

The article in this issue of *The Journal* by Beck, Amento, and colleagues (1) is a landmark in its conceptual approach to the use of peptide growth factors for experimental wound healing and presages important clinical applications in the future. As background, it has been known for more than 10 years that direct application of peptide growth factors (cytokines) to an experimental wound will accelerate healing, and the agent used in the present study, TGF- β , was one of the first cytokines shown to be effective for this purpose (2-4).

The present article is conceptually unique in that the authors have shown that direct application of a peptide growth factor to a wound is not necessary to enhance healing; systemic administration can be equally effective. The experimental design has been to use rats whose intrinsic capacity to heal wounds is defective, either as a result of old age or from treatment with a glucocorticoid, and to make standard dorsal incisional wounds. These rats have been treated intravenously with a single dose of TGF- β 1, while untreated wounded rats have served as controls. Significantly, TGF- β was effective in enhancing healing whether it was given at the time of wounding, 4 h after wounding, or, most surprisingly, even 24 h before wounding; this effect was measured either by increased tensile strength of the treated wound 1 wk later, or by increased deposition of extracellular matrix, particularly collagen.

What are the mechanisms whereby systemic administration of TGF- β , given before the creation of a wound, can accelerate its subsequent healing? Clearly this is a result that could be of major clinical significance, and further understanding of its mechanism is therefore needed. To begin, TGF- β is the prototypical multifunctional cytokine. Its receptors, actions, and effects are germane to almost every cell in the body involved in tissue injury and repair. Thus, α -granules of platelets are a highly concentrated source of TGF- β , while macrophages both react to TGF- β with a strong chemotactic response (concentrations as low as 10^{-15} M are effective) and also secrete several other cytokines when exposed to TGF- β . TGF- β is also a key regulatory molecule in the control of the activity of fibroblasts. TGF- β is strongly chemotactic for these cells and regulates their production of almost every known molecule of the extracellular matrix, including collagen, fibronectin, tenascin, as well as the integrins that are the receptors for these molecules. Furthermore, TGF- β blocks the destruction of newly synthesized extracellular matrix by upregulating the synthesis of protease inhibitors and downregulating the synthesis of matrix-degrading proteases such as stromelysin and collagenase, and of hydrogen peroxide. Another highly relevant action of TGF- β is its potent ability to induce angiogenesis (5-7).

How are all of these mechanisms brought into play when TGF- β is not administered directly to a wound, and in particular when it is given before the onset of wounding? This remains a major question. One important lead is the ability of TGF- β to induce its own synthesis, as shown in many studies, both in cell culture (8) and in vivo (9, 10). Thus, in the present experiments prior injection of TGF- β may have primed macrophages and fibroblasts throughout the body to respond more effec-

tively to a future injury. The initial endocrine action of the TGF- β would then be amplified by paracrine and autocrine mechanisms. Another important process in this regard is the activation of latent TGF- β ; two proteins that bind either latent or active TGF- β have recently been shown to participate in the activation of the latent TGF- β complex (11, 12), and one must consider whether prior administration of TGF- β enhances this process.

Whatever the mechanisms involved, these new studies suggest many important clinical applications. The need for more adequate treatment of chronic wounds, whether they be diabetic ulcers, decubitus ulcers, venous stasis ulcers, or related lesions, continues. The costs of these conditions to individual patients and the community as a whole, both in terms of personal pain and financial loss, are immense. It is indeed a sad commentary on our health care system that we have yet to find a successful way to use the immense amount of new knowledge obtained in cytokine research for the prevention of more than 50,000 amputations that are performed each year in diabetic patients.

Apart from treatment of chronic wounds, there remains the possibility to use peptide growth factors for treatment of acute wounds, particularly in a conventional surgical setting. What would the savings be to the health care system if we could shorten the hospital stay of the typical surgical patient by even one day? The studies reported here suggest that eventually one might be able to use a cytokine such as TGF- β in a prophylactic manner, to be given to the elective surgical patient before surgery to ensure the most rapid possible healing. Yet another prophylactic use of TGF- β to enhance healing would be its administration to patients with known impaired healing capacity, such as those undergoing high-dose radiation therapy or chemotherapy, as well as our increasingly aged population. Further development of TGF- β for prophylaxis or attenuation of tissue damage caused by myocardial (13) or cerebral (14) ischemia is also needed; both the myocardial and cerebral infarct can be viewed as special classes of wounds. Although chronic exposure to elevated levels of TGF- β may be associated with undesirable fibrotic reactions (15), there is no indication that a single priming dose of TGF- β is associated with any type of untoward response. Since TGF- β is one of the critical endogenous cytokines involved in physiological wound healing, such systemic treatment with TGF- β would represent a novel approach to endocrine replacement therapy.

In clinical practice, successful topical use of TGF- β to heal localized lesions in the human eye (macular holes) has recently been shown (16). There is now an immense opportunity to extend this knowledge for wider human application for many more common debilitating conditions, as well as for more routine uses. With increasing interest in preventive medicine and cost containment, TGF- β offers unique mechanisms for prevention of tissue injury and acceleration of its repair. Beck, Amento, and colleagues (1) have provided an imaginative and significant new approach to this problem.

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