Repair and regeneration: A contribution to clarify a terminological confusion

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The concept

The reconstruction of damaged or destroyed areas in the human body can be made by two different and not comparable mechanisms for it occurs in different situations, without competing with each other: The repair and regeneration.

What causes repair or regeneration?

What determines whether the lesion or destroyed area will suffer repair or regeneration is not if the final result was good or bad, but the type of damaged tissue. The connective tissues are the only ones vascularized and therefore are the only ones that have inflammation as a defense mechanism and of tissue reconstruction. The connective tissues are fibrous tissues, sort of dense, osseous, cartilaginous, adipose and others. The connective tissues when inflamed —or when blood coagulates inside as in surgery and trauma — immediately forms a fibrin network invaded by sprouts of endothelial cells that appear on the walls of blood vessels surrounding the damaged area and form a rich vessels net newly formed from this fibrinous reticular matrix. Angiogenesis — as this phenomenon of neovascularization is known — is one of the essential phenomena of tissue repair. Among the dental tissues the periodontal ligament tissue and pulp are classic connective tissues and assume specialized functions such as dentin and cementum matrix production. The dentin and cementum are synthesized matrix and mineralized by cells of this special tissues. The vascular component in the pulp and in the periodontal ligament is enormous, representing up to 50% of the periodontal volume. In the same anatomical region may exist adjacent tissues which may be reconstructed by regeneration or repair and the reconstruction process is harmonious, parallel and simultaneously, even with some synergism, when it is possible (Fig 1).

The concept of granulating tissue: The precursor of the mature connective tissue in areas to be repaired

In the connective tissues the invasion of damaged or destroyed areas — initially filled with fibrin — by the newly formed vessels or angiogenesis is followed by, almost simultaneously, the migration of undifferentiated tissue cells (stem cells tissue) and young cells. This migration of vessels and cells toward the center of the damaged area is due to the platelets and macrophages located centrally releasing large amounts of mediators stimulating proliferation and chemotaxis. The newly formed vessels and the migrating cells use fibrin as anchoring structure. The newly formed vessels, the undifferentiated and young cells, the stem cells and inflammatory cells fill destroyed or damaged parts of the body and form a red mass sort of gelatinous, fragile,

