TEXT ATLAS OF

WOUND MANAGEMENT

SECOND EDITION



EDITED BY

VINCENT FALANGA

CHRISTINA LINDHOLM • POLLY A. CARSON

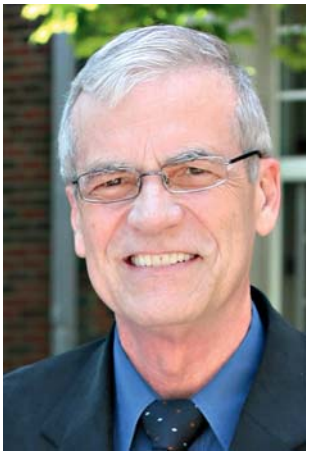
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Introduction

It has been almost 12 years since the first edition of *Text Atlas of Wound Management* came out, which focused mainly on chronic wounds. The need for this title *Text Atlas* remains, and is perhaps even more important in view of new diagnostic and therapeutic challenges. In constructing this largely new second edition, we have maintained the philosophy that led us to publish its first edition in the year 2000. *Text Atlas* remains a pictorial guide to wound management, and we have revised it with a broad audience in mind without sacrificing details. Therefore, the guide should remain useful to clinicians (physicians, nurses, health care students, other health care professionals, etc.) who are interested in knowing about wounds and how to approach them. Their interest may be in understanding wound healing and impaired healing, or in specific diagnostic approaches, or in procedures meant to diagnose and treat certain conditions.

We would like to think that, regardless of the professional background of the reader, our work will provide a fundamental framework for understanding the challenges presented by cutaneous wounds. In that respect, we remain aware that surgeons and physicians with a more internal medicine background often think differently about wounds. Still, they should gain confirmation and new perspectives from this informative pictorial guide and its informative text. The nursing profession has adopted an essential and increasingly important role in the management of wounds. We trust that this work will guide them in feeling even more comfortable about patient management and the details of therapy that, after all, are so critical to a successful management plan. We think that medical and nursing students are becoming increasingly aware of the medical and financial importance of chronic wounds; this Text Atlas should be an important primer for them as well, we hope. Regulatory agencies, including FDA officials, should benefit from this Text Atlas by gaining greater understanding of the therapies and pitfalls they are asked to evaluate. We would like to think that even professionals involved in the financial aspect of chronic wounds would draw from this work useful lessons that would enhance their knowledge of diseases that are becoming extremely expensive to treat. Last, but no less important, we sincerely hope that wound healing clinics and their personnel (physicians and surgeons, nurses, medical assistants, etc.) will feel more comfortable and confident after reading this Text Atlas.

Our intent in revising this Text Atlas has remained unchanged. We have strived to keep and project an open mind about wound management. As we had predicted in the first edition, we have now seen new and more thorough guidelines for wound management, particularly for venous, diabetic, and pressure (decubitus) ulcers. However, we have realized that inflammatory ulcers continue to present a tremendous challenge for many clinicians. Such ulcers still do not fall in well-defined categories, although this pictorial guide has made substantial advances in that regard. For example, the linear streaks of microlivedo should immediately raise the possibility of microthrombotic disease, such as cryofibrinogenemia, the antiphospholipid syndrome, livedoid vasculitis, etc. Undermining of the skin (other than in pressure ulcers) immediately raises suspicions about the diagnosis of pyoderma gangrenosum. These examples, like other situations regarding vascular ulcers, are presented as "clinical vignettes," which can stand on their own and are meant to deliver a teaching point or a point for discussion; we do not claim to have the answer in each and every case. Indeed, the conditions we present project the reality of wound management, from factitial disease, to poor compliance, to attempts in improving compression and dressing strategies, etc. In general, these "clinical vignettes" of the *Text Atlas* do not require the reader to refer back and forth to different portions of this guide. We do not claim that our work will take the place of other larger textbooks about etiology, pathogenesis, guidelines, treatment approaches and so on. However, we do feel strongly that this unique pictorial guide, which is supplemented with what we hope are thoughtful and informative comments (both in each legend and in the introduction to each of the eight sections) will be very desirable and worthwhile. In many cases, we have provided our own unique perspectives on the cases being shown and on the disease process. The rich bibliography can be used for more extensive reading, if so desired.

At the time of writing the first edition of *Text Atlas*, we formulated the unique concept of Wound Bed Preparation (WBP). With the advent of this useful concept, we think that the field of wound healing changed dramatically. WBP provided the foundation for making wounds heal more rapidly and, most importantly, for developing the conditions that allow advanced therapeutic products (including bioengineered skin and growth factors) to be more successful. Presently, WBP drives the field of chronic wounds, because it takes into account not only the overall diagnosis and definitive treatment, but the choice of dressings, compression bandages, elimination of biofilms, bacterial colonization and high bacterial burden, as well as the formation of proper granulation tissue and epidermal migration. Some clinicians may fall into the error of trying to correct each abnormality in sequence. However, WBP dictates that all aspects of the wound need to be addressed at about the same time, including the following: debridement by surgery, hydrosurgery, autolytic means with dressing and slow-release antiseptics, and enzymatic approaches; the use of stimulatory autografts and bioengineered skin; attention to the removal of edema and other local impediments to healing; correction of systemic components, including congestive heart failure, hyperglycemia, etc. This ongoing revolution of WBP has benefited chronic wound care in these and many other ways, and is likely to further improve the outlook and prognosis for difficult-to-heal wounds.

In the context of developing "clinical vignettes" we sort of invited the reader to be with us at the bedside, facing the same

problems and challenges we are dealing with. We have purposefully adopted a rather informal, narrative approach for that purpose. We do not stand at the podium, instructing clinicians about how to approach these challenging wounds. Rather, we invite thinking and an inner discussion about what we state in our narrative. A decade after our first edition, the management of some chronic wounds and practical problems is still an uncharted territory, and there is no absolutely right answer for their optimal management. Much depends not just on the condition being treated but also on the patient's circumstances and their environment.

This edition of *Text Atlas of Wound Management* is divided into eight sections, with each preceded by what we hope is a useful introduction and some key clinical points. The first section is about more acute wounds. We do not deal here with burns and major trauma, which are better dealt with in very specialized textbooks and surgical approaches. The second and third sections address wound infection and neuropathic ulcers, respectively. These are problems that commonly affect patients with diabetes but are also applicable to other clinically difficult wounds. The difficulty of distinguishing true infection from wound colonization, biofilm development, and from an inflammatory process is highlighted. We do not always have an answer for that, but we do discuss some helpful clues and approaches. Vascular ulcers and inflammatory ulcers are discussed in sections 4 and 5, respectively. It might at first seem easy to separate these two problems, and the challenge is made greater by frequent overlaps between the two etiologies and pathogeneses. We think we have provided a useful working approach to these challenging wounds. Indeed, we predict that the reader will develop a very good sense of how to deal with these problems, based on our experience and our struggles. Section 6 deals with wounds complicated by or caused by neoplasms. A high degree of suspicion must be kept when wounds do not heal. Even when a biopsy does not demonstrate a neoplastic process, the burden is on the clinician to ensure that a sampling problem did not occur or that the interpretation of the histology was difficult or flawed. In section 7 we devote ourselves to some practical points of wound management. This is an important section that both physicians and nurses must be quite familiar with. One may identify the etiology of the wound, but healing does not take place unless proper WBP is applied and the very practical aspects of patient care are addressed. Finally, we complete our Text Atlas with section 8, which deals with some procedures that are grouped together for the benefit of the reader. In that section, we conclude our work with a discussion of clinical trials, which are the fountain from which new treatments spring from. Over the years, clinical trials have become more demanding and challenging, in order to better address patient safety and to overcome regulatory hurdles. The clinician needs to have a working knowledge of these matters.

We humbly apologize for any shortcoming in preparing this second edition. However, we do hope that our patients' quality of life will improve as a consequence of our addressing these problems related to chronic wounds. Our patients tend to be elderly, are often unable to express themselves properly or unable to make themselves heard when suffering. They are often at the mercy of health systems that do not pay for the considerable expenses of wound management. They have pain, discomfort, and offensive odors from their wounds, and interestingly put up with these and other tremendous challenges with patience and silence. We dedicate this *Text Atlas of Wound Management* to them, our true teachers.

1 Acute wounds: Response to injury

In this section we have described some of the problems one deals with in the management of wounds caused by skin trauma or created by surgical intervention and radiation. The situations we have presented are common, and we hope that they provide the reader with reference points about how to manage some of these problems.

For the purpose of facilitating its understanding and for communicating concepts, the wound repair process is generally divided into three phases: (*i*) coagulation and inflammation; (*ii*) proliferation and migration; and (*iii*) remodeling. Overlap between these phases is considerable, however. The coagulation and inflammatory phase occurs immediately after the types of acute injury described in this section. Platelets enter the wound and release a host of mediators that recruit other cell types and amplify the initial response. In addition to a number of biochemical signals (e.g. fibrinogen, thrombospondin, and thromboxane A2, ADP), a variety of growth factors are released, including platelet-derived growth factor, transforming growth factor-β (TGF-β1), and connective tissue growth factor. The formation of a thrombus leads to the release of other inflammatory molecules, such as bradykinin, C3a, and C3b, which enhance vascular permeability. Ultimately, this phase of wound repair is characterized by platelet release and clot formation, wound debridement by neutrophils, and recruitment of macrophages, fibroblasts, and endothelial cells.

Macrophages, fibroblasts, and endothelial cells play a fundamental role in the second (proliferative) phase of wound repair. Collagen and other structural molecules are laid down, and the dermal matrix is reconstituted. Granulation tissue is formed. Angiogenesis takes place while the matrix makeup of the wound keeps changing. In turn, the change in matrix alters the angiogenic response. Certain growth factors, such as vascular endothelial growth factor and fibroblast growth factor, are key components of the angiogenic response. Integrins, the cell surface receptor molecules, are important in facilitating the interaction between cells and matrix and in cell migration, including that of keratinocytes.

Tissue remodeling represents the third and final phase of wound repair. This phase may go on for weeks, perhaps many months, and is characterized by the presence and activity of a host of enzymes that are able to break down matrix components. The matrix-degrading metalloproteinases are enzymes that need to be activated to function, and have specificity for different collagens and other matrix proteins. At the same time, fibroblasts continue to synthesize extracellular matrix components. Therefore, tissue formation and remodeling go on at the same time.

So far, a very brief summary and overview of what follows injury to the skin has been presented. However, it outlines the processes that take place following most of the surgical procedures described in this section. Based on the extent to which one can modify the wound repair response, one might obtain different and perhaps more desirable clinical results. We do not know how to control fibrosis yet, although experimental approaches to block the action of certain growth factors (e.g., TGF-βs) seem promising. At least in more superficial wounds, occlusive dressings and moisture-retentive dressings may downregulate the fibrotic response. They also create the moist environment which accelerates the healing process of acute wounds. Full-thickness grafts can be used to minimize contraction. Topical pretreatment of skin with retinoic acid (applied in a short-contact method) promotes the formation of granulation tissue in chronic wounds, but this approach has not been properly tested for acute wounds. This section shows a number of examples where facial wounds in a concave area of the face (versus convex) heal better and with less scarring when left to close by secondary intention. However, over the last decade most of these wounds are now managed by surgical reconstruction.

Nonsurgical trauma to the skin encompasses several situations, including injury from accidents, factitial disease or additional manipulation of the wound by the patient. Other common examples include the use of acids, such as trichloroacetic acid or phenol, for the purpose of creating a skin peel and the use of lasers. A fundamental difference of acute wounds not caused by the scalpel is their propensity for hyperpigmentation and hypopigmentation. In general, patients with dark skin are more susceptible to these complications, and this fact has to be kept in mind when discussing prognosis after trauma, treatment options, and possible side effects. In a therapeutic situation involving an elective procedure, it is often wise to first test a small area of the patient's skin to determine how it will repair in terms of hypo- or hyperpigmentation.

Postoperative pain seems peculiarly more prevalent after some procedures (e.g., laser treatment) than scalpel-induced injury. We do not know the reasons for this, but it might be that the damage is more diffuse and not confined or limited to the target area. Topical anesthesia with certain topical anesthetics (available in combination) can be very useful in some circumstances. Postoperative dressings, especially occlusive or moisture-retentive dressings, can also improve the pain in a very dramatic fashion. Another advantage of some classes of moisture-retentive or occlusive dressings in these types of wounds is that they can control exudate and can lead to remarkable decreases in the amount of crusting and even scarring. In our opinion, the beneficial effects of occlusion on postoperative scarring have yet to be fully recognized by many clinicians. How this anti-scarring effect comes about is not known. However, we do know that occlusion can decrease the inflammatory infiltrate, which can probably downregulate the deposition of excessive extracellular matrix proteins and even decrease pain.

A special clinical situation is that of wounds caused by the patient, either intentionally to gain attention and/or reap financial benefits, or in the course of deep psychological or psychiatric problems. In this section, we have presented several examples of these types of wounds, some of which are very dramatic. In our experience, clinicians are slow to recognize factitial wounds and, understandably, afraid to miss an important but unusual condition that they may not have seen before. When faced with a nonhealing or unusual wound, there is a tendency to assume that either the proper treatments have not been used or that the diagnosis is elusive and perhaps too difficult. We suggest that in these situations of failure to heal and no clear diagnosis, the opposite approach be used; we must be thinking of factitial disease while doing everything possible to arrive at alternative diagnoses. When using this approach, one can make use of wound-associated clues to factitial ulcers, in addition to paying attention to the patient's personality and associated medical problems. Ulcers characterized by a linear or geometric configuration and unusual location, and with a discrepancy between severe pain and rather insignificant clinical appearance, are suspect. One can make use of casts or certain short-stretch bandages to cover ulcers on the extremities that might be factitial. Improvement of the wound, while not necessarily proving it is factitial, is helpful in the management and suggestive of the possibility of some extrinsic factors.

While we have learned a considerable amount about the acute stages of classical wound repair (e.g., after scalpel surgery or burns), we know relatively little about the course of events following nonscalpel injury to the skin, including factitial disease and laser-induced wounds. This is also the case with other types of skin injury caused by intervention with acids and chemicals for cosmetic skin peels. The available information is at the histological level for the most part, with a paucity of knowledge about the cellular and molecular events that might be associated with these particular physical modalities. However, there is considerable interest in this area of research, and we continue to see steady progress in this field. From the clinical standpoint, we need to understand better what causes and controls pigmentary changes after cutaneous injury. Control of scarring is just as important, and it would be beneficial to know more about how occlusion seems to downregulate the fibrotic response.

Clinical points

- Tensile strength after complete wound repair can only be as high as 70% of that of uninjured skin.
- In secondary intention healing, concave areas of the face heal with less scarring than those in convex areas.
- Scalp ulcerations, for example after skin cancer surgery, are often difficult to heal if there has been a lot of actinic damage or radiation.
- Mohs surgery is quite effective in removing skin cancer completely, sparing as much noncancerous tissue as possible.
- Bioengineered skin can be used to speed up healing of facial Mohs surgery defects, decrease pain, and/or increase patient's comfort.
- The optimal time for dermabrasion or laser resurfacing for postoperative scars is about 2 months after surgery.
- The treatment of extensive and longstanding hidradenitis suppurativa generally involves extensive surgery to remove the apocrine glands and draining sinuses.
- Beefy red granulation tissue is not necessarily healthy and may signify bacterial overgrowth.
- Occlusive dressings are an established way to accelerate healing of acute wounds. The fear of infection associated with occlusive dressings is unwarranted.
- Redness of healed wounds can last for up to a year.
- Calcium alginate dressings and hydrofiber dressings can be useful in absorbing exudate.
- Factitial wounds generally have bizarre, angular shapes and cannot be totally explained by a defined underlying etiology.
- Clinicians must still be careful in determining that a wound is totally factitial. Mixed situations occur, whereby manipulation of the wound by the patient or the effect of some external therapy is superimposed on a true wound that has a clear and legitimate explanation.
- Occlusion of acute wounds is justified and indicated in the absence of obvious infection. The benefits of occlusive or moisture-retentive dressings are many: decrease in pain, more comfort, faster healing, and less scarring.
- It is difficult to predict whether acute wounds induced by means other than scalpel (i.e., laser, dermabrasion, chemical peels, etc.) will heal with appropriate return to near normal pigment. Often, testing a small area of the patient's own skin may be useful. Patients will often heal with exaggerated hyperpigmentation or hypopigmentation, which can be persistent.
- Low-potency topical steroids, used for a short period of time, can help reduce inflammation following certain procedures. However, topical steroids should not be used indiscriminately, but only when the clinically evident inflammation appears to be substantial and the risk of infection is low.
- The concomitant or recent use of oral isotretinoin is associated with the occurrence of exuberant granulation tissue after skin injury, be it by scalpel or other types of procedures or trauma.
- Trauma or surgical procedures in areas of skin that have previously (even years earlier) received gamma irradiation are often associated with nonhealing wounds.
- A net-like (livedo) pattern surrounding a wound may have been caused by heat injury. A rather typical example would be the prolonged use of a heating pad by an elderly patient with back pain.
- A topical anesthetic mixture of lidocaine/prilocaine, widely available, can help in the overall management of pain in certain wounds caused by trauma, such as burn or chemical injury.
- Surgery on the face for skin cancer removal can be done by the Mohs technique, which helps ensure a complete tumor removal before reconstruction or healing by secondary intention. The latter is more likely to yield acceptable cosmetic outcome in concave areas of the face.

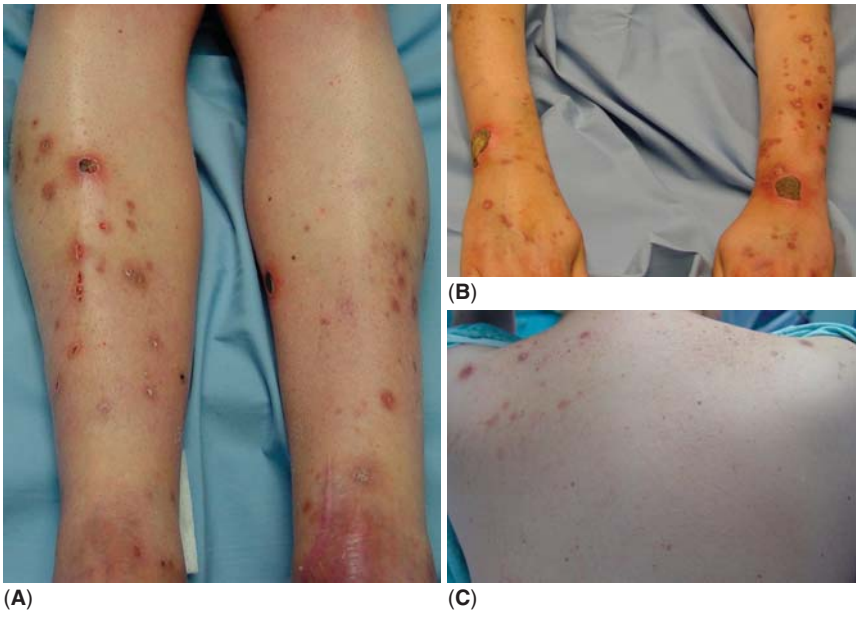


Figure 1.1 Factitial ulcers: clues.

Panel **A** might initially suggest lesions of ecthyma or pyoderma secondary to arthropod bites or other injuries. However, as shown in Panel **B**, the linearity of the lesions and the variation in ulcer size and depth suggest a factitial etiology. While other injuries (e.g., brushing against poison ivy leaves) might leave linear streaks, the diagnosis is almost certain when looking at the back of the patient (Panel **C**). Here we observe involvement of only areas that can easily be reached by the patient.

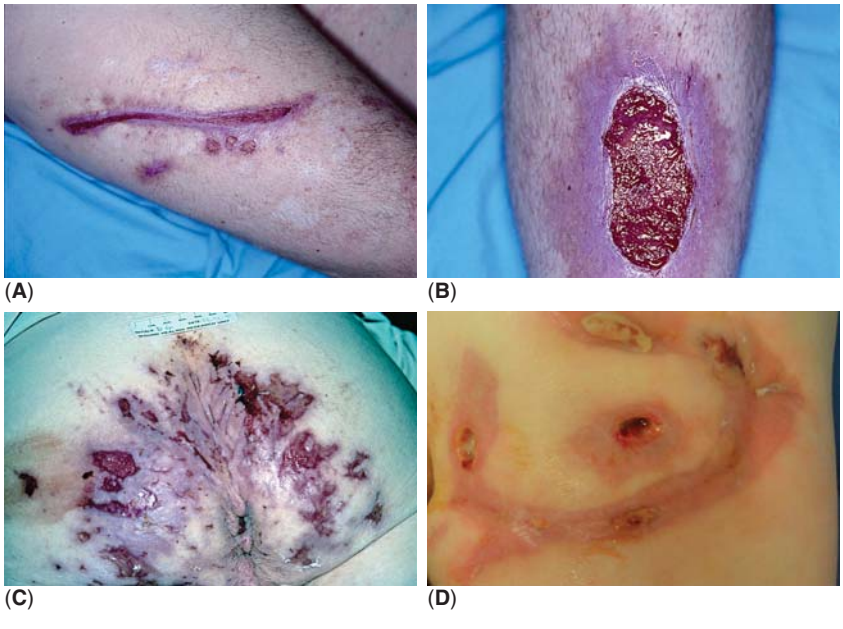


Figure 1.2 Several examples of factitial injuries.

Panel (**A**) This patient has a large linear wound on her thigh and some smaller ulcers around it. The large linear wound ulcer seems to have been produced with a sharp object. The plan is to treat her with pimozide, which is usually reserved for patients with delusional parasitosis but has worked in some patients with factitial ulcers. Sleep studies were normal and did not show EEG abnormalities or bouts of destructive behavior while the patient was asleep. Panel (**B**) This 32-year-old woman cannot stop from inducing these large ulcers on her leg. She clearly admits to doing it herself but states that she cannot stop when she has the urge to damage her skin. It is unclear how she induces these wounds. She denies using sharp objects and states that she simply keeps rubbing her skin off. Dressings have been of no value, and protecting the skin with bandages (like an Unna boot) has not worked; she easily removes all bandages. Panel (**C**) These extensive perianal ulcers and erosions were apparently self-induced by this elderly patient. There was no evidence of infection with herpes simplex viruses. The possibility of zinc deficiency dermatitis was entertained, but there was no other periorificial involvement or evidence for zinc deficiency; zinc levels were normal. Extensive use of hydrocolloids is probably the best way to protect these areas from further self-injury and manipulation. Panel (**D**) This young woman had multiple ulcers and several surgical procedures in an attempt to debride and resurface them. There were other self-induced systemic components to her medical history as well. For this chest area lesion we also entertained the possibility of a lymphomatous process because of the pink to red color and the C-shaped geometry that is occasionally seen with cutaneous lymphoma. However, there were other secondary lesions that originated from the outer margins of this incomplete circular area which also suggested factitial disease.



(**A**) (**B**)

Figure 1.3 A simple interventional step to determine factitial etiology.

This patient had recurrent necrotic ulcerations on her right forearm. Histological and laboratories studies did not show any evidence of vasculitis, cryoglobulinemia, cryofibrinogenemia, or antiphospholipid syndrome. She admitted to relentlessly scratching and picking her skin. In our experience, this type of problem is linked to some underlying psychiatric condition. It was decided to shield the area from further trauma by applying a type of short-stretch bandage (Unna boot, in this case) to the arm, from the wrist to the elbow. However, as shown in the photograph (Panel **A**), the bandage had a tendency to slip down, possibly as a result of further manipulation by the patient. Panel **B** shows the forearm after bandage removal. One can see that the inferior area, which had remained protected by the bandage, has healed. This clue told us that we were on the right track, both diagnostically and therapeutically.



Figure 1.4 Factitial ulcers/treatment with bandage.

We realized that a modification of the bandaging was needed to anchor the Unna boot in place. This was successfully achieved by applying the Unna boot from the upper arm to the wrist and then cutting a section over the elbow. This allowed the patient more freedom of movement and helped to ensure greater compliance and less slippage. The patient healed and, interestingly, did not continue to injure
her arm.



Figure 1.5 A burn injury in a quadriplegic patient.

This ulcer on the lateral portion of the fifth digit of the right hand was not self-induced (Panel **A**). The patient, who has no ability to feel pain in this location, inadvertently burned the area when sitting next to a heat radiator at his home. Panels **A** and **B** show the ulcer before and after surgical debridement, respectively. Subsequently, he was treated with a bi-layered living bioengineered skin construct, which led to progressive healing of the ulcer (Panels **C** and **D**).



Figure 1.6a Burn injury with livedo.

This area on the flank and back shows a livedo pattern (erythema ab igne) and ulceration. The patient had been applying a heating pad to this site in order to relieve back pain. This complication from a heating pad is not an uncommon clinical situation, particularly in the elderly. The livedo, net-like pattern represents damage to the superficial vasculature.



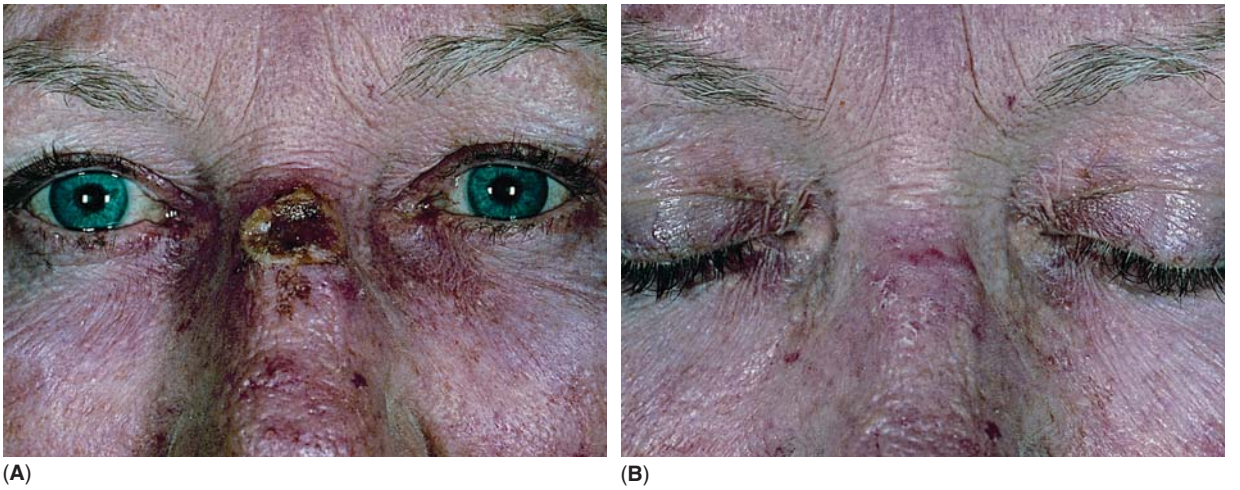
Figure 1.6b Burn injury/close-up.

The ulceration is surrounded by the livedo pattern and appears to be quite superficial. It healed with the use of hydrocolloid dressings.



Figure 1.7 Electrocautery burn.

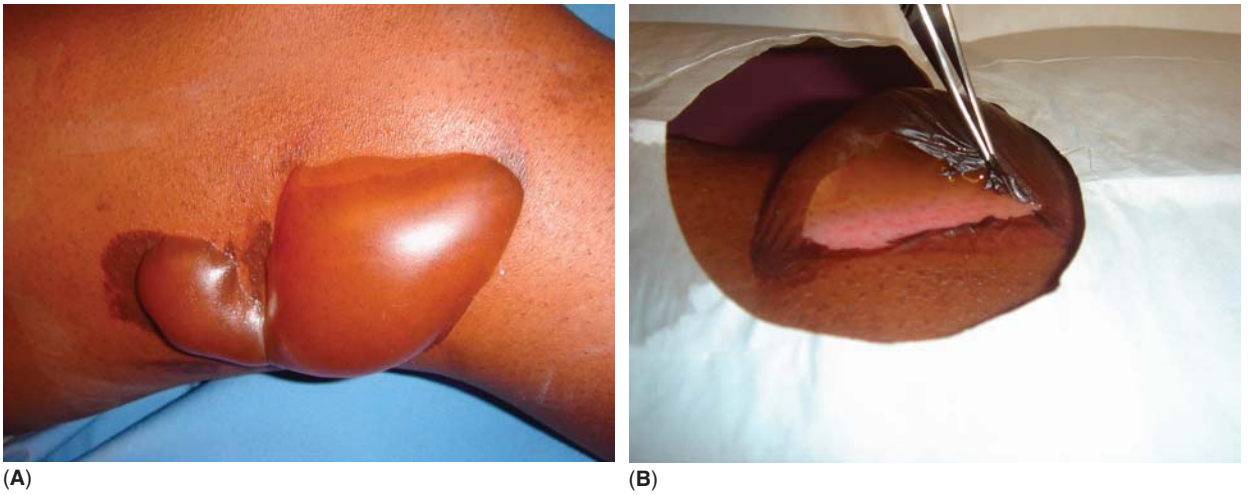
This represents a partial to full-thickness injury. Although the wound bed is still poor and shows what is probably denatured dermal structural proteins and nonviable tissue, there is evidence of epithelialization from the wound's edges.



(**A**) (**B**)

Figure 1.8 Ulcer from cryosurgery/follow-up.

A wound caused by cryosurgery usually starts as a hemorrhagic blister, followed by ulceration and crusting (Panel **A**). The surrounding tissue can become quite edematous. In this patient, liquid nitrogen had been used to treat an actinic keratosis. The wound has completely healed, as seen in Panel **B**. In other cases, healing is complicated by substantial hypopigmentation, presumably because of damage to melanocytes.



(**A**) (**B**)

Figure 1.9 Blistering from cold injury.

This middle-aged woman placed an ice pack for several hours on the medial aspect of her left knee, which she had injured during exercise (Panel **A**). This resulted in tense blisters, which were shown to be subepidermal on histology. Panel **B** shows the unroofing of the blisters, with clinical evidence of early epithelialization of the underlying wound bed. This is common in subepidermal blisters, so that the area under the blister is actually already resurfaced. Epidermal keratinocytes are able to migrate under blisters and crusts. There was no evidence of infection or immunological markers for bullous pemphigoid, a disorder that produces subepidermal blisters.

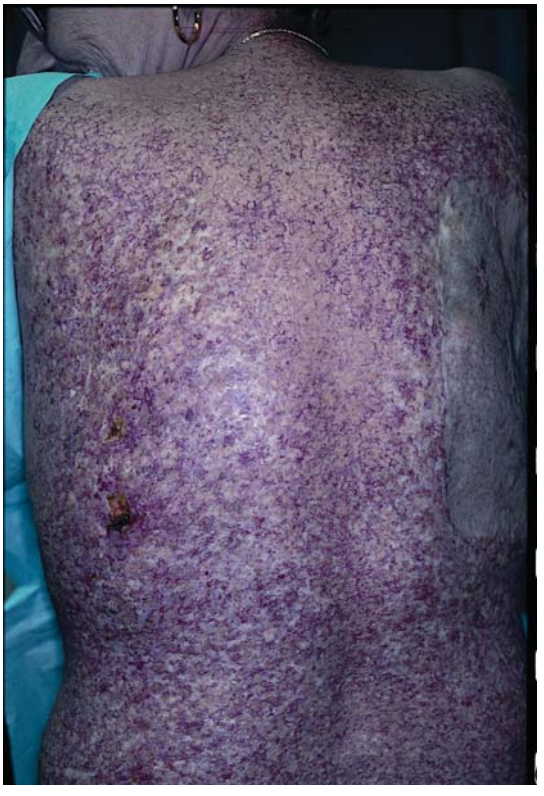
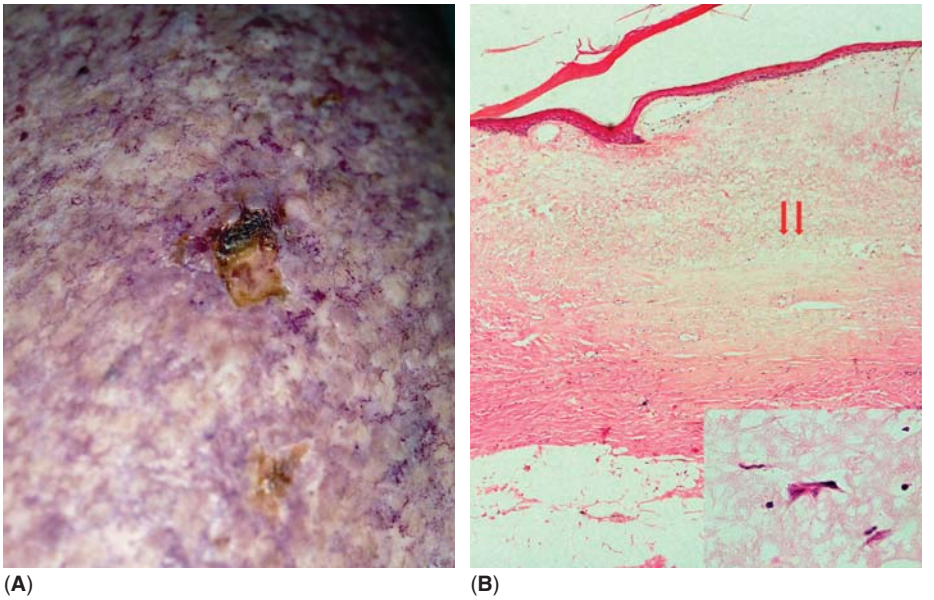


Figure 1.10a Radiation-induced wounds.

This patient had cutaneous T-cell lymphoma and received total body electron beam therapy several years ago. The lymphoma was under control. However, the radiation has caused the skin to become very atrophic. Skin breakdown within the atrophic areas has become a management problem.



(**A**) (**B**)

Figure 1.10b Radiation-induced wounds/close-up and histology.

This patient's skin is also indurated and shows a remarkable vascularity, which is probably due to blood vessel tortuosity and some vascular proliferation (Panel **A**). Histologically, these changes are seen as dilated vascular channels in the papillary dermis, loss of normal cellular compoents, hair follicles, and sebaceous glands, and effacement of the typically undulating epidermal rete ridges. There is homogenized collagen (red arrows). On higher magnification large, bizarre-looking "stellate" dermal and subcutaneous fibroblasts are appreciated (Panel **B** inset). These superficial wounds were very painful, and in this case did not respond to a variety of moisture-retentive dressings or to topical retinoic acid, which we have used in other patients; the retinoic acid stimulates the granulation tissue. Peculiarly, topical steroids appear to improve the symptoms and lead to healing in some of these patients. In our opinion, the epidermal and dermal cells are permanently damaged by the radiation. One hope is to use autologous grafting or bioengineered skin to re-establish a normal cell population. Though still investigational, autologous mesenchymal stem cells from bone marrow or adipose tissue may be worth trying.

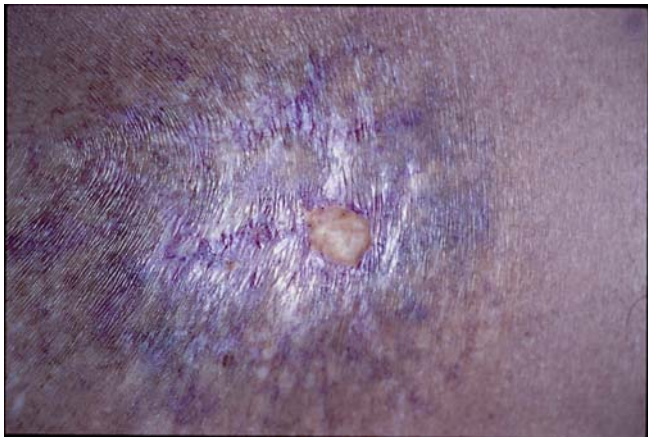


Figure 1.11 Fluoroscopy-induced wound.

This complication of intense exposure to x-rays during prolonged fluoroscopic procedures is not well recognized among radiologists or other clinicians. In this case, the patient had a liver transplant and many fluoroscopic procedures. This indurated lesion on his back, with a central nonhealing ulcer, was initially thought to be localized scleroderma (the morphea variant) by his physicians. However, the clues of vascular damage (net-like pattern) and the hyper- and hypopigmentation make it most compatible with radiation-induced damage, given also the history. He was helped by a medium-potency topical steroid, which markedly reduced his pain. A full-thickness graft taken from his thigh took initially but did not survive long term. We suspect that the intense immunosuppression from corticosteroids and other immunosuppressant for organ rejection also play a large role in preventing healing.

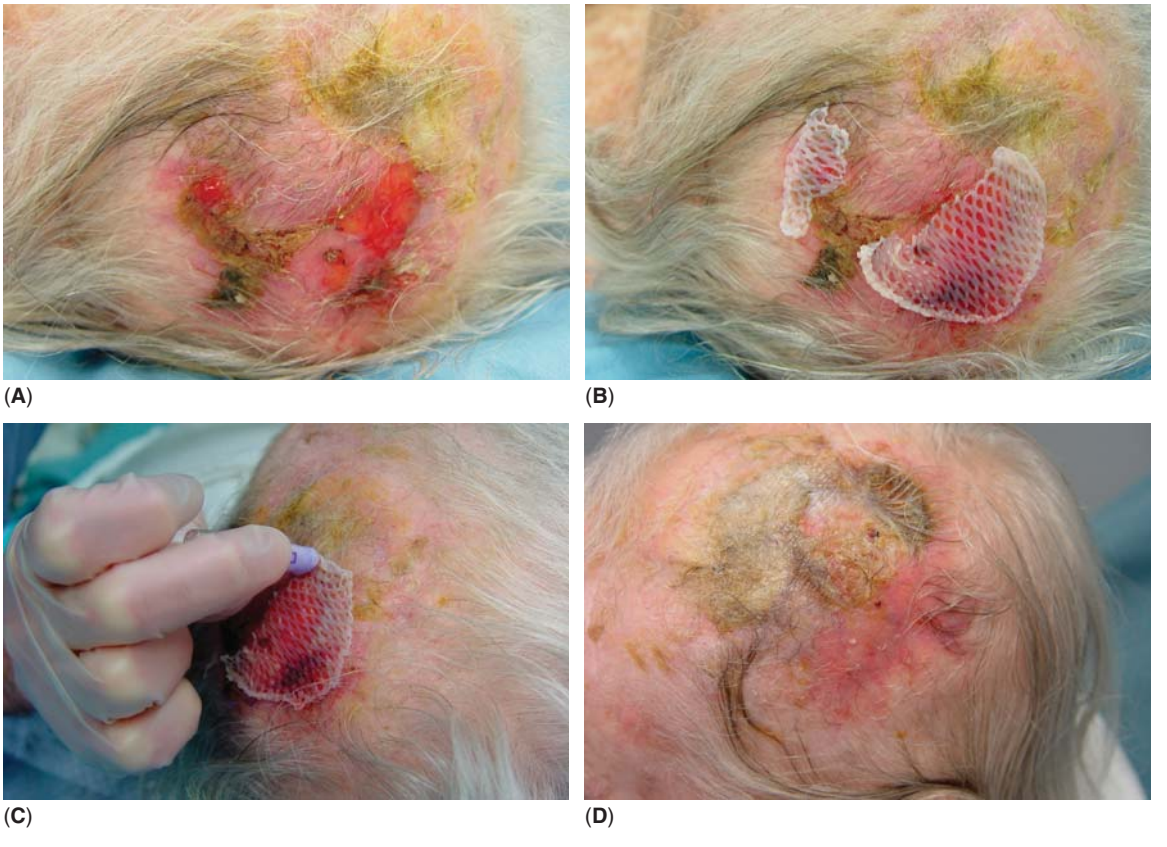


Figure 1.12 Sun-induced (actinic, chronic) damage to the scalp in an elderly woman.

She liked extensive sun exposure and boating for many decades of her life. Now in her 80s, she presented with extremely fragile, nonhealing erosions and ulcers of her scalp (Panel **A**). There was no evidence of skin cancer on repeated biopsies of her scalp. We have seen several patients having this clinical problem. In this particular case, as shown by the progression from Panels **B** to **D**, she was stabilized and healed with the application of a bi-layered living bioengineered skin construct (seen applied in Panel **B**). The bioengineered skin was meshed at a ratio of 1.5 to 1, and kept in place with a liquid bonding agent commonly used for wounds. During this clinical course, we also made rather extensive use of a polymer film spray. She would spray her remaining erosions, to avoid the use traditional dressings, which would inevitably stick to the wounds.



Figure 1.13a Wound from chemical injury.

This patient was injured by exposure to a chemical while at work. These and other wounds on his feet did not heal in spite of a number of therapeutic approaches. Pain was a persistent problem. The patient also had cirrhosis. Although the chemical injury may have been the inciting event, his clinical picture was one of venous insufficiency and ulceration. Generally, he tended to improve with compression therapy.



Figure 1.13b Wound from chemical injury/pain control.

Persistent pain was his greatest problem. In this and in other chronic wounds, we have found that a commercially available combination of lidocaine/prilocaine can be quite helpful in relieving pain. Here one sees the cream that has been placed on the wound and is being covered with an occlusive film (the paper supporting the film is yet to be removed). The use of the film is probably not absolutely necessary, because there is good absorption of this preparation in wounds.

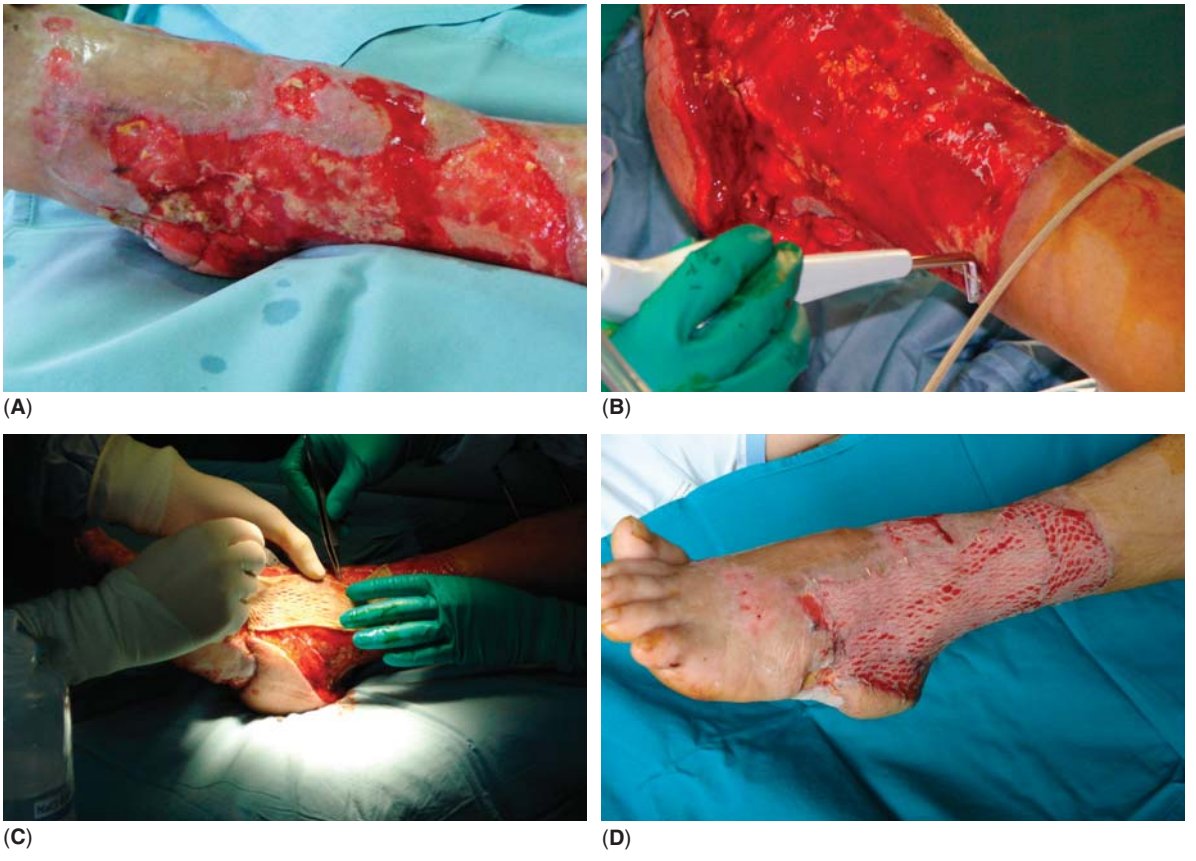


Figure 1.14a Injury to the leg from a work accident and surgical therapeutic steps.

This middle aged man sustained multiple fractures of the left lower leg and foot. The traumatic skin ulcerations were difficult to heal (Panel **A**). Panel **B** shows the use of hydrosurgery for surgical debridement in the operating room, while Panel **C** indicates the use of a flap rotation to cover the heel. A meshed autologous graft was used to cover the remainder of the ulcer (Panel **D**). He had a good outcome with almost complete take of the flap and graft, and this process was greatly aided by the use of negative pressure applied to the wounds with a polyurethane foam and up to 120 mmHg for 8 days.



Figure 1.14b Injury to the leg from a work accident and surgical therapeutic steps/results.

The results of these surgical and other therapeutic steps appear quite good after 4 months. The patient went through a rehabilitation program to recover function of the foot.



Figure 1.15 Dramatic salvage of the left hand after a 3rd-degree burn.

While working, this 63-year-old man sustained a 3rd-degree burn to the back of his left hand, with complete destruction of the 1st and 2nd phalanges of the thumb and the 1st phalanx of the 5th digit (Panel **A**). Not seen here are the extensive necrosis and subcutaneous loss of tissue of the palm. The patient was referred to us 14 days after ineffective attempts at treating the burn injury. The approach to this serious injury involved debridement by both scalpel and hydrosurgery, the application of negative pressure (Panel **B**; for 12 days with twice daily changes in dressings), the use of collagenase for further wound bed preparation, and repeated steps for cleansing and protection of exposed structures. Panel **C** shows the results obtained with surgical intervention 25 days after the initial burn. A reconstructive procedure with a free flap was used to cover the back of the hand. Surgical amputation of the 2nd digit and transposition of the 4th digit on the second were used to maintain apposition and functionality of the hand. Panel **D** shows the appearance of the hand 5 months after the injury. Liposuction was also required to reduce the amount of adipose tissue in the flap and to maintain function and reasonable range of motion of the fingers.

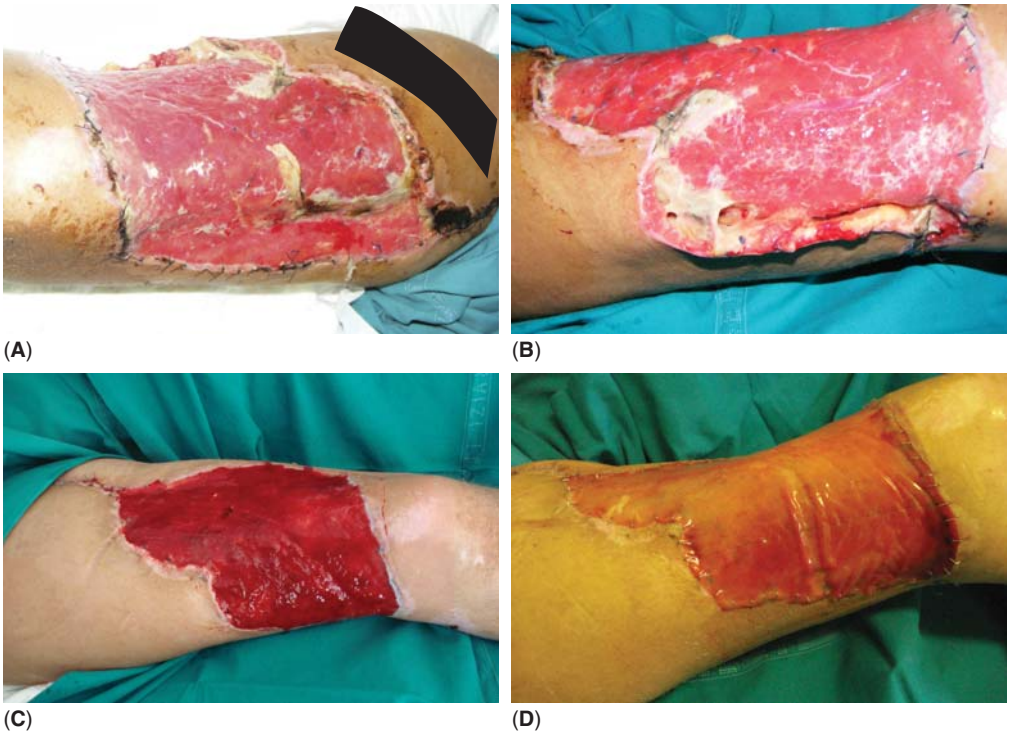


Figure 1.16 Extensive thigh injury following an automobile accident.

