Module VII - Apoptosis - The PATHOLOGY of CELL DEATH - CLINICAL IMPLICATIONS

APOPTOSIS, or programmed cell death is characterised by morphological and biochemical changes in the cell and plays a decisive role in maintaining cellular homeostasis in a physiological process. There are still many questions as to the entire and exact pathogenic processes involved.

Certainly, there is a gene involvement probably involving genes and molecular mechanisms that are both structurally and functionally homologous to human proto-onco-genes. Certainly, also, a variety of positive and negative regulators of apoptosis have been identified.

As Bichat (1803) and Dastre (1902) have stated "death is difficult to define = the cessation of the vents and phenomena which are characteristic of life". We, therefore, first need a definition of life - I would define it as " the life of an organism is constituted by the harmonious functioning of a community of organs, tissues and cells, and the concomitant use and emission of energy, expressed as measurable oscillations within a bio-field force system". Death is the dissolution of this community.

Thus, death is a progressive phenomenon which commences at some point and spreads throughout the organism - a situation created by cessation and disruption of the machinery of the organism (structure, function and immune system integrity), and less within the body of co-ordinated energy flow (meridians) and homeostatic control.

The death of a cell, too, is a similar progressive phenomena - a microcosmic counterpart of the death of a higher organism.

Apoptosis is a distinct form of cell death, controlled by an internally encoded suicide programme. It is a distinct event that triggers characteristic morphological and biological changes in the cellular life cycle. It is common during embryogenesis, normal tissue and organ unvolution, cytotoxic immunological reactions and occurs naturally at the end of the life span of differentiated cells.

Apoptosis can also be induced in cells by the application of a number of different agents, including physiological activators, heat shock (proteins), bacterial toxins, oncogenes, chemotherapeutic drugs, a variety of toxic chemicals, and ultraviolet and gamma radiation.

When apoptosis occurs, the nucleus and cytoplasm of the cell often fragment into the membrane-bound apoptotic bodies, which are then phagocytised by neighbouring cells. A landmark of cellular self-destruction by apoptosis is the activation of nucleases and protease's that degrade the higher order chromatin structure of the DNA into fragments of 50 - 300 kilo-bases and subsequently into smaller DNA pieces of about 200 base pairs in length. The magnesium/calcium- dependent endonuclease is partly responsible for this.

Apoptosis can also be characterised by changes in cell membrane structure. During apoptosis, the cell membrane's phospholipid asymmetry changes.

Apoptosis is induced by chemicals to control malignancy. Many chemicals have the capacity to bind to DNA, to form DNA adducts or DNA single strand. However, the body is equipped with many factors, enzymes, suppresser genes and cellular sensors, all with the capacity to prevent this action of chemicals on our DNA by activating apoptosis-inducing signals.

Ever since apoptosis was first described, a multiplicity of instigating factors have been identified. One group includes positive trigger mechanisms that stimulate apoptosis by means of positive signals, while the second group contains negative trigger mechanisms that hinder the programmed implementation.

The concept of programmed cell death implies the existence of genes that code for a cascade of proteins which in turn are capable of inducing the destruction of a cell. In eukaryotic cell systems, a great variety of genes can be identified that are directly or indirectly involved in inducing apoptosis.

Apoptosis is responsible for the programmed cell death in several important physiologic and patho-physiologic processes:

1/ Embryogenesis, as occurs in implantation, organogenesis, and developmental evolution.

2/ Hormone-dependent physiologic involution, such as the endometrium during the menstrual cycle, or the lactating breast after weaning; or pathologic atrophy, as in the prostate after castration.

3/ Cell deletion in proliferating populations, such as intestinal crypt epithelium, or cell death in tumours.

4/ Deletion of auto-reactive T cell in thymus, cell death of cytokine-starved lymphocytes, or cell death induced by cytotoxic T cells.

In detail, there are 5 stages of the postulated:

1/ The variety of intrinsic (including free radicals) and extrinsic stimuli, including the withdrawal of growth factors, the engagement of specific receptors and receptor-ligand interactions (FAS/FAS ligand, TNF/TNF-receptor) and intrinsic protease activation. The protease's include calpain 1, a calcium- dependent enzyme (explaining a role for increased cytosolic calcium in the processes, which calcium subsequently increases intracellular protease activity).

