ASSESSMENT OF THE IMMUNOLOGICAL ASPECTS OF CHRONIC HCV INFECTION

THESIS

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BY

AHMED NOAMAN HASSIB

(M.B., B.Ch.)

M.Sc.

Under Supervision of

Prof. Dr. NOAMAN MOHAMED HASSIB

Professor and Head of Tropical Medicine

Faculty of Medicine– Ain Shams University

Prof. Dr. ABD EL RAHMAN EL ZYADI

Professor of Tropical Medicine

Faculty of Medicine – Ain Shams University

Prof. Dr. OSAIMA EL SAID SELIM

Professor of Clinical Pathology

Faculty of Medicine– Ain Shams University

Prof. Dr. AHMED ABD EL HALEEM EL TAWEEL

Professor of Pathology

Faculty of Medicine – Ain Shams University

Faculty of Medicine

Ain Shams University

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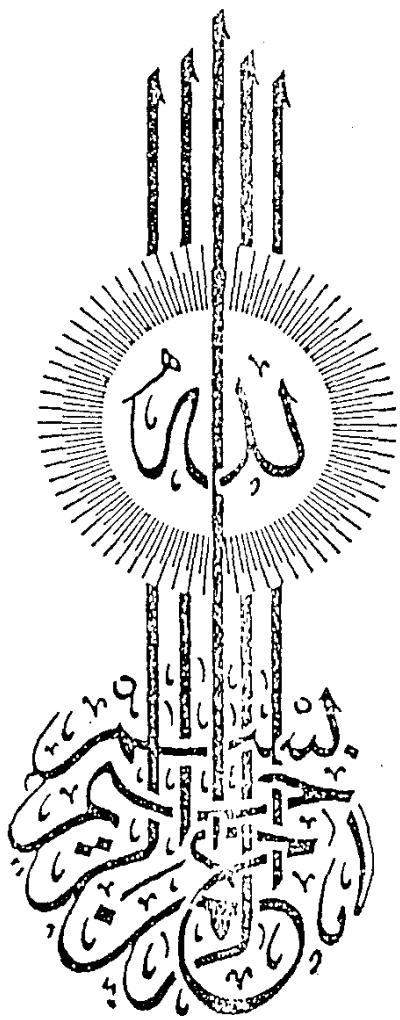

