CHLORAMPHENICOL DRUG FAILURE IN TYPHOID FEVER

THESIS

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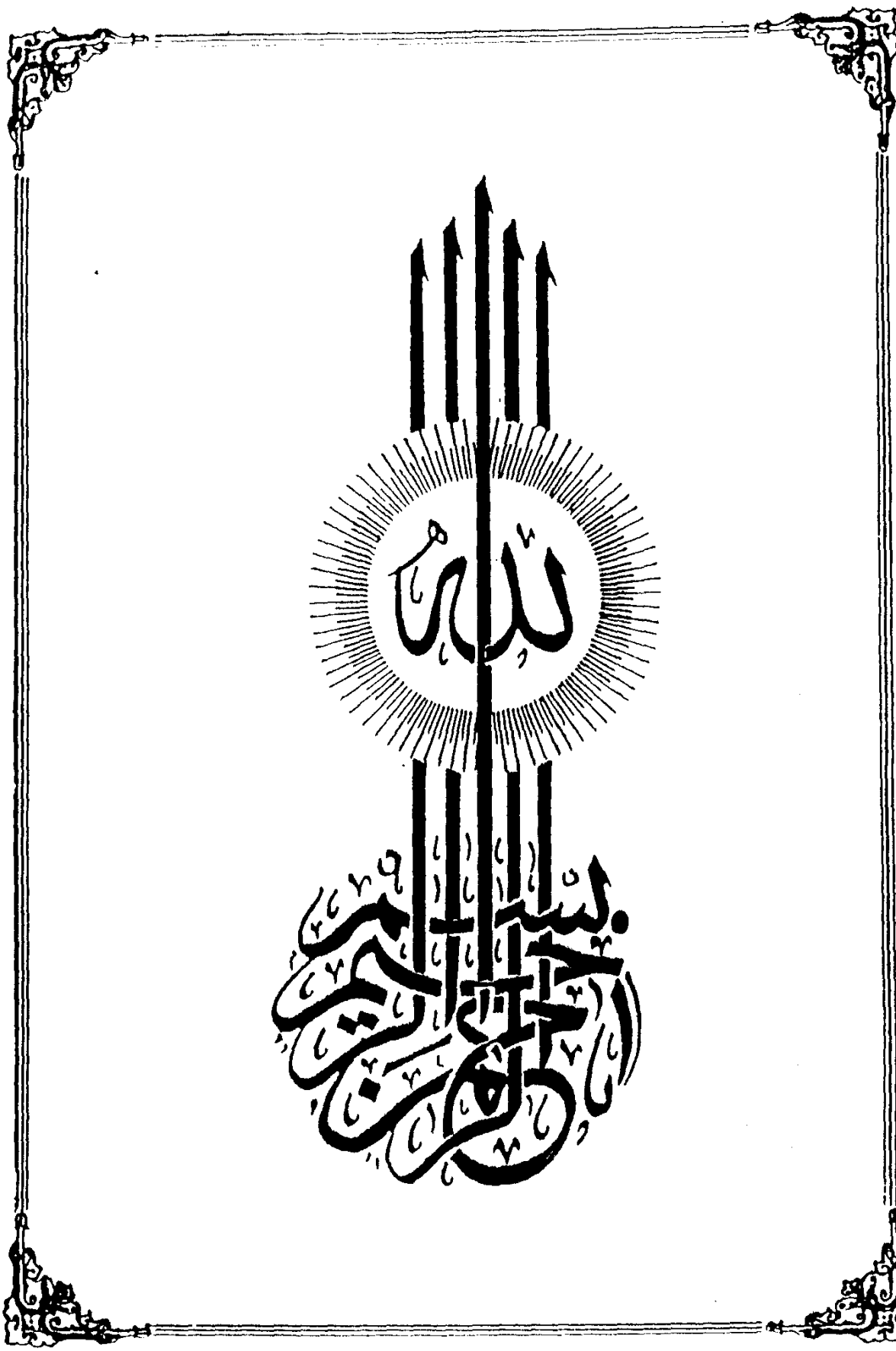

