CALCITONIN AND IRRITABLE BOWEL SYNDROME

Thesis

submitted for partial fulfillment of
The Master Degree in Internal Medicine

By

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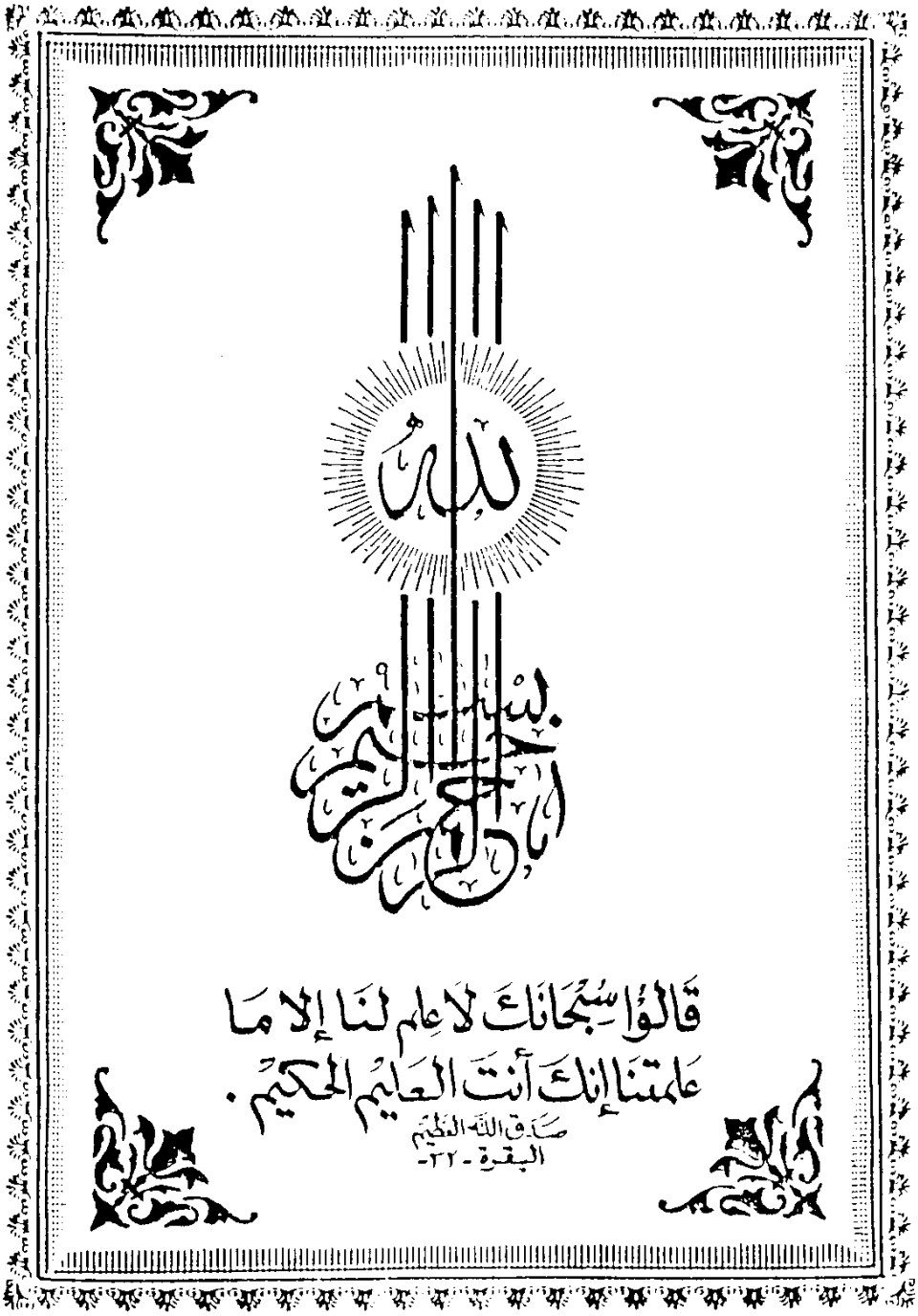
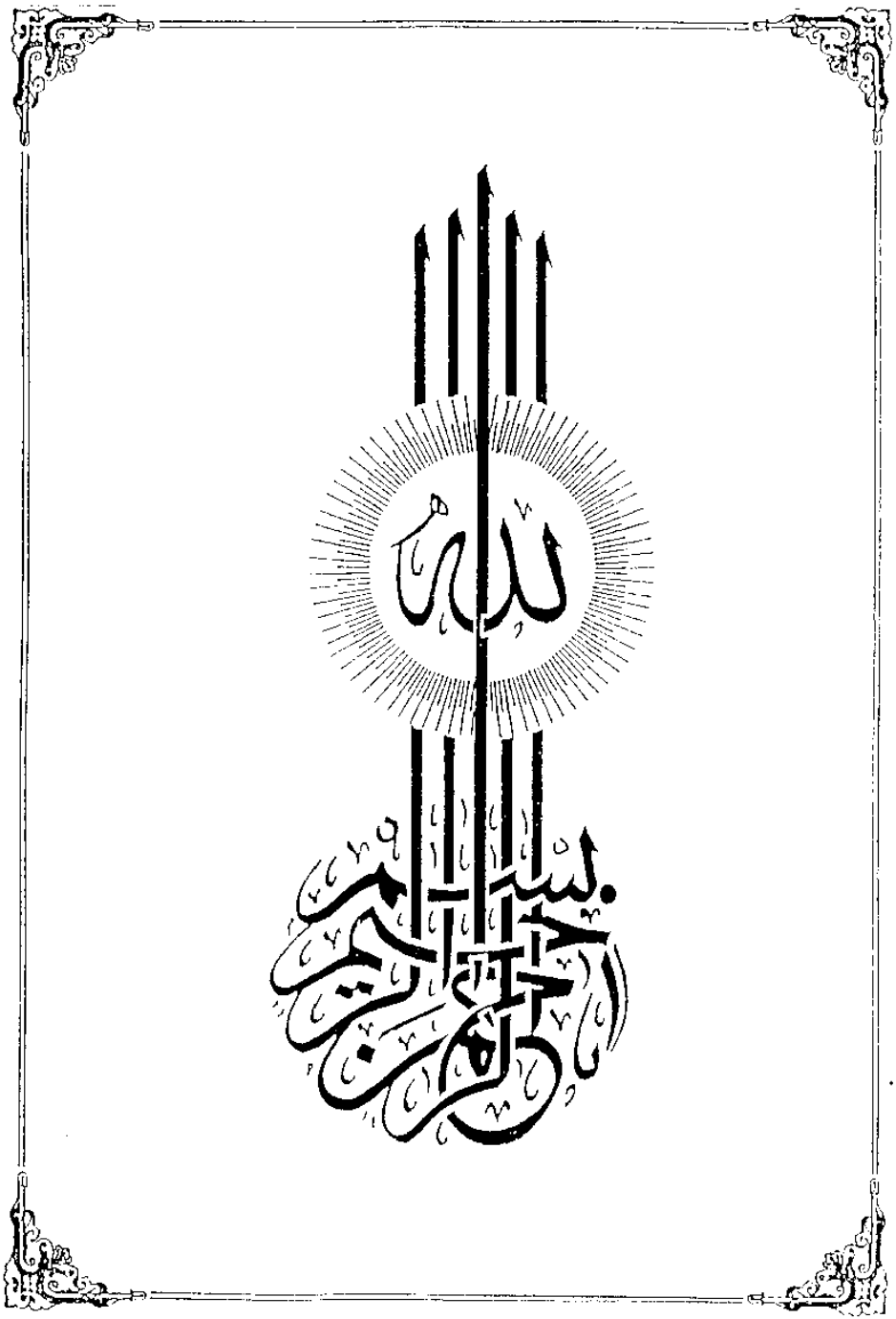
1994