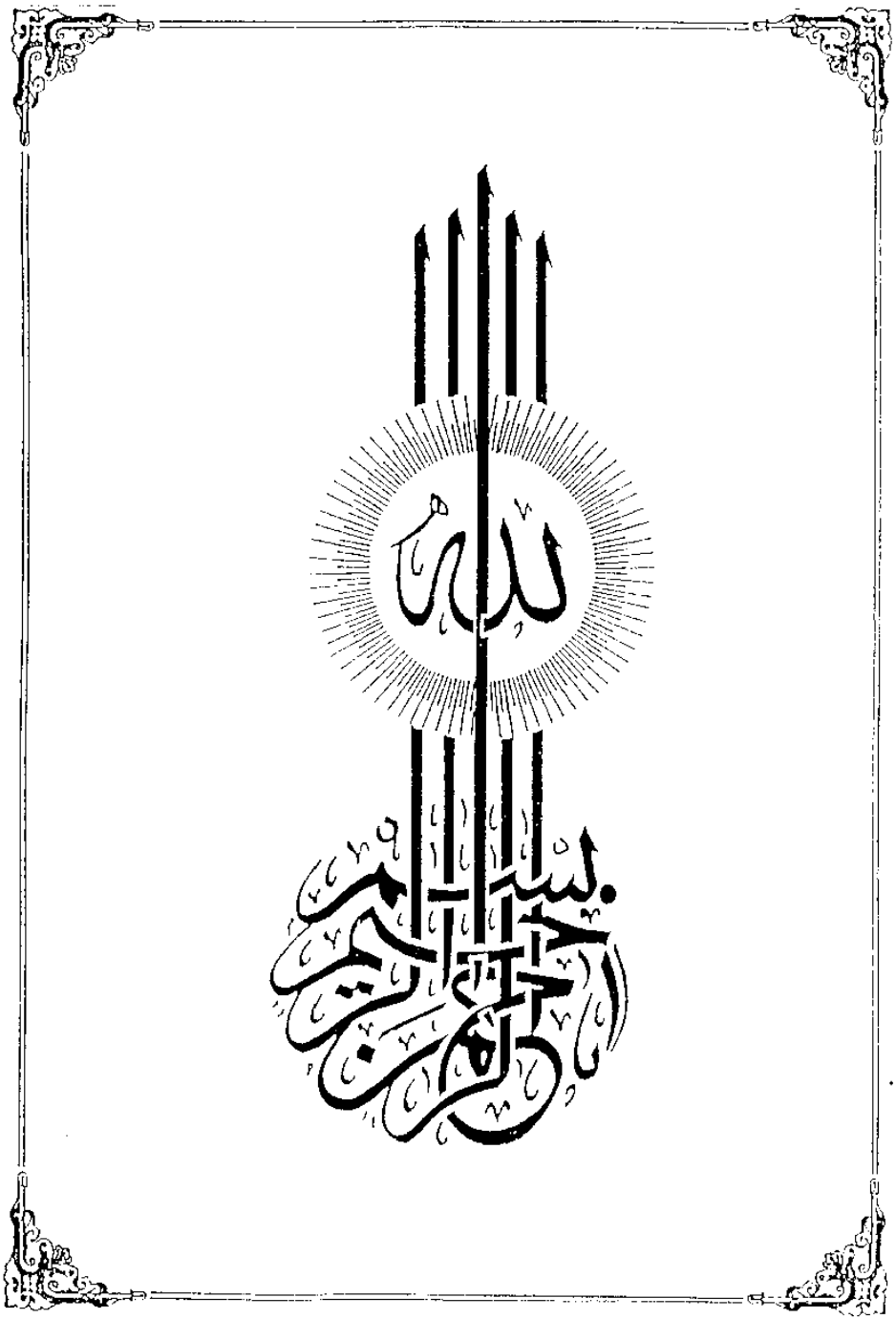

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ABBREVIATIONS

- AI	Autoimmune hepatitis.
- AI -CAH	Autoimmune chronic active hepatitis.
-ALT	Alanine amino Transferase.
- ALD	Autoimmune Liver disease.
- AMA	Antimitochondrial antibody.
- ANA	Antinuclear antibody.
- ANTI- ds	Antidouble Stranded.
- ANTI- HBs	Anti Hepatitis B surface.
-AST	Aspartate amino transferase.
- CAH	Chronic active hepatitis.
- CIE	Counter immunoelectrophoresis.
- CLD	Chronic liver disease.
- CSCL	Cesium chloride.
- DNA	Deoxyribonucleic acid.
- Ds-Ag	Double stranded antigen.
- DM	Diabetes mellitus.
- EIA	Enzyme immunoassay.
- ELISA	Enzyme linked immunosorbant assay.
- EM	Electron microscopy.
- FBG	Fasting blood glucose.
- FIG	Figure.
- GP	Glyco protein..
- HAV	Hepatitis A virus.
- HBV	Hepatitis B virus.
- HB	Haemoglobin.
- HBc Ag	Hepatitis B core antigen.
- HCV	Hepatitis C virus.
- HCA	Hepatitis C antigen.
- HCV-J	Hepatitis C virus- Japan.

- HEP Human epithelium.
- HIV Human immunodeficiency virus.
- HLA Human lymphocyte antigen.
- IDDM Insulin dependent diabetes mellitus.
- IF Immunofluorescence.
- IEM Immunoelectron microscopy.
- KD Killo dalton.
- LKM Liver kidney microsom.
- MF Microfilament.
- NANBH Non- A, non -B hepatitis
- NIDDM None Insulin dependent diabetes mellitus.
- OD Optical density.
- ORF Open reading frame.
- PBC Primary biliary cirrhosis.
- PCR Polymerase chain reaction.
- PPG Post prandial glucose.
- PT Post transfusion.
- RF Rheumatoid factor.
- RNA Ribonucleic acid.
- SGPT Serum glutamic pyruvic transaminase.
- SLE Systemic lupus erythematosus.
- SOD Superoxid dismutase.
- SMA Smooth muscle antibody.
- SMA- AIH Smooth muscle antibody- autoimmune hepatitis.
- SMA v Smooth muscle antibody- vessels.
- SMAG Smooth muscle antibody- glomeruli.
- SMAT Smooth muscle antibody- peritubular.
- US Ultrasonography.
- VS Viruses.

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AIM OF THE WORK

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Hepatitis C virus (HCV) has been identified as important cause of post-transfusion NANB hepatitis (PT-NANB hepatitis) **(Simmonds et al., 1990)**. ANTI-HCV antibodies have been often found in post-transfusion, autoimmune, alcoholic and cryptogenic chronic active hepatitis **(Esteban et al., 1989)**.

The specificity of diabetes-related anti-immunoglobulin-antibodies has been evaluated together with other autoantibodies in such cases that present with NANB related chronic liver disease. Those cases may be associated with organ or non-organ specific autoimmune disease e.g. Grave's disease, autoimmune hemolytic anemia and chronic autoimmune hepatitis **(Di Mario et al., 1990)**.

