At the Core of Surgery, the Fascinating Process of Wound Healing

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THE PRIMAL WOUND

The primal wound of every mammal follows undoubtedly the cutting of the umbilical cord, resulting in an inevitable scar: the navel. In humans, severing the birth cord can also be considered as the most ancient surgical operation,[1] in addition to having a great symbolic significance. During antiquity, there was a debate as to when and how to separate this life thread from the placenta. In the Kahun Gynecological Papyrus (1800 BC), the oldest known medical text in Egypt, it is said that the midwife should cut the cord with obsidian and bury the placenta under the threshold of the house. The Greek physician, Soranos of Ephesos (2nd century AC) advises to tie both ends before dividing the cord, to avoid bleeding. During the Middle Age, the distance as to where the cord should be divided is also of importance for the boys: "And let the umbilical cord be tied at a distance of 3 fingers from the belly, because according to the retention of the umbilical cord the male member will be greater or smaller!" wrote the women surgeons of Salerno in the Trotula.[2] In any case, the remnant of the cord will fall from the newborn after 5 to 8 days. A histological study carried out on neonates who died within 7 days of birth showed that the umbilical cord itself became dried and mummified. By and large, the fall of the stump corresponds to an aseptic necrosis, followed by a regular process of wound healing.[3]

ANTIQUE CONCEPT OF WOUND HEALING PHYSIOLOGY

Management of wounds has been a major concern since the beginning of humankind. Thousands of methods and recipes have been devised to dress and accelerate healing and avoid possible complications, in spite of the fact that very little was known on natural process of cicatrization (Fig. 1). The first physicians, however, did not hesitate to speculate on the origin and the way Nature reacts and responds to an injury causing an external wound. *Peri Helkon* is the title of a Hippocratic treatise about wounds and ulcers. Hippocrates believed that an organism is not passive to injuries or diseases, but regulates itself to counteract them. The body tends to overcome a disturbed equilibrium. It is this capacity of organisms to correct imbalances that distinguishes them from non-living matter. In cases of incisional wounds, the possibility to bring the tissues together by taping or suturing leads normally to a recovery called "by first intention." As for the wounds with disruption or deprived of substance, the Greeks had noted that after a period of hemorrhage and blood clotting, swelling invaded the surrounding tissues, followed by a white-yellowish secretion covering the wound. This has been called the period of *inflammation*, presenting the 4 cardinal symptoms: rubor, tumor, color, and dolor (redness, swelling, heat, and pain) defined by the Roman encyclopedist Celsus (25 BC–50 AC) in *De Medicina*. Following this phase of inflammation, the wounds could achieve healing by "secondary intention," which for the ancients necessitated the presence of whitish non-smelly good pus, the *phlegma*. It was considered as a good omen and became also for centuries the "pus bonum et laudabile" (the good and laudable pus). In case of infection, a turbid, sanious, muddy, and smelly variety of pus appeared, called *ichor.* This kind of corrupted blood could lead to sepsis, putrefaction or gangrene. Hippocrates and later on the Greek physician, surgeon, and philosopher Galen of Pergamon (129–199 AD) advised to promote the good white pus for a better healing and to fight only the bad and smelly pus.

Without knowledge of the cellular mechanisms that governed the filling of a wound, the ancient physicians had imagined a purely mechanical process such as that of the construction of a well by a mason. This theory was that the vessels adjacent to the wound, which had been divided by the injury, would continue to secrete a juice, a substance (the famous "good pus"), which would settle the way a mason deposits bricks on the wall of a well. This nourishing juice would gradually fill-up the cavity, coagulate, dry out, and stick the edges of the wound together and eventually be covered by a thin skin to form the scar.

FIRST RESEARCHES ON CICATRIZATION

The study of the physiological process of cicatrization took a new turn since the mid-eighteenth century, after the discovery of the

