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**Research Article**

# THE AGING PATIENT: PULP CAPPING IN THE ELDERLY

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**ABSTRACT**

Molecular and cellular changes occur during tooth aging. Odontoblasts, derived from ecto-mesenchymal cells of the dental papilla, are implicated in reactionary dentin formation. Direct or indirect pulp treatments are acceptable procedures for reversible pulp inflammation, and sealing leakage-free restorations. *In vitro* and *in vivo* experiments leading to reactionary or reparativeodontogenesis demonstrate that pulp cells may differentiate into new odontoblast-like cells implicated in pulp repair. The rationale for the use of calcium hydroxide (CH) and zinc oxide-eugenol paste (ZOE) evidences that these treatmentsarereserved to asymptomatic teeth. The ideal dressing material should be bactericidal, harmless to the pulp and surrounding structures, and should not interfere with the physiologic process of root resorption. Due to the deposition of successive new layers of reactionary dentin, the pulp volume is gradually reduced, asymmetrically. The highest reduction occurs in the occlusal roof, followed by the furcation zone. Less reactionary dentin is formed along the lateral walls. In association with the closure of pulp horn exposure, reparative dentin formation results from the transformation of pulp cells into odontoblast-like cells. The use of for mocresol was considerably decreased, whereas better results were obtained with MTA (Mineral Trioxide Aggregate) and/or with other pulp-capping materials. Internal root resorption, a finding seen both after ferric sulphate and for mocresol treatment, was not observed in MTA capped teeth. Due to the narrowing of the pulp in the root, endodontic treatments gain difficulties in the aging patient.



## INTRODUCTION

### *The aging patient: causes of aging, cellular mechanisms and theories*

Studies of aging have expanded becauseit was stimulated by 1) the lengthening of the average life span, 2)and the significant lengthening of the maximum human life span, 3) by the increasing percentage of elderly in the population, 4) and the increasing proportion of national health expenditures utilized by the elderly. According to the "programmed" theories, aging depends on biological clocks regulating the timetable of the life span through the stages of growth, development, maturity, and old age: this regulation would depend on genes sequentially switching on and off signals to the nervous, endocrine, and immune systems responsible for maintenance of homeostasis and activation of defense responses. The "error" theories identify environmental insults to living organisms that induce progressive damage at various levels (Weiner & Timers, 20 03).

Aging is the most commonly used term referring to post-maturational processes, leading to diminished homeostasis and increased organ vulnerability. Senescence and aging are used interchangeably, however senescence is the more correct term. Normal somatic cells cease replicating (Martin, a review- parts I and II, 1977). The life spans of human diploid embryonic lung fibroblast-like cells are 50 ± 10 mass population doublings. Replication ceases after 50 ± 10 doublings. Cell type-specific mitotic cell cycle inhibitors (or chalones) have been purified and characterized. Key proteins and pathways that regulate lifespan are members of the sirtuin family of NAD-dependent enzymes proteins, the Insulin/Insulin-like Growth Factor (IGF) signaling (IIS) pathway, including insulin and insulin-like peptides regulating development, body size and cellular growth. This includes the mechanistic target of Rapamycin (mTOR). The mTOR kinase is a serine/threonine protein kinase belonging to the phosphoinositide-3-kinase-related family highly conserved among eukaryotes, inhibited by the immunosuppressive drug rapamycin (Pan & Finkel, 2017). A phosphatidylinositol-3-OH kinase was cloned by the

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"longevity gene" *age-1* (Martin 2011). Cells could be essentially "immortalized" *via* transfected telomerase. Investigators haveshown that siRNA knockdowns of just two loci [(1) *Rb*and (2) an alternative reading frame of *Ink4a*)] was sufficient to induce the dedifferentiation of post-replicativeskeletal muscle myocytes to form mitoticallyactive myoblasts capable of making multinucleatedskeletal muscle.Sirtuins are a familyof $NAD^+$-dependent protein deacetylases. Intrinsic mutagenesis is regulated by DNA polymerases, DNA repair enzymes, activating enzymes for pre-mutagens (e.g., aryl hydrocarbon hydroxylases), inactivating enzymes for mutagens, "scavenger" enzymes that preferentially degrade abnormal proteins (including various proteases).The average lifespan (also known as life expectancy) is usually stated to be 90-100 years. In the United States an average life expectancy is about 80 years in 1980 (Troen, 2003).

**Table 1** Characteristics of Aging

1. Increased mortality with age after maturation.
2. Changes in biochemical composition in tissues with age (glycation and oxidation).
3. Progressive decrease in physiological capacity withage.
4. Reduced ability to respond adaptively to environmental stimuli with age.
5. Increased susceptibility and vulnerability to disease

***Mechanisms/Causes of aging***

Three categories of genes seem to be involved in senescence: 1) those that regulate somatic maintenance and repair, 2) negatively pleiotropic genes that enhance early survival but are disadvantageous later in life (antagonistic pleiotropic), 3) harmful late-acting mutations upon which little evolutionary selection is exerted (Johnson *et al*., 1999).

***Stochastic Theories***

Aging may be caused by random damage to vital molecules. Stochastic theories may be due to somatic mutations and DNA repair, error-catastrophe, protein modification, free radical (oxidative stress)/mitochondrial DNA. In addition, developmental-genetic theories play roles in the aging process. This is the case for longevity genes, such as accelerated aging syndromes, neuroendocrine theory, immunologic theory, cellular senescence and cell death (necrosis and apoptosis). Mutants with an increased lifespan revealed various genes playing relevant role: *age*-1 alters aging rate, *daf*-2and *daf*-23activate a delay in development, *spe*-26 reduces fertility, and *clk*-1 alters the biological clock.

Alterations with aging of molecular events may lead tocellular alterations, and contribute toorgan and systemic failure with evolutionary implications for reproduction and survival.

In complex multicellular organisms, the study of interactions among intrinsic (genetic), extrinsic (environmental), and stochastic (random damage to vital molecules) provides a fruitful approach conducive to a comprehensive and realistic understanding of the aging process. They include evolutionary, gene regulation, cellular senescence, free radical, and neuro-endocrine-immuno theories.

