OSTEOPOROSIS

Essay
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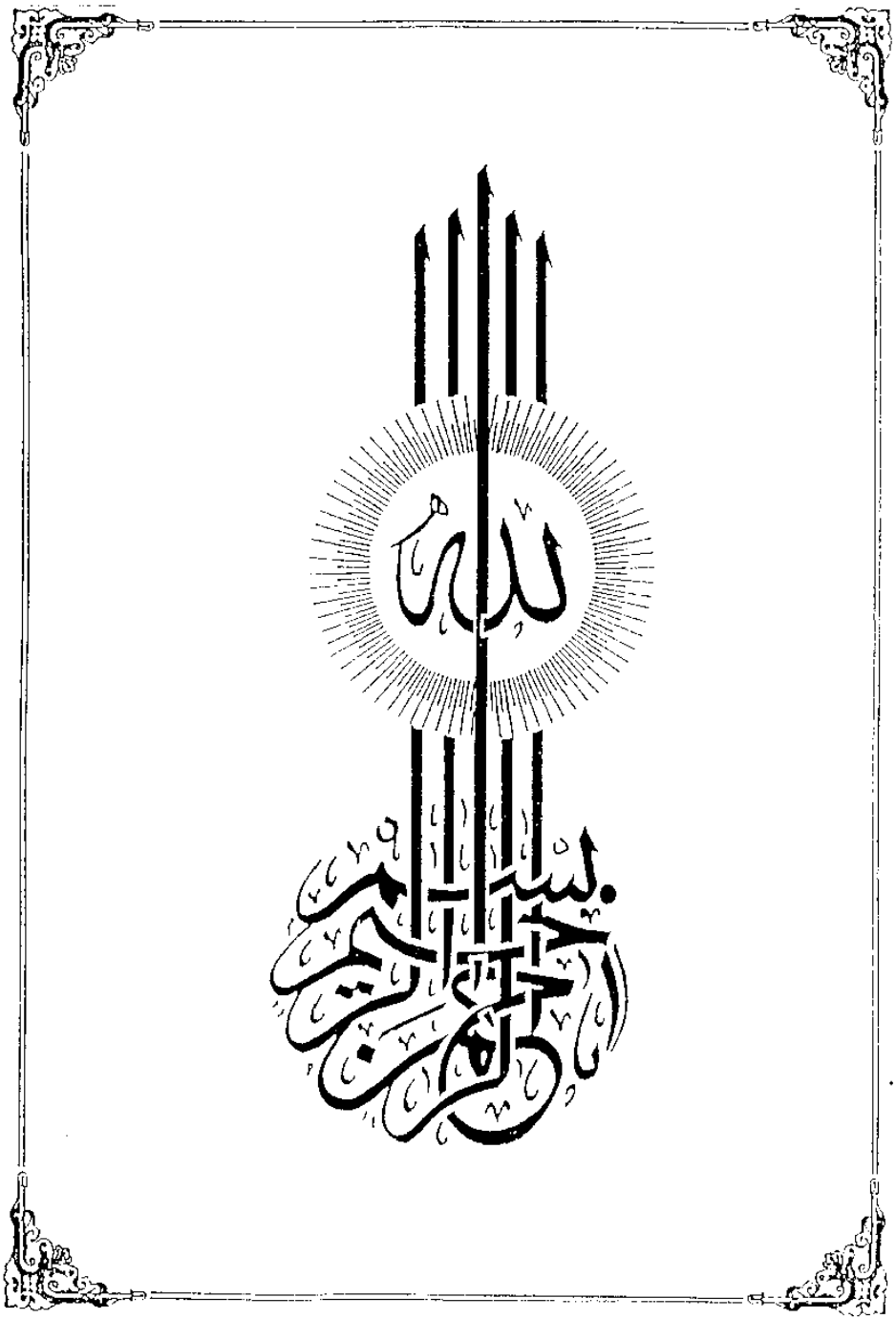

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INTRODUCTION AND AIM OF THE WORK

Osteoporosis is a generic term used to designate a metabolic bone disorder characterized by a decrease in bone mass and increased susceptibility to fracture with or without a recognisable causative medical back ground. The bone present is normally mineralised.

It is mainly characterized by a reduction in the total bone mass as compared with the normal values for the individual's age, sex and occupation and fractures primarily of vertebrae, hip and distal forearm.

In fact these two criteria (The low mass and fracture) must coexist in order to establish the diagnosis of the disease, and thus any attempt to discuss the problem must involve these two essential elements.

The aim of the work is to review the problem of osteoporosis, as regards its possible aetiology and pathogenesis, its morphologic and diagnostic features, and the method attempt for its prevention and treatment.

Bone Histology

It is usual to divide the cellular elements of the skeleton into osteogenic tissue and marrow tissue.

