THE VALUE OF TUMOUR MARKERS IN DIAGNOSIS AND TREATMENT OF TUMOURS

An Assay

Submitted in Partial Fulfillment of the requirements for the **Master Degree in General Surgery**

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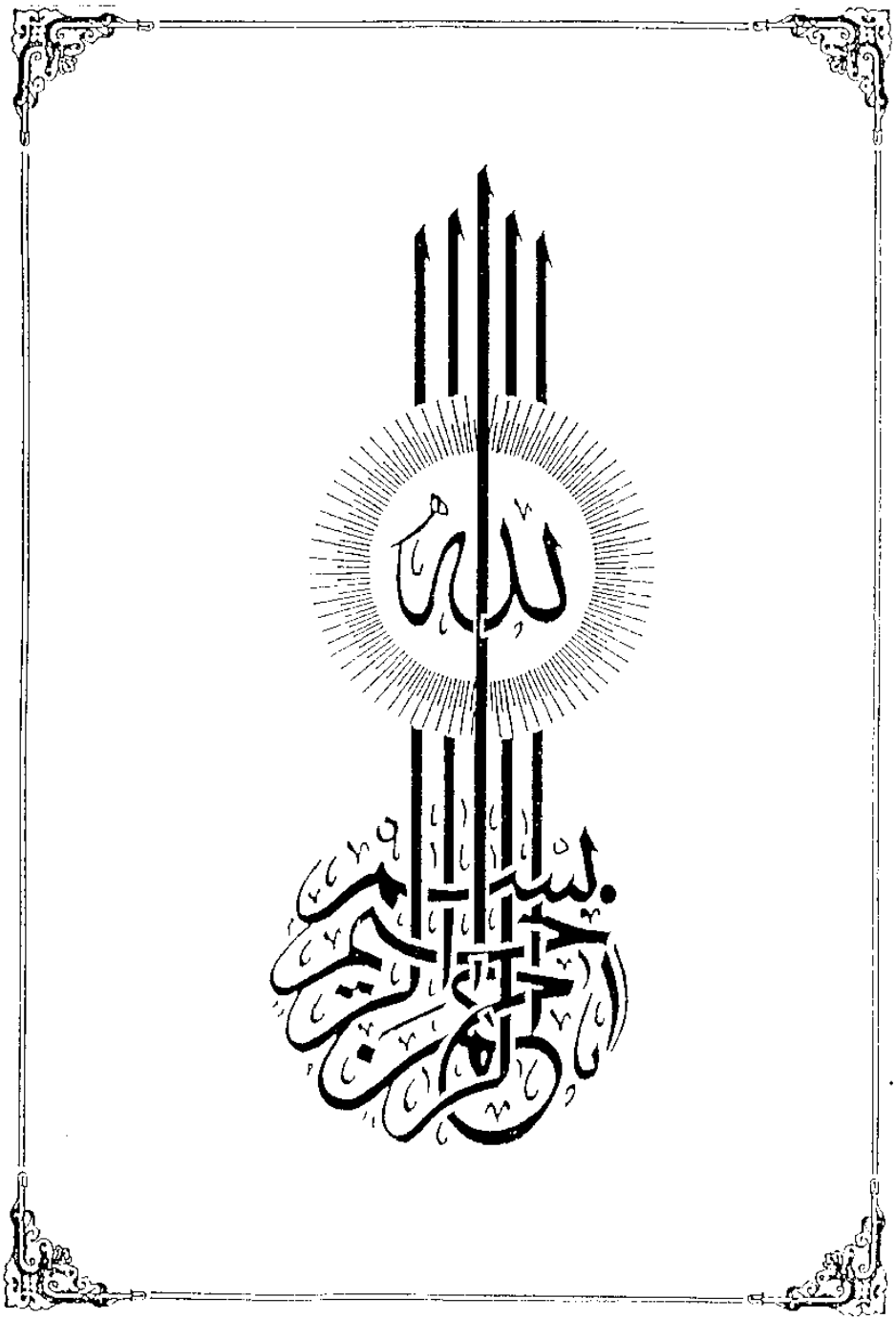

