HELICOBACTER PYLORI IN HEAMODIALYSIS AND POST RENAL TRANSPLANTATION PATIENTS

THIS IS

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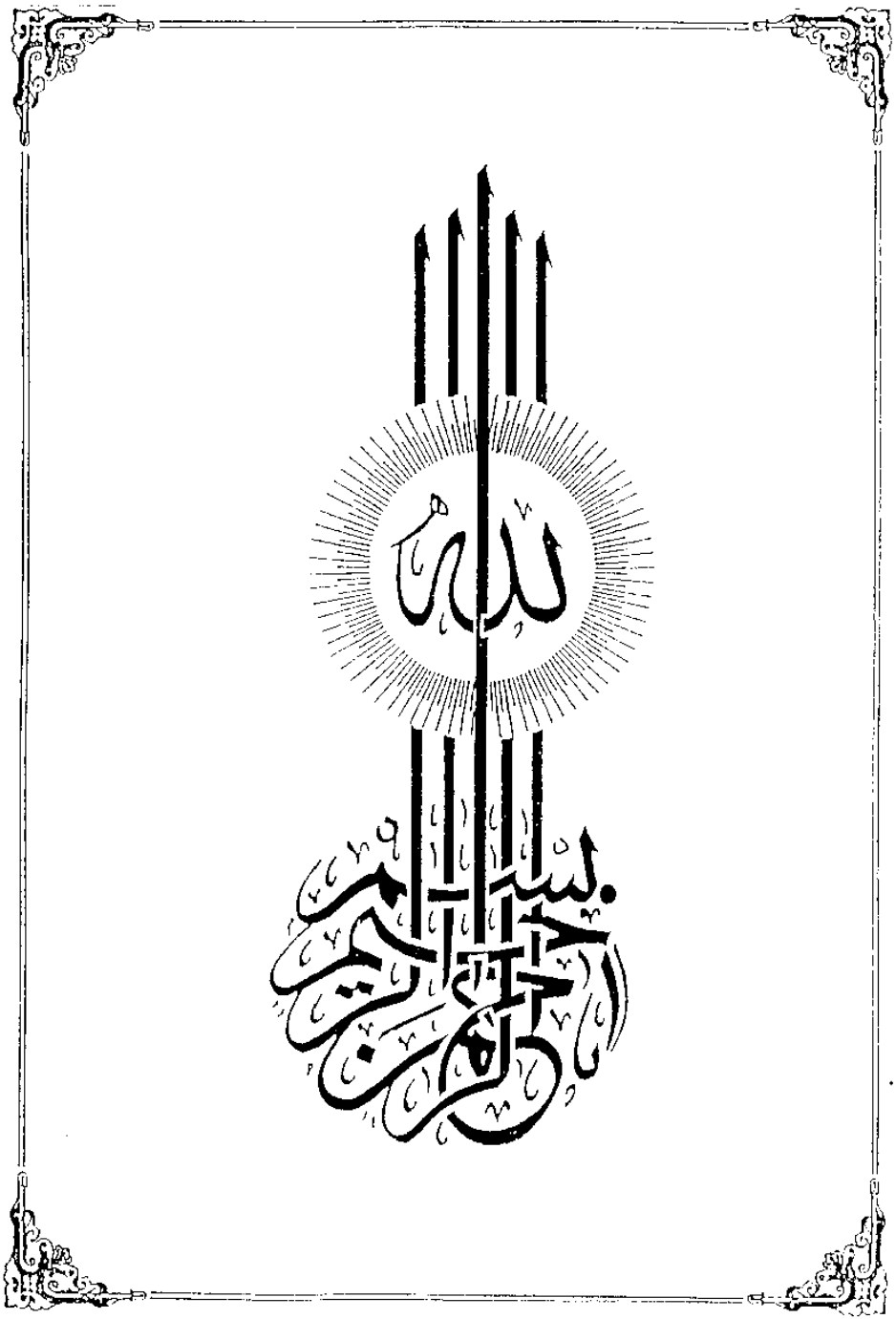

REVIEW OF LITERATURE

Helicobacter pylori (H.pylori) undergoes coccal transformation on exposure to air within 1-2 hours at room temprature 'like other Helicobacters' **[Langenberg, et al., 1984].**

By electron microscope, reveals a homogenous population of organisms 0.5 -0.9 µm wide and 0.3 µm long. **[Philips, et al.,1984].**

H.pylori is motile by means of one to five polar flagellae although dividing cells may have flagella at both poles **[Taylor, et al., 1987].** The flagella is sheathed, thus differing from all other known campylobacter species.

