Regenerative Medicine and Surgery, a Millenary Quest

Denys Montandon, MD,[*] *and Zoe Malvido*[†]

The authors are embarking in a great enterprise: the formation of a new field of medicine that will improve the lives of people everywhere by curing disease. [...] The seeds of regenerative medicine were planted by researchers in disparate disciplines. Yet there is also a unity to regenerative medicine, which stems from a common need. [...] The key insight of regenerative medicine is that every human being was once a single cell, with the potential to transform into an adult body. Each of our cells retains that remarkable potential in a latent form.

William Haseltine 2001.[1]

Regenerative medicine (surgery) is probably the fastest growing plastic surgery field. We have seen many advances in the last 20 years since the discovery of Adipose-Derived Regenerative Cells, especially when it comes to their application. The idea of using a patient's own regenerative potential is gaining more and more popularity among our patients so we have been witnessing an increase of number of indications. The results are very promising.

Dr. Katarina Andjelkov, January 2022

REGENERATIVE MEDICINE AND TISSUE ENGINEERING

The general principle of regenerative medicine is to allow the body to repair itself after an injury by developing the resources that it naturally possesses within itself. This process can be achieved by multiplying and differentiating its own cells, by developing its extracellular matrix, by using its inducing substances (growth factors) and by recreating the architectural supports that constitute the structure of the affected organs. it aims at replacing or regenerating human cells, tissues or organs, restore or establish normal anatomy or function. it is fundamentally based on tissue engineering, that is an interdisciplinary field, which applies the principles of engineering and the life sciences to the development of biological substitutes that restore, maintain, or improve tissue function.[2] Current strategies of this new field include 3 different approaches: cell-based therapy, use of biological or synthetic material leading to a repair process, and cell growth and implantation of scaffolds seeded with cells.[3] Cell therapy consists of injecting novel and healthy cells in pathologic tissues. it can rely either on already differentiated cells or on undifferentiated stem cells, which can differentiate depending on particular circumstances. The use of stem cells is a fundamental element of tissue engineering, whether they are totipotent from embryonic and extra-embryonic tissues, multipotent, unipotent or induced pluripotent. Biomaterials enriched with bioactive factors, such as growth factors and cytokines constitute the second axe of tissue engineering. Extracellular matrix has been shown to play a key role in many different functions, such as gene expression, survival, death, proliferation, migration, and differentiation. Biodegradable scaffolds play also an important role in creating a 3D environment to induce tissue formation (Fig. 1).

Many fields of medicine may benefit from these new technologies[4] In surgery, it has already been used to treat abdominal hernias, gastrointestinal tract diseases, the liver and the pancreas and, most important for plastic surgeons, artificial skin engineering. The extraordinary potential of adipose stem cells is also a matter of much interest and a field where a few plastic surgeons have greatly contributed.[5] The potential for using stem cells to stimulate human lens regeneration and improve visual function in case of cataract is also a promising application of regenerative medicine.[6] It is also important to recall that several methods, such as skin expansion or bone distraction used commonly in plastic and reconstructive surgery, although they do not refer to tissue engineering per se, induce artificially cellular multiplication and tissue growth.

Wound Healing Versus Epimorphic Regeneration

Among the multiple lines of research and investigation, which might increase our knowledge in regenerative medicine, the study of tissue repair in humans and different animals is of great interest.[7] The most extensively studied model for tissue repair is the wound healing response following acute traumatic injury. In most mammals, wound healing response achieves tissue repair through a series of complex

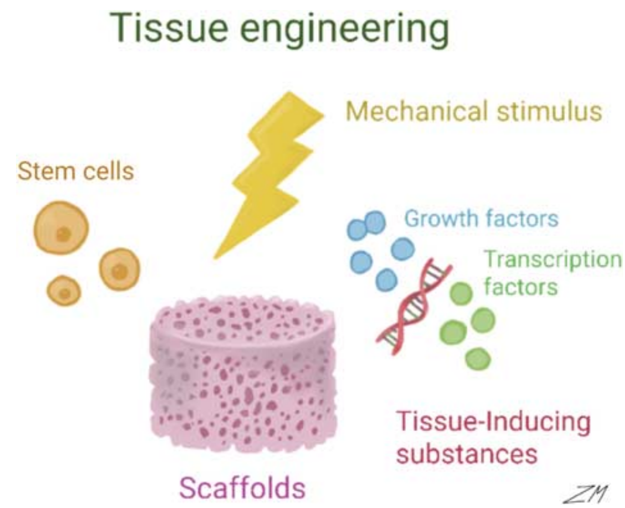

FIGURE 1. Principles of tissue engineering.