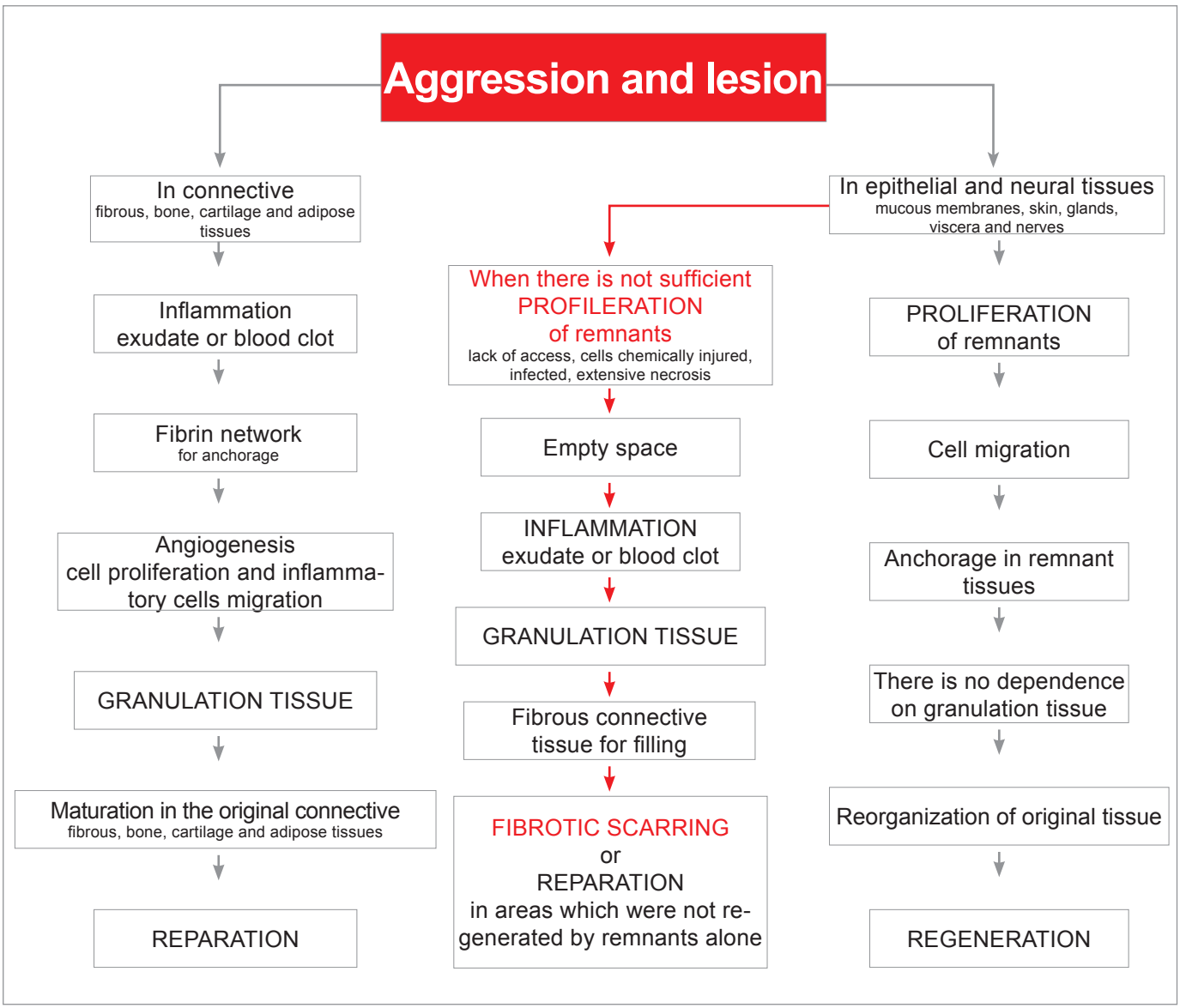

Figure 1. Diagram of sequential and differential phenomena of repair and regeneration.

with no resistance to tensile forces or pressure, known as granulation tissue. If we pay close attention in this tissue, there are dots more red than others, that stands out and create a grainy appearance, hence the doctors from yore in giving the name of granulation tissue for this structure. The granules represent the loops and curves of the vessels among the young and inflammatory cells. Any cavity of a body, when free of bacteria and other microorganisms, can be filled by exudate or blood clot, and then occupied by granulation tissue that gradually give place to a connective tissue (Figures 2 and 3).

The concept of connective tissue and its functions, including filling!

Or

The body has horror to empty spaces

The connective tissues are the only vascular ones and they might have mesenchymal origin. The connective tissues have many functions and one that deserves to be highlighted is the support and protection of fine tissues such as surface epithelia, organs such as liver, kidney and pancreas glands in general. Another important function of connective tissue in