Osteogenic tissue is often described as being made up of cells found lining bone surfaces and within bone lacunae. Marrow tissue is made up of the cells that fill the marrow cavities.

Recent experimental evidence suggests that marrow contains cells capable of differentiation into bone-forming cells **(Friedenstein, 1973)**, cells capable of differentiation into bone-resorbing cells and haemopoietic and other cell types derived from mesenchyme **(Hancox, 1972).**

1. **Origin and differentiation of marrow and haemopoietic stem cells.**

All bone begins as mesenchymal condensations during the early embryonic period (the term mesenchyme refers to the primitive C.T. cells and their intercellular matrix that derive from the mesoderm, the term condensation refers to an increase in the number of cells or intercellular fibres or both) (Vaughan, 1975).

Into the primitive osteogenic masses of cartilage and membrane bone, capillaries penetrate carrying with them primitive C.T. precursors forming a loose network with specialized capillaries and sinusoidal vessels.

Later these early capillaries become associated with venules and fully developed arterioles and arteries.

Haemopoietic stem cells are carried into this network by blood from the foetal liver. **(Moore and Metcalf, 1970).**

The stem cells leave the blood and colonize the interstices of the network formed by the invading capillaries and the associated loose connective tissue so forming the active haemopoietic marrow.

Much of this active haemopoietic tissue is replaced by fat cells propably differentiating from stem cells associated with the capillaries.

Large fixed tissue macrophages or histiocytes also differentiate within loose connective tissue.

The marrow is clearly then an extremely complex tissue that comes later in development than primitive osteogenic masses of cartilage and membrane bone.

2. Origin and differentiation of osteogenic stem cells:

a) Precursors of the osteoblast

Friedenstein described two types of osteogenic stem cells:

1. Determined osteogenic precursor stem cell (DOPC) which will form bone without inducer substance.

2. An inducable osteogenic precursor cell (IOPC).

The (DOPC) is a radiosensitive cell and following a radiation dose of 1000 r its osteogenic potency as tested by heterotopic transplantation is lost **(Friedenstein, 1973).**

As Friedenstein says "No reasonable hypothesis concerning participation of the inducable osteogenic precursor cell in the renewal of skeletal bone can be devised at present".

b) Bone-inducing substances

The nature of the inducing substance present in the transitional epithelium is at present unknown.

Vaughan has recently gone some way to characterizing the chemical nature of what he calls bone morphogenic protein, a material isolated from dead bone which is capable of inducing active bone formation when placed in connective tissue sites. Whether this material (BMP) acts on fixed mesenchymal cells or cells arriving at the site from bone marrow in the blood is still an open question **(Vaughan, 1975).**

c. **Precursors of the osteoclast**

At the present time there are two views:

1. It arises from precursor cells adjacent to the surface of the bone which may or may not coalesce to form the classical multinuclear cell lying in Howship's lacunae on the bone surface.

2. It arises from a mobile wandering cell like a macrophage or histiocyte or even a blood monocyte that reach the bone surface and there coalesce to form the classical multinuclear cell.

3. **Osteogenic cells**

The recognized and well defined cells associated with bone are:

a) The osteoblast that lays down the matrix of bone.

b) The osteocyte of doubtful function that lies in lacunae throughout bone.

c) The osteoclast that resorbs bone.

In addition there are the less well-differentiated precursor cells often called osteoprogenitor or mesenchyme cells and fibroblasts.

a) **Osteoblast**

The osteoblast is a fully differentiated cell whose function is to lay down bone matrix. It may well also be concerned in the mineralization process.

i) Structure

The layer of active osteoblasts near the surface of young bone is usually only one layer thick. The active osteoblasts tend to be columnar in shape with the nucleus at the end furthest from the bone surface. The cell shows an irregular contour particularly on the matrix surface where there are many fine protoplasmic processes which penetrate the adjacent osteoid and mineralized matrix via canaliculi. These processes finally rest on the cell membrane of deeper osteocytes or upon the osteocyte processes that meet them within the canaliculi (**Vaughan, 1975**).

Osteoblasts contain an abundance of rough-surfaced endoplasmic reticulum, a prominent golgi complex next to the nucleus, glycogen vesicles, and mitochondria.

Pinocytotic vesicles at the plasma membrane especially on the cell surface adjacent to the osteoid are easily seen.

Vaughan (1975) suggests that such intracellular vesicles are moving into the cell rather than out of the cell.

Matthews et al (1973) have described membrane-confined vesicles within the osteoid, some of which prove upon serial examination to be tangentially sectioned osteoblastic processes while others are completely dissociated from the cell.

Extensions from the osteoblasts within the osteoid have also been described by **Bernard and Pease (1969).**

ii) Origin and differentiation

The differentiation of osteoblasts from precursor osteoprogenitor cells has been studied by many workers.