From the *University of Geneva, Geneva, Switzerland; and †Department of Biology, Faculty of Science, University of Geneva.

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Address correspondence and reprint requests to Denys Montandon, MD, 112 Florissant, CH-1206 Geneva, Switzerland; E-mail: denys.montandon@bluewin.ch

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and well-established phases that include hemostasis, inflammation, cell migration and proliferation, angiogenesis, granulation tissue formation, wound contraction, and tissue remodeling. Although this physiological process is apt to repair a skin defect, it nonetheless fails to replicate the events of tissue growth and differentiation observed during development. Compared to organogenesis, scar tissue formation prioritizes wound closure over structural restoration. True mammalian regeneration is rare and it only occurs in a few privileged tissues particularly during the early stages of life. Compared to other animals, particularly invertebrates, humans have a much lower capacity of regeneration.

In mammals, a few privileged adult tissues including the liver, the bone marrow, and the epithelium of the gut have the ability to completely recover after mild to moderate injury. The liver is the only solid organ, which uses regenerative mechanisms to ensure that the liver-to-bodyweight ratio tends to reach 100% of what is required for body homeostasis. Other solid organs (such as the lungs, kidneys, and pancreas) adjust to tissue loss but do not return to 100% of normal. Unfortunately, this remarkable ability seems to be limited to tissues with high proliferative capacity and abundant stem cell reserve populations and, therefore, most adult mammalian tissues do not have the ability to regenerate. Instead, the default response to tissue injury typically results in scar tissue formation in the form dense collagenous tissue deposition.

Limb regeneration (Fig. 2)

Certain amphibians, such as salamanders, have the ability to regenerate entire limbs. What remains after amputation ultimately forms an apical epithelial cap, determinant for limb outgrowth. A mass of undifferentiated mesenchymal cells, a blastema, continues the process of limb regeneration similar to the initial formation of the limb bud. The formation of the blastema itself represents a transition phase in which limb cells respond to injury by dedifferentiating to become embryonic limb progenitor cells that can undergo redevelopment.[7] Blastema formation occurs via 3 methods: dedifferentiation, transdifferentiation, adult stem cell recruitment and combinations of these. The blastema gives rise to the differentiated tissues of the regenerating appendage. Whereas salamanders are capable of perfect tail regeneration, lizards can only regenerate an imperfect replica of the original appendage. In mammalians, regeneration is limited to the tip of the digits and is probably linked to the presence of stem cells in the nail bed. In humans, there has been a few reports of digital tip regeneration, particularly in young children, when the amputation was distal to the nail bed.[8,9]

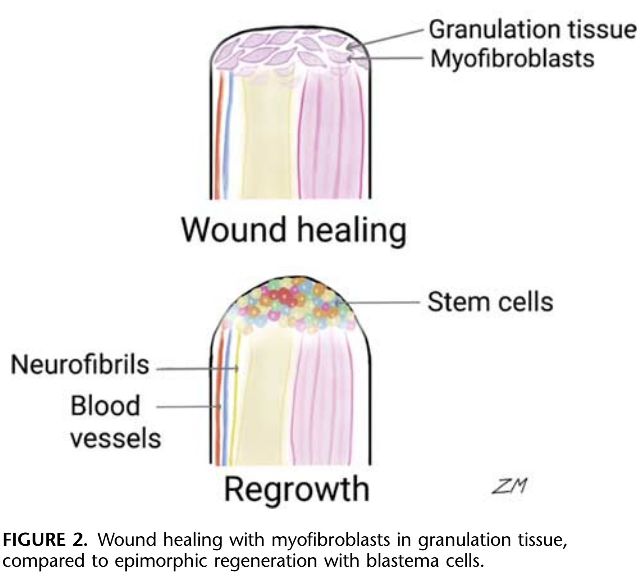

FIGURE 2. Wound healing with myofibroblasts in granulation tissue, compared to epimorphic regeneration with blastema cells.

