



Published in final edited form as:

Wound Repair Regen. 2009 ; 17(6): 763–771. doi:10.1111/j.1524-475X.2009.00543.x.

## Human Skin Wounds: A Major and Snowballing Threat to Public Health and the Economy

Chandan K. Sen, PhD<sup>1</sup>, Gayle M. Gordillo, MD<sup>1</sup>, Sashwati Roy, PhD<sup>1</sup>, Robert Kirsner, MD<sup>2</sup>, Lynn Lambert, CHT<sup>1,3</sup>, Thomas K. Hunt, MD<sup>4</sup>, Finn Gottrup, MD<sup>5</sup>, Geoffrey C Gurtner, MD<sup>6</sup>, and Michael T. Longaker, MD<sup>6</sup>

<sup>1</sup> The Ohio State University Comprehensive Wound Center, Department of Surgery, Columbus, OH

<sup>2</sup> Department of Dermatology, University of Miami Miller School of Medicine, Miami, FL

<sup>3</sup> National Healing Corporation, Boca Raton, Florida

<sup>4</sup> Department of Surgery, University of California- San Francisco

<sup>5</sup> Copenhagen Wound Healing Center, Department of Dermatology, Bispebjerg University Hospital, Copenhagen, Denmark

<sup>6</sup> Department of Surgery, Stanford University School of Medicine, Stanford, CA

### Abstract

In the United States, chronic wounds affect around 6.5 million patients. It is claimed that an excess of US\$25 billion is spent annually on treatment of chronic wounds and the burden is growing rapidly due to increasing health care costs, an aging population and a sharp rise in the incidence of diabetes and obesity worldwide. The annual wound care products market is projected to reach \$15.3 billion by 2010. Chronic wounds are rarely seen in individuals who are otherwise healthy. In fact, chronic wound patients frequently suffer from “highly branded” diseases such as diabetes and obesity. This seems to have overshadowed the significance of wounds per se as a major health problem. For example, NIH’s Research Portfolio Online Reporting Tool (RePORT; <http://report.nih.gov/>), directed at providing access to estimates of funding for various disease conditions do list several rare diseases but does not list wounds. According to the latest data from the National Center for Health Statistics, 40 million inpatient surgical procedures were performed in the United States in 2000, followed closely by 31.5 million outpatient surgeries. The need for post-surgical wound care is sharply on the rise. Emergency wound care in an acute setting has major significance not only in a war setting but also in homeland preparedness against natural disasters as well as against terrorism attacks. An additional burden of wound healing is the problem of skin scarring, a \$12 billion annual market. Current research advances in the field have led to solutions that have been effective in improving patient care. The immense economic and social impact of wounds in our society calls for allocation of a higher level of attention and resources to understand biological mechanisms underlying cutaneous wound complications. Investment in the detailed scrutiny of wounds presented clinically as well as in pre-clinical models seems prudent.

### Chronic Wounds

Chronic wounds are rarely seen in individuals who are otherwise healthy. In fact, chronic wound patients frequently suffer from “highly branded” diseases such as diabetes and obesity. The purpose of this article is to highlight the significance of investing in the development of wound sciences as an interdisciplinary field with lucrative translational opportunities to manage public health. The term co-morbidity refers to the association of two distinct diseases in the same individual at a rate higher than expected by chance. As a result, the true impact of chronic wound is diminished. From a funding standpoint it is seen only in parts, *i.e.* foot ulcers

as a complication of diabetes or pressure ulcers as a complication of spinal cord injuries and never as the sum of these parts. This seems to have overshadowed the significance of wounds per se as a major health problem. For example, NIH's Research Portfolio Online Reporting Tool (RePORT; <http://report.nih.gov/>), directed at providing access to estimates of funding for various disease conditions does list rare diseases such as Pick's but does not list wounds. Pick's disease is a rare neurodegenerative condition that is just one of the causes of the clinical syndrome now known as frontotemporal lobar degeneration<sup>1</sup>. Current advances in wound research have led to solutions that have markedly improved patient care<sup>2-8</sup>. Experimental observations have helped formulate guidelines of care providing the basis for uniform care across the country<sup>9-13</sup>. Strengthening of wound healing research, in light of the rapidly growing threat, deserve a higher level of prioritization.

Chronic wounds are those that have failed to proceed through an orderly and timely reparative process to produce anatomic and functional integrity of the injured site<sup>14</sup>. Often disguised as a comorbid condition, chronic wounds represent a silent epidemic that affects a large fraction of the world population and poses major and gathering threat to the public health and economy of the United States. In developed countries, it has been estimated that 1 to 2% of the population will experience a chronic wound during their lifetime<sup>15</sup>. In the United States alone, chronic wounds affect 6.5 million patients<sup>16, 17</sup>. In the Scandinavian countries, the associated costs account for 2-4% of the total health care expenses<sup>18</sup>.

The burden of treating chronic wounds is growing rapidly due to increasing health care costs, an aging population and, in the United States and beyond, a sharp rise in the incidence of diabetes and obesity worldwide. It is claimed that an excess of US\$25 billion is spent annually on treatment of chronic wounds<sup>19</sup>. To that add the rapidly expanding need for wound care of our veterans, and the need to prioritize wound care and research would appear to be compelling. At present, over 1000 outpatient wound centers are in operation in the United States, not including all the wound care rendered by clinicians in their offices, by inpatient acute care hospitals, long term facilities and nursing homes.<sup>20</sup> According to a new report by Global Industry Analysts, the annual wound care products market would reach \$15.3 billion by 2010. The United States represents the world's largest and the fastest growing market<sup>21</sup>. The amount of money spent on wound care, the loss of productivity for afflicted individuals and the families that care for them and their diminished quality of life come at great cost to our society.

## Pressure Ulcers

An infected pressure ulcer, secondary to spinal cord injury, caused the untimely death of the actor Christopher Reeve, known for playing "Superman". According to the National Pressure Advisory Panel, a pressure ulcer is localized injury to the skin and/or underlying tissue usually over a bony prominence, as a result of pressure, or pressure in combination with shear and/or friction. Vulnerable patients include the elderly, stroke victims, patients with diabetes, dementia, those in wheelchairs, bedridden or suffering from impaired mobility or sensation. Paralysis on the operating room table and sedentary stays in the ICU are also situations that can initiate pressure sore development in otherwise healthy patients. Patients 65 years of age and older accounted for 72% of all patients hospitalized during which pressure ulcers were noted. Of those patients with pressure ulcers who were hospitalized, nearly 9 of every 10 were covered by government health programs—66 percent by Medicare and 23 percent by State Medicaid programs. Patients with pressure ulcers are usually admitted to the hospital for a medical reason other than pressure ulcer. For patients with pressure ulcers the most common primary diagnoses for hospitalizations include: septicemia, pneumonia, urinary tract infections, congestive heart failure, respiratory failure and complicated diabetes mellitus<sup>22</sup>. It appears that the prevalence of pressure ulcers increases with underlying disease. By example, in the United States, the national pressure ulcer advisory panel report that the prevalence of pressure

ulcers in a critical care setting is 22%<sup>23</sup>. Comparably, the prevalence of pressure ulcers among hospital inpatients in Europe is typically above 20%<sup>24</sup>. Almost one-third were severe ulcers at grade 3 or 4 and most (50–80%) were hospital-acquired. In Scandinavia, the prevalence of open pressure ulcers vary between 13 and 27%<sup>25–28</sup>. In Denmark it was found that 58% of open pressure ulcers were not documented neither in the medical record nor in the nurse record<sup>25</sup>. This merely reflects that pressure ulcers and chronic wounds tend to develop in a debilitated patient population. Even though a great deal of effort is expended to try and prevent pressure ulcers, it is still extremely difficult and expensive to adequately relieve pressure<sup>29–33</sup>. This is a global problem that does not seem to be unique to any specific region of the world.