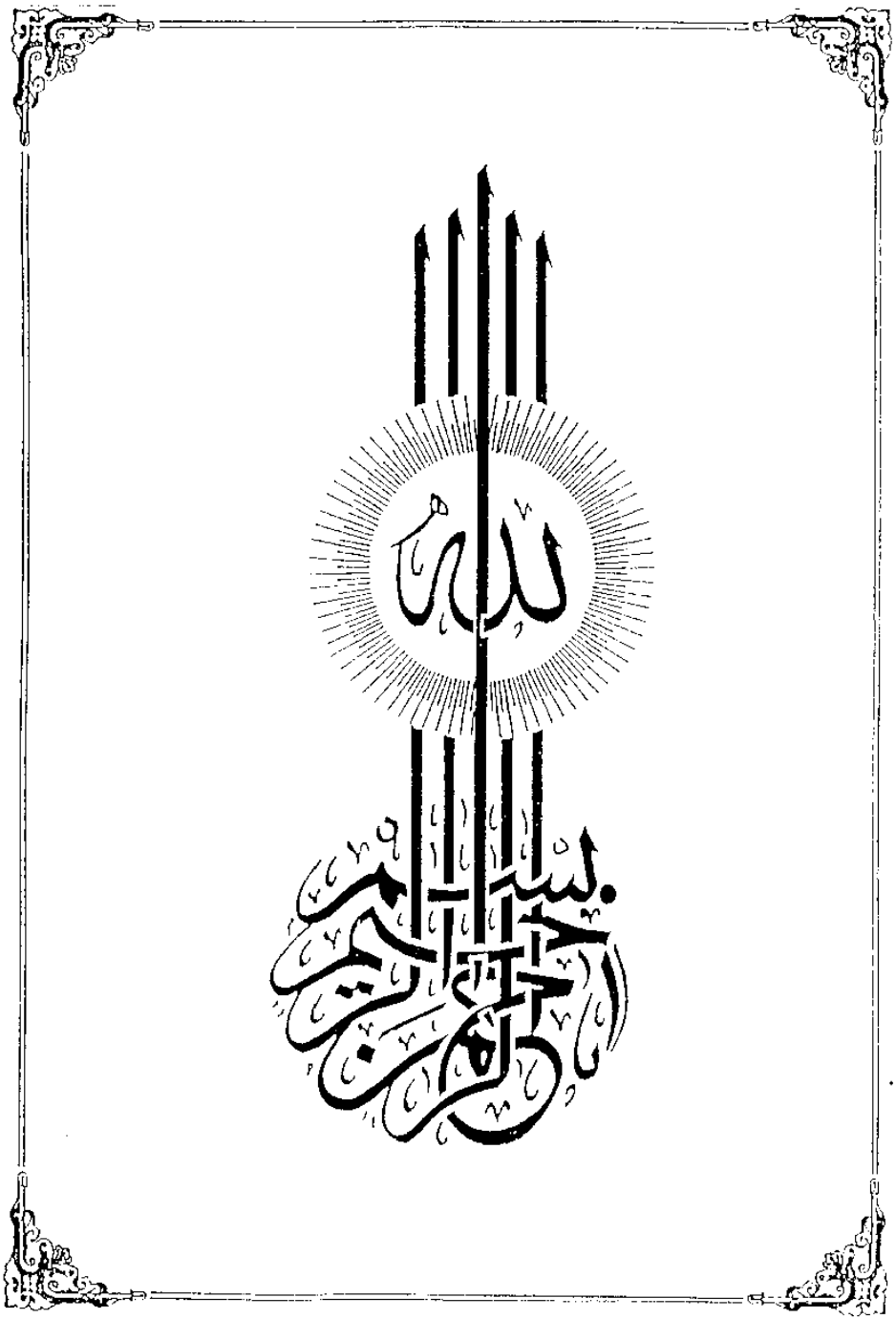

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INTRODUCTION

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Enteric fevers are endemosporadic diseases in EGYPT. The average number of reported cases of enteric fevers per year is 15000 (EL-AKKAD,1970). This reported number is far below the real one as many cases are treated in the private clinics without notification (ABDEL WAHAB. 1974) .

Since 1948 and until recently. chloramphenicol was the drug of choice for the treatment of enteric fevers. It is cheap, easily administered by various routes and is very effective. OMAR and ABDEL WAHAB (1967) in EGYPT reported that, the average defervescence period after chloramphenicol therapy increased from 3.2 days in 1950 to 6 days in 1964.

BOCTOR, et al. (1970) reported 0.7% chloramphenicol drug failure both clinically and bacteriologically in 300 typhoid patients in EGYPT. In ALEXANDERIA. MASSOUD. et al. (1982) found that strains of *Salmonella wein* isolated were mainly resistant to chloramphenicol and ampicillin. In 1991. EL SHERBINI. reported an outbreak of chloramphenicol resistant typhoid fever in GHARBEYA governorate at late 1990. Also IBRAHIM. et al.. (1991). reported 5 acute typhoid cases resistant in-vitro and in-vivo to chloramphenicol, ampicillin and trimethoprim sulfamethoxazole in ABBASSIA fever hospital. CAIRO.

