STUDY OF
EFFECT OF BRAN
ON COLONIC BACTERIAL FLORA
IN PATIENTS WITH LIVER CIRRHOSIS

THESIS

Submitted in Partial Fulfillment For

MASTER DEGREE

(GENERAL MEDICINE)

BY

TAREK MAGED EL- SAKATY

M.B, B.CH.

SUPERVISORS

Prof. Dr. Soheir Sheir
Prof. of Interanl Medicine
Ain Shams University

Prof. Dr. Ragaa Mahmoud Lashin
Prof. of Clinical Pathology
Ain Shams University

Prof. Dr. Mohamed Ramadan Baddar
Prof. of Internal Medicine
Ain Shams University

Dr. Mahmoud Ossman Abd El-Megid
Lecturer of Internal Medicine
Ain Shams University

FACULTY OF MEDICINE
AIN SHAMS UNIVERSITY
1992

ACKNOWLEDGMENT

I wish to express my sincere gratitude to **Prof. Dr. Soheir Sheir**; for her constant guidance, valuable advise and continuous support, without her creation and encouragement this work would have not been fulfilled.

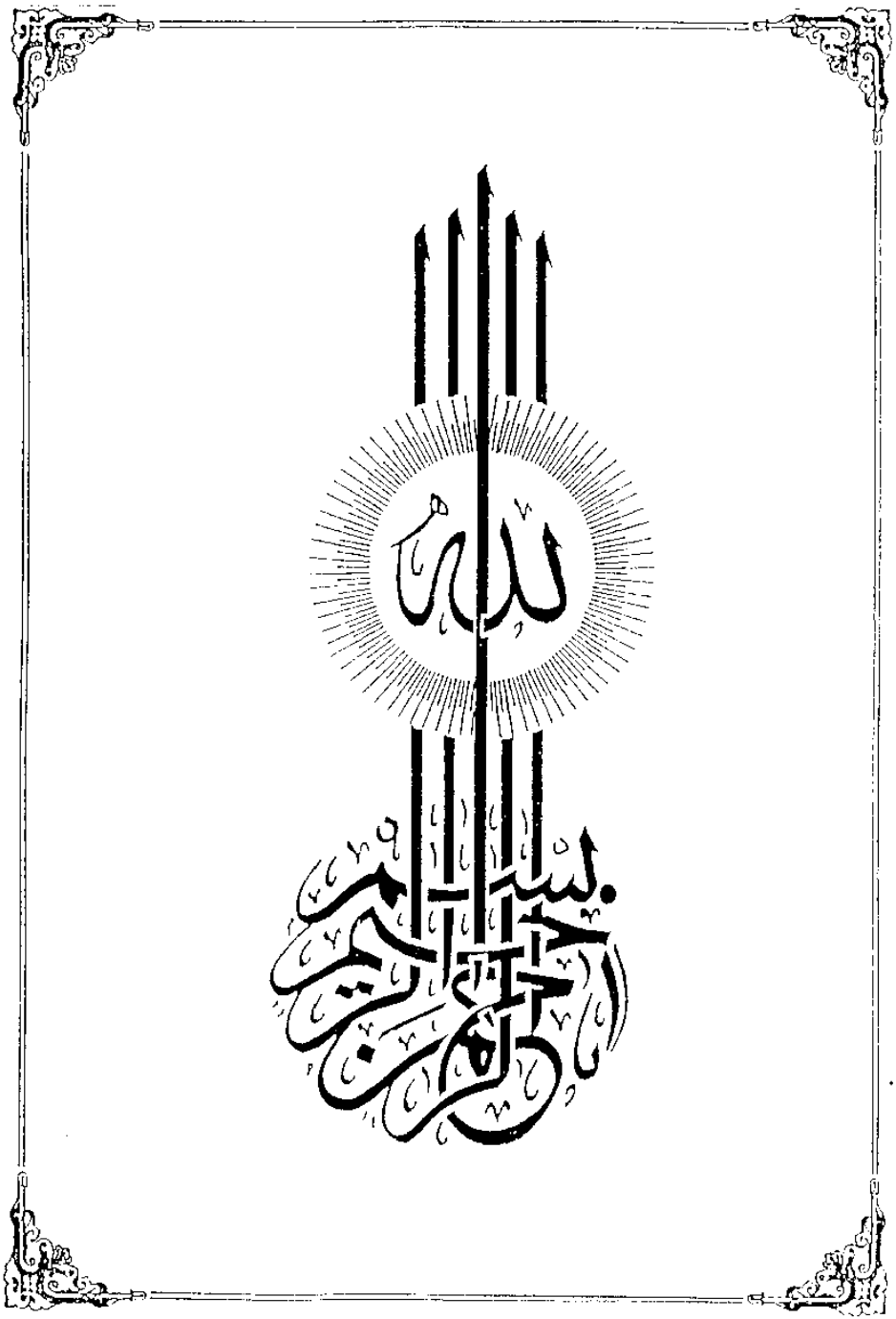
I would like to express my deepest gratitude to **Prof. Dr. Ragaa Mahmoud Lashin.** Thanks a lot to her for her close supervision and continuous guidance.