Pressure ulcers can be a major source of infection and lead to complications such as septicaemia, osteomyelitis and, even death. It is estimated that there are over 7.4 million pressure ulcers in the world where estimation was possible i.e. excluding the vast number of developing countries<sup>34</sup>. Annually, 2.5 million pressure ulcers are treated in the United States in acute care facilities alone<sup>35</sup>. According to data from the Department of Health and Human Services' Agency for Healthcare Research and Quality (AHRQ), the number of hospital patients with pressure sores rose by 63% during the period 1993–2003. The price of managing a single full-thickness pressure ulcer is as much as US\$70,000, and US expenditures for treating pressure ulcers have been estimated at \$11 billion per year<sup>36, 37</sup>. During the first two weeks of admission alone hospital acquired pressure ulcers occur in approximately 9% of hospitalized patients<sup>38</sup>. The average length of stay in the hospital for treatment of a pressure ulcer is 13 days<sup>22</sup>. Development of a pressure ulcer increases the mortality rate by 7.23%<sup>39</sup>. The additional average charge for a hospital stay per case related to pressure ulcers is \$43,180.<sup>40</sup> About 15% of patients in acute care facilities and up to 29% of patients in long-term care facilities will experience a pressure ulcer<sup>41</sup>. The development of pressure ulcers may also have important legal consequences. For example, the failure to prevent pressure ulcers in long-term care settings has resulted in increasing litigation, with settlements favoring long-term care residents in up to 87% of cases<sup>42, 43</sup>. The number of hospital patients who develop pressure ulcers has risen by 63% over the last 10 years and nearly 60,000 deaths occur annually from hospital-acquired pressure ulcers<sup>44</sup>.

Pressure ulcers now have even graver implications for health care<sup>45</sup>. According to the Centers for Medicare & Medicaid Services (CMS), in FY2007, there were 257,412 preventable pressure ulcers reported as secondary diagnoses in hospitals<sup>40</sup>. Starting October 2008, CMS no longer pays for hospital acquired pressure ulcers<sup>46</sup>, because they can “reasonably be prevented through the application of evidence based guidelines”. The financial implications of this new policy are substantial. Starting in October 2008, CMS discontinued assigning a higher payment to hospitals for pressure ulcers that develop during hospitalization<sup>46</sup>. This proposed ruling became final on August 1, 2007, when CMS included pressure ulcers as 1 of the at least 2 conditions that were required to be selected. CMS refers to this as the present on admission hospital-acquired conditions. Reduction of facility-acquired pressure ulcers and improvement of outcomes through better practices and research is therefore a matter of high priority.

## The Rising Threat Because of Diabetes

Over 23 million people or 7.8% of the U. S. population suffer from diabetes. While 17.9 million have been diagnosed, 5.7 million are unaware that they have the disease.<sup>47</sup> During the period 2005–2007, the total incidence of diabetes increased 13.5%<sup>48</sup>. Worldwide there are major differences in the prevalence of diabetes. The highest prevalence of diabetes was found in Nauru (30.7%) while the Middle East regions ranks among the highest with United Arab Emirates at more than 20%<sup>49</sup>. In Europe and the Scandinavia, the prevalence is estimated at 5–7%<sup>24</sup> and this is expected to increase significantly during the next 20 years, especially in

the elderly<sup>50</sup>. In Denmark, the prevalence of diabetes (types 1 and 2) is expected to double in the next 15–20 years (The Danish Diabetic Association).

Diabetic neuropathy, defined by damage to the foot's sensory nerves, contributes to foot deformities and/or ulcers that increase the chance of lower-extremity amputations unless treated. It is estimated that up to 25% of all diabetics will develop a diabetic foot ulcer<sup>51</sup>. About 71,000 non-traumatic lower-limb amputations were performed in people with diabetes in 2004<sup>47</sup>. Sixty-seven percent of all lower extremity amputation patients have diabetes<sup>52, 53</sup>. At \$38,077 per amputation procedure, diabetes-related amputations cost approximately three billion dollars per year<sup>54</sup>. Every year 5% of diabetics develop foot ulcers and 1% require amputation<sup>55</sup>. Recurrence rate of diabetic foot ulcers is 66% and the amputation rate rises to 12% with subsequent ulcerations<sup>55</sup>. The age-adjusted lower-extremity amputation rate for people with diabetes (5.5 per 1,000 people with diabetes) was 28 times that of people without diabetes (0.2 per 1,000 people). Diabetes-related lower-extremity amputations were on average age of 66 years, while non-diabetes-related LEA were on average age 71 years old.<sup>52</sup> Amputation rates rise with age. By example, in 2003, the lower-extremity amputation rate per 1,000 people with diabetes was 3.9 among people under age 65, 6.6 among people age 65 to 74 and 7.9 among people age 75 or older<sup>56</sup>. Amputation rates are also influenced by race, with the age-adjusted lower-extremity amputation rate per 1,000 people with diabetes was 5.0 among blacks compared with 3.2 among whites. Additionally it appears men are more likely to have an amputation with the age-adjusted lower-extremity amputation rate among men (5.8 per 1,000 persons with diabetes) approximately twice that the rate among women<sup>56</sup>. In Denmark optimal vascular surgery and wound management in a multidisciplinary set up resulted in a 75% decrease in the incidence of major amputations<sup>18, 57</sup>.

## From Foot Ulcers to Amputation

The diabetic foot constitutes a tremendous challenge for patients, caregivers and the health care system. Up to 25% of individuals with diabetes will develop a foot ulcer during their lifetime<sup>51</sup>. Adjusting for health-care inflation in 2007, foot ulcers cost between \$7,439 and \$20,622 per episode<sup>58</sup>. Ulcers and other foot complications are responsible for 20% of the nearly 3 million hospitalizations every year related to diabetes. Many of these patients eventually must undergo lower extremity amputations as a result of infection brought on by untreated foot ulcers<sup>59</sup>. It is estimated that 12% of individuals with a foot ulcer will require amputation<sup>55</sup>. The 5-year survival rate after one major lower extremity amputation is about 50%<sup>60</sup>. Once amputation occurs, 50% of patients will develop an ulcer in the contralateral limb within 5 years<sup>55</sup>. According to estimates, a total of \$9 billion were spent on the treatment of diabetic foot ulcers in 2001<sup>61</sup>.