**Table 2** Classification and brief description of main theories of aging

| Biological Level/Theory | Description |
|---|---|
| Evolutionary | |
| Mutation accumulation* | Mutations that affect health at older ages are not selected against. |
| Disposable soma* | Somatic cells are maintained only to ensure continued reproductive success; after reproduction, soma becomes disposable. |
| Antagonistic pleiotropy* | Genes beneficial at younger age become deleterious at older ages. |
| Molecular | |
| Gene regulation* | Aging is caused by changes in the expression of genes regulating both development and aging. |
| Codon restriction | Fidelity/accuracy of mRNA translation is impaired due to inability to decode codons in mRNA. |
| Error catastrophe | Decline in fidelity of gene expression with aging results in increased fraction of abnormalproteins. |
| Somatic mutation | Molecular damage accumulates, primarily to DNA/genetic material. |
| Dysdifferentiation | Gradual accumulation of random molecular damage impairs regulation of gene expression. |
| Cellular | |
| Cellular senescence-Telomere theory* | Phenotypes of aging are caused by an increase in frequency of senescent cells. Senescence may results from telomere loss (replicative senescence) or cell stress (cellular senescence). |
| Free radical* | Oxidative metabolism produces highly reactive free radicals that subsequently damage lipids, |
| Wear-and-tear | Accumulation of normal injury. |
| Apoptosis | Programmed cell death from genetic events or genome crisis. |
| System | |
| Neuroendocrine* | Alterations in neuroendocrine control of homeostasis and their results in aging-related physiologicalchanges. |
| Immunologic* | Decline of immune function with aging results in decreased incidence of infectious diseases but an increased incidence of autoimmunity. |
| Rate-of-living | Assumes a fixed amount of metabolic potential for every living organism (live fast, die young). |

(FromWeiner&Timers 2003)

***Molecular theories***

The insulin-like signaling pathway regulates life span in worms, flies and mice. Genetic rather than environmental or socio-economic factors have a genetic component. This gene was identified in a locus located on chromosome 4 that may contain gene(s), which contribute topromote longevity (Johnson *et al*., 1999).

Cell senescence/telomere theory limits the replicative capacity after a number of cell divisions. Cellular senescence may also occur in response to distinct molecular events. Replicative senescence results ultimately from loss of telomeres. With each cell division, a small amount of DNA is lost at each chromosome end. Activation of the telomerase enzyme regenerates telomeres, prevents replicative senescence, and

immortalizes human primary cell cultures (Oeseburg *et al*., 2010). Telomeres have been postulated as an universal biological clock that shortens in parallel with aging in the cells. Telomeres are located at the end of chromosomes and consist of an evolutionary conserved repetitive nucleotide sequence ranging in length from a few hundred base pairs to several kilobase pairs in vertebrates. Telomeres are special deoxyribonucleic acid structures (DNA) that "cap" the end of chromosomes in conjunction with specialized proteins, the telomere-shelterin complex. Telomere protects the chromosomes from erosion and end-to-end fusions shorten with each mitotic cycle resulting in cumulative telomere attrition during aging. Females have longer telomeres than men. Southern blot, polymerase-chain reaction (PCR) based techniques and in situ hybridization is the traditional method are still considered as the gold standard. Telomerase reverse transcriptase (TERT) and dyskerin increases the stability of the complex. Experimental evidence suggests that telomere shortening, uncapping, and cellular senescence results in an "aging" phenotype (Hayflick, 1980).

The tumor suppressor protein p53 is a key regulator of the cellular response to genome crisis. The type of p53-dependent cellular response to radiation-induced DNA damage (cell arrest, apoptosis, or senescence) is dependent on the type of cell examined. Mice mutated for p53 have an increase of cancer. The tumor–suppressor protein p53 is required for the early aging phenomenon-type. Treatments that inactivate p53 in senescent cells can trigger re-entry in the replication cycle and cell proliferation.Free radical theory remains controversial to this day.

### *Molecular Biology of Aging*

Aging is defined when two criteria are meet. Firstly, the probability of death increases with the age of the organism. Secondly, characteristic changes in phenotype occur in all individuals over time due to limiting processes. Identification of key genes and pathways follows a series of damages due to reactive oxygen species (ROS). It may be generated bycell metabolism, genome instability, genetically programmed extension mechanisms, cell death, and systematic aging.

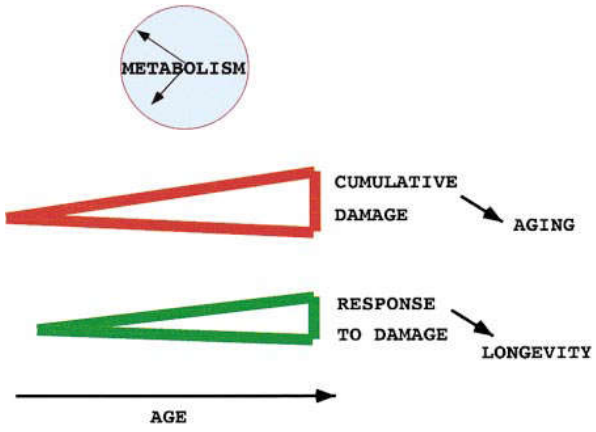


**Figure 1** Life span is determined by the balance of two opposing processes: 1) accumulation of damages causing aging, and 2) compensatory responses limiting or repairing the damage, thus promoting longevity (Johnson et al., 1999).
Mutation clk-1 slows developmentand rhythmic behavior. It extends life span. Clk-1 is a homolog of yeast CAT5, a gene involved in the synthesis of coenzyme Q, a component of the mitochondrial electron transport chain.

***Genome instability:*** Rearrangements and changes in the chromosome number have long been proposed as causes of aging. Ribosomal DNA constitutes a strong causal link between genome instability and aging. Cell division is asymmetric, giving rise to a large mother cell and smaller daughter cells. Telomeres, the repeated DNA sequences at the end of linear chromosomes, are unable to be fully replicated by DNA polymerases. Telomeres shorten with cell division, unless maintained via telomerase, an enzyme adding telomeric repeat sequences to chromosome ends. It has been proposed that telomere shortening could be a molecular clock that signals the eventual growth arrest, termed replicative senescence observed in all cultured primary human cells. Elevated secretion of metalloproteases by senescent fibroblasts may degrade collagen.