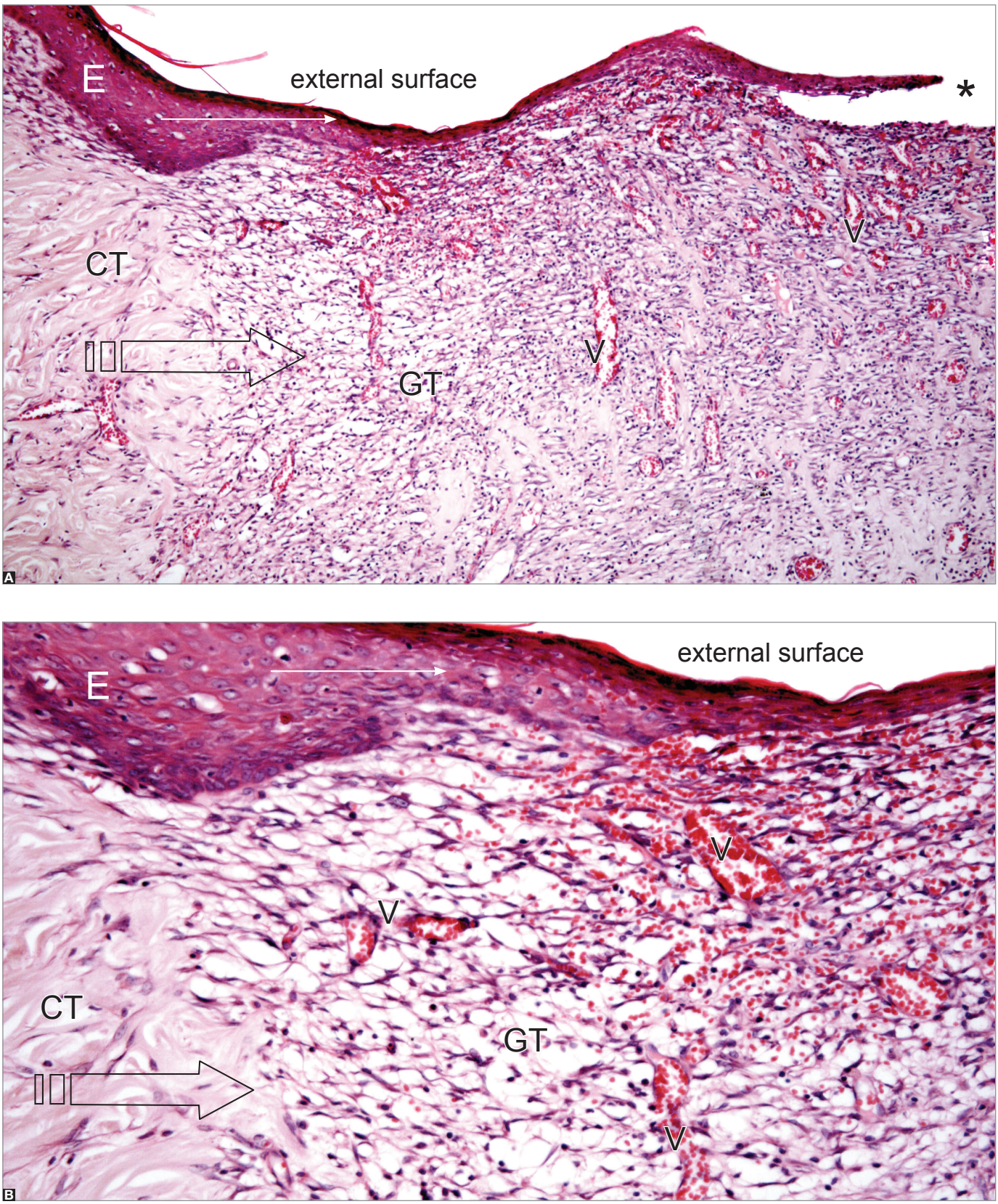

Figure 2. In skin wound with direct exposure of the conjunctive to the exterior, it is observed that in the epithelium (E) regeneration generates strips toward the center (*) from a proliferative burst in the margin of the lesion (smaller arrow). Angiogenesis (V), the migration of cells (greater arrow) of the connective tissue (CT) and inflammatory cells form the granulation tissue (GT), which represents the typical structure of the repair. (**A**=25X; **B**=40X; HE).