A section of H.pylori organism showed that the cell wall had a double membrane similar to that of other gram negative bacteria with terminal specialization.

Molecular Biology of H.Pylori:-

Fatty acids of H.pylori are markedly different from those of other campylobacter species. The major fatty acids of H.pylori are :-

- Tetradecanoic acid " 14.0 ".
- Cis 9,10 methyleneoctadecanoic acid " 19.0 ".
- And a very small amount of hexadecanoic acid " 16.0 " **(Goodwin, et al., 1989).**

Protein Profiles of H.pylori:-

H.pylori were found to share in a seven major protein bands of molecular weight 74000, 64000, 58000, 21000, 17000 and 12000 **[Taylor,**

By contrast, in developed countries infection in children is rare and adult rates are lower- about 50% at 50 - 60 years of age **[Tom and Leslie, 1991].**

Prevelance also varies between populations of different ethnic origin but how much is due to genetic rather than social factors is unknown **[Tom and Leslie 1991].**

H. pylori is found in 98 -100% of duodenal ulcer patients and in over 75% of gastric ulcer patients if drug-induced gastric lesions are eliminated **[Martin, et al., 1991].**

It is also found in 50 -60% of patients suffering from non ulcer dyspepsia "NUD", in contrast to 20 - 50% of asymptomatic individuals **[Graham, et al., 1987].**

In both asymptomatic and symptomatic populations the presence of H.pylori is strongly associated with gastritis as demonstrated by histological examination, those without gastritis are free of the organism **[Barthel, 1988].**

Natural Reservoir and Transmission of Infection:-

The human gastric mucosa is the only natural reservoir of H.pylori **[Tom and Leslie, 1991].** Gastric Helicobacter like organism have been observed in variety of animals, live rodents, primates and swan but not identical to those from human **[Blaser, 1990].**

Information of the infective dose and incubation period come from feeding experiments. A volunteer ingested " 10^5 CFU " H.pylori and on the seventh day following ingestion. He developed symptoms and endoscopic signs of gastritis. With higher inoculum " 10^9 CFU " another volunteer developed gastritis within 5 days **[Lee and Hazell, 1988].**

Site and Nature of Infection:-

The bacteria live in and beneath the mucus layer that covers the gastric mucosa. In this situation the pH is near neutrality. Any part of the stomach may become colonized, but the mucus secreting epithelium of the antrum is the favoured site. Areas of gastric metaplasia in the duodenum may also become colonized, but H.pylori never colonizes intstinal-type epithelium **[Tom and Leslie, 1991].**

H.pylori may be present deep in gastric glands as well as in superficial parts of the mucosa. Electron microscopic studies showed that some organsisms lie in intimate contact with mucus-secreting cells and their microvilli, sometimes with pedestal attachments **[Goodwin, et al., 1986].** Bacteria have also been seen in endocytic vacuoles and in the canaliculi of parietal cells. **[Chen, et al., 1986].**

Pathogenesis of H.Pylori

Although H.pylori is now recognized as playing an etiologic role in chronic gastritis and peptic ulcer disease, information on the pathogenesis and natural history of infection is limited. A model is proposed in which luminal H.pylori secrete substances that mediate inflammation that is beneficial to the organism but ultimately deleterious for the host, in addition to tissue damage, inflammation also affects gastric secretory function. In this model, the host may attempt to suppress the inflammatory response, and the adequacy of this postulated down-regulation determines pathological and clinical outcome. The effects of the inflammatory process on gastrinhydrochloric acid homeostasis may be of critical importance in the pathogenesis of peptic ulcer disease. **[Martin, 1992].**