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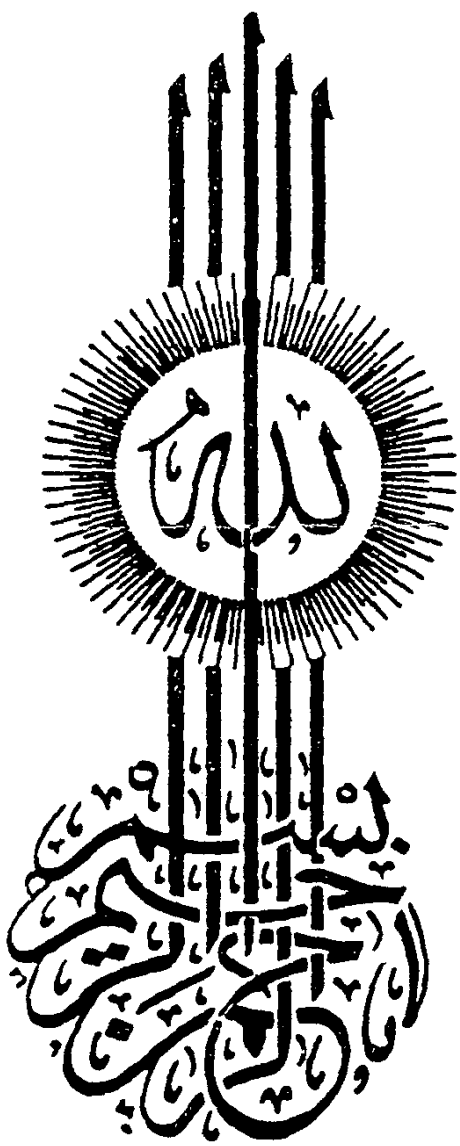

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ACKNOWLEDGMENT

I wish to express my deep gratitude and profound appreciation to Prof. Dr. ***ADEL ABDEL KADER***, Professor of general surgery, Faculty of Medicine, Ain Shams University, for his continuous encouragement endless support and precious advice, also for suggesting this interesting subject.

I wish to express my sincere gratitude and deep thanks to Prof. Dr. ***Sherif Omar*** Professor of Oncology, National Cancer Institute, Cairo University, for his valuable suggestions, kind assistance and unforgettable advice.

I would not miss to acknowledge Prof. Dr. ***Ali Khalifa***, Professor of Medical Biochemistry, Faculty of Medicine, Ain Shams University, he kindly and generously helped me in this work.

Lastly, I wish to express my deep thanks to all who helped me in accomplishing this work.

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LIST OF ABBREVIATIONS

AACT	: Alpha-1 antichemotrypsin.
AFP	: Alpha fetoprotein.
AGP	: Alpha acid glycoprotein.
CA	: Cancer antigen.
CDP	: Cystic disease fluid protein.
CEA	: Carcinoembryonic antigen.
CK-BB	: Creatine kinase BB.
FDA	: Food & Drug American Association.
HBV	: Hepatitis B virus.
HCC	: Hepatocellular carcinoma.
HCG	: Human chorionic gonadotropin.
5- HIAA	: Hydroxy indole accetic acid.
LCA	: Leucocytic common antigen.
LDH	: Lactate dehydrogenase.
NCI	: National cancer institute.
NMR	: Nuclear magnetic resonance.
NSE	: Neuron. Specific enolase.
PAP	: Prostatic acid phosphatase.
PIVKA-II	: Protein induced by vitamin K abscence or antagonest II.
PLAP	: Placental alkaline phosphatase .
PSA	: Prostatic specific antigen.
RIA	: Radioimmunoassay.
SCLC	: Small cell lung cancer.
TdT	: Terminal deoxynucleotidyl transferase.
TPA	: Tissue polypeptide antigen.
VIP	: Vaso active intestinal peptide.

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TUMOUR MARKERS

INTRODUCTION

Historical Aspects :

As understanding of the patho-physiology of cancer increases, the role of tumour markers becomes more important in the management of cancer patients. Biochemical measurements of substances in blood and body fluids have been used for these purposes for more than a century.

In 1847, Sir Henry Bence jones described in the urine of a patient what is referred to as the Bence jones protein. It is a useful marker in patients with myeloma. This protein is now to be identical with the light chain IgG, and most patients with myeloma excrete it in their urine whether or not the traditional "heat-cool" test is positive ***(Kahn, 1991)***.