I may convey my gratitude to **Prof. Dr. Mohamed Ramadn Baddar** for his creative guidance and help.

I am also very grateful to **Dr. Mahmoud Ossman Abd El-Megid,** Lecturar staff of internal medicine for his help.

I would like to express my gratitude to **Dr. Amira Mokhtar,** lecturar staff of clinical pathology for her cooperation

Tarek Maged



LIST OF CONTENTS

*INTRODUC*TION AND *AIM OF THE WORK*

INTRODUCTION
AND
AIM OF THE WORK

- Many studies were done in cirrhotic patients and their relation to the pattern of colonic bacterial flora, pointing out to the harmful effects of these flora specially urea splitting organisms as Klebsiella and Proteus which was found in one study to be more prevalent (10^8) in cirrhotic compared to (10^4) in normal control (*Montogomerie et al.*, 1970).
- The policy of treating cirrhotic patients with either chronic encephalopathy or hepatic coma by lactulose and/or Neomycin depends upon reducing the number of these bacteria to reduce Ammonia production.

  Wheat fibre (bran), is a natural material with a mild laxative effect, it was mentioned before that bran can affect bacterial flora in the colon. (*Pomare and Heaton*, 1974).
- The aim of this work is to study the pattern of colonic bacterial flora in cirrhotic and non cirrhotic subjects and to study the effect of short term use of wheat fibre (bran) on these flora, in a trial to find out its possible therapeutic role.

REVIEW OF LITERATURE

LIVER CIRRHOSIS

Definition

Cirrhosis is defined anatomically as a diffuse process with fibrosis and nodular formation ending in disruption of the normal lobular architecture of the liver. Functionally the disorder is characterized by a disturbance of hepatic hemodynamic associated with reduced functioning liver mass and with secondary alteration of extrahepatic circulation. the disturbance of hemodynamic is reflected as portal hypertension and reduced hepatic blood flow (*Popper*, 1977).

Pathogenesis and Structural Changes

Cirrhosis is initiated by injury and necrosis to the hepatocytes. The responses of the liver to necrosis are strictly limited; the most important are collapse of hepatic lobules, formation of diffuse fibrous septa, and nodular regrowth of liver cells. Thus, irrespective of the aetiology, the ultimate histological pattern of the liver is the same, or nearly the same (*Popper*, 1977).

The transition to the characteristic architectural disfigurement depends on processes common to many aetiological factor. There is passive development of fibrous septa from the collapse of the connective tissue framework due to death and loss of liver cells (*Popper*, 1977).

Sherlock (1989) said that hepatocellular necrosis is the stimulus to collagen formation. the factors con-

cerned are not known. Necrotic cells could produce a stimulating factor or there might be a preformed inactive precursor in the plasma.

Guzellian et al., (1984) reported that in monolayer culture, the rat hepatocyte can secrete collagen, raising the possibility that the hepatocytes may elaborate its own matrix and play a role in fibrogenesis.

In cirrhosis, synthesis of collagen is increased due both to a greater collagen synthesis per fibroblast and to an increase in the number of collagen producing cells. (*Sherlock*, 1989). She also added that, fibronectin is a cell surface glycoprotein serving the attachment of collagen fibrills and proteoglycans to hepatocytes. It forms part of the extracellular matrix collagen. It is deposited in areas of liver cell damage as early as one hour after injury. It stimulates fibrogenesis and its breakdown products are chemotactic for fibroblasts. It also modulates cell differentiation and function, particularly during the healing response. Fibronectin is found around all heaptocytes but not in portal tracts (*Sherlock*, 1989).

Sherlock, (1989) also added that laminin is a larger, rigid glycoprotein found principally in basement membranes of ducts, ductules and capillaries but forming a continous basement membrane around hepatocytes at times of regeneration or liver injury. The increased collagen is harmful by disrupting the hepatic architec-

ture and by converting sinusoids to capillaries, so impending metabolic changes through the basement membrane between liver cells and blood.

The fibrous septa may extend in bridge like fashion joining the central vein to the portal tracts and this results in disruption of the normal lobular architecture of the liver. There is proliferation of the remaining cells to produce nodular areas of hyperplasia with lack of the normal lobular architecture. This is accompanied by abnormal vascular connections. Shunts between branches of hepatic artery and portal vein are established. This abnormal vascular connection in the cirrhotic liver contributes to the abnormal function of the liver (*Sherlock*, 1989).

