A REVIEW ON
G-6-PD DEFICIENCY IN RELATION TO SICKLE-CELL ANAEMIA

THESIS
Submitted for Partial Fulfilment of Master Degree in Clinical Pathology

By

Hamid Ahmed Hamid

Supervised by

Prof. Dr. WAGIH NAGEEB IBRAHIM
Professor of Clinical Pathology
Ain Shams University

Dr. ZEINAB TAWFIK
Lecturer of Clinical Pathology
Ain Shams University

Faculty of Medicine
Ain Shams University

1986

A REVIEW ON G-6-PD DEFICIENCY IN RELATION TO SICKLE-CELL ANAEMIA

THESIS

Submitted for Partial Fulfilment of
Master Degree in Clinical
Pathology

By

Hamid Ahmed Hamid

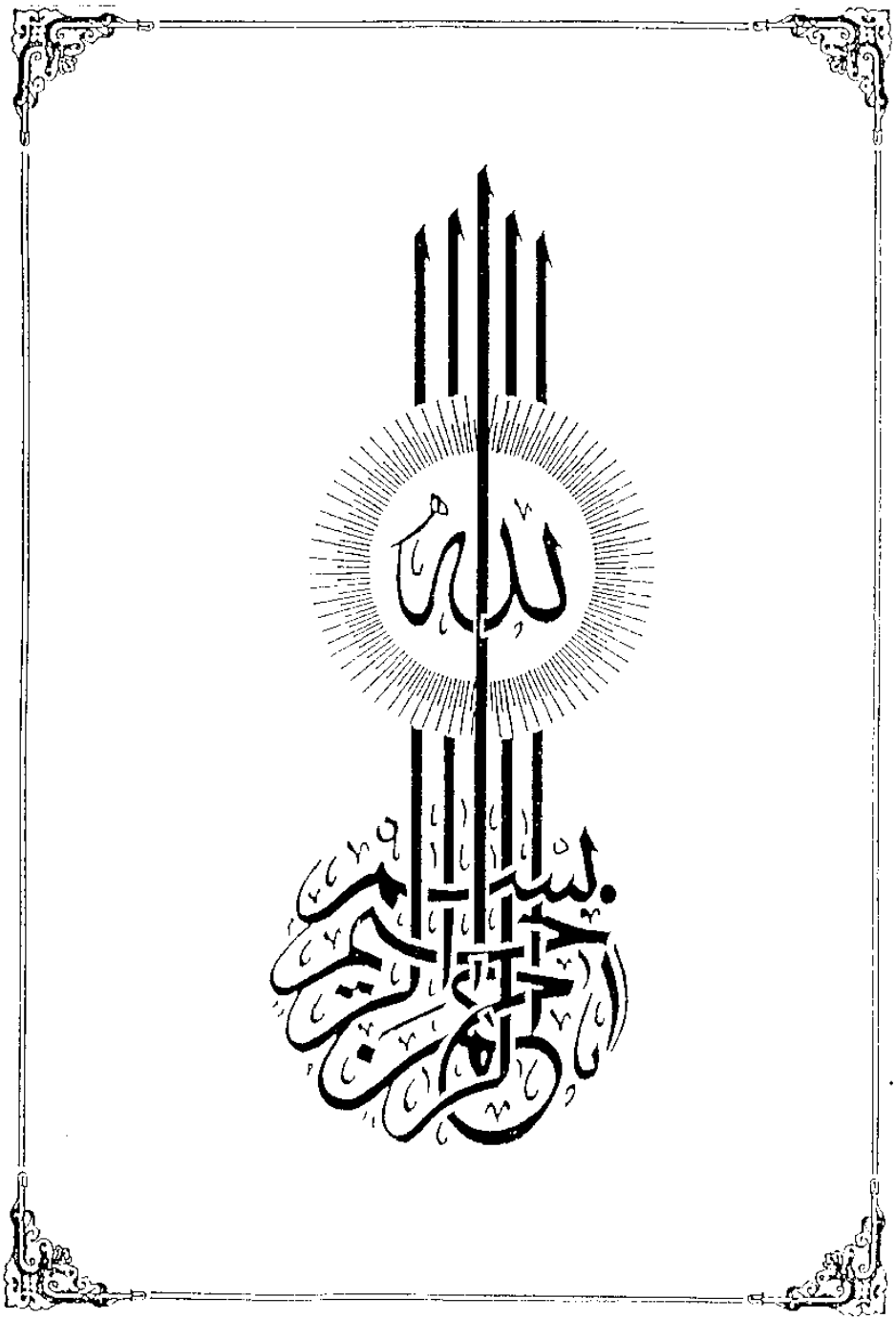
Supervised by

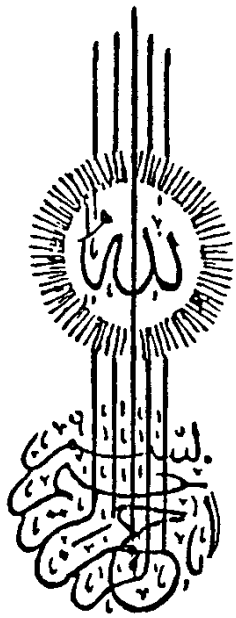
Prof. Dr. WAGIH NAGEEB IBRAHIM
Professor of Clinical Pathology
Ain Shams University

Dr. ZEINAB TAWFIK
Lecturer of Clinical Pathology
Ain Shams University

Faculty of Medicine
Ain Shams University

1986





قالوا

سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا

إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ

صَدَقَ اللهُ الْعَظِيمُ

سورة البقرة (الآية ٣٢)

ACKNOWLEDGEMENT

I am greatly honoured to have the chance to work under the supervision of Professor Doctor **Wagih Nageeb Ibrahim** *Professor of Clinical Pathology, Ain Shams University, whose supervision, guidance and creticism made the accompolishment of this thesis possible. I would like to express my thanks and gratitude to him.*

I am grateful also to Doctor **Zeinab Tawfik** *Lecturer of Clinical Pathology, Ain Shams University for her supervision, advice and careful follow-up till the completion of this thesis.*

My thanks are expressed to all teachers and colleagues.

CONTENTS

	Page
Introduction	1
Aim of Thesis	4
G-6-PD Deficiency, Sickle-Cell Haemoglobin and their Role in Causation of Disease	5
G-6-PD Deficiency, Sickle-Cell Anaemia and Malaria Hypothesis	16
Distribution of G-6-PD Deficiency, Sickle-Cell Anaemia and Frequency of Association	19
Clinical Features of Sickle-Cell Anaemia and G-6-PD Deficiency	30
Effect of Association of G-6-PD Deficiency and Sickle-Cell Anaemia	44