Two recent reports have given considerable information concerning the differences between cicatricial wound healing and epimorphic regeneration, and might provide new tools to stimulate the regeneration process in mammals and possibly in humans. Thanks to electro- microscopic, immune-fluorescent and chemical studies, the presence of modified fibroblasts within the granulation tissue of the healing wounds has been well documented since the 1970s. These contractile fibroblasts that have acquired features and potentialities of smooth muscle cells have been given the name of myofibroblasts and are in great part responsible of wound contraction.[10] Covering wounds and nerves in rodents with contraction-blocking scaffolds made of collagen, to inhibit the formation of myofibroblasts and their role in wound contraction, Yannas and Tzeranis have been able to show that, preventing natural healing with scar formation, increases regeneration.[11] Although in the early stage of development embryos can regenerate skin, nerves and conjunctival stroma without scars, adult mammals can do the same only if wound contraction and the proliferation of myofibroblasts is inhibited. The authors conclude that a relatively simple modification of the normal healing process, based on use of contraction-blocking scaffold, provides a reliable route towards regeneration of skin and peripheral nerves. In addition, elucidation of the molecular mechanism by which regeneration is induced provides a useful mechanistic basis for future development of regenerative science and medicine.

In the same line of research, Zhao et al[12] have compared the cellular basis of regenerative power in different models, in an attempt to answer the question: What determines the regenerative capacity in animals? They recall that simple animals like planarians, or hydrae have the ability to regrow the entire organisms, in response to injury. Their capacity depends of the abundant reserve of adult stem cells throughout their bodies. Under the influence of an organizing center, neoblasts accumulate to form a regeneration blastema and then convert into any cell type required for regeneration. This pluripotency of neoblasts is similar to that of embryonic stem cells in mammals. Primitive invertebrates (salamanders, xenopus laevis, newts, zebra fish) who may regrow substantial parts of their body, have more limited undifferentiated stem cells. Mammals (mice) have a low power of regeneration, which is depending mainly on age. The underlying reasons for differences in regenerative capacity is mainly based on the presence of stem or progenitor cells. As 1 of the goals of regenerative surgery is to replace or recreate new tissues or parts of the body, like a missing or amputated limb, it could be achieved by the activation of these progenitor cells with inducing substances to form a blastema like structure.

BACK TO THE PAST

The fact that humans cannot regenerate limbs, as certain animals can do, did not escape our ancestors as it is suggested by the 25.000 years old stencils of multiple hands with many of them missing a finger or part of a finger, in the French Gargas-Tibran cave complex and in Maltravieso Cave in Spain. Most archeologists interpret these disfigured Paleo-

FIGURE 3. Presumed amputated fingers, Gargas caves (circa 25000 BC).

lithic hands as being the result of a ritual, shamanistic amputation, as the 1 observed in at least 1 hunter gatherer society, the Dani of New Guinea, who cut off the tips of young women's fingers as part of a vengeance ritual, showing that the mutilation is irremediable (Fig. 3).

The phenomenon of natural wound repair and tissue regeneration has been a subject of preoccupation and wonder since prehistorical times. Descriptions and representations of wounds and their healing or their disruption can be found in many documents of antique civilizations, such as in Mesopotamia, ancient Egypt, Greece, Arabia, China, Alexandria, and Rome, and have continued during the Middle Age and the Renaissance. Improving, accelerating and avoiding complications, such as infections during the healing of wounds, have been the major concern of the first physicians, particularly the surgeons. For Hippocrates, who wrote a whole treaty on wounds and ulcers (Peri Helkon), an organism is not passive to injuries or diseases but tends to counteract them in order to overcome a disturbed equilibrium. This power of Nature, or God, has been a leitmotiv in the whole medical literature up to the 19th century.[13]

It was long recognized in ancient texts, that a few primitive animals like a salamander or a few crustacea do much better in their healing process than humans or mammals, as they are not only covering the wound and generating a scar, but in some cases regenerate a whole amputated limb. ARISTOTLE (384–322 BC), already noted that the tails of lizards and snakes, as well as the eyes of swallow-chicks, could regenerate.[14] Tissue or organ regeneration are also mentioned in the Greek mythology, like the legend of the Hydra, where Hercules slays the heads of the serpentlike monster and try to inhibit their regeneration by cauterizing the stump with a firebrand. Or the legend of the regenerating liver of Prometheus, punished by Zeus for having given fire to man (Fig. 4).

FIGURE 4. The myth of Prometheus' liver regrowth on a Laconian Kylix (560550 BC).

