EFFECT OF AGING ON THE IMMUNE SYSTEM SPECIALLY NEUTROPHIL CHEMOTAXIS

THESIS

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BY

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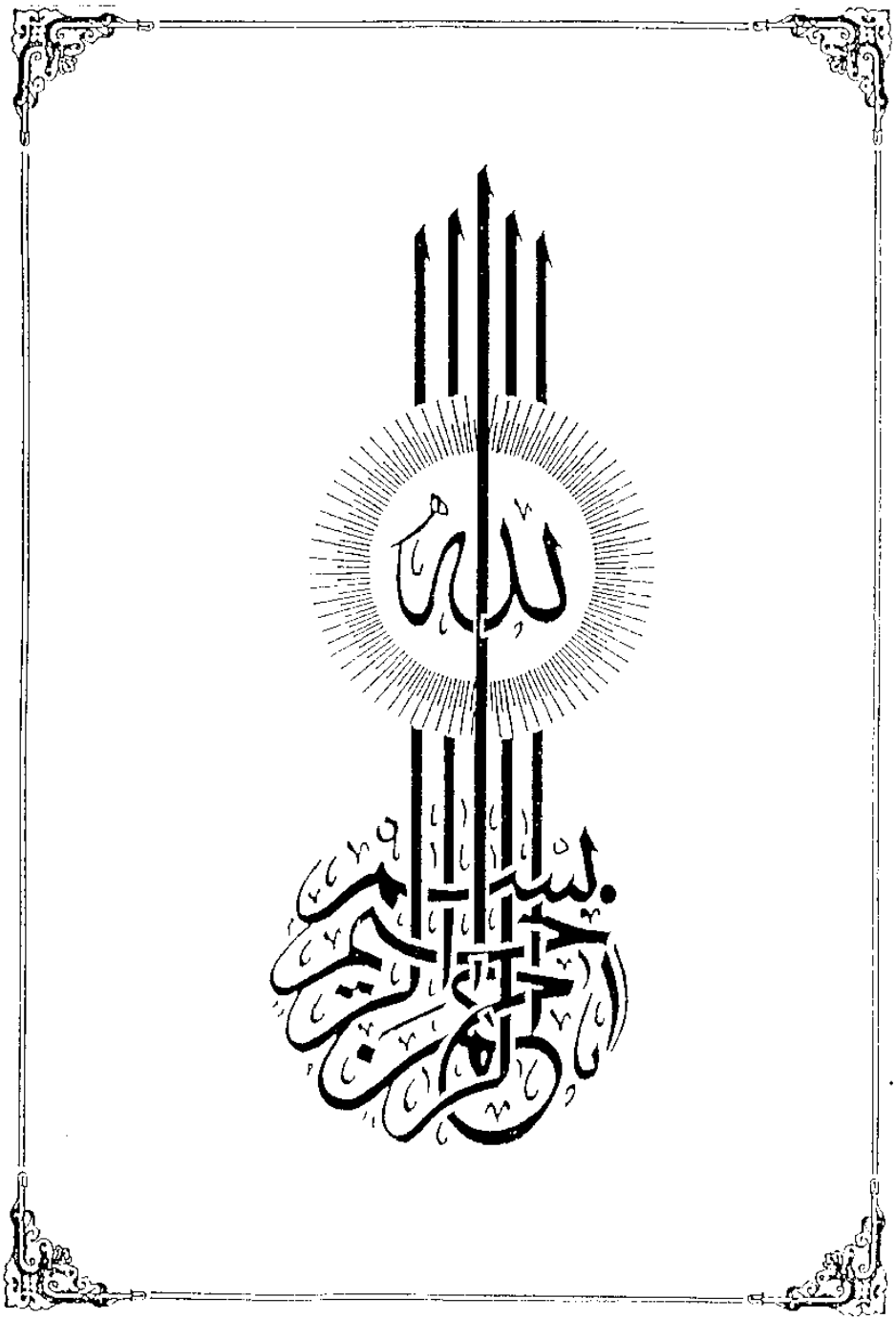

INTRODUCTION AND AIM OF WORK

What is aging, and what is its cause? are questions that have long fascinated men (and Women) ; the preoccupation is understandable, since human beings are the only living creatures capable of grasping aging as an idea and consequently of fearing it. Other animals accept in blissful unawarness only the physical actuality of the moment that is now.

One thing is certain, there is no single cause of aging Just as there never was a "philosopher's Stone" nor an Elixir of life " Aging is multiform and though death is the inevitable end result of aging, it seems likely that it is an incidental effect in the sense that it will occur when the aging process happen to impinge on something, however small which is vital for survival of the organism, the cells of the respiratory centre in Man for example. Keats' Poetic view that death is life's high meed, makes no scientific sense.