## Venous Ulcers

In the United States it has been estimated that venous ulcers cause the loss of 2 million working days per year<sup>62</sup>. Venous ulcers account for 70%–90% of ulcers found on the lower leg<sup>63</sup>. The prevalence of venous ulcers in the U.S. is approximately 600,000 annually<sup>64</sup>. In individuals 65 years and older, venous leg ulcers affect approximately 1.69% of the population in the U.S.<sup>41</sup>. Venous leg ulcers cost approximately \$9,600 to treat<sup>41</sup>. The annual cost of treating venous ulcers to the US healthcare system is estimated at \$2.5–3.5 billion<sup>63</sup>. Up to one-third of treated patients experience four or more episodes of recurrence<sup>62</sup>. These figures are consistent with what is observed in Europe and Scandinavia. In a Spanish study with mean age of patients of 76 years, 81% of all of the leg ulcers occurred in patients aged over 65<sup>65</sup>. In Ireland, the prevalence of leg ulcers in the general population is estimated at 0.12%. This rises to 1.2% in the population over 70 years of age<sup>66</sup>. The cost impact of leg ulceration is not well documented in Europe and estimates differ widely in their methodology<sup>24</sup>. The costs of treating patients

with a leg ulcer in specialized wound centres in Germany demonstrated that average cost per patient ranged from €9,900 to €10,800<sup>67</sup>. Most of the cost was contributed by the cost of inpatient treatment. In Scandinavia, the annual expenses per patient for treating a venous leg ulcer have been estimated to be 3,000 €– 6,000 €<sup>68, 69</sup>. Similar to that noted in the United States, a high recurrence rate is observed. One reason could be that it is estimated that almost half of the patients with an active open ulcer treat themselves in Sweden<sup>70</sup>.

## The Aging Population as an Increased Risk Factor for Chronic Wounds

The biomedical and socioeconomic burdens posed by wound complications are worsened by the aging global population. The populations of the aged in both Europe and the US is expected to rise 13–15% even as the overall population of Europe may experience a slight decline. As the global population ages, so does the nursing home population, and this will lead to more pressure ulcers. In Europe, similar to that in the US, aging of the population is associated with increase in the number of patients with a chronic wound. In the 17 years between 2008 and 2025, the total population of EU is expected to increase by less than 1%<sup>24</sup>. During that interval of time, the population aged 65 and above is expected to increase by 13% (25.5 million) and the proportion of the population aged 65 and above will increase from 17% in 2008 to 22% in 2025<sup>24</sup>. It is estimated that by 2050, the total population of Europe will be static or declining while the population aged 65 and above will have increased by 50 million (59%). The number of Americans aged 45–64, increased by 39% during this decade. The population 65 and over will increase from 35 million in 2000 to 40 million in 2010 (a 15% increase) and further increase to 55 million in 2020 (a 36% increase for that decade). The oldest old, those over 85 years old is projected to increase from 4.2 million in 2000 to 6.1 million in 2010 (a 40% increase) and then to 7.3 million in 2020 (a 44% increase for that decade)<sup>71</sup>. Peripheral artery disease, the circulatory disease commonly associated with non-healing wounds, affects about 8 million Americans and 12 – 20% of Americans age 65 and older<sup>72</sup>.

## The Rising Threat because of Obesity

According to the Center for Disease Control (CDC) and World Health Organization (WHO), in adults a body mass index (BMI) of 25 or more is considered “overweight” and a BMI of 30 or more is considered “obese”. In 2007, more than 1.1 billion adults worldwide were overweight and 312 million of them were obese<sup>73</sup>. The WHO estimates that by 2015, the number of overweight people worldwide will increase to 2.3 billion and more than 700 million will be obese.<sup>72</sup> According to the World Health Organization, the United States ranks fifth among all countries for obesity-related deaths. 1 Two-thirds of Americans are overweight, defined as having a body mass index (BMI) greater than 25. Americans spend close to \$117 billion on obesity related complications, with another \$33 billion spent annually in attempts to control or lose weight. Nearly half the costs of obesity are paid out by tax-supported health insurance. As the number of larger patients increases, so do the health problems related to obesity, including wound healing. Clearly, the prevalence of morbid obesity, along with related comorbidities, is sharply rising in the US, confounding wound care for persons at heightened risk for skin ulceration. Obesity-related changes in body systems impede wound healing<sup>74</sup>. Wound complications in the obese patients include infection, seromas, anastomatic leaks, and incision dehiscence. Limited tissue perfusion is also an issue of concern in most assessments<sup>75–77</sup>. Obesity is responsible for changes in skin barrier function, sebaceous glands and sebum production, sweat glands, lymphatics, collagen structure and function, wound healing, microcirculation and macrocirculation, and subcutaneous fat<sup>78</sup>. Obesity has a clear but not yet precisely defined effect on the immune response through a variety of immune mediators, which leads to susceptibility to infections<sup>79</sup>.



## Disabilities and Lost Wages Caused by Chronic Wounds

Patients suffering from chronic wounds frequently find themselves in situations of having to choose between commitments to their work and compliance with medical management for the ulcers<sup>80–82</sup>. Others that are less fortunate may be permanently impaired from performing their occupational job<sup>83, 84</sup>. As a whole on an annual basis, skin disorders account for 39 billion dollars of lost wages and medical care involving 65 million Americans<sup>85</sup>. Chronic wounds lead to disability and disability worsens wound outcomes resulting in a vicious cycle<sup>86</sup>.

Psychological status of mobile amputees is noted to be better than that of the diabetic foot ulcer patients<sup>87</sup>. Disability and loss of wages related to chronic wounds represents a heavy socioeconomic burden<sup>88</sup>. Venous ulcers alone lead to loss of an estimated 2 million workdays/year. It may also cause early retirement which is found in up to 12.5% of workers with venous ulcers<sup>89</sup>. It is estimated that chronic venous ulcers cost 2 billion dollars annually to lost wages an work days<sup>88, 90</sup>. Eighty-one percent of seventy-three patients interviewed with leg ulcer believed that their mobility was adversely affected by the ulcer. In younger, working patients, leg ulceration correlated with time lost from work, job loss, and adverse effects on finances. Fifty-eight percent of patients found caring for the ulcer burdensome. There was a strong correlation between time spent on ulcer care and feelings of anger and resentment. Sixty-eight percent of patients reported that the ulcer had a negative emotional impact on their lives, including feelings of fear, social isolation, anger, depression, and negative self-image<sup>80</sup>.

