THE PROGNOSTIC VALUE OF TUMOUR MARKER CARCINOEMBRYONIC ANTIGEN ESTIMATION IN SERUM AND CERVICAL MUCUS IN FLAT CONDYLOMA OF THE CERVIX

THESIS

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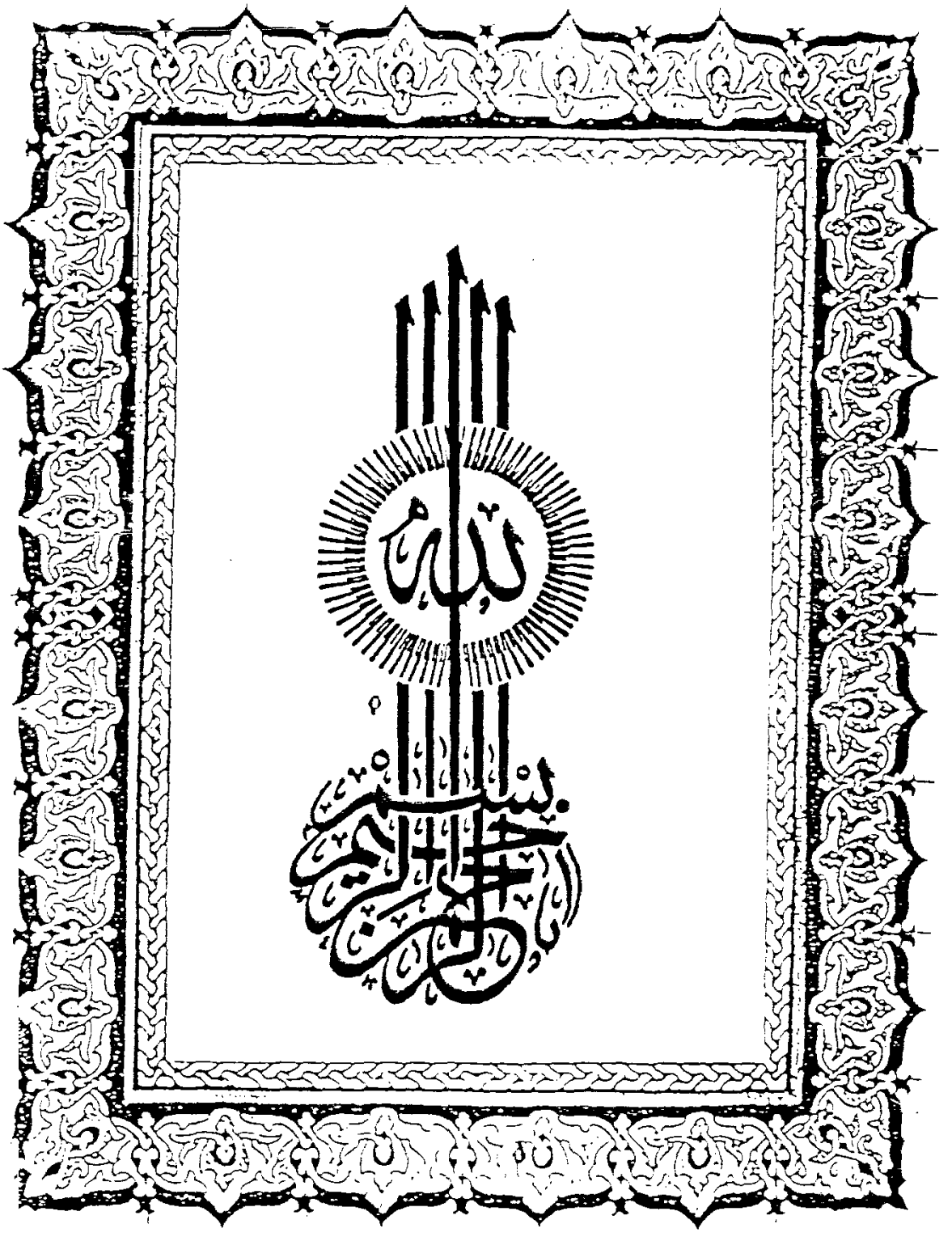