In spite of the fact that aging is like truth, 'a many sided thing', it is rational to look for one or few processes that could be the common denominator of aging.

It has to be admitted at the start that theories abound, facts are few and very little is known with certainty (Brocklehurst and Hanley (1976).

Most measeures of human function show on avarage an increase through childhood and early adult life followed by a decline at later ages. The age at which maximal avarage function is attained and the degree and timing of subsequent decline varies between individuals and also with the specific function being measured . In general,functions requiring the integrated actions of several body systems show greater decline than functions of single systems.

Homeostatic mechanisms tend to become slower, less sensitive and less accurate with age. Infections in the aged are characterized by being Commoner, Severer and Complicated.

The immune system is also affected with age and autoantibodies are more prevelant in old age. It is this duality of phenomena going in opposite directions that is unique and not obviously present in other physiological systems.

Therefore , the failing immune functions plus the autoimmunity would reinforce one another leading to an accelerated self destructive reactions.

Chemotaxis is the ability of motile cells to recognize and respond to a suitable chemical gradient with directional

migration. The accumulaton of leucocytes is an important aspect of normal host defence.

The aim of this work is to review the effects of aging on the immune functions specially neutrophil chemotaxis.

Review of Literature

THE BIOLOGY OF AGING

The central concept of aging is loss of adaptability of an individual organism with time so that on avarage the old are more vulnerable to environmental challenges than the young (Evans, 1981). Vulnerability is apparent clinically in the increase with age in the fatality of disease including truma, surgical operations and infections (Phair,1979) although in epidemic infections specific immunity may be a modifyng factor presumbly because the old had encountered an immunologically similar infection sometime before.

On a statistical definition human aging begins near the onset of puberty and is a continuous process thereafter without any discontinuity which mightprovide a rational basis for separating off a particular age group of adults as the elderly.

Aging Reflected in Function :

Most measures of human function show on average an increase through childhood and early adult life followed by a decline at later ages. The age at which maximal average function is attained and the degree and timing of subsequent decline varies between

individuals and also with the specific functions being measured. In general, function requiring the integrated actions of several body systems show greater decline than functions of single systems.

Homeostatic mechanisms tend to become slower, less sensitive and less accurate with age and these trends may be associated with secondary partly compensatory changes in body function.

(Helderman et al., 1978) have found evidence that osmoreceptor sensitivity increases with age possibly as an adaptive response to the age - associated diminution in the ability of the kidney to conserve salt and water (Mc Lachlan 1978).

True Aging :

Many text books attempt to draw a distinction between "normal" and "abnormal" aging or between normal aging and disease. This approach is unhelpful as apart from possible confusion between the implications of at least three entirely different meanings of the word "normal" there is no rational basis at present for defining normality and attempts to specify it emperically may be seriously misleading. There is no reason to assume that what is normal (i.e. healthy) will be found normally (i.e. most commonly) or that it will necessarily be within so many standard deviations.

Intrinsic Aging :

Observation and breeding experiments show that every species of animal has a characteristic life span sometimes referred to as specific life - span which is inherited in natural populations as a polygenic characteristic. The genetically controlled processes which place this upper limit on the life span of an individual comprise intrinsic aging.

A simple model of intrinsic aging might see it as a process analogous to the wearing out of components of a motor car, but a basic property of living matter is a capacity for self repair so a problem remains in why the body does not repair the revages of age.

Sacher (1975) has shown that in mammals characteristic maximal life span correlates with the ratio of brain weight to total body weight. Although this might suggest that the brain is the site of some biological clock the explanation is more likely to lie in the effect of large brain size in prolonging gestation and so reducing reproduction rate and in the probability that biological advantages of a large brain will not be apparant unless individual live long enough. Evans assumes that one of the significant advantages of a large brain is a greater capacity for learned as distinct from innate behaviour. Thus the genes

for large brain weight and the genes for long life are likely to become associated through selection.

Why should there be genes controlling aging ?

Theories proposed to account for the biological origin and significance of the genes coding for intrinsic aging process and maximum life span fall mainly into three groups. The first group propose that the genes represent a "self destruct" system specifically developed to prevent older organism competing with younger ones.

