PARATHYROID HORMONE IN MALES IN THE AGING PROCESS

A THESIS

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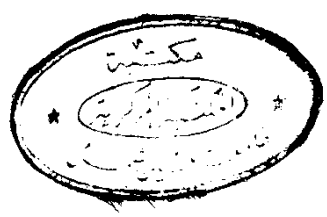


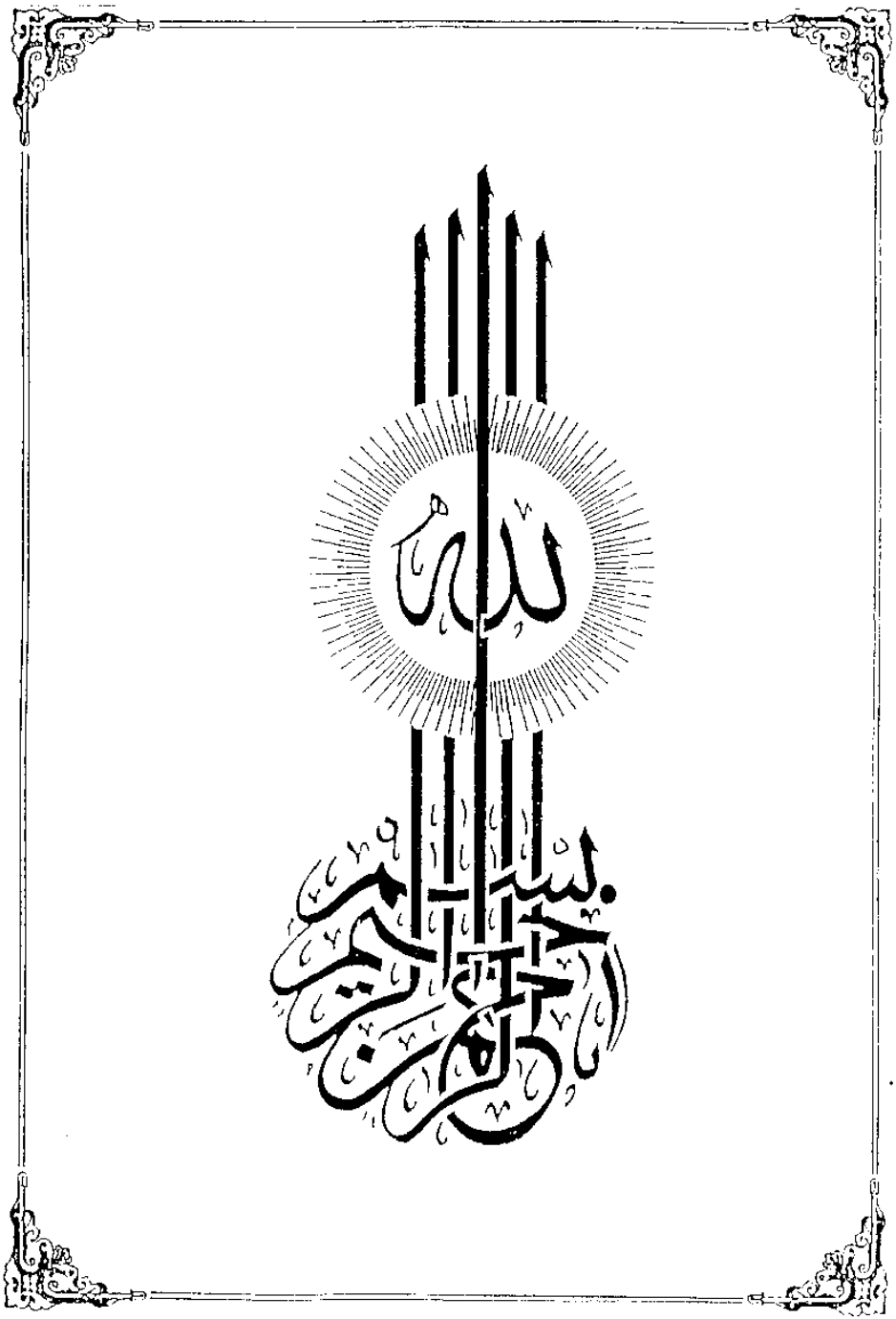
FACULTY OF MEDICINE

AIN SHAMS UNIVERSITY

DEDICATION

To My Family, To Whom

I Am So Grateful



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AIM OF THE WORK

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Aging was thought by some scientists to be the direct result of defeciency states resulting from age related insuffeciency of the endocrine glands.