In a car accident, this 19-year-old woman sustained extensive right thigh injury and loss of subcutaneous tissues. This would result in severe disfigurement and contractures, and also interfere with the function of the limb (Panel **A**). As soon as she arrived in the emergency room, the patient underwent surgical debridement by scalpel and hydrosurgery. Panel **B** shows the appearance of the wound 2 days after trauma and after the application of negative pressure to the wound with gauze dressings (80 mmHg for 6 days and changed twice per week). Panel **C** shows the wound after further surgical debridement with scalpel and hydrosurgery and after sustained (10 days) negative pressure with continuous use of polyurethane dressings (120 mmHg). Panel **D** shows the wound after the grafting of dermal tissue to diminish contractures and fill in the wound. Twenty days after this photo the patient underwent autologous skin grafting.

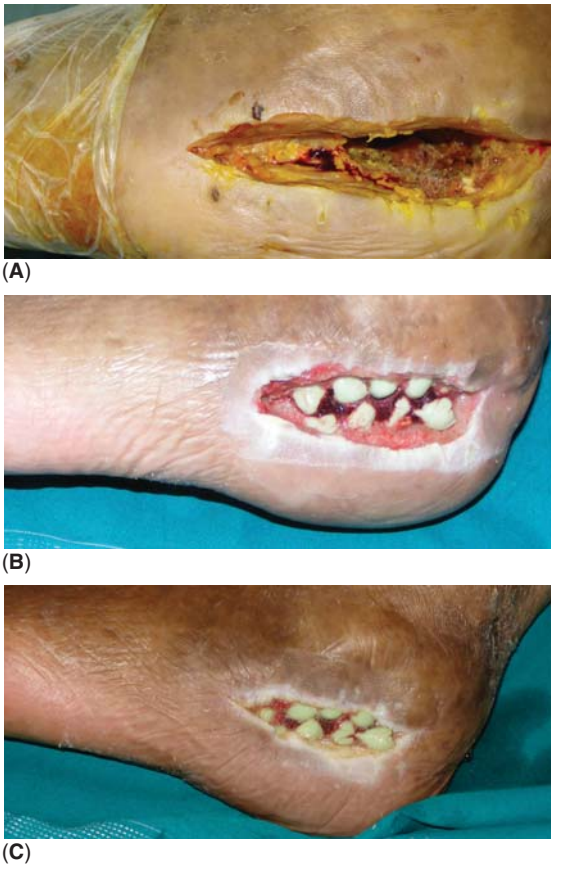


Figure 1.17 Stabilization of injury-induced osteomyelitis.

A 49-year-old man broke his heel and several areas of his ankle joint in an accident. Soon after the trauma, he received treatment with surgical screws to stabilize the joint. Two months after the accident there was persistent purulent drainage and nonhealing of the wound (Panel **A**). Radiological tests were consistent with the diagnosis of osteomyelitis. Antibiotic-loaded cement beads were used to deliver high concentrations of antibiotics to the underlying bone (Panel **B**). There was continuous application of negative pressure to 80 mmHg, which was used for 16 days with twice-a-week dressing changes. Casting was used to stabilize the ankle joint. Eight weeks after the injury, debridement was performed to remove tissue affected by osteomyelitis and the antibiotic beads (Panel **C**). The patient's ultimate outcome is still unknown at this time. This case highlights the difficulties involved with osteomyelitis after trauma and some steps that can be taken to try and salvage the limb.

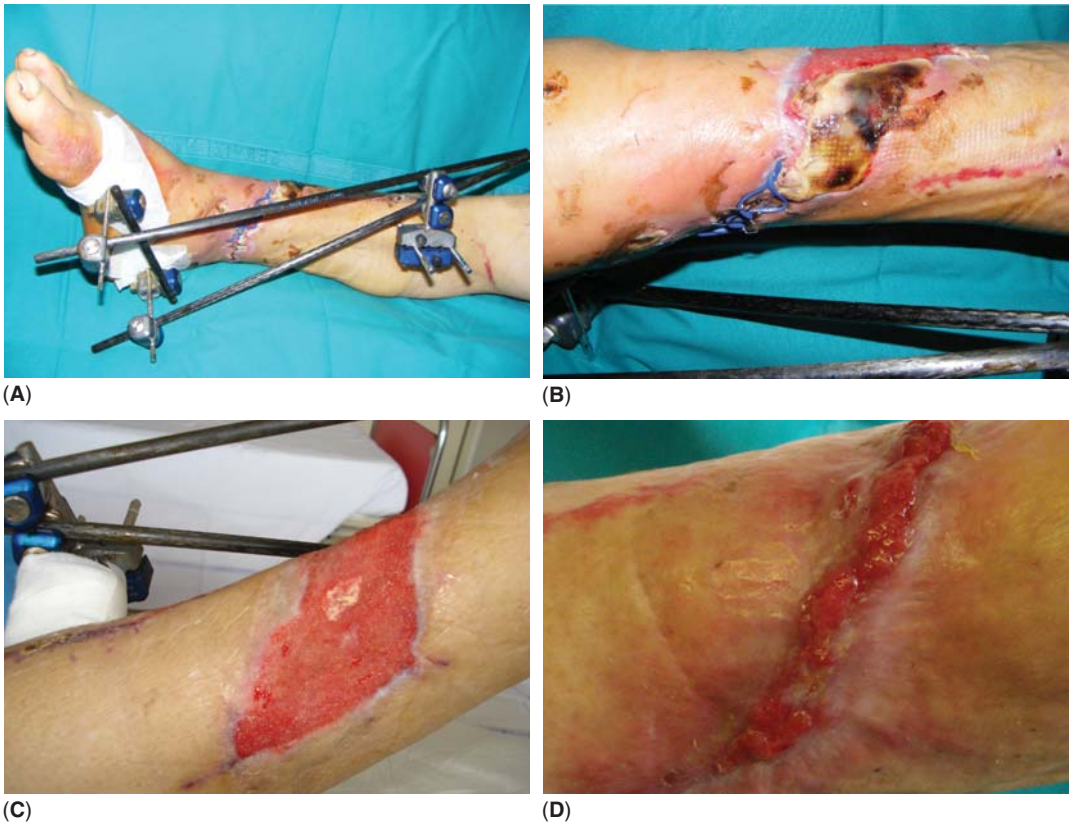


Figure 1.18 Complexities of trauma-induced wounds in a patient on anticoagulants.

The case of this 70-year-old man, who sustained compound fractures of the distal tibial and fibula of his right leg, illustrates the difficulties one encounters in trying to prevent complications, restore function, and ultimately salvage the limb. He was initially treated with an external device to stabilize the fractured bones (Panel **A**). It should be noted that the patient had undergone an abdominal aortic aneurysm repair approximately 1 month prior to the injury and the much needed anticoagulant therapy could not be stopped. The clinical course was complicated by the development of necrosis in the skin and subcutaneous tissues. In some areas of the wound (superiorly in Panel **B**) there was excessive granulation tissue. In our experience, the latter is associated with increased bacterial colonization and infection. The patient received extensive debridement by scalpel and hydrosurgery and the application of negative pressure (80 mmHg for 11 days and change of dressings twice a week). The wound responded well to these therapeutic measures (Panel **C**), where one sees a wound bed that is flush with the skin and is surrounded by new areas of advancing epithelialization. He was then treated with a bioengineered skin construct to stimulate the endogenous process of tissue repair. Panel **D** illustrates good results from the above therapeutic approach, and the wound is healing nicely.



Figure 1.19a Traumatic wound.

This was caused by a fall and became quite painful. The surface of the wound is yellow-white, suggesting bacterial colonization. However, there is no evidence of cellulitis.



Figure 1.19b Traumatic wound/pain management.

Gel dressings are ideal for this type of superficial but painful wound. These types of dressings are usually made of a polyethylene gel-like material sandwiched between two polyurethane films. Only the polyurethane film from the dressing side to be in contact with the wound is removed.



Figure 1.20 Traumatic wound.

This photograph was taken 2 days after the patient reported falling onto gravel. There is a great deal of swelling, bruising, and superficial skin loss on the forehead, cheeks, and nose. Generally, this type of injury heals without too much scarring, although keloid formation and tattooing from the particulate matter embedded into the skin are definite possibilities.



Figure 1.21 Nonhealing traumatic wound.

This patient had a surgical procedure to repair her Achilles tendon. Postoperatively, she was placed in a cast to immobilize her leg. This type of laceration just above the heel was present after the cast was removed and has not healed for several months. There is considerable induration and probable fibrosis around this wound. As in other situations like this, the fibrotic/sclerotic component may be interfering with the healing process. Topical retinoic acid (short-contact method) was used to stimulate granulation tissue, but did not improve this particular wound. She was lost to follow-up, but our plan was to surgically remove the fibrotic tissue around the wound and then perform an autologous graft.

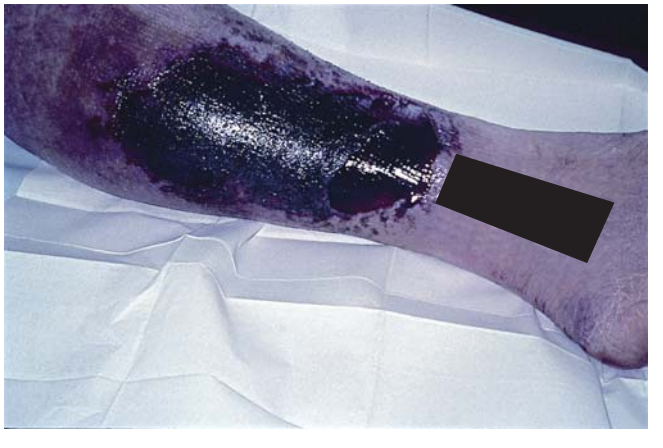


Figure 1.22 Warfarin (Coumadin) necrosis.

This is a well-known complication in patients on warfarin, which in this case was required because of atrial fibrillation and the possibility of strokes. Warfarin or coumadin necrosis is thought to be due to protein C deficiency during the initial phases of therapy. It will generally resolve even while continuing warfarin, but it can lead to substantial tissue necrosis and complications. Interestingly, the occurrence of this event does not preclude future use of warfarin.



Figure 1.23a Junctional epidermolysis bullosa (EB).

This genetic condition became apparent a week after birth and has plagued this child ever since. The variant of EB shown here (Herlitz variant) is characterized by excessive granulation tissue and lesions often occurring on the face. Scarring is the usual result. In this case, the excessive granulation tissue has led to obliteration of the nares. These patients may also suffer from gastrointestinal involvement. All forms of junctional EB are characterized by separation of the skin through the lamina lucida. There has been recent work, still preliminary, that children with this condition may be approached with allogeneic bone marrow transplantation. Living bioengineered skin constructs have been used to lessen the pain and stimulate healing. Patients with EB are at high risk of developing aggressive and quickly metastasizing squamous cell carcinomas from the skin.



Figure 1.23b Junctional epidermolysis bullosa (EB)/other features.

He also had wounds on his ears. A serious management problem in these patients is bleeding, which occurs readily as soon as the wound is touched or dressed. Trauma is important in the development of these wounds. We found petrolatum-impregnated gauze to be a reasonable and cost-effective dressing for most of these types of wounds. Slow-release antiseptics have been used to control bacterial colonization. In order to minimize the use of dressings, all of which stick to the wounds and cause further injury upon removal, we have used polymer film sprays.



Figure 1.24 Dystrophic epidermolysis bullosa (EB).

This photograph was taken when the patient was 63 years old. He first developed the condition at the age of 2. The pattern of inheritance was autosomal dominant. The cleavage and blister formation in this form of EB is below the lamina densa. Basically, the clinical course here is similar to what we see in chronic wounds, with trauma playing a major role in their initial development. In the management of these patients, and particularly in their first 3 or 4 decades of life, one should be aware of their propensity for developing aggressive and rapidly metastasizing squamous cell carcinomas in areas that have had recurrent ulceration and healing/scarring.



Figure 1.25a Full-thickness Mohs wound.

The wound is the result of Mohs surgery to remove a basal cell carcinoma located in the medial canthal area. A full-thickness graft is a good way to repair this defect.

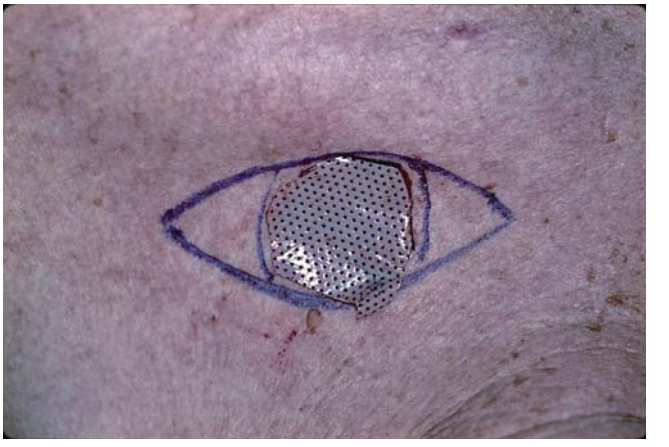


Figure 1.25b Full-thickness Mohs wound/donor site.

The area directly over the clavicle is a good source of full-thickness grafts for larger facial wounds. A template is used to mark the donor site of the graft. A sterile dressing or other suitable material can be used as template.

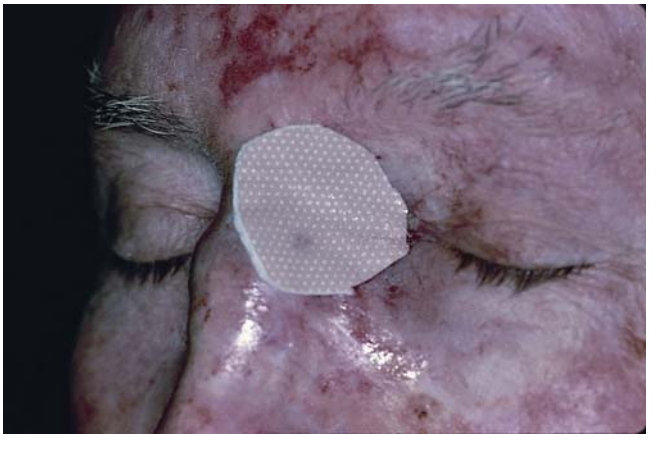


Figure 1.25c Full-thickness Mohs wound/grafted.

A nonadherent bandage is placed over the full-thickness graft.



Figure 1.25d Full-thickness Mohs wound/grafted.

Wadded-up gauze is used to maintain pressure over the graft and to minimize graft loss due to accumulation of blood or wound fluid.



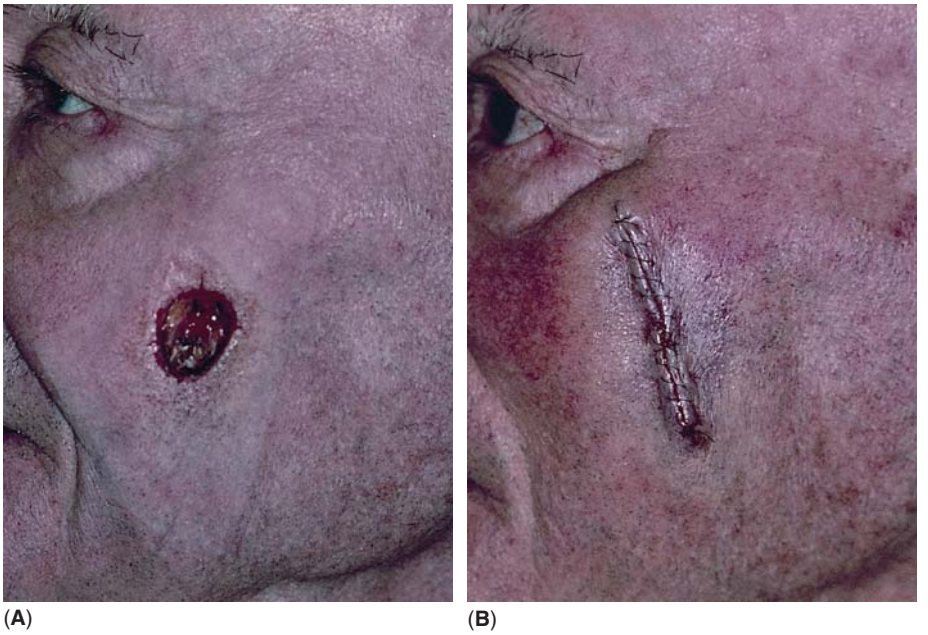
Figure 1.25e Full-thickness Mohs wound/grafted.

Here one sees the pressure dressing in place, covered and secured with paper tape and liquid adhesive.



Figure 1.25f Full-thickness Mohs wound/follow-up.

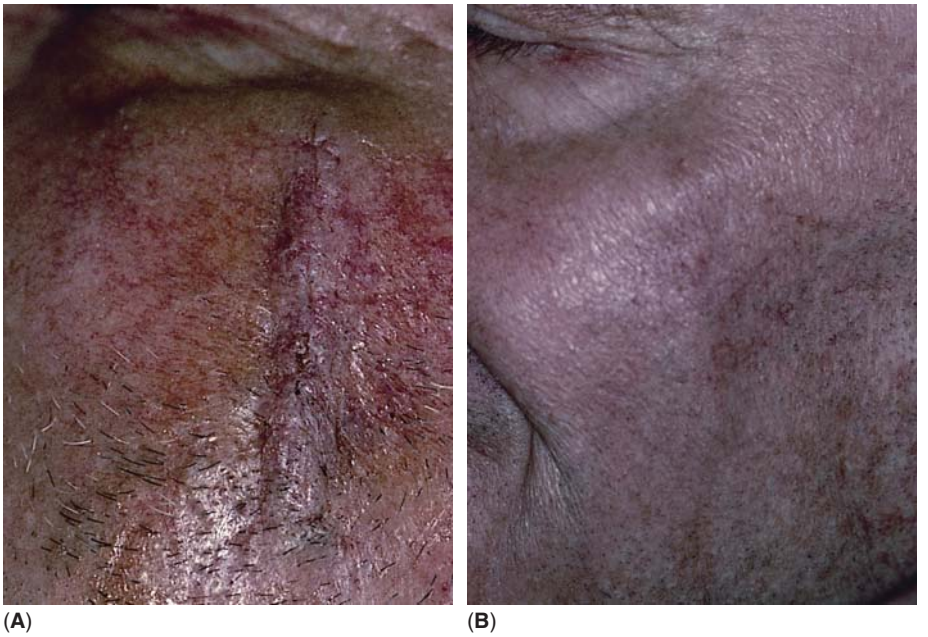
This photograph, taken 7 days after the procedure, shows an excellent graft take.



(**A**) (**B**)

Figure 1.26a Suturing of Mohs wound and follow-up.

This patient had a nonmelanoma skin cancer treated by Mohs surgery. This full-thickness defect on the cheek (Panel **A**) could be sutured in order to achieve a good cosmetic result, but several tissue re-arrangement options exist. Again, these convex areas do no heal well by secondary intention. If the wound is sutured flat, contraction will eventually create an indented scar. By suturing the wound with eversion of the edges (Panel **B**), later contraction and tissue remodeling tend to lead to a flat scar and a more desirable cosmetic result.



(**A**) (**B**)

Figure 1.26b Suturing of Mohs wound and follow-up.

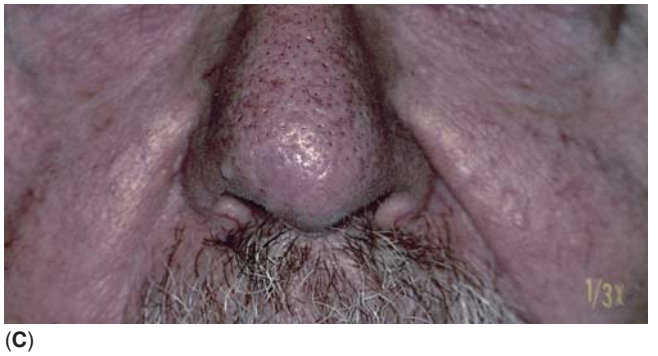
Panel **A** shows the surgical wound two months postoperatively and with an acceptable cosmetic result. Panel **B** illustrates an excellent cosmetic result several months later, also showing the extent of scar maturation over time. There are, of course, multiple ways of handling these types of surgical wounds. The principles to keep in mind are the benefits of rapid reconstruction after the skin cancer removal, predicting the extent of wound contraction, paying attention to pigment changes in the final outcome and, just as important, matching the type of surgery with the needs and wishes of the patient.



(**A**)



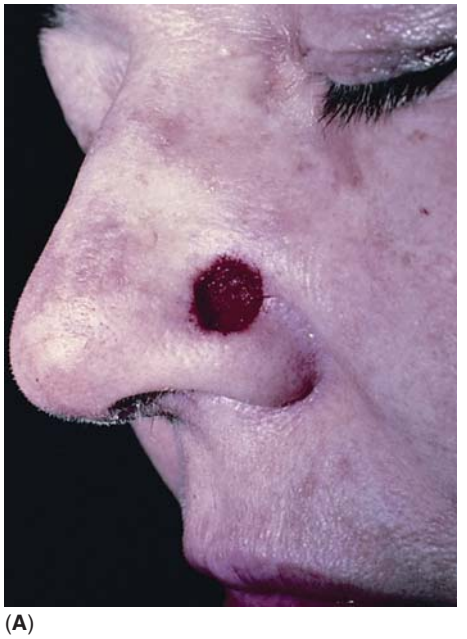
(**B**)



(**C**)

Figure 1.27 Full-thickness wound of the nasal ala and follow-up.

This photograph was taken immediately after Mohs surgery to remove a basal cell carcinoma (Panel **A**). The full-thickness wound near the nasal ala can cause alar rim distortion if left to heal by secondary intention. A full-thickness graft was sutured into the wound (Panel **B**). In this case, the donor site was the postauricular area. As shown here, the final result was quite acceptable (Panel **C**). The full-thickness graft helped prevent wound contraction. It is important, when choosing the donor site, to match as closely as possible the skin color and texture of the skin around the surgical defect.



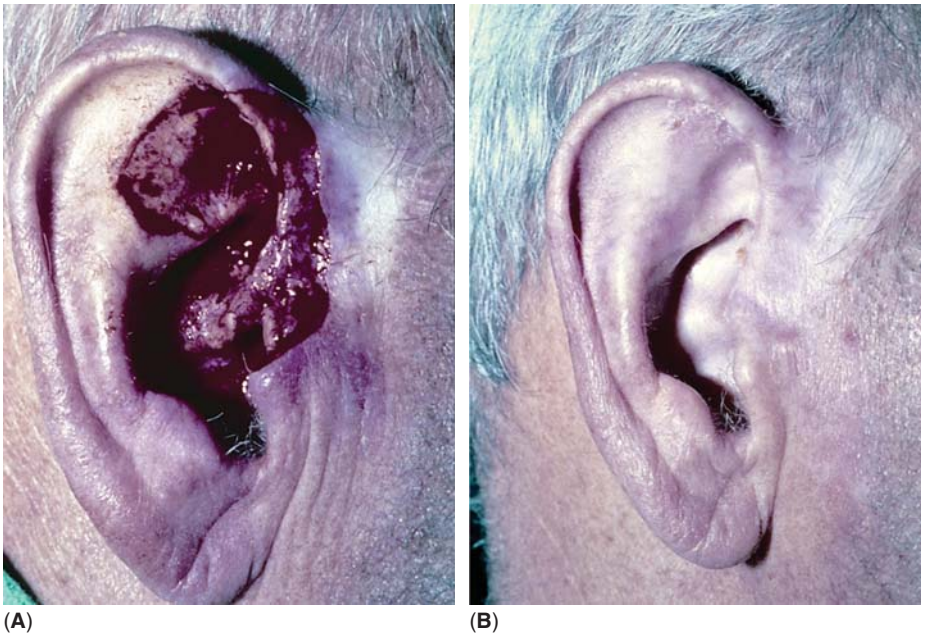
(**A**)



(**B**)

Figure 1.28 Nasal defect after Mohs surgery.

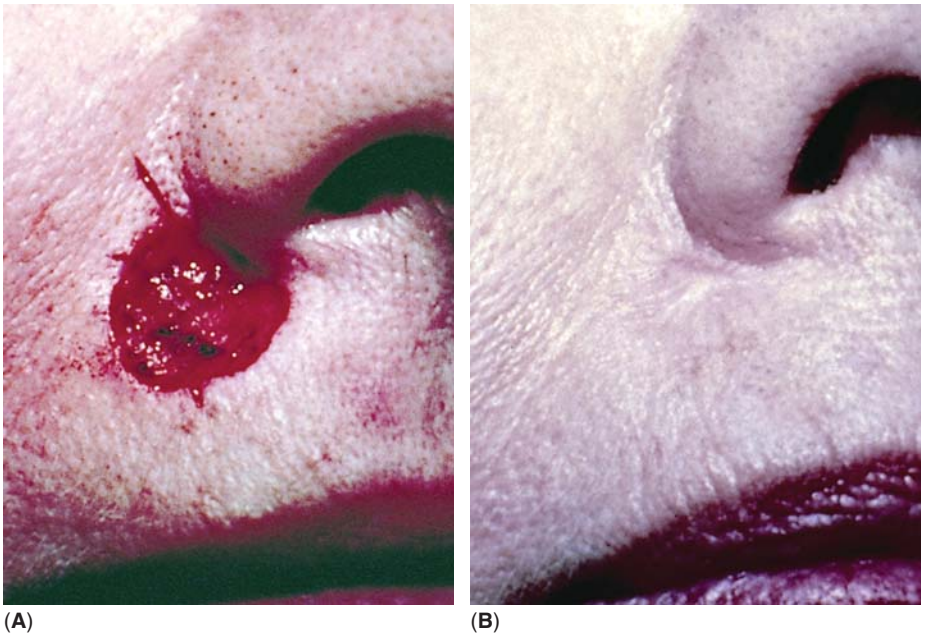
Unlike the situation in the previous case, this wound is in a concave area of skin (Panel **A**) and, therefore, can be expected to heal with acceptable scarring by secondary intention. In fact, an excellent cosmetic result was obtained with secondary intention healing. *Source*: Photo courtesy of John Zitelli, MD.



(**A**) (**B**)

Figure 1.29 Mohs surgery wound/follow-up.

Although it looks extensive, this type of ear wound (Panel **A**) heals quite well by secondary intention. This is what was done in this case (Panel **B**). Secondary intention healing may take a long time to achieve full wound closure, and this is of course associated with drainage, dressing changes, nursing attention, and visits to the doctor's office for follow-up. At times, an infection can occur in a wound that remains open for a long period of time. Therefore, clinical judgment and the patient's circumstances need to be taken into account when making the decision to use secondary intention healing versus a reconstructive procedure.



(**A**) (**B**)

Figure 1.30 Healing of a Mohs wound.

Skin cancers in these areas near the nasolabial folds can be very difficult to remove completely, and have a high chance of recurrence. Mohs surgery, by microscopically ensuring complete removal of the cancer, is often the treatment of choice in the United States (Panel **A**). Indeed, it should be noted that in most countries the treatment of basal and squamous cell carcinomas of the skin is approached by excision, histological attention to surgical margins, and reconstructive approaches to heal the wound. In this case, the wound was allowed to heal by secondary intention. As shown in Panel **B**, in this case there is a small scar after healing. This result is acceptable to most patients because the scar is small. However, some clinicians would correctly argue that a flap closure would have resulted in a better cosmetic outcome. The results obtained here by secondary intention are not entirely satisfactory. Therefore, even though the general guidelines about concave areas indicate that they heal well and acceptably by secondary intention, there are exceptions. It might also be that this wound was at the border of convex and concave areas.



(**A**) (**B**)

Figure 1.31 Large and multiple Mohs wounds and follow-up.

Even these large wounds after Mohs surgery for skin cancer (Panel **A**) can heal well by secondary intention (Panel **B**). Management of these acute wounds, particularly in the elderly, is very challenging. Although it has been shown that moisture retentive dressings are beneficial, it has been our observation that most surgeons prefer to use topical antibiotics and nonadherent dressings and gauze in the initial postoperative follow-up period. This preference may reflect concern over postoperative bleeding. One might argue that immediate surgical repair/reconstruction of these wounds, rather than healing by secondary intention, should be done instead, so as to minimize patient's discomfort. Overall, one should note that over the last decade there has been a shift in standard therapy of these patients to use immediate reconstructive surgery, even in the nonplastic surgery community.



(**A**) (**B**)

Figure 1.32 Wound in a convex area of the face and follow-up.

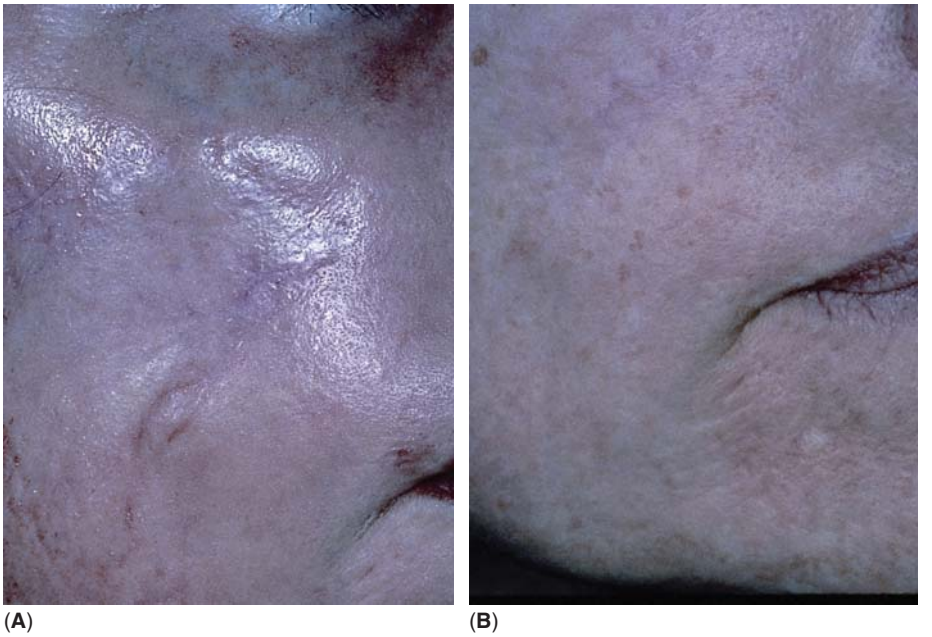
The wound is the result of removal of a skin cancer with Mohs surgery (Panel **A**).

As one might expect, secondary intention healing is not the appropriate way to treat these wounds over convex skin areas. Indeed, there is considerable scarring and contraction associated with that approach (Panel **B**). These findings are consistent with our previous statements, including those in the introduction, that reconstructive procedures are more appropriate in dealing with these facial wounds.



Figure 1.33 Sutured wound.

This patient had a traumatic scalp laceration that required sutures in the emergency room. The photograph was taken right after suture removal. The redness can persist for many months and often up to a year. The results do not appear to be acceptable in terms of cosmesis. However, surgical reconstruction can be addressed later on. Hair regrowth will likely hide much of the scar.



(**A**) (**B**)

Figure 1.34 Dog ear deformity.

A rhombic flap on the cheek has created scars and dog ear deformity at the inferior margin (Panel **A**). This photograph was taken 2 weeks after the surgical removal of a skin cancer.

The scar was eventually resurfaced with a CO_2 laser. The subsequent appearance is quite acceptable (Panel **B**).

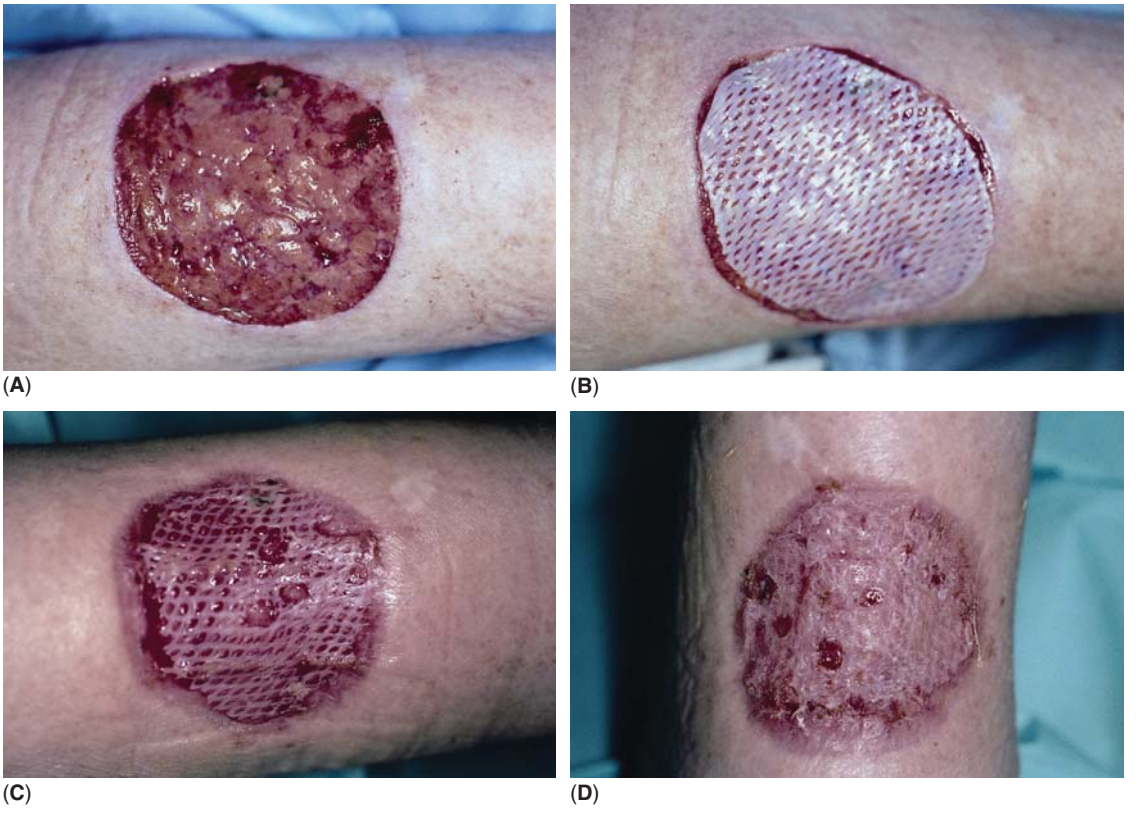


Figure 1.35 Mohs wound and bioengineered skin construct.

This woman in her 50s had a small papule on her right arm which, when biopsied, turned out to be a basal cell carcinoma. The tumor, removed by Mohs surgery, was surprisingly extensive. At the end of the procedure, she was left with this very substantial full-thickness wound (Panel **A**). Grafting with a full-thickness graft would be one way to approach this wound, given the risk of substantial contraction. However, it was decided to treat this wound with a living bi-layered bioengineered skin product. Here one sees the wound covered with the bioengineered skin construct, which was meshed at a ratio of 1.5 to 1 (Panel **B**). The pain improved immediately after the procedure. No sutures were used to hold the bioengineered skin in place, and the procedure was painless. Panel **C** shows the appearance of the wound 1 week after the application of the construct (Panel **C**). One can easily see the bioengineered skin in place over the wound, which is now less deep. Three weeks after application, there has been remarkable healing of the wound, and no further contraction (Panel **D**).



Figure 1.36 Seroma/hematoma after liposuction.

This patient developed a seroma after liposuction of the knee. The usual management of this complication involves draining of the clear or serosanguinous fluid. Repeated drainage is often required.

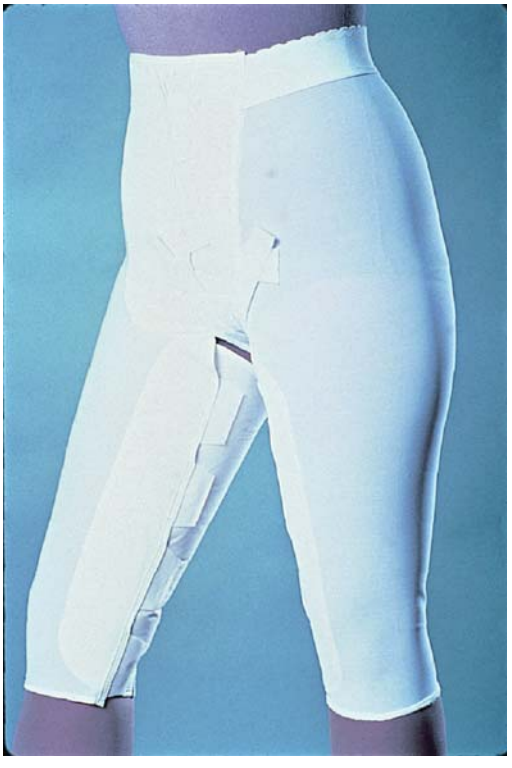


Figure 1.37 Compression garment.

This is a prototype of a garment that may decrease the frequency of hematomas or seromas after liposuction. These garments are worn by patients for at least 1 week after liposuction.



Figure 1.38 Sutured abdominal wound.

This extensive wound was treated with dry nonadherent dressings. In our opinion, better cosmetic results are obtained with the use of moisture-retentive or occlusive dressings. However, there is still substantial fear of using occlusion after such major surgical procedures. Many surgeons fear the development of infection and are concerned that the tensile strength of the wound does not develop normally in a moist environment. We believe that the fear of infection is generally unwarranted. However, further work needs to be done to study the tensile strength of wounds treated by this method.



Figure 1.39a Complication after urological surgery.

This photo shows dehiscence of the large surgical wound. By probing the two areas of dehiscence we found them to be undermined and connected.



Figure 1.39b Complications after urological surgery/clip removal.

The clips over the skin bridge between the two open areas had to be removed. This then allowed healing by secondary intention.



Figure 1.39c Complications after urological surgery/close-up.

This photo shows a stage of healing where granulation tissue has filled almost the entire wound. In such cases of extremely red and overly exuberant granulation tissue one should always consider the possibility of bacterial colonization with *Staphylococcus aureus.*



Figure 1.40 Pilonidal sinus surgery.

This wound will require several months to heal by secondary intention. Foam, calcium alginate, and hydrofiber dressings are among the wound dressings that may be beneficial here to absorb the exudate. Some foam or hydrocolloid dressings from various manufacturers are specifically shaped for this area. As in situations of extremely red granulation tissue, consideration should be given to the possibility of bacterial colonization.

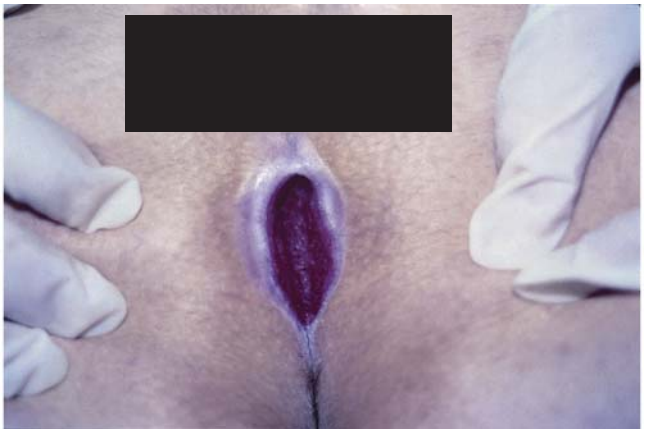


Figure 1.41 Pilonidal surgery/failure to heal.

This wound resulting from the excision of a pilonidal sinus did not heal completely, despite episodic decreases in the surface area. We have seen this happen before in patients with intragluteal ulcers. Whether the failure to heal is due to tension, fecal contamination, bacterial colonization, or pressure/friction is unclear. Grafting and tissue rearrangement may be suitable alternative treatments.



Figure 1.42 Granulating wound.

This excision became infected and a fasciotomy was required. The wound is now left open to heal by secondary intention.



Figure 1.43 Granulating wound after amputation.

This patient with diabetes mellitus required ray amputation of the second and third toe. The photograph shows the appearance of the granulating wound a week after surgery. One of the problems that will be encountered in this case is that other parts of the foot will now have to sustain greater pressure during ambulation and, therefore, will be subject to ulceration.



Figure 1.44 Complication of back surgery.

This patient was referred to us after corrective surgery for spinal deformity. The large wound had been closed primarily. Unfortunately, the upper portion became infected and had to be surgically re-exposed to allow for drainage and healing by secondary intention. A foam dressing was used to absorb the considerable amount of exudate. The development of osteomyelitis is a real concern here, especially because of the wound's proximity to the vertebral bodies, and it is probably wiser to let the wound heal secondarily.



Figure 1.45 Grafting after mastectomy.

Here too, after mastectomy, the wound became infected. After treatment with antibiotics for several weeks, a decision was made to use an autologous split-thickness graft and close the wound primarily. Most of the graft has taken and appears healthy. One would expect considerable contraction to occur.



Figure 1.46 Wound dehiscence.

This happens because of an infection or excessive tension across the wound. In this facial wound, dehiscence was due to infection. Lateral to the wound, one can see a finely sutured track. We prefer not to reclose these wounds primarily, and adherent strips or tapes can be used to approximate the edges, still allowing for drainage to occur.



Figure 1.47 Foot Abscess.

After drainage of the abscess, the wound was left to heal by secondary intention. Calcium alginate dressings or foams would be useful for this situation because they are able to absorb a considerable amount of exudate. A negative pressure regimen would also be used, perhaps prior to grafting and after the infection has been controlled.



Figure 1.48 Breast abscess.

A rather superficial infection eventually led to an abscess that needed to be drained. The photograph was taken after excision and drainage. Management of such a wound varies considerably among clinicians. Some still prefer the use of wet to dry dressings, while others might use calcium alginate material to absorb the exudate. In general, most wound healing experts do not advocate the use of wet to dry dressings, because they invariably cause trauma to the underlying and viable tissues and are painful. Still, there are unusual situations where one might find this strategy indicated. This is not one of those situations.



Figure 1.49 Hematoma after breast surgery.

This large hematoma developed following surgery for duct ectasia. The clot needs to be removed and all bleeding vessels need to be tied or cauterized. A pressure bandage will be applied. Consideration should also be given to the use of bioengineered constructs or tissue rearrangement.

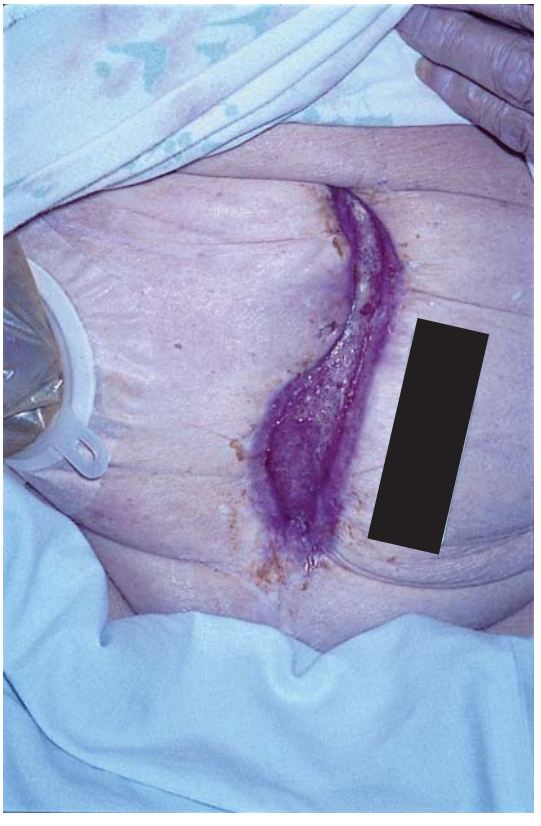
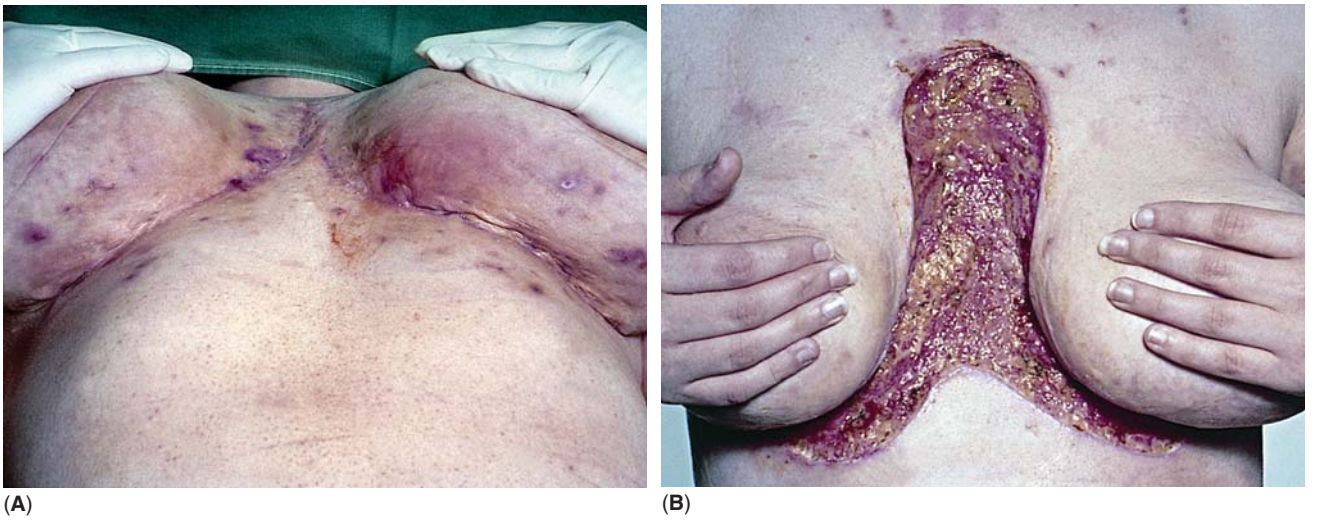


Figure 1.50 Healing abdominal wound after peritonitis and drainage.

Surgery was required for treatment of a ruptured viscus and peritonitis. The resultant wound shows a pink to red base and is healing well by secondary intention. Again, we would like to make the point that one should not expect a beefy red wound bed for optimal healing to occur.