***Mitochondrial theory of the aging process:*** Scientists primarily worked with two kinds of pluripotent stem cells, isolated from the inner mass of blastocysts, and non-embryonic somatic or adult stem cells found in various tissues. Aging affect the function properties, leading to cell death (apoptosis), senescence (loss of cell division and growth), or loss of regenerative potential. The regenerative power appears to decline with age, however they have a remarkable capacity to regenerate. In mammals, spontaneous and extrinsic mutational events occur on DNA on daily basis. There is an accumulation over time of some of the mutated DNAs in aging cells compared to young cells. Telomere shortening causes reduction in life span.

Mitochondria are the main source of cellular adenosine triphosphate (ATP) that plays a central role in a variety of cellular processes. Epigenetic refers to changes in gene expression, which are heritable without affecting the DNA sequence. Changes in DNA methylation and histone modifications influence the aging process. Retrotansposons are mobile DNA elements that can induce genetic instability and cause cellular dysfunction implicated in the aging process and aging-associated diseases (Asi *et al*., 2017).

***Systemic control of aging:*** Over the past two centuries, human life expectancy has more than doubled in developed nations due to advances in medicine and public health.

Figure2 is an illustration of the System-based theories of aging. Cell die via mechanisms that range from necrosis to apoptosis, which is an active and ordered process. This pathway involves activation of a family of proteases, termed caspases and nucleases, leading to the controlled degradation of cellular structures, followed by the removal of membrane-bound debris by phagocytic cells.

### *System-based theories of aging*

***Neuroendocrine and immune theories:*** The neuroendocrine theory propose that aging is due to changes in neural and endocrine functions that play crucial role in

1. Coordinating communications and responsiveness of organs or whole body to the external environment.
2. Programming physiological response to environmental stimuli,
3. Maintaining an optimal functional state for reproduction and survival while responding to environmental demands.

They regulate "biological clocks". The perception of the hypothalamus-pituitary - adrenal axis is to muster the physiological adjustments necessary for the preservation and maintenance of the internal homeostasis.

The so-called "disease of adaptation" and death is a theory. Aging would result from a decreasing ability to survive stress. Hypothalamus regulates 1) several important nerve functions, 2) behaviors, and 3) endocrine functions. With aging, the reduction of sympathetic responsiveness is characterized by 1) a decreased number of catecholamine receptors in peripheral target tissues 2) a decline of heath shock proteins, and 3) a decrease capability of catecholamine's to induce heath shock proteins.

The insulin/insulin-like growth factor-I*(IGF-I*) peptide and *Daf*- 2 gene are homologs of the human insulin and IGF-I receptor, *unc-64* and *unc-31*.They are homologous to human synthaxine and cataboliteactivator proteins that are involved in the release of neurotransmitters at the synapse.*Age-1* is related to a conserved phosphoinositol-3-kinase that responds toinsulin receptor activation, and *Daf-16* is the homologof the human fork head box, class-O transcription factor.

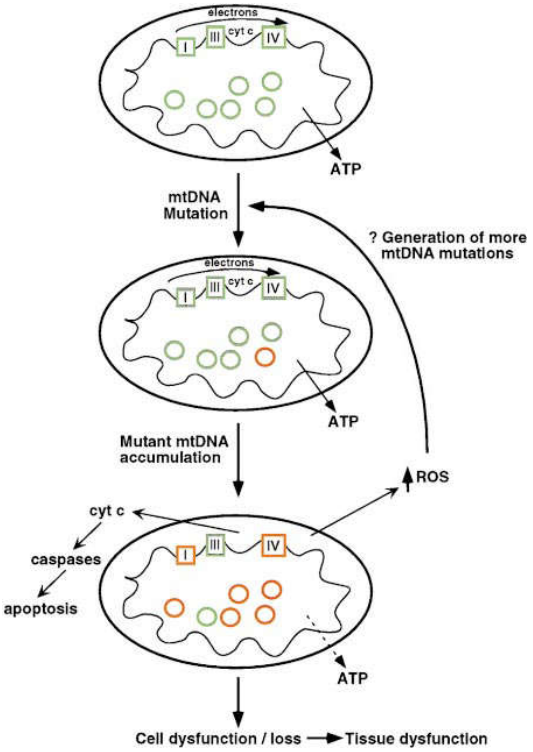


**Figure 2** Neuroendocrine-immuno theory
Otherfunctions, for example the activities of several types oflymphocytes (natural killer and dendritic cells, and/or macrophages)and the complement system, are well preservedin healthy centenarians. However, the ultimate causes of aging remain unknown.

There is a range of treatment options for the management of the pulp in extensively decayed teeth. Direct or indirect pulp capping, pulpotomy or pulpectomy are required. Pulp vitality is maintained in adults (Miyashita *et al*., 2008). Can we conservealive a dental pulp? Does it worth to be so? (Stanley 1989).

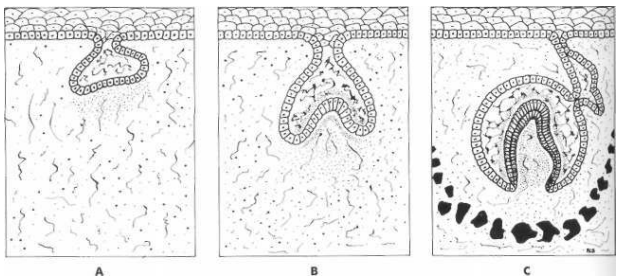


**Figure 3** Tooth development and aging is implicated in direct and indirect dental pulp capping

Diagrammatic representation of A (the bud), B (the cap) and C (the bell stages of tooth development) showing the outer enamel epithelium, stellate reticulum, inner enamel epithelium, dental papilla, cervical loop, successional lamina and dental sac.

