INTERFERONS IN DERMATOLOGY

Essay

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Dermatology and Venereology

By

Yasser Housein Aly

M.B.B.Ch.

Under Supervision of

Prof. Dr. MOHAMED GHOZZI

Asst. professor of Dermatology and Venereology

Faculty of Medicine,

Ain Shams University.

Dr. MAHA ABO EL-MAGD

Lecturer of Dermatology and Venereology

Faculty of Medicine,

Ain Shams University.

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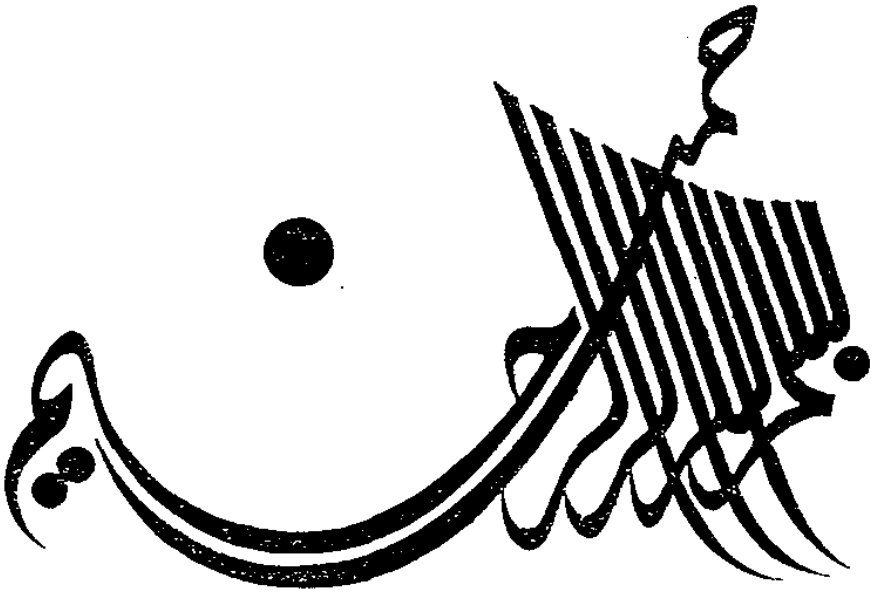

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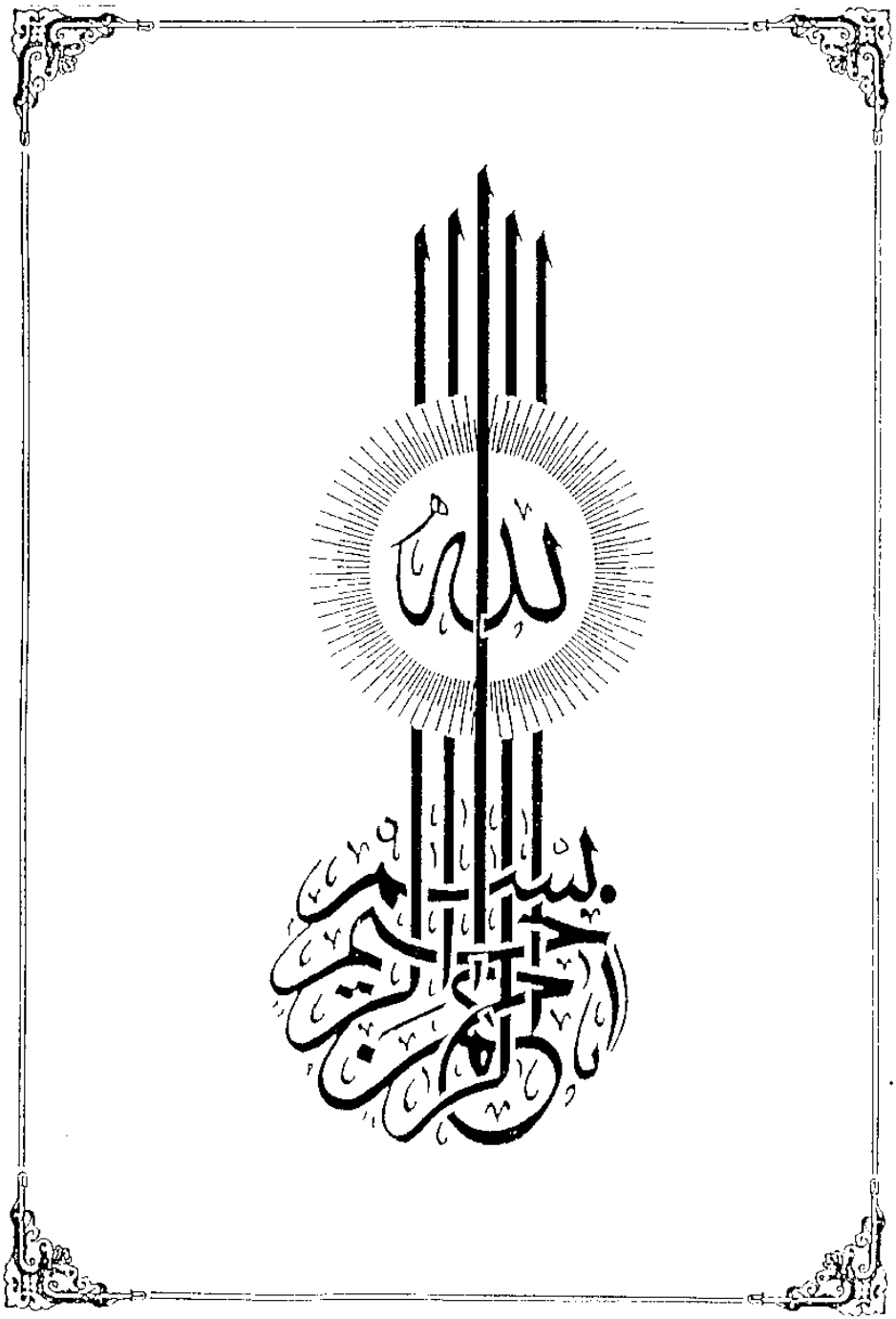