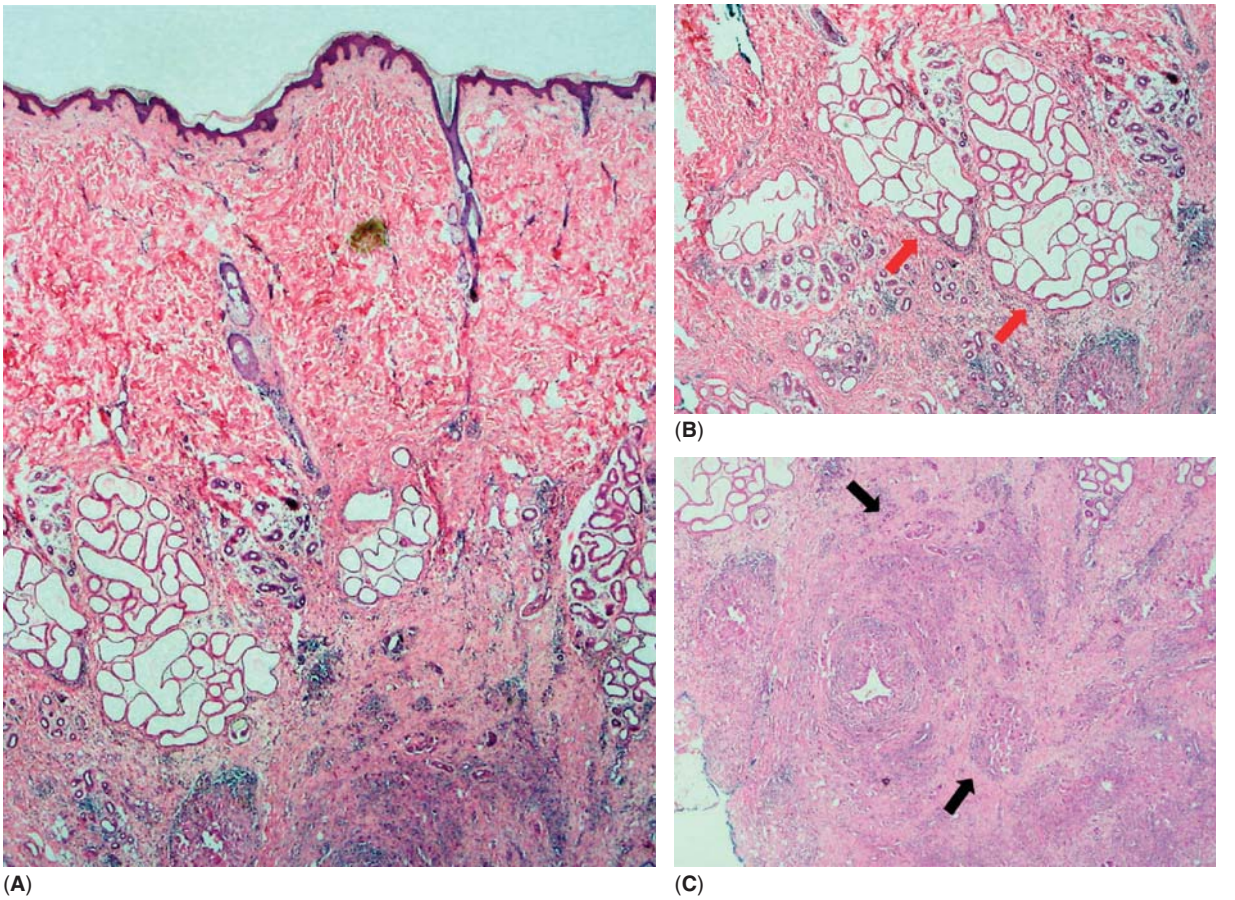


(**A**) (**B**)

Figure 1.51a Hidradenitis suppurativa/inframammary area.

This patient had a long-standing history of hidradenitis suppurativa. This condition affecting the apocrine glands is characterized by recurrent episodes of infection, sinus tracts, and draining abscesses (Panel **A**). Pain, foul-smelling exudate, and inability to wear certain clothes, all contribute to a poor quality of life. Although mild and early cases tend to respond to systemic antibiotics, intralesional injections of corticosteroids, and good wound care, patients with established and active sinus tracts need a more aggressive therapeutic approach.

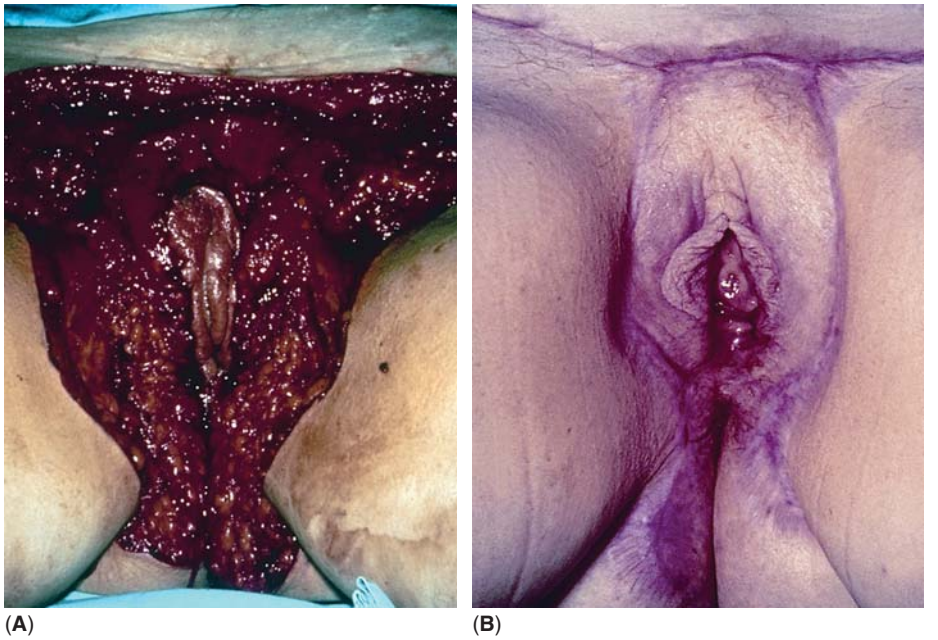
The entire area was excised to remove all sinus tracts and tunneling (Panel **B**). The patient healed well several months later. Also note the acneiform eruption on her chest. Patients often have both hidradenitis suppurativa and severe acne.



(A) (B) (C)

Figure 1.51b Hidradenitis suppurativa/histology.

This biopsy from an affected axilla shows some rather typical histological findings for hidradenitis suppurativa (Panel **A**). There are several apocrine glands (Panel **B**; red arrows) with surrounding chronic inflammation and fibrosis involving the deep dermis (Panel **C**; black arrows). These changes are seen in long-standing lesions.



(A) (B)

Figure 1.52 Radical excision for hidradenitis suppurativa and follow-up.

This was obviously a patient with a very extensive and severe case that required a radical surgical approach (Panel **A**). There was no choice but to remove the apocrine glands and all of the sinus tracts and fibrotic tissue that had formed over the years. Panel **B** shows very acceptable results months later and after reconstructive surgery.



Figure 1.53 Wound after excision for hidradenitis suppurativa.

The wound bed here may actually appear to be suboptimal. However, this particular wound shows evidence of healing and eventually healed completely. Apparent discrepancy between re-epithelialization and what we expect the wound bed to look like is not unusual. The general notion that granulation tissue in healing wounds should always be beefy red is probably an oversimplification. The red area lateral to the wound may represent an allergic contact dermatitis, possibly from a topical antibiotic.



Figure 1.54 Excised wound of hidradenitis suppurativa/grafting.

Grafting is another way to deal with excised areas of hidradenitis. The rather thin, autologous graft in this case may act as both tissue replacement and a stimulus for wound repair. In view of the beefy red color, there seems to be some surface bacterial colonization of the wound bed, but the wound healed very satisfactorily.



Figure 1.55 Excised wound of hidradenitis suppurativa/flap.

This example of a z-plasty is shown to illustrate that there are a number of surgical approaches to the repair of wounds after excision of areas of hidradenitis. Here, too, the results are quite acceptable but, unfortunately, recurrence in the upper horizontal scar line shows the difficulty of consistently obtaining a cure, even with radical excision.

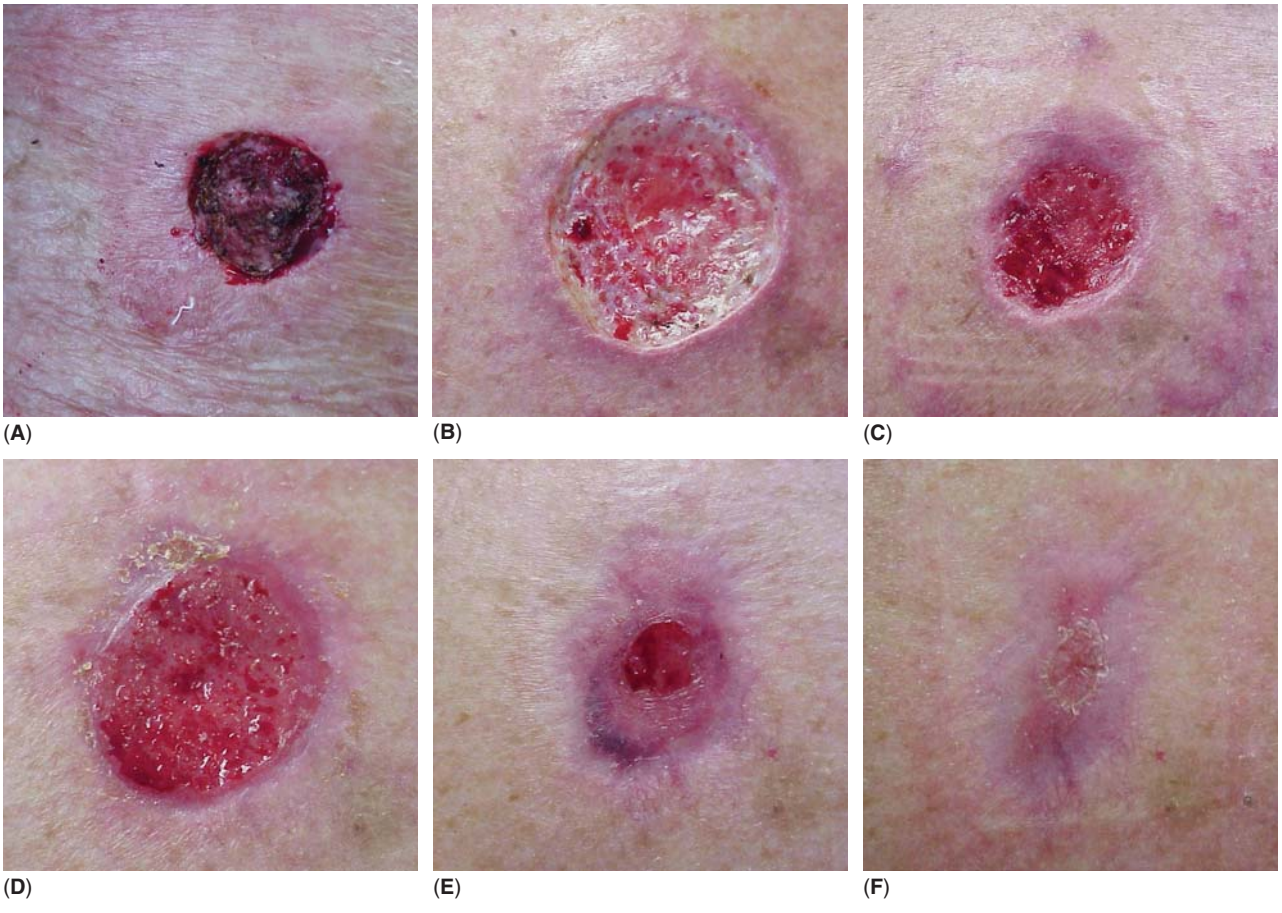
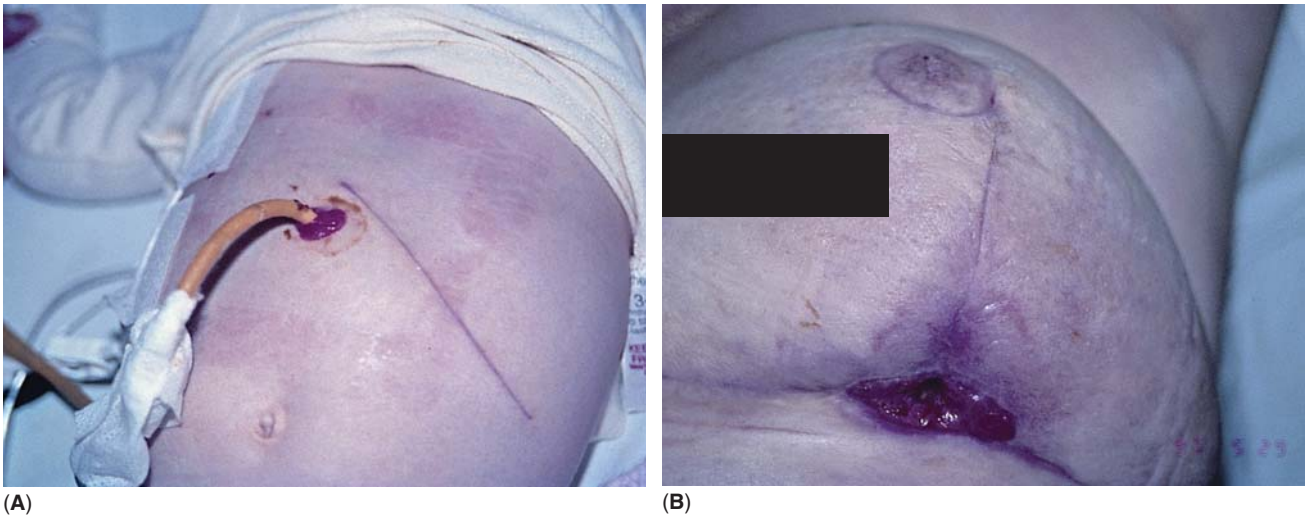


Figure 1.56 Clinical stages of healing in a full-thickness wound allowed to close by secondary intention.

Here we have a surgical wound after excision of a squamous cell carcinoma on the back. Panel **A** shows the appearance of the wound post excision; there are some necrotic areas caused by electrocautery. At 1 week post excision (Panel **B**), one can observe the fibrinous wound bed with areas of granulation tissue. The granulation tissue has persisted and there is some evidence of epithelialization from the wound's edges 2 weeks after excision (Panel **C**). It is to be noted that, for the most part, the process of epithelialization is largely dependent on epidermal migration and less so on the epidermal proliferation. In this photo, there is little or no contraction. At 4 weeks post excision (Panel **D**), the granulation tissue is well established and the wound bed is almost flush with the surrounding skin. There is increasing epithelialization from the wound margins. Panel **E** illustrates the appearance of the wound 6 weeks post excision; the process of resurfacing has continued but is now accompanied by the obvious beginning of wound contraction. This is a clear example of the fact that larger wounds may eventually contract because the epidermal resurfacing is not solely dependent on migration and has to rely on dermal events, including extensive extracellular matrix deposition. At 12 weeks post excision (Panel **F**), the wound has almost completely resurfaced and shows clear evidence of contraction in addition to epidermal migration. Because no skin appendages (hair follicles, sweat glands, etc.) with their reservoir of keratinocytes were left in the wound at surgery, all of the epidermis has to come in from the margins.



(**A**) (**B**)

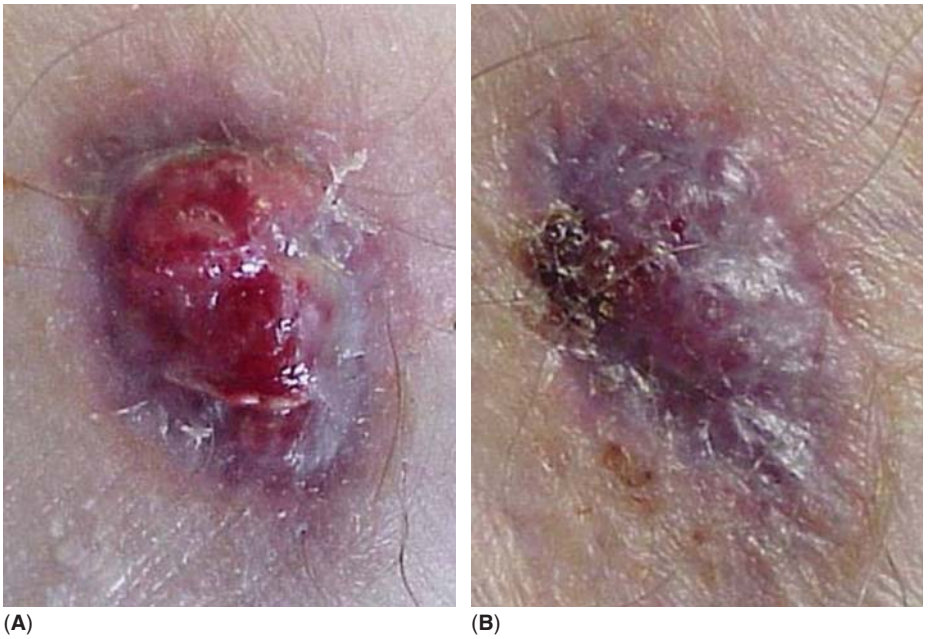
Figure 1.57 Excessive/abnormal granulation tissue.

This child has a gastrostomy feeding tube. Many believe that excessive granulation tissue, as seen here surrounding the orifice (Panel **A**), represents infection or bacterial colonization. *S. aureus* is commonly found in such cases and should be the initial target of antimicrobial treatment. Panel **B** shows a wound occurring after a reduction mammoplasty, as a result of the suture line becaming infected. This granulation tissue looks abnormal in that it seems to extend over onto the surrounding skin, and it looks like a pyogenic granuloma (Panel **B**). It may be necessary to remove this excessive granulation tissue and treat with antibiotics.



Figure 1.58 Excised area of hidradenitis suppurativa.

This wound would not heal. In our experience, this type of livid red granulation tissue is actually not ideal and is frequently associated with infection or a heavy bacterial colonization. *S. aureus* is a common pathogen in these cases.



(**A**) (**B**)

Figure 1.59 Example of an acute wound with exuberant granulation tissue.

This 74-year-old man with a wound on his leg after the removal of a skin cancer was healing by secondary intention and developed exuberant granulation tissue, which is still present 2 months after excision (Panel **A**). Removal of the exuberant granulation tissue led to healing after 2 or 3 more weeks (Panel **B**). It is often difficult to determine whether one is dealing with simple exuberant granulation tissue or bacterial colonization; clinical context and bacterial cultures are often required.



Figure 1.60 Acute wound caused by bandage removal.

This linear leg wound was caused by scissors that were used to remove the compression bandage in this patient with venous insufficiency. The patient also had a history of arterial disease, for which she had undergone revascularization. One must be exceedingly careful in removing bandages by cutting them with scissors. The wound show rather exuberant granulation tissue, but is healing well.

2 Wounds and infection

The diagnosis of infection in a wound is often obvious, but is based on clinical grounds and, for the most part, remains a subjective determination. One observes the cardinal signs of inflammation, the wound is not healing, and there may be systemic findings indicative of infection. However, the situation is not always clear-cut, especially in chronic wounds. Almost all chronic wounds are colonized with bacteria, many wounds are surrounded by redness and are warm to the touch, and their healing is often slow. Moreover, inflammation due to infection or noninfectious causes may be present. Particularly in the elderly, who are unable to mount a substantial response to infection, wound pain and failure to heal may be the only signs to show that an infection is present.

There is still considerable controversy regarding the best way to diagnose an infection. As mentioned, the mere presence of bacterial organisms within the wound is not sufficient. The clinical significance of redness and warmth surrounding the ulcer is often difficult to assess. Is it a contact dermatitis? Is it simply secondary to reflex vasodilatation, as one observes in arterial insufficiency? There have been attempts to arrive at the diagnosis of infection by obtaining a biopsy from the wound and by quantitating the number of organisms detectable in the tissue itself. With the help of an experienced laboratory (not always available), one can then determine the bacterial burden. Thus, with a bacterial burden of 10^6 organisms per gram of tissue, healing is judged to be definitely impaired. The level of impairment may be caused by even lower bacterial counts. It should be noted that, with this bacterial burden determination, it is the number of organisms, and not their species, that is important. An exception is the presence of beta hemolytic Streptococcus, which is always abnormal and at any level. Still, in addition to the difficulties involved in these technical measurements, the bacterial burden measures colonization and not infection, which implies the invasion of the surrounding nonulcerated skin and tissue by the organisms. Moreover, it seems (still unproven) that chronic wounds are able to sustain a higher level of colonization (without infection) than acute wounds.

Therefore, many clinicians are of the opinion that infection is a clinical diagnosis, and they tend to call a wound infected based on the appearance of the wound, the surrounding skin, the presence of certain organisms, systemic symptoms, and deterioration in the healing of the ulcer. There are other signs of infection that are not widely recognized but may be valid. For example, as shown by examples in this section, exuberant granulation tissue may signify infection rather than a good or excessive reparative response. In particular, *Staphylococcus aureus* is commonly cultured in exuberant and beefy red granulation tissue. Wound pain alone, as mentioned, may be a sign of infection. These difficulties in determining infection are a problem not only in clinical practice but also during clinical trials.

In this section, we describe the use of slow-release preparations of antiseptics, including iodine and silver. For years, elemental iodine and other antiseptics were used to treat wounds, until it was realized in the early 1980s that some of these agents could interfere with the wound-healing process. However, the outcome was that clinicians basically stopped using antiseptics altogether. We feel that a considered approach to the use of antiseptics is of value in certain patients. Cadexomer iodine, a slow-release iodine preparation, may be very useful in the management of wound infection and colonization, particularly in highly exudative wounds. Sophisticated preparations of silver dressings, capable of delivering silver in a slow-release fashion, are also very helpful in wound bed colonization. Overall, these products can play a major role in wound bed preparation.

Infection caused by bacteria is not the only one to complicate wounds. Astute clinicians must also think of more unusual infections. Particularly in the immunocompromised host, one must exclude infection with fungi, mycobacterial organisms, or even the presence of chronic infection with herpes simplex and cytomegalovirus. Rather than relying on swab cultures, one must often take biopsy samples to exclude these possibilities. Proper diagnosis demands that diagnostic material be taken immediately to the laboratory and plated appropriately and under conditions that optimize the growth of fastidious organisms.

Wound debridement and systemic antibiotics are often necessary to manage a significant wound infection. Hyperbaric oxygen therapy, combined with these approaches, is useful as well. It is often believed that hyperbaric oxygen therapy is overutilized and that there is no definite proof of its efficacy. However, for deep infection (e.g., with anaerobic organisms), hyperbaric oxygen therapy may play a useful role. Moreover, an increasing number of clinical trials are showing the effectiveness of hyperbaric oxygen to improve wound bed preparation and accelerate healing. Systemic antibiotics alone are generally not effective unless they are combined with proper wound care and surgical debridement. Also, systemic antibiotics may not achieve appropriate concentrations at the wound site or may not be effective in the wound microenvironment (e.g., pH conditions, fibrosis).

Severe streptococcal infection remains a serious infection complicating wounds. The "flesh-eating bacteria" continue to receive much attention. There is nothing to indicate that streptococcal infection and necrotizing fasciitis are on the rise. However, there are indications that, in addition to use of appropriate antibiotics and surgical approaches, the condition may benefit from systemic corticosteroids. At first, this may sound like a paradox, because systemic corticosteroids are often thought to predispose to or aggravate infection. However, the host response to infection may at times be a major problem, and systemic corticosteroids may help in dampening that damaging response. This approach remains controversial.

In the last several years, it is becoming apparent that for certain types of infection the number of bacteria is not

necessarily the key element; rather, the configuration in which they grow in tissues may be more relevant. In this context, the emergence of the "biofilm" as an important determinant of whether infection will take place is gaining acceptance. Biofilms certainly play a key role in bacterial endocarditis, middle ear infections, sinusitis, gingivitis, and other catheter-related complications. In wounds, particularly those that are chronic, the issue is not as clear. In part, any doubt is related to the difficulties involved in the detection of biofilms, which are colonies/aggregates of organisms within an extracellular polymeric substance which is composed of DNA, protein, polysaccharides, and probably other components. For example, placing a biofilm-containing tissue in formalin may abrogate the ability to detect it histologically or by special stains; special fixing and staining precautions must be taken. However, we believe that biofilms will probably turn out very important in the development of infection and in ulcer recurrence (i.e., biofilms may remain in tissues even after complete wound closure). The additional importance of biofilms, whose elimination is imperative for proper wound bed preparation, is that they render bacteria more resistant to antibiotics.

Clinical Points

- The mere presence of bacteria in a wound does not signify infection.
- Infected wounds can be associated with a number of clinical findings, either together or by themselves: failure to heal, pain, necrotic tissue, local signs of inflammation, and systemic symptoms and signs.
- The number of bacteria within tissue probably correlates with abnormalities in the way in which the host is dealing with microorganisms; the larger the number (e.g., greater than 10^6), the greater the possibility that the wound may not heal.
- Occlusive or moisture-retentive dressings may increase the number of microorganisms present in the wound fluid, but do not lead to infection.
- Exuberant granulation tissue, which at first may seem desirable, may actually represent infection.
- A translucent film over the wound tends to correlate with infection.
- Necrotic flaps may become infected, but with proper care and antibiotic therapy the tissue seems to recover and the results may be quite good.
- Not all antiseptics cause tissue injury. There are ways to deliver antiseptics in slow-release preparations; this helps keep the bacterial burden down.
- Surgical debridement is an excellent way to start treating infection in a wound.
- Hyperbaric oxygen therapy may be helpful in highly contaminated wounds.
- The only sign of necrotizing fasciitis is often exquisite tenderness, without any skin surface changes.
- Blistering around the wound may represent a contact dermatitis, but is also often seen with streptococcal infection.
- Blisters can also be caused by a staphylococcal toxin (as in staphylococcal scalded skin syndrome); this presentation is more common in patients with renal failure.
- Sharp demarcation of redness or blistering in the skin surrounding a wound can be seen with lymphangitis (erysipelas) and cannot be assumed to represent a contact dermatitis.
- The damage from streptococcal infection is often extensive and associated with a prolonged clinical course, in spite of antibiotic therapy. There is emerging evidence that in some cases systemic corticosteroids may be needed to decrease the host response to infection.
- Bites from brown recluse spiders can cause extensive necrosis and mimic a severe infection.
- Rapidly developing necrosis, especially on the extremities, should alert one to the possibility of meningococcal infection.
- Indolent necrotic ulcers, especially if present at multiple sites, may represent ecthyma gangrenosum, which is caused by bacteremias (commonly with *Pseudomonas aeruginosa*).
- When bone is exposed, it is fair to assume that it is infected (osteomyelitis).
- The development of puckering of the skin over an amputation stump may be associated with an underlying bone collapse from osteomyelitis.
- Cellulitis not responding to antibiotics should alert one to the possibility of opportunistic infection, such as from cryptococcal organisms.
- The clinical appearance of the foot in leprosy may resemble that observed with the Charcot foot in diabetic patients. However, leprosy is associated with substantial resorption of bones.
- The use of a Wood's light may be helpful in the diagnosis of infection or colonization with Pseudomonas (green fluorescence) or corynebacteria (coral red fluorescence).
- Myasis (presence of maggots) is often missed. It should be suspected in all cases where an exudative dermatitis is present around the wound or involves the foot.

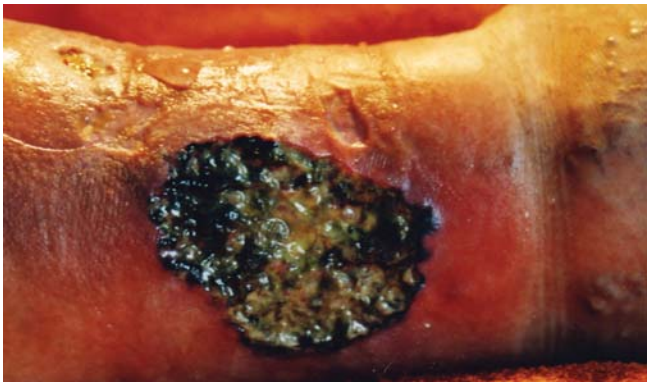


Figure 2.1 *Bacteroides melaninogenicus* infection.

This leg ulcer was found to be heavily colonized with *B. melaninogenicus* (presently classified in the *Prevotella* genus). The colonization became evident after the patient had been treated for 6 months with a potent topical corticosteroid (betamethasone valerate). Immunosuppression within the wound may have been the inciting factor. Ulcers colonized with this organism can show fluorescence under ultraviolet light (i.e., Wood's lamp). The patient began to improve with the application of topical antibiotics, but surgical debridement is generally required to eliminate the organism.

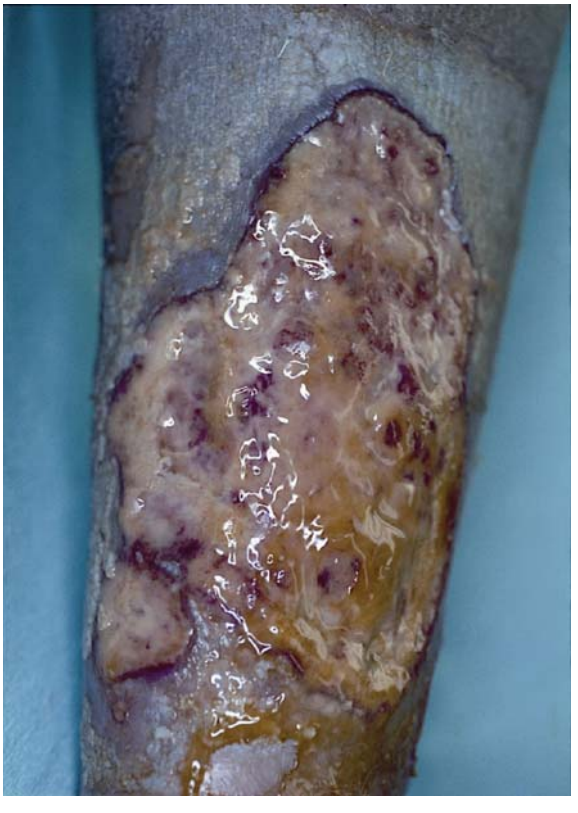


Figure 2.2 A heavily infected ulcer.

This venous ulcer is infected. The wound bed is purulent, necrotic, and appears to be heavily colonized with bacteria. The redness around the ulcer, particularly at the inferior border, suggests cellulitis. A biopsy from the wound bed showed acute inflammation and edema throughout the dermis and a deep abscess. Culture from the abscess grew both *P. aeruginosa* and *S. aureus*. The patient had to be hospitalized and required intravenous (IV) antibiotics and extensive surgical debridement. Slow-release antiseptics such as iodine or silver-based ones can be a helpful adjunctive therapy in this case.



Figure 2.3 An infected tumor.

This patient had cutaneous T-cell lymphoma. The skin tumor shown here ulcerated and became infected. The photograph shows a purulent wound that appears to be covered by a film-like membrane. Cultures from the wound grew *S. aureus*. She was treated with IV cephalosporins and the infection was controlled. When ulcerated, tumors frequently become infected.



Figure 2.4 A heavily colonized ulcer.

This patient with sickle cell anemia had a nonhealing ulcer which was thought to be largely venous in etiology. However, it is likely that the underlying sickling plays a role in the pathogenesis and persistence of such wounds. We feel that the pathogenesis of sickle cell ulcers includes both venous and arteriolar abnormalities. The ulcer became heavily colonized with *P. aeruginosa*, and required extensive surgical debridement and antibiotic therapy.



Figure 2.6 Recurrent erythema multiforme.

Not all infections are due to bacterial organisms. This 34-year-old woman has lesions on her lower legs that begin as red spots, enlarge, and forme a central blister. She was thought to have erythema multiforme, which in her case would occur periodically. This condition can develop with the use of many types of systemic drugs or viral infections, particularly herpes simplex. Hydrogel dressings had been used to decrease the intense pain present within her lesions. Many cases of recurrent erythema multiforme are now recognized to be a complication of infection with herpes simplex. She is being managed with the systemic administration of acyclovir, dapsone, and occasional courses of systemic corticosteroids.



Figure 2.5 A streptococcal infection.

The skin is denuded and there is considerable maceration. The patient had a streptococcal infection.



Figure 2.7 Infection after breast surgery.

This patient had undergone surgery to her left breast but the wound became infected. Here one can see the purulent exudate and the beginning of cellulitis in the surrounding skin. Systemic antibiotics will be required. In this particular case the location of the surgical sutures within the intertriginous region of the breast contributed to the development of the infection. There is considerable hemorrhage in the area surrounding the nipple.



Figure 2.8 Breast infection and necrosis.

Following mastectomy and breast reconstruction, the patient developed partial necrosis of the medial portion of the flap and cellulitis. Removal of the eschar and IV antibiotics are necessary to manage this complication. Surprisingly, after controlling the infection, the results are often acceptable despite suboptimal flap survival.



Figure 2.9 Contact dermatitis.

Of course, not all skin redness is the result of infection. Here the redness on his neck, within and surrounding the sutures, was due to a localized allergic reaction to topical antibiotics. The tiny and subtle blisters, particularly on the inferior border of the excision, are quite suggestive of a contact dermatitis, rather than cellulitis. Pruritus, rather than pain or tenderness, is another useful clue pointing to a contact sensitivity reaction; cellulitis is generally not itchy. Sometimes, however, the distinction between cellulitis and contact dermatitis is next to impossible. Another point is that the dermatitis is not very well demarcated, thus suggesting that an allergic process is taking place, with inflammatory mediators infiltrating the surrounding skin. With an irritant contact dermatitis, the opposite is true and the rash is better demarcated and has more defined borders.



Figure 2.10 Infection in the suture line.

In contrast to the previous case, this patient had no pruritus but developed intense pain a few days after this wound in his supraclavicular fossa was closed primarily. The vesicular reaction observed in the previous case was not present here. The patient was thought to have developed a cellulitis and was treated with systemic antibiotics.



Figure 2.11 Complication of abdominal surgery.

This woman has a large abdominal wound following emergency surgery for bacterial peritonitis. There is marginally healthy granulation tissue at the edges of the wound, but most of the wound bed shows suture material and adipose tissue that have become stained by a topical antiseptic. It will take about 2 weeks to develop good granulation tissue throughout. Hyperbaric oxygen is occasionally used in this type of severe wound. There is some undermining at the superior border, further complicating the management; bacteria tend to accumulate and persist beneath the undermined skin.



Figure 2.12 A graft failure.

An autologous skin graft was used to cover this defect after excision for a skin cancer. There is now almost complete failure of the graft, as shown by loss of graft take and necrosis. The reasons for this complication were not entirely clear, although infection may have played a role. Treatment requires removal of the graft and antibiotics.



Figure 2.13 A graft infection.

An autologous split-thickness graft was used to treat this heel ulcer due to radiation injury. The yellow color of the graft and the surrounding redness extending to the rest of the plantar surface suggest the presence of an infection. The graft will most likely fail, and one can already see the uplifting of the graft posteriorly. Removal of the grafted tissue is required, as it becomes a nidus for bacterial growth.



Figure 2.14 Erysipelas of the leg.

Fulminant infection of the leg with beta hemolytic streptococci is quite typical of erysipelas. This condition is actually an infection of the lymphatic channels, which explains the often well-demarcated borders of the redness and blistering. In contrast, cellulitis is an infection of the subcutaneous tissue and has poorly demarcated borders. The patient has severe pain and fever and was treated with systemic antibiotics. One would have to be careful here with the development of necrotizing fasciitis. However, in many cases, necrotizing fasciitis presents with exquisite tenderness of normal looking skin. Emergency CT scans or MRI can be done to exclude the presence of fasciitis.



Figure 2.15 Cellulitis.

This purpuric eruption was thought to represent a vasculitis, but there was a high fever and malaise. Histological evidence of vasculitis was not detectable, but infection can cause vasculitic changes also. Gram stain of the tissue can help if bacteria are present. He eventually responded to IV antibiotics. We have seen this type of purpuric presentation rarely, but believe it may represent a streptococcal infection (erysipelas). It points to the need for careful clinical and pathologic correlation.



Figure 2.16 Cellulitis with blisters.

The patient responded to IV antibiotics. Cultures were negative, but one would strongly suspect that this condition was due to streptococcal infection, particularly because of the blisters. This example illustrates the difficulty in identifying the causative organism in these situations.



Figure 2.17 An unusual cellulitis.

This patient was thought to have a cellulitis, but it took almost 3 weeks of IV antibiotics for her to improve. Brown recluse spider bite should be included as a diagnostic possibility, as should vasculitis. Histology, however, did not show a vasculitis.



Figure 2.18 Cellulitis.

The appearance of the wound itself is not always indicative of whether it is accompanied by an infection. Here the ulcer itself does not look heavily colonized or infected, but the redness and warmth around the wound indicate a cellulitis. In some cases, the physical findings of redness and warmth are missing, but the clinician should be concerned about the presence of pain. Some elderly patients present with pain alone in the setting of cellulitis. It's also important to point out that surface cultures cannot establish the diagnosis of cellulitis; almost all wounds have surface bacteria and thus are simply colonized. Surface cultures are also only partially helpful in guiding the choice of antibiotics. We have noticed that many clinicians jump to the erroneous conclusion that the patient has a cellulitis simply because of a positive swab culture of the wound's surface. Cellulitis remains a clinical diagnosis.



Figure 2.19 Cellulitis and lymphedema.

This 72-year-old woman has lymphedema. The clinical clue is that the leg is "tubular" in shape and does not show the typical exaggerated narrowing toward the ankle ("inverted champagne bottle") that one sees in venous disease. Because of the lymphedema, she suffers from repeated bouts of cellulitis that often require hospitalization. Her skin is warm and red. Usually, fever or leukocytosis is not present, but the absence of these findings is not uncommon in the elderly with infection. In order to prevent recurrence, she was eventually managed with the use of long-term oral penicillin therapy.



Figure 2.20 Cellulitis and punched-out ulcers.

The presence of cellulitis is rather obvious here. The warm and red skin extends from the foot to the midportion of the leg. She also had severe arterial insufficiency, which tends to explain the punched-out ulcers.



Figure 2.21 Chronic lymphedema and erysipelas.

This patient with chronic lymphedema developed erysipelas. This infection affects the lymphatic channels and, therefore, shows well-demarcated areas of redness and skipped areas. In particular, we have noted it to be very common for the redness to be present on the dorsum of the foot, skip the anterior portion of the ankle, and then involve the lower leg. We think this finding is due to the anatomy of the lymphatic vasculature, which dips deeper at the anterior aspect of the ankle.



Figure 2.22 Sickle cell ulcer.

Leg ulcers in patients with sickle cell hemoglobinopathy are typically very painful and resistant to treatment. Their pathogenesis is not fully understood, but most likely involves abnormalities in both the venous and arteriolar circulation. As in this case, sickle cell ulcers are long-standing and frequently become infected or heavily colonized with bacteria.



Figure 2.23 Sickle cell ulcer/cadexomer iodine dressing.

Initial attempts at debridement in the outpatient setting were difficult because of severe pain. Cadexomer iodine is a good way to debride these ulcers and decrease the bacterial burden. Cadexomer iodine is a slow-release preparation of iodine that is nontoxic to chronic wounds with considerable exudate. Therefore, it is particularly helpful in large and exudative wounds.



Figure 2.24 Perianal abscess.

This photograph was taken following extensive surgery for an abscess in the perianal area in a patient with inflammatory bowel disease. The extent of debridement is dictated by the severity of the problem and tunneling to the subcutaneous tissues. Sometimes, these patients are also treated with hyperbaric oxygen.



Figure 2.25 Extravasation of cytotoxic drugs.

He had severe soft tissue damage at the IV site on his forearm following extravasation of chemotherapeutic drugs. Adriamycin and 5-fluorouracil are particularly toxic agents that can cause this. The extensive erythema and swelling, suggesting a severe inflammatory response, are probably not due to infection. However, one generally ends up treating these patients with systemic antibiotics.



Figure 2.26 Meningococcemia.

This life-threatening infection can cause massive skin necrosis within hours. This 28-year-old man presented to the emergency room in shock and with signs of meningitis and was immediately admitted to the intensive care unit. Many of the fingers and toes became necrotic and began to ulcerate. Debridement was needed to manage some of these necrotic areas. He survived after a very prolonged hospital course.



Figure 2.27 Skin fragility in Ehlers–Danlos syndrome.

These disorders are characterized by features of hyperextensible skin and joint hypermobility. Six major types are recognized, some being more severe than others, depending on the way the mutations in various collagen genes affect the cardiovascular system. In patients with Ehlers–Danlos II (classical variant; autosomal dominant inheritance), type V as well as type I collagen are mutated. Skin fragility is a problem that can lead to spontaneous ulceration and necrosis, as shown in this photograph. Debridement and antibiotics will be necessary in this patient. Hyperbaric oxygen will also be an option. One has to be sure that there is no underlying osteomyelitis.



Figure 2.28 Ecthyma gangrenosum.

This man with leukemia has septicemia and has developed these dark ulcerated lesions of ecthyma gangrenosum. Ecthyma gangrenosum usually occurs due to infection with *P. aeruginosa*, but other types of bacteria can also cause it. The occurrence of this infection in immunocompromised patients portends a very poor prognosis.



Figure 2.29 Osteomyelitis of the face.

The possibility of osteomyelitis should always be considered in situations where healing is delayed. This woman had multiple surgical procedures for an extracranial tumor and required skin and bone grafting. She did not heal, and there was continued drainage at the wound site. Eventually, she was found to have osteomyelitis in the bone graft. In our opinion, when faced with a situation where bone might be infected, it is far better to obtain radiological studies at the very beginning of wound management and not take a wait-and-see attitude based on how well the wound responds to treatment. This is because healing of chronic wounds often fluctuates in its progression, and it is therefore better to have the possibility of osteomyelitis excluded at the beginning.



Figure 2.30 Osteomyelitis in a stump.

Sometimes, the presence of osteomyelitis is totally unexpected. In this man with an above-knee amputation, there were no obvious clinical signs of skin infection except for a dramatic puckering and "sinking" of the skin and some crusting. However, there was failure to heal, and further studies showed underlying osteomyelitis due to methicillin resistant *S. aureus*. The skin puckering or "sinking" was due to underlying bone collapse. Further amputation was required.



Figure 2.31 Systemic sclerosis and digital ulcers with osteomyelitis.

The sequence (**A**) through (**D**) shows a 50-year-old woman with systemic sclerosis (scleroderma). Scleroderma is caused by excessive deposition of collagen, which affects internal organs, renders the skin hard and stiff, and leads to severe hand contractures complicated by vascular occlusion. Her hands have been nonfunctional for several years. She then developed ulceration followed by worsening pain and swelling of the ring finger of the left hand. Imaging studies (MRI) showed osteomyelitis. The patient was admitted for IV antibiotics and required amputation of the ring finger. Both Panels **B** and **C** show the exposed bone. Generally, the clinical detection of the exposed bone strongly suggests osteomyelitis. When faced with these digital ulcers, it is our opinion to obtain imaging studies immediately and before embarking on the challenging management of these wounds.



Figure 2.32 Mycobacterium *ulcerans*.

There are multiple small ulcerations and draining sinuses. Some areas look healed, while others appear to be necrotic. There has been considerable scarring and the underlying tissues may be fibrotic, suggesting a prolonged clinical course. *M. ulcerans* grew from cultures of skin tissue. She was treated with a combination of clofazimine, clarithromycin, and trimethoprim/sulfamethoxazole. Some clinicians may opt for the use of rifampicin and streptomycin. Surprisingly, she was not immunocompromised. One must be alert to the possibility of infection with atypical mycobacteria and fungi. It should also be noted that biopsies and histology are not always helpful (organisms in the tissue could be rare and the histology not specific). Moreover, even the cultures could be negative initially and may need to be repeated if the suspicion is high or the patient is not improving.



Figure 2.33a Atypical mycobacterium infection.

There was no clear explanation for this man's bilateral foot ulcers and their failure to heal. The "no clear explanation" assessment is a definite clue that a more uncommon diagnosis needs to be pursued. He had these ulcers for about 8 months. The seemingly good granulation tissue and re-epithelialization at the edges of the wounds probably delayed the diagnosis. Multiple bacterial cultures taken from the wounds' surface showed a variety of organisms and he did not respond to systemic antibiotics chosen on the basis of culture sensitivity. Tissue taken from deep the wounds, however, grew an atypical mycobacterium (final determination *M. ulcerans*), and the ulcers responded to IV amikacin. The patient had diabetes mellitus, but there was no other known cause for immunosuppression.

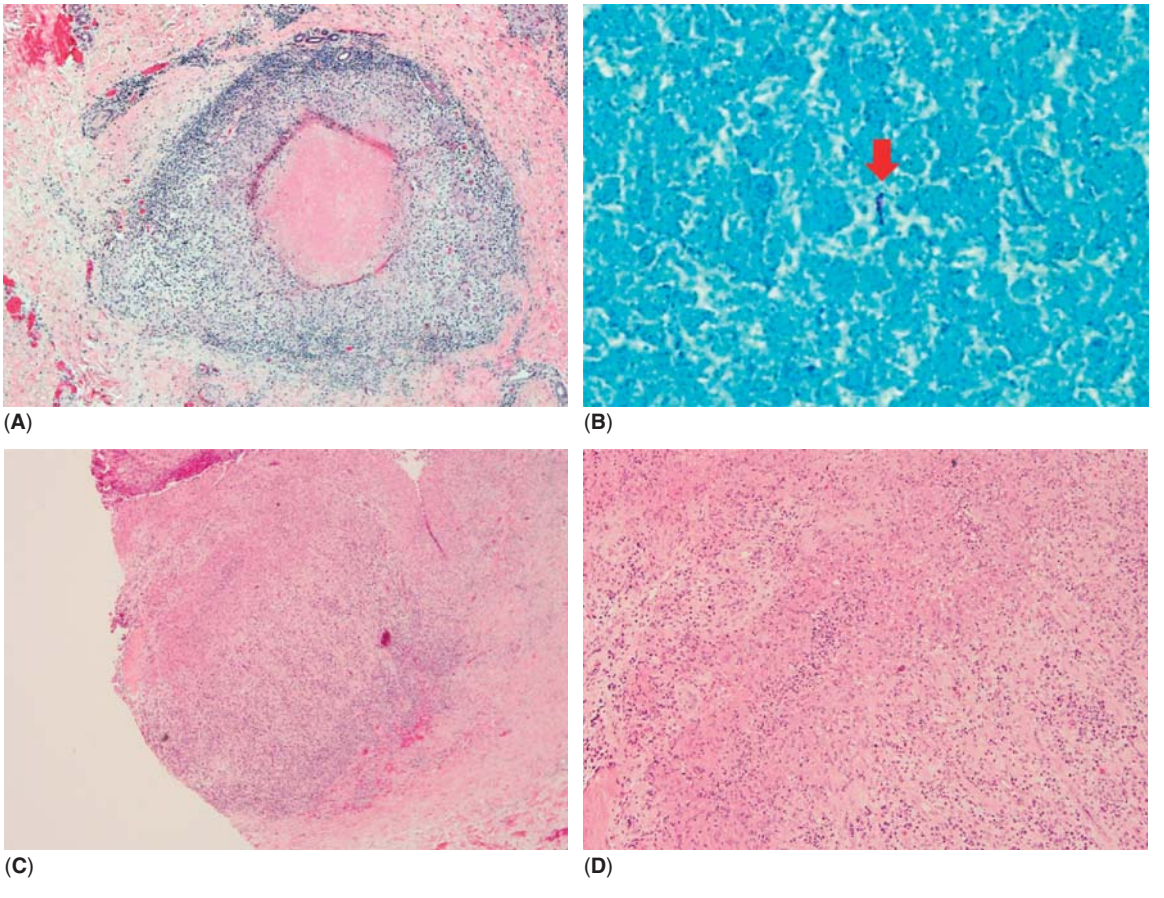


Figure 2.33b Mycobacterial infection/histology.