2/ The increased protease activity has homology to interleukin I Beta converting enzyme (“Ice”) (they are termed “ICE-like” because they structurally resemble the first member of the group discovered - interleukin I converting enzyme (ICE)).

Thus results the cascade of intracellular degradation, including endo-nuclease-mediated fragmentation of nuclear chromatin.

There is a series of apoptosis specific genes that can stimulate cell death (e.g. the bax gene). Also, there are genes whose products block apoptosis (bcl-2).

3/ The breakdown of the cytoskeleton.

4/ Formation of cytoplasmic bud.

5/ Formation of apoptotic body which expresses new ligands for phagocytic cell binding and uptake.

Various less complicated phenomena are associated or related to apoptosis and are covered in the lecture:

1/ Apoptosis in Autoimmune disease.

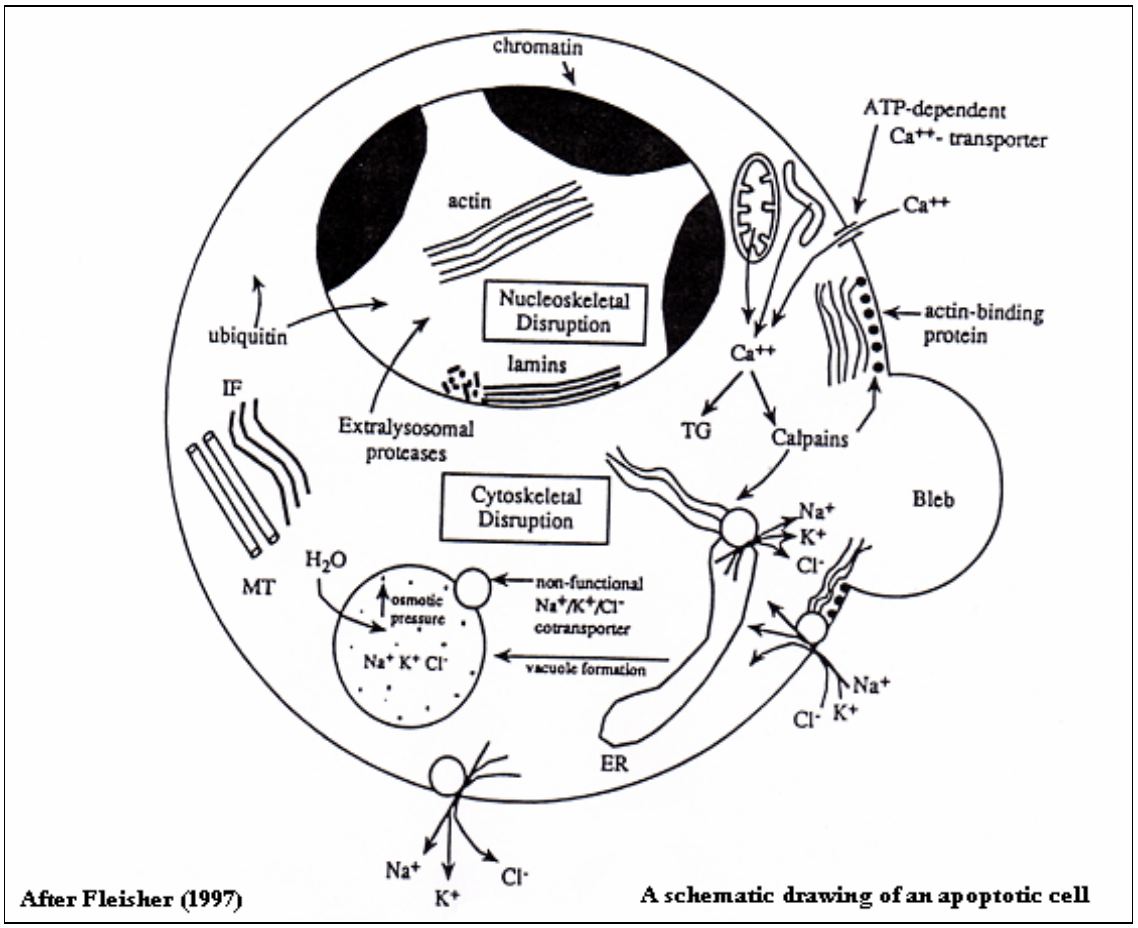
2/ Apoptosis during viral infection, including in AIDS.