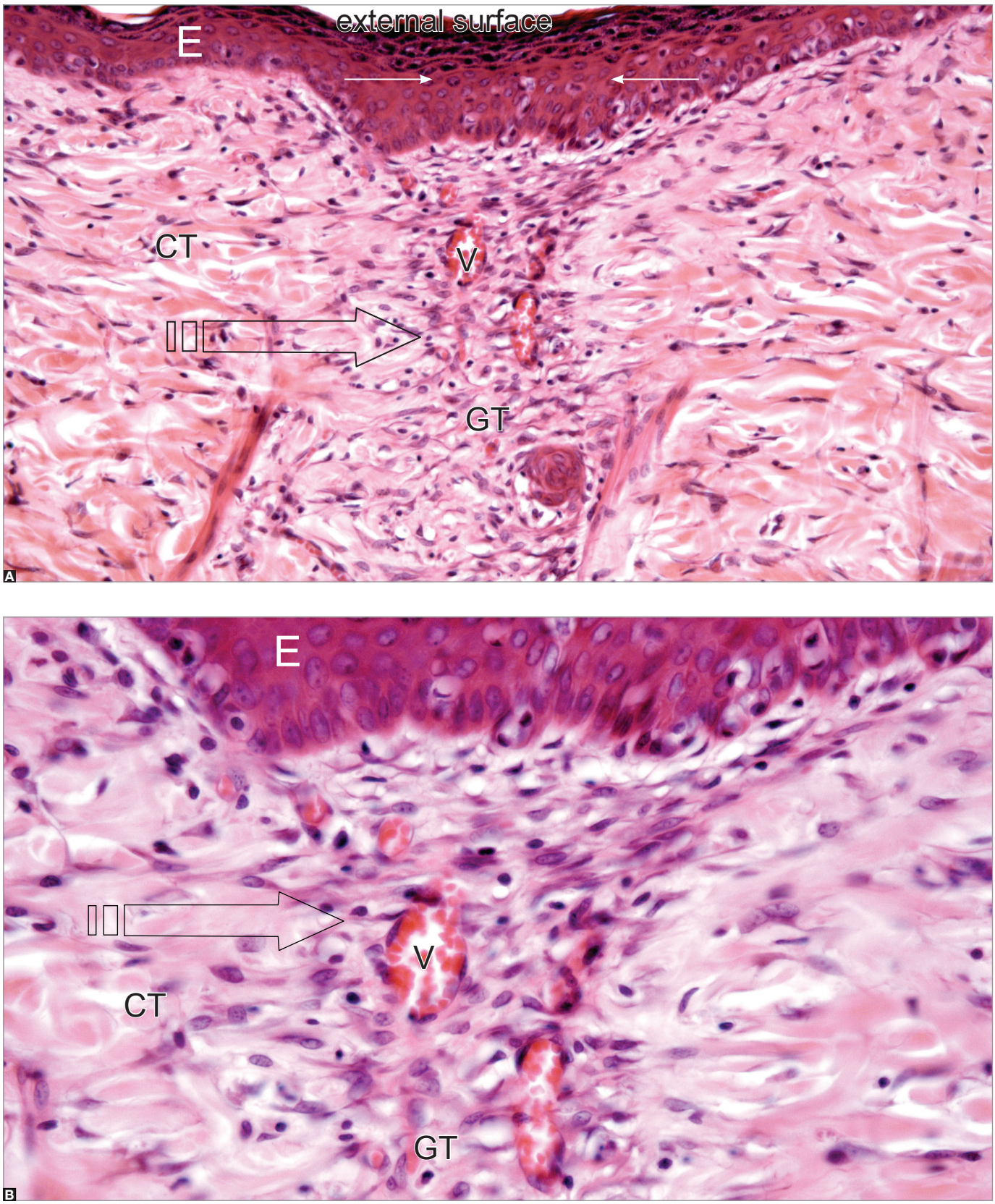

Figure 3. In skin wound suture, it is observed that in the epithelium (E) regeneration takes again the surface coating in a few hours from proliferative burst at the lesion margins (small arrows). Angiogenesis (V), the migration of cells (greater arrow) of the connective tissue (CT) and inflammatory cells form the granulation tissue (GT) in an area much smaller, accelerating the repair. (**A**=25X; **B**=40X; HE).

