Abstinence From Smoking Reduces Incisional Wound Infection:

A Randomized, Controlled Trial

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Sorensen et al. performed a randomized, controlled experiment to address the effect of smoking on wound healing. Nonsmokers were compared with smokers randomized into groups in which they continued smoking, abstained from smoking with a nicotine patch, or abstained from smoking with a placebo patch. Small sacral skin wounds were made and examined for evidence of wound infection or rupture at various times after wounding. The data in this article demonstrate what a number of scientific data and clinical anecdotes have suggested, that smoking results in impaired wound healing as evidenced by wound rupture rates. Furthermore, the authors demonstrate an increased risk of *wound infection* in the subjects who continue to smoke but not in nonsmokers or smokers using a nicotine or placebo patch. Importantly, the findings were made in "clean" skin wounds. They find that a short period of abstinence from smoking was sufficient to reduce the risks of wound infection in smokers to that of nonsmokers. Interestingly, this effect was not dependent on whether the abstinent smoker used a nicotine patch.

A number of studies have recently been published highlighting the relationship between active smoking and wound infection. The lead author of the current paper being discussed has previously published on the increased risks of wound healing complications, including infection after breast surgery in smokers in a prospective cohort study.[1] Another prospective cohort study found the same increased risk of wound infection in a variety of ambulatory surgical procedures.[2] Interestingly, they reported that ex-smokers also had an increased risk of wound infection that verged on significance. In a prospective, randomized trial of patients undergoing orthopedic procedures, preoperative smoking cessation intervention was found to significantly reduce postoperative wound infections only if the participants stopped smoking, but not if they merely decreased their level of smoking.[3] These studies were in patients undergoing operations with "clean" wounds who should experience few wound infection problems. In the current study by Sorensen et al., it can be argued that the wounds they are creating are far smaller and would be the sort of wound many surgeons would normally have little concern regarding infection.

New data about the biology of nicotine have raised a number of questions about the role of nicotine in smoking-related disease. There is much evidence showing that nicotine is the chemically addictive component in cigarette smoke. Recently, Heeschen et al. described nicotine as an angiogenic factor when used as a single agent in *in vitro* studies.[4] The same group has gone on to show that nicotine can enhance wound healing in the diabetic mouse model and promotes arteriogenesis in a limb ischemia model at a level

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comparable to fibroblast growth factor 2 (FGF2), a well-known angiogenic factor.[5] These data on nicotine are in contrast to the findings of Sorensen et al. and to previous laboratory models showing inhibition of angiogenesis by cigarette smoke.[6]

The data presented by Sorensen et al. suggest that, perhaps, we have been too simplistic in our assumptions about why cigarette smoking causes harm; we have equated the addictive nature of nicotine with the harmful effects of smoking. Although nicotine might be the reason why smokers have such a difficult time quitting the habit, it is clear that the clinical and physiological effects of cigarette smoke are the result of a complex interplay of the thousands of chemicals that are present.[7]

Before we leap to the conclusion that we might all benefit from having a nicotine patch, Heeschen et al. also noted that nicotine appears to promote growth in a murine lung tumor model and stimulates the growth of atherosclerotic lesions in a separate model of atherosclerosis.[4] This would appear to be consistent with the known association of smoking with lung cancer and atherosclerotic disease. By extension of the wound healing data, it would be equally naive to think nicotine is the only factor in cigarette smoke causing lung cancer or atherosclerotic disease.

Our laboratory has a significant interest in the role of hypoxia in wound healing. We see wound healing as a form of natural tissue regeneration and have been interested in better understanding wound healing as a way to help us design tissue-engineered solutions for deficits in somatic tissues. In a number of models of wound healing or tissue regeneration of skin and bone, it has become evident that the process of angiogenesis is critically important. Hypoxia has been identified as an important trigger for transcription of angiogenic factors.[8,9]

Hunt has long championed the importance of hypoxia in wound healing. We note that the senior author of the currently discussed paper and Hunt were among the first to report methodology for measuring oxygen tension in the wound environment.[10,11] They reported over a decade ago that significant declines in subcutaneous wound tissue oxygen in smokers could be detected.[12] Furthermore, the degree of hypoxia noted had been found to result in poor wound healing in animal models. The initial interpretation of these results was that this hypoxia was secondary to the vasoconstrictive effects of nicotine. The new data on nicotine would suggest that tissue hypoxia might be the result of additional factors. We note again that the use of a nicotine patch did not result in a wound-healing defect in the current study. An important set of adjunct experiments to the ones reported here would be to measure arterial blood gases and local cutaneous oxygen tension in these research subjects. This could help address the question of whether nicotine alone can cause local tissue hypoxia.

In the past 10 years, research has demonstrated that cells respond to hypoxia as a cellular stress and initiate a complex genetic cascade that is thought to have the goal of protecting the cell's integrity. Hypoxia-inducible factor 1 (HIF-1) was identified as a transcription factor that, as the name implies, is induced by conditions of low oxygen tension in studies of the transcriptional regulation of erythropoietin.[13,14] HIF-1 consists of a α and β subunit. Regulation of HIF-1 transcriptional activity is dependent on the α subunit. HIF-1α is constitutively made. In the presence of normal oxygen tensions, HIF-1α is ubiquinated and degraded. Low oxygen tension results in stabilization of HIF-1α and translocation of this subunit into the nucleus where it can participate in the transcriptional activation complex.[13] The exact molecular mechanisms of how low oxygen tension is sensed by the cell are still unknown.

The genes directly regulated by HIF-1 reflect the body's response to hypoxia. The initial identification of HIF-1 was in studies of the regulation of erythropoiesis. It makes teleologic sense that these genes would be upregulated in response to low oxygen tension. Under conditions of hypoxia, there is an upregulation of genes involved in glucose metabolism. A number of genes involved in angiogenesis are also upregulated by HIF-1, including vascular endothelial growth factor (VEGF) and flt-1, the receptor for VEGF.[9,13] In addition to the studies on wound healing, the role of hypoxia in cancer is a field of intense study. The central portions of tumors have long been known to suffer from relative hypoxia secondary to an inadequate blood supply to feed the growing tumor.[15,16]

In models of myocardial and cerebral ischemia, there is evidence that activation of HIF-1 functions to protect the cells from damage. Specifically, the phenomenon of ischemic preconditioning is known to extend some protection to a subsequent ischemic insult and is mediated by the inducible nitric oxide synthase (NOS2).[17] HIF-1 has been demonstrated to induce NOS2 in hypoxic cardiac myocytes and endothelial cells and is thought to be the mechanism by which these cells respond to hypoxia.[18] In addition to examining the oxygen tension in smokers, nicotine patch users, and nonsmokers, it would be of further interest to see how HIF-1 is regulated in these circumstances.

Sorensen et al. present a timely scientific study that seeks to address the question of the effect of smoking on wound healing and infection in a highly controlled manner. Even more striking is that Sorensen et al. find the potential for infection of even a minor, clean wound, as they performed, is affected by smoking. A number of surgeons already counsel their patients to stop smoking before major abdominal or thoracic procedures. Many plastic surgeons will not perform free tissue transfers in active smokers because of the concerns of poor wound healing. These data suggest that surgeons need to be even more active in recommending smoking cessation

programs to their patients because the impact of smoking on even minor incisions can be significant.

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