Acknowlegement

First and for the most I feel always indebted to "GOD", the most kind and the most merciful.

I wish to express my profound gratitude and sincere thanks to Prof. Dr. Soheir Sheir, prof. of Internal Medicine, Ain Shams University, as it was such a great honour to work under her guidance.

I wish to express my appreciation to Dr. Said Shalaby, ass. prof. of Internal Medicine, Ain Shams University, for offering the point of this research.

I wish to express my deepest gratitude to Dr. Yehia Elshazly, ass. prof. of Internal Medicine, Ain Shams University, for his valuable aid and close supervision throughout this work.

I wish to express my appreciation to Prof. Dr. Rashwan Mohamed Farag, prof. of Biochemistry, Ain Shams University, for his co-operation and generous attitude.

Yasser M. Abdel Halim
1994

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INTRODUCTION AND AIM OF THE WORK

INTRODUCTION:

Non organic ("functional") bowel diseases are the most frequent reason for referring patients to gastroenterologists; of several clinical variants irritable bowel syndrome is the most common; it is probably the most common chronic gastrointestinal disorder in developed countries (Almy, 1978). It is extremely common disorder accounting for more than 50% of cases seen by gastroenterologists (Harvey et al., 1983).

The term irritable bowel syndrome *can be defined as a symptom complex characterized by a chronically abdominal pain and abnormal bowel habit in the absence of any underlying structural or biochemical abnormality that explains the symptoms* (Switz, 1976; Alpers, 1981; Harvey et al., 1983; White et al., 1991; Talley et al., 1992). However it may occasionally coincide with organic gastrointestinal diseases (Kruis , et al., 1984).

Much work has been done to fined a pathologic marker to define the IBS. The diverse symptomatology suggest that there is a diffuse *disorder of smooth muscle function* (colonic, oesophageal, small intestinal, urinary bladder, vascular,...) which can explain both the colonic and the non colonic symptoms (Watier et al., 1983; Fielding, and Regan, 1984; Whorwell et al., 1986a; Whorwell et al., 1986b).

Calcitonin (CT) is one of a family of calcitonin gene related peptides which, although first found to be synthesized and secreted by thyroid C cells (Copp et al., 1961; Foster et al., 1964), now is known to be produced by neuroendocrine cells throughout the body. (Hirsch et al., 1963; Bussolatti and Pearse, 1967; Ayer-Le Lievre and Fontaine-Perus, 1982).

A variety of gastrointestinal effects of calcitonin have been described in some studies:

-*In rat*, intracerebroventricular (ICV) administration of calcitonin restored the fasted pattern which was disturbed by meal and inhibited gastric emptying and small bowel transit but not the large bowel transit (Bueno, 1982; Bueno et al., 1983a).

.-*In humans*, calcitonin given in doses reproducing the levels observed in medullary carcinoma of the thyroid, induced the appearance of phase III type activity and reduced the duration of the immigrating myoelectric

complexes (IMC) in the small intestine but not in the stomach of young volunteers (Demol et al., 1986).

AIM OF THE STUDY:

Irritable bowel syndrome is the most common motility disorder of the gastrointestinal tract.

Calcitonin has a central action to influence the gut motility.

S. calcitonin will be studied in both patients having symptoms of irritable bowel syndrome (subdivided into patients with predominant constipation and patients with predominant diarrhoea) and healthy controls.

REVIEW OF THE LITERATURE

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DEFINITION, CLASSIFICATION AND EPIDEMIOLOGY

DEFINITION?

IS IT AN IDENTIFIABLE ENTITY?

The nature of the irritable bowel syndrome (IBS) is controversial patients complain of many symptoms but objective abnormalities are elusive and no diagnostic test is available (Thompson, 1984; Drossman et al., 1985; Oettle and Heaton, 1986; 1987; Read, 1987). Therefore, IBS defies definition.

Nevertheless, at our present state of knowledge (or lack thereof), there is an alimentary disturbance that we call the IBS which *can be defined as a symptom complex characterized by a chronically abdominal pain and abnormal bowel habit in the absence of any underlying structural or biochemical abnormality that explains the symptoms* (Switz, 1976; Alpers, 1981; Harvey et al., 1983; White et al., 1991; Talley et al., 1992). However it may occasionally coincide with organic gastrointestinal diseases (Kruis , et al., 1984).

SYNONYMS FOR IBS. ARE THEY CORRECT?

Numerous terms have been used to describe the syndrome. Many of them are either inadequate, inaccurate or both.

Nervous colon (Alvarez, 1943), *Irritable colon* (Jordan and Kieffer, 1929), *Unhappy colon* (Hurst, 1935), and *Spastic colon* (Ryle, 1928) are

inadequate because they describe only some possible etiologic influences (such as nervous factors) or some signs (e.g., spasticity). Furthermore, they ignore the involvement of areas other than the colon.