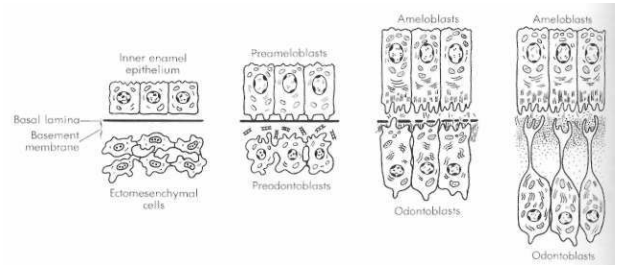


**Figure 4** Diagrammatic representation of the successive stages of odontoblast differentiation.

Direct capping is a method for treating exposed vital pulp, which facilitate the reparative dentin formation and maintain vital the dental pulp: caries, mechanical sources and trauma (Komabayashi *et al*., 2016). Growth factors and extracellular matrices should be considered. Bone sialoprotein, matrix extracellular phosphoglycoprotein (MEPE), amelogenin and dentin phosphophorynmay induce the formation of reparative dentin. The consequences of pulp exposure from caries, trauma or tooth preparation are severe, with pain and infection (Hilton, 2009).

### *The aging pulp*

Aging implies a substantial decreased volume in the dental pulp. Clearly, in young teeth, the floor includes the furcation zone, lateral walls, and occlusal roof. These surfaces are already formed. They are reduced in the occlusal direction (reduction in height). During aging, secondary dentin is formed at slower rate than on the occlusal surface. Far less is formed in the lateral walls. Variations are detectable among species.

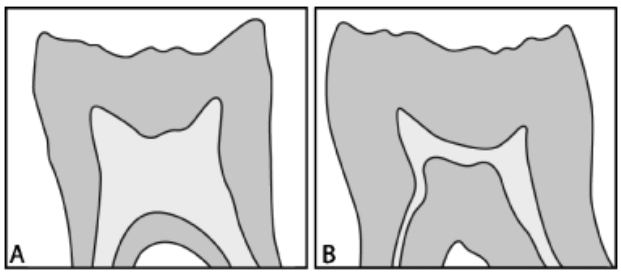


**Figure 5** Difference in the pulp volume between A (a very young teeth) and B (a very old teeth).

There is a decrease in the occlusal roof and even more at the furcation area. Pulp stones are formed either in the central part of the pulp, or as false denticles bound to the lateral walls.

They are located as diffuse mineralization, adding to endodontic difficulties. The mesio-distal diameter remains stable, pulp horns staying as permanent structures despite a general reduction of the pulp volume and anasymmetric closure of the pulp (Goldberg 2017).

Nerves and blood supply becomes more fibrous and less cellular in the pulp tissue. Mediators of inflammation include lymphocytes, plasma cells, and macrophages. Specific and non-specific mediators (prostaglandins, thromboxanes, leukotrienes, histamine, bradykinin, serotonin, interleukins) are released by cells within the pulp. Branches arising from the maxillary and mandibular divisions of the trigeminal nerve contain both large myelinated A-δ and also A-β fibers. They form the Raschkow plexus beneath odontoblast cell bodies and between sub-odontoblastic cells (Hoehl's cells). Nerves are present within the first 150 microns of the inner dentin layer, butnever present in the dentin outer layers.

***Age estimation from physiological change of teeth: a reliable age-marker?***

Modified Gustafson's criteria were used for estimation of age: degree of attrition, root translucency, secondary dentin deposition, cementum apposition, and root resorption (Singh *et al*., 2014). Age calculation results from Tooth Cement Annulations (TCA) and it is possible to examine the correlation between the estimated age and the numerous incremental lines in human cementum. Correlations were made by calculating cementum lines and the thickness of secondary dentin (Gupta *et al*., 2014).

***The aging pulp (Allen & Whitworth, 2004)***

Old pulps are described as being "sclerosed" or "calcified". Pulp space is reduced by reactionary and reparative dentine (formerly classified as tertiary or irritation dentine), laid down to reduce the porosity of dentinal tubules. It is predicted that 25% of the population in developed countries will be over the age of 65 years by 2025.Primary dentine is the original tubular dentin formed prior to eruption of a tooth. Secondary dentine is formed after completion of root formation. Tertiary dentine is found in dentin that has been subjected to trauma or irritation (Tsurumachi *et al*., 2008).

Developmental dentine is classified as orthodentine, the tubular form of dentine found in the teeth of most of the dentate mammals.

- **Mantle dentine** is located immediately subjacent to the enamel or cementum. The width of mantle dentine is estimated to vary between 30 and 100 micrometers. The hyaline circumpulpal layer contributes also to the formation of the thin outer layers. This superficial layer is subjacent to the ameloblast layer (sub-ameloblasts layer) and to the Hopewell-Smith layer (8-15µm). Immediately beneath, the granular Tomes's layer displays calcospherites or globular structures, together with the bending of thin minute tubuli. The peripheral dentin is atubular, whereas circumpulpal dentin is tubular.
- **Circumpulpal dentine** constitutes the major part of developmental dentine. Collagen fibrils are closely packed and form an interwoven network. In coronal dentine, the tubules have a S-shape as they extend from the DEJ to the pulp. Dentine may be atubular in the primary dentin, or tubular in the secondary dentin.
    1. Peritubular dentine is lining the periphery of the tubules, whereas
    2. Intertubular dentine is formed between the tubules. It is highly mineralized and more quickly dissolved in acids than intubular dentine. Intertubular dentine constitutes the bulk of circumpulpal dentine, consisting mainly of collagen fibrils having diameters of 500 to 1000Å. The collagen fibrils are oriented approximately at right angles to the dentinal tubules.

Dentinal sclerosis is easily recognized in histologic ground sections because of its translucency, both matrix and tubules being mineralized. There is a decreased permeability of dentine. Peritubular dentine formation is accelerated. This form represents a physiologic process, appearing in the apical third of the root and developing as a function of age. Dentinal tubules are filled with mineral precipitation of hydroxyapatite and whitlockite within the tubules. They constitute "pathological sclerosis". Interglobular dentine refers to unmineralized globules failing to coalesce. In vitamin D-resistant rickets and hypophosphatasia, large areas of interglobular dentinebeing the characteristic feature of this structure (Goldberg, 2014).

Dental erosion and abrasion, demastication, attrition and abfraction provide overview of tooth wear. Non-destructive processes affecting the teeth include all these factors. They are based on etiology (extrinsic, intrinsic, idiopathic), on clinical severity (classes I to III), on pathogenic activity (manifest or latent) or on localization (perimolysis). Interactions between erosion, abrasion, demastication, attrition, and abfraction are linked to teeth aging (Imfeld, 1996). Several specific features facilitate the identification of lesions in old teeth.