Accurate assessment, prompt treatment and suitable follow-up are essential components in minimizing the potential long-term disability caused by chronic wounds<sup>84, 91, 92</sup>. Pain is also a major problem for venous leg ulcer patients<sup>93</sup>. Persisting pain and pain at dressing changes is commonly encountered<sup>94</sup>. Pain results in lower activity, depression, irritation and reduced social activity. Furthermore 73% has a disturbed sleep and 50% had their mood affected.

Recently a foam dressing containing Ibuprofen has been introduced in order to solve some of the pain problem<sup>95</sup>.

## Acute Wounds

Acute wound care is indicated in all patients with surgical and traumatic wounds, abrasions, or superficial burns. Every time an incision is made a wound is created. Wound infections are the most expensive complications following surgery and still after many years are a major source of bacteria that drive the nosocomial infection rates in hospitals. We must develop and apply new concepts of preventing and treating these wound infections. According to the latest data from the National Center for Health Statistics, 40 million inpatient surgical procedures were performed in the United States in 2000, followed closely by 31.5 million outpatient surgeries. The need for post-surgical wound care is sharply on the rise with the expectation to reach more than 38.0 million by 2012<sup>96</sup>. Furthermore, the long term infections that follow the implantation of prosthetic devices is currently an unconquerable problem faced by an increasing number of patients. In European hospitals, the overall rates of Surgical Site Infection (SSI) range between 3% and 4% of patients undergoing surgery. Depending on the nature of surgery in question, the incidence of SSI ranges between <1% to >10%<sup>24</sup>. In the future, as the population ages, the incidence of SSI is expected to sharply rise because the incidence is connected to age with a doubling of the rate in patients older than 64 years<sup>97</sup>.

Emergency wound care in an acute setting has major significance not only in a war setting but also in homeland preparedness against natural disasters as well as against terrorism attacks. The soft tissue and musculoskeletal systems have the highest incidence of bodily injury in survivors of bombings. The most extreme of these injuries, the traumatic amputation, is reported to occur in 1%–3% of blast victims<sup>98</sup>. Acute wound care may be of very high value in occupational health because of the nature of related infection. An important factor in the failure of a sore to heal is the presence of multiple species of bacteria, living cooperatively in

highly organized biofilms. The biofilm protects the bacteria from antibiotic therapy and the patient's immune response. Among others, cutaneous wounds lend themselves to infection by methicillin-resistant *Staphylococcus aureus* (MRSA)<sup>99</sup>. Comparison of infectious complications in patients with mutilating wounds due to trauma during corn harvesting with those in patients with factory-related hand injuries of similar severity showed that more gram-negative rods were recovered from environmental cultures of corn-harvesting machines and corn plants than from those of factory machinery<sup>100</sup>. Many species of Gram-negative bacteria are pathogenic. This pathogenic capability is usually associated with certain components of Gram-negative cell walls, in particular the lipopolysaccharide which triggers an innate immune response characterized by cytokine production and immune system activation. Gram-negative rod infection poses substantial public health threat, more so than that posed by factory wounds themselves. Hospital discharge data derived from the 2002 Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project were reviewed by Hostetler et al to look at the demographics and healthcare resource utilization for this patient population. Data were collected for 55,795 injury-related hospitalizations with an acute wound, representing an estimated 272,278 such hospitalizations in the United States. Overall, 96.9% of patients had an open wound and 5.8% of those acute wound patients and 17.8% of burn wound patients were discharged to home health care. After controlling for demographics, co-morbidities, and hospital characteristics, the likelihood of having an acute wound that required home health care referral was significantly increased with: increased age (odds ratio [OR]:up to 10.91), insurance (OR:2.08–7.04), diabetes (OR:1.26–2.81), and obesity (OR:1.41)<sup>101</sup>. Thus, a significant number of acute wounds do not go on to resolve uneventfully and consequently utilize significant health care resources.

## Scar and Fibrosis

An additional burden of wound healing is the problem of scarring, which can have profound functional and aesthetic consequences<sup>102</sup>. Hypertrophic scarring commonly occurs following burns<sup>103</sup>. A scar represents the sum of the injury, the reparative process and subsequent interventions to improve the scarring process<sup>104</sup>. Scars may have long lasting functional, cosmetic as well as psychological consequences for the patient. Both normal and hypertrophic scars remain difficult to treat and impossible to prevent. Analysts at Nomura Code, the investment bank that focuses on life sciences, “conservatively” estimate the market for an anti-scarring drug at \$12 billion in skin application alone<sup>105</sup>.

## Education

At present, American medical students receive very little education on the science and care of wounds during their medical studies. The mean hours of education in physiology of tissue injury at fifty American medical schools are 0.5 hours and 0.2 hours, respectively, in the first year and second years and none in the third and fourth years. The mean hours of directed education in the physiology of wound healing are 2.1 hours and 1.9 hours in the first and second years<sup>106</sup>. In Europe, at present there is no consensus on the minimum education program necessary to qualify as an acceptable expert in wound care. For medical doctors, a standardized pre-graduate and postgraduate education is essential. In Denmark, medical students have the option to follow the work at the two existing major national wound healing centers during their rotation between specialties<sup>107</sup>. A specialized 2 year postgraduate wound care education program for physicians is currently under development. In Europe, different initiatives have been launched. The umbrella organization for European societies (European Wound Management Association, EWMA) has developed an educational program primarily directed at nurses. It is the hope that this program will establish European standards of wound care education. Given the current and projected burden that wound related complications may place

on our public health and economy, it is important to objectively revisit the investment needs in education of wound care.

## Closing Remarks

The immense economic and social impact of wounds in our society calls for allocation of a higher level of research resources to understand biological mechanisms underlying the complexities noted in problem wounds. Listing of such allocation in databases such as the NIH RePORT will enable year-by-year tracking and should help attract a wider interdisciplinary interest in the science and care of wound healing. For detailed experimental queries, the development of animal models would enable in-depth study of biological mechanisms as a function of time<sup>108–110</sup>. Wound healing represents the outcome of a large number of interrelated biological events which are orchestrated over a temporal sequence in response to injury and its microenvironment. Investment in approaches that query global changes in wound tissue proteome<sup>111, 112</sup>, as well as coding<sup>109, 113–115</sup> and non-coding<sup>116, 117</sup> genome seems prudent. Effective application of systems biology tools<sup>82, 118</sup> to manage vast “omics” datasets will facilitate supervised generation of novel hypotheses. The study of chronic wounds presented clinically is highly valuable but poses numerous practical challenges. Development of technologies such as laser capture microdissection enables the collection of “omics” data from single as well as multi-cellular regions of a tissue biopsy<sup>115</sup>. Approaches directed at the mathematical modeling of wound healing lend themselves to systems biology tools and have the potential to contribute to clinical wound management in the near future. Finally, the rapidly developing field of tissue engineering and stem cell biology represents the backbone of the future of wound sciences<sup>119, 120</sup>.

## Acknowledgments

Supported by research funds from NIGMS and NIDDK.