Nervous colitis, Spastic colitis, and Mucous colitis (Bockus, 1928; White and Jones, 1940) have two additional faults. They are *physiologically incorrect*, because inflammation is not present, and they are *frightening to the patient* because they are easily confused with ulcerative colitis. Therefore the term "colitis" is to be sharply condemned as both inaccurate and psychologically damaging (Schuster; 1989).

Irritable bowel syndrome is *the most suitable and accurate* term currently available, as it emphasises that the condition is a motor disorder manifesting irritability, that it is not a single disease but a syndrome, and that many areas of the gut are involved.

IS IT A DISEASE?

Patients commonly complain of erratic bowel habits, but bowel function varies from day to day in healthy people and it has not been shown to vary more in patients (Heaton et al., 1992).

Furthermore, many healthy people suffer symptoms of the irritable bowel syndrome from time to time and it is only when a person goes to a doctor with these symptoms that he becomes a patient (Drossman et al., 1982; Sandler et al., 1984; Bommelaer et al., 1986; Drossman et al., 1986; Johnson et al., 1986). Then he has tests, is treated with diet, drugs, consultation; in short he is considered to be ill (Thompson, and Heaton, 1980).

Therefore, it is still unclear whether IBS is abnormal perception of normal events or normal perception of abnormal events? Can a complaint which is so common in the community, be so subjective in manifestations, and which has as yet no defined aetiology or mechanism, be considered a disease? We shall not be able to settle these questions until we establish the presence or absence of pathophysiologic abnormalities which are present only in sufferers (Thompson et al., 1989).

However, disease means "*absence of ease; uneasiness; inconvenience, annoyance, disturbance, trouble*----", and sufferers will readily agree this is present, therefore, *IBS is a disease on the semantic ground.* Furthermore, any complaint that represent 20-50% of out patient gastrointestinal consultations *is a disease in epidemiological and economic sense* (Harvey et al., 1983).

WHAT IS IT'S NATURE?

Much work has been done to fined a pathologic marker to define the IBS. The diverse symptomatology suggest that there is a diffuse *disorder of smooth muscle function* (colonic, oesophageal, small intestinal, urinary bladder, vascular,...) which can explain both the colonic and the non colonic symptoms (Watier et al., 1983; Fielding, and Regan, 1984; Whorwell et al., 1986a; Whorwell et al., 1986b).

IS IT COLONIC OR SYSTEMIC DISORDER?

It was commonly regarded that the irritable bowel syndrome (IBS) is a disturbance of the colonic motor activity (Connell, 1962; Snape et al., 1976; 1977), but patients with IBS compared with healthy control subjects suffer from a wide variety of symptoms of more general nature and these seem to originate outside the colon and possibly outside the bowel altogether. These led to the concept that *IBS is not a disorder confined to the colon* (Fielding 1977a;b; Watson et al., 1978; Rubin et al., 1979; Murney and Winship, 1982; Thompson, 1984a; Whorwrell et al., 1986a).

IS IT FUNCTIONAL OR ORGANIC?

The label "functional" depends upon exclusion of any known morphologic, histologic, microbiologic, or biochemical abnormalities in patients. As the irritable bowel syndrome (IBS) fits these criteria *till now it can be labelled as a functional disorder* (Read, 1987a). However, before the recognition of lactose intolerance (McMichael et al., 1965; Weser et al., 1965) patients with that disorder would have been considered to have IBS, one-third of 27 patients referred with unexplained diarrhoea were found to be surreptitiously using laxatives (Read, 1980), further, idiopathic bile salt malabsorption is another organic explanation for symptoms in a small group of patients previously thought to have a functional disorder (Taysen and pederson, 1976). These lead us to suspect that *those conditions which we now call functional will one day have a rational explanation and what is thought "functional" today may be found "organic" tomorrow* (Haubrich, 1989).

CLASSIFICATION

To a clinician, there appear to be several subgroups of IBS and these subgroups may have very different pathophysiologic relationship.
Fielging (1984), *classified the irritable bowel syndrome into three main clinical subgroups according to the site wherein the patient's main symptoms and signs reside:*

I. IRRITABLE ORO-PHARYNX SYNDROME (UPPER IBS)

Manifested by globus, sore throat, excessive coating of the tongue, bad breath in absence of halitosis, excessive dryness of the tongue or mouth without clinical evidence of such dryness exist, and/or bad taste.