The prevalence of impaired glucose metabolism and DM among patients with chronic active hepatitis and cirrhosis in the absence of any known diabetogenic risk factors has been reported before **(Cacciatore et al., 1990)**. Inoculation hepatitis (HBV, HCV) in diabetes treated with insulin has also gained interest **(Pusztai et al., 1990)**.

Insulin autoantibodies (IAA) may cause false positive results in the indirect immunofluorescence test with islet cell antibody (ICA) **(Scott-Morgan et al., 1990).**

Based on the above data and other studies, it has been aiming to explore the immunological background of chronic HCV infection and whether it imposes an effect on the immune system (much like HBV) or not?

To fulfil the aim of this work, about 50 cases suffering from chronic HCV infection will be submitted to:

* Clinical evaluation.
* Serological detection of HCV (anti-HCV-RIBA test).
* Liver biopsy studies.
* Immunological survey (AMA, ASMA, ANA, LKM1, anti-actin).

REVIEW OF THE LITERATURE

Non-A, Non-B hepatitis (NANBH)

An independently developing idea for evidence of more than two immunologically distinctive viruses of human hepatitis (i.e agents in addition to HAV and HBV) was found in the fact of multiple episodes of acute disease. **Havens (1956)** described a drug addict who had 3 distinct attacks of acute hepatitis, separated by intervals of apparently complete recovery. The distribution of incubation periods following transfusion of the whole blood or its unpooled derivatives did not conform to the bimodal pattern expected from experimental studies and epidemiologic findings.

Three explanations might be considered briefly:

1- **Prince et al. (1974)** found that cases of transfusion associated hepatitis seropositive for HBV markers had a mean incubation period of 10.4 weeks, while sero-negative cases had a mean incubation period of 8.0 weeks.

2- Purcell (cited by **Prince et al., 1974)** did not find serological evidence for HAV infection by immune electron microscopy in any of 28 transfusion-associated cases also seronegative for HBV markers.

3- A substantial proportion of transfusion-associated cases of hepatitis were caused by an agent having a model incubation period in the range 45-49 days **(Mosley, 1975).**

Mosley et al. (1977) later reported a 16 bouts of acute viral hepatitis not attributable to either of the two recognized hepatitis viruses. None of these "non-A, non-B" episodes evaluated for infectious mononucleosis and cyto-megalovirus infections, could be ascribed to either. From that evidence, therefore it appeared that the clinical syndrome of viral hepatitis was produced not only by the two viruses (HA and HB) (hepatitis A and hepatitis B) recognized since the 1940's but also, in all probability by 2 non-A, non-B agents as 3 patients whom had 4 attacks of acute hepatitis proved to have 2 attacks of non-A, non-B hepatitis (NANBH) which were immunologically distinct from each other.

Shirachi et al. (1978) reported an evidence for a new hepatitis-specific antigen by double immunodiffusion assays between acute and convalescent sera obtained from patients with PT-NANBH. The designation hepatitis C (HC) antigen was proposed. HC was found in the acute-phase sera of all 13 PT-NANBH patients with longer incubation and duration

periods (type 2) tested, but only transiently in 4 out of 10 acute phase sera from patients with (type 1) NANBH, with shorter incubation and duration periods.

Antibodies against HC antigen were found in only 30% of the type 2 PT-NANBH patients and did not persist for long. However, these antibodies were directed specifically against HC antigen and moved in a manner similar to 7 S globulin on rate zonal centrifugation. Type 2 can be called NANBH of longer incubation and duration periods, also SGPT was characterized by a plateau pattern. They finally, suggested that there might be more agents in the aetiology of PT-hepatitis.

Diagnosis of NANBH

Maugh (1980) reported that the difficulties of unidentified immunological markers of NANBH were compound because the presumed NANB virus apparently produced much less antigens than did the HBV, even when the disease was in the acute stage. Furthermore both agar gel diffusion and counterelectrophoresis types of assays were estimated to be a 100 fold less sensitive than the radioimmuno assays used for detecting HA (hepatitis A) and HB (hepatitis B) viruses.

Dienstage (1983) reported that the most compelling evidence for the existence of NANBH agents derived from experimental transmission of infection to volunteers and unhuman primates. Although routine availability of specific serologic markers for the diagnosis and prevention of NANBH remained an elusive goal, promising loads were certain to arise from the preliminary studies already reported.

1- Immunodiffusion (ID): one of the first approaches to be apparently successful was agar gel ID using convalescent serum as antibody, **Shirachi et al. (1978)** detected a hepatitis C antigen "HCA" in acute phase serum samples from 17 of 23 patients with PT-NANBH. Adding further to the confusion, **Ishida et al.(1980)** had reported that the HCA