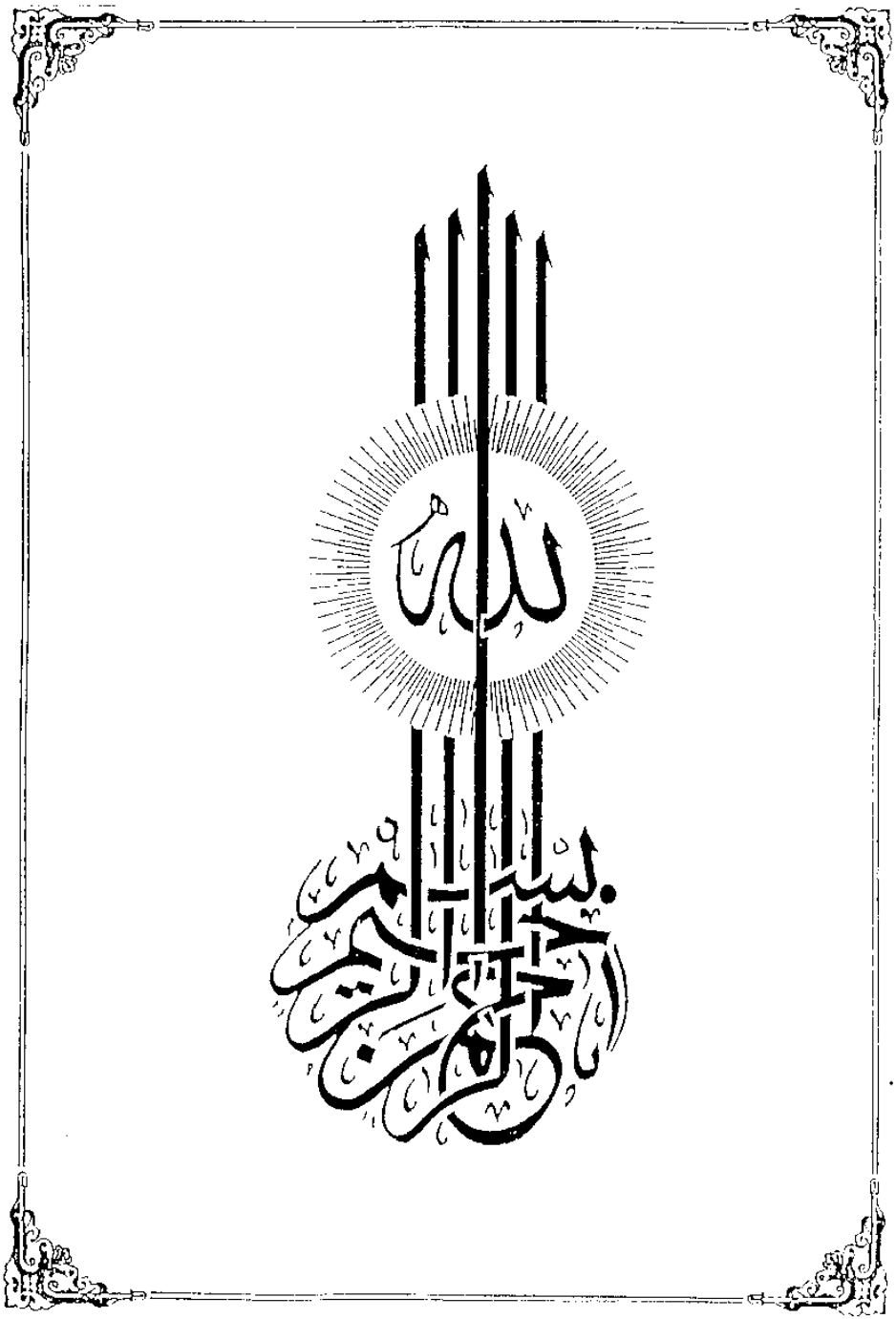

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CONTENTS

INTRODUCTION

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In the last 12 years knowledge of human papillomavirus (HPV) infections has expanded at a breathtaking pace . This is due to an interplay of several branches of the Natural Sciences and Medicine including Biochemistry, Molecular Biology, Virology, Immunology, Pathology, Epidemiology and clinical Medicine.

The relation between HPV and cervical cancer is one of the hot topics in current gynaecological research . Recent data have provided strong evidence to implicate HPV in the aetiolgy of cervical intra-epithelial neoplasia (CIN) and cervical cancer . DNA sequences of certain HPV types are frequently demonstrated in CIN and cervical cancer spicemens (Durst et al,1983).

Many investigations have shown that ploidy analysis and viral typing could predict those HPV infections associated with a definite malignant potential. Unfortunately, access to these tests is not widely available, and they cannot be applied to routine clinical material (Reid,1987).

Recent studies have shown that plasma carcinoembryonic antigen (CEA) level is elevated in a high percentage of cancer cervix, and it may also be elevated in some precursors of cervical malignancy. Kjorstad et al (1988) reported slightly elevated plasma CEA levels in patients with CIN .

Normally, the cervical mucus contains extremely high levels of cancer antigen (CA) 125 as a normal constituent and low levels of CEA and CA19-9; whereas , in cervical adenocarcinomas, the cervical mucus shows low CA125 levels with extremely high levels of CEA and/or CA19-9. The cervical mucus samples from patients with squamus cell carcinoma exihibit slightly elevated levels of CEA which is possibly derived from the destructed squamus cells (Fujii et al,1985) .