our body is filling empty spaces, of which our body has horror. If any empty space "appears" inside the body every effort will be made to fill it with the finest tissues of the original body of that region. When all mechanisms fail to restore the area with more specialized tissues from that region, the connective tissue will form in the area starting from the formation of granulation tissue. This does not represent an "invasion" of connective tissue as we use to refer at this process, instead it is a filling, a form of anatomical accommodation for which the connective tissue was primarily designed. The human connective tissues are dense and loose according to the density of the collagen fibers, the bone tissue, cartilage and adipose. All these tissues have some common characteristics: They are vascularized and nourished directly by blood, they have lymphatic drainage, mesenchymal origin, present an extracellular matrix between their cells which is produced by them. One common point of the connective tissues refers to its formation and reconstruction when necessary: A network of vessels is formed and it invades the to be reconstructed area, being followed by undifferentiated and young cells, attracted to the site where they start to produce extracellular matrix and fills the place (Figs 2 and 3). The common feature most important refers to the ability of the connective tissue to form granulation tissue. In other words, all the connective tissue is reconstructed by formation of granulation tissue. This form of tissue reconstruction is called repair.

The bone reconstruction is made with granulation tissue: Bone does not regenerate!

In the damaged or destroyed bone area, endothelial cells and stem cells migrate to the clot (or exudate) in exuberant fibrin network to establish a granulation tissue. Once anchored in the fibrin, the cells take the form and function of osteoblasts and some, after a while, of osteocytes. In the middle of the neoformed vessels and inflammatory cells — which numerically decrease gradually — newly differentiated osteoblasts will deposit bone matrix and then mineralize it (Fig 4). The bone tissue repairs itself and this is the only known mechanism of bone formation. The osteogenesis is dependent on prior angiogenesis, of fibrin anchoring and the migration of stem and young cells.

In the pulp cavity with wide opening to the periapical tissues: Reconstruction is made with granulation tissue

In teeth with incomplete root formation, or as such, with a wide opening into the periapical tissues and free from microorganisms and their products on their walls and tubules, endothelial cells and undifferentiated and young periodontal cells migrate to the clot, in an exuberant fibrin network to establish a granulation tissue. Once anchored in the fibrin, the cells take the form and function of fibroblasts and synthesize new extracellular matrix, organizing connective tissue in the region. In cases where the pulp cavity with a wide apical opening is in contact or interface with periapical tissues such as dental papilla and dental follicle — which remained alive in spite of the aggression in the pulp of teeth with incomplete root formation — the cells that may invade the fibrin network together with the endothelial cells to form the blood vessels, may originate cementoblasts and odontoblasts. This possibility of reconstructing the apical tissues with formation of new odontoblastic and cementoblastic layer exists only if in the periapical tissues remain the embryonic tissues such as the dental papilla and dental follicle.

A granulation tissue that fills a pulp cavity in the apical third with wide opening at the interface with mature periodontal ligament will not be invaded by cells with potential to differentiate into odontoblasts and or cementoblasts. Where this interface is made only with the dental follicle, without dental papilla, there is potential to reconstruct surfaces of the pulp cavity with new cementoblastic layer and deposition of new cementum in their walls. After recomposed the odontoblast and/or cementoblastic layers in the surface of this apical pulp cavity free of bacteria and their products, we may have the deposition of reparative dentin and neocementum respectively, reorganizing or rebuilding the apical third. But even so, this process of tissue reconstruction, having been made based on granulation tissue, is characterized and must be named repair. In order to call the reconstruction process of tissue regeneration, in all periods of occurrence should not be observed formation or dependence of granulation tissue. Regeneration is one of two mechanisms of tissue reconstruction and makes it directly from the