Laboratory Diagnosis of G-6-PD Deficiency and Sickle-Cell Anaemia	49
Management of sickle-Cell Anaemia and G-6-PD Deficiency	70
Summary	76
References	80
Arabic Summary	

INTRODUCTION

INTRODUCTION

Glucose-6-phosphate dehydrogenase (G-6-PD) enzyme is the first enzyme in the hexose monophosphate shunt, and is required for the formation of reduced nicotine amide adenine dinucleotide phosphate (NADPH). This in turn, is essential for the maintenance of an intact red blood cell membrane (Zilva and Pannall, 1984).

Numerous variants of G-6-PD deficiency have been described. In many cases haemolysis is precipitated by drugs, notably certain antimalarial drugs, such as primaquine and also sulphonamides, penicillin, streptomycin, isoniazid and analgesics. In other cases haemolysis can be precipitated by vicia faba ingestion, infection or administration of oxidant compounds (Otienol et al., 1983).

Sickle-cell anaemia occurs as a result of the presence of haemoglobin S (HbSS). The abnormality in the haemoglobin structure lies in the β-chain, in which the sixth amino acid normally glutamic acid, is replaced by valine. This alteration leads to sickling of the red cells when are faced with low oxygen tension; and their removal from the circulation by reticuloendothelial cells resulting in haemolytic anaemia (Rooks and Pack, 1983).

G-6-PD deficiency and sickle-cell anaemia are hereditary disorders and they are inherited independently. The gene for G-6-PD activity is located on X-chromosome and that for sickle-cell anaemia on an autosomal chromosome (Ozsoylu, 1978).

It has often been claimed that malaria exerts a selective pressure for the maintenance of higher frequencies of sickle-cell and G-6-PD genes. Concurrent occurrence of higher frequencies of these genes is found in malarial areas in Africa (Rao and Goud, 1979). Outside Africa, they are found in American Negroes, West Indies, in the indigenous population of the Mediterranean Sea, Middle East and in some parts of India (Black, 1985).

