STEROID THERAPY IN THE MANAGEMENT OF RHEUMATOID ARTHRITIS

Thesis

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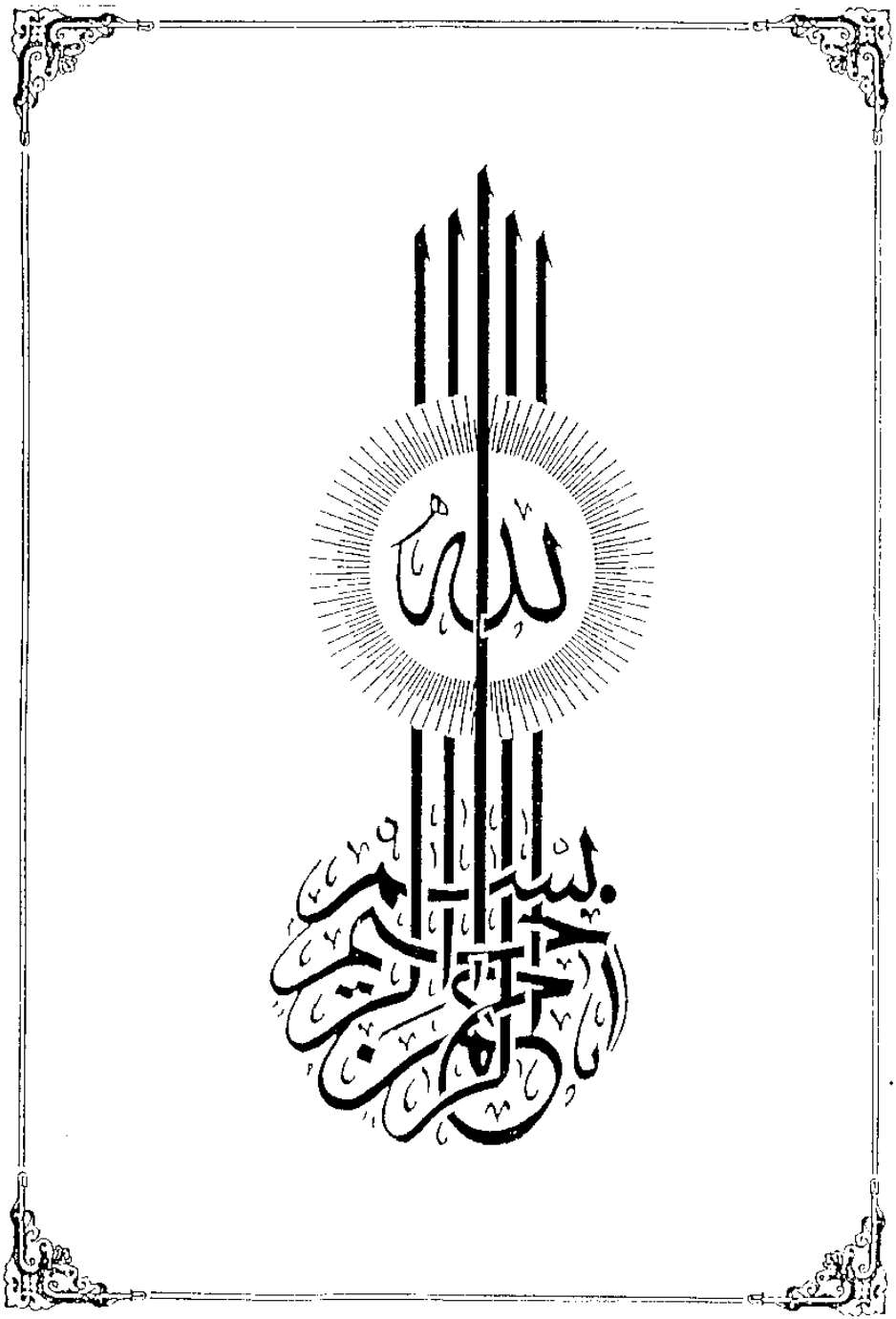

CONTENTS

INTRODUCTION

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Rheumatoid arthritis is a wide spread rheumatic disease of non-specific aetiology but may be of an atuoimmune origin.

In spite of decades of research, a specific cure for rheumatoid arthritis has not been found. Our inability to eradicate this disease is reflected by its prevalence.

According to a survay by the national centre for health statistics ten years ago, there were 3.6 millions adults in the united stetes who where classified as having definite or probable rheumatoid arthritis, and more recent estimates bring the figure closer to 5 millions (**Gifford,1973**).

Fortunately, most of these patients have mild disease which is self-limiting and nondeforming, and requires little or no medical treatment. For many others, however, this inflammatory joint disease is persistant, aggressive, and debilitating , demanding medical attension.

Since chronic synovial inflammation is the principal feature of rheumatoid arthritis, and since the inciting agent is unknown, therapy has been described primarily at various means to control the inflammatory response. Physical measures such as splints, local heat, and rest are often effective but frequently overlooked by

the physician in his search for a more dramatic, systemic form of therapy that will quickly relieve the agony of inflammed joints.