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TO

MY MOTHER

MY WIFE

MY DAUGHTER

CONTENTS

		Page
INTRODUCTION & AIM OF THE THESIS		1
NATURE & TYPES OF INTERFERONS		3
CHEMISTRY & PRODUCTION OF INTERFERONS		5
MECHANISM OF ACTION & PHARMACOKINETICS		8
THERAPEUTIC ACTION & EFFICACY		14
I.	Interferon and Papilloma virus	14
II.	Interferon and Herpes viruses	40
III.	Interferon and Basal cell carcinoma	46
IV.	Interferon and Actinic Keratoses	51
V.	Interferon and kaposis sacrcoma	53
VI.	Interferon and Cutaneous T cell lymphomas.	57
VII.	Interferon and Malignant Melanoma	61
VIII.	Interferon and other skin conditions	64
SUMMARY		73
REFERENCES		78
ARABIC SUMMARY.		

INTRODUCTION
&
AIM OF THE THESIS

INTRODUCTION

Nearly 4 decades have passed since interferon (IFN) was first described by Isaacs and Lindenmann (1957). They observed that virus infected cell lines released a protein that protects other cells from infection with the same virus, and they called this phenomenon "virus interference" or interferon. It soon became apparent that interferon is not a single protein but a large family of proteins or glycoproteins, which differed from one animal species to another, and which was synthesized only in hormone like amounts *(Stadler et al., 1989)*.

Interferons are naturally occurring or artificially produced by recombinant biotechnology. Their antiviral, antiproliferative, antitumoral, and immunomodulatory activities are induced by alteration in cell metabolism after binding to specific membrane receptors. Interferons have been used for the treatment of viral papillomas (e.g. verruca vulgaris and condyloma acuminatum), human immunodeficiency virus (HIV)- associated Kaposi's sarcoma and cutaneous tumors (e.g. melanoma, cutaneous T cell lymphoma, and basal cell carcinoma), and inflammatory dermatoses as psoriatic arthropathy *(Rudolf et al., 1989)*.

THE AIM OF THE THESIS

Review of the literature concerning interferons, their nature, types, chemistry, action and their therapeutic uses as a new method of treatment in various skin diseases.

NATURE & TYPES OF INTERFERONS

NATURE AND TYPES OF INTERFERONS

On the basis of some experiments, IFN are defined as proteins or glycoproteins with a non virus specific antiviral activity in homologus cells through induction of cellular RNA and protein synthesis *(Pestka, 1983).*

There are 3 major classes of IFN. Alpha interferon "IFN-α", of which there are a number of species, is produced by peripheral blood leukocytes. Beta interferon "IFN-β" is produced by fibroblasts or epithelial cells. They are induced by viral infections or agents containing double stranded RNA. Gamma interferon "IFN-γ" is produced by T lymphocytes in response to mitogens, antigens and interleukin-2. Several additional types of IFN have been described but their exact role remains unclear *(Rachlis, 1989).*

It is important to note that IFN produced by any type of cell may have more than one kind of chemical makeup and more than one type of activity *(Jawetz, 1989).*

Interferon- gamma is also known as immune IFN. The alpha family has 20 subtypes that differ in their amino acid composition *(Stadler et al., 1989).*

Because the amounts of IFN synthesized by induced cells are quite small, it has been difficult to purify and characterize the proteins. With recombinant DNA techniques, cloned IFN genes are being expressed in large amounts in bacteria and in

yeast, and the availability of genetically engineered IFN makes clinical studies feasible *(Merigan, 1982)*.