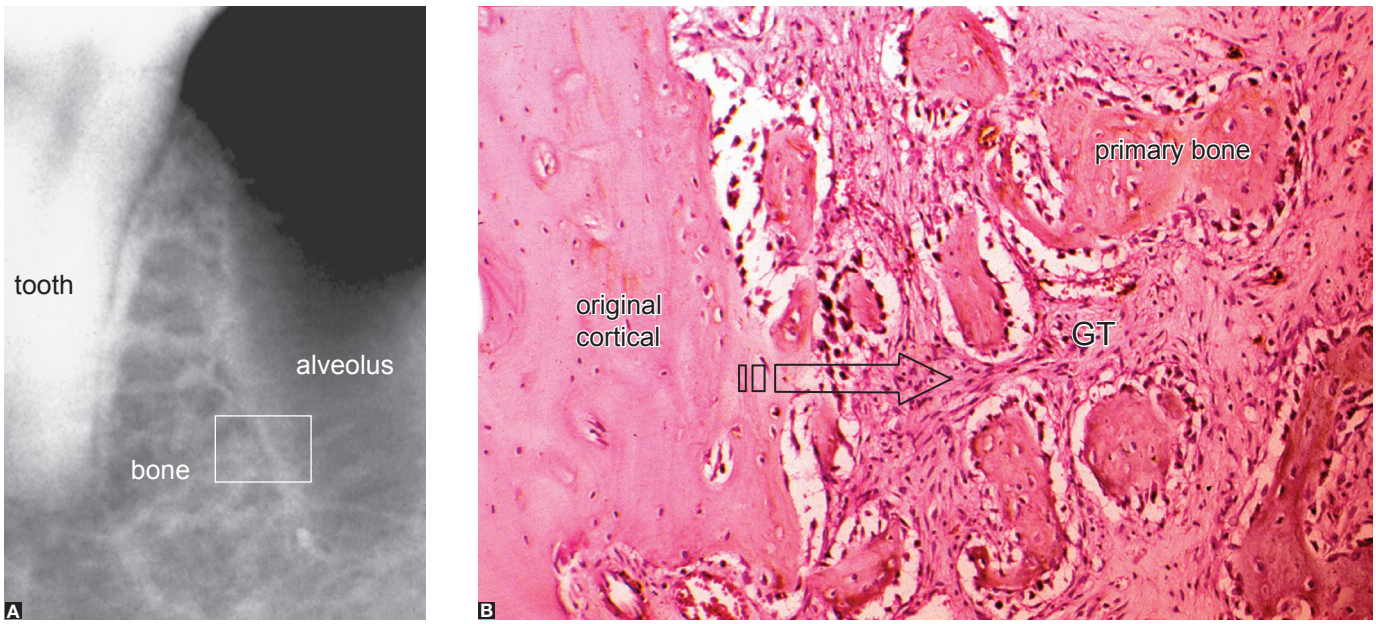

Figure 4. In an intra-alveolar clot, granulation tissue (GT) is formed from the periodontal remnants and bone wall with the same phenomena: Angiogenesis and cell migration (arrow) of the osseous connective tissue to the center of the clot. The bone matrix, initially synthesized by the first migrants osteoblasts in the region, gives rise to the embryo or primary bone to fill the alveolar space. (**B**=25X; HE).

remnants of the damaged tissue in the region. Both processes — the regeneration and repair — should not be compared in terms of efficiency, competence or quality, because both can rebuild all or part of a region and they can still fail and/or leave marks, scars or warning signs in a certain region.

Repair: Rebuilding of damaged connective area

The reconstruction happens in previously damaged areas. The damage or injury in connective tissues leads to inflammation and once it is eliminated the cause of the injury, the process progresses to the final stage represented by the repair process. The repair must be considered as part of the successful inflammatory process in the defense of the organism. The processes of reconstruction of damaged tissues, regardless of whether to repair or regeneration, are also eventually classified under the term bioengineering or tissue engineering. These two terms are used mainly when there is interference of man in the process as placing materials, membranes and other products in order to accelerate or improve the process.