## Literature Cited

1. Odawara T, Iseki E, Kanai A, Arai T, Katsuragi T, Hino H, Furukawa Y, Kato M, Yamamoto T, Kosaka K. Clinicopathological study of two subtypes of Pick’s disease in Japan. *Dement Geriatr Cogn Disord* 2003;15:19–25. [PubMed: 12457075]
2. Wu SC, Armstrong DG. Clinical outcome of diabetic foot ulcers treated with negative pressure wound therapy and the transition from acute care to home care. *Int Wound J* 2008;5 (Suppl 2):10–6. [PubMed: 18577133]
3. Melling AC, Leaper DJ. The impact of warming on pain and wound healing after hernia surgery: a preliminary study. *J Wound Care* 2006;15:104–8. [PubMed: 16550663]
4. Stojadinovic A, Carlson JW, Schultz GS, Davis TA, Elster EA. Topical advances in wound care. *Gynecol Oncol* 2008;111:S70–80. [PubMed: 18793796]
5. Armstrong DG, Ayello EA, Capitulo KL, Fowler E, Krasner DL, Levine JM, Sibbald RG, Smith AP. New opportunities to improve pressure ulcer prevention and treatment: implications of the CMS inpatient hospital care present on admission indicators/hospital-acquired conditions policy: a consensus paper from the International Expert Wound Care Advisory Panel. *Adv Skin Wound Care* 2008;21:469–78. [PubMed: 18836326]
6. Andros G, Armstrong DG, Attinger CE, Boulton AJ, Frykberg RG, Joseph WS, Lavery LA, Morbach S, Niezgoda JA, Toursarkissian B. Consensus statement on negative pressure wound therapy (V.A.C. Therapy) for the management of diabetic foot wounds. *Ostomy Wound Manage* 2006;(Suppl):1–32. [PubMed: 17007488]
7. Broughton G 2nd, Janis JE, Attinger CE. Wound healing: an overview. *Plast Reconstr Surg* 2006;117:1e-S–32e-S. [PubMed: 16404237]
8. Clemens MW, Parikh P, Hall MM, Attinger CE. External fixators as an adjunct to wound healing. *Foot Ankle Clin* 2008;13:145–56. vi–vii. [PubMed: 18328418]



9. Barbul A. Genesis of the prevention guidelines project. *Wound Repair Regen* 2008;16:145–6. [PubMed: 18318799]
10. Hopf HW, Ueno C, Aslam R, Burnand K, Fife C, Grant L, Holloway A, Iafrazi MD, Mani R, Misare B, Rosen N, Shapshak D, Benjamin Slade J Jr, West J, Barbul A. Guidelines for the treatment of arterial insufficiency ulcers. *Wound Repair Regen* 2006;14:693–710. [PubMed: 17199834]
11. Robson MC, Barbul A. Guidelines for the best care of chronic wounds. *Wound Repair Regen* 2006;14:647–8. [PubMed: 17199830]
12. Steed DL, Attinger C, Colaizzi T, Crossland M, Franz M, Harkless L, Johnson A, Moosa H, Robson M, Serena T, Sheehan P, Veves A, Wiersma-Bryant L. Guidelines for the treatment of diabetic ulcers. *Wound Repair Regen* 2006;14:680–92. [PubMed: 17199833]
13. Whitney J, Phillips L, Aslam R, Barbul A, Gottrup F, Gould L, Robson MC, Rodeheaver G, Thomas D, Stotts N. Guidelines for the treatment of pressure ulcers. *Wound Repair Regen* 2006;14:663–79. [PubMed: 17199832]
14. Lazarus GS, Cooper DM, Knighton DR, Percoraro RE, Rodeheaver G, Robson MC. Definitions and guidelines for assessment of wounds and evaluation of healing. *Wound Repair Regen* 1994;2:165–70. [PubMed: 17156107]
15. Gottrup F. A specialized wound-healing center concept: importance of a multidisciplinary department structure and surgical treatment facilities in the treatment of chronic wounds. *Am J Surg* 2004;187:38S–43S. [PubMed: 15147991]
16. Singer AJ, Clark RA. Cutaneous wound healing. *N Engl J Med* 1999;341:738–46. [PubMed: 10471461]
17. Crovetto G, Martinelli G, Issi M, Barone M, Guizzardi M, Campanati B, Moroni M, Carabelli A. Platelet gel for healing cutaneous chronic wounds. *Transfus Apher Sci* 2004;30:145–51. [PubMed: 15062754]
18. Gottrup F, Holstein P, Jorgensen B, Lohmann M, Karlsmar T. A new concept of a multidisciplinary wound healing center and a national expert function of wound healing. *Arch Surg* 2001;136:765–72. [PubMed: 11448387]
19. Brem H, Stojadinovic O, Diegelmann RF, Entero H, Lee B, Pastar I, Golinko M, Rosenberg H, Tomic-Canic M. Molecular markers in patients with chronic wounds to guide surgical debridement. *Mol Med* 2007;13:30–9. [PubMed: 17515955]
20. Fife, CE.; Weitr, D. Today's Wound Clinic. Today's WoundClinic; 2007. Getting Started. <http://www.todayswoundclinic.com/2007/06/getting-started/>
21. Global Industry Analysts I. Wound Care Products: A Global Strategic Business Report . Global Industry Analysts; 2008. [http://www.strategy.com/Wound\\_Care\\_Products\\_Market\\_Report.asp](http://www.strategy.com/Wound_Care_Products_Market_Report.asp)
22. Agency for Healthcare Research and Quality DHHS. Number of Hospital Patients with Pressure Sores Increasing. Department of Health and Human Services; 2006. <http://www.ahrq.gov/news/nn/nn041806.htm>
23. Shahin ES, Dassen T, Halfens RJ. Pressure ulcer prevalence and incidence in intensive care patients: a literature review. *Nurs Crit Care* 2008;13:71–9. [PubMed: 18289185]
24. Posnett J, Gottrup F, Lundgren H, Saal G. The Burden of Chronic Wounds in Europe. *Journal of Wound Care*. 2009 In Press.
25. Bermark S, Zimmerdahl V, Muller K. Prevalence investigation of pressure ulcers. *EWMA Journal* 2004;4:7–11.
26. Gunningberg L. Risk, prevalence and prevention of pressure ulcers in three Swedish healthcare settings. *J Wound Care* 2004;13:286–90. [PubMed: 15977770]
27. Wann-Hansson C, Hagell P, Willman A. Commentary on Wann-Hansson C, Hagell P, Willman A (2008) Risk factors and prevention among patients with hospital-acquired and pre-existing pressure ulcers in an acute care hospital. *Journal of Clinical Nursing* 17, 1718–1727 Response. *Journal of Clinical Nursing* 2008;17:3257–58.
28. Wann-Hansson C, Hagell P, Willman A. Risk factors and prevention among patients with hospital-acquired and pre-existing pressure ulcers in an acute care hospital. *Journal of Clinical Nursing* 2008;17:1718–27. [PubMed: 18578778]