AIM OF THE STUDY

This study aims to estimate CEA in the blood and cervical mucus in patients with cervical HPV infection .

REVIEW OF LITERATURE

VIROLOGY OF

HUMAN PAPILLOMA VIRUS

Human papillomaviruses (HPV) are a heterogenous group of DNA tumour viruses associated with hyperplastic (warts, condylomas, papillomas), dysplastic (CIN) and malignant lesions (carcinomas) of squamous epithelium in susceptible individuals (Baird, 1988).

HISTORICAL BACKGROUND

Ciuffo (1907) was the first to identify the virus in the wart and condyloma extracts as submicroscopic infectious agents able to pass through filters fine enough to intercept bacteria, protozoans and other microorganisms.

[illegible] squamous epithelia from skin warts by electron microscopy.

Similar viral particles were also found in genital wart material (Dunn, 1968).

Williams (1961) used three methods to demonstrate the particles of HPV (thin sectioning, shadow casting and negative staining) by which he could detect the detailed characterization of the virus.

Using nucleic acid hybridization techniques, Zur Hausen started to study HPVs and their possible role in squamous carcinomas in the early 1970s. After that , the genetic heterogeneity of papillomas was established in 1976 and led to the identification of different HPV types (Krebs, 1989).

TOXONOMY

Human papillomavirus (HPV) represents a complex group of small DNA tumour viruses that belong to genus A of the family papovaviridae (Melnick et al , 1974). The name papova was suggested by Melnick(1962) as a group name for the small icosahedral oncogenic viruses with circular, double stranded DNA. They include papilloma, polyoma and simian vaculating viruses.

TYPES

Virus type and subtype classification is based on species specificity and polynucleotide sequence homology ; viruses with less than 50% homology are defined as different viral types, whereas viruses with greater than 50% but less than 100% homology are recognised as subtypes (Coggin and Zur Hausen, 1979).

During recent years, an even increasing number of types and subtypes of HPV have been isolated using hybridization. To date, over 50

HPV types have been identified (Krebs, 1989).

Each type has a predilection for infection of a particular site. More than seven different types are known to infect the genital tract of both sexes. These include: HPV 6,10,11,16,18,31 and 35 (McCance, 1986). HPV 6 and 11 mainly induce benign exophytic genital condylomata, flat condylomas and low-grade dysplasias (Gissmann et al, 1982). HPV 16,18,30,31,33,34,35 and some recently described types are associated with grades II and III intraepithelial neoplasias, primary invasive carcinomas and secondary metastasis (Khan et al, 1986) .

STRUCTURE AND PHYSICAL PROPERTIES

VIRION STRUCTURE

By electron microscopy, the viruses are icosahedral particles (i.e with 20 equilateral triangular faces) approximately 45-55 mu in diameter (Williams, 1961). The surface capside is composed of 420 structural units and 72 capsomers (Klug and Finch, 1965).

There is a major capside protein with a molecular weight of about 45,000 daltons and a minor species with a weight of about 76,000 daltons (KOMLY et al,1986).They don't contain any lipid or membrane and therefore resist inactivation by lipid solvents e.g ether (Melnick,1962).

HPV DNA

HPV chromosomes are covalently closed circular, double stranded DNA molecules with a molecular length about 7900 base pairs, a molecular weight of about 5×10^6 daltons and an adenosine : thymen to guanosine: cytosine base pair ratio of approximately 58 to 42% (Broker, 1987). The DNA constitute about 12% of the virion by weight (Baker and Howley, 1987).

HPV genomes contain random runs of nucleotides that will be recognized by specific bacterial restriction endonucleases, resulting in cleavage of the DNA into either a full length linear molecule or a set of subgenomic fragments that are characteristic for each viral type (Broker, 1987).

PHYSICAL STATE OF HPV - DNA IN LESIONS

In benign lesions HPV - DNA persists as self replicating extra-chromosomal plasmids. Within the cancer cells, it is covalently linked to cellular DNA sequences (Durst et al, 1985). The integration within the human genome usually occurs near a cellular proto-oncogene (C-src, C-raf, C-myc) (Durst et al, 1987).

The copy number of viral DNA in individual cell nuclei within a wart can vary over several orders of magnitude and there is no meaningful equivalent to average copy number as can be reported for homogenous cell cultures. The limit of detection of the most sensitive of radioactively labeled probes is perhaps 50 copies of viral DNA per cell nucleus, and the viral DNA in the basal cells of condyloma usually remains below level of detection (Broker, 1987).

DNA CONTENT OF THE HPV INFECTED CELL

Condylomas without epithelial atypia , all had a diploid or polyploid nuclear DNA distribution; whereas , about 45% of condylomas with epithelial atypia/dysplasia had aneuploid DNA distribution which is thought to be a pre neoplastic pattern (Fu et al ,1983).