Possible association between G-6-PD deficiency and sickle-cell haemoglobin among various population has been a subject of controversy. Barclay et al. (1970) from Zambia, Luzzato and Allan (1968) from Nigeria, Nhonoli et al. (1977) from Tanzania and Gibbs et al. (1980) from Jamaica, found no relationship between G-6-PD deficiency and sickle-cell haemoglobin. On the other hand, Lewis (1967) from Ghana, Piomelli et al. (1972) from America and Beutler et al. (1974) from America also, reported that G-6-PD deficiency was much more frequent in patients with sickle-cell anaemia than in the general population. Warsy (1985) from Saudi Arabia reported a stepwise increase in the frequency of G-6-PD deficiency from haemoglobin AA (adult Hb) through haemoglobin AS (sickle-cell trait) to haemoglobin SS (sickle-cell anaemia).

It has been claimed by many workers that this association will affect the course of each disease. Thus, Piomelli et al. (1972) reported that the survival of patients with sickle-cell anaemia

might be improved if they were also G-6-PD deficient. According to Konatey (1972), quite the contrary was true. He noticed that G-6-PD deficient patients with sickle-cell anaemia were hospitalized more frequently owing to the greater severity of the disease, and also die more quickly from anoxic liver necrosis, cardiac failure and intrahepatic cholestasis. On the other hand, Bienzle et al. (1975) stated that, the coexistence of G-6-PD deficiency in patients with sikle-cell anaemia will not influence the course of the disease.

AIM OF THE WORK

AIM OF THESIS

The aim of this thesis is to review the literature and see the recent work on the distribution of both defects in the world and the possible aetiological association. It is also aimed to throw light on the pathogenic features of both defects, and the resultant effect of the simultaneous coexistence of both disorders on the affected individuals. The laboratory diagnosis and the management of these defects will also be included in the thesis.

G-6-PD DEFICIENCY SICKLE-CELL Hb AND THEIR ROLE IN CAUSATION OF DISEASE

G-6-PD DEFICIENCY, SICKLE-CELL Hb AND THEIR ROLE IN CAUSATION OF DISEASE

A) G-6-PD:

Since G-6-PD enzyme is sex-linked, it is seen predominantly in males (Black, 1985). In females, it is thought that only one of the two X-chromosomes present in each nucleated cell is active. Inactivation of the second accounts for the finding that normal females have the same activity of the enzymes coded for by the X-chromosome as do normal males, even though females have twice the number of X-chromosomes. So heterozygous females have red cells with either full normal activity or completely deficient activity. Cells do not have intermediate levels of enzyme activity. In most heterozygous females, about half the cells are deficient so that the total G-6-PD activity of the blood is intermediate between that of hemizygous males and normal males (Gordon-Smith, 1983).

Homozygous females are not uncommon. They may be as severely affected as men, rarely a heterozygous woman may be affected clinically (Black, 1985).

G-6-PD variants:

Many different isoenzymes of G-6-PD have been described, and it may be that the different isoenzymes result from the substitution of single amino acid. Isoenzymes may show the same

activity, less activity or even more activity than the common or normal isoenzymes, though those variants which have normal or increased activity are only discovered in population surveys and not associated with clinical disorders. There are two main isoenzymes which produce no abnormality In the black population is designated type A^+ and in caucasian type B^+ (Gordon-Smith, 1983).

Three main types of G-6-PD deficiency variants are recognized. The mild disorder known as A^- is found in tropical Africa and in American blacks. The other variety is Mediterranean type which is found around Mediterranean Sea. The third variety is found in China and is designated the Canton variety. Both the B^- variety and the Chinese type are much more serious disorders than the A^- or African variety (Otienol et al., 1983).

G-6-PD type A^+ has fast mobility and normal activity, G-6-PD type B^+ with normal (slow) mobility and normal activity, while G-6-PD type A^- has fast mobility and moderately low activity (Piomelli et al., 1972). G-6-PD type A^- has normal Michaelis constants for NADP and Glucose-6-phosphate and also has increased in-vivo lability (Steinberg and Dreiling, 1974).

Role of G-6-PD:

There are two energy releasing metabolic pathways in a mature red blood cell i.e. the Embden-Meyerhof or glycolytic pathway