29. Conine TA, Hershler C, Daechsel D, Peel C, Pearson A. Pressure ulcer prophylaxis in elderly patients using polyurethane foam or Jay wheelchair cushions. *Int J Rehabil Res* 1994;17:123–37. [PubMed: 7960335]
30. Hook O, Gabrielsson L, Lagerman U. Prophylaxis and treatment of decubitus ulcers with a rocking bed. *Scand J Rehabil Med* 1982;14:33–7. [PubMed: 7063819]
31. Lippert-Gruner M. Gluteal neuromuscular stimulation in therapy and prophylaxis of recurrent sacral pressure ulcers. *Spinal Cord* 2003;41:365–6. [PubMed: 12746744]
32. Torrance C. Pressure sores: pathogenesis, prophylaxis and treatment. 3. Medical Management and surgical intervention. *Nurs Times* 1981;77(suppl):1–4.
33. Torrance C. Pressure sores: pathogenesis, prophylaxis and treatments. 2. Predisposing factors: the 'at-risk' patient. *Nurs Times* 1981;77(suppl):5–8. [PubMed: 6907932]
34. MedMarket Diligence AWBR. Worldwide Wound Management, 2007–2016: Established and Emerging Products, Technologies and Markets in the U.S., Europe, Japan and Rest of World. MedMarket Diligence; 2007. Report #S245 <https://www.mediligence.com/rpt/rpt-s245.htm>
35. Reddy M, Gill SS, Rochon PA. Preventing pressure ulcers: a systematic review. *Jama* 2006;296:974–84. [PubMed: 16926357]
36. Gordon MD, Gottschlich MM, Helvig EI, Marvin JA, Richard RL. Review of evidenced-based practice for the prevention of pressure sores in burn patients. *J Burn Care Rehabil* 2004;25:388–410. [PubMed: 15353931]
37. Kuhn BA, Coulter SJ. Balancing the pressure ulcer cost and quality equation. *Nurs Econ* 1992;10:353–9. [PubMed: 1465158]
38. Frankel H, Sperry J, Kaplan L. Risk factors for pressure ulcer development in a best practice surgical intensive care unit. *Am Surg* 2007;73:1215–7. [PubMed: 18186374]
39. Niezgoda JA, Mendez-Eastman S. The effective management of pressure ulcers. *Adv Skin Wound Care* 2006;19 (Suppl 1):3–15. [PubMed: 16565615]
40. Centers of Medicare & Medicaid Services. Medicare Program: Changes to the Hospital Inpatient Prospective Payment Systems and Fiscal Year 2008 Rates - Final Rule. *Federal Register* 2007;72:47130–8175.
41. Hodde J, Allam R. Submucosa Wound Matrix for Chronic Wound Healing. *Wounds* 2007;19:157–63.
42. Bergstrom N, Horn SD, Smout RJ, Bender SA, Ferguson ML, Taler G, Sauer AC, Sharkey SS, Voss AC. The National Pressure Ulcer Long-Term Care Study: outcomes of pressure ulcer treatments in long-term care. *J Am Geriatr Soc* 2005;53:1721–9. [PubMed: 16181171]
43. Voss AC, Bender SA, Ferguson ML, Sauer AC, Bennett RG, Hahn PW. Long-term care liability for pressure ulcers. *J Am Geriatr Soc* 2005;53:1587–92. [PubMed: 16137292]
44. Greenwald, L. Medicare Deadline Spurs Hospitals to Prevent Pressure Ulcers. E-Zine. 2007. <http://ezinearticles.com/?Medicare-Deadline-Spurs-Hospitals-to-Prevent-Pressure-Ulcers&id=846302>
45. The Wall Street Journal. New Medicare Payment Rules Spur Push for Prevention; The 'Four-Eyed Body Check'. *The Wall Street Journal*; 2007. Hospitals Combat Dangerous Bedsores. [http://online.wsj.com/article/SB118894998795817515.html?mod=rss\\_The\\_Informed\\_Patient](http://online.wsj.com/article/SB118894998795817515.html?mod=rss_The_Informed_Patient)
46. Services CfMaM. Changes to the Hospital Inpatient Prospective Payment Systems and Fiscal Year 2008 Rates: Final Rule, 72. Services, CfMaM Centers for Medicare and Medicaid Services; 2007. p. 47201-06.
47. Center for Disease Control and Prevention. National diabetes fact sheet: general information and national estimates on diabetes in the United States, 2007. U.S. Department of Health and Human Services, CfDCaPCenters for Disease Control and Prevention; Atlanta, GA: 2008.
48. American Diabetes Association. Direct and indirect costs of diabetes in the United States. ADA; 2007. <http://www.diabetes.org/diabetes-statistics/cost-of-diabetes-in-us.jsp>
49. Diabetes Atlas. International Diabetes Federation; 2003.
50. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004;27:1047–53. [PubMed: 15111519]

51. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. *Jama* 2005;293:217–28. [PubMed: 15644549]
52. Amputee Coalition of America. National Limb Loss Information Fact Sheet; Diabetes and Lower Extremity Amputations. Amputee Coalition of America; 2008. [http://amputee-coalition.org/fact\\_sheets/diabetes\\_leamp.html](http://amputee-coalition.org/fact_sheets/diabetes_leamp.html)
53. CDC. Hospital Discharge Rates for Nontraumatic Lower Extremity Amputation by Diabetes Status — U.S., 1997; MMWR Weekly. 2001. p. 954-58. <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5043a3.htm>
54. Shearer A, Scuffham P, Gordois A, Oglesby A. Predicted costs and outcomes from reduced vibration detection in people with diabetes in the U.S. *Diabetes Care* 2003;26:2305–10. [PubMed: 12882853]
55. Stillman, RM. Diabetic ulcers. 2008. <http://www.emedicine.com/med/topic551.htm>Medicine from WebMD
56. CDC. Hospital Discharge Rates for Nontraumatic Lower Extremity Amputation per 1,000 Diabetic Population, by Age, United States, 1980–2003. Centers for Disease Control and Prevention; National Center for Chronic Disease Prevention and Health Promotion; Atlanta, GA: 2008. [http://www.cdc.gov/diabetes/statistics/lea/diabetes\\_complications/fig4.htm](http://www.cdc.gov/diabetes/statistics/lea/diabetes_complications/fig4.htm)
57. Holstein P, Ellitsgaard N, Olsen BB, Ellitsgaard V. Decreasing incidence of major amputations in people with diabetes. *Diabetologia* 2000;43:844–7. [PubMed: 10952455]
58. Rogers LC, Lavery LA, Armstrong DG. The right to bear legs--an amendment to healthcare: how preventing amputations can save billions for the US Health-care System. *J Am Podiatr Med Assoc* 2008;98:166–8. [PubMed: 18348977]
59. American College of Foot and Ankle Surgeons. Foot Ulcers Affect 15 Percent of All Diabetic Patients. 2006. ([http://www.footphysicians.com/diabetes/diabetes\\_foot\\_ulcers.htm](http://www.footphysicians.com/diabetes/diabetes_foot_ulcers.htm)). [footphysicians.com](http://www.footphysicians.com)
60. Lyon, L. Preventing foot ulcers caused by diabetes: the personal and economic costs of foot infections and amputations are enormous. *U.S. News & World Report*. 2008. <http://health.usnews.com/articles/health/diabetes/2008/01/28/preventing-foot-ulcers-caused-by-diabetes.html>
61. Gordois A, Scuffham P, Shearer A, Oglesby A, Tobian JA. The health care costs of diabetic peripheral neuropathy in the US. *Diabetes Care* 2003;26:1790–5. [PubMed: 12766111]
62. Fishman T. How to manage venous stasis ulcers. *Podiatry Today* 2007;20:66–72.
63. Fife C, Walker D, Thomson B, Carter M. Limitations of daily living activities in patients with venous stasis ulcers undergoing compression bandaging: problems with the concept of self-bandaging. *Wounds* 2007;19:255–57.
64. Abbade LP, Lastoria S. Venous ulcer: epidemiology, physiopathology, diagnosis and treatment. *Int J Dermatol* 2005;44:449–56. [PubMed: 15941430]
65. Soldevilla J, Torra JE, Verdu J, Rueda J, Martinez F, Roche E. Epidemiology of chronic wounds in Spain: Results of the First National Studies on Pressure and Leg Ulcer Prevalence. *Wounds-a Compendium of Clinical Research and Practice* 2006;18:213–26.
66. Clarke-Moloney M, Keane N, Kavanagh E. An exploration of current leg ulcer management practices in an Irish community setting. *J Wound Care* 2006;15:407–10. [PubMed: 17044358]
67. Augustin, M.; Herberger, K.; Purwins, S.; Debus, ES. Cost-of-illness of venous leg ulcers in Germany - a nationwide cross-sectional study. EWMA Annual Meeting; Lisbon. 2008.
68. Kjær, M. Evidence-based medical technical care for patients with venous leg ulceration. Copenhagen University; Denmark: 1995.
69. Lindholm C. Leg ulcer treatment in hospital and primary care in Sweden: cost-effective care and quality of life. *Adv Wound Care* 1995;8:48, 50–52. [PubMed: 7582337]
70. Nelzen, O.; Bergqvist, D. Leg Ulcers: definitions, classification, differential diagnosis and epidemiology. Uppsala, Sweden: Medical Products Agency; 1995. p. 186
71. Administration on Aging A; Services, DoHaH. A profile of older Americans. 2007. p. 1-19. <http://www.wvseniorservices.gov/Portals/0/pdf/ProfileOfOlderAmericans.pdf>
72. American Heart Association. Peripheral Arterial Disease Statistics - 2008 update. American Heart Association; 2008.

73. Hossain P, Kavar BEI, Nahas M. Obesity and diabetes in the developing world--a growing challenge. *N Engl J Med* 2007;356:213–5. [PubMed: 17229948]
74. Brown CV, Neville AL, Rhee P, Salim A, Velmahos GC, Demetriades D. The impact of obesity on the outcomes of 1,153 critically injured blunt trauma patients. *J Trauma* 2005;59:1048–51. discussion 51. [PubMed: 16385276]
75. Fife CE, Benavides S, Carter MJ. A patient-centered approach to treatment of morbid obesity and lower extremity complications: an overview and case studies. *Ostomy Wound Manage* 2008;54:20–2. 24–32. [PubMed: 18250484]
76. Wilson JA, Clark JJ. Obesity: impediment to postsurgical wound healing. *Adv Skin Wound Care* 2004;17:426–35. [PubMed: 15492679]
77. Gallagher S, Gates JL. Obesity, panniculitis, panniculectomy, and wound care: understanding the challenges. *J Wound Ostomy Continence Nurs* 2003;30:334–41. [PubMed: 14615764]
78. Yosipovitch G, DeVore A, Dawn A. Obesity and the skin: skin physiology and skin manifestations of obesity. *J Am Acad Dermatol* 2007;56:901–16. quiz 17–20. [PubMed: 17504714]
79. Falagas ME, Kompoti M. Obesity and infection. *Lancet Infect Dis* 2006;6:438–46. [PubMed: 16790384]
80. Phillips T, Stanton B, Provan A, Lew R. A study of the impact of leg ulcers on quality of life: financial, social, and psychologic implications. *J Am Acad Dermatol* 1994;31:49–53. [PubMed: 8021371]
81. Lanzafame RJ. Business. *Photomed Laser Surg* 2007;25:371–2. [PubMed: 17975949]
82. Ghanassia E, Villon L, Thuan Dit Dieudonne JF, Boegner C, Avignon A, Sultan A. Long-term outcome and disability of diabetic patients hospitalized for diabetic foot ulcers: a 6.5-year follow-up study. *Diabetes Care* 2008;31:1288–92. [PubMed: 18390801]
83. O'Donnell TF Jr, Browse NL, Burnand KG, Thomas ML. The socioeconomic effects of an iliofemoral venous thrombosis. *J Surg Res* 1977;22:483–8. [PubMed: 140274]
84. Lanzafame RJ. Forces and photonics. *Photomed Laser Surg* 2007;25:135–6. [PubMed: 17603851]
85. Society for Investigative Dermatology. Priorities for skin iology and disease research. 2005. <http://www.sidnet.org/pdfs/Priorities%20for%20SKin%20Biology%20and%20Disease%20Research.pdf>
86. Unger, PG. The Physical Therapist's Role in Wound Management. In: Krasner, DL., editor. *Chronic wound care*. Vol. 4 . Vol. Chapter 39. Rodeheaver: GSibbald, RGCWC; 2007. <http://chronicwoundcarebookcom/>
87. Carrington AL, Mawdsley SK, Morley M, Kincey J, Boulton AJ. Psychological status of diabetic people with or without lower limb disability. *Diabetes Res Clin Pract* 1996;32:19–25. [PubMed: 8803478]
88. Eberhardt RT, Raffetto JD. Chronic venous insufficiency. *Circulation* 2005;111:2398–409. [PubMed: 15883226]
89. DaSilva A, Navarro MF, Batalheiro J. The importance of chronic venous insufficiency: various preliminary data on its medico-social consequences. *Phlebologie* 1992;45:439–43. [PubMed: 1302319]
90. Patel NP, Labropoulos N, Pappas PJ. Current management of venous ulceration. *Plast Reconstr Surg* 2006;117:254S–60S. [PubMed: 16799394]
91. Fivenson D, Scherschun L. Clinical and economic impact of Apligraf for the treatment of nonhealing venous leg ulcers. *Int J Dermatol* 2003;42:960–5. [PubMed: 14636194]
92. Lanzafame RJ. Issues in the acquisition, development, and use of technology in health care. *Jsls* 2006;10:401–8. [PubMed: 17575747]
93. Margolis DJ, Bilker W, Santanna J, Baumgarten M. Venous leg ulcer: incidence and prevalence in the elderly. *J Am Acad Dermatol* 2002;46:381–6. [PubMed: 11862173]
94. Nonan L, Burge SM. Venous leg ulcers: is pain a problem? *Phlebologie* 1998;3:14–9.
95. Gottrup F, Jorgensen B, Karlsmark T, Sibbald RG, Rimdeika R, Harding K, Price P, Venning V, Vowden P, Junger M, Wortmann S, Sulcaite R, Vilkevicius G, Ahokas TL, Ettler K, Arenbergerova M. Reducing wound pain in venous leg ulcers with Biatain Ibu: a randomized, controlled double-blind clinical investigation on the performance and safety. *Wound Repair Regen* 2008;16:615–25. [PubMed: 19128256]