On the periosteal surface there is an outer layer of fibroblasts enclosing several layers of undifferentiated cells, the preosteoblasts and on the mineral matrix surface a layer of differentiated cells the osteoblasts. At the electron-microscope level **Scott,** has shown that there is clear distinction between the osteoblast and the preosteoblast **(Scott, 1967).**

In order to study the pattern of cell proliferation and differentiation, injections of [^{3}H] glycine and [^{3}H] thymidine DNA were given to young rabbits and the animals were killed at intervals of 1-5 days (**Vaughan, 1975).**

The [^{3}H] glycine labelled the position of the bone surface at the time of injection since it was taken up into new collagen, and the [^{3}H] thymidine labelled the cells that were synthesizing D.N.A.

It was therefore possible to analyse first, the relative proliferative activity of the different cells on the bone surface and secondly the pattern of differentiation and rate of movement of the different cells. Little thymidine was taken up by the fibroblasts which therefore play no significant role in increasing the cell population.

The active proliferating cells which showed an initial high level of labelling were the osteoprogenitor cells or preosteoblasts the majority, but not all, of these preosteoblasts subsequently divided to give rise to the osteoblasts which contained only half the amount of label seen in the preosteoblasts (**Vaughan, 1975**).

About 3 days later a few of the cells embedded in the matrix adjacent to the mineral surface are labelled and subsequently these labelled osteocytes increase in number as more labelled osteoblasts become incorporated into bone matrix.

In the young animal an osteoblast may remain on the surface for 3 days during which time it will lay down 3 times its own volume of matrix.

iii) Functions

It has long been recognized that the function of the osteoblast is to lay down matrix, both collagen and ground substance **(Vaughan, 1975).**

More recently the osteoblast has been implicated in the deposition and exchange of calcium and phosphorus **(Matthews et al, 1973).**

a) Collagen synthesis

Osteoblasts rapidly incorporate tritium-labelled amino-acids injected I.V. these labelled compounds are first found on the bone surface **(Leblond and Weinstock, 1971),** and later in a clearly defined line in the osteoid at varying depths depending on the time after injection and the rate of growth.

Autoradiographic studies made at the electron microscope level indicate that the collagen fibril precursors are synthesized by the osteoblasts and released extracellularly to the osteoid **(Leblond and Weinstock 1971).**

b) Protein-polysaccharide synthesis

Sulphur-35 is rapidly incorporated into growing bone and at least a part of this is found in the chondroitin sulphate fraction (Vaughan, 1975).

At the level of the electron microscope ^{35}S is taken by the Golgi apparatus and the sulphated mucopolysaccharide is propably released into the extracellular matrix by way of Golgi-derived vesicles **(Leblond and Weinstock, 1971).**

c) Glycoprotein synthesis

Tritium-labelled fucose and glucosamine have both been used to study glycoprotein synthesis since they are known not to be metabolized in both rat and rabbit , both are components of bone sialoprotein, a matrix constituent.

They can be demonstrated in the osteoblast immediately after injection and subsequently in the osteoid **(Leblond and Weinstock 1971).**

d) RNA synthesis

The job of the preosteoblast is to differentiate or divide in order to maintain the osteoblast population.

The job of the osteoblast is to synthesize and possibly calcify the matrix. The rate of the labelling of the cytoplasmic RNA has been shown to be similar for the two cell types but the maximum level of labelling in the cytoplasm of osteoblasts is 2-3 times than in the preosteoblast. **(Leblond and Weinstock, 1971).**

e) Transfer of calcium and Phosphate.

Much recent evidence suggests that osteoblastic activity may be deeply involved in the in vivo formation of bone mineral (Vaughan, 1975).

It is agreed that the osteoblast contains both calcium and phosphate **(Matthews et al, 1973).**

Matthews finds the calcium particularly associated with the mitochondria and suggests that within the cell, the mitochondria probably act as reservoirs for both calcium and phosphorus. In his view the ions are not permanently sequestered but exchange continuously with the cytoplasmic pool.

Vaughan has suggested that mineralization can be visualized in two phases:

First phosphate accumulation within the matrix vesicle through the enzymic hydrolysis of inorganic pyrophosphates and then the accumulated phosphate reacts with available Ca possibly associated with the lipids to form apatite. In the second phase the crystal (within the vesicle) grows until it perforates the vesicle membrane and becomes exposed to the cartilage or bone fluid which at least in the case of cartilage is supersaturated with respect to apatite crystals (**Vaughan, 1975**).

The vesicle contents then act as a nucleating site.

f) Enzymes

The cell is characterized by its extremely high content of alkaline phosphatase known to be capable of acting as a pyrophosphatase and therefore may be concerned in the initial calcification process.

g) Biological control factors:

Factors recognized as affecting osteoblast activity are: