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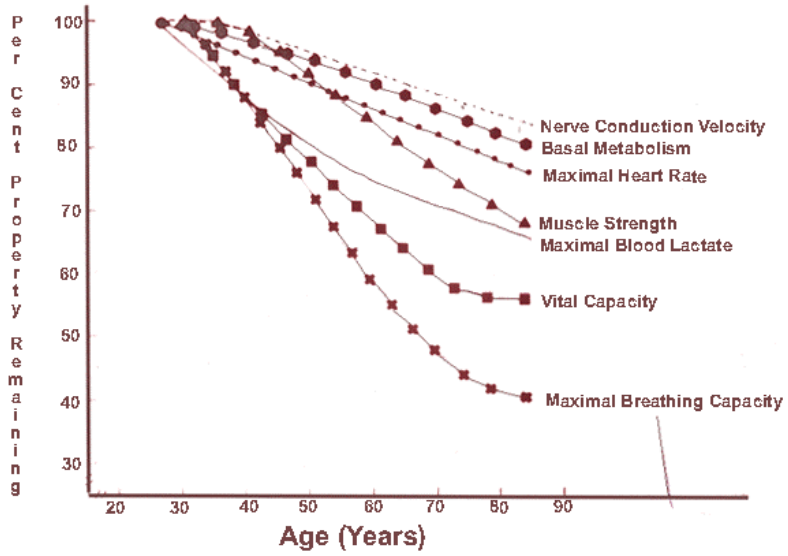
Theories of Ageing

According to *Kenney* "The physiologic hypothesis of aging and its termination by eugeric death is that the decline of function proceeds to the point where an internal environment compatible with the life of the cell can no longer be maintained".

> NOTE: Function can include adaptability, impairment, loss in reserve of physiological capacities and eventually death.



Rates of Decline of Functions With Ageing Per Decade After Apex	
Nerve conduction velocity	15%
BMR	20%

Cardiac index	30%
Vital capacity	50%
Renal blood flow	50%
Max O2	60-70%
Stature (height)	1 cm
Lean body mass	10%

We observe a loss of function with ageing:

- Functions totally lost
  - Female reproduction
  - Menstruation
  - High frequency hearing

- Structural changes - functional loss
  - Units of function lost but remaining units maintain normal function
  - Kidney nephrons
  - FT fibre number
  - Skeletal muscle diameter

- Reduced efficiency of a unit
  - Decreased conduction velocity in nerve fibres

- Control systems
  - With feedback, control loss of female sex hormones e.g. estrogen and increased gonadotropins
  - The system, when exposed to stress has reduced reserve as well

Biological ageing refers to the slow, progressive, structural and functional changes that take place at the cellular, tissue, and organ levels, ultimately affecting the performance of all body systems.

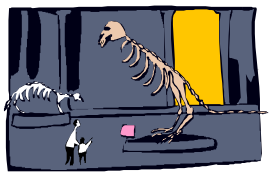
Strehler (1959) characterized ageing by four (4) main features:

i) It is destructive - compromising functionality
ii) It is progressive, and irreversible
iii) It is intrinsic, i.e. determined by internal rather than external factors
iv) It is universal, i.e. all individuals of the same species display a largely uniform ageing pattern, with all

living beings displaying the aging phenomenon.

Esposito (1983) Devised modern theoretical approaches to ageing into three (3) distinct sub-groups:

i) *CAUSATIVE MECHANISMS*, which seek to explain ageing in terms of small, sporadic, individually non-significant physiochemical changes which accumulate in complex organisms and lead to manifestation of the ageing phenomena.
ii) *SYSTEMIC EXPLANATIONS*, which characterize ageing in terms of interaction on the organ and system levels of complex organisms.
iii) *EVOLUTIONARY EXPLANATIONS*, which speculate the existence of an active genetic "ageing and death" program for each species.



History

- Hippocrates (460-377 B.C.)
  - Defined ageing as an irreversible and actual event dictated by the gradual loss of heat.
- Erasmus Darwin (Grandfather of Charles)
  - Established one of the earliest theories of ageing (1795), observed that older organisms had reduced responses to stimuli and explained as a loss of excitability over time.
- Pearl (1928)
  - Offered a variant based on the inverse relationship between metabolic rate and life expectancy, the so-called *rate of living* theory of ageing, which assumes a genetically determined metabolic potential that is used up at a rate determined by the actual metabolic rate of the animal.
- Kunze (1933)
  - Organ wear is caused by cosmic irradiation
- Henshaw (1947)
  - Demonstrated that irradiation of laboratory animals at a dosage far below that which would cause actual damage caused an acceleration of the ageing process.
- Failla (1960)
  - Observed that the number of chromosomal aberrations increased with age led to the *somatic*

mutation theory which attributes ageing to accumulation of genetic errors in postmitotic cells over the life span of the cells.

- Notes
  - Most theories developed before 1960 are considered obsolete and would have fallen under the general headings listed above but most would be considered "wear and tear" theories. For example, experimental results cast the somatic mutation theory into doubt as it was shown that the effect of any irradiation dose is considerably diminished if its application is spread out over time. As well, it is now known that there exists a chromosome repair mechanism. In order to shorten the life span of animals, irradiation doses of 12-20 times that found in a normal life span were required. This suggests that mutation effects may contribute to ageing, but do not explain the results alone.
  - The *Somatic Mutation Theory* led to the *Genetic Mutation Theory* that attributed a causative role in ageing to the same types of mutations, but in premitotic stem cells rather than in postmitotic mature cells.
  - The Somatic Mutation Theory made no mention of the source of mutation, merely that genetic errors came into being and resulted in defective protein synthesis. Proteins of erroneous structure then began to accumulate within cells. This model was popularized by Orgel (1963) who used the term "error catastrophe" to describe the process. However, extensive research on the fidelity of transcription and translation demonstrated a higher efficiency of DNA damage repair than this could.

Categories of Ageing Theories

<u>WEAR AND TEAR THEORIES</u> (Damage Theories)

Body parts (cells, organs etc.) wear out with continued use and stop functioning e.g. neurons and other cells lose ability to regenerate which results in mechanical or chemical exhaustion. Perhaps too simplistic (organ based

theory).

NOTE: These theories are based upon the fact that the damage may be extremely as well as internally casual.

- Chemical micro insults - air, food, smoke, metabolism
- Viruses, trauma, free radicals, environmental radiation, high body temperature
- Damage probably results from an accumulation of incompletely repaired insults

- **Free radical**
    - Naturally produced chemical elements from metabolic processes
    - Highly reactive and disruptive at cell level
    - Highest concentration in cell mitochondria
    - Damaging to DNA membrane and ability to synthesize proteins
    - Also produced by external exposure to radiation and chemical toxins such as ozone, hydrogen peroxide, aluminum
    - Antioxidants include vitamins A & C, beta-carotene
    - Chemical reactions (natural) produce irreversible objects in molecules
    - Unpaired electron in outer orbit
    - Could lead to damage because of accumulation of incompletely repaired insults
    - The power of this theory lies in that it does not belong or depend on any one biomacromolecule, cell, tissue, or system as the initiating step in a failure cascade

- **Cross-Linking** (Collagen 33% of body protein)
    - Tough fibrous protein holding cells together becomes stiffer with age, perhaps through a molecular process producing "cross-links" with DNA strands
    - Cross links = tangles of protein: stiffening of tissues, rigidity of blood vessels, tight ligaments and tendons, cataracts, and atherosclerosis
    - A cross-linking agent may "oxidize" cellular

components
  - Cross linking of proteins in presence of high blood glucose has been noted;
  - Receptors in pancreas (perhaps related to insulin) become less sensitive to blood glucose levels
  - Glucose can bind to proteins and nucleic acids - hence cross links
  - Note: the cross linking can be intra or intermolecular
  - This cross link formation may be caused by or stimulated by the action of oxygen free radicals

GENETIC THEORIES

Genes program ageing from birth to death; that is, cells have a biological clock. Examples include puberty and menopause. It has been suggested there may be one or more positively acting gene(s) for longevity. Genes dictate cellular ageing within the nucleus of the cell, or are expressed or repressed with normal development.

- **Programmed Cell Death** (apoptosis)
  - The Hayflick limit (1977)
  - Probably the most accepted, proven theory to date
  - Pre-programmed in genetic code i.e. cells genetically programmed to reproduce a limited number of times
  - As cellular maintenance degrades, apoptosis is turned on and a decrease in cell number occurs
  - Telomeres on ends of chromosomes (protective coating) start to degrade and lose their integrity - therefore, with loss, the number of divisions of fibroblasts in culture lessen from approximately 100 to 50 and 20 as the cell ages until the telomere is lost - then zero

- **Genetic Mutation**
  - Post mitotic mature cells
  - Somatic cells undergo mutational changes

which accelerate ageing (DNA mutations of the mitochondria)
    - Genetic structure of cell chromosome is damaged which results in synthesis of the wrong proteins and mutated cells
    - Mutagenic agents damage the orderly process of cell formation which results in an ability of cells to manufacture essential enzymes for maintenance of the cell life.
    - Best (or worst) example is found in cancer research - radiation therapy to prevent or subside the increased mutation rate.