Regeneration: The other mechanism of tissue reconstruction, but not in connective tissues

In other tissues without connective nature as surface and glandular epithelium, the visceral organs, muscles and peripheral nerves, the reconstruction process happens directly from the proliferation of these tissues remnants that persist in the attacked region without an intermediate phase represented by the formation of granulation tissue. The reconstitution of tissues from direct proliferation of its remainings is known as regeneration. In the regeneration the lost tissues are directly reconstructed also with the proliferation of specialized neighboring cells, but without the participation or formation of granulation tissue. Damage to any anatomical area rarely will involve only connective tissues, leading them to inflammation without jeopardizing the normality of the epithelia and peripheral nerves. In reconstructing tissue in a skin wound, for example, there will be repair of the connective tissue of dermis and epithelial regeneration in the epidermis. Even in the dermis, the lesion certainly will jeopardize any peripheral neural fiber that rebuilds itself by regeneration in the nerve stumps.

Likewise, in the visceral organs such as liver, kidneys and glands, there will hardly be a tissue injury or inflammation without affecting the stroma and fibrous capsule that correspond to parts of connective tissue responsible for support of the noble part of the viscera. In this situation the connective tissue will be reconstructed by repair from the formation of granulation tissue and visceral epithelial portion from the remnants that will proliferate and rebuild the noble part lost. When the noble part cannot recompose itself in area, the neighboring connective tissue serves to fill the empty space and with granulation tissue formed in the area, it is established.

Classification of cells and the ability to promote tissue regeneration

The greater or lesser capacity of a tissue or organ to promote regeneration is in its capacity and speed of cell proliferation. The greater the easiness or capacity of proliferation of cells in a certain tissue entering mitosis, the greater the regenerative capacity. As for the capacity and speed of proliferation, cells can be classified into:

» Labile cells: Cells that proliferate rapidly, which practically do not leave the cell cycle. Some cells proliferate in cycles of 16 to 24 hours. The epidermal and mucous surface of epithelium, the hematopoietic tissue and lymphoid organs represent tissues with very high proliferative potential (Figs 2 and 3). In these tissues the replacement of lost cells is rapid, although not all cells proliferate continuously, but an important part does sufficiently to maintain the cell turnover. In the tissue composed by labile cells, approximately 1.5% or more are at mitosis. Cells in constant mitotic activity derive daughter cells. One of these cells will assume a terminal differentiation and the other will follow a proliferative rhythm which is called stem cell. This occurs, for example, with the epithelial basal cells. In the surface epithelia, as well as in other tissues, when the stem cell is capable of giving rise to a single cell type it is classified as unipotent, but when the stem cell is able to give more than one cell type, such as bone marrow stem cells — originating the erythrocytes, leukocytes and megakaryocytes — can be identified as pluripotent. In remaining tissues in the injuries, the regeneration depends on the local persistence of stem cells

» Stable cells: Those that constitute the tissues with up to 1.5% of its population constantly in mitosis as glands, liver and endothelium.

Although the number of stem cells is not so great, its regenerative capacity is significant when stimulated by growth factors. In the liver, even the loss of 75% of its structure, can be recomposed; among its cells, in each 15,000 one is in mitosis.

» Permanent cells: Cells that definitely left the cell cycle and has no ability to proliferate even with certain stimuli by growth factors. If injured, this cells are not naturally replaced by other cells and the same occurs with the neurons, the cardiac and skeletal muscle cells and lens.

The concept of cicatricial fibrosis

The glandular epithelium and visceral tissues are more specialized, or differentiated; their proliferation is slower and limited by several factors, among these is the size of the lesion. In the regeneration of large lesions in these tissues more differentiated, slower proliferation can leave empty spaces that the body does not accept and quickly demand to fill it somehow. In areas where tissues are damaged and it does not regenerate by itself, supporting connective tissues surrounding, known as stroma and/or fibrous capsule, are induced to angiogenesis, to cell proliferation and migration to form a granulation tissue at the site. Thus, in the site, the granulation tissue will lead to the filling of the region with fibrous connective tissue that will occupy a part that will "replace" anatomically an specialized component of visceral tissue. The biology of the organism does not tolerate gaps in our organs and tissues, for this reason the connective tissue has the function of filling. This property of the organism can be expressed in Latin as *horror vacui*. The region of fibrous connective tissue that fills these spaces will be called fibrosis or cicatricial fibrosis and even cicatricial fibrous tissue. The term fibrosis does not mean that the collagenized tissue is thicker, only that it was formed in the body where previously it did not exist. In a healthy liver, for example, when there are lesions the hepatocytes rapidly replenish the lost cells. In alcoholics or in patients with viral hepatitis this may not occur, because the neighboring hepatocytes are injured and unable to proliferate to the point of replacing the cells that died. In these areas the spaces of these cells will be filled by granulation tissue arising from the stromal and capsular connective tissue unaffected by the aggressors and