> …in fast bondage, he bound Prometheus, the obvious planner, whipping the painful bindings over a column at midpoint, and against him sent a long-winged eagle to feed on his liver, which was immortal: but whatever this longwinged bird ate during the day grew during the night again in perfection. Hesiod's Theogony (circa 900 BC)

Although the mechanisms by which the various tissues and organs repair themselves after injury in humans and mammals differs from the epimorphic regeneration observed in worms, lizards and some crustaceans, the similarities between these 2 restorative processes had often been noticed. For humans, it was somehow anticipated by the 16th century war surgeon Ambroise PARE in his observations of the amputees. The phenomenon known as "phantom limb," which suggests that a missing part of the body can be felt as a painful regenerated limb reflects, may be, the amputees' mental hope of its regeneration:

> "For the patients, long after the amputation has been made, still say they feel the pain of the dead and amputated parts: and they complain a lot, something worthy of admiration and almost impossible to believe for those who have not had this experience."[15]

The Microscope and the First Biological Experiments

Whether it concerns the study of healing or epimorphic regeneration, the end of the 17th and beginning of 18th century was a landmark for the development of research in these fields, a date that coincides also with what has been called the Age of Enlightenment in literature and philosophy. As a starting point, it is certainly the discovery and use of the microscope that magnified objects from about 25- to 250 fold, following the publications between 1665 and 1683 by Robert HOOK (1635-1703) and Antoni VAN LEEUWENHOEK (16281694) marking the onset of this new era of animals and vegetal investigations. Physician, mathematician and astronomer, Hook is also credited with the first description of a biological cell made from the observation of plants. He describes in 1665 a cell of cork,[16] and was the first to use the word "cell" in 1667. At the same period, the famous Italian anatomist and histologist Marcello MALPIGHI (1628–1694) used the microscope for his studies of the skin, kidneys, and liver. His book on the structure of the silkworm and its meta- morphosis[17] is a model of ultra-conscientious biological observation. The phenomenon of change in the form or structure of some animals or insects, which happens as the animal or insect becomes an adult, has also been studied later by Leeuwenhoek in his letter on the flea, tracing the whole story of the biological metamorphosis of this insect with very precise drawings.[16]

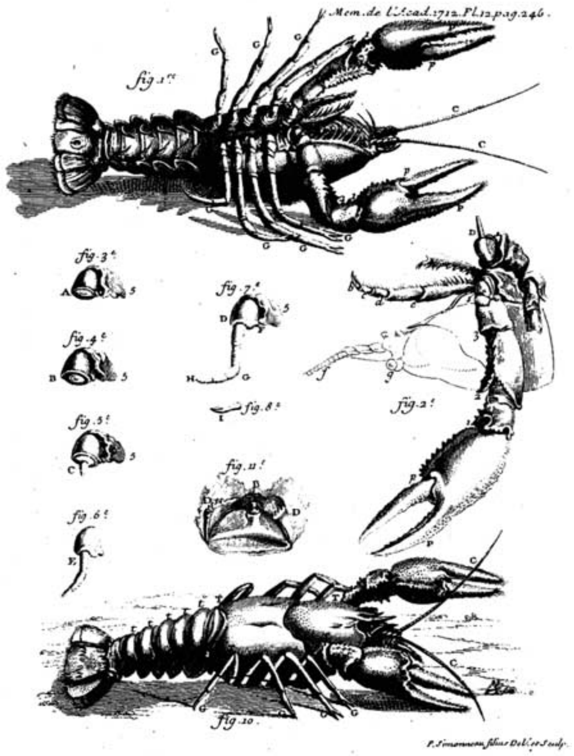

FIGURE 5. Crayfish's limb regeneration illustrated by Réaumur 1712.