1. In erosion, some healthy enamel is generally preserved on the palatal/vestibular cervical margin; when erosion occurs on the occlusal surfaces.
2. In attrition, the pattern of tooth substance loss matches the morphology of the teeth in the opposing arch.
3. Abrasion lesions do not show wear facets, but non-anatomically specific wear areas, and they are usually associated with gingival and periodontal recession.
4. Abfraction usually takes the form of a wedge-shaped lesion located at cervical level. (Levrini *et al*., 2014).

***Pulp cell composition***: Macrophages, and dendritic cells are found in many tissues including the epidermis. They are called Langerhans' cells. They are antigen-presenting cells and characterized by dendritic cytoplasmic processes and by the presence of class II antigens. They are implicated in phagocytosis. The processed antigens are weakly phagocytic. Together with lymphocytes (T- and B- lymphocytes in the normal pulp from human teeth), T8 (suppressor) lymphocytes are the predominant T-lymphocytes. The presence of macrophages, dendritic cells, and lymphocytes indicates that the pulp is well equipped with the cells required for the initiation of immune responses. Undifferentiated mesenchymal cells give rise to new fibroblasts. Mast cells are weakly distributed in connective tissues. They contain heparin, an

anticoagulant, as well as histamine, an anti-inflammatory mediator.

Fenestrations are implicated in a rapid transport of fluid and metabolites from the capillaries to the adjacent odontoblasts. Arterio-veinous anastomoses are present both in the coronal and radicular portions of the pulp. Areas irrigating successive pulp domains about 180-200 micrometers have the capacity to constitute arterio-veinous shunts. Alongside the lateral pulp border, capillaries may drain a thrombus, and favor the reactivation of vascular repair.

Reparative dentin is formed at the periphery of the coronal pulp chamber by the odontoblasts. This dentin may be tubular or in some cases atubular. As it is the case for bone, odontoblasts may be isolated within osteocyte forming lacuna, with minute processes forming a thin network. Dentin containing cells being of the osteodentin type.

Reactionary dentin is associated to a pulp exposure. Pulp wound can stimulate pulp closure. Pulp cells differentiate into odontoblast-like cells. They adopt an odontoblastic shape, and become elongated fibroblastic-like structures. These odontoblast-like cells migrate toward the exposed pulp horn and become elongated. A bone-like structure fills the top of the pulp exposure. Again this is a tubular structure, filling the top of the pulp horns, and expressing extracellular bone molecules, and not dentin matrix molecules.

***Vascularization***

**Figure 6**: Vascular network in the radicular pulp showing the terminal capillary network. Capillaries are organized as a fisher net in the outer region of the root.

**Figure 7** Subodontoblastic terminal capillary networks (TCN) (AL arterioles and VL (venules) of a coronal canine pulp.

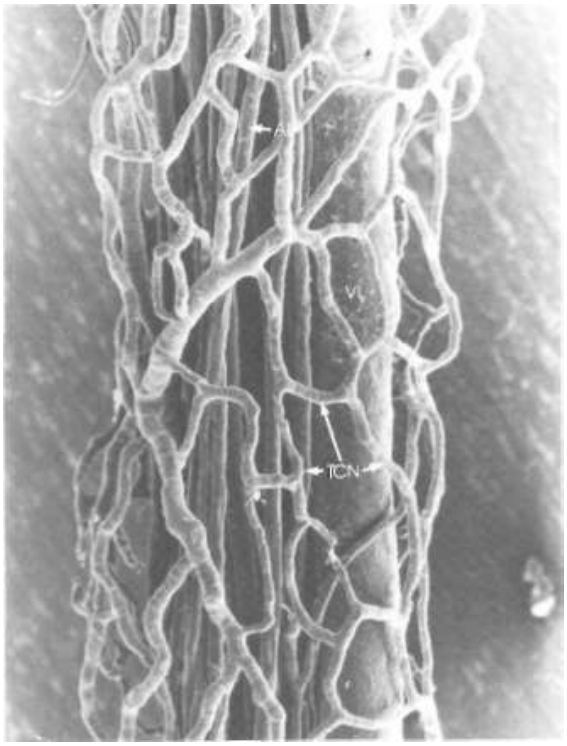


**Figure 6** In the root, capillaries form a network, leaving empty spaces, filled with intracellular/extracellular network. The fisher-like network favors the basal diffusion of the ground substance.

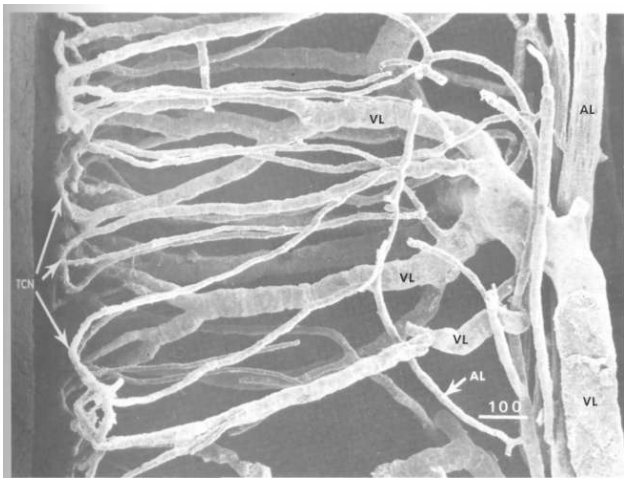


**Figure 7** Capillaries in the coronal pulp. Terminal capillary network (TCN). Bar: 100 micrometers. U-turn loop. The functional regulation of the pulpal blood may be complex.

***Lymph vascularization***

The presence of lymphatics capillaries has for a long time be a matter of debate, now clarified by light and electron microscopic methods (Trowbridge & Kim 1994). Unclosed gaps junctions between endothelial cells are widely open, displaying large intercellular gap junctions, allowing dentinal fluid leakage. The basement membrane covering the capillaries is discontinuous, and this favor plasmatic blood diffusion between the dentinal lymph, outward and/inward flow in the tubules, and the pulp lymph vascularization directed toward the lymph ganglions of the jugular chains.

Pulp stones occur more in the coronal region, but are also found in the radicular pulp (Goga *et al*., 2008). Pulp stones (calcospherites) are classified as true and false pulp stones. They may be diffuse or amorphous. They are in close association with blood vessels. Laminations around blood vessels reflect also a hierarchical organization.