It is wrong to think that the histology for mycobacterial infections is uniform and similar to what is observed in tuberculosis, which is caused by *M. tuberculosis* and typically affects the lungs, kidneys, and occasionally skin. The histological hallmark of tuberculosis infection is caseation necrosis (pink material in the center of the inflammation), as seen in a case of cutaneous tuberculosis (Panel **A**). With the typical acid fast bacilli special stains one can detect the mycobacterium as small red rods (Panel **B**). In contrast to tuberculosis, the histology of atypical mycobacterial infection shows suppurative granulomas (Panels **C** and **D**) or a diffuse mixed infiltrate of inflammatory cells. The diagnosis can be quite challenging.



Figure 2.34 Disseminated mycobacterial infection.

This woman with chronic myelogenous leukemia developed septicemia and this nonhealing ulcer. She did not respond to usual wound care and was referred to us. Eventually, tissue from the ulcer grew an atypical mycobacterium that was resistant to multiple antibiotics and could not be properly identified. Dramatic improvement occurred with kanamycin, Biaxin, and interferon therapy.



Figure 2.35 Mycobacterial infection and immunosuppression.

This patient was immunocompromised from the use of long-term systemic corticosteroids and methotrexate for psoriasis. Initially, the referring clinician thought that this eruption on the patient's left upper arm looked like a folliculitis and treated him with oral antibiotics. However, the patient did not respond to this therapy and actually developed multiple abscesses on his left upper arm and leg. The photograph mainly shows nodules and ulcers. Culture of tissues from these areas grew *M. fortuitum.* This microorganism is often associated with subcutaneous and intramuscular injections. Therefore, the infection could have been the result of an injection.



Figure 2.36 Mycobacterium infection and immunosuppression/healed ulcers.

An indwelling catheter was used to deliver antibiotics intravenously for over a year. His infection slowly resolved, although considerable scarring is present.



Figure 2.37 Venous ulcers complicated by myasis.

This elderly woman with venous ulcers was being cared for at home by her sister. She was hospitalized because of cellulitis. There was considerable maceration in the interdigital spaces of her feet. Maggots were seen in that location.



Figure 2.38 Venous ulcers complicated by myasis/larval forms.

This photograph shows the maggots obtained from the patient (Figure 2.37). She did very well with whirlpool and IV antibiotics, and was discharged after a few days. There has been a revival of the use of maggots for the purpose of debriding wounds. The maggots do not actually eat or suck tissues, but secrete fluid containing a number of proteolytic enzymes that are able to break down only necrotic tissues. However, maggots also affect keratin; so, the nonulcerated skin is also damaged by these larval forms.



Figure 2.39 Chronic lymphedema with cellulitis.

This 54-year-old morbidly obese woman has severe lymphedema and recurrent bouts of cellulitis, an association that is very common. A possible entry point of bacteria in this particular patient's skin and subcutaneous tissues is the maceration between the skin folds in the midcalf region. In addition, the patient has been applying topical bacitracin and may very well have developed a contact dermatitis from this medication. The patient improved with systemic antibiotics and a combination of acetic acid and aluminum acetate soaks and miconazole powder to the folds, as well as compression to decrease the edema. Although we cannot prove it, we think that lymphedematous legs, such as seen here, probably have a reservoir of bacteria in the subcutaneous tissues and that these patients have a constant low-grade cellulitis.



(**A**)



(**B**)



(**C**)

Figure 2.40a Candida infection of the breast.

Inframammary intertrigo can be a very challenging clinical problem and can be complicated by infection with surface organisms. This 85-year-old woman has intertrigo and candida colonization. Periodic erosions would occur. The key to treatment, in addition to topical antimicrobials directed against yeast (such as nystatin or ketoconazole), is to use absorbent powders and to keep the inframammary area "open" to air by the use of dressings. Some patients are told to use a hair dryer (on cold air setting) a few times a day to keep the area dry. The sequence of photographs (Panels **A**, **B**, and **C**) shows the eventual improvement of this condition.

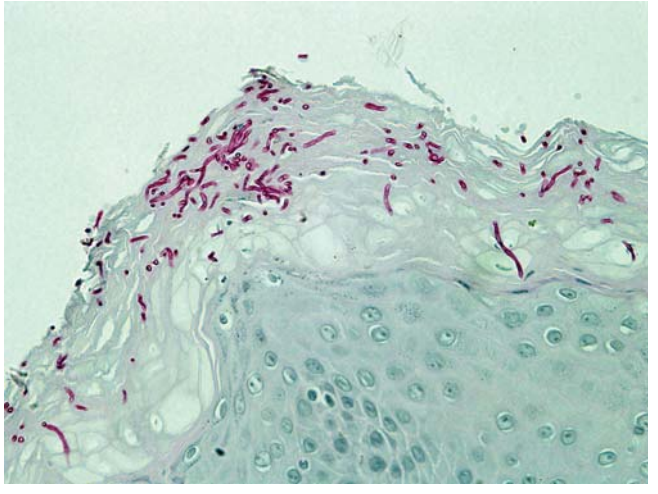


Figure 2.40b Cutaneous candidiasis/histology.

Candida is a genus of yeasts. On biopsy, special stains are often required to identify fungal elements as well as bacteria. In this case, we see multiple individual spores and pseudohyphae (nonseptate), which are quite suggestive of a yeast infection. Please note that the yeast forms are confined to the stratum corneum, above the epidermis. The special stain used here is periodic acid Schiff.



Figure 2.41 Mucormycosis.

The patient had chronic myelogenous leukemia and had been on systemic immunosuppression after receiving a heterologous bone marrow transplant. In addition, he had diabetes. He suddenly developed this deeply necrotic area of skin on his face. Biopsies done in the operating room showed typical findings of mucormycosis (inset: hyphae show broad hyphae at a 90 degree branching pattern). The patient was therefore diagnosed as having mucormycosis (also called zygomycosis), which is caused by several species of the *Mucorales* fungal order. It is an opportunistic infection, generally fatal, which is peculiarly much more common in patients with diabetes. Clinically, as in this case, mucormycosis starts as an erythematous, swollen plaque or nodule on the face, with a rapid development of necrosis. It invades underlying structures rapidly, and will extend to involve brain tissue. When it involves the periorbital tissue, it may initially cause visual impairment. In spite of the timely diagnosis and treatment with antibiotics and surgical debridement, the patient did not survive the infection.

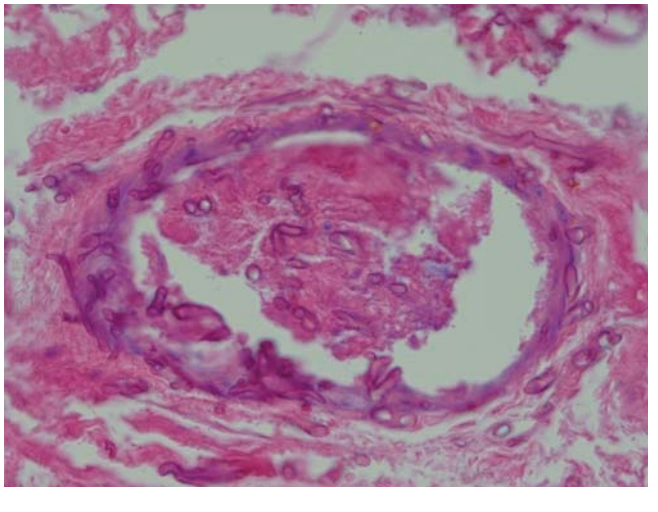


Figure 2.42 Mucormycosis/high-power photomicrograph of the histology.

The hyphal elements are infiltrating the wall of this blood vessel, as well as being present as an aggregated mass within the lumen. The obstruction of blood vessels and their destruction explain how mucormycosis is characterized by tissue infarction and necrosis.



Figure 2.43 Aspergillus infection.

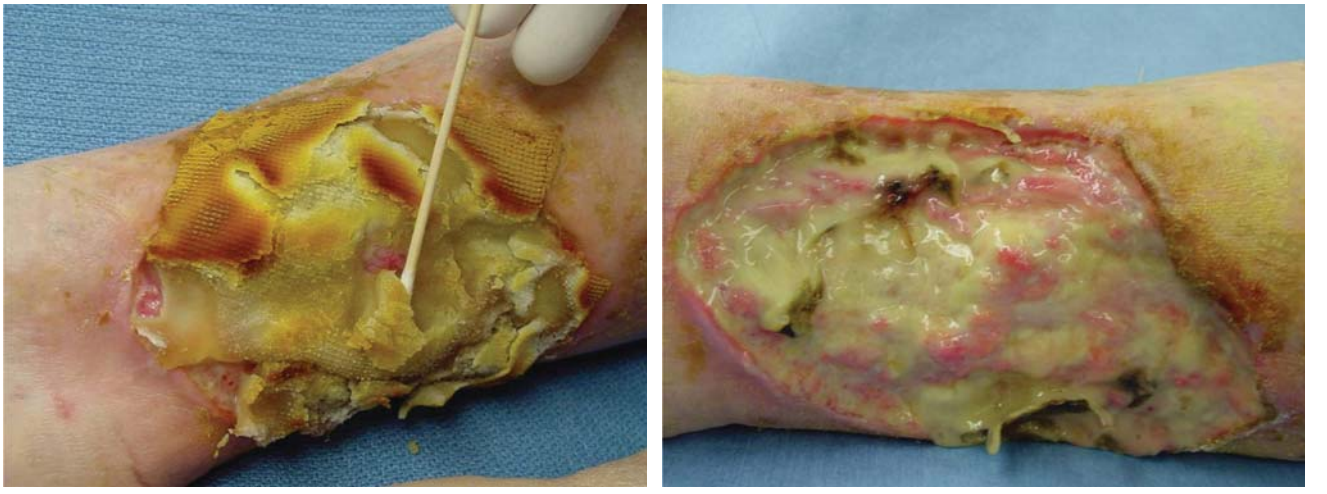
These pustules with an unusual necrotic center and distributed in a linear pattern were found to be due to *Aspergillus* infection. The patient had received a liver and pancreas transplant and was on intense immunosuppressive therapy. He responded quite well to systemic antifungal therapy. One must always be alert to the possibility of unusual infections in immunocompromised patients. Sudden areas of necrosis should alert one to the possibility of *Aspergillus* infection. We cannot explain the linearity of the lesions in this patient. More typically, *Aspergillus* infection involving the skin (probably from hematogenous spread) presents as an ecthyma-like necrotic ulceration or a crusted plaque.



(**A**) (**B**)

Figure 2.44 Use of Gentian blue.

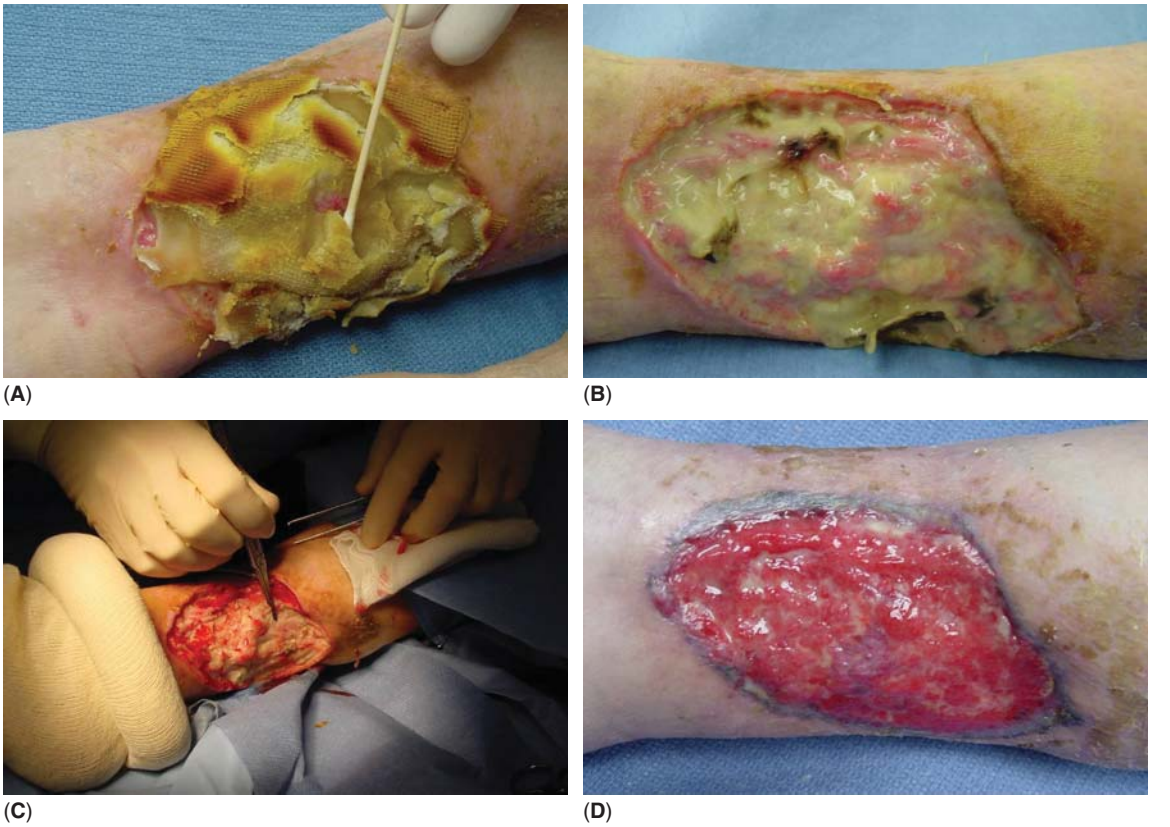
Lymphatic disease, often in the setting of venous insufficiency, is often associated with foot swelling. This poses a problem because maceration between the toes (Panel **A**) can be a portal of infection and lead to cellulitis of the leg and sepsis. Frequently, the infection is caused by multiple bacteria as well as fungi. We find that the use of Gentian violet, an old treatment which has antibacterial and antifungal properties, is quite useful in these circumstances (Panel **B**).



(**A**) (**B**)

Figure 2.45 A heavily colonized wound treated with debridement, antibiotics, and a bioengineered skin construct.

Here we have a large ulcer on the leg. She was diagnosed as having pyoderma gangrenosum. However, the wound also appears to be heavily colonized by bacteria (Panel **A**). Initial management attempts with the use of cadexomer iodine, which delivers iodine to the wound from microscopic cadexomer beads, seemed helpful but was not entirely sufficient in creating a proper wound bed (Panel **B**).



(**A**) (**B**)

(**C**) (**D**)

Figure 2.46 Heavily colonized wound treated with debridement, antibiotics, and bioengineered skin construct/sequence.

The patient was then admitted to the hospital for IV antibiotics and surgical debridement under general anesthesia (Panel **C**), with immediate postoperative application of a living bi-layered bioengineered skin construct. This was done to achieve proper wound bed preparation and to further stimulate healing. In addition, after we were satisfied that the bacterial colonization was getting under control, the patient was started on oral prednisone to help with the pyoderma gangrenosum. There was rapid improvement within a month. This case illustrates how one needs to remain flexible and open minded, often utilizing multiple concomitant approaches, to achieve proper wound bed preparation in patients with difficult wounds.

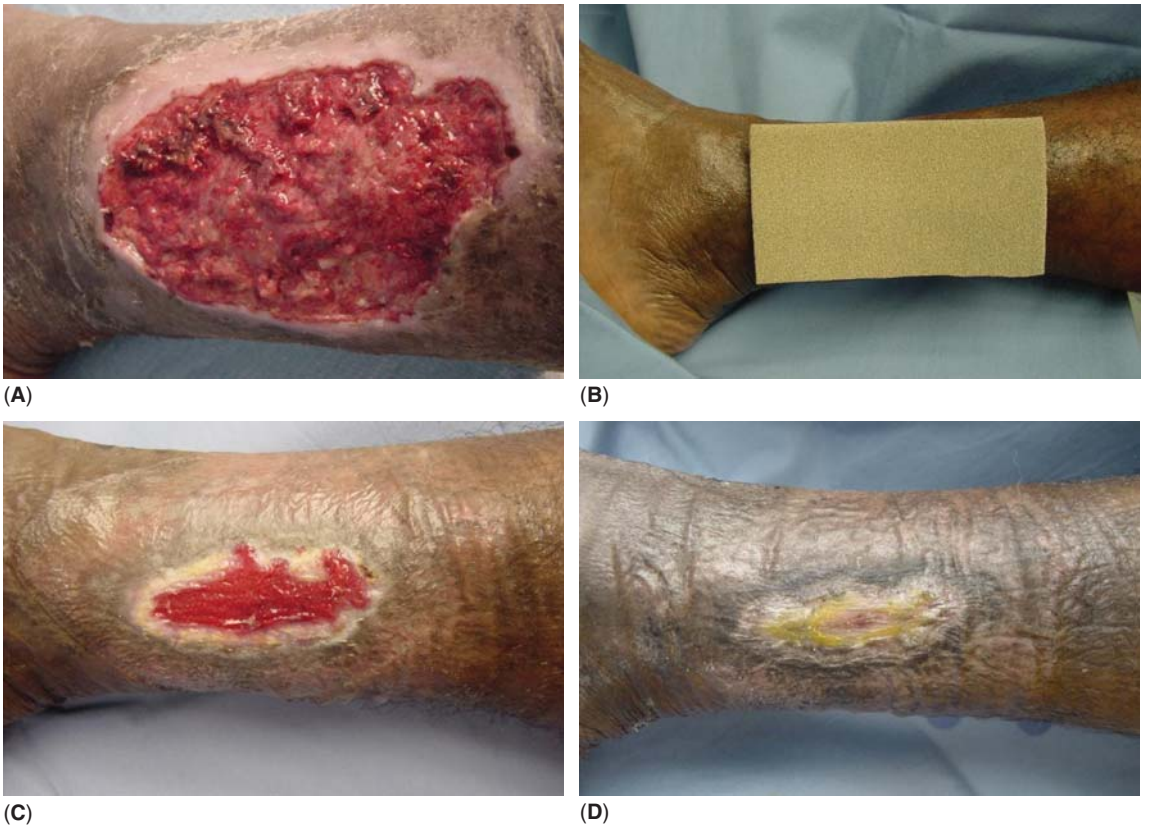


Figure 2.47 Colonization with *S. aureus.*

This patient had a very large venous leg ulcer with bright red granulation tissue (Panel **A**) which we correctly assessed to be due to *S. aureus* colonization. The patient was started on oral antibiotics and silver-releasing dressings (Panel **B**). We also began compression therapy and pentoxifylline (at high doses of 800 mg 3 times a day). She tolerated the pentoxifylline well, except for some heartburn, which we treated and monitored. She healed in 4 months (Panels **C** and **D**).



Figure 2.48 Hyperbaric oxygen chamber.

This type of monoplace hyperbaric chamber can be found in many hospital settings or specialized clinics. Hyperbaric oxygen is often used for difficult-to-heal wounds, particularly if they are heavily colonized. In a way, the delivery of oxygen at more than one atmosphere is acting as an antimicrobial agent. There is evidence that hyperbaric therapy can be effective in many types of ulcers, particularly complex wounds and difficult-to-heal ulcers in patients with diabetes. Multiple treatments (i.e., 20 or more) lasting a couple of hours a day are often necessary.

3 Pressure and neuropathy

The injury caused by simple pressure is often underestimated, both in terms of the time required for tissue necrosis to develop and for the extent of necrosis to become apparent. It is good to keep in mind that pressure injury leads to ulcers characterized by deep tissue necrosis and loss of volume that are disproportionately greater than the overlying skin defect. Therefore, the area of ulceration may be misleading and will tend to lead to underestimation of the true extent of the problem. There is a well-described pressure-induced "cone of injury" with its base toward the underlying bone. This might explain the skin undermining which characterizes pressure ulcers; the skin is less susceptible to injury than the underlying tissues. Muscle and other subcutaneous tissues are highly susceptible to pressure injury because of direct or shearing forces on large segmental and perforator arteries; it has been argued that skin necrosis from pressure is less likely because the cutaneous blood supply benefits from nearby anastomozing vessels. This is only one explanation for why skin and subcutaneous tissues differ in their susceptibility to pressure. For example, in experimental animal models, degeneration of muscle fibers and full-thickness skin necrosis occur after 60 mmHg for 1 h and 600 mmHg over 11 h of contact pressure, respectively. As clinicians are well aware, the anatomic location of pressure is also an important variable, as pressures over 2500 mmHg are reached immediately over bony prominences. Also, and not surprisingly, patients with neurologic or vascular abnormalities such as diabetes or spinal cord injury are more susceptible to pressure injury.

As in diabetes, many ulcers due to pressure are thought to result from loss of a protective sensory input. The neuropathy of diabetes leads to many structural changes in the foot. Extensor function is altered, and this causes excessive prominence of the metatarsal heads. Autonomic failure is likely to play a pathogenic role as well. Thus, there is decreased sweating and more easily damaged skin. However, whether the "insensate foot" alone fully explains the development of ulceration remains somewhat unclear. Patients with diabetes have a host of abnormalities (metabolic, vascular, neurologic, and so on) and these deficits are likely to play a fundamental role in creating the conditions leading to pressure injury and ulceration. For example, patients with diabetes have long been thought to have "small vessel disease." The role of this abnormality in the development of pressure injury is unclear. We do know that an obstructive vascular lesion of small blood vessels is unlikely. We also know that there are structural and functional abnormalities of the endothelium and blood vessels in patients with diabetes. These include, for example, excessive thickness of the basement membrane, endoneural capillary damage, and vascular leakage of albumin and other proteins. Hyperviscosity and fibrin deposition are also described. In addition to neuropathy, patients with diabetes suffer from increased susceptibility to vascular abnormalities, including atherosclerosis and medial sclerosis. Because of this, many clinicians now believe that the ankle to brachial pressure index, which is often used to exclude severe arterial insufficiency, is not useful and is often unreliable in patients with diabetes. However, the realization that an obstructive "small vessel disease" in patients with diabetes was a myth perpetuated by retrospective studies and anecdotal experience was a major breakthrough. Once this myth was eliminated, the vascular surgical approach to diabetic patients with vascular insufficiency changed dramatically and for the better. Now, diabetic patients are offered vascular reconstruction as other nondiabetic patients, and this more positive approach has saved many limbs.

Throughout this section, we describe clinical cases where control of infection is a critical component of care in patients with pressure (decubitus) or diabetic ulcers. Extensive surgical debridement removes infected and necrotic tissue and stimulates the healing process. Debridement should remove the undermined edges of the ulcer, because these areas act as a pocket for bacterial growth. Also, in patients with neuropathic diabetic ulcers, one should remove the cells surrounding the ulcer. This process of "saucerization" creates a wound that has flatter edges and contains healthier tissue. In this regard, a popular notion is that aggressive surgical debridement transforms a chronic wound into an "acute wound." This may be partly true, but it is probably too simplistic. Different explanations are possible. One that we favor is that removal of tissue from within and around the wound may actually be removing cells that have been adversely altered by the long-standing pathogenic event (i.e. pressure and ischemia). Bringing new young cells in may provide the wound with healthier and more active cells, at least for a period of time. We discuss this further in the section on vascular ulcers. However, it is important to note here that surgical debridement (and debridement by other means including enzymes and autolytic approaches) should not be thought of as a one-time or two-time procedure. We have proposed that the clinician needs to think of "maintenance debridement," and have written extensively about this notion. This concept points to the fact that we, as clinicians, are not very good at identifying what is an optimal wound bed and whether proper wound bed preparation has been achieved. Therefore, in the setting of a persistently nonhealing wound, it may just be that a more continued debridement is needed ("maintenance").

The metabolic abnormalities associated with diabetes (e.g., impaired migration of neutrophils and macrophages) do seem to predispose to infection. From the practical standpoint, it is important to achieve maximal glucose control. It is also worthwhile to try and correct clinical abnormalities that might lead to infection. For example, although this has not been studied in detail, it is probably important to treat tinea pedis and onychomycosis in patients with diabetes. By decreasing skin dryness and fissures associated with fungal infection, one might also

decrease the chance of bacterial entry and infection. Certainly, this approach is worth pursuing in patients with recurrent cellulitis.

Clinical Points

- Diabetic ulcers can develop as a result of ill-fitting shoes and from sharp objects which end up inside shoes. Patients with diabetes should always shake their shoes before wearing them, to ensure that no object is present in them.
- Treatment of tinea pedis and onychomycosis may help patients with diabetic ulcers by preventing the development of cracks (especially between the toes) in the skin and bacterial entry leading to cellulitis.
- Off-loading is essential to ulcer care in diabetic patients. The notion of the insensate foot is generally poorly understood by patients (no matter how bright or educated) and requires continuous reinforcement.
- Total contact casting is a useful first approach in the management of Charcot foot, with evidence that this approach accelerates ulcer healing.
- The area of ulcers in pressure injury is often misleading; there is often a deeper component that is not immediately obvious, particularly if undermining of the edges is present.
- Pressure ulcers in the heel are often complicated by vascular problems.
- Exposed and visible bones generally mean osteomyelitis.
- Proper debridement of diabetic ulcers should include complete removal of the surrounding callus, which may contribute to the level of pressure.
- Because they may provide an ideal pocket for infection, the undermined edges of pressure ulcers should be removed surgically.
- Especially in the elderly, hip fracture and hospitalization are major risk factors for pressure ulcers.
- Measurements of pressure ulcers require that volume be assessed. An easy way is the use of alginate material to obtain a mold of the ulcer.
- Because of noncompressible or only partly compressible arteries, the ankle to brachial pressure index in patients with diabetes does not reliably exclude arterial insufficiency. Vascular studies in patient with diabetes should focus on color duplex scanning, pulse volume recordings, and pulse volume recordings. Arteriography is the gold standard, but one must keep in mind that it may cause or complicate renal failure.
- The use of negative pressure for pressure ulcers can be quite helpful.



Figure 3.1 Arterial insufficiency in diabetes.

The red appearance of the foot may suggest a cellulitis. However, it is not uncommon for the redness to be due to arterial insufficiency and reactive hyperemia. There is also extensive fungal infection. Maceration between the toes is also a problem here, and is due to edema of the toes and poor blood supply. This patient may require systemic antibiotics and antifungal agents, whirlpool treatment, and cautious separation of the toes with cotton material or a toe comb. He was being evaluated for arterial stenting or angioplasty. We now recognize that "small vessel disease" is generally a myth in diabetes. This has now been recognized by prospective studies and has improved the prognosis and the way clinicians approach the diabetic foot and perform revascularization. However, there are indeed endothelial physiologic abnormalities in diabetes.



Figure 3.2 A diabetic ulcer and Charcot foot.

This patient had long-standing diabetes mellitus and neuropathy. He presented to us with an ulcer on the sole of his foot. The midfoot is collapsed, giving a flat appearance to the sole. In these circumstances, progressive damage to the tendons and collapse of the bones leads to excessive pressure and persistent ulceration. Charcot foot is seen in several diseases characterized by neuropathy, such as diabetes, syphilis, and leprosy. The etiology of the Charcot foot remains unknown but is thought to be initiated by an inflammatory process. In this particular case, the patient has some redness on the plantar surface, suggesting that one needs to investigate whether this represents a chronic Charcot foot or whether an inflammatory process is still present.



Figure 3.3 The effect of pressure on blood flow.

Pressure causes very substantial decreases in local blood flow, and this photograph is a vivid demonstration of this. A glass slide was placed for a few seconds against this elderly woman's sole. Although not much pressure was applied, blanching of the skin was quite evident. One can extrapolate this finding to the situation encountered by patients with diabetes or other neuropathies. These patients unknowingly place sustained pressure on their feet and, as a consequence, develop prolonged ischemia and necrosis. The technique shown here can be used as a teaching tool to show patients how pressure compromises blood flow.

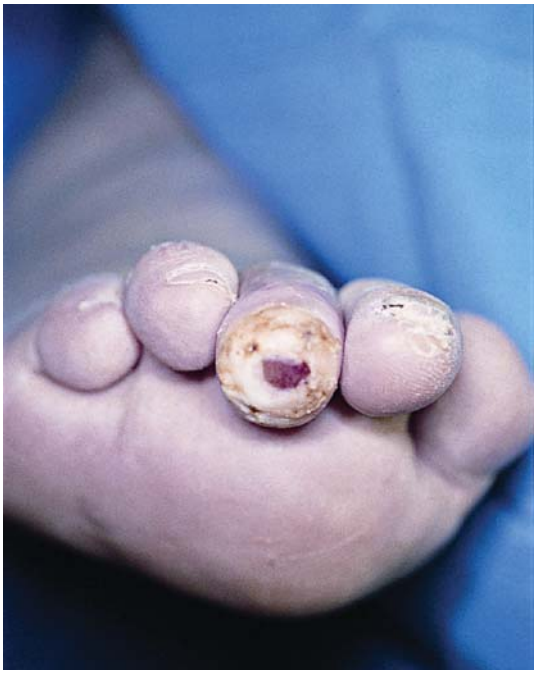


Figure 3.4 A pressure ulcer on the third toe.

This patient with long-standing diabetes and peripheral neuropathy has had this pressure ulcer from a hammertoe deformity for several months. The ulcer goes through periods of partial healing and enlargement. Ideally, one should remove the surrounding callus and have the patient evaluated for correction of the hammertoe. One should realize that it is important to warn patients that, while debridement is necessary, it will create a much larger ulcer. Topical platelet-derived growth factor or bioengineered skin, in addition to protective measures and off-loading, will be good therapeutic options here.



Figure 3.5 A diabetic foot after multiple surgical procedures.

This patient had several operations to remove metatarsal bones. The toes were not removed, however. This is probably not ideal, because the nonfunctional toes merely create a situation where pressure from the shoes or within the toes leads to further ulcerations as well as maceration.



Figure 3.6 A large neuropathic ulcer.

This young man with diabetes developed this ulcer about 9 months ago. The ulcer is surrounded by an extensive and thick callus. He has complete loss of sensation in his feet. Application of a Weinstein filament, seen here at 7 o'clock, does not elicit any sensation. Treatment of the ulcer requires extensive debridement of the callus and saucerization of the wound in order to achieve better wound bed preparation.



Figure 3.7 A large callus and ulcer formation in a diabetic patient.

Here the amount of pressure has been substantial, and the clinical appearance cannot really be used to assess the full extent of the ulcers and the amount of necrosis of the underlying tissues. For management, one needs to remove this entire callus and debride down to the subcutaneous tissues and bone. It is quite possible that an abscess or osteomyelitis is present at this stage.



Figure 3.8 Pressure injury to the back of the ankle.

She was from a nursing home and had very deep pressure ulcers over the Achilles tendons, which have a green hue (*left*) or are within an eschar (*right*). She also had severe arterial insufficiency. Although this is an extreme case, it does highlight the need to monitor patients with neurologic deficits for the development of ulcers in any areas of pressure. For example, we have seen pressure ulcers developing on the calf of diabetic patients undergoing hemodialysis and while in a recliner for several hours at a time. The extent of the ulcers in this particular case makes management very difficult. Most likely, the Achilles tendons would have to be cut and the entire area debrided extensively. Attention must be paid to revascularization prior to extensive surgical debridement.



Figure 3.9 Pressure ulcers from ill-fitting shoes.

In diabetic patients with severe neuropathy, ulcers do not develop only at the bottom of the foot and toes. In this case, the shoes were the culprit, and this woman developed ulcers at pressure points on the dorsal aspect of her feet.



Figure 3.10a A sequence of events in the case of arterial insufficiency and diabetes.

The sequence of photographs shows the progression from ischemia to necrosis of the second and third toe and surrounding cellulitis (Panel **D**, plantar aspect) in a patient with severe arterial insufficiency and diabetes. This could be considered dry gangrene of the toes. Frequently, autoamputation takes place, as shown in Panels **D** through **F**. The patient received several courses of systemic antibiotics. The retention of the big toe provides the important function of initiating walking.



Figure 3.10b A sequence of events in the case of arterial insufficiency and diabetes/follow-up.

The patient was fitted with a prosthesis 6 months after healing took place. The toe prosthesis helps with balance, gait, and ambulation.



Figure 3.11 Osteomyelitis of the calcaneous.

The heel is commonly affected by pressure injury, and ulcerations occurring in this area are frequently complicated by vascular problems and osteomyelitis. Therefore, one should not think of heel ulcers as simply being secondary to neuropathy. In this case, radiographic examination confirmed the presence of osteomyelitis.



Figure 3.12 A diabetic ulcer with good granulation tissue.

Some clinicians might be content with the way this neuropathic ulcer looks, because of the "good" granulation tissue in the ulcer base. However, we strongly advise removing the surrounding callus to minimize infection (bacteria tend to grow under the undermined skin) and achieve optimal ulcer healing. The presence of callus generally implies poor compliance with off-loading. There are, however, some cases where we have observed continued callus formation despite immobilization and proper off-loading. Studies are needed to evaluate this phenomenon and whether it might represent chronic alterations in the cellular phenotype of the involved skin. In addition, because of its red and dusky color, the "good" granulation tissue might possibly represent colonization with *S. aureus*.

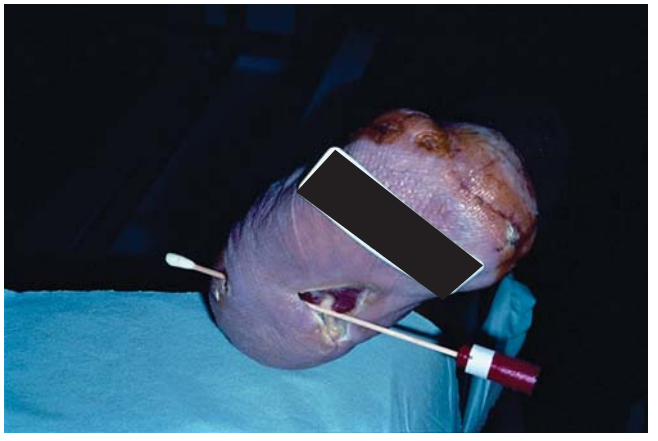


Figure 3.13 A sinus tract in a neuropathic diabetic foot ulcer.

One needs to be aware of the possibility that ulcers in the same location might be communicating through sinus tracts, as illustrated here. The presence of these subcutaneous tunnels alters management dramatically, and this complication requires extensive debridement. The patient has previously lost his toes because of pressure injury. There is also vascular insufficiency in this patient.



Figure 3.14a A patient with leprosy.

The neuropathy in this patient was secondary to Hansen's disease (leprosy). The ulcer is due to pressure because of the insensate foot. While at first this clinical picture may resemble the neuropathic ulcers due to diabetes, in fact resorption of the toes (as observed here) is more typical of Hansen's disease.

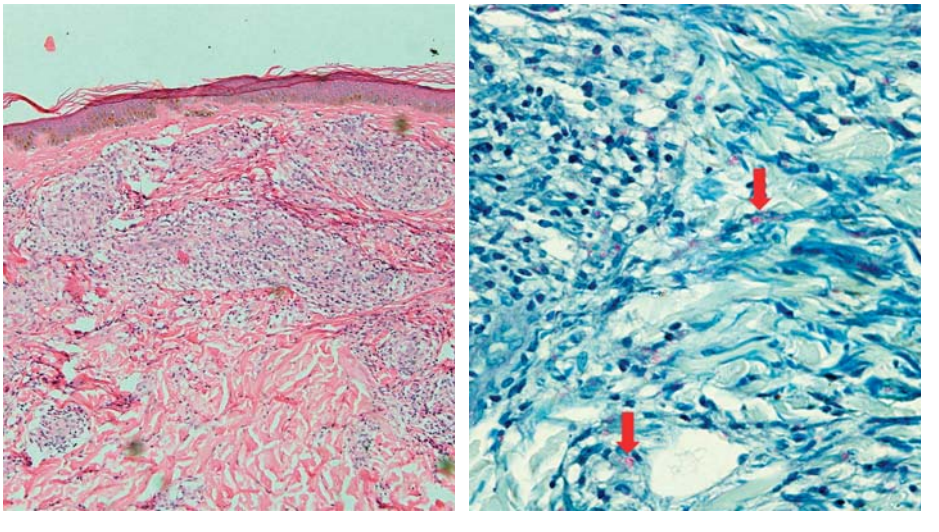


Figure 3.14b A patient with leprosy (Hansen's disease)/histology.

Here in the left panel we see aggregates of foamy histiocytes forming several granulomas. The epidermis appears unaffected. These granulomas frequently involve the nerves, resulting in the typical neuropathy of leprosy. In the right panel a Fite stain highlights the *Mycobacterium leprae*, which are seen as red globules (arrows).



Figure 3.15 A neuropathic ulcer from leprosy.

At first, this foot ulcer looks very much like what one might see in patients with diabetes mellitus and neuropathy. However, in this case the neuropathy was due to Hanson's disease (leprosy). The ulcer is very deep and the patient will require extensive surgical debridement.



Figure 3.16 An exudative diabetic ulcer.

Neuropathic ulcers in the diabetic patient are often not very exudative. In this case, however, the considerable drainage necessitated the use of an absorbant dressing, such as an alginate. Alginates are capable of absorbing large amounts of wound fluid. There is still some controversy over whether diabetic ulcers should be occluded, but most clinicians appreciate that moist wound healing accelerates healing and leads to painless autolytic debridement. The use of negative pressure devices could also be very helpful.



Figure 3.17 A diabetic foot ulcer treated with a bi-layered living bioengineered skin construct.

This man had recurrent neuropathic ulcers on the metatarsal heads. Here the baseline ulcer (Panel **A**) is surrounded by callus, which needs to be removed because it causes further pressure on the ulcer. After debridement, a living bi-layered bioengineered skin construct was applied to the ulcer (Panel **B**). This living skin equivalent is bi-layered and made up of human keratinocytes and dermal fibroblasts derived from neonatal foreskin. The fibroblasts are embedded in a type I bovine collagen matrix. Slits are often made in the bi-layered bioengineered skin construct, so as to allow the escape of exudate from the wound, or else the "graft" (there is no actual take with these biological constructs) would be uplifted. Overlapping of the living skin equivalent onto the wound edges seems to increase its adherence and prevents it from shifting. The photograph in Panel **C** was taken 3 days after the application of the construct, and it shows the construct to be firmly in place. Complete healing of the ulcer occurred within 2 weeks (Panel **D**). At this point, there is no exudate appearing on the dressing. We could not be sure as to whether the living skin equivalent remained on the wound or whether it provided a stimulus for wound repair, but our published PCR data show that the allogeneic cells of these constructs are no longer detectable at 4 weeks. Tissue engineering technology and its application to the treatment of wounds have emphasized that grafts act not only as replacement, but also as cell therapy, capable of delivering growth factors and other stimulatory substances.



Figure 3.18 Treating a nonhealing ulcer with a bi-layered living bioengineered skin construct.

This man in his early 30s has a severe neuropathy from his diabetes, and his work does not allow him to adequately off-load his foot. As a result, his neuropathic ulcer had not healed for 9 months. It is surrounded by a callus, which has a green color in some areas, suggesting hemorrhage and possible colonization with *Pseudomonas* bacteria (Panel **A**). The callus around this wound has to be removed in its entirety and the wound needs to be saucerized (Panel **B**). Panel **C** shows a photo taken several weeks later, illustrating a more shallow ulcer and better granulation tissue. A bioengineered skin construct has been placed in the middle of the ulcer; in our experience it is effective even when it is not extending to the surrounding edges. Panel **D** shows the ulcer almost completely healed after several weeks.

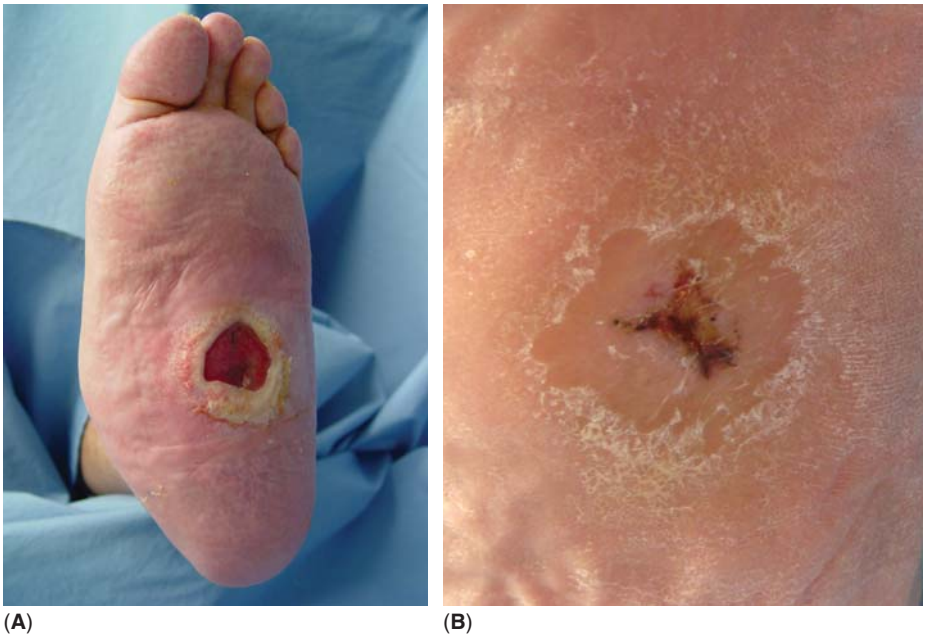


Figure 3.19 Diabetic ulcer and Charcot foot.

Here is an example of an elderly patient with a chronic Charcot foot and ulceration (Panel **A**) that was treated with bioengineered skin and went on to become much smaller (Panel **B**) and ultimately heal. As in other cases, weekly debridement of the callus was done with off-loading of the foot. Compliance with treatment, particularly off-loading, was difficult. Consistent use of off-loading devices are difficult in the elderly, as such devices (or even contact casting) are often cumbersome.

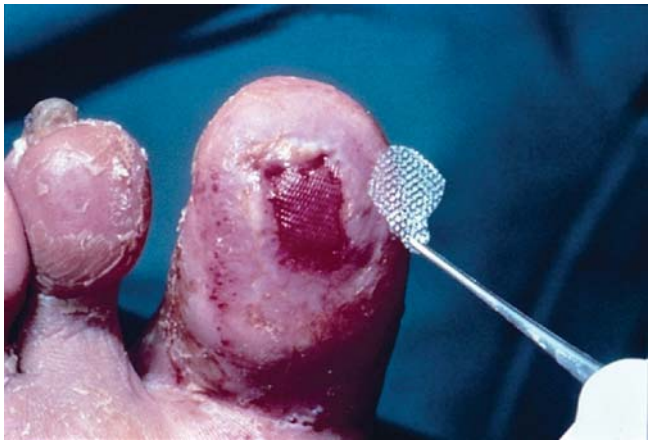


Figure 3.20 Treatment with a living dermal construct.

In this photograph the neuropathic ulcer on the big toes of this patient with diabetes is being treated with a dermal substitute consisting of living human neonatal dermal fibroblasts in an absorbable matrix material. Besides the living bioengineered skin constructs we show, there will be other types in the next few years. Some of these constructs will be modifications of the existing ones, (i.e., adding endothelial cells, re-engineering with certain growth factors or matrix gene constructs that are constitutively expressed or whose expression can be regulated by the wound environment). We have also developed the idea that a "priming" step is required, whereby the construct is activated and allowed to develop its full program (increased gene expression for proliferation, migration, and chemotaxis) in vitro before being placed in the hostile ulcer microenvironment.



Figure 3.21a A diabetic wound treated with a living dermal skin substitute.

This neuropathic heel wound in a diabetic patient shows excellent granulation tissue. Because of the beefy red wound bed, we were concerned about colonization with *S. aureus*, but bacterial cultures proved negative. The wound should heal with appropriate off-loading measures. Bioengineered skin products can be used to accelerate the healing process.



Figure 3.21b A diabetic wound treated with a living dermal skin substitute/follow-up.

The wound was treated with a living dermal skin substitute, and the photo shows its appearance and size at 5 weeks. The wound is healing and there is an "edge" effect, consisting of epidermal migration from the wound's margins.



Figure 3.21c A diabetic wound treated with a dermal skin substitute/healed.

There has been complete healing of the ulceration after 10 weeks. It is important to note that off-loading measures will need to be continued for the rest of this patient's life, or else the foot will likely reulcerate.



Figure 3.22 A stage II pressure ulcer.

There is partial thickness skin loss on the hip, down to the dermis. The ulcer is superficial and presents clinically as an abrasion, blister, or a shallow crater. The photograph was taken in a hospitalized patient who could not be moved/shifted easily because of a hip fracture. Removal of pressure, proper positioning in bed, flotation mattress, and use of protective dressings (i.e., a hydrocolloid) are measures that could be used to treat this condition and prevent it from worsening. However, as in this case, medical and surgical conditions can make the nursing task of shifting the patient's position in bed extremely challenging and sometimes almost impossible.

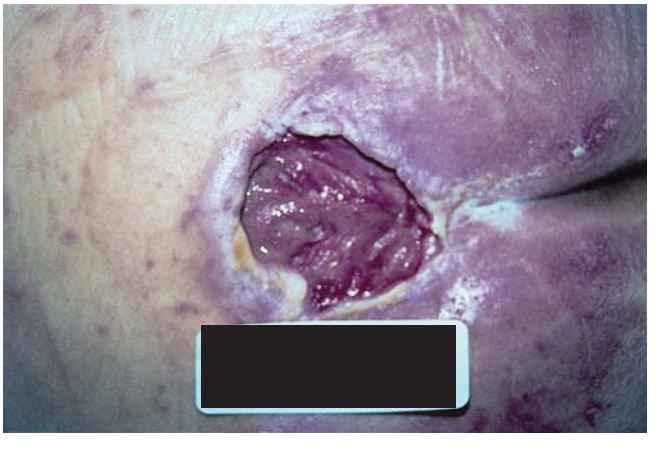


Figure 3.23 A stage III pressure ulcer.

There is seemingly healthy granulation tissue in the base of this sacral ulcer, which extends down to the subcutaneous tissues. There is undermining, which is quite typical of pressure ulcers because of the increased susceptibility of deeper tissues to pressure injury, compared to skin. The redness around the ulcer may represent the early stages of pressure injury (stage I), but one must keep in mind infection and abscess formation. A thorough debridement of the ulcer and undermined portions need to be done. Indeed, bacterial overgrowth often develops under the undermined edges. Proper positioning and frequent changes in the way the patient is lying in bed are imperative.



Figure 3.24 A stage IV pressure ulcer.

This young girl of 7 was in an automobile accident and became paraplegic. The ulcer developed from prolonged pressure, as she spends most of the day in a wheelchair. Pressure relief devices placed over the seat of the chair did not help. The ulcer extends down to bone. When faced with such ulcers, it is best to excise all of the necrotic tissue and bone in the operating room.