- **Cellular Error** (Error - Catastrophe)
    - Cell death from errors in the sequence of information transfer which result in non-identical protein formation and an inability to carry out normal cell function
    - Faulty proteins accumulate in the cells - error catastrophe - which results in changes with age and ultimately cell death
    - Repair failure leads to premature cell death

Poor, poor Dolly, old before her time

by Robin McKie

SO FAR, SO GOOD. "Dolly's doing fine. The world's most famous sheep is shaping up." So ran the headlines marking the first birthday of the Earth's most distinguished clone.

In a few weeks time, Dolly will be three. But this time round, the greeting may be a little more muted - for Dolly has a problem. Her telomeres have come up short.

Sounds nasty and you might be right. Telomeres are the bits of DNA that cap the ends of the chromosomes found inside the cells of all living creatures. Every time a cell divides, it sheds a little bit of telomere. You can judge an animal's age by the lack of length of its telomeres.

And Dolly's have been found wanting. They are 20 per cent too short for a three-year-old sheep, and are more like those of a nine-year-old - a striking finding given that Dolly was cloned

from a six-year-old sheep's udder cell. In other words, she appears to have inherited all the wear and tear that would normally be found in her mother's cells.

And that is a crucially important finding for two reasons. First, it suggests that Dolly is destined to play a critical role in understanding that most baffling and dispiriting of phenomena: ageing. Scientists have wondered whether it is a cellular business. In other words, do the building blocks of living beings contain the seeds of their own destruction, and after their allotted span, just die out, triggered by telomere depletion? Or is ageing more to do with larger processes; the failure of repair mechanisms to correct the accretion of physiological flaws, for example?

Sheep when not merged with mint sauce, live for about 14 years

Dolly offers us a chance to find out. Sheep, when not merged with mint sauce, live for about 14 years. Dolly has 11 to go, and if she fails to make it, her stunted telomeres may be blamed. Equally, if she lasts through to her sheepish dotage, then scientists will also have learned an important lesson.

There is, however, a second point to be noted from the discovery of Dolly's truncated telomeres. When her creation was announced in February 1997, the world and its pundits went into a lather of pipe-sucking hysteria about the creation of human clones. It was assumed a monstrous regiment of Identikit humans would soon be marching in step towards global domination. In vain, scientists tried to point out that it took 277 attempts before they succeeded in making Dolly. Researchers have still not mastered the ability to clone mice, never mind an ape or a monkey.

And now comes news of Dolly's telomeres. Clone a 50-year-old man and by the time his son is in his teens, his cells would have the age of an OAP's. Not much cop really, or as Dolly's creators put it last week, "It's another good reason to stop talking about human cloning." And not before time...

<u>GENERAL IMBALANCE THEORIES</u>

- Found in brain, endocrine glands, or immune system
- Systems gradually fail to function

- Different rate in different systems
- Remember CNS and neuroendocrine systems are regulators and integrators of cell function and organ systems
- Failure of immune system to challenge control systems leads to susceptibility to disease

- **Neuroendocrine Regulatory Systems**
    - Integrate cells, tissue and organ activities to adapt to challenges e.g. temperature, work loads etc.
    - Hypothalamus - Pituitary Axis
        - Hypothalamus - releasing and inhibiting hormones
        - Acts on pituitary (master gland)
        - Regulates growth hormone, thyroid, glucocorticoids (metabolic rate), adrenal and sex hormones (estrogen and testosterone)
        - With age endocrine imbalances lead to physiological and metabolic imbalances

- **Autoimmunization**
    - Decline in immune system function
    - Antibodies develop that destroy cell structure and function with
        - Failure of antibodies to recognize normal cells
        - Errors in formation of antibodies
            - React against normal cells, as well as deviant cells
    - Examples include: mature onset diabetes (type II), rheumatoid arthritis, types of anaemia, certain cancers
    - NOTE: via animal research this is not a favoured thesis because of the following:
        - Ageing of lower animals with immune systems much less complex than that of humans
        - Immune cells frequently turned over versus (for example) nervous system
        - Lack of evidence of age dependence in immune function and auto aggression

ACCUMULATION THEORIES

- **Lipofuscin**, age pigment
  - An insoluble cross-linked lipoprotein accumulates in lysosomes and takes up useful cytoplasmic volume and thus impairs cellular function
  - Accumulates due to insufficient lysosomal function
  - Lipofuscin accumulates first in nerve cells and myocardial cells
  - Many consider this accumulation as the most characteristic biomarker of ageing
  - However leupeptin, a lysosomal thiol proteinase inhibitor causes accumulation of lipofuscin
  - Like granules in nerve and pancreatic cells of young animals, which demonstrates that lipofuscinogenesis is not exclusively an ageing phenomenon
    - The difference is that younger cells can eliminate it effectively, where in older cells its lysosomal decomposition slows, like any other cellular function with age

- **Free Radical**
  - Some consider the Free Radical Theory an accumulation theory.

- **Membrane permeability to potassium** (K+)
  - This is a variant of the Free Radical Theory
  - Proposed by Zsolt Nagy (1978, 1991)
  - Theory is based on the observation that membrane permeability to K+ decreases over the lifetime of an organism
  - Since the membrane is the most vulnerable structure to attack by free radicals
  - And since lipid-lipid, protein-lipid and protein-protein cross-links are continuously being formed, and since they form more efficiently in dense structures than in dilute ones, (for kinetic reasons contact between

molecules is more frequent) this affects the probability of cross-link formation (Remember: membrane proteins display the shortest half-life among all cellular proteins)

NOTE: Membrane Hypothesis of Ageing (MHA) models limit ageing affects to the cellular level only and do not attempt to explain how ageing might be occurring throughout the different systems of an organism.

DYSDIFFERENTIATIVE HYPOTHESIS OF AGEING & CANCER (DHAC)

- Cutter (1985) postulated that underlying most of the vast complexities of ageing is a primary ageing process: the drifting away of cells from their proper state of differentiation
- This is thought to be due to Aregulatory changes (not gene mutation) of highly differentiated cells (Specialized genes)
- Dysdifferentiated cells in important regulatory systems initiated a cascade of changes throughout the organism. The summation of these changes is the ageing process.

DHAC differs from other genetic-based models in three key ways:

i) The model is not dependent upon gross changes in genes themselves, lacking the gross impairment of vital functions

ii) The majority of DNA in a cell is involved with gene regulation; a higher probability of getting >hit= by a mutagen. Regulatory changes, not gene mutation, lead to dysdifferentiation.

iii) Very small changes occur in the genetic apparatus, insufficient to alter genes responsible for >housekeeping= functions, but sufficient to alter specialized >luxury= genes in highly differentiated cells

- DHAC postulates special stabilizing mechanisms for maintenance of differentiated state of cells. Such mechanisms are considered more effective in longer-

lived species and similar in mammalian species. Species differences are likely quantitative rather than qualitative.

- There may be a relationship with antioxidant capability
- In humans, the pituitary, hypothalamus, and other regulatory regions of the brain have highly differentiated characteristics
- Therefore, small changes would result in massive functional changes (defective) in an organism dependent upon them
- *DHAC suggests a common mechanism behind ageing and cancer: cell dysdifferentiation.*
- Properties consistent with a dysdifferentiated state include:
    - Synthesis of foreign proteins
    - Loss in sensitivity to normal controlling elements in cell division
    - Altered isozyme patterns
    - Shifts in membrane properties
- IN FACT ageing shows cell types of one tissue are found in others (metaplastic cells) and
    - Altered membranes
    - Altered proteins
    - Autoimmune
- Arguments in favour of the DHAC Theory:
    - Older cells do show a greater tendency toward dysdifferentiation with age
    - metaplastic cells - intestinal cells found in stomach lining
    - Membrane composition and properties become altered, abnormal proteins appear
    - Age-dependent increase in autoimmune phenomenon

<u>MISCELLANEOUS THEORIES</u>

- **Caloric Restriction**
    - It has been observed that laboratory animals with restricted diets (60%) have extended lifespan
    - The mechanism is unclear

- **Dolly**
  - Her telomeres have come up short
  - Dolly was cloned from a 6 years old ewe and today she is three but her telomeres are comparable to a 9 year old
  - Dolly appears to have inherited all the wear and tear found in her mother's cells

- **London Free Press Article** (Dec. 27/99 Section C page 1)
  - The slow downhill slippery slope of ageing 45
  - Disorders to consider: sleep, brain, skin, eyes, smell, libido, feet, urination, bones
  - Add to this muscle, heart, hearing, taste, fat, nerves, endocrines, organ function
  - That is the inevitable - ageing with or without taxes!