The different IFN are similar in size, but 3 classes are antigenically distinct. Interferon- gamma and IFN-β are resistant to low pH. Interferon-beta and IFN-γ are glycosylated, but the sugars are not necessary for biologic activity. So, cloned IFN produced in bacteria are biologically active *(Jawetz et al., 1987)*.

Interferon is a protype of a family of similar substances now called cytokines that all appear to function as regulatory molecules. It was held that the production of IFN constituted a specific response to a viral infection. Today it is believed that IFN is an integral part of a cytokine network and that they and other cytokines may be produced regularly at low levels *(Ion, 1990)*.

By general agreement, natural IFN are now distinguished from recombinant IFN as shown in the table below

""Interferon nomenclature"*

Type	Producing cells	Naturally occurring interferon (IFN)	Recombinant interferon (rIFN)
Alpha	Leukocytes	IFN Alpha [LE]	
	Lymphoblastoid (Namalva) cells	IFN Alpha-N_1	
	Transformed *Escherichia coli*		Alpha-2a (lysine at position 23)
	Transformed *E. coli*		Alpha-2b (arginine at pos. 23)
	Transformed *E. coli*		Alpha-2c (arginine at pos. 23, 34)
	Transformed *E. coli*		Alpha-2d (29 variations from αA)
Beta	Human fibroblasts cell lines	IFN Beta	
	Transformed *E. coli*		Beta cystine (cystine at pos. 17)
	Transformed *E. coli*		Beta serine (serine at pos. 17)
Gamma	T lymphocytes from normal blood	IFN Gamma	
	Transformed *E. coli*		Gamma

(Stadler et al., 1989).

CHEMISTRY & PRODUCTION OF INTERFERONS

CHEMISTRY AND PRODUCTION

Alpha-interferon comprises a group of at least 14 compounds that share a 75 percent amino acid homology. Their molecular weight ranges from approximately, 15,000 to 20,000 daltons. These compounds originate in various white blood cells, principally the macrophages and the non-comitted lymphocytes carrying neither T-nor B-cell identifying marker (Landow, 1988).

Only one protein species of IFN-β has been identified (Hawkins et al., 1984). Its site of synthesis seems well established as being either the fibroblast or epithelial cells. This compound weighs approximately 20,000 daltons and shares a 30 percent amino acid homology with the α-IFN group (Yancey and Smith, 1980).

Gamma interferon exists as a unique strain weighing approximately 40,000- 46,000 daltons. It has a different cell surface receptor and appears to share little in structural homology with other IFN. Previously termed "immune interferon", this substance originates in T lymphocytes or natural Killer (NK) cells (Ortaz, 1986).

Irrespective of the degree of similarity, these compounds may posses, or seem to have their own unique chemical and biological activities. In the early years of IFN research, most authors thought that production of these compounds was stimulated only by exposure to viral products. However, it

rapidly became apparent that a large number of triggers exist to enhance their synthesis. These include a wide array of antigens ranging from those of bacterial, fungal, or parasitic origin to specific chemical inducers such as the now well-known polyriboinosinic (Poly. I), polyribocytidylic (Poly. C) and even non specific mitogens *(Landow, 1988)*.

Depending on the host's genetic characteristics, response to any of these stimuli results in production of multiple species of IFN. The central control mechanism appears to reside on chromosome 5 and 9, with some input from chromosome 2 and a total of at least 17 other genes as well (Yancey and Smith, 1980). The large time from stimulus to production of IFN ranges from 2 to 3 days *(Ortaz, 1986)*.

The introduction of recombinant DNA technology has changed the use of IFN. Only limited quantities of natural leukocyte, fibroblast or lymphocyte IFN could be produced from cultures of human cells. Clinical research was hampered by limited supplies, enormous expenses, and uncertainity about the purity of the derivative. Recombinant DNA technology in the early eighties, allowed production of enough IFN to renew interest in clinical investigation *(Ringenberg and Anderson, 1986)*.

Leukocyte - derived IFN can be obtained from stimulated white cells extracted from units of donor whole blood (Yarbov, 1982). Leukocytes respond to interferogens by producing a variety of IFN. These can be extracted to produce a solution