At first sight one reason why such competition might be undesirable is that if aging did not exist old organisms would be highly adapted by learning and natural selection to a particular environment and so would compete successfully with the younger more variable individuals and this would render the species vulnerable to changes in enviromental conditions. This proposal contains the implicit assumption that natural selection can act for the survival of the species as well as of the gene and this is a doubtful, Possibly untenable, hypothesis (Dawking 1976). Furthermore, (Medawar, 1952) and others have pointed out that even without aging, death from disease, accident and predation will always result in there being fewer older than younger organisms in competition for reproductive and other resources so there

would be no biological need for older organism to be further handicaped by the evolution of aging processes. The idea that aging may include a specifically evolved self destruct element is still advanced from time to time but is generally considered improbable.

The second group of theories takes an opposite view and suggests that the general trend of evolution within a species is to lengthen life span and that intrinsic aging process represent uneradicated determinants of non adaptive metabolism. (Culter 1972) in relation to human aging, Medawar(1952) and others have proposed that the genetic component of aging represent the action of deleterious genes whose effects have been postponed until later life through selection. This idea has been mathimatically evaluated by Hamilton (1966). A deleterious gene which acts near puberty will be at a reproductive disadvantage compared with agene producing the same effect later in life when the organism carring it will have had more chance to reproduce. Through successive generations of evolution the effects of deleterious genes will therefore tend to accumulate in later life.

The third group of theories suggest that intrinsic aging represent "side effects" of genes which have other benificial effects that have been favoured by evolution. One type of theory in this group is to regard aging as a direct consequence

of the cessation of growth or of cellular diffrentiation. It is suggested that both these states involve switching - off genes which would be requried to replace cell components damaged by heat, radiation or accident. (Calow, 1978) & (Kirkwood, 1977) have recently produced theories of this type. (Kirkwood, 1977). Contrasts the inevitable senescence of somatic cells with the apparent immortality of germ - line cells. He suggests that accurate repair of cellular damage is "expensive" in terms of energy and metabolic materials required so that although high accuracy of repair is essential in the germ-line there has been little selection pressure to prevent damage accmulating in somatic cells after the age of reproductive maturity.

"Side effect"theories have been proposed at an organismic as well as at a cellular level. "Williams (1957) has pointed out that a gene which has a beneficial effect early in reproductive life may be selected for, even though it has a deleterious effect later in life . So far with the doubtful exception of Huntington's chorea no pleiotropic genes of this type have been definitely identified. It may also be relevant that human evolution took place under environmetal conditions very different from todays world so that the early beneficial effect of Williams's postulated pleomorphic genes may no longer be apparant. (Neel 1962) suggested the existence of a thrifty gene which enables individuals possessing

it to survive periods of famine by storing excess food energy as fat but which in time of overadequate food supply leads to obesity, diabetes and arterial disease later in life. The recently demonstrated lower thermogenesis of obese subjects compared with the non obese may reveal the thrifty gene at work (Jung et al., 1979).

(Burnet, 1974) has also proposed what is essentially a 'side effect' theory of intrinsic aging. He suggests that aging is due to accumulating errors in cellular DNA generating somatic mutation. The errors come about because of inaccuracies in the DNA repair system and the rate of inaccuracy is a genetically determined characteristic. Burnet suggests that the beneficial effect of this inaccuracy which have led to its persistence, include the genesis of germ-line mutations making evolution possible, and a contribution through somatic mutations to immunocyte variability broadening and individual organisms range of immune response.

Few or Many Genes ?

It is of interest to know whether aging and maximum life span are under the control of many or few genes, for if only few genes are involved the modification of aging rate or pattern is

a more realistic possibility. (Walfard, 1974) has commented that when a viral infection renders a tissue culture immortal, the amount of genetic information entering the cell from the virus must be small and that therefore the mortality of the cultured cells may be determined by a small number of genes, possibly only four to six. Clearly, however, the control of senescence in isolated fibroblasts may be an inadequate model of aging in whole organisms.

(Culter 1975) has argued from current knowledge of higher primate evolution that the maximum life span of the direct line ancestors of Homo Sapiens increased so rapidly over a period about 100.000 years ago that given reasonable estimates of mutation rates relatively few genetic loci must have been involved. He suggests approximatly 250 which is equivalent to about 0.6 percent of the genome.

(King and Wilson, 1975), have drawn attention to the very close correspondence in peptide sequances between the proteins of man (maximum life span 110 years) and the corresponding proteins of chimpanzee (maximum life span 45 years). On average, human polypeptides are more than 99 per cent identical with those of the chimpanzee. The implication is that a relatively small number of changes in systems controlling expression of genes coding for structured proteins may explain the difference between man and the lower primates. In this we may be witnessing the sophisticated rebirth of an old idea that man is merely an overgrown fetal ape.