the severity of *H. pylori* associated antral gastritis as measured by histological scoring and MPO activity. These results suggest that an up-regulation of the OPP and increased GSH levels may protect the mucosa against the oxidant load during *H. pylori* infection in the mouse. However, in the adult patient (chronic infection) this proposed mechanism may have be overcome allowing the onset of pathological changes associated with the infection.

**DECLARATION**

I declare that this thesis is a record of original work and contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution. To the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being available for loan and photocopying.

Geoffrey Mark Matthews.

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