II. IRRITABLE OESOPHAGEO-GASTRO-DUODENUM SYNDROME (MIDDLE IBS)

Manifested by heartburn, dysphagia, oesophageal angina, and "nutcracker oesophagus" as a result of oesophageal dysfunction (Rubin et al., 1979; Obrecht and Richter, 1984) and non-ulcer dyspepsia as a result of gastroduodenal dysmotility (Ayres et al., 1989).

III. IRRITABLE COLON SYNDROME (LOWER IBS)

Manifested by gaseousness, abdominal pain, and diarrhoea as a result of disordered function of the small and large bowel (Lasser et al., 1975; kellow et al., 1988); spastic colon and constipation as a result of colon dysmotility ; proctalgia fugax as a result of spasm of the anal canal or supporting striated muscles (Thompson, 1984a; prior et al., 1990).
Within the lower IBS itself, clinicians (Thompson, 1984b; Drossmam, 1982; Harvey, 1983) have recognised five syndromes categorised according to bowel habits.

They including the following:

A. Spastic colon syndrome

Consists of Abdominal pain, Three of the Manning criteria, Constipation defined by straining on more than 25% of occasions, and/or Diarrhoea defined by loose stool more than 25% of occasions.
The rectum is often empty or contains scybala (Fielding, 1981a).

B. Painless diarrhoea syndrome

Might be defined as loose, runny stools on more than 25% of occasions, with a total daily stool volume of less than 300 gm. It may be associated with urgency and more than three movements per day (Cann et al., 1983).
It was recognised as a separate entity (Esler and Goulston, 1973).

C. Atonic constipation syndrome

May be defined as staining at stool more than 25% of the time. The rectum is usually full. There may be one of: less than three movements per week, laxative abuse, or melanosis coli (Bockus et al., 1933).

D. Lower GIT gaseousness syndrome

Consists of distension due to the products of colon bacterial digestion; hydrogen, carbon dioxide and in some cases methane. This is improved by starvation and relieved by flatus on more than 25% of occasions. There appears to be no intestinal gas in some gaseous patients and the sensation of gaseousness may be simply another manifestation of gut dysmotility (Lasser et al., 1975).

E. Chronic abdominal pain syndrome

Defined as pain more than three days per week and lasting more than one year; usually unrelated to meal, defecation, diarrhoea or constipation. The chronic abdomen has the least understood pathophysiology in that it sometimes occurs without any evidence of gut dysmotility. This is often said to be "psychogenic" or to occur in "pain-prone" person, and may not be a bowel syndrome at all (Thompson et al., 1984b).
Each of these syndromes occurs without known organic explanation and may only be defined by its symptoms. These disparate syndromes should not be lumped together when searching for causes or mechanisms of the IBS, nor indeed when studying methods of treatment (Drossman et al., 1982; Harvey et al., 1983; Thompson, 1984).

EPIDEMIOLOGY OF THE IBS

Irritable bowel syndrome is probably the most common chronic gastrointestinal disorder in developed countries (Almy, 1978). It is extremely common disorder accounting for more than 50% of cases seen by gastroenterologists (Harvey et al., 1983).

IS IT PREVALENT?

Irritable bowel syndrome is *extremely common in the general populations*. A number of studies (Tab. 1-1) have been estimated the prevalence of IBS, but most of them were not obtained from truly representative samples of subjects identified through random sampling techniques.

TABLE 1-1
Prevalence of IBS using restrictive symptom Criteria [1]

STUDY	*PERCENTAGE*
Thompson and Heaton (1980)	13.6
Drossman et al., (1982)	7.3
Talley et al., (1990b)	10.4
Whitehead et al., (1990)	7.1
Talley et al., (1991)	13.0

IS IT PREVALENT IN CERTAIN AGE GROUP?

The people most prone to irritable bowel syndrome are *under the age of 25 years* (Fielding, 1977). However, above the age of 25 years, there is no age group particularly prone to irritable bowel syndrome (Talley et al., 1990; Talley et al., 1992).

[1] .Defining the IBS as three or more of the six Manning criteria in those with abdominal pain six or more times in the prior year.