3/ Regulation of Apoptosis - see illustrations for details.

4/ Mitochondrial implications - see diagrams.

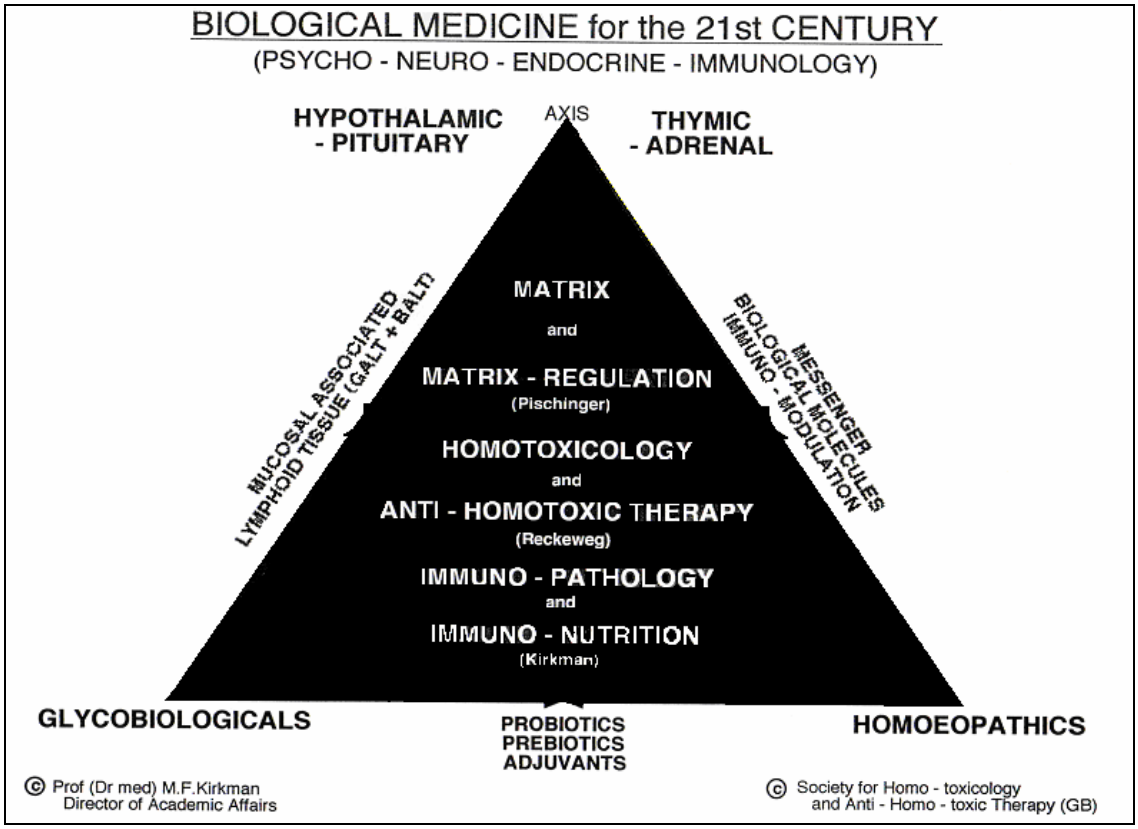
5/ Antioxidants and ageing.

6/ Remedial factors in ageing - pathological implications
- a) Heavy metal intoxication.
- b) Lack of essential nutrients and imbalance.
- c) Loss of calcium for bones.
- d) Accumulation of metabolic residues.
- e) Loss of normal immunity.
- f) Loss of neurones and nerve conduction, Alzheimer's and Parkinson's disease.
- g) Cross linking of collagen fibres and other biological matrix deterioration's.