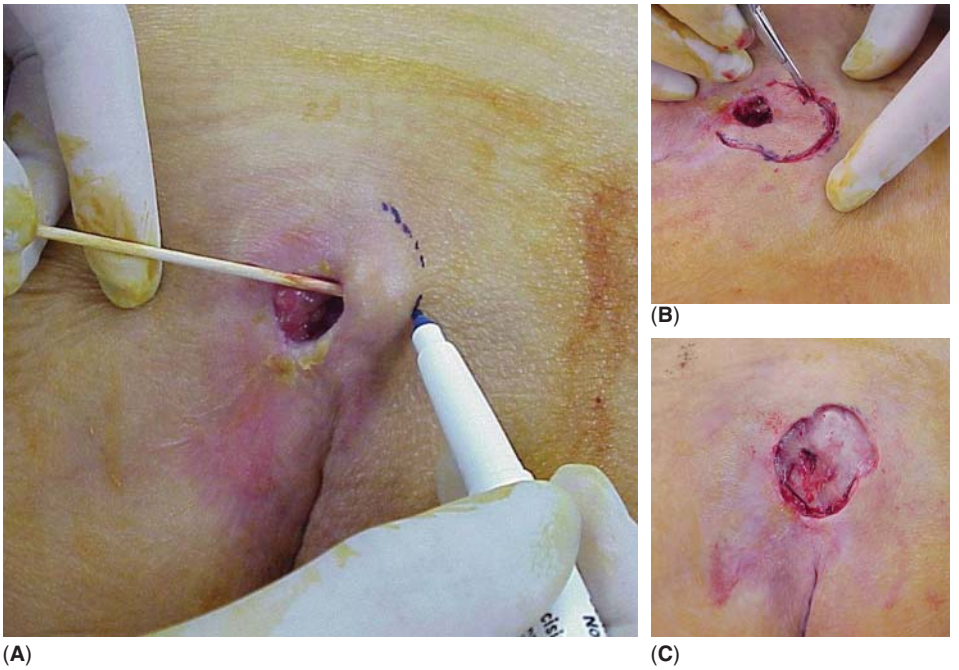


Figure 3.25 Removing undermined tissue from a pressure (decubitus) ulcer.

This patient had a pressure (decubitus) ulcer that may appear superficial upon early inspection. However, careful examination of the wound edges and the use of a sterile cotton applicator show that the ulcer was undermined by about 2 cm, almost circumferentially (Panels **A**–**C**). It is important that undermining of pressure ulcers be assessed carefully and that proper debridement be done to remove the undermining. Some clinicians may disagree with the need to remove the undermining, but we feel that bacteria thrive under that skin overhang. The undermining also suggests that unwanted pressure to the wound is continuing to occur.

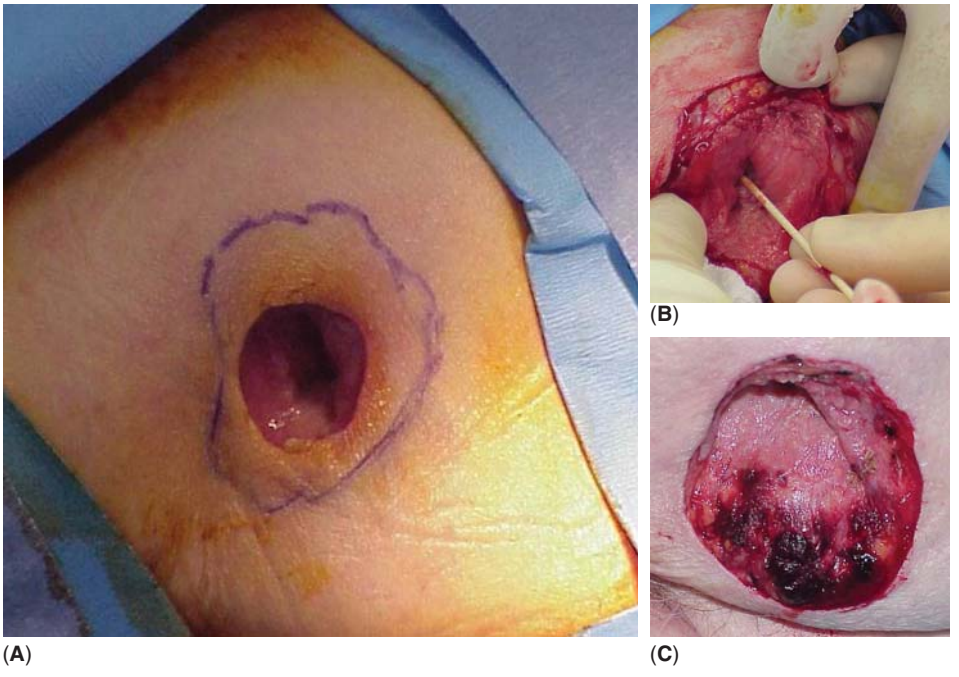
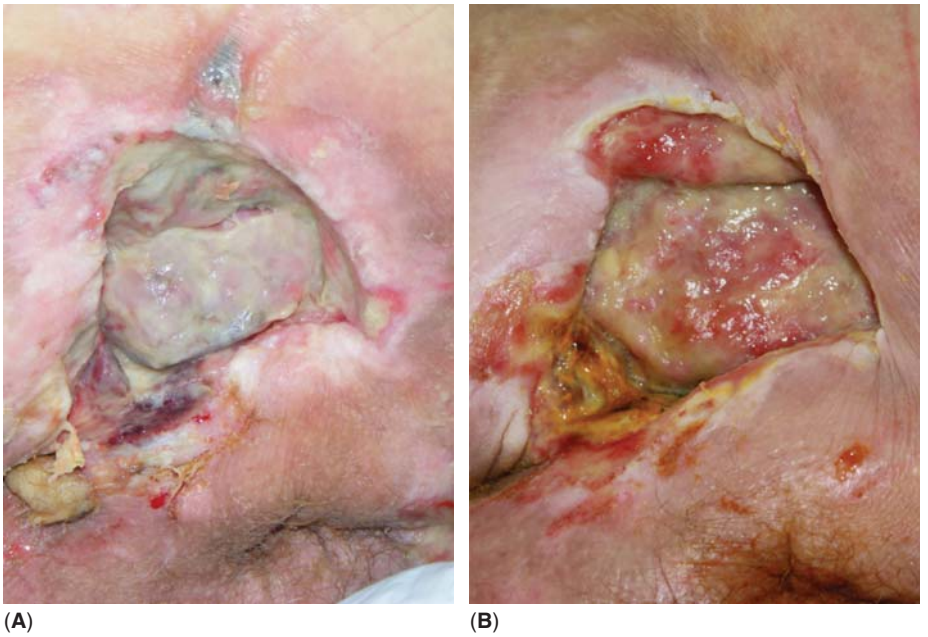


Figure 3.26 A sinus tract in a pressure (decubitus) ulcer.

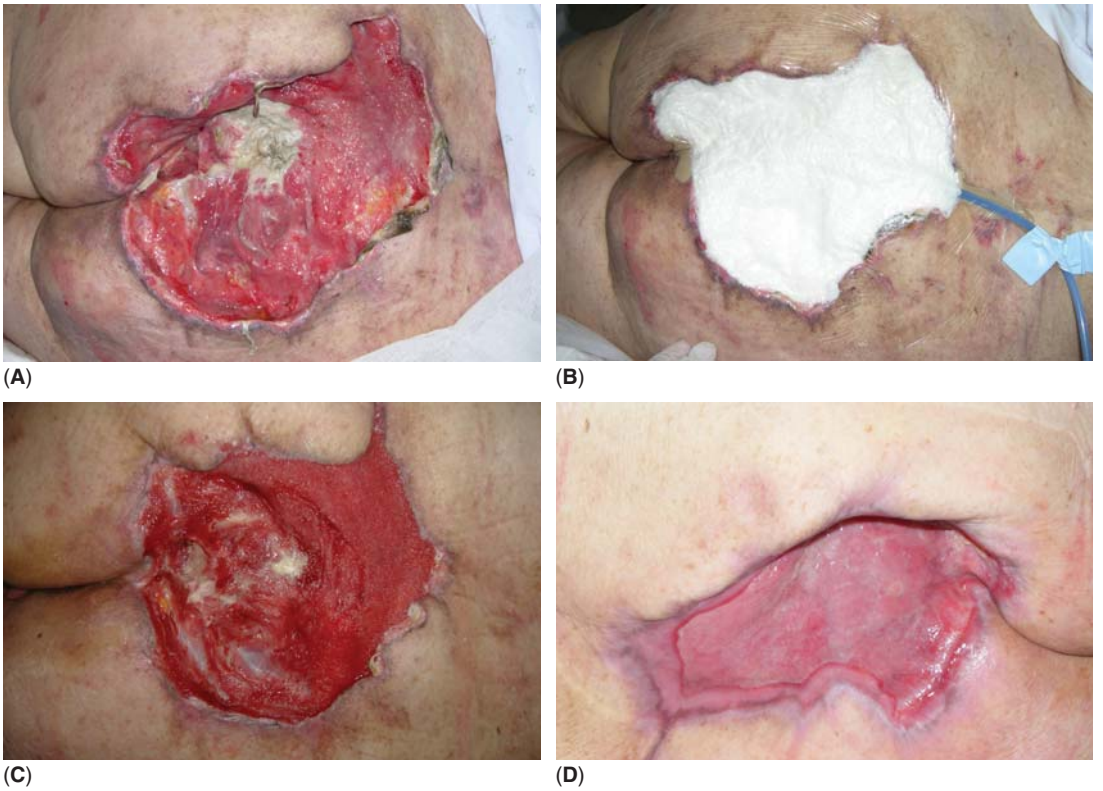
In this patient the undermined area has been mapped out and removed (Panels **A**–**B**). However, there is a sinus tract in the middle of the ulcer (Panel **B**). The sinus tract was then excised (Panel **C**). In addition to adequate debridement, the reduction of pressure against the ulcer with the use of specialized surfaces and proper positioning of the patient are essential to healing. Medical management of a patient with a pressure ulcer includes careful attention to wound bed preparation. This even includes proper attention to optimization of the patient's nutritional status and appropriate surgery for urinary or fecal diversion. Frequent assessment for possible infection should always be done. One unresolved question is whether certain dressings, particularly those that are rigid or quite adhesive, add to the effect of pressure. It's sadly ironic that dressings could contribute to the amount of pressure against the wound. In our experience and experimentation, it might be that gel dressings are less likely to do so, but more work is required to make a final determination.



(A) (B)

Figure 3.27 An ischial pressure (decubitus) ulcer.

Wound bed preparation is critical in these cases of very difficult-to-treat pressure (decubitus) ulcers. Treatment requires a combination of approaches, including surgical debridement, negative pressure, and appropriate dressings that do not augment the level of pressure by forming a rigid unit with the ulcer. In this particular case (Panel **A**, at baseline) there was improvement with these approaches and with the use of a hydrogel dressing (Panel **B**), which tends to be more flexible than other dressings. However, the granulation tissue seen in Panel **B** is still not optimal, and the plan is to use additional treatment with negative pressure and bioengineered skin. More surgical debridement will be required, as there is undermining and the possibility of sinus tracts.



(A) (B)

(C) (D)

Figure 3.28 A sacral pressure (decubitus) ulcer.

This woman developed a large pressure ulcer due to immobility from a fractured right femoral condyle (Panel **A**). Treatment was instituted with negative pressure (Panel **B**) and a gauze filler. Panel **C** shows that the ulcer has better granulation tissue at 1 month. At this point the negative pressure treatment was discontinued. Hydrogel dressings were then continued and resulted in further improvement at 3 months, with a definite decrease in ulcer depth and with evidence of epithelialization from the margins (Panel **D**).

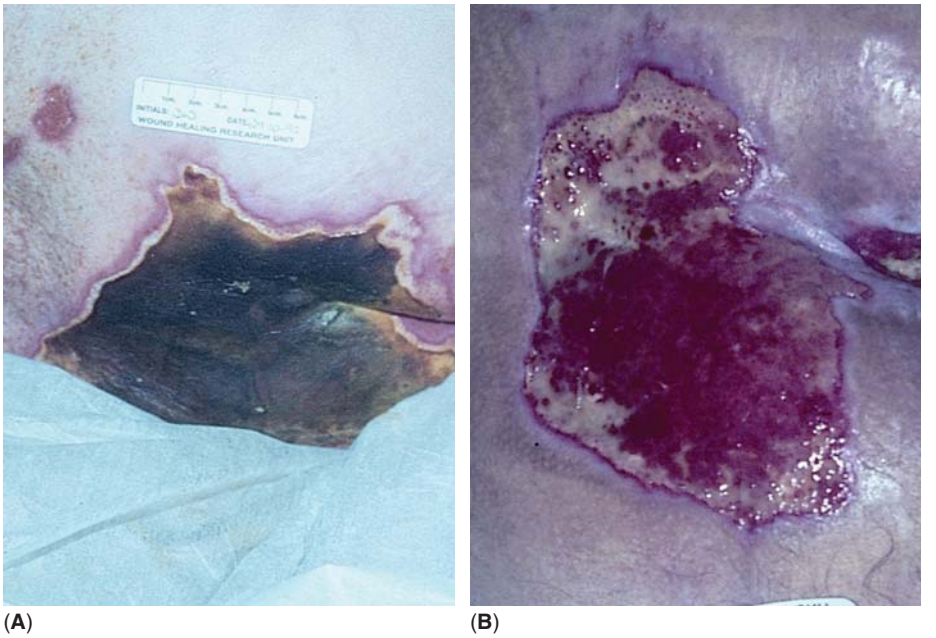


Figure 3.29 Massive necrosis due to pressure.

This large sacral ulcer in a nursing home patient needs immediate attention to remove the eschar and drain any possible underlying abscess (Panel **A**). In Panel **B** one sees the same ulcer 2 weeks later, after surgical debridement and nursing attention to relieve the pressure. This patient has a good chance to heal. Portions of the wound bed are still becoming necrotic, and will probably require additional surgical debridement. However, removal of the unwanted nonviable tissue could also be achieved with autolytic debridement with a hydrocolloid or hydrogel. We have developed the concept of maintenance debridement, which suggests that debridement (by a number of means) needs to be continued as long as there is nonviable tissue or lack of healing.



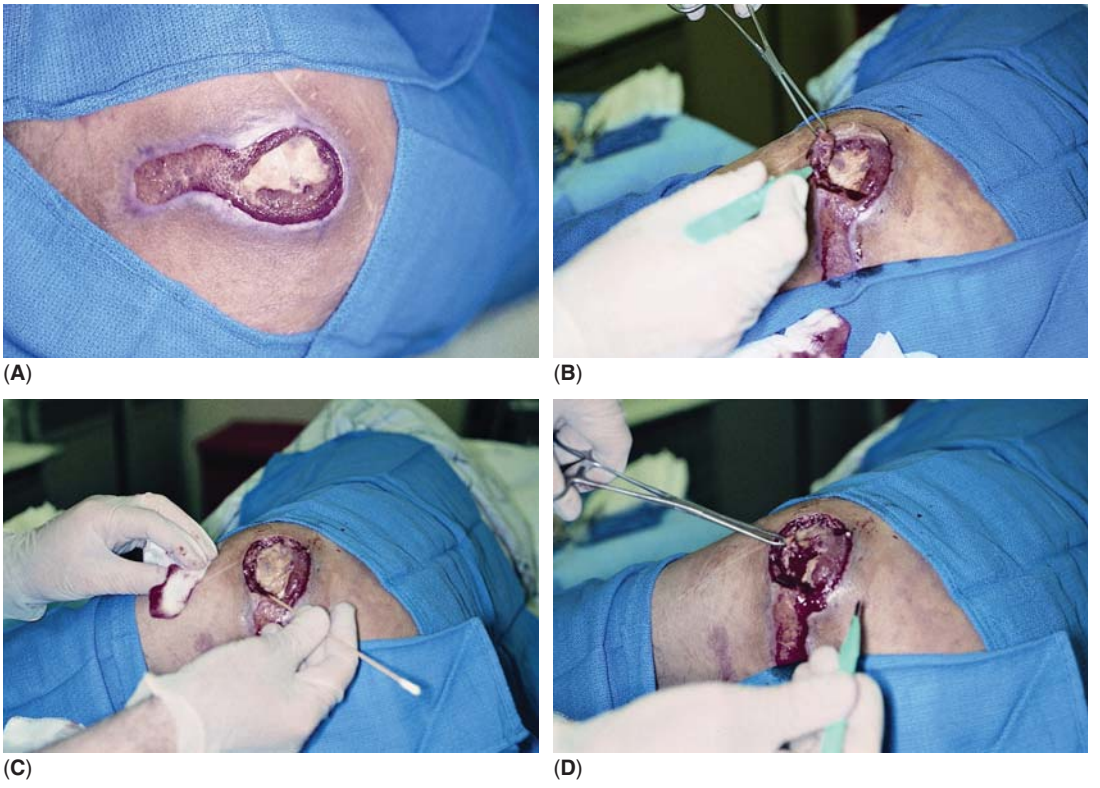
Figure 3.30 An ischial pressure (decubitus) ulcer in a paraplegic athlete.

The ulcer has minimal exudate, but the patient was still started on negative pressure therapy. However, after several weeks there was marginal improvement. Imaging studies were done to rule out osteomyelitis. X-ray examination of this area showed a bony spur over the femur. At this point, the patient was referred to a plastic surgeon with expertise in pressure ulcers, and extensive debridement and a flap were performed to close the wound.



Figure 3.31 Debridement and a simple method of measurement of pressure ulcers.

There is still no easy way to measure the extent (size, depth) of a pressure (decubitus) ulcer without resorting to expensive equipment that is not easily available in nursing homes and other usual clinical settings. This patient with multiple sclerosis had a stage IV pressure ulcer on his hip (Panel **A**). The eschar was removed, and the wound bed still showed a fibrinous material that required further surgical debridement (Panel **B**). This dental alginate material (Panel **C**) has commonly been used to obtain an impression and a volume measurement for deep wounds, such as pressure ulcers. The material, consisting of a powder, is mixed with water and then applied in its semi-liquid form into the wound. Occasionally, it is helpful to cover the wound first with a film dressing, and then apply the alginate solution through a slit in the film, using a large-bore syringe. The alginate solidifies quickly. It can then be easily removed from the wound and weighed to obtain an objective measurement at baseline and follow-up. Panel **D** shows the alginate mold soon after removal from the patient's ulcer and being weighed. The weight can be used to objectively assess the progress of the ulcer (Panel **E**).

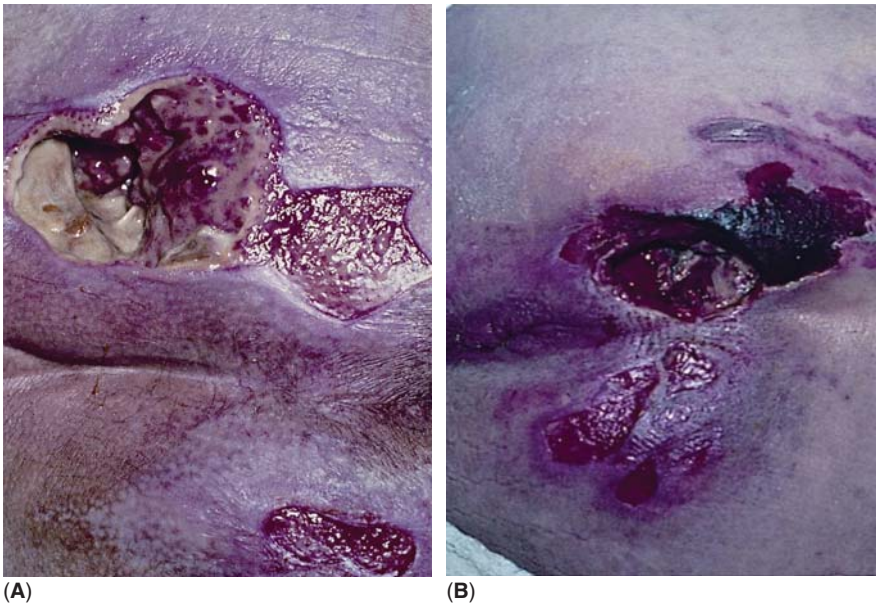


(**A**) (**B**)

(**C**) (**D**)

Figure 3.32 A pressure (decubitus) ulcer over a hip prosthesis.

This had been a recurrent ulcer. The white area was immediately over the prosthesis (Panel **A**). Extensive debridement with a scalpel and scissors showed the ulcer to be much larger and deeper than initially assessed (Panel **B**). Probing of the edges is always a useful maneuver to judge the extent of deep tissue injury. This is often done repeatedly during debridement, to be sure of removing all necrotic and undermined tissues (Panel **C**). Further debridement over the middle of the ulcer showed that the hip prosthesis was directly exposed (Panel **D**). The patient had to be taken to the operating room to have the hip prosthesis removed. We felt that there was no choice at that point.



(**A**) (**B**)

Figure 3.33 A multistage pressure (decubitus) ulcer.

These sacral pressure (decubitus) ulcers are in different stages of development, from nonblanching erythema (stage I), to partial thickness skin loss (stage II), to extension into the subcutaneous tissue (stage III), and bone involvement (stage IV) (Panel **A**). Some of these ulcers are necrotic and covered by an eschar, while others show some evidence of re-epithelialization (Panel **B**, inferiorly). The blisters above the necrotic sacral ulcer may be secondary to friction injury. A multistage ulcer also points out the problem of classifying it for both clinical purposes and for clinical trials. A logical solution is to classify according to the worst aspect of it, and therefore as stage IV. Another problem may arise when a pressure ulcer recurs in the same location. Due to the underlying scarring, which may alter its natural size and depth, it becomes unclassifiable.

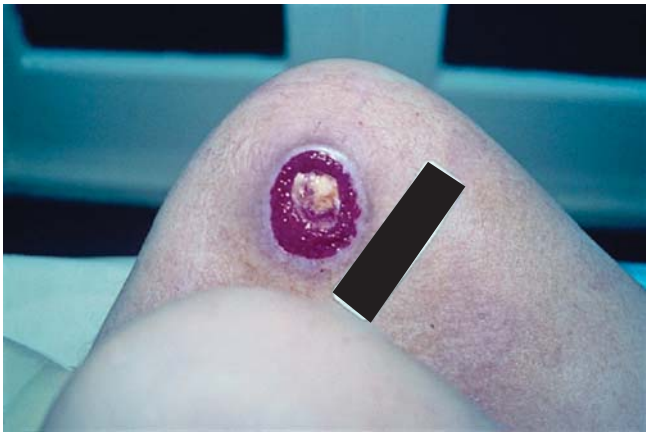


Figure 3.34 A pressure ulcer on the knee in a paraplegic patient.

Such ulcers on the medial aspects of knees are not uncommon in patients with spinal cord injury and spastic paralysis. In this case, there was almost constant trauma to the medial aspect of both knees. Although much of the ulcer has excellent granulation tissue, the center is necrotic and in need of debridement. Management of these ulcers involves the use of protective dressings, such as hydrocolloids, or foam padding.



Figure 3.35a A pressure ulcer in a patient with multiple sclerosis.

This woman suffered from severe multiple sclerosis and sustained pressure injury to her knee. Her course was also complicated by the development of eosinophilia myalgia syndrome, which was secondary to the ingestion of L-tryptophan and had led to the development of fibrotic skin and subcutaneous tissue, down to the fascia.



Figure 3.35b A pressure ulcer in a patient with multiple sclerosis/wound dressing.

This special pressure relief dressing, which combines a hydrocolloid with foam rings on top, can be modified and cut to accommodate the contour of the area to be treated. It seems to work best in situations such as this, where intermittent trauma, and not constant pressure, is the problem. In many ways, clinicians have gotten away from treating pressure ulcers with dressings or devices that completely encircle the wound. There is fear that such an approach might produce more ischemia by compressing the blood vessels around the wound. However, there needs to be some flexibility in our approach to difficult cases, and this patient with a difficult neurological problem is an example of that.

4 Vascular ulcers

Many ulcers occur on the extremities, and most of them are due to vascular abnormalities. Therefore, not surprisingly, this section of our *Text Atlas* is more extensive than the others. This section deals with arterial, venous, and lymphatic ulcers. We also discuss ulcers which occur due to obstruction of small blood vessels with fibrin thrombi (i.e., cryofibrinogenemia, antiphospholipid syndrome, calciphylaxis, etc.).

Venous insufficiency is the most common etiology for ulcers of the lower extremities. The fundamental abnormality is venous hypertension, which refers to failure of the venous pressure to decrease in response to calf muscle pump action (e.g., during walking). Failure of the calf muscle pump could be due to a problem either with veins, such as retrograde blood flow, or the calf muscles themselves, as in a neurologic illness. We still do not fully understand how venous hypertension causes leg ulceration, but several hypotheses have been proposed. An early observation was that dermal capillaries in the fibrotic skin affected by venous disease (lipodermatosclerosis or LDS) were surrounded by fibrin cuffs. This led to the notion that venous hypertension causes leakage of fibrinogen, which then polymerizes to fibrin. It has been thought that the fibrin cuffs might reduce the proper exchange of oxygen and other nutrients between the dermis and blood. It remains unclear whether this "fibrin barrier" is truly operational in venous disease; our recently published evidence with confocal microscopy shows that the cuffs are incomplete around the dermal vessels. However, one could envision that, under conditions of poor microcirculation, fibrin could indeed act as a barrier. Most importantly, this hypothesis and subsequent studies showing defective tissue and systemic fibrinolysis in patients with venous disease did much to increase interest in chronic wounds.

Another interesting hypothesis for venous ulceration suggests that endothelial cells are damaged by venous hypertension, which then leads to adherence of circulating mononuclear cells, release of mediators, and further vascular permeability and tissue damage. Tumor necrosis factor-α (TNF-α) is probably one of these mediators. This hypothesis is also associated with clear therapeutic implications. For example, venous ulcers have been shown to heal faster with high systemic doses of pentoxifylline, which can inhibit the action of TNF-α. A third prominent hypothesis for venous ulcers proposes that macromolecular leakage (fibrinogen, albumin, α2-macroglobulin) leads to trapping of growth factors within the wound. The idea here is that, although they are present in the wound, growth factors are no longer available for proper wound repair. Interestingly, α2-macroglobulin is an established scavenger for growth factors and does leak into the dermis. There are other interesting hypotheses for the pathogenesis of venous ulcers, including oxidative processes and the excessive iron deposition from extravasated blood.

Within this section are examples of ulcers that cause considerable diagnostic difficulties, and which are characterized by obstruction of dermal capillaries with thrombi or other material (e.g., cholesterol emboli). Clinically, these ulcers present with areas of "microlivedo," purple discoloration of the foot and skin around the wound, and areas of dark necrotic tissue in the wound itself or at the edges. One of us (VF) has labeled ulcers having this clinical/histologic picture as "microthrombotic ulcers." Those ulcers that are due to cryofibrinogenemia responded dramatically to the anabolic steroid stanozolol, in terms of both pain and ulcer healing. We present several examples of these conditions. Unfortunately, due to the unrelenting abuse of stanozolol to enhance physical performance, this drug is no longer available. There are a few countries where it can still be obtained, but we would be concerned about quality control. Fortunately, there is enough clinical experience to suggest that danazol may also be effective in conditions where we used stanozolol.

Anabolic steroids, including danazol, also seem to help the pain and other symptoms and signs of inflammation associated with acute (or early) LDS. These patients often present with a picture resembling cellulitis but which is unresponsive to systemic antibiotics. We believe that this clinical condition is the acute counterpart of chronic LDS. Patients with acute LDS have evidence of venous insufficiency and will generally develop the intense fibrosis associated with long-standing venous disease. Ulcers often develop within the lipodermatosclerotic tissue. It may not have been emphasized enough in the literature or even in our legends, but vein surgery can be quite effective in both LDS and in the treatment of venous ulcers. There has been considerable progress in this area. Thus, referral to vascular surgeons and others who can remove or block perforators is worthwhile, particularly when the ulcers are recurrent. Bioengineered skin is also helpful, and a living bilayered skin construct has been shown to accelerate the healing of venous ulcers.

In this section, we have also tried to dispel some of what we regard as clinical myths regarding venous and other types of ulcers. For example, venous ulcers are not invariably associated with hyperpigmentation in the surrounding skin, and the absence of this finding should not exclude a venous etiology for the ulcer. Pain is very commonly associated with venous ulcers, contrary to what students, physicians, and other clinicians are generally taught. The verrucous changes associated with lymphedema can develop rather rapidly, within a few months after lymphatic obstruction. What looks like great granulation tissue in chronic vascular ulcers is not always desirable; it may represent infection or some other process (e.g., basal cell carcinoma). Autologous split-thickness skin grafts are often used in the treatment of vascular ulcers. However, it is not fully appreciated how painful the donor sites can be; patients are very reluctant to undergo additional grafting procedures.

Other sections describe wound dressings in more detail. Here we give several examples of how compression bandages are applied. There has been considerable progress in the development of better and more effective compression bandages. Compression remains the established treatment for venous ulcers, but there is considerable controversy regarding what constitutes the ideal bandage. Some experts favor elastic compression, often multilayered, while others believe that rigid or semi-rigid (non-elastic) bandages (short-stretch) are optimal. The majority of venous ulcers heal with compression therapy alone, and there is evidence that occlusive or moisture-retentive dressings may add to the beneficial effects of compression. There is increasing interest in methods or measurements which may allow us to predict which ulcers will go on to heal with these traditional and conservative methods. We have paid considerable attention to this in the context of wound bed preparation, and have indeed developed a wound bed score that might be useful (section 8). Confirmed work points to evidence that the extent of healing within the first 3–4 weeks is a very useful marker for complete healing several months later. This type of work is very important from a number of aspects. Measurements of healing rates in the first few weeks could be used as a guide for the use of different treatment modalities, for example grafting. Also, it is possible that pilot clinical trials in the treatment of some chronic wounds could make use of healing rates within the first few weeks as surrogate markers to guide further drug development.

Bioengineered skin constructs have redefined the way in which we treat chronic wounds, including vascular ulcers. We are actually perplexed that this treatment modality is not used more often in ulcers that are difficult to heal. There is increasing evidence that mesenchymal stem cells can lead to faster healing, again in patients who have failed other therapies. Negative pressure is now used commonly in vascular ulcers and in other types of acute and chronic wounds. This approach is useful, but the challenge will be to determine when negative pressure is clearly useful and effective, especially in preparation for other therapies including bioengineered skin, stem cell treatment, or traditional autologous split-thickness grafts. As with all new technologies, work is still required to identify how best to create and use such therapy. Here we give some examples of what might be expected with the use of bilayered skin constructs composed of living keratinocytes and fibroblasts. Many of these novel treatments, including bioengineered skin constructs and stem cell therapy are very attractive because they allow clinicians to use living cells to modify the wound microenvironment. Increasing evidence has shown the existence of abnormalities in the phenotype of cells within chronic wounds (e.g., increased senescence, unresponsiveness to some growth factors, etc.). Bioengineered skin constructs and stem cells may work, at least in part, by providing new wound cells which are "smart" and capable of adapting to the needs of the wound.

Clinical Points

- Wound bed preparation is key for all kinds of therapies and to make them successful. Without proper wound bed preparation, even highly sophisticated therapies are likely to fail.
- The ankle–brachial index is not reliable in patients with noncompressible arteries, as in diabetes. It is very helpful in venous disease.
- Biopsies are a safe and often necessary way to evaluate chronic wounds, including those due to vascular abnormalities. Biopsy sites at the edges of the wound heal readily and often upto the original margin.
- The presence of exposed tendons or a black eschar within a wound basically rules out a venous etiology.
- Microlivedo refers to a pattern of small linear streaks, often purple and not fully reticulated in configuration. It is associated with the formation of dermal thrombi, such as in cryofibrinogenemia and the antiphospholipid syndrome. We have labeled these conditions "micro-thrombotic ulcers."
- Venous insufficiency is the most common etiology for ulcers of the lower extremities.
- Acute lipodermatosclerosis (LDS) is red and painful and resembles cellulitis. Occasionally, it is also mistaken for localized scleroderma (morphea). It can respond dramatically to treatment with anabolic steroids, such as danazol (stanozolol is no longer available).
- Compression bandages remain the established treatment for venous ulcers and should be part of any therapeutic program.
- When taking a biopsy from fibrotic skin, as in LDS, a long and thin excision closed primarily gives the best chance of healing. A punch biopsy can create an ulcer.
- Pericapillary fibrin deposition is a hallmark of LDS and can be easily demonstrated by direct immunofluorescence.
- Arterial insufficiency should be suspected when ulcers are punched out or necrotic in appearance.
- Livedo reticularis or microlivedo are seen in almost 90% of patients with cholesterol embolization.
- Widespread cutaneous necrosis can be seen in a number of disease processes: connective tissue disease, vasculitis, disseminated intravascular coagulation, and so on.
- Venous ulcers do exist without the "typical" hyperpigmentation and LDS surrounding the ulcer.
- Localized supplemental pressure is directly applied to ulcers that are in concave locations on the leg and where compression bandages are often not able to achieve optimal treatment. Ulcers around the malleoli fall in this category.
- Multilayered bandages are preferred in patients whose legs have a "bowling pin" appearance. The noncompressive components can be used to "fill-in" certain areas on the leg and thus allow the compression bandages to work better by not slipping down.
- When venous ulcers are in the "healing mode," the wound edges become flat and the epithelium begins to migrate toward the center.
- Dermatitis is a major therapeutic problem in patients with venous insufficiency. It remains unclear whether dermatitis is a true manifestation of venous disease or a complication of sensitization to topically applied agents. Patch testing and, indeed, the establishment of a clinic to test patients for allergies is very useful in the management of patients.

- Lymphedema complicates many cases of venous disease. Chronic use of systemic antibiotics may sometimes be required to control the associated recurrent cellulitis.
- Sickle cell ulcers are probably due to both venous insufficiency and an arteriolar component. They do not respond readily to treatment. A comprehensive program of blood transfusion, grafting, hyperbaric oxygen, and pentoxifylline may be necessary.
- High doses of pentoxifylline (800 mg 3 times a day) have proven effective in the treatment of venous ulcers.
- Autologous grafting is an acceptable way to treat difficult-to-heal venous ulcers. Graft take is only about 50%, but it is important to maintain adequate compression for the grafts to spread and remain in the wound.
- Negative pressure can increase the survival of autologous skin grafts and their effectiveness.
- Autologous grafts in general can act as both tissue replacement and a stimulus for wound healing (the "pharmacologic" effect).
- Bioengineered skin has revolutionized the way in which we treat difficult-to-heal venous ulcers. Actual initial "take" of the bioengineered skin is occasionally seen, but the main mode of action appears to be stimulation of healing. Within four weeks, the cells comprising bioengineered skin are no longer detectable by PCR methods.
- It is possible that with both bioengineered skin and autologous grafts a "priming" step will bring about even greater effectiveness in the future. This is because the wound microenvironment can be quite hostile to cells and, therefore, initiating a healing program of these therapies in advance of their placement within the wound can be more beneficial.
- Mesenchymal stem cells, either from bone marrow or from adipose tissue, offer the promise of healing difficult wounds. The number of cells may be critical. The use of programmed pluripotent cells (i.e., derived from adult fibroblasts) or the use of adult-derived very small embryonic-like stem cells is very promising because of their ability to differentiate into a variety of cells within the wound. Safety studies and clinical trials will be required.
- The "edge effect" refers to stimulation of the ulcer edge to start migrating and resurface the wound. Bioengineered skin often leads to an edge effect.
- Debridement of necrotic tissue and nonviable areas of the wound is essential. In addition to enzymatic and traditional surgical methods, we can now use hydrosurgery to remove nonviable tissue.



Figure 4.1 Arterial ulcers.

In this 68-year-old man, these necrotic and punched-out ulcers developed within a few weeks. He was found to have severe arterial insufficiency by angiography. The necrosis is a valuable clue. For example, venous ulcers would hardly ever show this type of black eschar. Embolization (i.e., cholesterol emboli) could give a similar clinical picture but is generally associated with livedo reticularis or at least a microlivedo pattern. The same considerations apply to cryofibrinogenemia and the antiphospholipid syndrome. Another possibility would be polyarteritis nodosa and other types of vasculitis.



Figure 4.2a Ulcers after surgical arterial reconstruction.

This 52-year-old man with severe claudication and arterial insufficiency underwent an arterial bypass procedure. Possibly, angioplasty and stenting would be other therapeutic considerations. Shortly thereafter, he developed numerous ulcerations, in spite of adequate pulses. Some of these ulcers were near grafted sites.



Figure 4.2b Ulcers after surgical arterial reconstruction/ follow-up.

His blood flow was adequate and good wound care should enable these ulcers to heal. He was treated with hydrocolloid dressings. A few months later, he was completely healed. We have seen many patients develop ulcers after surgical reconstruction, particularly within the surgical excisions. Often, conservative therapy or small and thin autologous grafts can help the situation.



Figure 4.3 Eschar in ulcer bed.

Again, the presence of an eschar argues against venous disease alone as the etiology. There is also no hyperpigmentation, which is common in venous insufficiency. The patient is an 82-year-old woman with widespread atherosclerosis and inoperable peripheral vascular disease. This tibial ulcer was very painful. The pain did not respond to pentoxifylline and to occlusive dressings. She required narcotic analgesics to control the pain. We have found the topical use of anesthetics under occlusion to be helpful. This case also illustrates the fact that, while often effective, occlusive dressings do not always relieve pain. Another therapeutic approach to improve pain here would be the use of autologous grafts (very thin) or bioengineered skin.



Figure 4.4 Scleroderma ulcers.

Patients with systemic sclerosis (scleroderma) commonly develop hand and finger ulcerations. The ulcers on the tips of the fingers, as seen here, are probably due to a fixed vascular narrowing and do not readily respond to vasodilators. Ulcers on the knuckles are usually precipitated and perpetuated by trauma. Moisture-retentive dressings can lead to pain control and painless debridement of these ulcers. One must always ensure that osteomyelitis or septic arthritis is not present. This may require an MRI.



(**A**) (**B**)

Figure 4.5 Arterial ulcers.

This 79-year-old woman presented with multiple nonhealing ulcers. It was unclear whether the etiology was related to her history of CREST (calcinosis, Raynaud's phenomenon, esophageal problems, sclerodactyly, and telangiectasia) syndrome. CREST can be thought of as an exaggerated form of the limited variant of systemic sclerosis (scleroderma), and it's also associated with anticentromere antibodies. The deep, punched out appearance of the ulcers, together with the visible tendon sheath and pain on exposure to air pointed to an arterial component (Panel **A**). Vascular studies confirmed that the ulcers were due to arterial occlusion. In order to restart/reset the healing process, extensive debridement with hydrosurgery was performed. Thereafter, topical negative pressure was applied to stimulate the granulation tissue, and a stent was placed in the left leg. Five weeks later there was definite improvement in the wound bed and tendon (Panel **B**). A plan was made to continue the topical negative pressure until there was substantially more granulation tissue that would allow us to graft the ulcers.

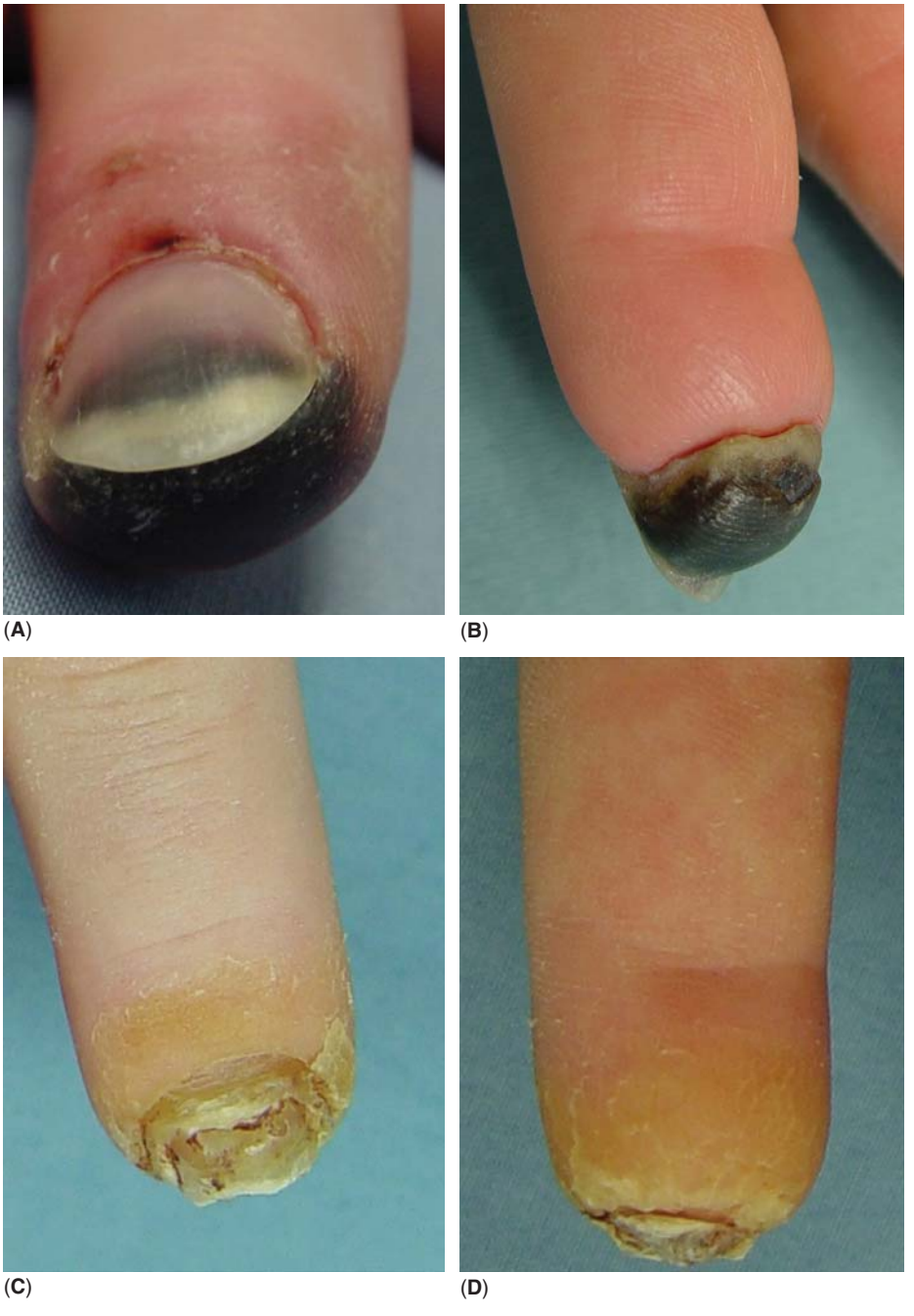


Figure 4.6 Gangrene of the digits.

Given the history of mixed connective tissue disease, repeated and inevitable trauma from daily activities were enough to precipitate ischemia and damage to the distal aspect of the second digit (Panels **A** and **B**). Treatment with pentoxifylline, calcium channel blockers, and sildenafil had been used prior to this presentation. Regardless of measures taken to salvage the finger, the distal phalanx of the index finger could not be saved and the patient underwent autoamputation over the course of several months (Panels **C** and **D**).

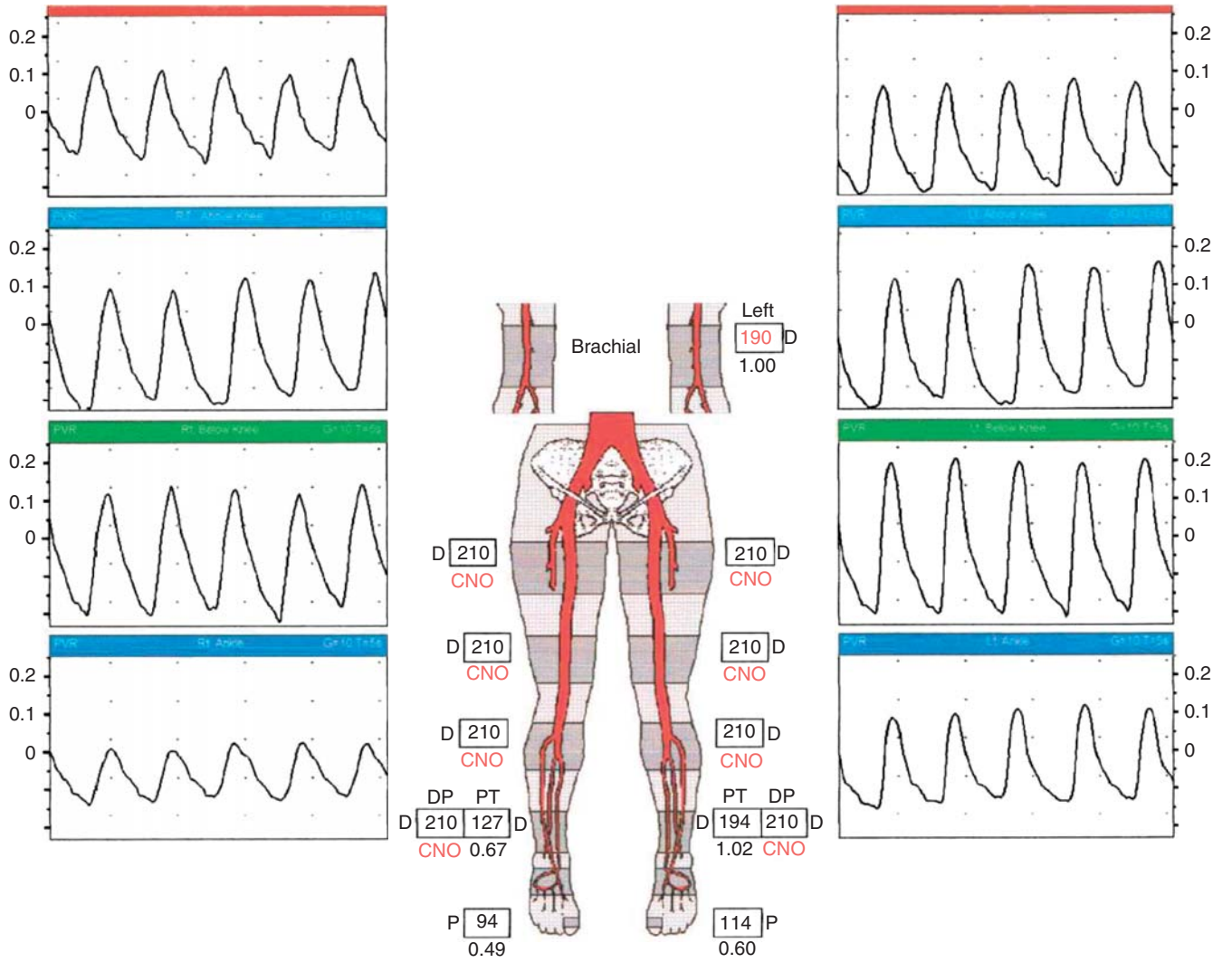


Figure 4.7 Normal pulse volume recordings.

This diagram and set of results are an example of a normal arterial pulse, as shown by pulse volume recordings, and are typical of the evaluations obtained in a vascular laboratory. In this example, one can appreciate a rapid rise in upstroke during systole, a sharp peak at maximum amplitude, and a gradual downstroke following peak amplitude. In some areas one can appreciate the presence of a dichrotic notch.