Pathogenic mechanisms of H.pylori:-

The success of H.pylori as a gastric pathogen is dependent on virulence (maintenance) factors and pathogenic mechanisms. Virulence factors are those that allow H.pylori to survive in the hostile environment of the gastric lumen, such factors include spiral shape and motility, adaptive enzymes and proteins, and ability to adhere to gastric mucosal cells and mucus. Pathogenic mechanisms are those that lead directly to disruption of the gastric mucosal barrier, including toxins and mediators of inflammation, or contribute to gastric acid activity **[Table 1].**

Table (1): Outline of proposed pathogenic mechanisms of H.pylori. after **Dunn 1993.**

❐ **Decrease mucosal integrity " Leaking roof hypothesis"**

- Toxins and potentialy toxic enzymes:-
  - Cytotoxins.
  - Urease.
  - Mucinase.
  - Lipopolysaccharide.
  - Lipase and phospholipase A.
- Inflammation:-
  - Mucosal invasion.
  - Neutrophil activation.
  - Activation of monocytes, macrophages, lymphocyte and plasma cells.
  - Pophospholipase A.
  - Leukotriene B_4.
  - Leukocyte migration ingibition factor.
  - Platlet activating factor.
  - Autoimmune phemomena.
- Increased gastrin level.
- Pepsin secretion.

❑ **Lipopolysaccharide:-**

Laminin is an extracellular matrix protein required for maintenance of epithelial integrity. H.pylori lipopolysaccharide **[LPS]** inhibits binding of liposome incorporated laminin receptors to laminin coated surfaces in a dose dependant manner. Inhibition of binding of laminin with its specific receptor may contribute to the loss of gastric mucosal integrity in H.pylori infection. **[Slomiany, et al., 1991].**

❑ **Lipase and phospholipase:-**

Mucosal lipids and phospholipids play important roles in maintenance of the viscosity of gastric-mucus, prevention of back diffusion of H^+ ions and maintenance of the hydrophobic lining of the stomach. H.pylori filtrates exihibit both lipase and phospholipase activity and thus, may seriously impair the protective function of the gastric mucus gell **[Goggin, et al., 1990].**

Inflammation:

Inflammation is thought to decrease the integrity of the gastroduodenal mucosal barrier. A variety of putative mediators of inflammation have been identified in H.pylori infection:-

1) Mucosal invasion:-

Mucosal invasion by H. pylori occurs rarely **[Wyle, et al., 1990, Kazi, et al., 1990].** Invasion may be a mechanism allowing presentation of H.pylori antigen to the immune system **[Dunn, 1993].**

physiology may be that ammonia production by H.pylori neutralizes the environment adjacent to the G cell or the somatostatin-secreting cell that monitors luminal acidity. Another hypothesis is that chronic antral inflammation up-regulates gastrin production. **[Graham, et al.,1990].** Interestingly, gastrin promotes growth of both gastric and colonic carcinoma primary cells and cell lines **[Sumiyashi, et al., 1984].**

● ***PEPSIN SECRETION:-***

Increased luminal pepsin activity resulting from elevated gastrin concentration could degrade the gastric mucus layer which in turn might enable other aggressive factors. **[Cave and Cave, 1991].**

Speculations About The Role of H.pylori in The Pathogenesis of Specific Upper Gastrointestinal Pathology:

Chronic Superficial Gastritis:-

Studies of the natural history of superficial gastritis suggest that this process may progress over decades to atrophic gastritis. H.pylori infection is highly associated with each stage of this progression until infection rates decline with sever atrophy **[Faisal, et al., 1990].** This significant association leads to the hypothesis that gastric inflammation may be advantageous for H.pylori. One possibility is that inflammation, with disruption of mucosal barriers, may facilitate the release of nutrients into the mucus gel **[Hazell, et al., 1986].** However, inflammation disrupts epithelial function and therefor is deleteriuos to the host. The apparent predominance of CD8 lymphocytes suggests that the host may be attempting to down-regulate the exuberance of the inflammatory response. In the proposed model, successful downregulation could be defined as occuring in infected persons who no longer have neutrophils in the lesions because pyogenic infection is in general a most destructive host-pathogen interaction **[Weiss, 1989].**