In 1867, Sir Michael Foster reported the prescence of amylase in human blood, and urinary amylase was proposed even earlier as a marker for pancreatic cancer ***(Schwartz M K, 1973)***.

In the 1930s, acid phosphatase was used in evaluating men with cancer of the prostate, and serum alkaline phosphatse gained wide acceptance in diagnosis of osteogenic sarcoma and other bone cancers ***(Schwartz MK, 1973)***. Urinary chorionic gondotropin became a standard test in evaluating and monitoring

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choriocarcinoma; vanillyl mandelic acid and catecholamines become essential markers in neuroblastoma and pheochromocytoma; and 5- hydroxy indole accetic acid was used in carcinoid and a variety of hormones in neuroendocrine tumors.

In the 1950s, glycolytic and other enzymes were used as indicators of liver metastases. However, it was only after the availability of immunoassays that cancer-related or cancer-specific tests were proposed, and the tumour marker era began. The introduction of carcinoembryonic antigen in 1965 and the report of its high sensitivity and specificity in colon cancer led to an ever-increasing number of tumour-associated antigens that were proposed by their developers as useful in cancer diagnosis and therapy ***(Thompson et al., 1969).***

Several scientific advances during the past 20 years were instrumental in the developement of clinically useful tumor markers. First, **Yalow and Berson** developed the technique of Radioimmunoassay (**RIA**) for which they later received the Nobel prize. (**RIA**) allowed the reproducible, sensitive, and specific detection of minute amounts of substances in serum based on structural immunogenic characteristics of the marker as opposed to more cumbersome and less specific assay based on bioactivity. Second, the descripition of hybridomas that secrete monoclonal antibodies ***(Kohler, G., et al., 1975)*** has been applied to tumor antigens, which has greatly facilitated detection and charaterization of new tumor markers. Finally, with recently developed molecular biology methods, tumour markers can be

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charaterized at the gene level. ***(Thompson, J.A., et al., 1987) (Viola, M.V. et al., 1986).***

DEFINTIONS:

What is a tumor marker ?

* Tumour markers are substances that can be measured quantitively by biochemical or immunochemical means in tissue or body fluids to detect a cancer and possibly the organ where it resides, to establish the extent of tumour burden before treatment, and to monitor the response to therapy. Many substances can be identified as tumor markers. These include tumor-associated antigens, enzymes, specific proteins, metabolites and oncogenes and oncogene products.

Some terms are essential to an understanding of the clinical use of tumor-markers, such as sensitivity and specificity.

What is sensitivity ?

Analytically, sensitivity is the lowest amount of analyte that can be detected. Epidemiologically, it is a measure of the ability to detect the cancer.

What is specificity ?

Analytically, specificity means the degree of intereferance in the assay by extraneous substances that may be present in the sample.

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Epidemiologically, it is the ability of the test to identify the population without cancer.

In any evaluation of tumor markers, the prevalence of the cancer in a given population and the analytic precision of the assay must be known.

The calculated predictive value can give information concerning clinical utility and cost effectiveness.

Positive Predictive Value

The positive predictive value of a test is the number of true positive values divided by the sum of the true positives and false positives.

Negative Predictive Value

The negative predictive value of a test is the number of false negatives divided by the sum of the false negatives and true negatives.

For a population of 100.000 in whom the prevalence of the cancer is 10% (i.e., 10.000 expected cases) and for whom the test has a sensitivity of 75% and a specificity of 95%, the positive predictive value (i.e., probability) of the marker is 7500 (true positives) / (7500 true positives + 4500 false positives) = 62.5%. The negative predictive value is 2500 false negatives / (2500 false negatives + 85.500 true negatives) = 2.8 % ***(Sox HC, 1986).***

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Ideal tumor marker

Coombes and Neville (1978), have suggested specific criteria of an ideal tumor marker, in that it should :

(a) Be specific to the tumor studied and commonly associated with it.

(b) Have a storchiometeric relationship between plasma level of the marker and tumor cell burden.

(c) Have an abnormal plasma and/or urine levels that are stable i.e. not subjected to wild fluctuations.

(d) Be abscent in health and benign disease or present in much lower conscentration than that found in association with all stages of cancer.

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