Is There a Field of Wound Pharmacology?

Major improvements in almost all branches of surgery have occurred during the past 50 years. Pioneering developments in cardiovascular surgery, organ transplantation, and in the repair of congenital anomalies, to name but a few, are now embedded in everyday surgical practice. Driven by technological advances as well as by new science, this progress has permitted surgeons to restore to health patients who were previously untreatable. These advances also have allowed smoother recovery and reduced morbidity rates for those undergoing conventional operative procedures.

Progress in improving wound healing *per se* has been more moderate. It has centered mainly on the prevention of vitamin, trace metal, and protein deficiencies that delay wound healing or lead to wound breakdown. Beyond attempts to reduce or prevent pathologic scar formation, few active interventions in wound management have fundamentally affected the outcome of healing. Although novel suture materials have been a most important contribution to microsurgery and to vascular surgery, these advances have only marginally affected the healing of surgical wounds and of chronic wounds or ulcerations.

The existence of this relatively static status of wound management has not been for lack of research effort. In fact, in the past two decades we have witnessed elegant studies of the mechanisms of wound healing, not only at the cellular level, but at the biochemical and molecular levels as well. Many of these investigations have been conducted by surgeons in collaboration with basic scientists.[1,2] Until the past 3 to 5 years, however, the conventional wisdom was that for most clean wounds, healing occurred at ceiling rates and by optimal incorporation of cellular and matrix components. Almost no one thought that normal wound healing could be further enhanced by any biochemical or therapeutic manipulation.

The discovery in 1962 of the first growth factor,[3] epidermal growth factor (EGF), did not immediately alter this thinking. More than a decade passed before this growth factor was tested in animal wounds, and it was more than a quarter of a century before the first clinical trial of EGF was reported.[4] Subsequently, other growth factors were discovered and produced in large quantity by recombinant technology. These included platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and transforming growth factor-beta (TGF-β). Once it was recognized that angiogenesis, fibroblast proliferation, and collagen production could be stimulated by these polypeptides, they were applied to experimental wounds.

Thus, it was revealed for the first time that clean surgical wounds could undergo *accelerated* healing. It was soon found that each of these molecules could accelerate healing of chronic wounds or wounds with specific healing deficiencies.[5–7] Because of the many similarities between chronic wounds and chronic duodenal ulcers, accelerated healing of ulcers was also stimulated by administration of an angiogenic factor.[8] Taken together, these results kindled intense activity in university and pharmaceutical laboratories to determine which was "the optimum" growth factor for wounds. The drive to find a single growth factor that could accelerate wound healing was heavily influenced by the potential of clinical application, but also by the added difficulty of obtaining Food & Drug Administration (FDA) approval for mixtures of multiple growth factors. This search for a therapeutic growth factor, however, led to a new concept of "wound pharmacology." The developers of this young field have begun to recognize that optimum promotion of wound healing may require the administration of more than one growth factor.[9] Nevertheless, these efforts have been focused almost exclusively on acceleration of wound healing.

In this issue of the *Annals,* Adzick and Longaker[10] now propose that the field of wound pharmacology deserves a wider focus. They argue that it may soon be possible to therapeutically modify other characteristics of wound healing, for example, scar formation. Such therapy could prevent or reverse many types of pathologic scars, including hepatic cirrhosis, pulmonary fibrosis, and burn contractures. The authors base this proposal on their own studies of fetal wound healing. Fetal wounds in animals and humans heal with greatly diminished scar formation. In its simplest form, the Adzick-Longaker hypothesis says that at least one essential difference between fetal and adult wounds is the level of hyaluronic acid. Fetal wounds heal with a persistently elevated level of hyaluronic acid. Hyaluronic acid in the wound matrix may organize the deposition of collagen in a unique fashion so that little or no scarring or contraction ensues. In contrast, adult wounds have only a transient elevation of hyaluronic acid. The point that should be emphasized is that a thorough

understanding of the mechanisms of fetal wound healing may provide a novel approach to prevent pathologic scar formation in adult wounds. The authors quote interesting preliminary experiments in which topical hyaluronic acid was able to modify scar formation in animals. It is also interesting that different fragments of hyaluronic acid can either stimulate or inhibit angiogenesis.[11,12]

It often matters less that a hypothesis is right or wrong, than that it is fruitful. The hypothesis presented here is important especially because it is likely to be very productive for the field of wound pharmacology. As this field develops, it may introduce the next revolution of fundamental advances in surgery.

References

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