Superficial gastritis caused by H.pylori, with or without neutrophils, may persist for years and therefor may represent a long-term equilibrium between a host's inability to remove a noxious stimulus and ability to contain the damage **[Morris, et al., 1991].**

Clearly, the presence of activated T cells in a host unable to eradicate a particular antigenic focus may be deleterious. Furthermore, in the presence of chronic infection antibodies to host-specific epitopes may develop and contribute to the pathological process. **[Davis, et al., 1990].**

This observation suggests that the ability of parietal cells to respond to the gastrin signal may be impaired possibly by H.pylori-induced inflammation of the fundus . **[Cave, and Vargas, 1989].**

The factors that determine the consequences of the disordered regulation of acid production induced by H.pylori infection are not presently known. Differences in H.pylori characteristics are one possibility, but host genetic factors also could play a role as they do for other chronic infectious diseases with inflammatory sequels **[Steere, et al., 1990].**

Persons with minimal parietal cell destruction may maintain the new homeostasis indefinitely if on a functional level parietal cell [fundal] hypoproduction of acid and G cell [antral] hyper production of gastrin are roughly in balance. For such person, the clinical consequences of chronic superficial gastritis may be minimal. Another group of infected persons may have more extensive antral inflammation. One subset of these persons may develop chronic G-cell hyperfunction in the face of a relatively spared fundus, capable of responding to gastrin. This hyperstimulation may result in increased parietal cell mass and acid production, which may then contribute to duodenal ulceration. **[Soll, 1990].** Another subset may develop high-intensity antral inflammation, leading to local ulceration as well as to G-cell damage or death and this result in hypoacidity and independently lead to local (gastric) ulceration. **[Sipponen, et al., 1989].**

The regulation of anatomic and functional consequences of antral and fundal inflammation may have an inherited basis or be related to hormonal status. Such hypothesis would explain both the familial tendency to ulceration and the male predominance of duodenal ulceration **[Soll, 1990].**

Diagnosis of H.Pylori in Clinical Samples

A variety of diagnostic procedures are used for the identification of H.pylori in clinical samples. No single test is optimal because of length of time required to perform the test, lack of sensitivity or irreproducibility **[Marten, et al., 1992].**

The major categories for identification of H.pylori are:-

1) Histological examination of multiple mucosal biopsy specimens.

2) Culture and biochemical identification.

3) Rapid urease tests.

4) Carbon isotope breath tests **[James, 1990].**

5) Serodiagnosis.

6) Detection by the polymerase chain reaction (PCR) **[Marten, et al., 1992].**

Histological Exanimation of Multiple Mucosal Biopsy Specimens:

Histological detection of H.pylori is based on the identification of micro-organisms with appropriate morphology location and staining characteristics in mucosal biopsy specimens. **[James, 1990].**

The organism is typically located within or beneath the gastric layer of mucus adjacent to the gastric epithelium within the antrun, body or fundus **[Marshall, et al., 1984].**

H.pylori organisms are found adjacent to the surface epithelium in the gastric pits, and in necks of gastric glands, the bacteria tends to congregate near intercellular junctions **[Hazell, and Lee, 1986].**

All endoscopic specimens were obtained, placed in 10% buffered formalin, each biopsy was serially sectioned and then backed at 75°C for 24 hours befor being stained with different stains **[Maden, 1988].**

Different types of stains were used for visualization of H.pylori and mucus penetrated by the organism. The following stains were applied:-

1. Giemsa stain.
2. Hematoxylin and eosin stain.
3. Warthin-starry silver stain.
4. Gram stain.

   In all above stains light microscopy can be used for examination of specimens.**[Coudron, 1989].**
5. Acridine-orange stain. Flourescent microscope used for examination of specimens. **[Walters, 1986].**
6. Phase contrast microscopy. **[Pinkard, 1986].**

The appearance of the organsim varied with the staining:-

1- Hematoxylin and Eosin Stain:-

H.pylori appears as faintly visible hematoxylin positive spiraled rods in tissue sections, but it is less sensitive for H.pylori demonestration. **[Marshall., et al., 1984].**