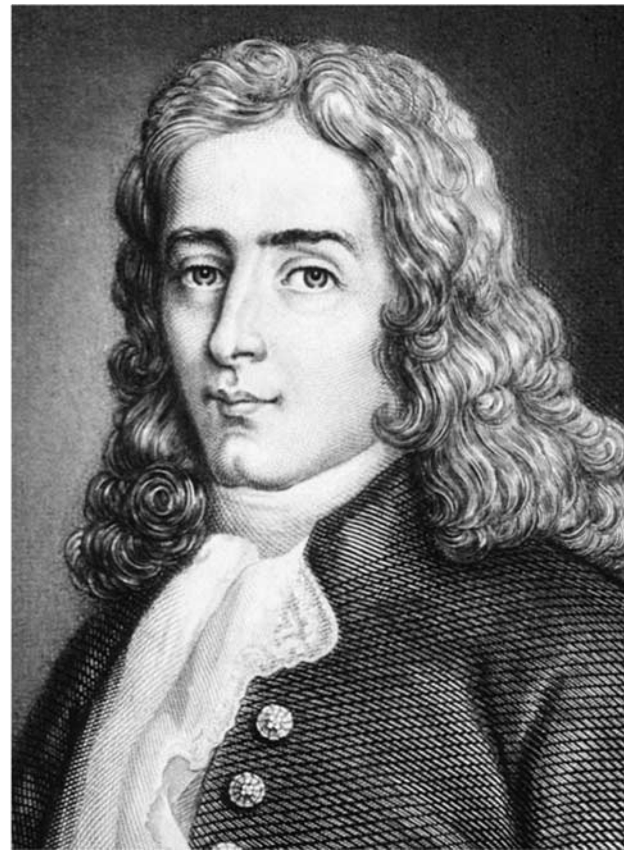

FIGURE 6. René-Antoine FERCHAULT DE RÉAUMUR (1683–1757).

It was already in 1686, that the French naturalist Melchisédech THÉVENOT (1620–1692) made a public demonstration of a lizard undergoing tail regeneration to the Paris Academy of Sciences. The public could follow day after day how the amputated animal was able to regenerate a small part of his body. This fascination for appendices and limb amputation, followed by their regeneration became a legitimate area of scientific inquiry in 1712, when the French scientist Rene-Antoine FERCHAULT DE RÉAUMUR (1683–1757) published his seminal work on crayfish limb and claw regeneration[18] (Fig. 5). Réaumur was a genial scholar with multiple interests encompassing several branches of science. He wrote extensively on natural history, particularly on regeneration, describing for example the locomotor system of echinoderms and showing their ability to replace their lost limbs. One of his greatest works on this subject is the Mémoires pour servir à l'histoire des insects,[19] published in 6 volumes, with 267 plates (Amsterdam, 1734–42).[17] It served as an inspiration for a century of research in this field (Fig. 6).

However, for several historians of science, another event took place in 1740, representing a marked shift in the life science and the foundation of experimental zoology: "With a single snip of the scissors across the middle of an extended hydra in November 1740, the young Swiss tutor Abraham Trembley initiated the modern study of regeneration"[20] (Fig. 7). This single slip of scissors was followed by numerous experiments published in several articles and a groundbreaking book in 1744: Mémoires pour servir à l'histoire d'un genre de polypes d'eau douce.[21] It became also the starting point of an intense and lasting correspondence between the most prominent scientists of the 18th century: Réaumur, Trembley, Bonnet and Spallanzani. Abraham TREMBLEY (1710–1784) (Fig. 8), a young mathematician from Geneva, whereas tutoring natural science in Holland, started experimenting on the fresh water hydra, which he called initially a polyp of

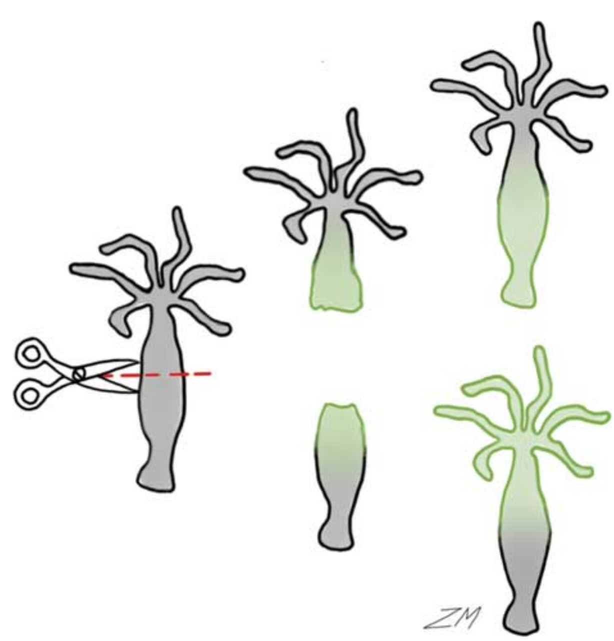

FIGURE 7. Head and tail regeneration after division of a hydra.

FIGURE 8. Abraham TREMBLEY (1710–1784).