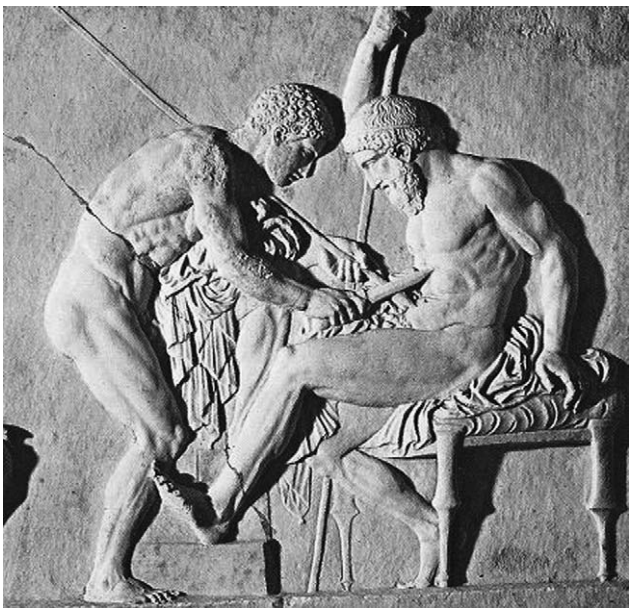

FIGURE 1. Achilles healing Telephos' wound with rust (copper) from his spear.

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microscope and the observation of the red blood cells and microbes by the Dutch Antonie van Leeuwenhoek (1632–1723). However, as expressed later by the French veterinarian Emile Griolet (1869): "Of all the questions related to the art of healing, few have been the subject of as many diverse explanations as the mechanism of wound healing. In each era, there is a theory; each author has his own opinion on this work of nature, even if it looks simple in appearance, as it offers the observer the advantage of being outside the body."[4]

At the end of the 18th century, during the same decade (1760–1770), the French doctors L. Fabre and A. Louis published 2 lengthy articles: the first was: *Memoir where it is proven that there is no regeneration of flesh in wounds and ulcers with loss of substance*,[5] and second: *On the consolidation of wounds with loss of substance*,[6] where they affirm their belief in a purely mechanical deposit of inert material to fill the wound defect, in analogy with masonry. Contrariwise, François Quesnay (1694–1774) wrote a 400 pages book called *Treatise on suppuration*,[7] where he taxes the *mason* theory as being gross and purely imaginary. Quesnay does not question the necessity of good pus, but this helps to stimulate the regeneration of the flesh, that is the production of living tissues and capillaries, that he had observed under the microscope. Regeneration of the tissues starts when the bleeding and the inflammation have stopped, and should be compared to a minor degree to the growth of the young shoots after the section of a tree's branches, or the growth of a limb in a salamander: "Our parts can extend beyond their ordinary boundaries, where, however, they retain this organic structure on which depends the action and life that preserves these parts." He states that with the microscope, when the suppuration is perfectly established, small elevations on the surface of the flesh, which resemble snail horns, can be seen and that it is also evident that the newly former flesh is formed with small vessels and veins, where blood is circulating. François Quesnay has been an important figure of his time as a personal physician of Madame de Pompadour, and King Louis XV. Today, he is best known as an economist, as the second part of his adult life was entirely devoted to the Physiocracy Theory of economics.

WAR WOUNDS

Wound healing has always been of primary concern for the surgeons during the wars. Since the days of the ancient Greeks and especially the Romans, surgeons have almost always accompanied troops in battles. They were mainly responsible for dressing and suturing the wounds, reducing dislocations and fractures, sometimes for amputating a limb. Usually, after amputation, the stumps were left open to allow a good drainage, and left for secondary healing. A few surgeons practiced cutting the bone more proximal than the soft tissues, to facilitate wound contraction around the stump. After the advent of firearms, injuries and their cares became more complicated. The first accounts of wound treatments on battle fields were the noteworthy books written by Ambroise Paré during the sixteenth century, and we are indebted to the British surgeon John Hunter (1728–1793) for having collected his conceptions, his experiments, and his experience on the battle field in a voluminous treatise entitled: *A Treatise on the Blood, Inflammation and Gunshot wounds*,[8] published after his death. Throughout the nineteenth century, this treatise was considered as the most important study on inflammation and has been widely quoted since. After a section on the nature of blood and the circulatory system, in which he describes the vascular supply in detail, Hunter proceeds to an extensive survey of inflammation, which he divides into 3 groups. "Inflammation is capable of producing 3 different effects, viz. adhesions of the parts inflamed, suppuration in the parts, and ulceration of those parts; which I have called the adhesive, the suppurative, and the ulcerative inflammation; the last, or ulcerative, is, properly speaking, only a secondary effect of inflammation, not being performed by the same vessels. In the first instance, healing is due to extravasation of coagulable lymph. The others correspond to more or less severe wound infections . . .". His ideas on suppuration lead us to think that he did not consider pus absolutely necessary for healing a wound: "This is contrary to the commonly received opinion, but it is according to my idea of suppuration, for I have all along considered inflammation as the disease, and suppuration only as a consequence of that disease; and have supposed the disease to be gone when suppuration has taken place: but according to the common opinion, suppuration was the thing to be wished for; because all diseases arose from humors; but as we have not once mentioned humors, and therefore made it no part of our system, we must also drop it at present." Hunter does not adopt the concept of "regeneration of the flesh" described by Quesnay, but he proposes a mechanism of wound contraction by the granulations forming in the wound: "Immediately upon the formation of the granulations, cicatrization would appear to be in view. The parts which had receded, in consequence of a breach being made into them, by their natural elasticity, and probably by muscular contraction, now begin to be brought together by this new substance; and it being endowed with such properties, they soon begin to contract, which is a sign that cicatrization is to follow. The contraction takes place in every point, but principally from edge to edge, which brings the circumference of the sore towards the center; so that the sore becomes smaller and smaller, although there is little or no new skin formed."