After Fleisher (1997)

A schematic drawing of an apoptotic cell


BIOLOGICAL MEDICINE for the 21st CENTURY
(PSYCHO - NEURO - ENDOCRINE - IMMUNOLOGY)
HYPOTHALAMIC - PITUITARY
AXIS
THYMIC - ADRENAL
MUCOSAL ASSOCIATED LYMPHOID TISSUE (GALT + BALT)
MESSENGER BIOLOGICAL MOLECULES IMMUNO - MODULATION
MATRIX
and
MATRIX - REGULATION
(Pischinger)
HOMOTOXICOLOGY
and
ANTI - HOMOTOXIC THERAPY
(Reckeweg)
IMMUNO - PATHOLOGY
and
IMMUNO - NUTRITION
(Kirkman)
GLYCOBIOLOGICALS
PROBIOTICS
PREBIOTICS
ADJUVANTS
HOMOEOPATHICS
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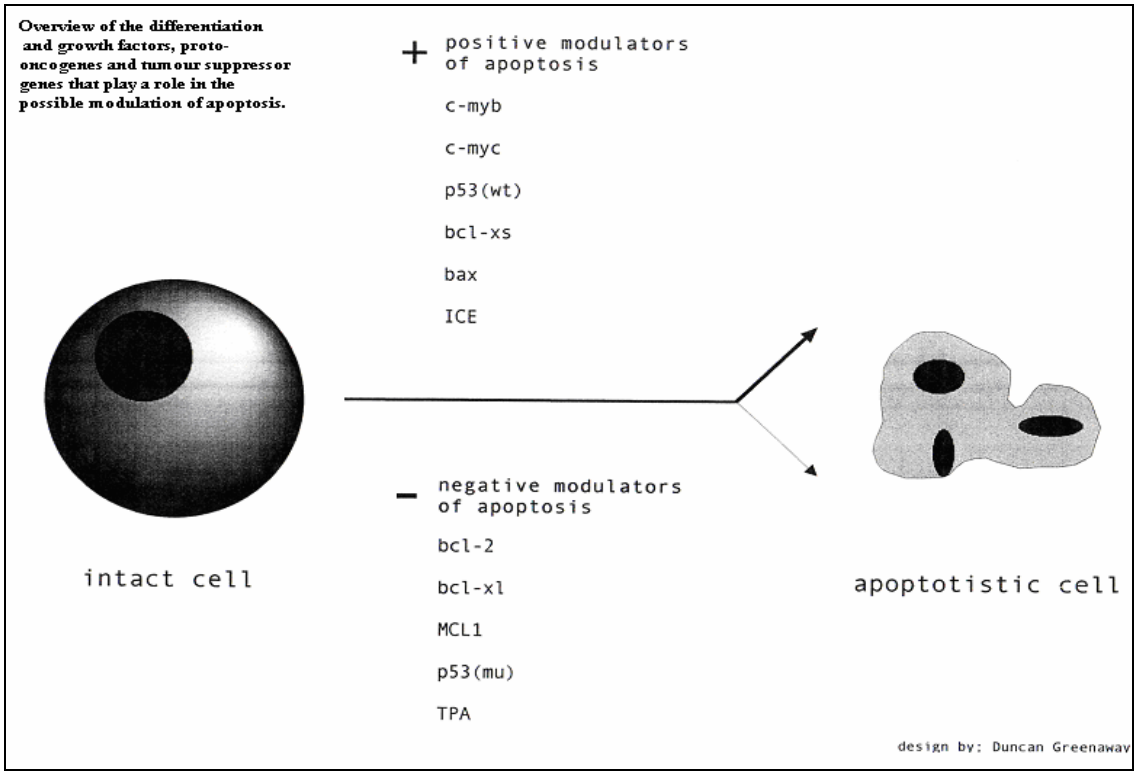
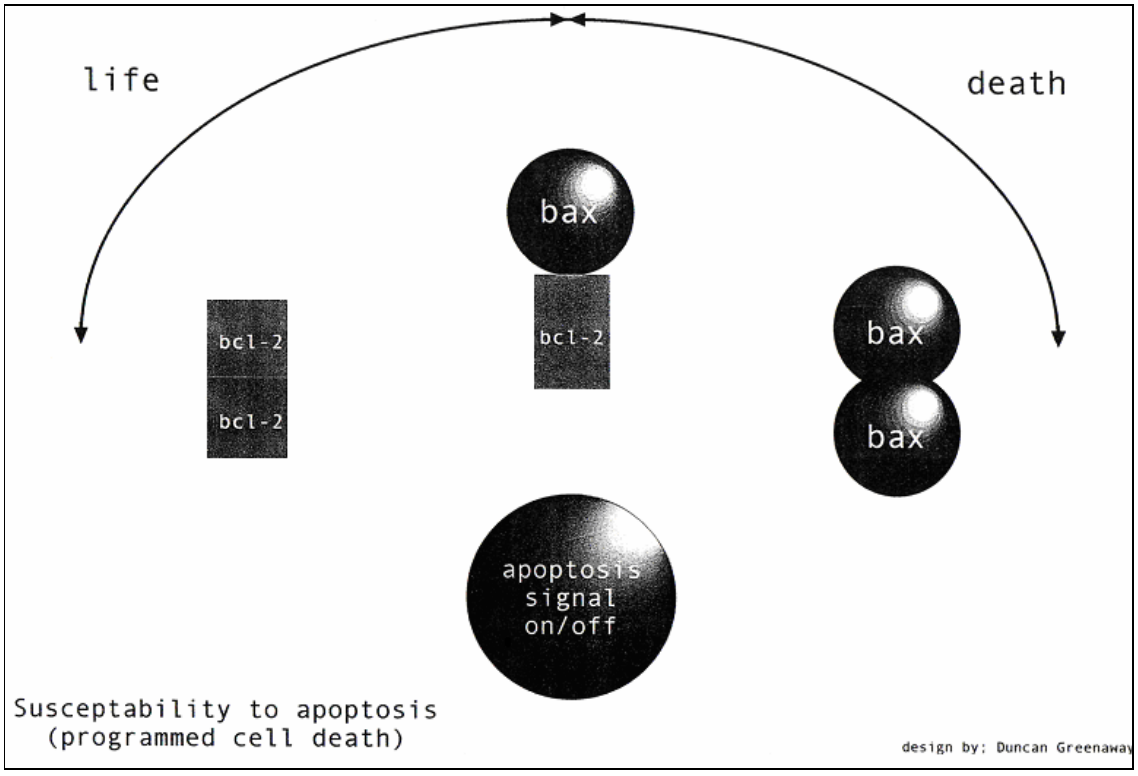