Pulp stones and canal calcifications may be manifestations of degenerative aging. The main changes in dentine associated with aging are an increase of peritubular dentine, dentinal sclerosis, and the number of dead tracts? There is a general decrease in dentinal permeability as the dentinal tubules become progressively reduced in diameter.

Pulp stones and canal calcifications may provide evidencesof degenerative aging. The main changes in dentine associated with aging are the increase in peritubular dentine. There is a general decrease in dentin permeability as the tubules aregradually reduced in diameter.

***Terminology of pulp stones***

Pulp stone True Made of dentin and lined by odontoblasts False Formed by degenerating cells which mineralize Free Stone not related to the pulp space wall, surrounded by soft tissue Adherent Stone attached to the wall of pulp space, not fully enclosed by dentin. Embedded Stone enclosed within canal wall, less attached than above Denticle Alternative term for pulp stone Fibrodentine Produced by fibroblast-like cells, prior to generation of a new generation of odontoblast-like cells.

Dystrophic calcification Inappropriate biomineralization of the pulp in the absence of mineral imbalance. (Trowbridge & Kim, 1994; Goga *et al*, 2008; James 2008).

***Pulpal calcifications***

Six basic appearances were categorized on the basis of typical SEM photomicrographs of the superficial dentinal pulpal wall. Type I- Partially fused calcospherites: they were observed on the buccal and lingual surfaces of dentinal pulp walls. Type 2- almost or completely fused calcospherites. They seemed to be scarcely present or decreased in number in older teeth. Type 3- Network-like mineralized appearance. They form a mesh. Type 4- Ridge-like mineralized appearance. They are found on the proximal surface of dentinal pulpal walls near the apical-root location, especially in older teeth. Type 5- Spherically mineral appearance. The small spherical minerals are seen to coalesce in the apical region, especially in old teeth. Type 6- Structureless mineralized appearance, located in the apical location especially in old teeth.

***Innervation***

Nerves penetrate the pulp through the apical foramen. They are ascending in the central part of the pulp, and fan out in the subodontoblastic plexus (Raschkow 's plexus), cross the odontoblastic intercellular junctions and penetrate into and cross the pre-dentine. Later they are found in the first 150 micrometers of the inner dentin layer (Goldberg, 2014).

Acellular and cellular cementum forms around the apical dentin. Alternating layers of cellular and acellular cementum may be found, forming the cellular mixed stratified cementum (CMSC). Incremental lines contribute to increase the overall volume of cementum. Ring-like layers are added annually. The shape of this additional tissue appended to the root display the outlineof a gulf club. Hypercementosis (cementum hypertrophy, cementum hyperplasia) reflects aging processes in the apical region of the roots. Myelinated and unmyelinated axons look degenerating. They appear swollen and lack neurotubuli, with a reduced population of microfilaments and mitochondria.

***Indirect & direct pulp capping: dental biomaterials***

Pulp inflammation is the result from direct pulp capping, the initial horn exposure being due to mechanical reasons rather than caries. Asymptomatic pulp exhibits no clinical nor radiological signs of pathology. Pulp bleeding after the initial exposure occurs prior to the placement of the pulp-capping agent. Itreduces the capacity for pulp repair. In addition, contamination of the exposure site due to bleeding prevents subsequent bacterial exposure. Saline, sodium hypochlorite at concentrations ranging from 0.12% to 5.25%, hydrogen peroxide, ferric sulfate and chlorhexidin contribute to efficient pulp capping.

Direct pulp capping biomaterials have been used in close association with direct pulp capping. Zinc Oxide Eugenol (ZOE) has been used in dentistry as bases, liners, cements and temporary restorative materials. Biomaterials such as Glass Ionomer (GI) / Resin-Modified Glass Ionomer (RMGI) have also been used. It should be noted that most components of adhesive systems are cytotoxic. MTA in the form of tricalcium silicate, dicalcium silicate and tricalcium aluminate, with the addition of bismuth oxide playing a role to increase the cement radio-opacity, white or grey, are contributing to seal the tooth structure. MTA is superior to calcium hydroxide for pulp capping on mechanically exposed human teeth. MTA-like materials are composed of artificial synthetic calcium silicates instead of a hydraulic Portland cement. Of note, calcium hydroxide is the gold standard for pulp capping.

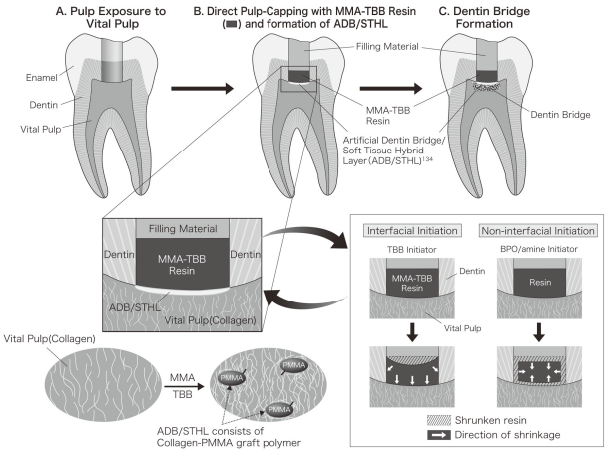


**Figure 8** Indirect and direct pulp capping biomaterials.

When normal human embryonic fibroblasts are cultured *in vitro*, 50 ± 10-population doublings occur. This maximum potential is diminished in cells derived from older donors and they appears to be inversely proportional to their age. The 50-population doublings limit can account for cells produced during a lifetime. The limitation on doubling potential of cultured normal cells is also expressed *in vivo*. A direct correlation may be established between the mean maximum life spans of several species and the population doubling potential of the cultured cells (Hayflick, 1980). The study of events leading to functional losses in cultured normal cells may provide useful insights into the biology of aging (Fuks, 2002). Histologic evaluation of direct pulp capping was carried out 14 days after the surgical procedure. The sections were evaluated for pulp tissue disorganization (PTD), and also for inflammatory cell infiltration (ICI), dentin bridge formation (DBF), and bacterial penetration (BP). The dental pulps showed various degree of tissue disorganization, inflammatory cell infiltration, dentin bridge formation and bacterial penetration, depending on the capping material. There were no complete dentin bridges. On the opposite, pulps capped with MTA showed no disorganization or/and inflammatory cell infiltration. Dentin bridges were complete in all except one specimen (Shinkai *et al*., 2017).