Afflicted patients and concerved physicians dream of an instant cure. Many are impatient with standard treatment .

Salicylates, the cornestone of anti-inflammatory therapy, tend to be prematurely discarded as ineffectual.

Anti-malarial drugs and gold salts, both of proven worth, are often considered too dangerous, or too slow in their effects. Thus it is not surprising that many physicians rapidly turn to the agents that are most dramratic in relieving the distressing inflammation and pain of active rheumatoid arthritis, adrenal corticosteroids.

It has been noted for years that rheumatoid arthritis was often ameliorated by jaundice,pregnancy , surgical operation, and other types of stress that may stimulate the adrenal cortex.

Dr. Hench and his later associates came to recognize the antirheumatic effect of cortisone and ACTH through a series of peritent clinical observations and investigations. These began about 1925 when the weakness, fatigue, and low blood pressure of certain patients with rheumatoid arthritis suggested that somehow the adrenal glands might be responsible.

Steroids are chemical hormones secreted by the human adrenal cortical gland.

cortisone, originally designated compound E, along with several other adrenocortical hormones was isolated in crystalline form in DR.E.C. kendall's laboratory in Rochester, in December 1933.

Though animal studies were pursued directly after the hormones were isolated and the physiological properties of cortisone were clearly defined,more than another decade elapsed before the clinical use occured. It is of considerable interest that the first substantial clinical experience with adrenal corticoids in the therapy of human disease was with rheumatoid arthritis on 21 September 1948 (Polley,1970), the response was dramatic.

Steroid therapy has been used in various clinical situations in which its anti-inflammatory and immuno-suppressive effects have proved effective.

Researchs have been channeled that structural change of natural cortisone have resulted in the production of synthetic dervatives of steroid that characterized by increased biological potency.

Hollander and his colleagues in 1951 (Polley, 1970), first reported the use of hydrocortisone given by intrasynovial injection

and this has been followed by various steroid analogues and their esters as locally injected drugs in the treatment of articular and extra-articular lesion in rheumatoid arthritis.

However, the use of steroids has many hazards where its complication is common, so it is preferable that it should never be the initial agents in the treatment of rheumatoid arthritis, they only should be described after failure of other measures of treatment.

Anatomy of the suprarenal glands:

The suprarenal glands are two small, flattened bodies of a yellowish colour, situated one on each side of the median plane, at the posterior part of the abdomen, behind the peritoneum and immediately above and in front of the upper end of the kidney.

They are surrounded by areolar tissue containing a considerable amount of fat, they are enclosed together with kidneys, in the renal fascia, but are separated from the kidneys by a little fibro-areolar tissue.

Each gland consists of an outer cortical portion, which is rich in lipoids and contains no chromatin tissue, and an inner medullary portion which stains deeply with chromatin salt.

Structurally, and functionally, the cortex and the medulla of the suprarenal gland are distinct from each other, but together

they consistitute a single entity anatomically.(**Davis, 1964**).

Histology of the adrenal cortex:

The adrenal cortex is composed of 3 layers namely, the zona glomerulosa, zona fasciculata, and zona reticularis. The zona glomerulosa secretes mineralocorticoids (aldosterone), while the glucocorticoids and sex hormones (androgens) are secreted by the zona fasciculata and zona reticularis (***Guyton*, 1981**).

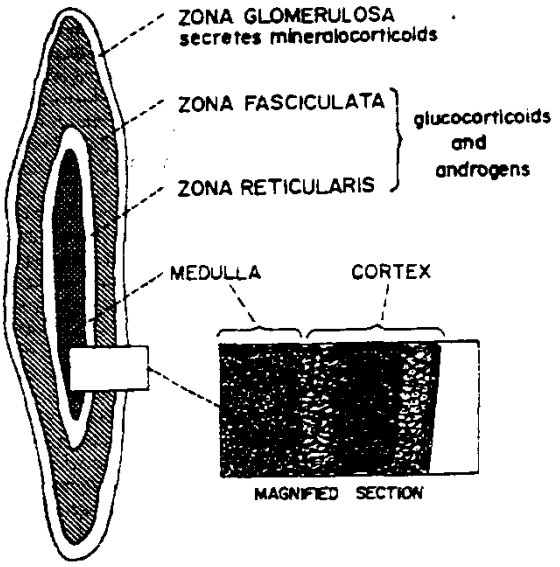


Fig. (A) : Histology of the adrenal gland.