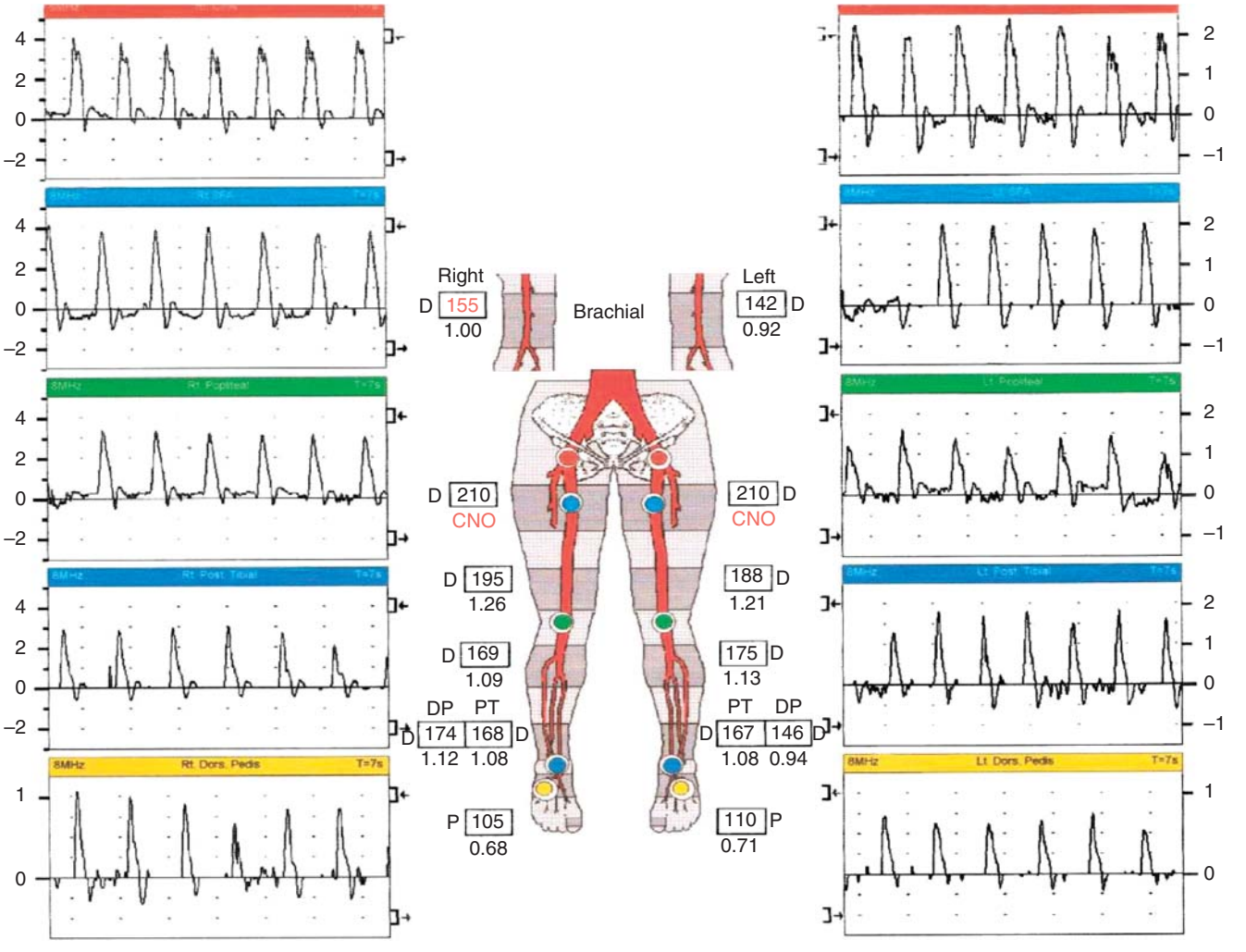


Figure 4.8 Normal arterial Doppler testing.

This is another example of a normal arterial study using arterial Doppler testing. It shows a characteristic tri-phasic flow profile. The tri-phasic flow evaluates and allows for comparison of the arteries in the lower extremities from the abdominal aorta to the tibia and to the ankle. As mentioned before, there is a quick upstroke during systole, followed by a brief reversal of flow in early diastole (dichrotic notch) and a gradual decrease in waveform in later stages of diastole.

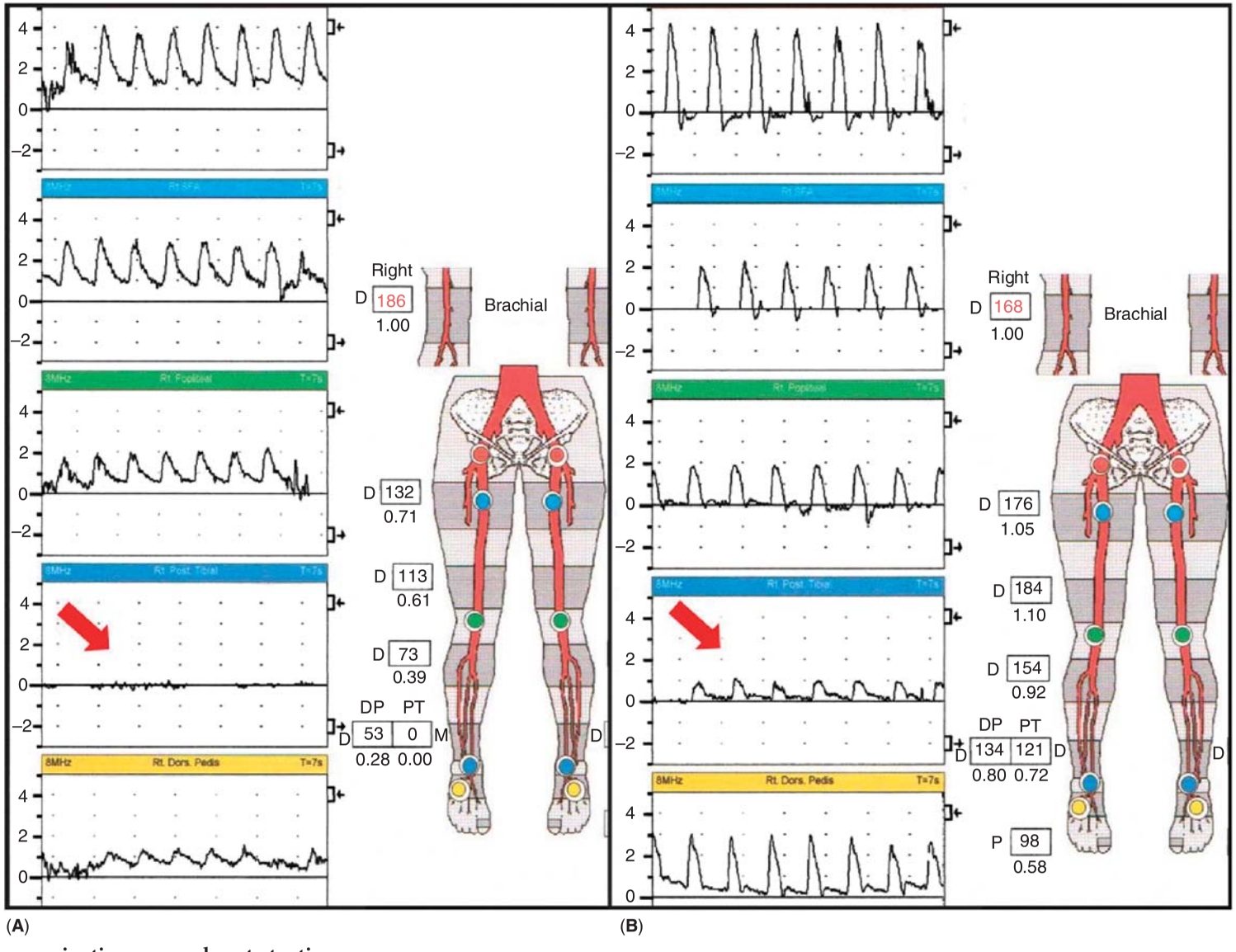


Figure 4.9 Doppler examination pre- and post-stenting.

We suspected arterial obstruction, based on the patient's symptoms (resting pain) and signs on physical exam (ulcers refractory to care, nonpalpable pulses, decreased pulses with the use of a handheld Doppler). Blood flow was estimated with pulse volume studies. The diagrams refer solely to the testing of the right leg. Some of the actual readings are not easily seen, but the main point is to indicate the value of this type of testing. There is an obvious localized occlusion or stenosis in the right leg at the level of the calf. A decrease in pressure between 2 consecutive levels (greater than 30 mmHg) suggests arterial occlusive disease of the artery proximal to the cuff (Panel **A**). After a stent was placed, there was a significant positive change; no longer was the pulse wave close to flat line. A rapid systolic upstroke, gradual downstroke, and dichrotic notch can be better appreciated as well (Panel **B**).

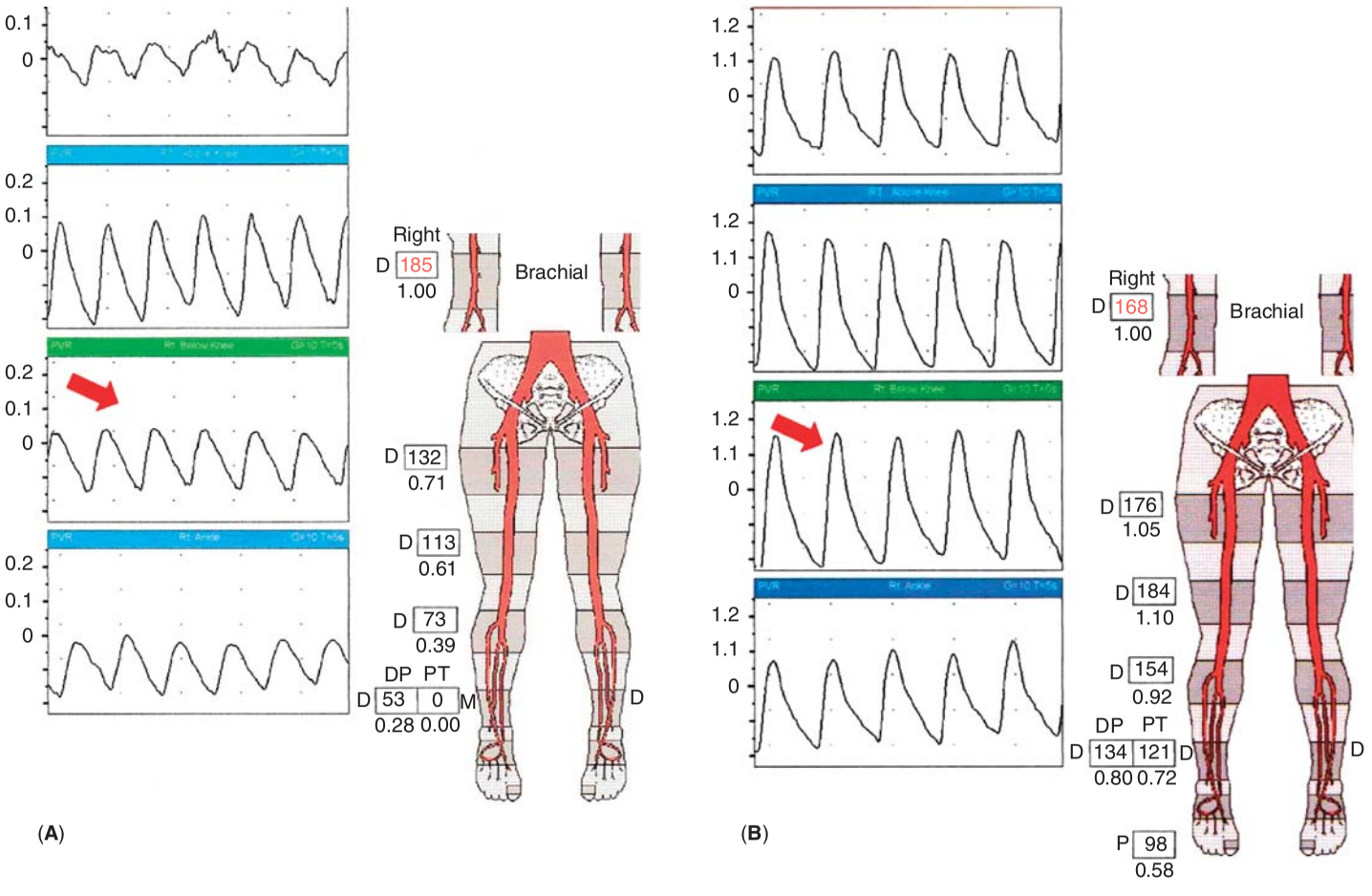


Figure 4.10 Pulse volume recordings pre- and post-stenting.

In this study (Panel **A**) there is evidence of significant arterial occlusion or stenosis. There is a consistent absence of the dichrotic notch. Also, there is flattening of the waveforms with a decreased slope of the ascending and descending segments and a rounding of the systolic peaks, especially in the right leg above the knee. Panel **B** represents pulse volume recordings post-stenting in the same patient. On review of the study, there is evidence of improvement in the waveform.



(A) (B)

Figure 4.11 Successful treatment of arterial ulcers.

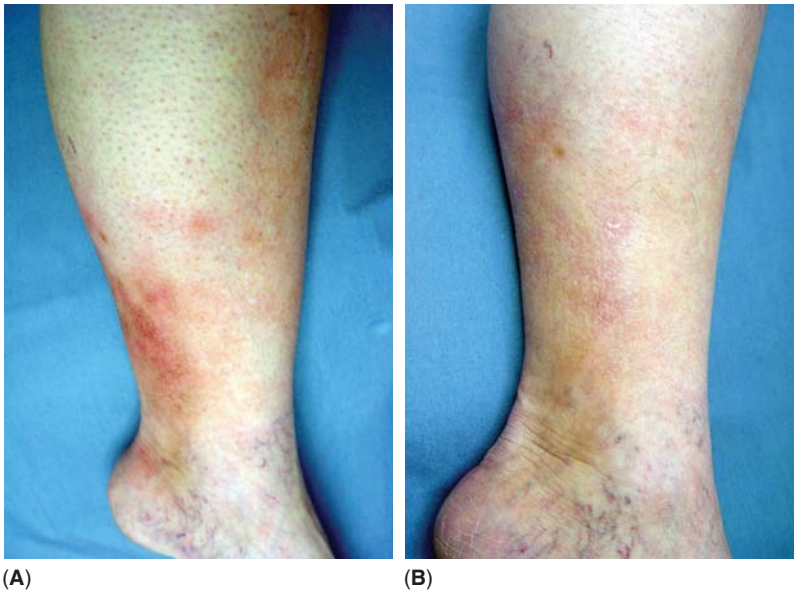
Prior to revascularization (Panel **A**), the skin is shiny, taut, and hairless. These findings are consistent with arterial ulcers, which in this patient were extremely painful. Panel **B** shows complete wound closure after revascularization.



(A) (B) (C) (D)

Figure 4.12 Debridement of an arterial ulcer and stimulation with pinch grafting.

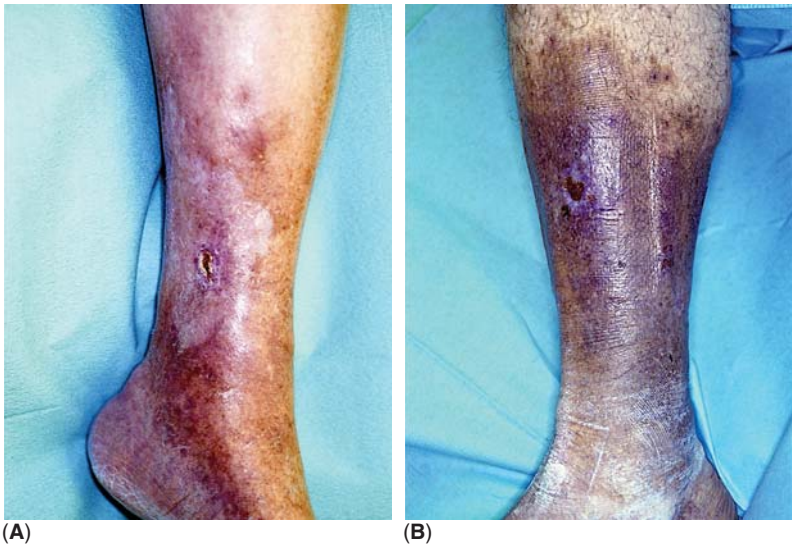
This 70-year-old woman had inoperable arterial insufficiency, diabetes, and this nonhealing ulcer of the big toe (Panel **A**). She also had severe neuropathy and an insensate foot. The ulcer developed after she stepped on a sewing needle that was stuck in her carpet. She repeatedly refused amputation, even when imaging studies suggested the possibility of osteomyelitis. Systemic antibiotics were given intravenously for 6 weeks, with some improvement. Here one sees substantial necrosis of the ulcer bed. There is also a yellow area of exudate and fibrinous material in the center of the wound bed. No sinus tract was present and the underlying bone was not visible. After the application of a lidocaine/prilocaine anesthetic combination followed by infiltration with local lidocaine infiltration, a scalpel was used to remove the necrotic areas (Panel **B**). Right after the debridement in the outpatient setting, a few pinch grafts of skin from her abdomen were applied to the ulcer bed with the goal of activating the wound bed and stimulating healing (Panel **C**). The photograph in Panel **C** was taken a week after pinch grafting. The applied skin has not taken and has mostly fallen off. However, the "pharmacologic" action of the autologous grafts may have stimulated ulcer healing (Panel **D**). This approach is simple, cost-effective, and worth trying in difficult situations like this one.



(**A**) (**B**)

Figure 4.13 Acute lipodermatosclerosis treated with danazol.

Lipodermatosclerosis (LDS) is for the most part secondary to venous insufficiency. The term was coined by British vascular surgeons Browse and Burnand, at St. Thomas Hospital in London. With that term, they described the indurated skin of the lower extremities in patients with long-standing venous disease. One of us (VF) noted that there is a painful acute form of LDS, which may have been described in the past with a number of names, including sclerosing panniculitis. In many cases, we found that it responded dramatically to anabolic steroids, particularly stanazolol. This patient developed acute LDS with excruciatingly painful, tender, red patches on the calf (Panel **A**). We could not use stanozolol, since it is no longer available but, based on our anabolic steroid experience, we treated her with danazol; she improved dramatically in the next 3 months (Panel **B**). As with stanazolol, one needs to follow liver function tests in patients on danazol. Typically, enzymes will increase to almost double but will return to normal after the therapy has been discontinued. Copyrighted, V. Falanga, 2010.



(**A**) (**B**)

Figure 4.14 Examples of acute (early) lipodermatosclerosis.

Here we have two examples of patients with acute lipodermatosclerosis (LDS). The 58-year-old woman in Panel **A** had persistent pain in her leg for over a year. Typically, some clinicians thought she might have localized scleroderma (morphea). Because of recurrent bouts of worsening pain associated with redness, she was hospitalized unnecessarily multiple times for treatment of presumed cellulitis. This is also quite a typical error in the management of these patients. Instead, these patients have acute (or early) LDS, which is associated with venous insufficiency. We have achieved successful treatment with anabolic steroids. Because stanazolol is no longer available, we now use danazol. Another option is the combined use of pentoxifylline and colchicine. In our experience, most of these patients cannot use graded stockings because of the pain and tenderness. The ulcer in the middle of the fibrotic plaque was due to a punch biopsy (Panel **A**). In these patients, it is preferable to perform excisional biopsies at the periphery of the indurated areas and close the biopsy defect primarily. The 55-year-old patient in Panel **B** ran into the same problem with a biopsy-induced chronic wound before she was referred to us. The success of anabolic steroids may be due to their fibrinolytic as well as immunologic properties.



Figure 4.15 Chronic lipodermatosclerosis with ulcer.

This patient in her 60s has had venous insufficiency for many years. The fibrotic component involving most of the medial aspect of the leg is generally painless and is not tender. It represents the chronic form of lipodermatosclerosis (LDS). Ulcers develop within LDS, recur within LDS, and their failure to heal correlates with the severity of LDS. Trauma is often a precipitating event in causing the ulcers.



Figure 4.16 Healed ulcer and chronic lipodermatosclerosis.

There are several presentations of chronic lipodermatosclerosis (LDS). The hypopigmented area on the medial aspect of the lower leg is an ulcer that has healed recently. Interestingly, it takes several months or even years for the pigment to return to the previously ulcerated site. The surrounding hyperpigmentation and the hardness of the skin are classic for chronic LDS. There is usually little pain at this point, although some discomfort can be felt upon prolonged walking. This 64-year-old man needs to wear graded compression stockings for the rest of his life, so as to avoid recurrence of the ulcer.



Figure 4.17 Chronic lipodermatosclerosis and dermatitis.

In colder climates, the clinical picture of venous disease can be somewhat different, in that the involved skin is dry and scaly. This 82-year-old man had a very distinctive scaly plaque on his shin, which was not painful or tender. These plaques were present bilaterally, and we also thought of the possibility of pretibial myxedema. However, a biopsy showed no evidence of increased hyaluronic acid (as in pretibial myxedema) and there were typical histological findings of venous disease (i.e., increased tortuous vessels, hemosiderin deposition).



Figure 4.18 Lipodermatosclerosis and atrophie blanche.

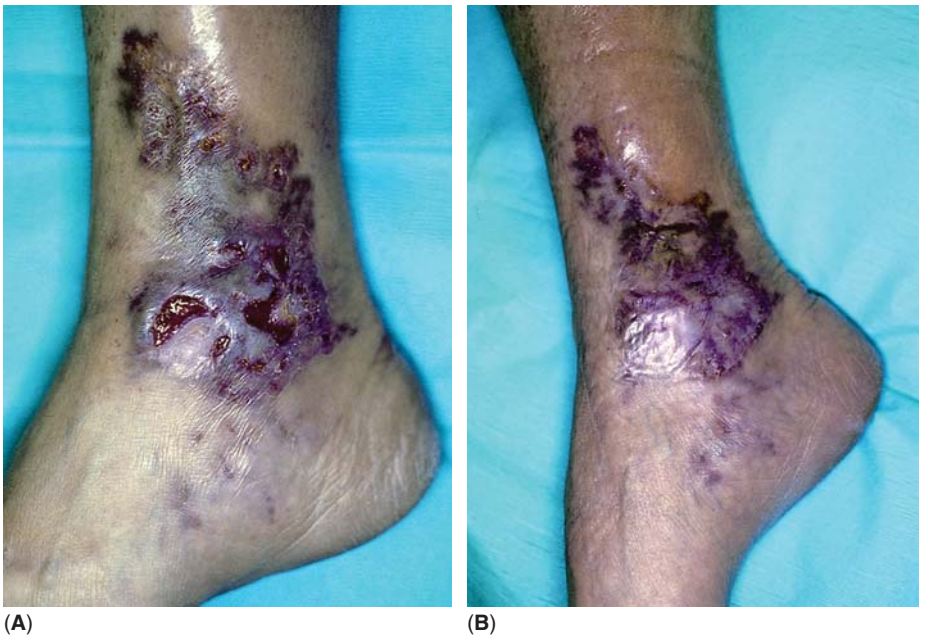
The separation between the acute and chronic forms or stages of lipodermatosclerosis (LDS) can be somewhat artificial. There are patients who have a more sub-acute course, such as this patient. She has areas of induration (around the small ulcer), as well as other features of venous disease; these have been present for years. Note also the white atrophic lesions studded with prominent small blood vessels (atrophie blanche). Atrophie blanche, in our opinion, is not a defined entity with a clearcut etiology. It can be seen with venous, arterial, vasculitic diseases, and cryoproteinemia. It has been stated that patients with venous insufficiency go through a clinical course of either LDS or atrophie blanche (without skin induration). This may be true to a certain extent, but in our experience some patients have both conditions.



(**A**) (**B**)

Figure 4.19 Chronic lipodermatosclerosis.

The patient in Panel **A** has venous insufficiency, left lower extremity ulcers that have healed, and a history of left lower extremity deep vein thrombosis. Note the clearly demarcated areas of violaceous to pink and brown plaques with left lower extremity edema. The sharp pigment demarcation speaks for the chronicity of the condition. In order to prevent any breakdown of the skin, graded compression stockings will be needed indefinitely and the patient will need to be followed on a routine basis. As stated, chronic lipodermatosclerosis (LDS) often has this sharply demarcated border. A useful clinical step for the clinician is to palpate the skin several centimeters above the superior edge of the plaque. A characteristic "cliff," with a sharp separation between the softer skin above and the hard skin below, will be felt. The patient in Panel **B** has LDS and a dermatitis. We are generally reluctant to use the term "stasis" dermatitis, because studies have shown that there is actually increased venous flow in such patients. However, we are occasionally forced to use that term because of its widespread recognition.



(**A**) (**B**)

Figure 4.20 An unusual presentation of lipodermatosclerosis and ulcers.

We mentioned earlier that lipodermatosclerosis (LDS) can have a spectrum of presentations. This case was highly unusual. This 34-year-old woman sustained an injury at work and developed painful and highly inflammatory lesions with ulcerations (Panel **A**). The history of trauma did not fit with the clinical observations, and we thought she might have a vasculitis or small vessel obstructive disease from cryoproteins. However, her laboratory studies were normal and several biopsies from the inflamed and ulcerated areas were mostly consistent with venous disease and LDS. Although initially treated with anabolic steroids, this patient did not respond to this therapy alone, even at high doses of stanozolol (one may use danazol now because stanozolol is no longer available). Her ulcers, however, did heal with foam dressings and compression therapy over a period of about 4 months (Panel **B**). Another therapeutic option here is colchicine and pentoxifylline at high doses (800 mg 3 times a day).



Figure 4.21 A typical venous ulcer.

Most clinicians are used to this more classic presentation of a venous ulcer. In this 62-year-old man with proven venous insufficiency (by color duplex scanning) the skin is hyperpigmented and the ulcer has the typical irregular borders. This ulcer has been present for over 10 years by history, but patients often forget that it may have healed on occasion. Note how the edges are steep, with a sharp cutoff between the edges and the ulcer bed. We mention that because these ulcers are not in a "healing mode." When the ulcer begins to heal, the edges become flattened and the epithelium begins to migrate toward the center. Wound bed preparation, when properly accomplished, will result in epithelial migration from the margins.



Figure 4.22 Another typical venous ulcer.

The surrounding hyperpigmentation is what one expects in venous ulcers. Although rather small, this ulcer was extremely painful and was not responding to treatment with compression bandages, which caused additional tenderness. The pain may be due to the proximity of the skin breakdown to the periosteum over the malleolus. Ulcers such as this, near or below the malleoli, are more resistant to therapy with compression bandages. It might very well be that compression, as it is generally applied, does not take into account the concave nature of this location, which then is not properly compressed. Therefore, it is important to use extra dressings or wool wraps to make this area more cylindrical before applying compression.



Figure 4.23 Venous insufficiency and systemic lupus erythematosus.

This patient began having leg ulcers at age 24, at about the time she was diagnosed as having systemic lupus erythematosus. Now, almost twenty years later, she continues to have recurrent ulcerations. Clinically, some of the features (i.e., hyperpigmentation, irregular ulcers, and hard skin) are suggestive of venous ulcers. However, many of the ulcers are small and punched out and resemble ulcerations due to vasculitis or the antiphospholipid syndrome. She has venous insufficiency (both superficial and deep veins) and a biopsy of the ulcers showed changes most consistent with venous disease (i.e., tortuous blood vessels, hemosiderin deposition, etc.). She had no detectable cryoproteins (cryofibrinogen and cryoglobulin) or anticardiolipin antibodies, and eventually improved with compression bandages. This case illustrates the fact that it is difficult sometimes to have a definite diagnosis, and one may need to rely on the response to treatment. Another point is that the ulcers may look factitial because of their linear configuration (like from scratching). However, we also see linear configuration of wounds in patients with collagen vascular diseases.



Figure 4.24 An unusual venous ulcer.

Along the lines of atypical venous ulcers, this one too has unusual features. There is no definite hyperpigmentation but the ulcer is located in an area of intense lipodermatosclerosis (LDS). The shape of the ulcer is also unusual, because it is narrow and long. The undulating edges point to the possibility of a rheumatoid ulcer, but she did not have rheumatoid arthritis or other connective tissue diseases. She did not have plasma or serum cryoproteins (i.e., cryoglobulin and cryofibrinogen) and a biopsy did not show vasculitis. She improved dramatically with compression therapy. The edges here are seen to be in a "healing mode" in that they are flat and flush with the ulcer bed. Many of the translucent areas in the ulcer bed represent new epithelium.



Figure 4.25 An ulcer with purple edges and venous insufficiency.

This 59-year-old woman has venous insufficiency and lipodermatosclerosis (LDS) involving the lower leg. The ulcer is on the medial aspect of the leg. Taken together, these clinical findings suggest that the ulcer is venous in etiology. Although she eventually responded to hydrocolloid dressings and compression bandages, we could not be absolutely certain that this was a venous ulcer. The edges are purple, like in pyoderma gangrenosum, and the inferior border is necrotic, like we see in vasculitis, cryoproteinemias, or the antiphospholipid syndrome. However, laboratory testing could not confirm any of these possibilities, and the biopsy was more consistent with venous disease.

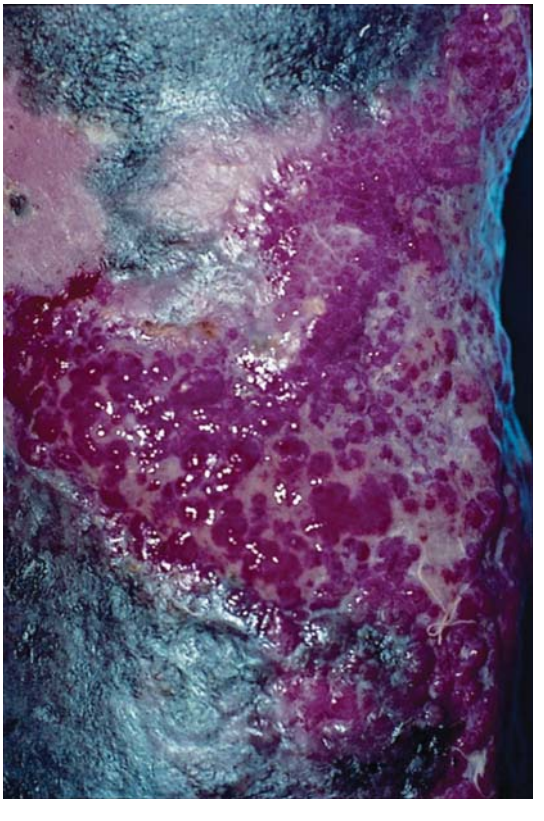


Figure 4.26 A venous ulcer and exuberant granulation tissue.

There is overgrowth of granulation tissue that developed after the use of an occlusive dressing. We do use occlusive (or moisture-retentive) dressings to create a moist wound environment and to promote granulation tissue, but we would regard this extent of granulation tissue as undesirable. Some believe that bacterial overgrowth may be responsible for exuberant granulation tissue. However, it should be noted that the superior edge is in a "healing mode," because it is flat and flush with the ulcer bed, while the lower edge shows absence of healing. This case also illustrates the fact that different areas of ulcers can be in different stages of healing. In addition to compresssion, this patient was treated with a foam dressing, which creates a less moist environment.



Figure 4.27 A venous ulcer in different stages of healing.

There are several points for discussion here. First, the upper and midportion of the ulcer are healing well and the edge is flat (in a "healing mode"). In fact, the hypopigmented skin represents an area that has recently re-epithelialized. The inferior and more dependent part of the ulcer shows poor granulation tissue and a steeper edge (not in a "healing mode"). Although the tendency has been to dress wounds with one type of dressing, one can see here that the needs are different in these two areas of ulceration. One could use a protective foam dressing in the upper part and a hydrocolloid dressing to stimulate debridement and better granulation tissue in the lower part of the ulcer.



Figure 4.28 Venous ulcer resistant to treatment with compression.

Some ulcers, like this one, are small but do not heal readily with compression bandages. This 82-year-old woman has not responded to elastic or short-stretch compression bandages. A common denominator for these small nonhealing ulcers is that they are present near or below the malleolus. This site is difficult to wrap in a way that achieves proper compression. The concave areas need to be "filled" with other dressing material before compression is applied.

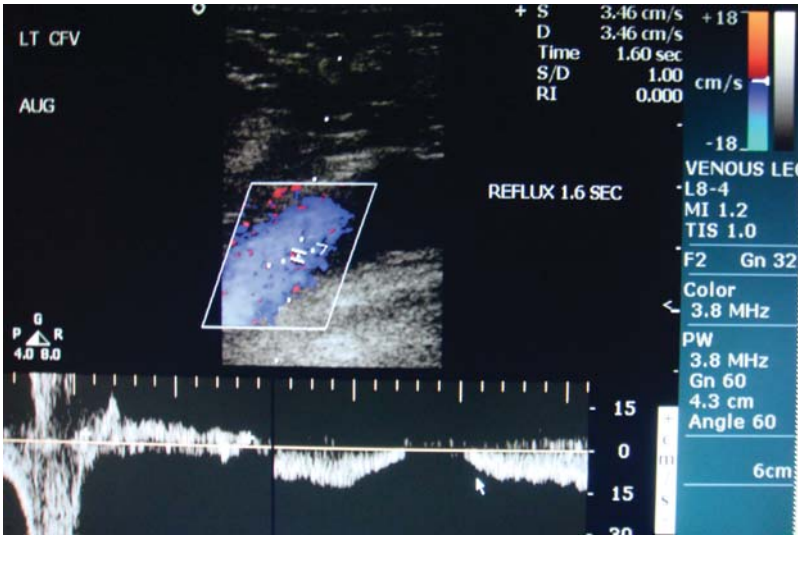


Figure 4.29 Venous testing.

This is an example of the image produced in duplex ultrasonography. The color-flow duplex imaging uses Doppler information to color code the sonogram, thus enabling us to assess venous flow relative to the transducer. Using this device, venous flow can be mapped out and reflux can be measured. Reflux is defined as an outward flow of blood from the deep to the superficial venous system. Clinically relevant reflux varies from 0.3 to 1.0 sec, with most authors considering >0.5 sec as evidence for incompetence. In addition, the color duplex ultrasound is also a useful screening tool to assess deep venous thrombosis. Thus, it is important for the clinician to specify the purpose for the examination in order to obtain relevant results.



(**A**)



(**B**)

Figure 4.30 Biopsy of the wound edge.

In order to gain a better insight into the etiology of an ulcer, a tissue biopsy is taken (Panels **A** and **B**). Our concern for taking a biopsy from the wound bed is often minimal, as research has shown that healing is not adversely affected by this procedure. We do not suture these biopsy sites.



(**A**)



(**B**)

Figure 4.31 Punch biopsy of the wound bed.

This patient had a nonhealing ulcer on the leg. In cases where there has not been any improvement after optimal treatment, a wound biopsy is necessary to rule out a malignancy. Here is an example of a punch biopsy encompassing both the wound bed and the ulcer's margin (Panels **A** and **B**).



(**A**)



(**B**)

Figure 4.32 Multiple biopsies needed to avoid sampling error.

This patient had a large leg ulcer for about 2 months. Multiple biopsies of the wound bed were done to check for malignancies and to exclude an unusual infection (Panels A and B). Sometimes multiple biopsies are necessary to minimize sampling errors in biopsying a large wound. The histology in this case did not show any malignancy. The patient improved with intravenous antibiotics and compression therapy.



Figure 4.33a A nonhealing ulcer biopsied to rule out malignancy.

A 66-year-old man with long-standing leg ulcers and documented venous insufficiency did not improve with compression. Biopsies of the ulcer bed and edges were done to exclude malignancies. Punch biopsies of the ulcer bed were also done for quantitative bacterial cultures. The patient had methicillin-resistant *Staphylococcus aureus* and healed with a combination of intravenous antibiotics and compression.

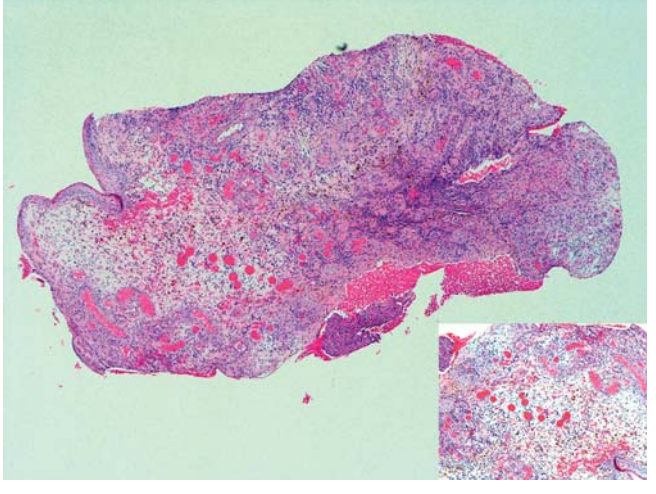


Figure 4.33b A nonhealing ulcer biopsied to rule out malignancy/results of biopsy.

Punch biopsy of the ulcer showed numerous small blood vessels (note red areas) with an inflammatory infiltrate characteristic of granulation tissue. No evidence of a malignancy was present. Gram stains of the histological section did not detect bacteria, in spite of the positive cultures for MRSA.

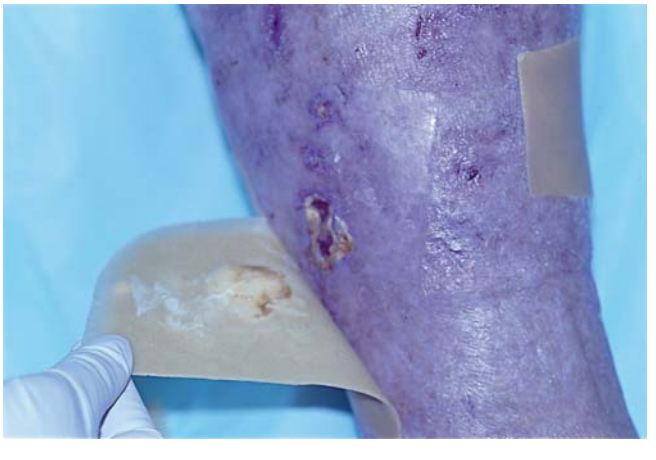


Figure 4.34 Debridement with occlusive dressings.

This is now a well-established property of occlusive dressings. In many cases, occlusive dressings are able to stimulate painless debridement of the wounds. Here hydrocolloid dressings are being used to cover ulcers that were previously necrotic. The hydrocolloid "melts" into the wound and often produces a brown exudate that may be mistaken for infection.



Figure 4.35 A sickle cell ulcer.

This 35-year-old man with sickle cell hemoglobinopathy has had persistent and excruciatingly painful ulceration on the medial aspect of his leg. The surrounding hyperpigmentation suggests venous disease, and in fact the etiology of these ulcers is probably venous insufficiency and arteriolar disease. Compared to pure venous ulcers, these are more painful, more resistant to treatment with compression and autologous grafting, and can be deeper. In some very resistant cases, we have combined split-thickness autologous grafting with hyperbaric oxygen and transfusion, with considerable success. Panel (**A**) Baseline ulcer with a poor wound bed and requiring debridement. Panel (**B**) Use of lidocaine/prilocaine cream to achieve anesthesia for debridement. Panels (**C** and **D**) Debridement performed with a curette. Panels (**E** and **F**) Evidence of progressive healing, as shown by the new hypopigmented skin at the margins of the wound.

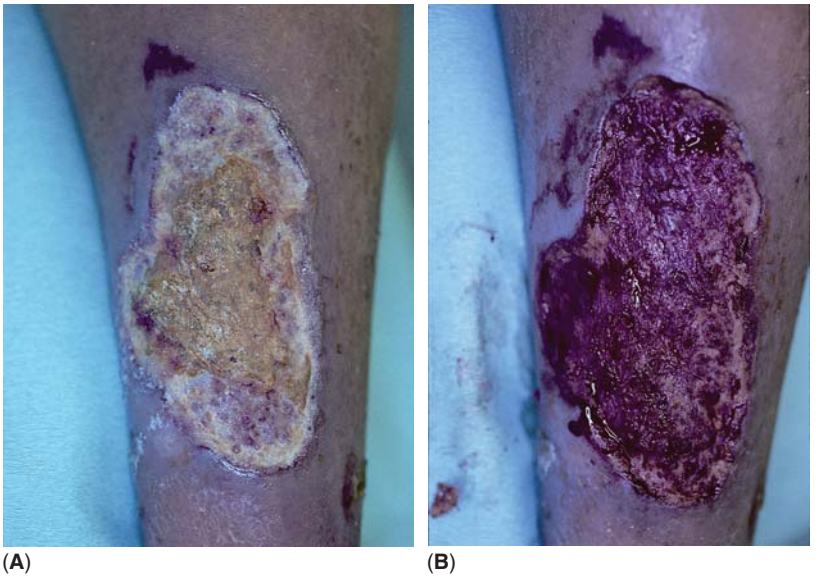


Figure 4.36 Failed split-thickness autologous graft.

This 68-year-old woman has an ulcer with an undulating (scalloped) edge, which is consistent with ulcers occurring with rheumatoid arthritis. She has failed many therapies, including methotrexate. Compression therapy, in the hope that this may represent an unusual venous ulcer, also did not help. Histology from the ulcer's edge was nonspecific but failed to show a vasculitis. Vascular studies showed venous insufficiency but good arterial flow. She was finally grafted (Panel **A**) but, as can be seen in the photographs, the graft did not take and was surgically debrided (Panel **B**). These ulcers in patients with rheumatoid arthritis are extremely challenging. The next step would be the repeated applications of bioengineered skin to stimulate the wound bed. We have also considered experimental therapy with topically applied autologous bone marrow-derived cultured stem cells.



Figure 4.37 Dermatitis and infection.

This is a common combination in patients with venous ulcers, and it is necessary to address both conditions. The wound is debrided and systemic antibiotics are administered. We prefer to treat the dermatitis by avoiding all topical agents, including topical steroids, which could have ingredients that make the dermatitis worse. Gel dressings can be very helpful and soothing, but one must watch out for the development of infection/colonization with *Pseudomonas* organisms with these types of dressings. On occasion, after treating the infection, we have used systemic corticosteroids for 2–3 weeks to get the dermatitis under control.



Figure 4.38 Dermatitis and infection/another case.

Here, too, there is cellulitis as well as dermatitis. The dermatitis is in the foot, mainly in the inferior portion, a feature we have often associated with retention of fluid by the primary dressing. The reasons for this remain unclear. When we have collected wound fluid from an ulcer and applied it to the patient's own normal forearm skin (as in a patch test), we have been unable to elicit a reaction at that site. The granulation tissue here looks exuberant and has areas of necrosis; the ulcer bed is heavily colonized by bacteria.



Figure 4.39 A venous ulcer and compression bandages.

This photograph shows a self-adherent elastic bandage in place from the base of the toes to just below the knee. Underneath is a nonelastic zinc-impregnated short-stretch bandage (Unna boot) (Panel **A**). This combination has become popular in the United States, while there is a difference of opinion among European countries about the value of elastic versus short stretch bandages. When ulcers have healed and patients do not yet have elastic stockings, it is still necessary to provide compression to avoid ulcer recurrence. In some cases, we simply continue the compression bandages until stockings are obtained. In other cases (Panel **B**), it may be possible to use the shaped support bandages shown here. These ready-to-wear graduated bandages provide less pressure but can be useful in the management of healed patients. An alternative method to achieve compression, especially when the bandage tends to slip down, is the use of the device shown in Panel **C**. Individual straps are applied from the toes to below the knee. There is a backstrip behind the leg to which the individual units attach by means of a velcro material.

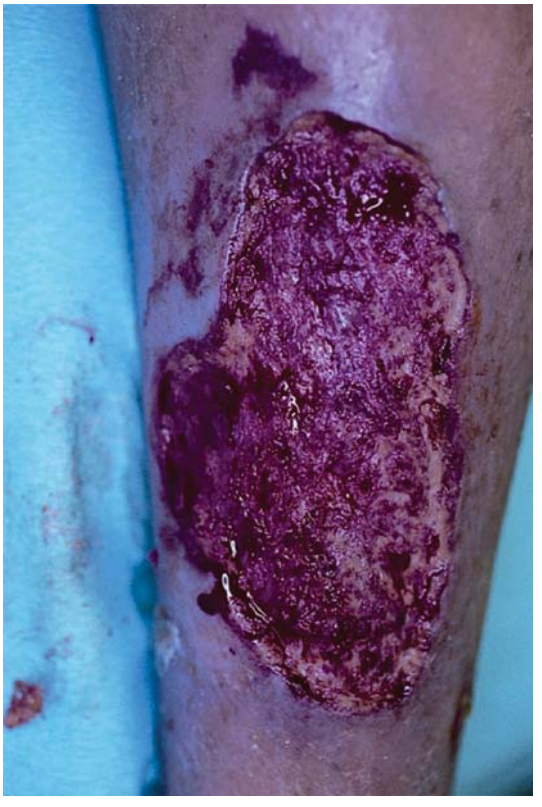


Figure 4.40 A failed split-thickness autologous graft followed by initiation of healing.

This photograph was taken many weeks after the failed graft and shows clear evidence of re-epithelialization. Debridement may have also stimulated healing. It is tempting to think that, even though it failed, the graft may have stimulated the healing process. We have long recognized that grafts act as both tissue replacement and as "pharmacologic" agents capable of stimulating healing.



Figure 4.41 A meshed split-thickness autologous graft.

Of course, a more elegant and accepted way to graft ulcers is with meshed grafts. This large venous ulcer was grafted with an autologous split-thickness graft meshed at a ratio of 1.5 to 1. The photograph was taken one week after the surgical procedure. Most of the graft seems to have taken and to be viable. Meshing is desirable when grafting these chronic wounds, or else the wound fluid accumulating beneath the graft will lift it off. We feel that grafting is an underutilized procedure for the management of nonhealing or large ulcers. Although recurrence of the ulcer is not uncommon, the procedure provides patients with an ulcer-free interval of time and a better quality of life.



Figure 4.42a Living bi-layered bioengineered skin construct to stimulate healing.

This photograph shows the construct in place. In this case, it was not meshed, but small slits (0.5–1.0 cm in length; fenestration) were made in it with a scalpel before application to allow the escape of wound fluid and prevent uplifting and rapid loss of the construct.

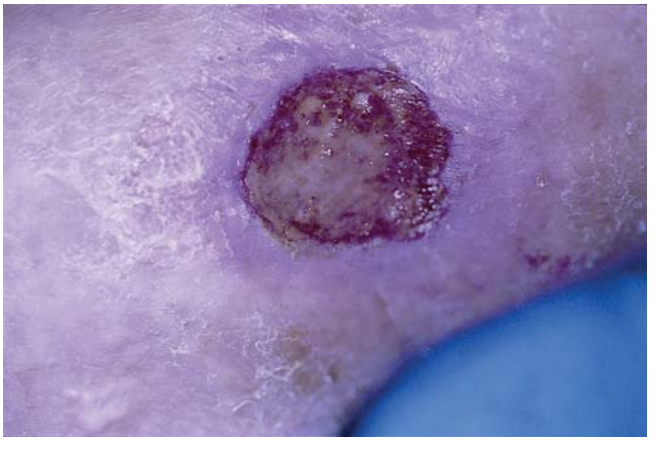


Figure 4.42b Living bi-layered bioengineered skin construct to stimulate healing/follow-up.

In some cases, the construct can still be visualized after a week or two. In other cases, like this one, the construct is not visible but is beginning to stimulate the wound bed. The yellow material represents the hydrated remnant of the construct and, in some cases, can be mistaken for necrotic and/or infected tissue. Clinicians need to be aware of this phenomenon and must not debride the wound at this point.



Figure 4.43 Progression of healing with compression.

This 55-year-old woman presented with a chronic venous leg ulcer of more than 2 years in duration. There is noticeable swelling and red-to-purple skin around the ankle. We felt that she had a severe contact dermatitis (Panel **A**). It is important to rule out infection in this case, as this is a common complication. Topical agents were eliminated, and dressings consisted of a foam pad wrapped with cotton gauze and a compression wrap. No cause for the dermatitis was found by patch testing with over 100 allergens, including dressing materials, but the patient healed with a 4-layer bandaging system over a period of 6 months (Panels **B** and **C**). The dermatitis persisted and this example shows that complete wound closure can still take place with this complication.