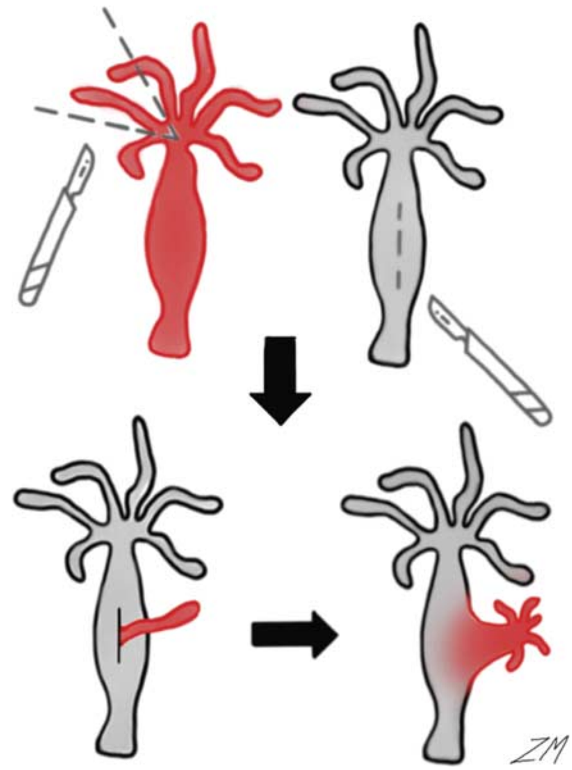

FIGURE 9. Homografting of a hydra's tentacle and regeneration.

freshwater with arms shaped like horns, not knowing if it was a plant or an animal. He soon recognized its animality when he saw it moving and, to study the possibility of regeneration, started sectioning them in every possible way, transversely, longitudinally, and into many pieces, observing the newly formed individuals. He obtained 2 living hydras after sectioning 1 in the middle. Repeating the operation, he obtained 4, then 8 individuals. He was also able to achieve the fusion of fragments of 2 different animals by grafting, producing for example hydras with 16 limbs instead of 8. He thus demonstrated the infinite capacity of these animals to duplicate and regenerate, and their possibility to reproduce asexually by budding. He then sectioned through animals developing buds, eventually creating a 7-headed monster, which he named "Hydra" after the monster in Greek mythology. Grafting part of an individual to another was the first animal allotransplantation duly recorded[22] (Fig. 9). Trembley's Memoirs, published with multiple illustrations drawn and engraved, had an enormous success throughout Europe, particularly at the Royal Society in London, where he was elected as a fellow and was awarded the Copley Medal in 1743. Réaumur in Paris repeated his experiments and confirmed them, and engaged a correspondence with Trembley for several years. But the main support and continuity of Trembley's experiments came from his younger cousin in Geneva, Charles BONNET (1720–1793), (Fig. 10) who was soon to be known as 1 of the leading naturalists of the 18th century. Bonnet, began performing experiments with insects on his own, whereas studying both philosophy and physics. Also very influenced by reading the History of insects by Reaumur, he became the first to discover the parthenogenesis in aphids, proving that asexual reproduction of offspring was possible, and published also a Treaty of insectology in 1745.[23] As soon as Trembley wrote to him about his experiment, Bonnet repeated the same kind of cutting on worms and found that animals bigger than hydra, divided in 2 parts, could also regenerate and give 2 individuals. In fact, for Bonnet, it was not only a discovery of regeneration but also of generation.

"I almost do not know what to admire more, the miracles of Nature contained in this work or the acumen with which they are described, I can recommend this work to all researchers in the natural sciences as the best paradigm of method, out of which they can learn the still too little-known art to investigate the truth of Nature."

Although Bonnet continued to write books and texts on natural sciences and philosophy, he became handicapped by the loss of hearing and diminished sight. Not being able to pursue his experiments, he started an intense correspondence with Lazzaro SPALLANZANI (1729–1799) (Fig. 11) a younger catholic Italian priest and philosopher teaching in Modena, who had already acquired a reputation for his concepts on regeneration. Stimulated by Bonnet, Spallanzani undertook experimental studies of regeneration on a great number of earthworms, freshwater worms, garden snails (slugs), salamanders, and tadpole's tails. Every experiment was recorded in detail with drawings of his own hand. In several regenerated body parts that he observed under microscope, he could see and describe the anatomy of the circulatory system, a domain that rendered him famous later on. Three years before summarizing his results in a publication (announcing a future book which was never published) Prodromo di un'opera da imprimersi sopra le riproduzioni animali,[24] he sent extensive letters to Bonnet, giving him all the details, illustrations and interpretations he could draw from a scientific and a

FIGURE 10. Charles BONNET (1720–1793).