THE ADVENT OF SCIENTIFIC MEDICINE

It is during the nineteenth century, particularly after 1850, that major progress have been made in the understanding of wound infections, with the theory of the germs of Louis Pasteur and the antiseptic method described by Joseph Lister in the seventies. Before that, several theses were written on the mechanism of inflammation and cicatrization, as the ones of GJ Gutherie in 1827,[9] *A treatise on gunshot wounds, on inflammation, erysipelas, and mortifications,* and FG Lafosse in 1836,[10] *History of healing, its formation methods and the pathological and therapeutic considerations that follow.* For Lafosse, inflammation, that is soft heat, increased sensibility and vascular supply, leading to subsequent healing, was considered as the exaltation of the vital properties of the bodies, a surge of life, in analogy to the reproductive organs: erection of the penis and clitoris, engorgement of the nipple during breast feeding. In a word, *a turgor vitalis*, leading to life and health. The process of wound healing was also compared to the closure of the branchial arches of the face, the closure of the Botal canal of the heart and the function of the placenta during fetal life. Lafosse also quotes the Dutch biologist Swammerdam (1637–1680) who described wound healing as a "miracle of Nature," and the French scientist Jean Cruveilhier (1791–1874) who spoke about the "law of integrity, or restorative, conservative law of repair."

Emilien Griolet was a veterinarian and wrote his thesis in 1869 *On the mechanism of wound healing in the soft tissue.*[4] For him, wound healing "is not a simple physical phenomenon, but a complex work carried out with the help of all the forces of the economy, the vital properties of tissues, which combine and contribute to the same goal, the repair of the injured party." Although unaware of the process of germ infection, the idea of an exclusive role of a yellowish sticky juice, coagulating lymph, pyogenic-membrane or good pus, a substance that will dry out, solidify, and ultimately glue the wound to obtain healing by primary intention as it was the rule previously, is not accepted anymore. As initiated by Quesnay a century earlier, Griolet emphasizes the necessity to use the microscope in order to observe the presence

of the cells and capillaries in the bed of a healing wound; but the belief that this cellular network is formed by spontaneous generation of new cells is abolished and replaced by the multiplication of preexisting cells brought to the wound and stimulated by the nutritive secretions arising from the dilated capillaries, (an anticipation of the growth factors of modern biology?). A serous exudation soaks the connective tissue around the wound; this modifies the fibrous tissue, which permits the agglutination of the wound edges, and at the same time provokes a multiplication of the cells destined to achieve a definitive wound closure. For Griolet, the process of secondary healing is similar to the primary, with the addition of cellular bourgeoning and suppuration. The wound covers itself by a membrane, which bears different names: granulose membrane, fleshy bourgeons membrane, pyogenic pseudo-membrane. This bourgeons or cellular granulations are growing and join a finely red surface. An important feature follows: it is the progressive shrinking of the wound, that some have attributed to the growth of the peripheral skin. Griolet, however, considers it as a forceful attraction of the wound edges to the center. The effect of this contraction is such that the traumatic zone may be reduced to a third, a quarter; even a tenth of is initial surface, as a result of which, it may produce a retraction of the eyelids, of the lips, deviation of the limbs and the like, a phenomenon often observed after extensive burns. Griolet affirms that this force of attraction resides in the membrane of fleshy granulation and not in the retraction of the scar.