Parathyroid normone was found to increase significantly with age irrespective of change in glomerular filtration rate.

The aim of our work is to study the level of parathyroid hormone, calcium and phosphorus in the process of aging in males.

REVIEW OF LITERATURE

AGING

BIOLOGY OF HUMAN AGING

Aging is a complex, time dependent, inevitable process. There are so many definitions of aging. Makinodan (1977) defined aging as active dependent process in which there is loss of physiologic adaptability to environmental stress and change.

Watkin (1978) defined aging as a process that begins as early as conception and continues until death.

Alfin-Salter (1979) described aging as a complex biological process in which there is a reduced capacity for self maintenance, a reduced ability to repair body cells.

Young (1983) thought of aging as the progressive physiologic, cellular, biosocial, cultural and psychological changes that start at least from conception until death.

Aging studies may take one of two forms:

A. Longitudinal studies:-

In these studies serial measurements are done on the same individual at two or more points of time . Idealy, the longitudinal study requires that measurements should be repeated at standarized time intervals throughout the whole life span of the individual. (Exton-Smith, 1982).

B. Cross sectional studies:-

This means the study of different subjects of different age groups. Age differences are established by comparing the results of measurements made on individuals in different age groups.

These studies are useful in establishing normal values for biochemical or heamatological data, but they do not describe accurately the course of aging of individuals, since the observed age differences may be due to the operation of different factors (Exton-Smith, 1982).

THEORIES OF THE MECHANISM OF AGING

Ideally, human aging should be studied longitudinally by following the changes occuring in individuals as they grow older. Studies of this type are expensive and present several methodological problems due to difficulties in maintaining methods over time and loss of subjects under study by death, migration and non-cooperation.

Most available evidence on the effect of human aging is derived from cross sectional studies. The most serious hazard of this method is that an important part of what appears as aging in cross sectional studies is due to the differences in cultural backgrounds of successive generations especially in developing societies. This is what is referred to as "Pseudo-Aging" (Evans, 1981).

Since aging is indicated by the organism ability to respond optimally to environmental challenge, its effect may be amplified if environmental chellenges are greater for older people than for younger ones. This is what is referred to as "aggravated aging" (Collins et al., 1977).

True Aging

Human aging is regarded as arising from intrinsic and extrinsic factors and from the interaction between them.

Intrinsic Aging :

There have been many theories proposed to account for the biological origin and significance of the genes coding for intrinsic aging processes and maximum lifespan.

The first theory proposes that the genes represent a self destruct system specifically developed to prevent older organisms competing with younger ones (Dawkins, 1976).

The second theory suggests that the general trend of evolution within a species is to lengthen lifespan and that intrinsic aging processes represent uneradicated determinants of non-adaptive metabolism (Cutler, 1972). The genetic component of aging may represent the action of deleterious genes whose effects have been postponed until later life through selection (Medawar, 1952).

The third theory suggests that intrinsic aging represents side effects of genes which have other beneficial effects that have been favoured by evolution. Aging may be considered as a direct consequence of the cessation of growth or of cellular differentiation (Kirkwood, 1977).

Mechanisms of intrinsic aging :

The theories on the mechanisms of intrinsic aging have been divided into those which propose "programmed" aging and those which are based on "random error" mechanisms.

(a) Programmed aging :-

This concept implies that aging comes about through the action of an orderly sequence of genes acting essentially without error (Evans, 1981). The original programmed aging theories imagined senescence and death as being coded directly in the gene sequence.

Such theories then propose mechanisms of senescence as the perminant locking of cells into a non cycling phase (Gelfant and Grove, 1974).

Many programmed aging theories propose the existence of a biological clock in the organism which paces the changes of senescence.

An early fashion for placing this clock in the endocrine system has been overtaken by increasing attention to the immune system (Burnet, 1974). Age associated changes in the

immune system are complex but in general are dominated by a decline in T-cell function. The onset of T-cell decline begins at sexual maturity with the involution of the thymus which is therefore seen by some as the main pacer for senescence (Evans, 1981).

(b) Random-error theories :-

These propose that aging is a consequence of damage to cell components and particularly to those components concerned with control and repair (Evans, 1981). A number of specific mechanisms of damage have been proposed including thermal denaturation, radiation and free radicle reactions.

Damage to molecules involved in information transfer in the cell requires a special consideration. Damage to a single molecule of RNA or a synthetase might lead to the creation of many molecules of mis-specified protein of aberrant function. Accumulation of informational errors over time might then lead to accellerating dysfunction of the cell which would eventually die of an error-catastrophe (Orgel, 1970).