***Guyton* 1981**

CHEMISTRY OF THE ADRENOCORTICAL STEROIDS

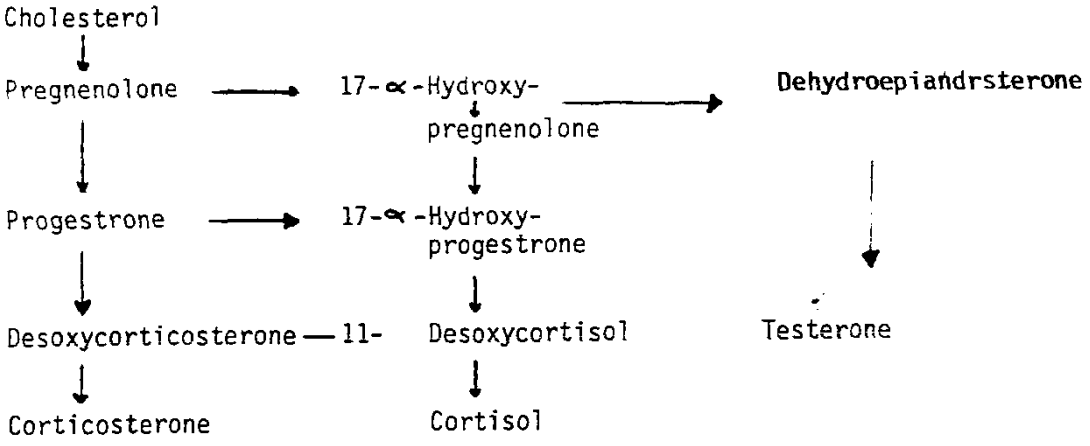
CHEMISTRY OF THE STEROIDS

The adrenal cortex synthesizes two classes of steroids:

1. the corticosteroids with 21 carbon atoms.
2. The adrenal androgens with 19 carbon atoms (sex hormones).

We shall restrict our study only on the corticosteroids. Most naturally occuring steroids contain alcohol side chain and are therefore usually referred to as sterol.(**Harper et al.,1978**).

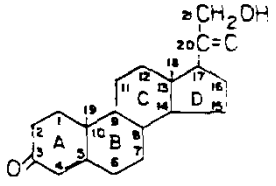
Cholesterol is an obligatory intermediate in the biosynthesis of corticosteroids, where most of the reactions are catalyzed by mixed function oxidases that contain cytochrome and require NADPH and molcular oxygen. (**Haynes et al.,1981**).



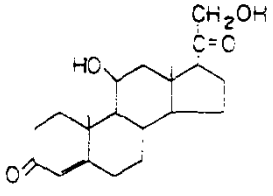
Of these natural steroids are :

1. Deoxycorticosterone
2. Corticosterone or compound (B)
3. Hydrocortisone or cortisol or compound (F)
4. Cortisone

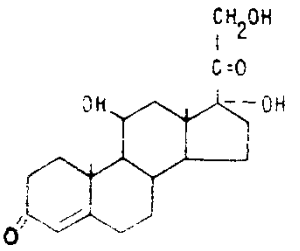
Deoxycorticosterone



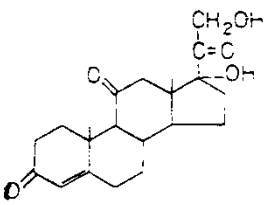
Corticosterone



Cortisol :



Cortisone:



So, it is clear that these natural steroids are composed of 4 rings system (Cyclopentanoperhydrophenantherne ring), with a common presence of a double bond between C_{4-5}, and a ketone group at C_3.

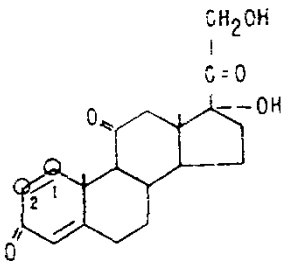
In addition to the anti-inflammatory effect of basic natural steroids, they exert multiple physiological actions. When they are administrated in amounts sufficient to produce a desired anti-rheumatic influence, signs of hormonal excess frequently intervene, such unwanted side-effects may interfere with the use of effective dosage and the maintenance of satisfactory improvement. (**Boland,** 1960).

However, it is noted that structural alteration of cortisol have resulted in the creation of new preparations that characterized by increased biological potency with another advantage over cortisol

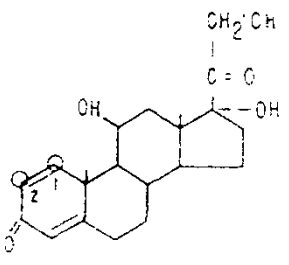
where soidum retension is not so marked, although all of other undesirable side-effects of cortisol overdosage have been observed with synthetic analogues (**Melby, 1974**).

Of these synthetic dervatives we have prednisolone, methylprednisolone, fluorcortisone triamcinolone, and dexamethasone.

prednisone and Prednisolone:



PREDNISONE



PREDNISOLONE

The introduction of a double bond at C_1-C_2 positions of cortisone and hydrocortisone causes enhancement of anti-inflammatory potency and glycogen deposition without corresponding increase in electrolyte activity. (**Herzog et al, 1955**).

That is supported by the notce of **Boland . in 1960**, that the incidence and degree of salt and water retension and blood pressure elevation are much less with prednisone and prednisolone, however unfortunately these analogues are not free of other major deleterious effects.