CONTROVERSIES OF THE 20TH CENTURY

During the early twentieth century, a dispute arose as to whether cellular multiplication during healing is due to internal or external factors. For the eightieth birthday of the famous German pathologist Hans Virchow in 1901, Felix Jacob Marchand, 1 of his pupils, published an authoritative survey of evolution of medical knowledge concerning healing of wounds, [11] supporting the doctrine of his master, that inflammatory cell growth is the result of the action of external stimuli upon cells, the so-called inflammatory irritants, which thereby directly incite cells to grow and multiply. However, 3 years earlier, William Welch (1850–1934), 1 of the founders of the John Hopkins Hospital, in a memorable conference entitled *Adaptation in pathological processes*,[12] had duly questioned this theory. To describe the morbid processes, which bring about some sort of adjustment to change conditions due to injury or disease, Welch prefers the epithet *adaptative*, instead of compensatory, regenerative, self-regulatory, protective or healing. He recalls that some scientists deny absolutely the power of external agents to stimulate directly cells to proliferation. For them, it would be equivalent to spontaneous generation of living matters, they argue. Therefore, 2 hypotheses remain for the surge of acute inflammation: injuries either remove natural resistance to cellular growth or increase the formative energy resident within the cells. Welch is also puzzled by the fact that inflammation may initiate healing, but may also be the equivalent of a destructive infection: ''How far are we justified in regarding acute inflammation as an adaptative or protective morbid process?'' He questions.

Alexis Carrel (1873–1944), Nobel Prize winner of physiology and medicine in 1912, is best known for his experiments on vascular sutures, cell cultures, and organ transplantations. Between 1910 and 1921, he published a series of articles on wound healing. One of his experiments: *Cicatrization of wounds. XII. Factors initiating regeneration*[13] deals precisely with the dilemma introduced by Welch: Can we attribute resumption of cell proliferation in the wounded tissues to the removal of resistance to growth, in consequence of the defect from loss of tissue? Is regeneration following an injury started by forces within the organism, or can it be logically attributed to external factors, meaning that cells are directly stimulated to grow and multiply by forces outside the organism, acting on tissues deprived of their natural protection by the injury. Following a poorly designed experiment on a few dogs, Carrel concludes that the second theory (defended before by Virchov and Marchand) is the good one. The wounds protected by dermal grafts had a delayed healing, whereas local application of certain irritants, such as turpentine and staphylococci on unprotected wounds apparently reduced the latent period of regeneration and demonstrated, according to Carrel, the importance of external factors in the initiation of cicatrization. This incredible conclusion on the influence of external factors, meaning that staphylococci could accelerate wound healing, was then criticized by subsequent studies like by Burrows in 1924,[14] who considers that cell crowding or stagnation are the fundamental factors of the body, which regulate the normal balance between tissues, local hyperplasia and hypertrophies, atrophy, hyalinization, development, wound healing, and cancer. The differences in the end result are due merely to quantitative differences in these fundamental factors.

Among the series of research projects on cicatrization published up to the sixties, the article entitled *Contracture and intussceptible growth in the healing of extensive wounds in mammalian wound skin*[15] is particularly interesting, not so much for its content, but more for its authors, Peter Medawar, Laureate of the Nobel Prize in Physiology and Medicine in 1960, for his discovery of acquired immunological tolerance, and Rupert Billingham, his longtime friend and collaborator. If Medawar devoted most of his carrier to study the possibility of transferring tissues from 1 individual to another, it is not without reason. As he recalled in his autobiography[16], as a young researcher at the Pathology Department at the Ratcliffe Infirmary during the war, he witnessed the crash of an airplane, and the subsequent saving of the burned pilot by skin grafting, noticing: ''Only the patient's own skin could ''take as a graft and grow upon himself.'' He pursues: ''This conjunction of events had first made me aware of the body's exquisite powers of discrimination, also fixed my career of scientist. I was henceforward to devote the great part of my time, thought and creative energy to discover how the body discriminates between its own and other living cells. . .I understood now how much of my time had been wasted on unimportant projects, intellectual pastimes, and reveries. . . A scientist who wants to do something original and important must experience, as I did, some kind of shock that forces upon his intention the kind of problem that it should be his duty and will become his pleasure to investigate.'' Thus, thanks to the observation of the healing of burn wounds, we are indebted to this great scientist, major discoveries on organ transplantations.[17]