Classification of Cirrhosis

There are many classification of liver cirrhosis but the most common one is based on aetiology, morphology and function (*Anthony et al.*, 1977)

I) Morphological Classification

The simplest morphological subdivision of cirrhosis is according to the nodular size by which three types are recognized

1. *Micronodular Cirrhosis*

   It is characterized by nodules of equal size, up to 3 mm in diameter associated with regular, thick septa and by involvement of every lobule (*Scheuer*, 1988)

2. *Macronodular Cirrhosis*

It is characterized by the presence of nodules which are variable in size and larger than those of the micronodular type. Regeneration is reflected by larger cells with larger nuclei and by cell plates of varying thicknesses (*Scherlock*, 1989)

3. *Mixed Cirrhosis*

Regeneration in a micronodular cirrhosis results in a macronodular or mixed appearance with time, micronodular cirrhosis often convert to macronodular (*Fauerholdt et al.*, 1983)

II) Aetiological Classification

1. *Established Aetiological Associations:-*

These include viral hepatitis, alcoholism, some metabolic diseases eg. haemochromatosis, hepatolenticualr degeneration (Willson's dis), Alpha antitrypsin deficiency, glycogen storage disease, galactosaemia, hereditary fructose intolerance and a beta-lipoporteinemia. Also, prolonged cholestasis, hepatic venous outflow obstruction eg. veno-occlusion disease and Budd-Chiari syndrome. Toxins and drugs are also included together with intestinal bypass operation for obesity (*Anthony et al.*, 1977).

2. *Cirrhosis with debatable Causes*

* Auto-immunity
* Parasitic disease
* Malnutrition (*Sheuer*, 1979)

Malarial parasites don't cause cirrhosis, the co-existence of malaria and cirrhosis probably reflects malnutrition, virus hepatitis and toxic factor in the community

* syphilis causes cirrhosis in neonates but not in adults
* In schistosomiasis the ova excites fibrous tissue reaction in the portal zone the associated cirrhosis in certain countries is probably related to other aetiological factors. (*Sherlock*, 1989). Ghaffar et al., in 1984 added that the incidence of cirrhosis was found to be higher in patients with mixed schistosomiasis and HBV infection or non A non B viral infection than viral hepatitis alone.

* **Cryptogenic Cirrhosis**

The aetiology is unknown and this is clearly a heterogeneous group (*Sherlock*, 1989). Gial Bongi Vanni in 1983 said that it may be often difficult to establish a cause and effect relationship even unless an aetiological factor is found. Likewise, in case

where a well substantial causal relationship is demonstrated, the exact pathogenic mechanism may remain unclear.

* It is important to keep in mind that

[A] Clinical and histopathologic features may overlap among forms of cirrhosis

[B] One liver may simultaneously exhibit several histopathologic pathways leading to cirrhosis

[C] The final diagnosis of cirrhosis should be made considering:

1- Clinical setting of the patient.

2- Epidemiological informations.

3- Specific laboratory tests.

4- Liver biopsy when available.

III) **Functional Classification**

(1) ***Clinically Latent Cirrhosis***

* In this case the disease may be discovered at a routine examination or biochemical screen or at operation undertaken for some other condition

* Cirrhosis may be expected if the patient has pyrexia, vascular spiders, palmar erythema or unexplained epistaxis or edema of ankles. firm enlargement of the liver and splenomegaly are helpful diagnostic signs.

* Vague morning indigestion and flatulent dyspepsia may be the early feature in alcoholic cirrhosis.

Biochemical tests may be quite normal in this group.

the most frequent changes are slight increase in the serum tranaminases or gamma G.T level and constant excess of urobilinogen in the urine. Diagnosis is confirmed by needle liver biopsy. Those patients may remain compensated until they die from another cause. Some proceed, in a period from months to years, to the stage of hepatocellular failure. In others the problem s portal hypertension with oesophageal bleeding. Portal hypertension may be present even with normal liver function tests. The course in individual patient is very difficult to predict. (*Sherlock*, 1989)

(2) ***Decompansated Cirrhosis***

the patient usually seeks medical advice because of ascites and/or jaundice. General health fails with weakness, muscle wasting and weight loss. Continous mild fever. (37.5 -38 °C) is often due to gram -negative bacteremia, to continuing hepatic cell necrosis or to complicating liver cell carcinoma, foetur hepaticus may be present. Cirrhosis is the commonest cause of hepatic encephalopathy. Jaundice implies that liver cell destruction exceeds the capacity for regeneration and is always serious. The deeper the jaundice the greater the inadequacy of the liver function.

The skin may be pigmented due to increase amounts of melanin, clubbing of the fingers is occasionally seen. Purpura over the arms, shoulders and chins may be associated with a low platlets count. Spontaneous brus-

ing and epistaxis reflect a prothrombin deficiency. The circulation is over active, the blood pressure is low. Sparse body hair, vascular spiders, palmar erythema, white nails and gonadal atrophy are common. Ascites is usually preceded by abdominal distension. Oedema of the legs is frequently associated. The liver may be enlarged, with a firm regular edge or contracted or impalpable. the spleen may be palpable (*Sherlock*, 1989). The heaptocellular function in cirrhosis and its prognosis was assessed by Child's classification into 3 group:

Child's Classification of Hepato-cellular Function in Cirrhosis

Group Designation	A	B	C
Clinical Observation			
Ascites	none	easily controlled	poorly controlled
Neurological disorder	none	minimized	advanced coma
Nutrition	excellent	good	poor "wasting"
Laboratory investigation			
Serum bilirubin (mg%)	below 2.0	2.0 - 3.0	over 3.0
Serum albumin (mg%)	over 3.5	3.0 - 3.5	under 3.0

The one year survival in good-risk (Child A and B) patients in about 70% and in bad risk (Child C) about 30% (*Infante-Rivard et al.*, 1987).