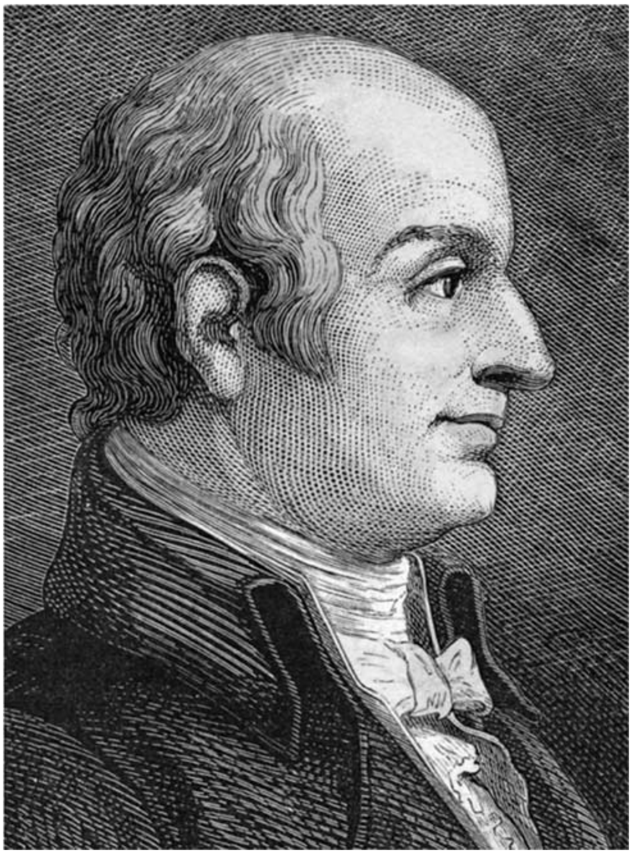

FIGURE 11. Lazzaro SPALLANZANI (1729–1799).

philosophical point of view: salamanders could regenerate their limbs, tails, and jaws; premeta- morphic frogs and toads could regenerate their tails and legs; slugs could regenerate their horns; and snails could regenerate their heads. This last discovery caused quite a stir in 18th century France, leading to an ''unprecedented assault'' on snails as both naturalists and the general public participated in the quest for scientific knowledge by reproducing Spallanzani's intriguing results.[25]

Regeneration Philosophy: Preformation Versus Epigenesis

The 18th century could very well be considered as the golden era in regeneration and generation research. But it was also the theater of a fight between 2 philosophical currents: preformation (or ''over'') theory, and epigenesis, which both started during the previous century.[26] Gottfried Wilhelm von LEIBNIZ (16461716), among other thinkers, described his New System of Nature,[27] expanding on his ideas regarding the union or unity of the soul and the body. That, animals had souls, was for Leibniz, like for Bonnet later on, a given assumption. Every living body had to be created by the Supreme Being. The idea of preformation, that is the ''emboîtement'' or encasement of multiple so-called germs, that could be at the origin of the regeneration in case of amputation, duplication or reproduction, fitted with their religious beliefs. It asserted that all species were structurally complete at the time of the creation, but represented as germs enclosed 1 within the other. ''There is a mechanism that [...] an organic body never could be produced altogether new and without any preformation.'' Réaumur and Bonnet were preformationists and, in fact, Réaumur believed that germs were contained within parts responsible for regeneration. It was thought that the finished being with all its organs was hiding in the germ cells, waiting to unfold like a bud, that the germ cells must already contain the germ cells of all the future descendants nested inside other germ cells. For Bonnet, Trembley's experiments with Hydra and his own with worms supported the preexistence of germs present in the divided parts before the cutting. He encouraged also his pupil Spallanzani to adopt the preformation theory. This last 1 accepted with diplomacy the idea of his elder, that all new ''animalicules,'' or a regenerating limb, arise from an ''egg'' containing a minuscule preformed limb ready to expand when needed, lying at the base of an amputated stump (Fig. 12).

The second view, epigenesis, derived from Aristotelian views, was championed by the physician William HARVEY (1578–1657), asserting that new organisms (and limb regeneration) arose from previously undifferentiated matter, as a completely new generation. During the 18th century, Naturalists like the French Georges-Louis Leclerc conte de BUFFON (1707–1788) and the English microscopist John Tuberville NEEDHAM (1713–1761) developed the conception that a force-like moule intérieur (internal mold) was to organize the material into the various forms of life. This idea was ready-made for epigenesis, since the lost part could be regenerated because the moule intérieur restored the integrity of organisms by reorganizing the organic molecules resident within them[26] (Fig. 13).