Somatic mutation is a specific random error mechanism postulated as a basis of aging and there is evidence for the accumulation of somatic mutations in human fibroblasts in tissue culture (Fulder, 1979). It may prove to be the basis of malegnancies and of some diseases of later life that appear to be due to clones of cells with disordered function as Paget's disease of bone.

(c) Combining programmed and random error theories :-

The rate of random error occurance may be genetically determined. This view provides a combination between programmed and random error theories. Specific genetic systems would activate degenerative process at a programmed point in the life cycle of a particular given species.
This theory explains the fact that different species have different lifespan (Hayflick, 1973).

It should be noted that most of the available data are obtained from studies done on human tissue cultures in vitro. Comparison between aged in vivo and in vitro cells suggests that the two processes may not derive from the same mechanism.

Extrinsic aging :

There is convincing evidence that many age associated changes in man are at least partly extrinsic in origin arising from environmental factors and from aspects of a culturally-determined way of life (Evans, 1981).

Many authors have proposed that carcinogenesis is a consequence of intrinsic aging processes. However it may be that the longer an individual lives, the more likely he is to accumulate a carcinogenic dose of an environmental factor, and variations in incidence and in sex ratio of cancer around the world suggest that most malignancies are partly extrinsically caused (Boyland, 1980).

To simplify all these data, intrinsic aging determines maximum lifespan and extrinsic factors determine how close to lifespan an individual reaches.

It is to be expected that the relative importance of extrinsic factors in determining differences in morbidity and mortality between individuals of the same age will decline in old age.

LEVELS AT WHICH AGING CAN BE STUDIED

1- Cellular level :-

The failure of proliferation of aged human diploid fibroblasts in vitro had directed the attention towards the study of the changes in cell cycle with aging. Krohn (1962)

showed that the length of the cell cycle increases with aging.

Lesher (1961) stated that not only the duration of the cell cycle increases, but also there is prolongation in the stages of RNA synthesis (G. phase) and DNA synthesis (S. phase)

The replicative potential of the cell was studied in relation to aging. Price and Makinodan (1972) stated that aging can reduce the replicative potential of certain cell types in vivo and suggested the possibility that the aging phenomenon might be due to such limitations imposed on a specific, highly important cell population.

Experiments utilizing the radio active precursor, ^{3}H-thymidine showed that DNA synthesis had stopped in senescent cells, suggesting that replication of the cellular genetic material may be one of the first processes which is affected by aging (Denny, 1975).

It has been shown that there is increase in number and size of lysosomes within the cells with increasing number of cell doublings. Also it has been shown that there is a concomitant increase in their enzymatic activity suggesting that the autolytic capacity within the cell might be one of the major factors in limiting cell proliferation (Denny, 1975).

Martin et al., (1970) found a regression of replicative potential of human skin cells occurs with age.

Experiments were performed on cells from patients with Werner's syndrome or progeria which are characterized by what might be described as accelerated senescence. The cell doublings for patients with Werner's syndrome were below the mean of the control cultures for the same age group (Martin, 1970). Skin cells derived from a 9 years old boy with progeria could undergo only two cell doublings whereas

control experiments using cells from young adults were capable of 20-30 doublings (Goldstein, 1969).

The failure of mitosis and the observed deterioration of cellular integrity with aging were tried to be explained by two approaches. The first approach explained the condition to be of nuclear origin, being the expression of specific genetic programming or exhaustion of programme. The second approach put into consideration a cytoplasmic origin of the condition and suggested that it was mainly due to accumulation of non repairable damage with time (Smith & Rubenstein, 1981).

Wright and Hayflick (1981) developed the ability to enucleate populations of human fibroblasts and to fuse the resulting enucleate cytoplasms to whole cells of different in vitro age. They found that young enucleate cytoplasm was not able to rejuvenate old cells. They interpreted this finding as evidence that cellular senescence is not a result of selective depletion of cytoplasmic function. They also found inability of old enucleate cytoplasm to age young cells.

From these findings they suggested that cellular senescence is intranuclear rather than intracytoplasmic in origin although it is possible that artefacts affect the results.

2- Tissue and organ level:-

Not all cells and tissues age in the same way. Some body cells retain the ability to reproduce all through life such as: skin, lining of the gut, liver and bone marrow. Even in these tissues the capacity for regeneration does slow down.

Some cells lose this capacity before birth or shortly thereafter such as: neurons, muscle and kidney cells. With the death of these cells, fewer functional units remain for body processes, this loss could theoretically result in a less