AIM OF THE WORK:

Typhoid fever is endemic in Egypt and a considerable number of cases was reported to be resistant to chloramphenicol, however the magnitude of the problem was not statistically assessed. So the aim of this work is to study the cause of this resistance from the clinical, bacteriological, and therapeutic points of view

REVIEW OF LITERATURES

TYPHOID FEVER

DEFINITION :

Typhoid fever is an acute systemic illness caused by infection with *Salmonella typhi*. It is characterized by: (1) Prolonged fever. (2) Sustained bacteremia without endothelial or endocardial involvement, and (3) Bacterial invasion of and multiplication within the mononuclear phagocytic cells of the liver, spleen, lymph nodes and Peyer's patches. Paratyphoid fever is a pathologically and clinically similar, but generally milder.Enteric fever refers to either typhoid or paratyphoid (Hoffman, 1991)

ETIOLOGY:

Salmonella typhi is a gram-negative, flagellated, non capsulated, non sporulating, facultative anaerobic bacillus. It ferments glucose: reduces nitrate to nitrite. Synthesizes peritrichous flagella when motile: has a somatic (0) antigen (oligosaccharide), a flagellar (H) antigen (protein) and an envelope (K) antigen (polysaccharide) and has a lipopolysaccharide macromolecular complex called endotoxin that forms the outer portion of the cell wall. The endotoxin is composed of three layers: outer (O. oligosaccharide), middle (R-core), and basal (lipid A). *S.typhi* is also capable of developing R-plasmid-transmitted antimicrobial resistance (Hoffman, 1991).

Salmonella enteritidis: Paratyphoid fever is caused by organisms of the species *S.enteritidis*. The bacteria that most frequently cause paratyphoid fever are formally named *S.enteritidis* bioserotype *paratyphi A*. *S. enteritidis* bioserotype

paratyphoid B. and *S. enteritidis* bioserotype *paratyphi C*. but they are commonly referred to as *S. paratyphi A, S. schottmuelleri,* and *S. hirschfeldii* respectively (Hoffman. 1991).

Characteristics and Classifications: All *salmonellae* grow on simple media: however. specimens are usually cultured on a selective media. such as *Salmonella-Shigella* agar, to avoid the overgrowth of *salmonellae* by other enteric bacteria. The various *salmonellae* are differentiated on the basis of biochemical reactions and by serologic reaction, i.e., agglutination patterns with O, H, and Vi homologous antisera. The biochemical differences between *S. typhi. S. paratyphi A*. and *S. schottmuelleri* (*paratyphi B*) are summarized in table (1)

Table (1) Biochemical Differences Between *S. typhi. S. paratyphi A. and S. schottmuelleri* (After Sonnenwirth. 1980).

	S.typhi	***S.paratyphi A***	***S.schottmuelleri***
Acid from glucose	+	-	+
Gas from glucose	-	+(trace)	+
Hydrogen sulfide	+ (trace -5%)	- (10% late +)	+
Citrate utilization	-	- (25% late +)	+
Lysine decarboxylase	+	-	+
Ornithine decarboxylase	-	+	-

Serologic classification using the kauffman. White agglutination scheme of antigenic analysis is summerized in table (2) Among the *salmonellae*. only *S. typhi* and *S. paratyphi C* have the important (k) antigen called the Vi antigen. Vi stands for virulence. and *S. typhi* microorganisms with this antigen are thought to be more

virulent than those without. possibly because the envelope protects the somatic O antigen from bactericidal antibody (Hoffman 1991).

Table (2) Antigenic Analysis by the Kauffman. - White Scheme of the Organisms Causing Typhoid and Paratyphoid Fever (After Sonnenwirth, 1980)

	O antigens Group.	O antigens	H antigens		K antigens
			Phase 1	Phase 2	
S.paratyphi A	A	1.2.12	a		–
S.paratyphi B	B	1.4.5.12	b	1.2	–
S.paratyphi C	C	6.7	c	1.5	Vi
S.typhi	D	9.12	d		Vi

EPIDEMIOLOGY :

Typhoid fever is a disease of world wide prevelance especially in Asia, Africa and north America.