Another famous physician and naturalist of Swiss origin Albrecht VON HALLLER (1708–1777), was initially an early adherent of epigenesis. Arguing against several preformationists

FIGURE 12. Picture of the "homunculus" in the human sperm, supporting the ovid or preformation theory.

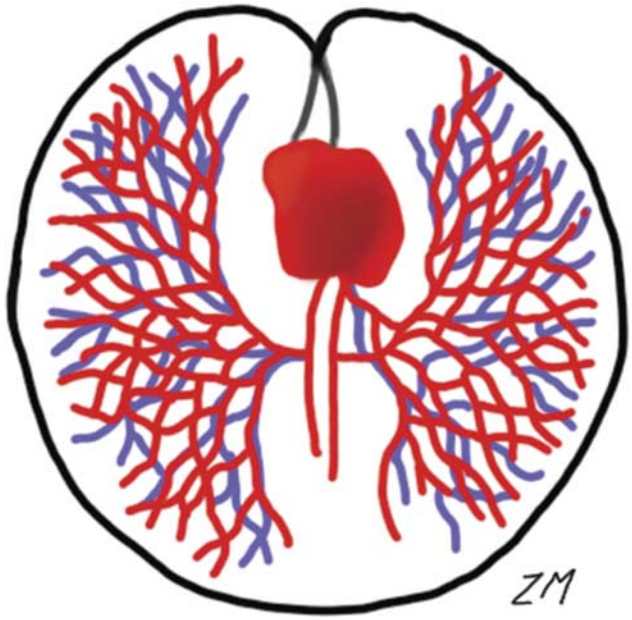

FIGURE 13. Development of blood circulation in the embryo supporting the epigenetic theory.

who used microscopical observations to demonstrate their position, Haller quoted from Aristotle and Harvey to support his view that generation occurred epigenetically from undifferentiated organic fluids. In his First elements of physiology,[28] he adopted a Buffon-like force explanation. A few years later, Haller became skeptical about epigenesis. Later, to seek an academic post,[29] he changed positions and adopted Charles Bonnet's ovist preformation stand in which the egg contained preformed parts and the sperm provided the activation for the coalescence of the part. In fact, neither the preformation theorists nor the epigenetic theorists had observed the germs or the molecules used to explain regeneration. For them, it was mainly an attempt to explain the mystery of life and of the healing power of Nature, either as religious believers or materialist un-thinkers.

From the 18th century to the present time

Research and fascination for the capacity of animals to regenerate parts of their body did not stop since the pioneer's works of the 18th century. Numerous outstanding scientists have tackled this subject with the technological tools and the physiological knowledge of their time, as for example the neurotrophic phenomenon in limb regeneration initiated by the English physician Tweedy John TODD in 1823 or the relationship of bioelectricity and epimorphic regeneration studied mostly since the beginning of the 20th century. There is however a considerable change of paradigm by the late 1830s, when botanist Matthias Jacob SCHLEIDEN (1804–1881) and zoologist Theodor SCHWANN (1810–1882) were studying tissues and proposed the unified cell theory stating that all living things are composed of 1 or more cells, that the cell is the basic unit of life; and new cells arise from existing cells.

Regeneration in the 18th century and regeneration in our time do not carry the same semantic charge, do not cover the same fields, and it would be a damaging "precursoritis," to seek in Réaumur, Trembley and Bonnet the premises of a debate that they could not in any way formulate: that of the regenerative potential of stem cells. Although it is tempting to make a parallel between Bonnet germs and ovid theory and the presence of stem cells that we know today, or the epigenesis of Harvey and Buffon and the modern epigenetic theory, 1 has to be aware that these terms had different meanings throughout the ages. Several terms describing animal modifications, like epimorphosis, morphallaxis, (w)holism, organizing center and even generation and regeneration, have been used by different authors to express sometimes different significations. It is nevertheless certain that the scientists of the 18th century paved the way of experimental biology and possibly to some of the most significant advances of modern medicine. Charles Bonnet was a visionary when he wrote in 1745:

> "Modern anatomy has done much work on this great mystery of Nature, the generation of Animals. We may presume that the number of ancient discoveries with which it has been enriched, will increase by what Physicists do not fail to make on insects (word given at that time for small animals), which are multiplied by cutting them into pieces. […] Physicians and Surgeons will be able to study better than in any other part of our body, or of that of animals, all that concerns the theory of wounds, the manner in which they heal and consolidate. Who would know if this will not lead them to some discovery that will perfect Medicine and Surgery?"[23]

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