instead form a filling connective tissue. This process can be slow and eventually occupy most of the liver that gradually loses its function. The liver fibrosis is known as hepatic cirrhosis. A mythological example of regeneration can be the story of Prometheus, who stole fire from the gods and passed it to humans, and for it Zeus condemned him to a long life chained to a cliff, but every day an eagle would come to his body and would eat a small portion of his liver. As the portion was small, every day the hepatocytes regenerated and thus life perpetuated and with it also his punishment.[13] This story serves to illustrate and demonstrate that when important organs, formed by well-differentiated cells are damaged, since these lesions are small, it can regenerate. But if this happens in connective tissues there will be granulation tissue formation and this features repair.

Healing is not synonyms of repair

Both processes of tissue healing — repair and regeneration — can leave signs in the affected area. The term signal can also be replaced by marks or scars. It is very common to use the term scar as a synonym for repair, however this does not seem to be precise, for during regeneration in some situations remain permanent sequelae, depending on the extent and location of the process. In the skin, in cases of fistula and accidents, it can be noted areas of epithelial atrophy, loss of hair and melanin pigmentation; in these cases there was not complete regeneration of all epithelial structures, including the hair follicles and melanocytes. They are true scars resulting from tissue regeneration. In many of these areas, by analyzing the subjacent connective tissue, it is normal, without fibrosis or different organization, although it has undergone repairs. In most situations, the repair and regeneration occur simultaneously and both processes may leave signs. These terminological mistakes arise from the frequent, erroneous and simplistic statement: "The repair restores the anatomy and regeneration restores the anatomy and physiology of the region."

If we apply this expression in the reconstruction of epithelial tissue, connective and peripheral nerve as in the skin, mucous membranes and bones, it will be totally wrong, because both processes can return to complete normality to the affected region. But if we analyze the reconstruction of organs such as liver, kidney and pancreas, regeneration will lead to restoration of function and anatomy. However, if part of the reconstruction is made from the fibrous capsule tissue or from stroma it will occupy a portion of the lost part and functional restoring will not be complete, but also the anatomy won't be complete and the cicatricial fibrosis will be morphologically revealed. In the anamnesis, the patient is questioned about his ability to heal wounds when they occur. The answer "yes" by the patient, if taken in extreme level of precision of the true meaning of healing, implies understanding that the patient has a great ability to form exuberant scars. The healing terminology should be interpreted as the process by which is formed the signs, marks or scars.

Final considerations

The words or terms such as healing, regeneration, repair, cicatrization and cicatricial fibrosis have specific meanings and are often mistakenly used as synonyms. In other situations are applied with inverted concepts resulting in a lot of confusion, especially in clinical language. Understanding the reasons and origins of each of these terms facilitates the understanding and solidify universal concepts. There are no specific concepts of a particular specialty or area of study, all areas should follow the principles and concepts established by the basic sciences that serve all science. The conceptual and terminological precision facilitates communication among clinicians and researchers and also allows a more critical reading of the works on the subject, developing a greater selectivity of the products available to the clinician, especially biomaterials. Some advertisements use the confusion in terminology for a commercial persuasion, impossible if professionals present well-founded concepts. Repair and regeneration are biological processes that reconstruct different tissues and are not subject to comparison on which is best. Both processes may occur in partial and imperfect way, leaving marks, signs or scars, but in most cases reconstitute perfectly the tissues in their anatomy and normal function.

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