Regenerative endodontic procedures can be defined as biologically based procedures aiming to replace damaged, diseased, or missing structures, which restore the normal physiologic functions of the pulp-dentin complex. They play important roles in permanent immature traumatized teeth (Garcia-Godoy & Murray, 2011). Progresses in this field have been rapid. The regenerative endodontic procedures include revascularization, apexogenesis, and /or partial pulpotomy.

***Regenerative procedures***

Osteogenic differentiation of human dental pulp stem cells is due to antibacterial properties of the anti-bacterial resin monomer (MAE-DB). Portland cement interferes also with the

viability, adhesion, migration according to the wound healing, and Trans well migration assay. They all induce dentin bridge formation and excellent biocompatibility (Yu *et al*., 2016).

Pulp revascularization is a promising procedure for the treatment of adolescents'immature permanent teeth with necrotic pulp and/or apical parodontitis. No evidence of root lengthening or thickening was detectable. In contrast, successful revascularization was achieved in a middle-aged patient's teeth (Wang *et al*., 2015).

***Apexification****:* If the tooth is non-vital with a necrotic pulp, periapical lesion or has a carious lesion extending into the root canal, other types of regenerative endodontic procedures should be considered. Pulp necrosis is often asymptomatic but may be also associated with episodes of pain and discomfort. MTA apexification may be more beneficial for severely injured teeth than a regenerative endodontic procedure. Many revitalization/regeneration procedures are using a triple antibiotic paste (also called Hoshino's paste). The paste contains 200mg ciprofloxacin, 500mg metronidazole, and 100mg minocycline. The triple antibiotic is placed in contact with the necrotic pulp inside the root canal for up to 1 month prior to revascularization procedure. Calcium hydroxide is equally as effective as the antibiotic at promoting root lengthening and thickening. The borders of the Hertwig's root sheath are gradually reduced in diameter, and merge. They contribute to apexogenesis (or apexification).

***Direct and indirect pulp capping in young permanent teeth****:*

***Direct or indirect capping***

Inflammation is an important factor and in many cases a prerequisite for pulp healing and regeneration. These inflammatory factors includes MTA, calcium hydroxide as well as other biomaterials (Goldberg *et al*., 2015).

Mineral Trioxide Aggregate (MTA) may treat carious pulp exposure. At 24 months, the clinical and radiographic success rate was 93% with evidence of continued root growth (Farsi *et al*., 2006). MTA is non-resorbable, and have superior sealing ability compared to amalgam, ZOE, or IRM.

Direct pulp capping with calcium hydroxide is another option. However some calcium hydroxide bases disintegrate over time and microleakage can take place through tunnel defects in reparative dentin bridge. These irritants can compromise pulp vitality, often leading to dystrophic calcification, root canal therapy, or potential extraction.

Partial pulpotomy and wound dressings were similar for the 4 capping agents so far investigated in this study (Ledermix, an anti-inflammatory non-steroidal compound, calcium hydroxide, and zinc oxide-eugenol). The results didn't evidenced any difference between the 4 capping materials. Pulpectomy after 3.5-4 years were similar than after 1 year observation. No difference was also found between deciduous and permanent teeth following direct or indirect capping. However, the consequences obtained from these comparative study are limited, or contradictory, or insufficient (Bergenholtz *et al*., 2013).

***Indirect pulp capping***

Formocresol pulpotomy is frequently used to treat asymptomatic caries near the pulp in primary teeth. Pulpotomy is indicated on non-vital teeth, especially those with reversible pulpitis. In Indirect Pulp Therapy (IPT), the carious lesion is left in place and covered with a biocompatible material (James, 2008).

This study aimed to compare the clinical and radiographic outcomes of an adhesive resin system vs. a calcium hydroxide liner for protection of the dentin-pulp complex of primary molars treated with indirect pulp treatment (Falster *et al*., 2002). The teeth were divided into two groups: an adhesive resin system (Scotchbond Multipurpose) and calcium hydroxide liner (Dycal). The overall success rate of indirect pulp treatment was approximately 90% after 2 years in primary posterior teeth.

***Direct pulp capping***

When used as direct pulp capping, calcium hydroxide ($Ca(OH)_2$), resin composite (RC) and Resin-Modified Glass-Ionomer (RMGM) material were compared, namely concerning healing defects between these materials. Healing defects were recorded putting emphasis on 5 points. The following aspects were pointed: 1) bacterial leakage, 2)operative debris, including dentin fragments and particles of capping material, 3) pulpal inflammatory activity, 4)area and absence of dentin bridge formation, and 5) presence of tunnel defects in bridge. (Murray & Garcia-Godoy, 2006).

$Ca(OH)_2$ and amalgam were chemically simple pulp capping materials, with limited scope for technological development. Further improvements to adhesive systems mediate pulp repair, antibacterial activity, improved sealing, bond strengths and caries prevention. They have some impact on gaining acceptance of RC materials for all types of pulp capping situations.

***Biomaterials used asdental capping materials***

**Biodentine™** consists of a power containing tricalcium and dicalcium silicate as well as calcium carbonate. Zirconium dioxide serves as contrast medium. The liquid consists of calcium dichloride in aqueous solution with an admixture of polycarboxylate. Mixed for 30 seconds, Biodentine™ is set in approximately 12 minutes. Biodentine™ is used for direct pulp capping. It stimulates tertiary dentin formation (Dammaschke 2010).

Evaluation of wound healing process following direct pulp capping with demineralized bone matrix (DBM) and calcium hydroxide ($Ca(OH)_2$) indicates that after 1, 3, 7, 14 and 28 days, Runx2, type I collagen (Col1), osteocalcin and dentin sialoprotein (DSP) expression of reparative dentinogenesis-related transcription factor were under focus. The expression of the four factors in the Reparative Dentine Formation (RDF) was stronger than in the $Ca(OH)_2$ group during the same observation periods.