Overview of the differentiation and growth factors, proto-oncogenes and tumour suppressor genes that play a role in the possible modulation of apoptosis.
+ positive modulators of apoptosis
c-myb
c-myc
p53(wt)
bcl-xs
bax
ICE
intact cell
apoptotistic cell
− negative modulators of apoptosis
bcl-2
bcl-xl
MCL1
p53(mu)
TPA
design by: Duncan Greenaway



two types of cell death

necrosis	apoptosis
"accidental cell death"	"programmed cell death"
overwhelming insult that depletes (ATP) + prevents normal cell function	cytokines (cell death hormones) or lack of growth factors. stresses e.g. toxins, hypoxia
depletion of ATP, disruption of ionic homeostasis + mitochondrial membrane potential. nucleus remains intact but diffuse with random degradation of DNA (smearing), swelling of cell + organelles, cytosol becomes electron-lucent, non-specific proteolysis + phospholipase activity, blebbing + final rupture of plasma membrane.	ionic homeostasis maintained chromatin condensation + nucleus sometimes fragments, DNA cleavage into large fragments, no swelling of cell of organelles, cytosal condensed + may form apoptotic bodies, specific pattern of proteolysis (caspases), plasma membrane remains intact but with surface alterations. mitochondrial membrane potential usually maintained.
inflammatory	non-inflammatory