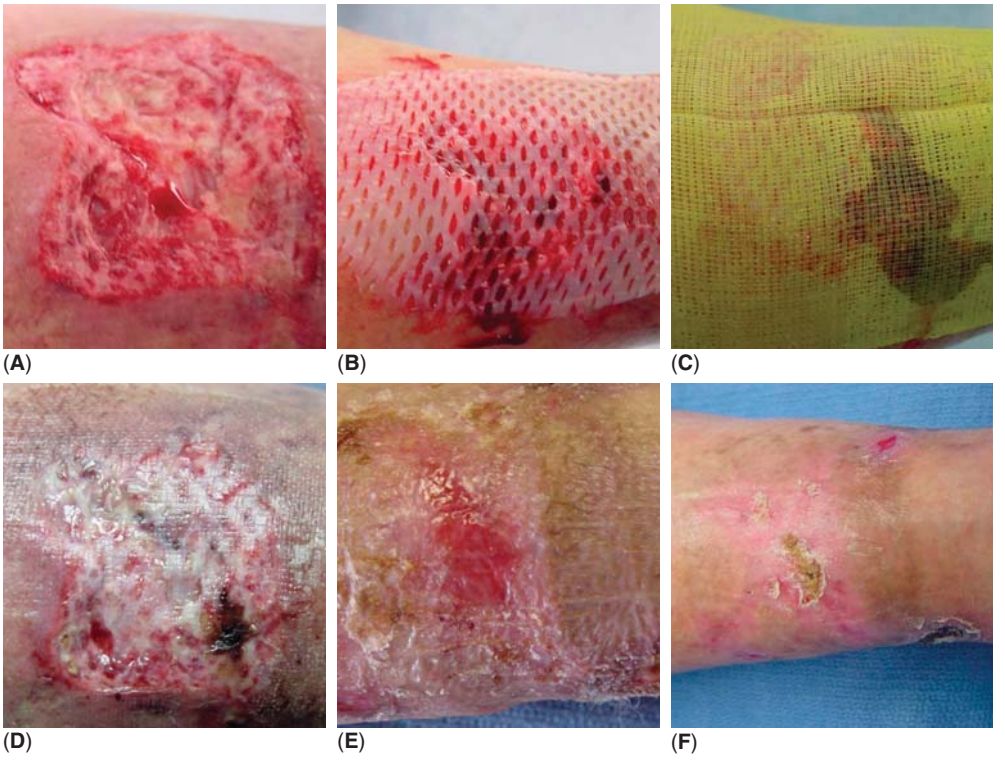


Figure 4.44 Bioengineered skin treatment and sequence of healing.

This series of photographs illustrates the treatment of a venous ulcer with a bi-layered bioengineered skin construct (Panels **A** through **F**). The ulcer was debrided (Panel **A**), treated with the meshed construct (Panel **B**), and dressed with a petrolatum- and bismuth-impregnated gauze (Panel **C**). This treatment resulted in complete closure after 2 months (Panels **D** and **E**) and remained healed after 4 months (Panel **F**).

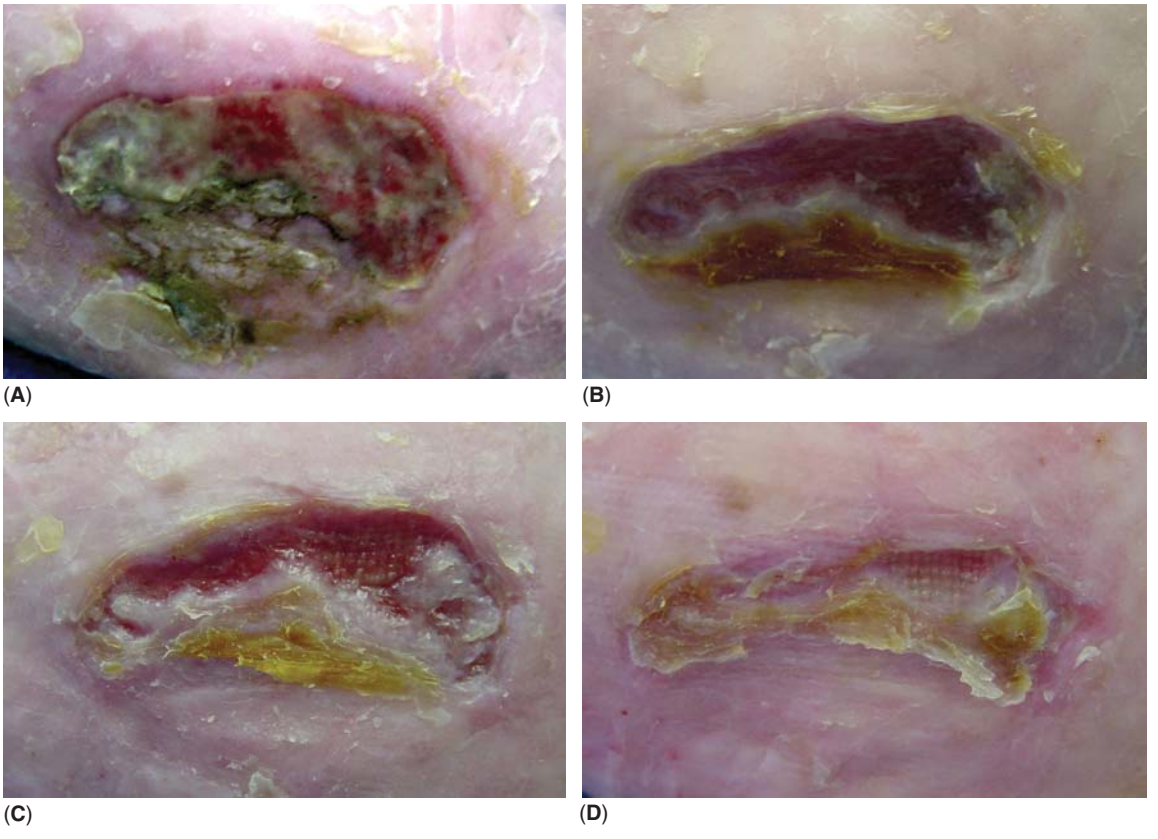


Figure 4.45 Development of a venous ulcer parallel to the fibrotic tissue component.

In the setting of lipodermatosclerosis, venous ulcers can commonly develop along the parallel axis of fibrosis. Compression can help. In this particular sequence of an ulcer near the medial malleolus, the wound margins were steep (Panels **A–C**), suggesting poor epidermal migration. The ulcer finally began to heal with a combination of cadexomer iodine and elastic compression (Panel **D**).



Figure 4.46 Contact dermatitis and venous disease.

This patient was being treated with a zinc-impregnated compression bandage and developed a bullous eruption consistent with contact dermatitis. This occurrence would lead one to use elastic bandages (preferably latex-free) instead of wraps that contain topical agents. It is important to realize that patients with venous disease have a high potential for contact sensitization. Patch testing can be a very important procedure. We have found useful to establish a dedicated clinic to patch test patients to over 100 allergens, including wound dressings.



Figure 4.47 Dermatitis and swollen toes.

Multilayered bandages are a good way to deliver high levels of compression in patients with venous insufficiency and ulcers. However, because of their high resting pressures, elastic bandages should be used cautiously in patients with concomitant lymphatic disease. This 75-year-old man with a venous ulcer and lymphatic disease developed a substantial dermatitis and swollen toes after repeated application of high elastic compression. We have observed this problem in a few patients. In some cases, it has not been possible to apply any type of elastic compression because of this complication. Short stretch bandages and pneumatic pumps are a useful alternative.



Figure 4.48 Contact dermatitis in venous disease.

As mentioned earlier, patients with venous disease are particularly susceptible to contact dermatitis. Clinicians have always thought that "stasis" dermatitis is an intrinsic component of venous disease. However, we and others have come to the conclusion that "stasis" dermatitis may not be a real entity but the result of sensitization to topical agents, particularly in cold climates that may require the use of emollients. Once patients stop using the topical allergen, it may take months before the dermatitis improves. Unfortunately and almost invariably, patients or caregivers end up using emollients and other topical agents again in between visits even one application of potential allergens perpetuates the problem and leads to confusion during management.



(**A**)



(**B**)

Figure 4.49 Allergic contact dermatitis to mercaptobenzathiol (rubber accelerator).

This is an elderly woman with severe venous insufficiency, treated with multilayered compression bandages. The swelling of her legs was improving. However, she developed this severe dermatitis of both legs in areas where the compression bandages were applied, but which could not be easily separated from a case of cellulitis (Panel **A**). Patch tests with multiple chemicals applied to her back showed a positive reaction to mecaptobenzathiol at 48 hours (Panel **B**). This chemical is a rubber accelerator that is commonly used in many products. As a result of this allergic component, the application of compression bandages became very difficult. One could opt for short stretch bandages not containing the rubber accelerator.



(**A**) (**B**)

Figure 4.50 Allergic contact dermatitis.

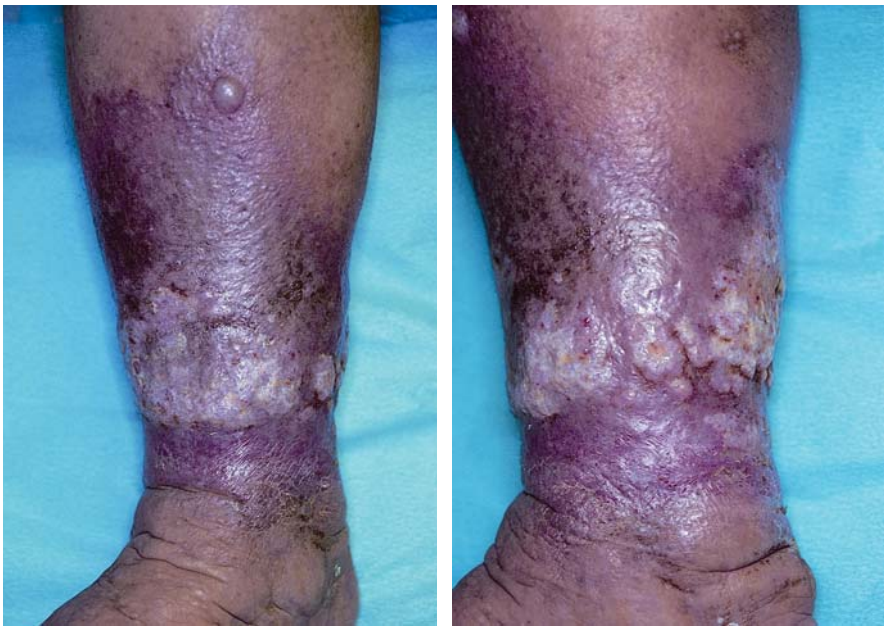
This 76–year-old woman with a chronic venous ulcer had an allergic contact dermatitis (Panels **A** and **B**) to her foam dressing (proven by patch testing), which was quickly discontinued. She had other allergies to neomycin, gentamycin, and wood tar mix. The patient was treated with systemic corticosteroids, which were tapered over 3–4 weeks. However, there was not much improvement until we used a regimen of clobetasol ointment and a nonadherent dressing with compression. Note the dramatic ulcer size increase occurring during this complication.



(**A**) (**B**)

Figure 4.51 Venous and lymphatic disease.

This ulcer is caused by mixed venous and lymphatic etiology, which is a common combination (Panels **A** and **B**). The clinical features suggesting lymphatic disease are the presence of these verrucous changes and the fact that the leg is more cylindrical in shape and does not have the "inverted bowling pin" or "inverted champagne bottle" appearance that is so common in venous disease and lipodermatosclerosis.



(A) (B)

Figure 4.52 Lymphedema and erysipelas.

Erysipelas and cellulitis are very common complications of lymphatic obstruction. As in this 62-year-old man, leg infection is often recurrent and severe (Panels **A** and **B**). In some cases, "chronic" low-grade cellulitis develops. The lymphatic system can become so damaged that bacteria cannot be properly cleared. The presence of chronic biofilms is possible, but not proven yet, as playing a major pathogenic role. Chronic systemic antibiotics have been used to prevent recurrences of cellulitis and erysipelas (lymphangitis). The photograph in Panel **A** also shows a blister (bulla) superiorly and a large anterior area of early breakdown. Leg elevation and systemic antibiotics are needed at this point.



(A) (B)

Figure 4.53 Injury and a lymphatic ulcer.

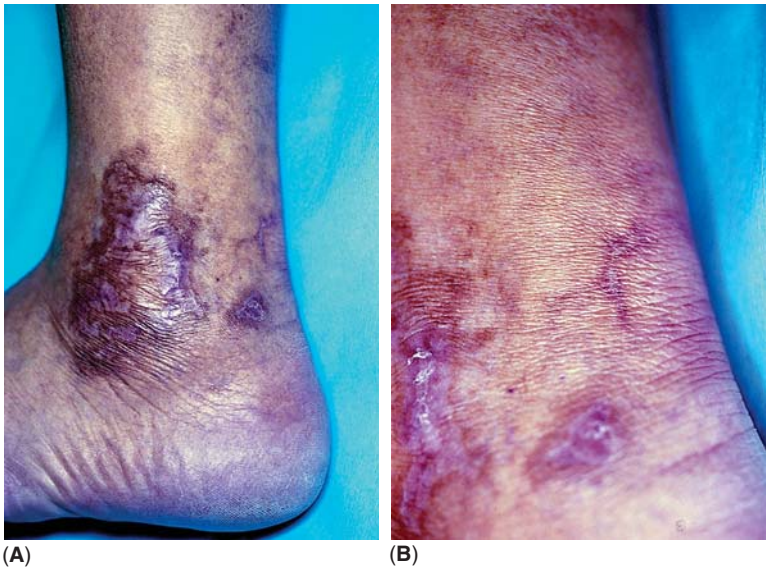
Some cases of lymphatic obstruction start with trauma. In this case, an automobile accident caused a fracture of the tibia and subsequent ulceration and chronic swelling of the anterior portion of the leg. The redness around the ulcer represents an infection. The ulcer bed shows a yellow exudate (Panel **A**). He improved while hospitalized and receiving systemic antibiotics. We think that the improvement patients get from being hospitalized is more than just due to the use of intravenous antibiotics. Hospitalization allows patients to rest and keep their legs elevated, and places the clinician in charge of the situation. For example, the use of topical agents can then be better controlled. The infection was treated and the patient was followed in the outpatient setting. Foam dressings were used to provide absorbancy and protection for the ulcer. The raised areas surrounding the ulcers, which might have suggested an infiltrative process (such as lymphoma, granulomatous reaction, etc.) have become less prominent; the ulcer is healing (Panel **B**).



(**A**) (**B**)

Figure 4.54 Lymphedema years after Charles procedure.

This 68-year-old woman was referred to us with a long history of lymphedema (see the verrucous changes, particularly on her toes) in the lower extremities and after extensive surgical procedures. She had multiple therapies over the years, including antibiotics, lymphedema pumps, massage therapy, and compression bandages with minimal improvement. She eventually underwent an aggressive debulking operation known as the Charles' procedure. This intervention involves complete removal of subcutaneous and fascial tissues, followed by full-thickness autologous skin grafting. This treatment modality is used in extreme cases to improve quality of life (such as being able to wear pants) by reducing the size of the extremity and restoring ambulatory activity. Panels **A** and **B** were taken many years after the procedure. There are some long-term complications which include venous/lymphatic insufficiency, ulceration, hyperkeratosis, and chronic exudative dermatitis. We excluded the presence of skin cancers and used silver dressings to minimize bacterial colonization within the ulcers. Her motivation is quite good, and she has adjusted well to these palliative measures.



(**A**) (**B**)

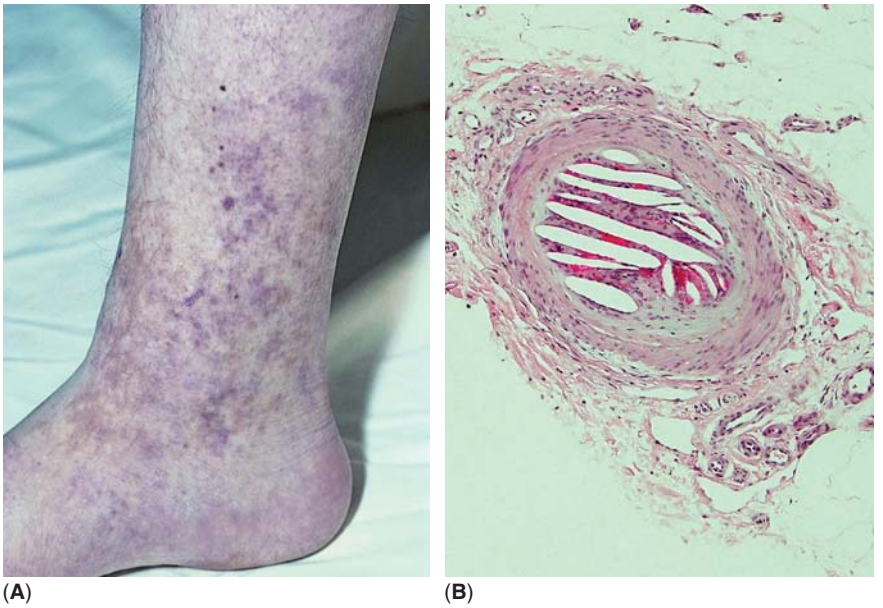
Figure 4.55 Livedo pattern (microlivedo).

The pattern of microlivedo (Panels **A** and **B**) is worth looking for when evaluating ulcers of the lower extremity. Microlivedo is not a specific clinical finding, and can be seen with cholesterol embolization, vasculitis, the antiphospholipid syndrome, cryofibrinogenemia, cryoglobulinemia, and septic embolization. Microlivedo can be quite subtle. Instead of the intense livedo reticularis which, like a net, involves a large area of skin, one sees often faint linear streaks which are purple and do not form a complete "net." These lesions have been called "microlivedo" and are commonly observed on the lower leg and foot in cases of obstruction of small blood vessels. Biopsies and blood studies are necessary to look for the specific conditions causing microlivedo. In this particular patient the ulcers were due to cryofibrinogenemia. His plasma showed increased cryofibrinogen levels, and a biopsy of the large ulcer (Panel **A**, which is now healed) showed the typical fibrin thrombi in small dermal vessels, without much inflammation. He was successfully treated with the anabolic steroid stanozolol. Since this drug is no longer available, our preference now would be to treat with danazol. We do have evidence that danazol is effective in cryofibrinogenemia.



Figure 4.56 Calciphylaxis.

This 62-year-old woman presented with painful livedo-like lesions (microlivedo) in the setting of renal failure and secondary hyperparathyroidism. The livedo pattern, the necrotic areas, and the clinical setting suggest calciphylaxis. A biopsy showed calcium deposition in and around the blood vessel walls. However, we have found that the histology is highly variable, sometimes without definite pathological findings, suggesting that cause and effect in terms of these findings are not clear-cut. Patients can have a high mortality, and calciphylaxis may occur as an end-stage event. Calciphylaxis may develop in patients with normal renal function and after successful kidney transplantation. In recent years, intravenous treatment with sodium thiosulfate or bisphosphonates has shown promise. We have also successfully used debridement followed by application of bioengineered skin. The ulcers are very painful.



(**A**) (**B**)

Figure 4.57 Cholesterol embolization.

The clinical hallmark of cholesterol embolization is livedo reticularis, which is present in up to 90% of patients (Panel **A**). Ulcerations of toes and legs are not uncommon. The condition occurs as a result of dislodging of atherosclerotic material from atheromas, either spontaneously, or after angiography, or even after initial treatment with warfarin. The less than 100-μm emboli obstruct the microcirculation and give a clinical picture of livedo reticularis and ulcers, and systemic disease (especially kidney and brain involvement). Interestingly, the blood pressure is usually normal in these cases, and peripheral pulses are palpable. Biopsies of the areas of livedo may show the typical cholesterol clefts in subcutaneous vessels, as observed in Panel **B**. Serial sectioning of biopsy specimens may be necessary to detect the typical histology of cholesterol clefts (Panel **B**), which represent the empty spaces of cholesterol emboli that do not survive the formalin and fixation process.



Figure 4.58 Massive necrosis of fingertips.

This type of fulminant presentation is often associated with connective tissue diseases, such as rheumatoid arthritis. It generally represents a vasculitis, but coagulopathies may coexist or even be the primary cause. The patient improved considerably with systemic immunosuppressive therapy and wound debridement. She did not lose function of her hand or fingers. This clinical presentation could also be consistent with purpura fulminans (like after varicella infection), leprosy (Lucio's phenomenon), disseminated intravascular coagulation, frostbite, etc.



(**A**)



(**B**)

Figure 4.59 Disseminated intravascular coagulation.

This is a serious complication of sepsis (i.e. with meningococcemia), other generalized infections (i.e. varicella), or widespread malignancy. The cutaneous necrosis can be so extensive as to require amputations. Toes, fingers, or entire extremities may become gangrenous almost overnight. In this 42-year-old man with malaria (falciparum), hemorrhagic blisters developed on toes, fingers, and truncal areas. Panel **B** is a close-up of the dorsal areas, showing well-demarcated necrosis without livedo areas, which would be more common in vasculitis. In meningococcemia, this dramatic purpura and necrosis can evolve very quickly, and be associated with a fatal outcome within hours.



Figure 4.60 Ulcer due to microthrombi.

The necrosis (eschar) and the lack of hyperpigmentation argue against a venous etiology. This patient had dermal microthrombi, but there was no associated laboratory abnormality (i.e. cryofibrinogen, anticardiolipin antibodies). In such cases, these patients may have an idiopathic form of microthrombotic disease, which we call livedoid vasculitis. He improved with surgical debridement, wound care with hydrocolloids, and anabolic steroids. There have been reports of successfully using systemic tissue plasminogen activator (tPA) in such cases.



Figure 4.61 A dramatic case of cryofibrinogenemia.

Again, the extensive necrosis is a clue to the diagnosis, and the pain is rather typical in that it is excruciating and is peculiarly relieved by the patient gently rubbing the surrounding skin. He was an elderly man with many other medical problems, including congestive heart failure. He was admitted to the hospital and treated with stanozolol; due to the unavailability of this drug at this point, we now use danazol. A similar clinical picture would be caused by other conditions we have discussed, including the antiphospholipid syndrome, calciphylasis, vasculitis, etc.



Figure 4.62 Congenital noninvoluting hemangioma.

Shown here is an example of an extensive congenital hemangioma. As an adult, the patient then developed persistent pain, limitation in function of the arm, and recurrent 3–5 mm ulcerations. A chest CT scan showed a complex vascularity of the left anterior chest wall with no other abnormalities. A biopsy from the lesion showed a benign hemangioma with overlying ulceration. There is evidence that laser therapy can help some of these vascular lesions even when they are so dramatic.

5 Inflammatory ulcers

In this section we review a number of conditions which lead to chronic and often dramatic ulcerations. It is probably fair to state that inflammatory ulcers present a major challenge to most clinicians and to specialized wound healing centers, simply because health care professionals have been trained much more thoroughly in the management of the other wounds addressed in this *Text Atlas*. Inflammatory ulcers demand expertise in recognizing morphological features and subtle clues, correlation with unusual systemic conditions, and much more attention to the patient's overall appearance and medical problems. As a result, inflammatory ulcers are a major source of morbidity for patients and become expensive to treat because of delays in diagnosis. Still, it is possible for clinicians to become quite familiar with these conditions and to acquire the visual skills and attention to subtle details that are required in the management of these chronic wounds.

Excruciating pain is generally a hallmark of some of these ulcers. Proper diagnosis is essential here, because therapy is quite varied, depending on the underlying process. For example, ulcers due to cryofibrinogenemia tend to respond well to anabolic steroids. We had long used stanozolol in their management. However, because this anabolic steroid is no longer available, we are now using danazol. The latter seems to work well, but we will need more clinical experience with it. Cryoglobulinemia may be treated with interferons and immunosuppressive agents, and pyoderma gangrenosum responds dramatically to intravenous pulse steroid therapy and, most dramatically, to the new biological agents that interfere with the action of tumor necrosis factor α (TNF-α). We used to use cyclosporine much more for these conditions, but this immunosuppressive drug takes longer than the biologics in improving certain inflammatory conditions, such as pyoderma gangrenosum. Moreover, cyclosporine requires extreme attention to blood pressure, renal function, and the presence of diabetes.

As alluded to already, the evaluation of patients with inflammatory ulcers actually starts before we remove the bandages covering the wound and examine the wound itself. Indeed, the mental process leading to proper diagnosis and management starts as we are entering the examining room. We should look for signs of rheumatoid arthritis, for the typical features of systemic sclerosis (scleroderma) affecting the face and hands, and the cutaneous findings of lupus erythematosus. Hands affected by rheumatoid arthritis will tell us that the patient may have pyoderma gangrenosum or vasculitis. The malar rash of lupus erythematosus should lead us to expect the possibility of a wound associated with the presence of the antiphospholipid syndrome (lupus anticoagulant). We look for the Cushingoid appearance resulting from the chronic use of systemic corticosteroids, as wounds in these patients will typically have poor granulation tissue and respond to topical retinoids. Because the topical application of retinoids is associated with considerable irritant contact dermatitis in and around the wounds, we have successfully pioneered the use of short-contact treatment with retinoids, which improve the granulation tissue. Thus, we apply the compound to the wound for only 5–10 minutes before washing it off.

A number of connective tissue disorders are associated with a livedo (net-like) pattern in the affected extremity; this clinical finding may be the result of dermal thrombi, cryofibrinogenemia, or cryoglobulinemia. Often, it presents as an incomplete livedo pattern, with only linear hyperpigmented and subtle streaks. In that case, we refer to it as microlivedo. Its presence speaks for occlusion of dermal blood vessels, which could be caused by the antiphospholipid syndrome, cryofibrinogenemia, cryoglobulinemia, vasculitis, and hypercoagulable states. Together, we have grouped those conditions under the terms of "microthrombotic diseases." There are many other clues to look for before focusing on the wound itself. Simply shaking the patient's hand will tell us about the possibility of scleroderma (indurated digits) or rheumatoid arthritis. A patient rubbing the skin next to the wound, in an effort to obtain pain relief, may have cryofibrinogenemia. Once we remove the bandages or primary dressing, we are able to determine whether the above clues are indeed valid. The appearance of pyoderma gangrenous with rolled purple borders and undermined edges is typical. Ulcers due to the antiphospholipid syndrome have necrotic areas and are surrounded by areas of microlivedo due to occlusion of small blood vessels. Location of the ulcers is also helpful. For example, erythema induratum, which has been associated with systemic tuberculosis infection, commonly presents on the calf. Intensely painful ulcers, due to thrombocytosis or treatment with hydroxyurea, are generally on or around the malleoli. These and other clues can be of great help, before any laboratory tests or biopsies.

Biopsies are often of great help in the evaluation of this group of inflammatory disorders. The biopsy site has to be chosen carefully. We generally biopsy the edge of the ulcer, and would choose skin immediately adjacent to necrotic areas. Histology may confirm the presence of dermal fibrin thrombi, and hence lead us in the direction of microthrombotic ulcers (cryofibrinogenemia, the antiphospholipid syndrome, and cholesterol embolization). A mild inflammatory component around the occluded dermal vessels is seen in ulcers due to the antiphospholipid syndrome. The diagnosis of pyoderma gangrenosum, although based for the most part on clinical features, is also helped by histologic evaluation; histology will exclude an infectious process and will at least be consistent with pyoderma gangrenosum (i.e., neutrophilic infiltrate and no vasculitis). Biopsies should be taken down to the subcutaneous tissue, so as not to miss the chance of diagnosing medium-sized vessel vasculitis (e.g., polyarteritis nodosa).

It will be noted that there is some overlap between this section and the previous one on vascular ulcers. This is because ulcers are often complicated by an inflammatory component, even though the etiology and pathogenesis are primarily

related to the occlusion of arteries or venous insufficiency. An obvious example of this is atrophie blanche. This painful condition is associated with vasculitis, arterial as well as venous disease; some clinicians even regard it as an entity in itself. In our experience, atrophie blanche tends to respond to high doses of pentoxifylline, sometimes in combination with colchicine. Lividoid vasculitis refers to an idiopathic condition where dermal blood vessels are occluded and for which there is no clear explanation. Cholesterol embolization is another example where there can be a substantial inflammatory component even though the primary process is occlusion of small dermal and subcutaneous vessels by cholesterol crystals.

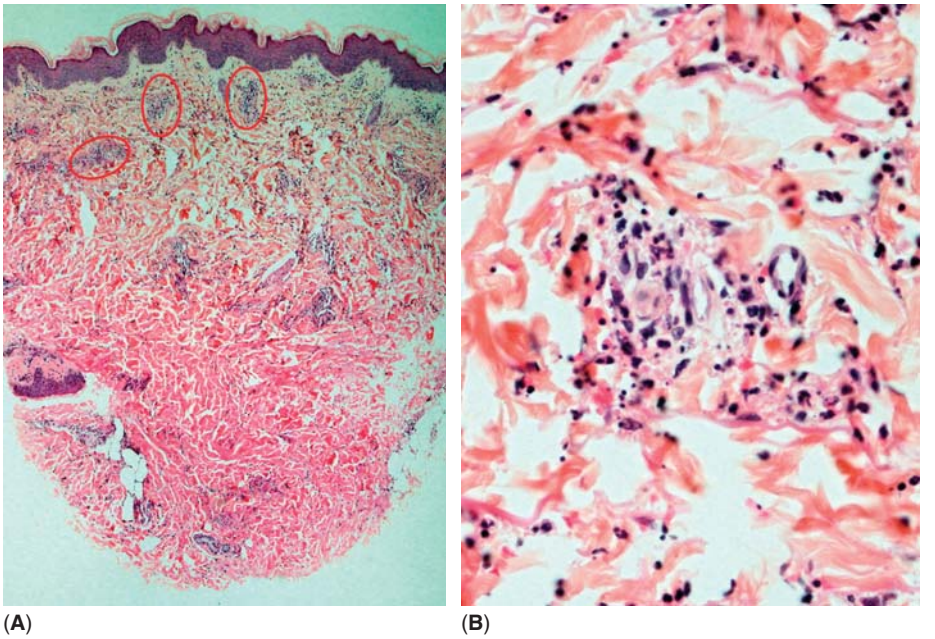
Clinical Points

- Lipodermatosclerosis probably represents a spectrum of diseases, ranging from an acute and intensely painful panniculitis to a more chronic and rather painless form associated with more established signs of venous insufficiency. It may be more common in patients with the limited variant of systemic sclerosis (scleroderma).
- Anabolic steroids, such as danazol, may provide dramatic clinical improvement and pain control to patients with cryofibrinogenemia. An alternative is the use of high doses of pentoxifylline (800 mg 3 times a day) and colchicine.
- The differentiation between dermatitis and cellulitis of the leg is often difficult. It is often necessary to treat with systemic antibiotics.
- Clinicians should include split-thickness skin grafting as therapy for inflammatory ulcers, such as erosive lichen planus or necrobiosis lipoidica diabeticorum. Pain control is often very dramatic after grafting, and the grafts stimulate healing.
- Some ulcers of the lower leg have clinical features of both pyoderma gangrenosum and necrobiosis lipoidica diabeticorum.
- Biological agents that interfere with the action of TNF-α have emerged as powerful agents for the treatment of inflammatory conditions, including pyoderma gangrenosum.
- Ulcers of erythema induratum (nodular vasculitis) are often on the calf and are associated with systemic tuberculosis. Many clinicians treat these patients with isoniazid.
- Cutaneous calcinosis has no recognized effective treatment. Low-dose warfarin and calcium channel blockers may be worth trying. The low-dose warfarin (in doses not enough to alter coagulation) appears to help the associated pain and inflammation.
- Calciphylaxis is classically associated with renal disease and secondary hyperparathyroidism. It has also been linked to a high mortality. However, the recognized spectrum of calciphylaxis is changing. Some patients hardly have the classical clinical and histologic findings, although the necrotic appearance and microlivedo is still suggestive of the disease.
- Cutaneous injections of pentazocine can lead to severely fibrotic skin changes. Patients tend to inject this drug in the inner aspect of the thigh for some systemic painful condition or because they are addicted.
- Microlivedo refers to an incomplete pattern of lacy (net-like) hyperpigmentation. This feature is common in ulcers due to occlusion of dermal vessels (microthrombotic ulcers).
- Cryoglobulinemia with ulceration is often associated with hepatitis C infection.
- Intravenous pulse steroid therapy can be an extremely effective and rapid treatment for pyoderma gangrenosum. We almost always monitor the cardiac rhythm by telemetry, due to fluctuations in electrolytes. We would not use this therapy in patients on diuretics.
- Cutaneous ulcers in patients with collagen vascular diseases often have unusual shapes and can mistakenly be thought to be factitial.
- In patients with systemic sclerosis (scleroderma), distal digital ulcers are usually due primarily to ischemia, while those on the metacarpal phalangeal joints are more likely the result of trauma.
- Ulcers secondary to blistering conditions can present with persistently crusted lesions on the skin.



Figure 5.1a Vasculitis resembling septic emboli.

This 38 year-old-man had fevers, arthralgia, and cutaneous lesions that were initially thought to represent septic emboli. However, there was no evidence of endocarditis, and the biopsy showed leukocytoclastic vasculitis. The vasculitis may have been due to antibiotics he had received for an unrelated problem.



(**A**) (**B**)

Figure 5.1b Vasculitis resembling septic emboli/histology.

There is evidence of leukocytoclastic vasculitis in the two photomicrographs of different magnification shown in Panels **A** and **B**. The encircled areas in Panel **A** (10x) refer to dermal blood vessels that have been destroyed by the vasculitic process. This is observed at a higher (40x) magnification in Panel **B**. As is typically observed in this type of small-vessel vasculitis (angiitis), there is extravasation of red blood cells, leukocytes, nuclear fragmentation, and destruction of the configuration of dermal blood vessels.



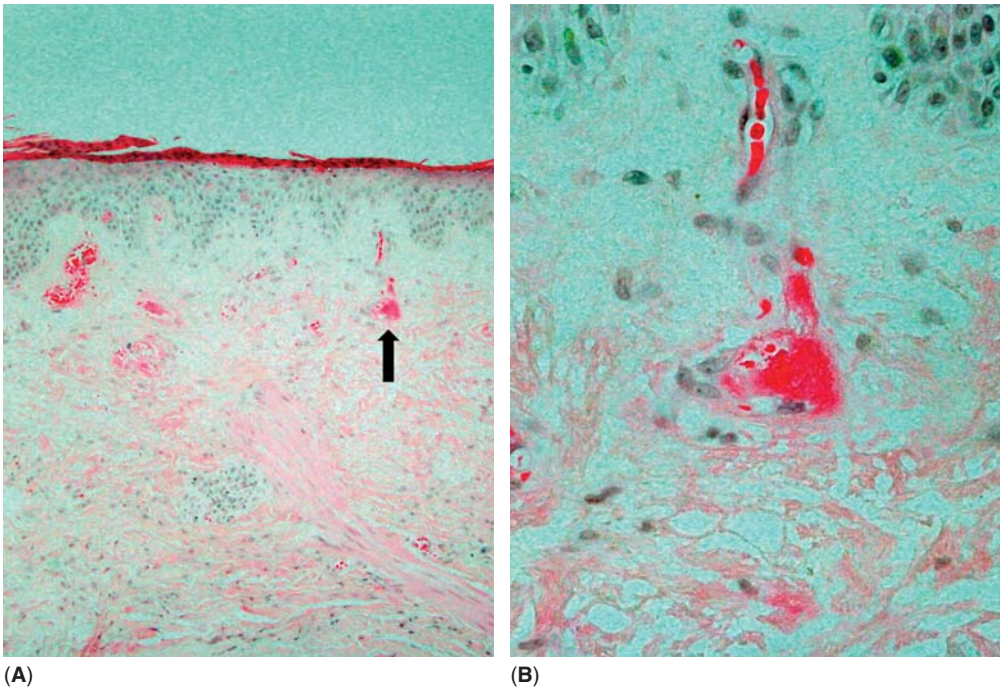
Figure 5.2 Vasculitis due to rheumatoid arthritis.

The edges are purple and, in the setting of rheumatoid arthritis, the initial diagnostic consideration was pyoderma gangrenosum. However, a biopsy showed definite leukocytoclastic vasculitis. She required treatment with systemic corticosteroids.



Figure 5.3a Livedoid vasculitis.

This middle-aged woman had very painful purple macules and plaques on the lower aspect of her right leg. They would periodically ulcerate. Histologically, there were fibrin thrombi within the dermal vessels. These thrombi can be seen in the setting of cryofibrinogenemia or the antiphospholipid syndrome. However, there was no plasma cryofibrinogen or detectable anticardiolipin antibody. The acute phase of this problem was treated successfully with anabolic steroids (same class as danazol), which have fibrinolytic properties. She was also maintained on pentoxifylline. This clinical picture is generally associated with occlusion of small cutaneous vessels; we have called it a microthrombotic disease.



(**A**) (**B**)

Figure 5.3b Lividoid vasculitis/histology.

The two photomicrographs were taken at different magnifications (Panel **A** at 4x; Panel **B** at 40x) to show clearly the plugging of dermal blood vessels with fibrin or fibrinous thrombi. This histological picture is not diagnostic of lividoid vasculitis, but could also be consistent with the antiphospholipid syndrome, cryofibrinogenemia and, in a more general sense, in conditions manifested by microthrombi. Here we don't see any substantial inflammatory infiltrate around the occluded dermal vessels, and that is quite typical.

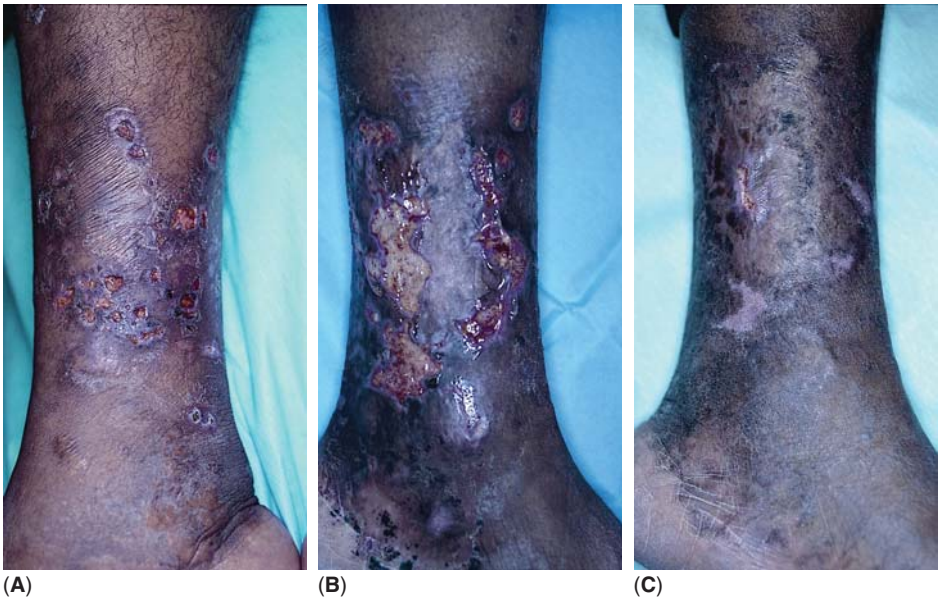


Figure 5.4 Polyarteritis nodosa.

This 61-year-old man (Panels **A–C**) has polyarteritis nodosa and renal involvement. He has been on methotrexate and other immunosuppressive agents. Complicating his clinical picture are these painful and recurrent ulcerations on his legs (Panels **A** and **B**). New lesions would appear as purple areas and show histological evidence of leukocytoclastic vasculitis. It is not uncommon for both medium (polyarteritis nodosa) and superficial (leukocytoclastic vasculitis or angiitis) blood vessels to be present in the overall setting of polyarteritis nodosa. He was treated with a combination of methotrexate and cycloporine but did not respond adequately. He was also treated with a gel dressing to promote moist wound healing, and which helped in autolytic debridement. It was important to keep the wound from drying because the pain would worsen with drying of the wound bed. His ulcers stabilized, became less painful, and began to heal (Panel **C**).

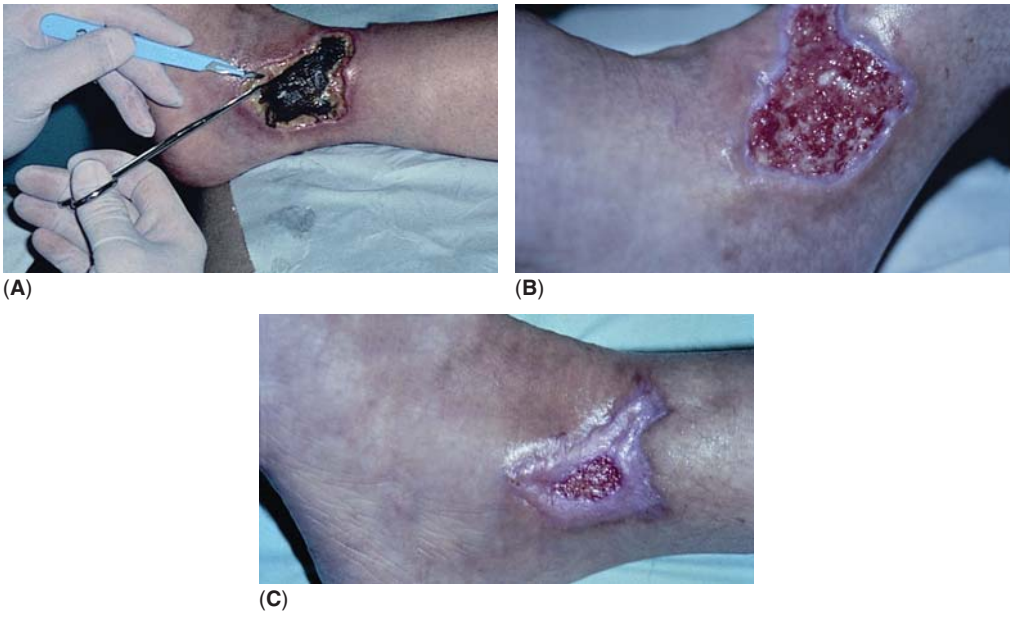


Figure 5.5 Wegener's granulomatosis/importance of local wound care.

She has an established diagnosis of Wegener's granulomatosis. Patients with this condition develop sinusitis, pulmonary disease, and renal involvement; these findings do not occur in a uniform sequence. The condition is commonly associated with serum autoantibodies to cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA). The photograph shows a large necrotic ulcer that needed surgical debridement to accelerate healing (Panel **A**), and Panel **B** indicates the appearance of the ulcer about 3 weeks after the initial debridement. There is now good granulation tissue and some evidence of re-epithelialization. Six weeks after the initial presentation, there has been rapid healing (Panel **C**). She was kept on her systemic immunosuppressive therapy for Wegener's granulomatosis, which generally includes prednisone and cyclophosphamide; sulfa drugs are used occasionally. This case illustrates the importance of following basic wound care principles in conditions that are inflammatory. We find that some clinicians often emphasize systemic therapy in these cases without proper attention to basic wound care.



Figure 5.6 Widespread necrosis in Hansen's disease (leprosy).

He developed necrosis of his fingertips and toes, together with extensive necrosis of truncal areas. This patient was in his 40s and had leprosy. This clinical picture represents Lucio's phenomenon, a serious immune complex reaction associated with ulcerations in the setting of lepromatous leprosy. Here one sees necrosis of the ear (Panel **A**). Distal areas are particularly prone to this complication of leprosy (Panels **B** and **C**), which leads to severe pain. He was treated with dapsone, rifampin, and clofazamine and made a remarkable recovery.



Figure 5.7 Polyarteritis nodosa.

She had a long history of inflammatory bowel disease and leg ulcerations, which were thought to represent pyoderma gangrenosum. She improved dramatically on treatment with cyclosporine, but worsened with tapering of this drug, which was necessitated by the development of early renal disease. Some of these ulcers (Panel **A**, superiorly) were necrotic. A biopsy of the ulcers showed classic findings for poyarteritis nodosa, with destruction of the blood vessel wall of medium sized vessels, which was also suggested by elastin stains (inset in Panel **B**). Serial sectioning of the biopsy specimens is often necessary to detect this blood vessel destruction. In many cases, coexistence of leukocytoclastic vasculitis and medium sized blood vessel destruction is present in polyarteritic nodosa. This is not very common, however.

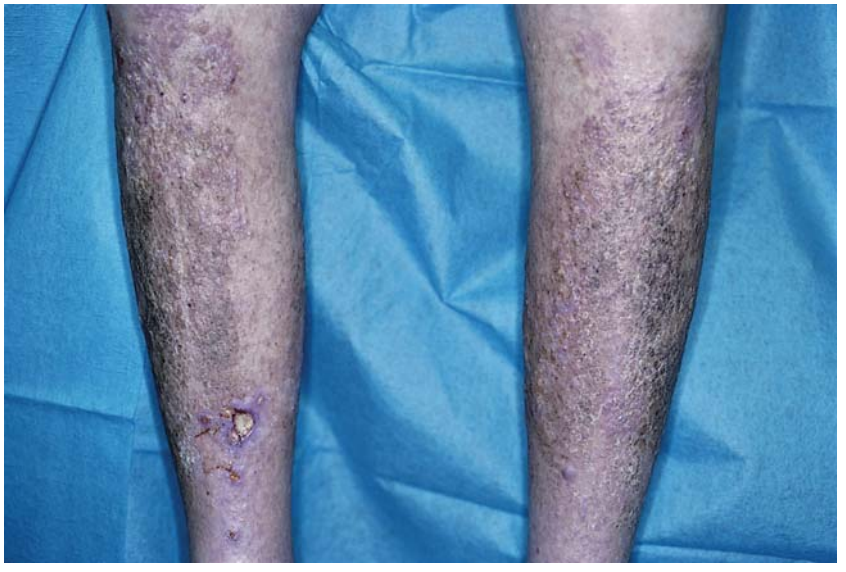


Figure 5.8 Eosinophilic fasciitis.

This elderly woman had eosinophilic fasciitis (EF), with typical leg swelling and sparing of the toes, very extensive (>60%) peripheral blood eosinophilia, and muscle pain. In a matter of a few weeks, she had ankle contractures and extensive fibrosis of the involved skin. She had not taken L-tryptophan, which is implicated in many cases of EF, but had been on nicotinic acid. Since the removal of L- tryptophan from the market, new cases of EF are hardly seen. This photograph shows ulceration within the very fibrotic skin. Among many treatments, she received up to 50 mg a day of corticosteroids, which healed the ulcer and was continued at small doses. Four years later, the fibrosis has diminished, and the ankle contractures have improved.



Figure 5.9 Pentazocine-induced ulcers.

This 52-year-old health care professional used subcutaneous injections into her thigh (shown in the photo) of pentazocine to relieve the pain of an unrelated condition. Over the next several years, she developed an extremely local fibrotic reaction, which encompassed most of her thighs and extended down to muscle. Ulcerations, sinus tracts, and frequent infections were major problems leading to numerous hospitalizations and chronic use of antibiotics. This is a rare but well-established complication of pentazocine injections. It is more common in health care professionals.