Source of Infection: *S. typhi, S. paratyphi A* and *S. schottmuelleri* infect only humans. Thus , all cases of typhoid fever, most cases of paratyphoid fever could theoretically be traced back to another infected human .The stool and less commonly, the urine of carriers and those with or recovering from acute infections are the source of the organism. It is generally believed that 3% of patients with

acute typhoid fever become carriers. The carrier rate increases with increasing age and prevalence of gallbladder disease. Fecal carriers usually outnumber urinary carriers 10 to 1. but in areas endemic for *Schistosoma haematobium* urinary carriers are often more common (Hathout,et al.,1967 and Hoffman, 1991).

Method of Transmission: The infection is most commonly acquired by ingestion of contaminated food or water but may rarely be transmitted by direct finger to mouth contact with the feces, urine, respiratory secretions, vomitus or pus from an infected individuals. The stools of chronic carriers usually contain from 10^6 to 10^9 organisms per gram *S. typhi* can survive for several weeks in water, ice, dust, or dried sewage and on clothing but survives in raw sewage for less than a week. It can also survive and multiply in milk or milk products without altering the appearance of the milk. (Hoffman, 1991).

Food can be infected directly by water used to wash it or prepare it, by carriers, by fomites and dust and probably by flies. In many cases, the initial concentration of organisms is too low to cause human disease, but under optimal environmental conditions, the organisms can multiply in food. In the case of shellfish such as oysters and mussels, the polluted water in which they live may not have a high enough concentration of organisms to cause disease in a swimmer who ingests small amounts of water.However, since the shellfish filters up to 50 gallons of water per day and concentrates the microbial content, the aficionado of raw shellfish from polluted water may be presented with an enormous dose of *S. typhi* (Hoffman, 1991)

Factors That Influence Infectivity: Studies done in human volunteers using the Quailes strain of *S. typhi* showed that in healthy, previously unvaccinated male adults ingestion of 10^5 organisms led to clinical disease in 25% of volunteers (ID_{25}); ingestion of 10^7 organisms caused disease in 50% (ID_{50}) and 10^9 organisms caused disease in 95% (ID_{95}). As the number of organisms increased, the incubation period decreased, but the clinical syndrome was unchanged. Nothing is known about the relationship between differences in strains of *S.typhi* and infectivity except that strains that do not have Vi antigen are less infective and less virulent. A gastric pH of < 2 will kill most of the organisms: those patients who chronically ingest antacids, have had a gastrectomy or have low gastric acidity for other reasons require lower numbers of organisms to produce clinical disease.(Hoffman, 1991).

PATHOGENESIS:

Mucosal Penetration: After ingestion, the organisms pass through the upper gastrointestinal tract to the small intestine, where they attach preferentially to the tips of villi and either invade directly or multiply for several days before invading. Since less than 5% of the villi are involved, it is hypothesized that there are specific receptor sites on the villi, but these receptors have not been identified. Stool cultures are positive for several days after *S. typhi* ingestion and then become negative until after the onset of clinical illness. Human volunteer studies have shown that invasion can take place in the jejunum and animal studies suggest that it occurs in the ileum. After penetration (mechanism unknown), the organisms pass to

the intestinal lymphoid follicles and the draining mesenteric lymph nodes: some also pass into the systemic circulation, where they are filtered out by the reticuloendothelial cells of the liver and spleen. The *salmonellae* then multiply within the mononuclear phagocytic cells of the lymphoid follicles, lymph nodes, liver, and spleen. At this stage there are subtle degenerative, proliferative and granulomatous changes in the villi, crypt glands and lamina propria of the small bowel and in the mesenteric lymph glands. These changes are reversible and unassociated with clinical symptoms (Hornick and Greisman, 1978 and Hoffman, 1991).

Dissemination and Organ Invasion: At a critical point (which is probably a function of numbers of bacteria, bacterial virulence and the host's immune response) a sufficient number of organisms and possibly other mediators that induce clinical symptoms are released from this sequestered intracellular habitat in the intestinal and mesenteric lymph system and pass through the thoracic duct into the general circulation This marks the end of the incubation period, which may last from 3 to 60 days but is usually 7 to 14 days (Hornick and Greisman, 1978 and Hoffman, 1991).

During this bacteremic phase, the organisms may invade any organ but are most commonly found in the liver, spleen, bone marrow, gall bladder and Peyer's patches in the terminal ileum. They invade the gall bladder either directly from the blood stream or from the bile and then reappear in the intestine, where they are excreted in the stool and reinvade through the intestinal wall. At most tissue sites,