However, Ca $(OH)_2$ has its own limitations, such as inducingcoagulation necrosis and pathologic calcification, and also leading to pulp chamber obliteration. DBM, which derives from natural bone tissue, is a biocompatible material and has beenused in bone defect treatment. DBM is mainly comprised of type I collagen (COL I) and bone morphogenetic proteins (BMPs). BMPs have been confirmed to promotethe dental pulp stem cell differentiation into odontoblasts, which is the

foundation ofreparative dentine. BMPs not only regulate the development of tooth embryonic stem cellsand odontoblasts differentiation but also participate to the dentin matrix secretion and mineralization. The results showedthat DBM induced less inflammatory cell infiltration (ICI) and pulp tissue disorganization(PTD), suggesting the therapeutic possibility for DBM to be used as a new pulp-capping agent (Liu *et al*., 2017). Enamel Matrix Derivative (Emdogain) allows the healing process to take place and ensure the closure of the pulp chamber. The formation of a dentin bridge was observed in the experimental and control groups. A mild to moderate reaction was observed in both groups. Necroses were not observed, nor were bacteria present in the pulp. Pulp reaction was similar to that of MTA (Popovic Bajic *et al*., 2015). After 6 months, favorable effects of calcium hydroxide were detectable. Less inflammation was seen, together with a greater thickness of the dentin bridge. Inflammatory cells were seen in the coronal and radicular pulp. In the control group, where pulp was capped with MTA, lymphocytes, plasma cells and macrophages were observed. Experimental angiogenesis was observed in the pulp, together with regenerative processes and successful tissue remodeling. Odontoblast-like cells were observed. Altogether, this provides valuable confirmation of the favorable therapeutic effect of EMD similar to MTA.

***Reactionary dentine***

Diminished co-expression of CX43 and zonula occludens implies a reduced level of intercellular connectivity between odontoblasts (Couve *et al*., 2014). DMP1 and DSPP were more abundant in carious than in sound samples. High expression of DMP1 and DSPP inside tubules suggestsa high expression of DMP1 and DSPP inside the tubules, and consequently an active dentin biomineralization by odontoblasts (Martini *et al*., 2013). DSPP was found to be expressed in bone and cementum. DSPP is secreted as a multi-domain extracellular matrix protein of dentin sialoprotein (DSP). At the N-terminus. MMP-2 was also implicated in this processing. Membrane type-1 matrix metalloproteinase (MT1-MMP) and tissue inhibitor of metalloproteinase-2 (TIMP-2) were also implicated in the process.

Reactionary dentine and reparative dentine are secreted by odontoblast-like cells and used by the dentin-pulp complex. Reactionary dentin is secreted by the original odontoblasts, while reparative dentin is formed by odontoblast-like cells.

Osteopontin (OPN) is a non-collagenous protein present during repair of mineralized tissues. Reactionary dentin is tubular and share similar aspects with primary and secondary dentin. Reparative dentin has a dystrophic atubular matrix with cells entrapped in the mineralized matrix (Aguiar & Arana-Chavez, 2007). Bovine bone morphogenetic protein-induced dentinogenesis induced the formation of cartilage and bone when implanted in muscle tissue. BMP is also found in dentin matrix. Four conclusions might be drawn from a series of experiments: 1) BMP exists in odontoblasts, ameloblasts, and dentin matrix, 2) BMP promotes incorporation of (3H) thymidine and increases the activity of alkaline phosphatase in cultured dental pulp cells, 3) BMP-induced dental pulp cells differentiate from mesenchymal to odontoblast-like cells, and 4) BMP induces the formation of osteodentin and tubular dentin when used as a pulp capping agent (Lianjia *et al*., 1993).

In response to an appropriate stimulus, reactionary dentin may be formed in response to significant amount of TGF-□, a growth factor previously shown to influence odontoblast differentiation and secretion. TGF-β initiates the stimulatory effect on the odontoblasts. Composition differences in tertiary dentin matrices beneath carious lesion indicate modulation of odontoblast secretion during reactionary and reparative dentinogenesis (Smith *et al*., 1995).

Fibronectin is redistributed during odontoblast polarization and interacts with cell-surface molecules. Under this influence, reparative dentin is formed (osteodentin and/or tertiary dentinogenesis). Application of dentin matrix components or growth factors stimulates the up-regulation of reactionary dentin formation. Growth factors such as TGFβ–1, –2 –3 / BMP2, 4 6, during of the. IGF-1 also intervene (Tziafas 2004). Immunolocalization of fibronectinduring reparative dentinogenesis involves unclarified mechanisms (Yoshiba *et al*., 1996).

***Reparative dentine***

Reparative dentin formation may be induced on exposed dental pulp by dentin phosphophoryn/collagen composite (Koike *et al*., 2014). Dentin Phosphoprotein (DPP) cross-linked with collagen fibers was applied to direct pulp capping in rats. Slight pulp inflammation was seen, and calcium hydroxide induced severe inflammation at 3 weeks. Anecrotic layer was formed, adjacent to the capping material. This demonstrates a potential for DPP/collagen composite as rapid biocompatible inducer for the formation of reparative dentin of excellent quality in rats.
The potential of bioactive agents such as BMP-2, BMP-4 and BMP-7, dentin matrix protein-1 (DMP-1), matrix extracellular phosphoglycoprotein (MEPE), bone sialoprotein (BSP), enamel matrix derivative, or stem cells is currently under study. The current study provides confirmation that porous reparative dentin have tunnel defects, failing to provide hermetic seal, and allowing recurring infection due to microleakage. This reparative dentin has a bone-like structure, does not possess odontoblast layer and consequently is deprived of dentinal tubules.

Tertiary dentin, also called reactionary dentine when alkaline phosphatase activity was highly reactivated. Pulpal progenitor/stem cells revealed alkaline phosphatase activity in areas encircling inflamed pulp sections. Hydrolases, transaminases, metalloproteinases, and dehydrogenases are expressed during primary dentinogenesis (Larmas & Sandor, 2014).

Pulp stem cells are implicated in reparative dentin formation (Dimitrova-Nakov *et al*., 2014). They lead to the formation of reparative dentinogenesis. Bone sialoprotein (Decup *et al*., 2000) has the capacity of inducing reparative dentin. Extracellular matrix proteins may constitute tools for regenerative dentistry (Goldberg *et al*., 2009).

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