WOUND CONTRACTION, THE MYOFIBROBLAST

Every major technical discovery or invention, like optic and electronic microscopes, cell cultures, immunological reactions, molecular biology, immune-fluorescent methods, has contributed to a better understanding of normal and pathological wound healing. However, the principal phases of wound repair described several centuries ago are still recognized by the modern investigators, that is: a phase of inflammation or exudation, a phase of proliferation, a phase of contraction and epithelialization and a phase of remodeling of the scar. Although contraction and epithelialization might occur during the same phase, they are 2 distinct processes that are usually studied separately. We have already seen the polemic that arose concerning cell growth, between the tenants of the external or the internal stimuli; a similar debate arose in the 1970s concerning the origin of wound contraction or contracture. It was usually agreed that the wound bed, with the granulations embedded in the connective tissue deposit, was responsible for the shrinking of the wound

by a pull mechanism attracting the edges toward the middle. The idea that this forceful attraction could be attributed to the drying out of the tissues has long been abandoned. Two hypotheses remained: do collagen fibers contract under the influence of chemical stimuli, as they do under heating, or is there a cellular process similar to red or smooth muscle cells contraction at the origin of this process? As often, the solution arose from a set of circumstances, which have been recalled with scientific mastery and humor by its own discoverer,[18] Guido Majno, known for his monumental account on *Men and wound in the ancient world*.[19] Without entering into details, this discovery was the collaboration, at the University Medical School of Geneva, between Majno, another outstanding scientist Giulio Gabbiani, and several young researchers. As a model of inflammation in animals, they used the granuloma pouch described by Hans Selye, with whom Gabbiani had worked before. Thanks to electromicroscopic, immune-fluorescent and chemical studies, they were able to show the presence of modified fibroblasts within the wounds, fibroblasts that have acquired features and potentialities of smooth muscle cells. These contractile fibroblasts have been given the name of *myofibroblasts*, As a young plastic surgeon, I had the privilege to work with this team and confirm the presence of these myofibroblasts during cicatrization in human wounds, as well as in Dupuytren's and La Peyronie's diseases.[20,21] These cells are also known today for playing a major role, not only during the contraction phase of wound healing, but also in a series of pathological situations, like liver cirrhosis, pulmonary, heart and kidney fibrosis, and other fibromatoses. It is now established that the presence of these myofibroblasts within the connective tissue is responsible for the contraction of the wound and the subsequent scar contracture.[22]

During the last 50 years, considerable advances have been made in the understanding and improvement of the healing of wounds. It is now recognized that this is a dynamic process involving the integrated action of a number of cell types, the extra cellular matrix, and soluble mediators termed cytokines, which are proteins that act as internal cellular signals to allow cells to communicate with one another. Growth factors are a subclass of cytokines that specifically stimulate the migration and proliferation of cells and the synthesis of new tissue. Growth factors are believed to exert their specific effects through specific receptors present on the surfaces of target cells. Most of the research on wound healing is now centered on biology at the molecular level.[23]

THE PARADIGM SHIFT OF WOUND HEALING

The concept of *paradigm shift* has been identified by the American philosopher of science, Thomas Kuhn. In his essay *The Structure of Scientific Revolutions*,[24] Kuhn saw the sciences as going through alternating periods of normal science, when an existing model of reality dominates, a protracted period of puzzle-solving, and revolution, when the model of reality itself undergoes sudden drastic change.

In case of injury, the phenomenon of wound healing, whether by first or second intention, was in accordance to the finalistic Hippocratic paradigm: Nature is the physician(s), which became in Latin: Vis medicatrix naturae, (the healing power of nature). Nature finds for itself and does what is necessary for the safeguard of the body. In the ancient Greek and Roman nosology, the Human body contains humors, such as blood, phlegm, yellow bile, and black bile. These are the things that make up its constitution and cause pain and health. Health is primarily the state in which these constituent substances are in the correct proportion to each other, both in strength and quantity, and are well mixed. The role of the physician was to allow and help Nature to achieve healing by regaining a good equilibrium between the humors. The role of the surgeon in treating wounds was to accompany Nature or God's will. Hence the often-repeated sentence of the 16th-century surgeon, Ambroise Paré: "I dressed him, God cured him." In case of infection, 1 of the treatments attempting to remove the bad humors, transported by blood flooding to the wound, was to let blood escape from the body, even at a distance from the wound. This method is at the origin of the traditional surgical veno-sections or the application of leeches, which have been practiced up to the nineteenth century.