96. US Surgery. Executive Summary. US Surgery. 2008.  
<http://www.touchbriefings.com/cdps/cditem.cfm?cid=5&nid=2358>
97. Moro ML, Morsillo F, Tangenti M, Mongardi M, Pirazzini MC, Ragni P. Rates of surgical-site infection: an international comparison. *Infect Control Hosp Epidemiol* 2005;26:442–8. [PubMed: 15954481]
98. CDC. Blast Injuries: Blast extremity. 2008.  
[emergency.cdc.gov/masscasualties/pdf/BlastExtremityInjuries.pdf](http://emergency.cdc.gov/masscasualties/pdf/BlastExtremityInjuries.pdf). CDC- Emergency Medicine
99. Loh JV, Percival SL, Woods EJ, Williams NJ, Cochrane CA. Silver resistance in MRSA isolated from wound and nasal sources in humans and animals. *Int Wound J* 2009;6:32–8. [PubMed: 19291113]
100. Agger WA, Cogbill TH, Busch H Jr, Landercasper J, Callister SM. Wounds caused by corn-harvesting machines: an unusual source of infection due to gram-negative bacilli. *Rev Infect Dis* 1986;8:927–31. [PubMed: 3797937]
101. Hostetler SG, Xiang H, Gupta S, Sen CK, Gordillo GM. Discharge patterns of injury-related hospitalizations with an acute wound in the United States. *Wounds* 2006;18:340–51.
102. Wadman M. Scar prevention: the healing touch. *Nature* 2005;436:1079–80. [PubMed: 16121148]
103. Bloemen MC, van der Veer WM, Ulrich MM, van Zuijlen PP, Niessen FB, Middelkoop E. Prevention and curative management of hypertrophic scar formation. *Burns*. 2008
104. Powers PS, Sarkar S, Goldgof DB, Cruse CW, Tsap LV. Scar assessment: current problems and future solutions. *J Burn Care Rehabil* 1999;20:54–60. discussion 53. [PubMed: 9934638]
105. Times, T. Renovo shares plunge as new scar prevention drug fails second trial. 2008.  
[http://business.timesonline.co.uk/tol/business/industry\\_sectors/health/article3479317.ece](http://business.timesonline.co.uk/tol/business/industry_sectors/health/article3479317.ece) The Times
106. Patel NP, Granick MS. Wound education: American medical students are inadequately trained in wound care. *Ann Plast Surg* 2007;59:53–5. discussion 55. [PubMed: 17589260]
107. Gottrup F. Trends in surgical wound healing. *Scand J Surg* 2008;97:220–5. discussion 25–6. [PubMed: 18812270]
108. Lindblad WJ. Considerations for selecting the correct animal model for dermal wound-healing studies. *J Biomater Sci Polym Ed* 2008;19:1087–96. [PubMed: 18644233]
109. Roy S, Biswas S, Khanna S, Gordillo GM, Bergdall V, Green J, Marsh CB, Gould LJ, Sen CK. Characterization of a Pre-Clinical Model of Chronic Ischemic Wound. *Physiol Genomics*. 2009
110. Sullivan TP, Eaglstein WH, Davis SC, Mertz P. The pig as a model for human wound healing. *Wound Repair Regen* 2001;9:66–76. [PubMed: 11350644]
111. Aden N, Shiwen X, Aden D, Black C, Nuttall A, Denton CP, Leask A, Abraham D, Stratton R. Proteomic analysis of scleroderma lesional skin reveals activated wound healing phenotype of epidermal cell layer. *Rheumatology (Oxford)* 2008;47:1754–60. [PubMed: 18829709]
112. Caldwell RL, Opalenik SR, Davidson JM, Caprioli RM, Nanney LB. Tissue profiling MALDI mass spectrometry reveals prominent calcium-binding proteins in the proteome of regenerative MRL mouse wounds. *Wound Repair Regen* 2008;16:442–9. [PubMed: 18282264]
113. Roy S, hanna S, Rink C, Biswas S, Sen CK. Characterization of the acute temporal changes in excisional murine cutaneous wound inflammation by screening of the wound-edge transcriptome. *Physiol Genomics* 2008;34:162–84. [PubMed: 18460641]
114. Roy S, Khanna S, Yeh PE, Rink C, Malarkey WB, Kiecolt-Glaser J, Laskowski B, Glaser R, Sen CK. Wound site neutrophil transcriptome in response to psychological stress in young men. *Gene Expr* 2005;12:273–87. [PubMed: 16358416]
115. Roy S, Patel D, Khanna S, Gordillo GM, Biswas S, Friedman A, Sen CK. Transcriptome-wide analysis of blood vessels laser captured from human skin and chronic wound-edge tissue. *Proc Natl Acad Sci U S A* 2007;104:14472–7. [PubMed: 17728400]
116. Roy S, Khanna S, Hussain SR, Biswas S, Azad A, Rink C, Gnyawali S, Shilo S, Nuovo GJ, Sen CK. MicroRNA expression in response to murine myocardial infarction: miR-21 regulates fibroblast metalloprotease-2 via phosphatase and tensin homologue. *Cardiovasc Res* 2009;82:21–9. [PubMed: 19147652]
117. Shilo S, Roy S, Khanna S, Sen CK. MicroRNA in cutaneous wound healing: a new paradigm. *DNA Cell Biol* 2007;26:227–37. [PubMed: 17465889]



118. Sun T, McMinn P, Coakley S, Holcombe M, Smallwood R, Macneil S. An integrated systems biology approach to understanding the rules of keratinocyte colony formation. *J R Soc Interface* 2007;4:1077–92. [PubMed: 17374590]
119. Gurtner GC, Werner S, Barrandon Y, Longaker MT. Wound repair and regeneration. *Nature* 2008;453:314–21. [PubMed: 18480812]
120. Riboh J, Chong AK, Pham H, Longaker M, Jacobs C, Chang J. Optimization of flexor tendon tissue engineering with a cyclic strain bioreactor. *J Hand Surg [Am]* 2008;33:1388–96.