The concept that wound healing is purely mechanical could not be abandoned before the identification of the presence of living cells into the wounds and the observation that repair and regeneration in most animals are more effective that in humans. Although still under the influence of the old theories of humors and good suppuration, surgeons and scientists of the 19th century acknowledged the fact that cicatrization is a dynamic process, accomplished by the extravasation of various cells and substances following the phase of inflammation.

During the recent years, taking advantage of the new methods and discoveries in the fields of biology, physics, and chemistry, researchers have acquired a better understanding of the intimate processes of wound healing and its complications. Moreover, as tissue repair is universal across all multicellular organisms, conserved mechanisms may be identified in models more experimentally tractable than humans and subsequently extrapolated to the clinic.[25] From a symphony of cellular intelligence, we have now reached a new paradigm, which includes the complexity of molecular biology and even nanotechnology[26] to understand how our body reacts to an injury.

As we have seen, many outstanding scientists and surgeons throughout the years have been fascinated by the phenomenon of wound healing. Since Hippocrates and probably even before, the philosophical question was to figure out how an injury provoking a wound might trigger a response of the body to counteract the damage, in other words, a self-healing process. The medieval surgeon Guy de Chauliac formulated this concept in his Chirurgia Magna (1363): "The common purpose in every solution of continuity is union, as is said in the Third of the Technic (Galen). This general and first intention is accomplished in 2 ways: by Nature as the principle worker, which operates by its own powers and suitable nourishment, and by the physician as a servant working with 5 purposes…" For Hunter, several centuries later,[8] the animals possess in themselves this power of repair: "An animal in perfect health is to be considered a perfect machine, no part of it appearing naturally weaker than another. As the animal is liable to accidents, it becomes absolutely necessary for its continuance that it should possess, within itself, the power of repair."

The French physiologist Claude Bernard in his introduction to the study of experimental medicine (1865) introduced the paradigm: "All vital mechanisms, whatever they are, have only 1 goal that is to maintain the unity of the vital conditions in the internal environment."

The American physiologist Walter C. Cannon (1871–1945) gave a name to this concept, *homeostasis.* In his book *The Wisdom of the Body*[27] he recalls: "The fathers of medicine made use of the expression, the "healing force of nature," the vis medicatrix naturae. It indicates, of course, recognition of the fact that processes of repair after injury… go on quite independent of any treatment, which a physician may give. All that I have done…is to present a modern interpretation of the natural vis medicatrix." Hans Selye (1907–1982), who had been a pupil of Cannon, spent his life to study the reactions of the body to an injury, an aggression, a stressor, describing the General Adaptation Syndrome (GAS), which he later renamed "stress." For him, when tissues are damaged, for example the skin is burned, there is a specific general body reaction with discharge of adrenalin, and a non specific one,

inflammation, that is decrease in selective permeability of membranes (capillaries) with leakage of chemical (and later even cellular) blood constituents into extra-cellular spaces, giving rise to an increase in phagocytic power. Inflammation largely depends upon systemic defense reactions and particularly upon production of corticoids, according to Selye. Somehow, the directly affected organ must have sent out a message notifying the pituitary-adrenal system of an increased cortical hormone secretion. The response to this signal is given by the inflammation: ''Inflammation is a reaction to injury. If so, it must be something active. It is not merely the passive result of injury, but a positive reaction against it. By calling it reaction, we also imply that it has a purpose; apparently, its object is to repulse the aggressor and mend whatever damage has been caused.'' It can be compared with a fire alarm. ''Even the mending of the wound, if you have cut your hand, will depend on inflammation. The innocuous sting of a mosquito, just as an almost fatal exposure to the atomic bomb, is met by the body with what we called inflammation.''[28]

From birth to death, the capacity of the body to heal its wounds is essential to our development and survival, and invasive surgery would not exist without it. Simple animals do much better than complex mammals in that they may even regenerate part of their bodies. A salamander can afford to lose a whole limb because it will grow a new one. Man's wounds, however, heal mainly by patching up, but the basic processes of repair appear to be similar. Many of the most outstanding scientists throughout the years have been fascinated by this ''miraculous'' biological phenomenon and tried to understand its intimate mechanism, which involves a series of physiological and pathophysiological events. The complex process of inflammation seems to be 1 of the keys to the wound-healing enigma.

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