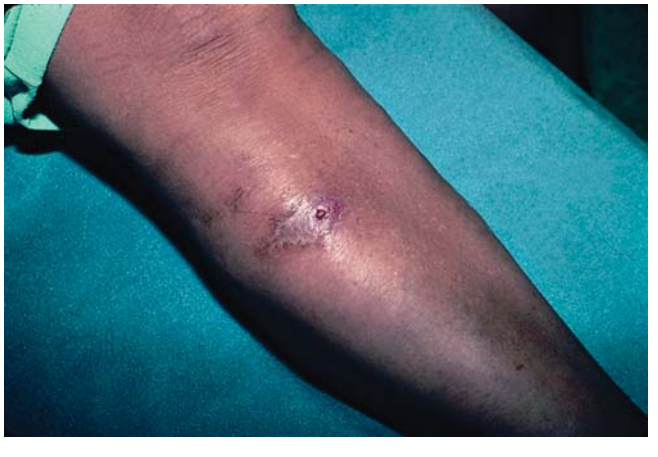
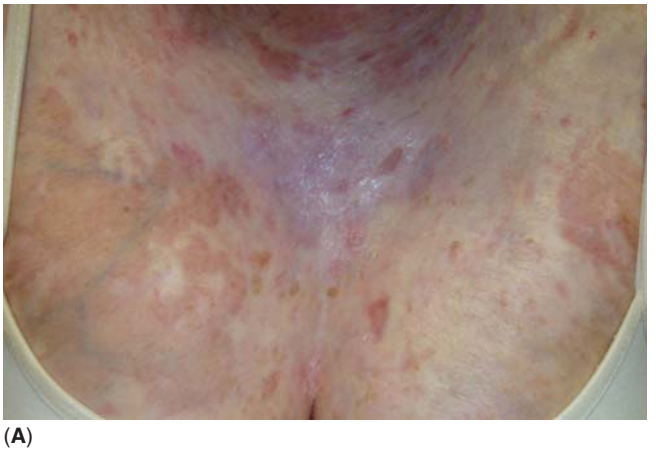


Figure 5.10 Erythema induratum/nodular vasculitis.

Ulcers of erythema induratum can look rather nonspecific and are usually located on the calf. When not associated with a history of tuberculosis (still a controversial matter), the term "nodular vasculitis" is preferred. Clinicians still tend to treat these patients with antituberculous drugs. This particular patient had a positive tuberculin test and has been improving on isoniazid.



(**A**)



(**B**)

Figure 5.11 Sclerodermoid presentation of late graft vs. host disease.

Panel **A** shows poikilodermatous (hyper-/hypopigmentation and atrophy) changes and hard, shiny areas on her chest, and histologically would show fibrosis (increased fibroblasts and collagen) or sclerosis (increased collagen alone). Panel **B** shows an early erosion on the back associated with much indurated skin.



Figure 5.12 Stage 3 (out of 4) graft vs. host disease vs. toxic epidermal necrolysis.

This 59-year-old man with chronic lymphocytic leukemia developed acute graft versus host disease (GVHD; at first intestinal symptoms) 50 days after bone marrow transplantation. The skin showed widespread erythema with areas of sparing (almost like a drug eruption), and histological findings of epidermal necrosis and a subepidermal split on biopsy. These clinical and histological findings were consistent with advanced GVHD, but toxic epidermal necrolysis (TEN) could not be excluded. The patient was treated with intravenous immunoglobulin G, but developed multiorgan failure and died.



Figure 5.13 Stage 4 graft vs. host disease vs. early toxic epidermal necrolysis.

There are generalized erythematous macules coalescing into patches with areas of erosions. Sloughing of skin, as in toxic epidermal necrolysis, was not clinically evident. The patient was very ill.

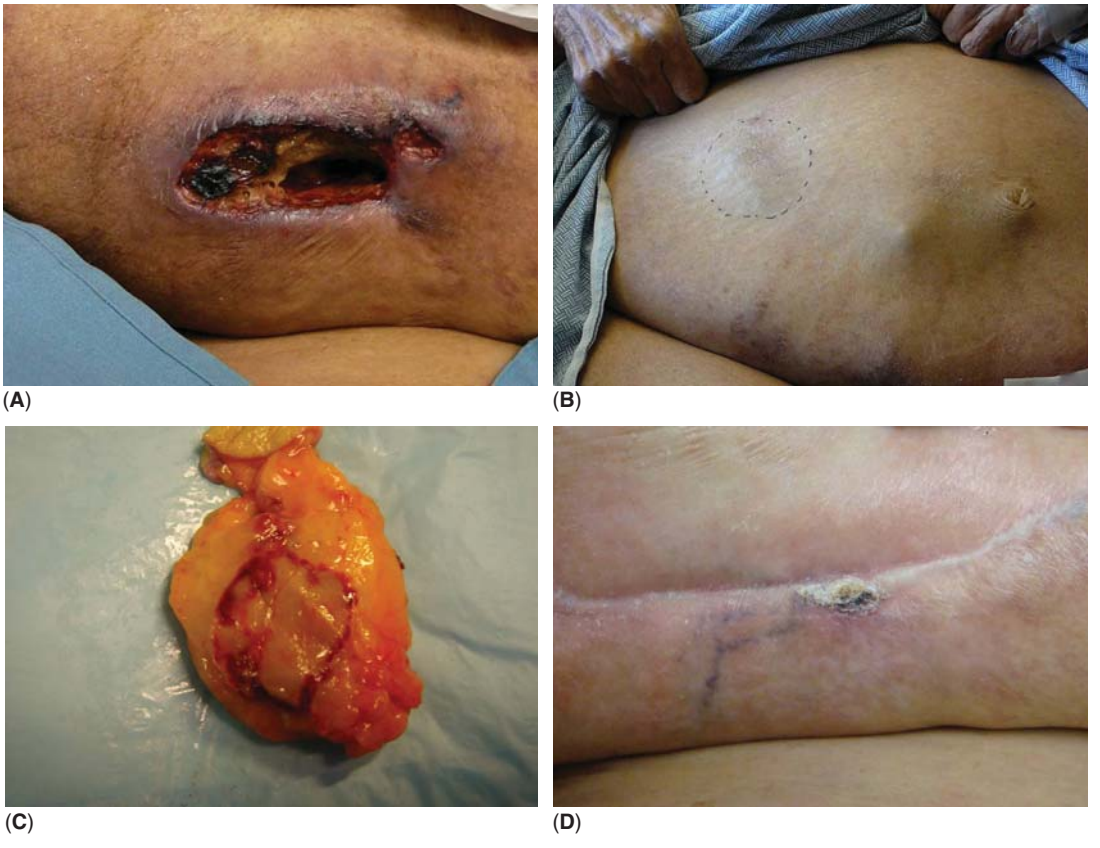


Figure 5.14 Expanding the spectrum of calciphylaxis.

This 81-year-old woman with chronic renal failure, secondary hyperparathyroidism, and cirrhosis had a one-year history of a large abdominal ulcer (Panel **A**) and multiple subcutaneous nodules on her breasts, abdomen (Panel **B**), and thighs. Panel **C** represents the gross specimen of a nodule excised from her abdomen, while Panel **D** is the healed excision of the abdominal nodule. This and multiple other biopsies showed a septal and lobular panniculitis. Based on her history, calciphylaxis was considered, but we could not identify histological calcium deposition within her blood vessels. The large abdominal ulcer healed with debridement and bioengineered skin in 4 weeks. She continued to develop new ulcers, but was successfully treated with cinacalcet to handle her elevated parathyroid hormone. We have seen a number of patients in the setting of renal disease who most likely have calciphylaxis, but do not display the typical histological findings described in the literature. Therefore, we believe that there is a wide-spectrum of disease presentation in calciphylaxis.

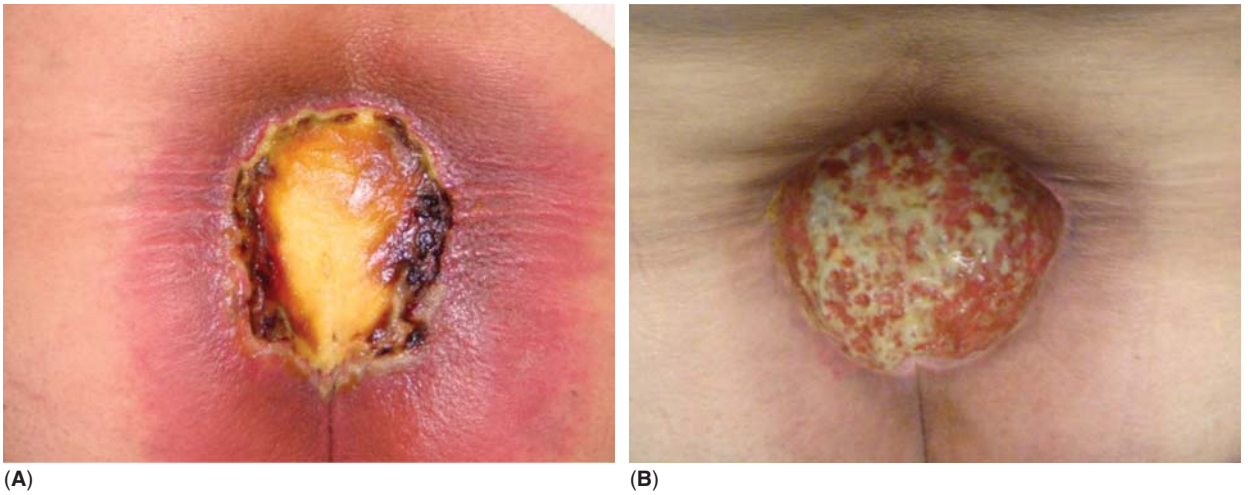


Figure 5.15 Radiation (fluoroscopy)-induced ulcer.

This 51-year-old ambulatory man developed a non healing ulcer on his back Panel **A**). He had previously undergone repair of an abdominal aneurysm that required a very lengthy fluoroscopic procedure. Subsequently, a nonhealing ulcer developed in the same location. Initially, the patient was thought by other clinicians to have pyoderma gangrenosum, but high doses of systemic corticosteroid steroid therapy failed to heal the wound, although the ulcer was generally improved (Panel **B**). Based on other patients we have seen, we strongly believe his clinical presentation is consistent with radiation (fluoroscopy)-induced chronic ulceration. A biopsy from the wound bed showed no evidence of malignancy but did show the bizaree "stellate" fibroblasts we generally see in radiation-induced ulceration.

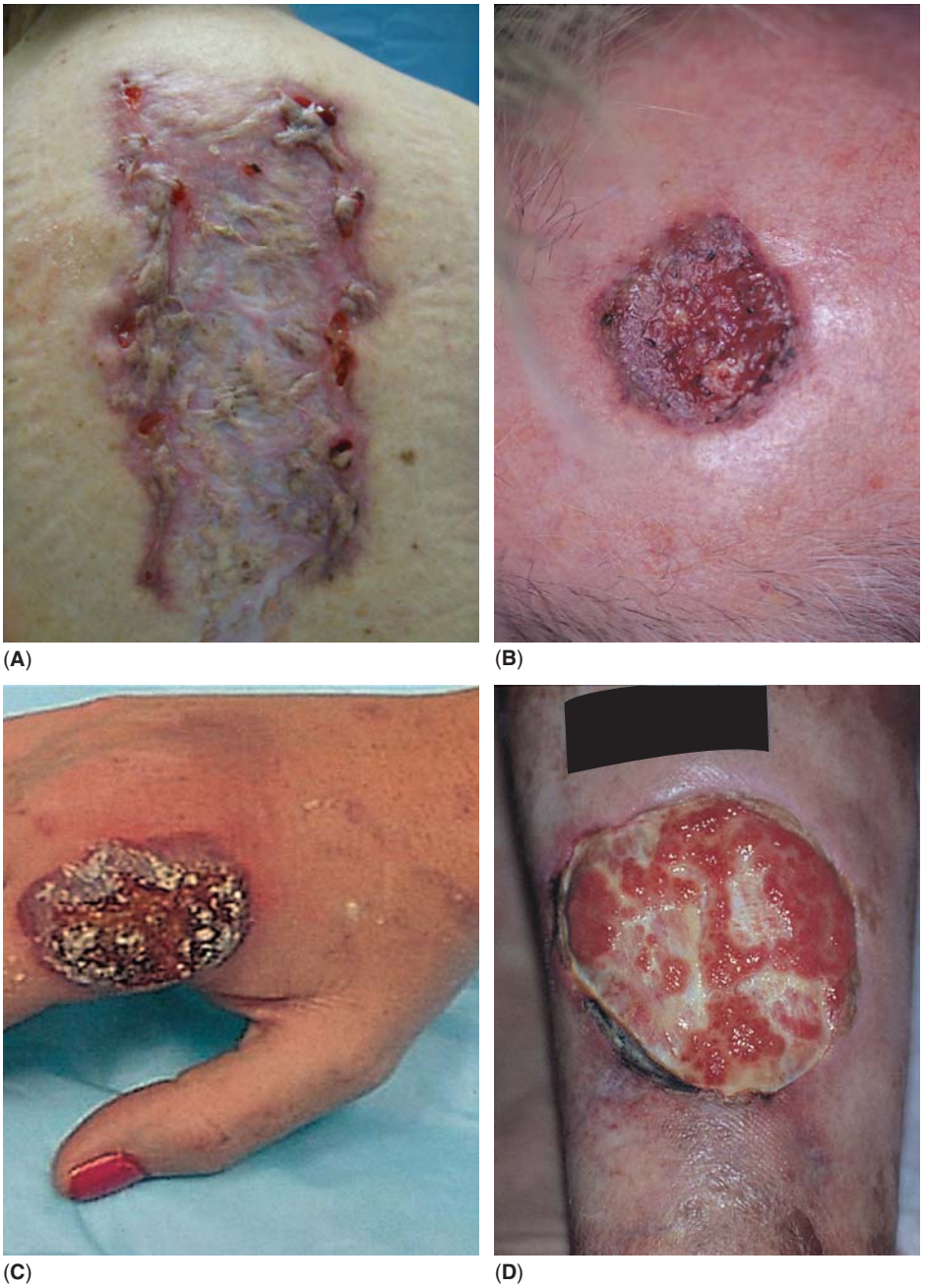


Figure 5.16 Several examples of pyoderma gangrenosum.

The patient shown in Panel **A** had an ulcer on his back for several years that developed after the removal of a cyst. The ulcer, which gradually enlarged with successive surgical debridement, still shows the typical cribriform appearance (bridges of epithelium across the wound). He has largely healed, but breakdown of the tissue continues at the ulcer's margins. There has been improvement with the use of topical tacrolimus and local corticosteroid injections. In another patient (Panel **B**) the purple edges, the raised border, and the attempts at re-epithelialization within the ulcer bed are extremely suggestive of pyoderma gangrenosum (PG). This man did not have associated diseases like rheumatoid arthritis, inflammatory bowel disease, leukemia, multiple myeloma, Behcet's disease or IgA gammopathy. Initial lesions of PG can begin as blisters, at which time intralesional corticosteroids can help (Panel **C**). This woman had a number of medical problems, including inflammatory bowel disease. The clinical course of the systemic problem often parallels that of PG. In the past, cyclosporine was a major breakthrough in the treatment of PG. However, PG is now treated more effectively and rapidly with the use of biological agents. The 45-year-old man shown in Panel **D** presented with multiple rapidly enlarging ulcers with a violaceous and undermined border, which are typical for PG. No associated systemic involvement could be found. The condition improved with large doses of systemic corticosteroids. In general, oral prednisone at a dose of at least 60 mg a day is required for initial treatment. Sometimes, methylprednisolone has to be used in patients with liver disease.



(**A**) (**B**)

Figure 5.17 Pyoderma gangrenosum and purple edges.

This clinical feature is particularly evident in this 44-year-old woman with idiopathic pyoderma gangrenosum (PG). The ulcer shows a violaceous undermined border (Panel **A**). For a while, she was thought to have had a brown recluse spider bite. However, the clinical findings and histology were more consistent with PG. It should be noted that the diagnosis of PG is mainly clinical and that histological results (i.e., neutrophilic infiltration or the granulomatous variant) are only suggestive. Cultures for mycobacteria and fungi are required; PG is a diagnosis of exclusion. She healed after a 4-day course of intravenous pulse steroid therapy. The photo in Panel **B** was taken 1 week later. During her hospital course, each day she received 1 g of methylprednisolone, with careful attention to electrolytes and cardiac rhythm (including telemetry). Patients on diuretics are more susceptible to electrolyte shifts during treatment with massive doses of corticosteroids, and arrythmias can develop in that setting. We generally prefer not to use pulse therapy with corticosteroids in patients on diuretics.



(**A**) (**B**)

Figure 5.18 Pyoderma gangrenosum with wound bed necrosis.

It is not unusual for patients (such as in Panel **A**) to be surgically debrided by clinicians unfamiliar with the condition. The problem with extensive debridement of pyoderma gangrenosum (PG) is that it can dramatically worsen the ulceration by a process known as pathergy, whereby trauma dramatically enlarges the ulceration. This woman had rheumatoid arthritis and developed her PG in a few weeks. She was treated with cyclosporine and healed after several months (Panel **B**). The puffy appearance of the hand is suggestive of rheumatoid arthritis. Although cyclosporine can be effective, it usually requires many weeks of treatment. We now prefer to use biological agents.



(**A**)



(**B**)

Figure 5.19 Pyoderma gangrenosum worsening with withdrawal of immunosuppressive therapy.

This 58-year-old woman had a one-year history of a non-healing left breast ulcer after breast reduction surgery (Panel **A**). She had no history of inflammatory bowel disease, IgA gammopathy, or hematologic malignancy. She was started on high doses of oral prednisone, with only minor and temporary improvement. Moreover, she developed stress fractures; she was then switched to cyclosporine. Her clinical course was complicated by the development of multiple abscesses (Panel **B**) that required antibiotics, drainage, and reduction of immunosuppression. Do note the bridging of skin across the wound bed superiorly and inferiorly, which we call cribiform pattern. We were able to achieve almost complete closure with the use of biologics, but the course was very prolonged and she opted for mastectomy. We finally agreed with that decision because the scarring was considerable and, moreover, we thought that the tissue changes, fibrosis, and scarring would make almost impossible the detection of any future breast malignancy.



(**A**)



(**B**)

Figure 5.20 Pyoderma gangrenosum and intralesional corticosteroids.

She is in her late 40s and has no disease associated with pyoderma gangrenosum. She develops recurrent blisters, and these result in ulcers with purple edges and undermined borders (Panel **A**). This photograph shows a typical blister, days after its initial appearance. Panel **B** shows the lesion being injected with 20 mg/ml of triamcinolone acetonide.

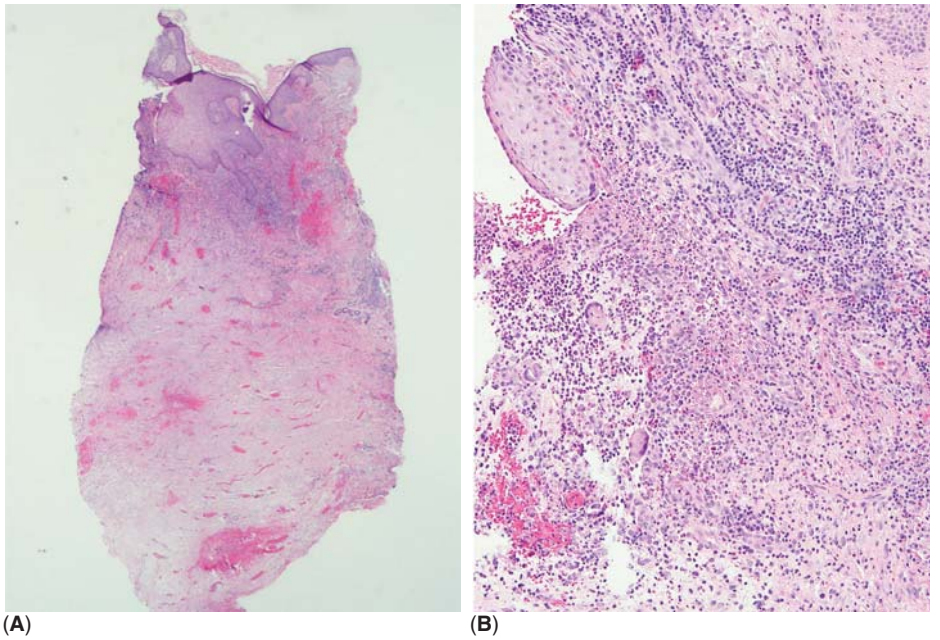


Figure 5.21 Histology of pyoderma gangrenosum.

Biopsies are done in pyoderma gangrenosum (PG) to exclude other etiologies, particularly infection and vasculitis (Panels **A** and **B**). Accordingly, the higher-magnification photomicrograph in Panel **B** shows heavy infiltration with neutrophils and some chronic inflammation. Special stains and cultures are always required. We wish to stress that the histology of PG is never truly diagnostic, and that the clinician needs to correlate the clinical findings, associated systemic conditions, the histology, and the absence of infection with mycobacteria or other unusual organisms.

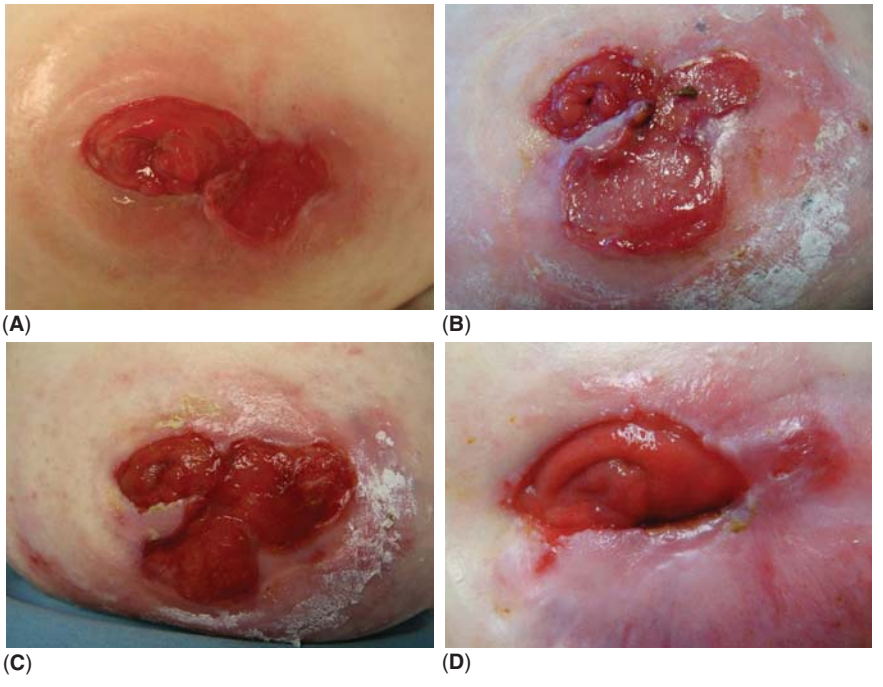


Figure 5.22 Parastomal pyoderma gangrenosum: difficult to treat.

This 77-year-old woman developed an ulcer adjacent to the site of a colostomy performed for diverticulitis. She had no evidence of inflammatory bowel disease, rheumatoid arthritis, or other conditions associated with pyoderma gangrenosum (PG). In addition, she had an underlying, large abdominal hernia that was causing pressure against the ulceration. A major difficulty was ensuring adhesion of the colostomy bag to the abdominal wall; constant irritant dermatitis and bacterial colonization from fecal material was the result (Panels **A** through **C**). We believe that the ulcer adjacent to the abdominal stoma was PG, possibly experiencing pathergy from the underlying abdominal hernia. However, the PG proved unresponsive to short courses of systemic immunosuppression; we were afraid of the immunosuppression because of a nodular melanoma on her back that had been excised 2 years earlier. Panel **D** shows promising re-epithelialization with a trial of topical tacrolimus, and that was the therapy of choice in this difficult case. We also advised her to have the abdominal hernia repaired.

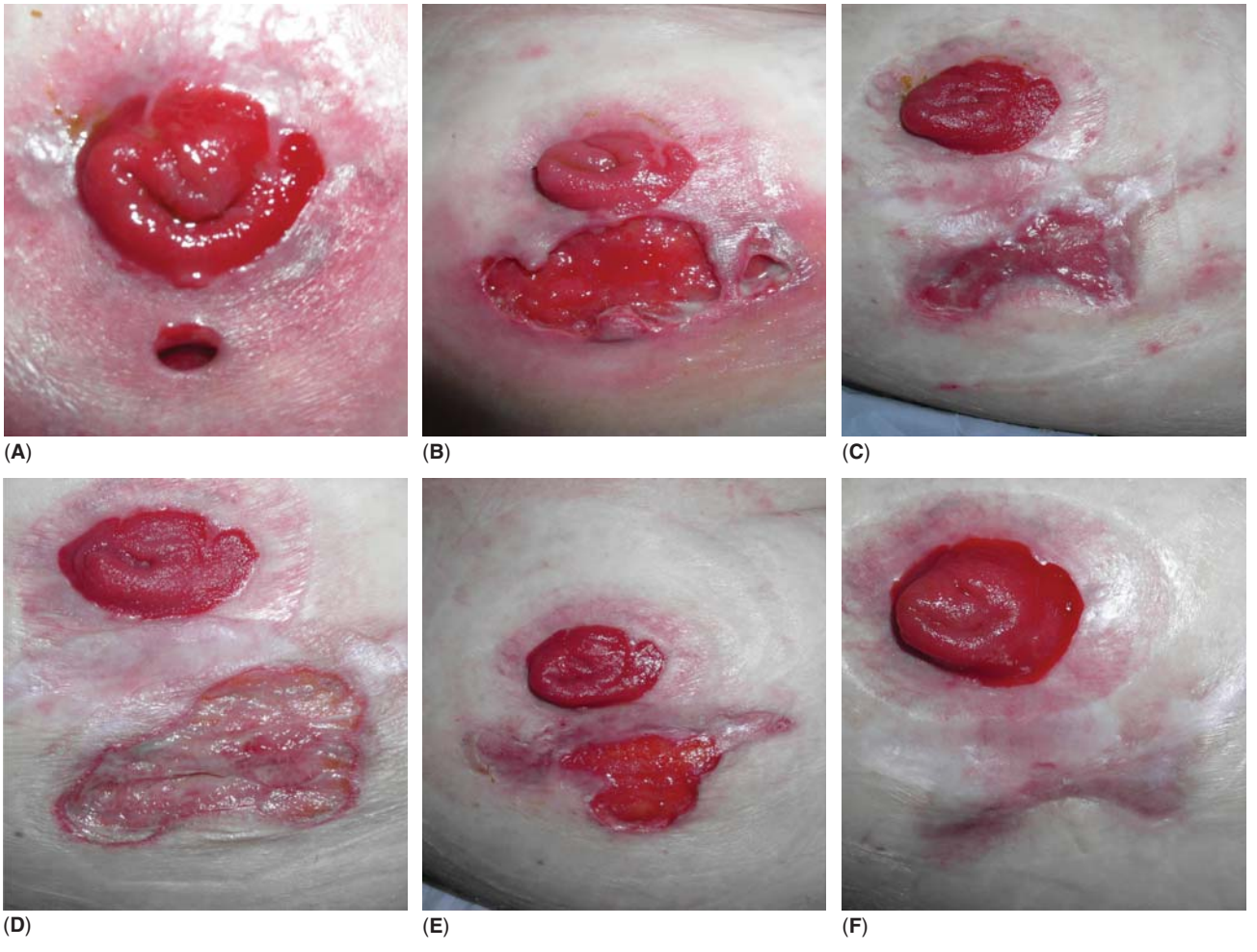


Figure 5.23 An example of parastomal pyoderma gangrenosum treated with an anti-TNF-α agent.

(Panel **A**) The patient presented with an ulcer around her colostomy site and an inferior satellite ulcer, both consistent with pyoderma gangrenosum (PG). She had Crohn's disease. She was initially treated with a potent topical corticosteroid. However, the satellite ulcer worsened (Panel **B**) and the patient was started on oral prednisone 50 mg with an initial rapid improvement (Panel **C**). However, and not surprisingly, worsening of the ulcerations occurred (Panel **D**) and particularly in the inferior satellite ulcer, as the prednisone was being tapered. Treatment with oral cyclosporine was then started. As there was no consistent improvement in 5 months (Panel **D**), cyclosporine was discontinued and the patient was started on adalimumab and topical tacrolimus. The PG healed in 4 months (Panel **F**).



Figure 5.24 Pyoderma gangrenosum-like ulceration in a young person.

He was seen at multiple medical centers for Wiskott–Aldrich syndrome, and X-linked recessive disease associated with thrombocytopenia, diarrhea, and eczema. Apparently, this ulceration developed after treatment with intravenous immunoglobulin. Clinically, the ulcer is most consistent with pyoderma gangrenosum (PG), although cutaneous lymphoma should be considered, due to the purple color. A biopsy specimen showed histological findings of a lymphocytic vasculitis with fibrinoid necrosis, consistent with livedoid vasculitis. The ulcer healed after discontinuing immunoglobulin therapy and with local care with a hydrocolloid dressing plus leg compression. The case illustrates the importance of basic wound care and diagnostic steps, even in rare diseases.



Figure 5.25 Pyoderma gangrenosum and Behcet's disease.

She had incapacitating arthritis and oral and genital ulcers, consistent with Behcet's disease. Skin ulcers had developed and healed in the past, as shown by the scar in the photograph. The small inferior ulceration seen here shows the classical purple edges of pyoderma gangrenosum. She healed with intravenous pulsed steroid therapy.



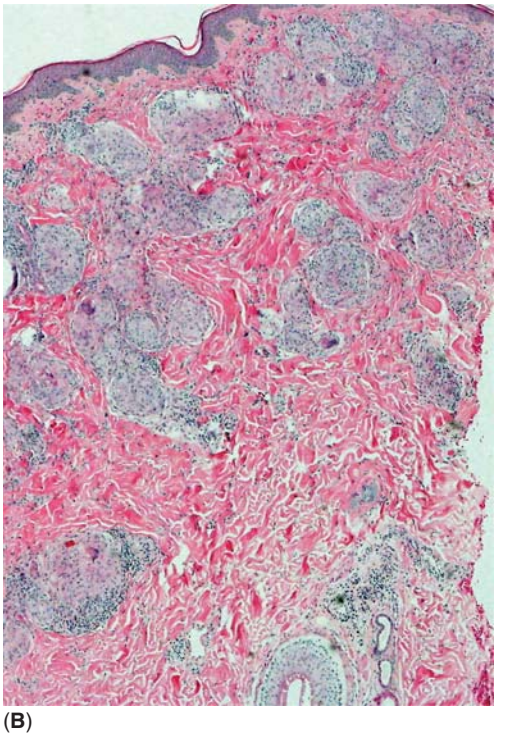
(**A**) (**B**)

Figure 5.26 Pyoderma gangrenosum and Sweet's syndrome.

He presented with extensive ulcers on both legs that began as bullae one day after he received an intramuscular injection of penicillin. During his clinical course, the lesions evolved to what is seen in the photographs (Panels **A** and **B**) and he was thought to have pyoderma gangrenosum or Sweet's syndrome. Biopsy of the ulcerations showed an intense neutrophilic infiltration that could be consistent with either condition. Shortly thereafter, he was diagnosed as having a very rare form of leukemia (chronic neutrophilic leukemia). His wounds were very painful, and improved with systemic corticosteroids. However, his prognosis was very poor and he succumbed to his rare leukemic condition.



(**A**)



(**B**)

Figure 5.27 Sarcoidosis.

It is not common for the granulomatous cutaneous lesions of sarcoidosis to ulcerate. (**A**) This 38-year-old woman had approximately 30 ulcers on her legs. A biopsy showed noncaseating granulomas, quite consistent with sarcoidosis. (**B**) There was liver and lung involvement. She was treated with oral prednisone and plaquenil. Eventually, the nonhealing ulcers responded to treatment with cultured epidermal allografts. Bioengineered skin may be a promising treatment for inflammatory ulcers, but we find that clinicians don't often entertain this therapeutic approach.

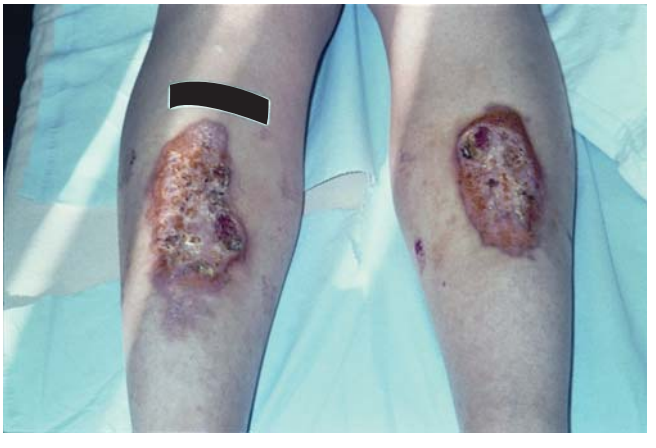


Figure 5.28 Necrobiosis lipoidica.

Necrobiosis lipoidica (NL) commonly ulcerates, as shown here in this woman with diabetes mellitus. NL is a rather specific marker for diabetes. It develops in patients who have diabetes, or will develop diabetes, or who have a strong family history of diabetes. The tibial location is typical, as is the yellow/orange color of NL lesions. Occasionally, NL can resemble pyoderma gangrenosum and we believe there are cases where a definite overlap occurs. NL ulcerations are difficult to treat. There have been reports of the successful use of autologous split-thickness grafts. Nicotinamide has been reported to be helpful. Occlusive dressings, for example hydrocolloids or foams, can accelerate healing and protect these areas from trauma. In ulcers on the anterior tibial surface, we often advise the use of shin guards that are normally used when playing soccer (football).



Figure 5.29 Necrobiosis lipoidica (the term diabeticorum is sometimes added)/small punched-out ulcers.

This woman with insulin-dependent diabetes presented with bilateral atrophic plaques over both shins, classical for NL (sometimes also called necrobiosis lipoidica diabeticorum). As one would expect, the NL was yellowish in color and, probably due to the skin atrophy, showed the underlying dermal blood vessels quite well. Commonly, her ulcerations occurred at the periphery of the NL. A biopsy confirmed the diagnosis of. If the ulcerations are relatively small, as in this patient, they can be managed with intralesional corticosteroid injection. However, continued use of corticosteroids may worsen the atrophy.



Figure 5.30 Necrobiosis lipoidica/recurrent.

Ulcerations often recur within necrobiosis lipoidica (NL), as in this case. She responded initially to intralesional corticosteroid injections at 5 mg/mL of triamcinolone acetonide. In some cases, we have treated such patients with systemic anti-inflammatory agents, for example methotrexate. In general, one tries to avoid systemic corticosteroids or cyclosporine because of the almost invariable presence of diabetes mellitus.



Figure 5.31 Necrobiosis lipoidica/healing ulcer.

She has had necrobiosis lipoidica (NL) as well as diabetes for many years. Biopsies have confirmed the diagnosis of NL. However, some of the histological features have also been consistent with granuloma annulare. The histological, and sometimes clinical, overlap between NL and granuloma annulare is well known. It is also known that patients with disseminated granuloma annulare may have diabetes.



Figure 5.32 Necrobiosis lipoidica/pyoderma gangrenosum.

We have seen a number of patients with tibial lesions and ulcerations resembling necrobiosis lipoidica, but with clinical features also suggestive of pyoderma gangrenosum. This elderly woman with many medical problems, including diabetes, is an example of this clinical presentation. Intralesional corticosteroid injections would heal the injected areas, but new lesions (see the necrotic dark areas) would develop next to it. Potent topical corticosteroids under occlusion seemed to help the situation for a period of time and prevent further ulcerations from developing.



Figure 5.33 Necrobiosis lipoidica treated with topical tacrolimus.

Here is an example of a patient with recurrent ulcers on her shins and no personal or family history of diabetes mellitus. A previous biopsy only showed fibrosis/sclerosis consistent with a scar. A re-biopsy established the diagnosis of necrobiosis lipoidica (NL). The patient was treated with topical tacrolimus, so as to prevent further atrophy of the skin from corticosteroids, and which was well tolerated and produced a durable response. This young patient was very much bothered by the telangiectasia within the areas of NL. A possibility would be to try pulsed dye laser treatment of those areas.



Figure 5.34 Histopathology of necrobiosis lipoidica.

This is a photomicrograph from a punch biopsy specimen of the case just described above but is quite typical of other necrobiosis lipoidica (NL) cases. In the superficial to deep dermis there is a broad band of altered pink-colored collagen (necrobiosis) with an eosinophilic sclerotic appearance. There is a dense inflammatory infiltrate composed of lymphocytes and plasma cells. The pattern of layered necrobiotic collagen with inflammation is consistent with NL.



Figure 5.35 Erythema multiforme.

Multiple such blisters developed in a 34-year-old woman with recurrent erythema multiforme (EM). These inflammatory lesions can be associated with recurrent oral or genital infection with Herpes simplex. Early treatment with antiviral agents can be helpful. Another major precipitating cause of EM is medications, including antibiotics. The therapeutic use of systemic corticosteroids in EM is controversial.

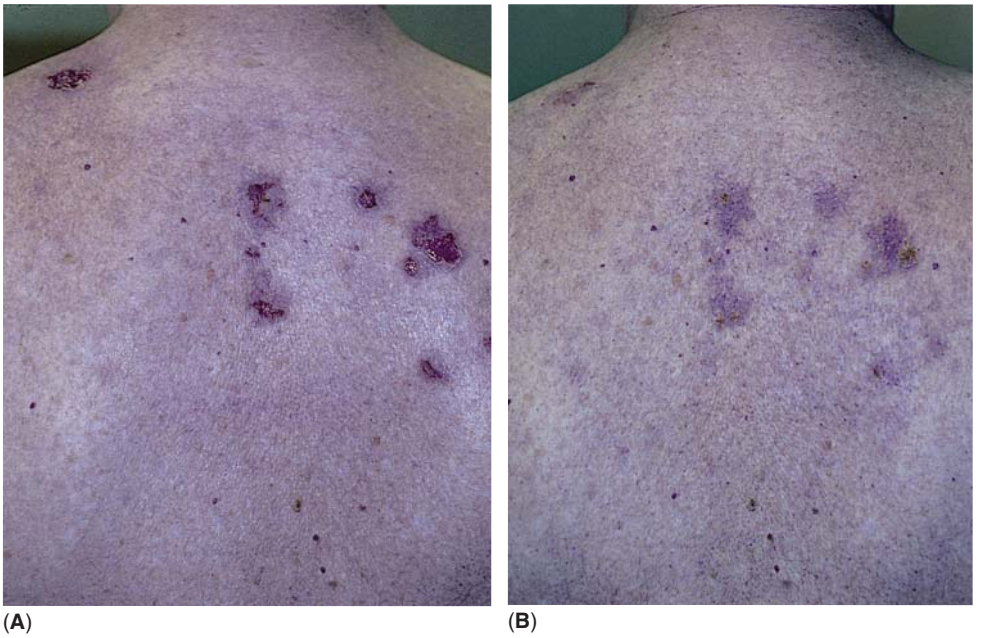


Figure 5.36a Pemphigus vulgaris.

This life-threatening blistering disorder generally involves the oral mucosa and, not uncommonly, the nonmucosal skin as well. It can be a life-threatening condition, due also to the potent drugs needed to control the blistering process. Foam dressings were used in this case with mucosal and nonmucosal skin (Panel **A**) involvement. Pemphigus vulgaris is an immunological disorder associated with autoantibodies against structural proteins in the skin (desmoglein 1 and 3). The skin erosions seen in this photograph look mild and easy to heal, but can persist for months. Oral erosions and ulcers often require treatment with high doses of systemic corticosteroids and other immunosuppressants, such as azathioprine and even alkylating agents such as chlorambucil. The skin erosions in this case healed with systemic corticosteroids (Panel **B**).



Figure 5.36b Pemphigus vulgaris/histology.

The autoantibodies directed against desmosomal proteins cause the keratinocytes to round up (acantholysis) and separate from the basal cell layer of the epidermis, creating a blister whose floor is lined up by the remaining keratinocytes still attached to the basement membrane. This histological picture, as shown well in this photomicrograph of a typical case, has been compared to a "tombstone row" of basal cells. Direct immunofluorescence will show IgG deposition within the intercellular spaces of the epidermis.



Figure 5.37a Examples of bullous pemphigoid.

Bullous pemphigoid (BP) is a blistering disorder more common in the elderly. There has been controversy about whether it is associated with systemic malignancies. Autoantibodies are directed against specific hemidesmosome proteins and other components of the basement membrane. Separation of the epidermis takes place in the lamina lucida of the basement membrane. Like in pemphigus vulgaris, the treatment of BP generally requires the use of systemic corticosteroids. Mucosal involvement is uncommon. The examples of BP shown here were proven both by histology (H&E) and direct immunofluorescence. Panel **A** here shows BP in an 85-year-old man with dementia; he presented with eroded areas on his upper back. The initial assessment was neurotic excoriations. However, new blisters developed on his trunk, away from easily reachable areas. The patient was treated with prednisone and mycophenolate mofetil (as a steroid sparing agent). This patient reminds us that we should consider a blistering disorder when we see crusted lesions on the skin, as the blisters are not always evident. Panel **B** shows BP involvement on the arms and hands of an elderly man. Panels **C** and **D** refer to an elderly man with diabetes mellitus and BP. While prednisone was initially required to control his symptoms, the addition of topical clobetasol and tetracycline plus niacinamide was helpful in discontinuing the oral prednisone. Local successful wound care consisted of white petrolatum and minimally adherent dressings.

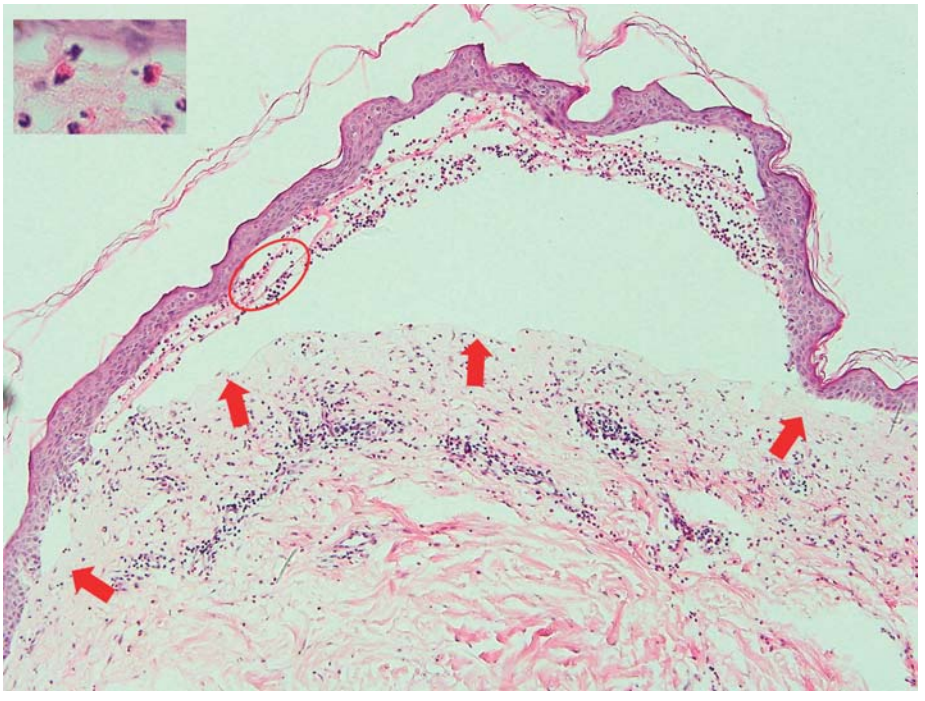


Figure 5.37b Examples of bullous pemphigoid/histology.

This H&E section from a biopsy of a patient's blisters shows a subepidermal blister. The red arrows indicate the dermal floor of the blister, with no keratinocytes remaining attached. There are other typical findings, such as the presence of eosinophils (see also upper left inset). Direct immunofluorescence of skin taken next to the blisters will typically show linear deposition of complement (C3) and immunoglobulin (IgG) at the basement membrane. A clinically similar condition (epidermolysis bullosa acquisita) will have similar histological and immunofluorescence findings but can be distinguished from BP by the location of the immunoreactants (roof vs. floor of the blister) after a salt-split skin preparation step.



Figure 5.38 Erosive lichen planus healed with skin grafting.

Lichen planus (LP) is an inflammatory condition generally occurring in the oral and genital mucosa or as a widespread eruption of the skin. Rarely, it involves mainly the palms and soles, as shown in this middle-aged man (Panels **A**–**D**). There can be an overlap of LP and lupus erythematosus of the palms and soles. This man had no clear histological evidence of LP on his plantar surface (Panel **A**), and we had to rely on our clinical judgment and diagnosis. Occlusive wound dressings and intralesional injections of corticosteroids provided no relief from pain, and there was an ongoing breakdown of the involved skin. We feel that clinicians do not often use grafting as a means of healing ulcerations due to inflammatory processes. However, in selected situations, split- thickness autologous skin grafting (as in this case; Panels **B**–**D**) can be very valuable in healing the ulcerations or, at the very least, in stimulating healing. It is now recognized that grafts can not only provide new cells for the nonhealing wound, but also improve wound bed preparation and stimulate the endogenous healing process.



(A) (B)

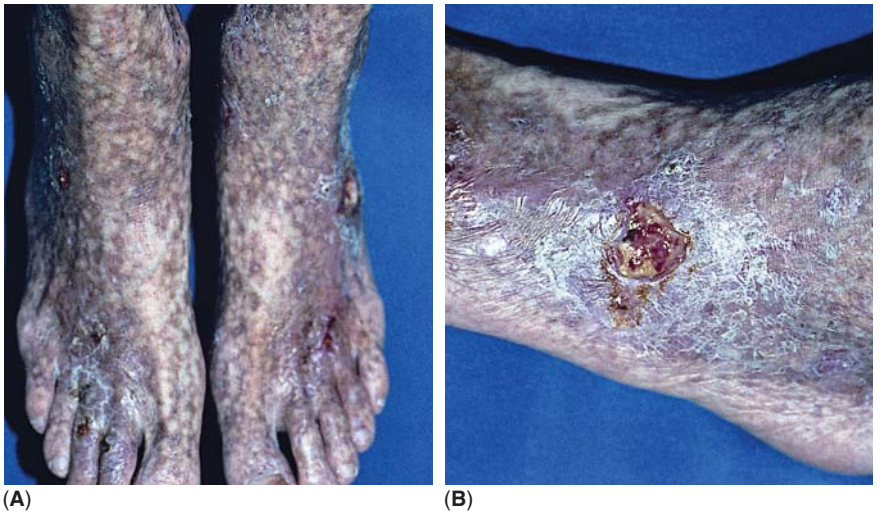
Figure 5.39 Cutaneous lupus erythematosus.

The medial aspect of the right thigh (Panel **A**) is studded with necrotic and painful ulcers and is surrounded by areas of microlivedo. Clinically, these ulcers are consistent with a number of conditions, including pyoderma gangrenosum, panniculitis, and cryofibrinogenemia. She did have plasma cryofibrinogen, but the histology was most consistent with a lobular panniculitis. Panel **B** is a close-up focusing on necrotic areas and the microlivedo pattern after initiating debridement. Pain was very severe and was managed with hydrocolloid dressings. The hydrocolloids can debride painlessly, with substantial improvement and eventual disappearance of the necrotic tissue and the development of granulation tissue. She required systemic immunosuppression therapy for this condition.



Figure 5.40 Lupus panniculitis.

She has systemic lupus erythematosus and has developed numerous small thigh ulcerations that are very painful. Biopsy showed a lobular panniculitis, and she responded to systemic corticosteroids. It is important not to dismiss such ulcers as factitial; their odd shape and distribution may initially suggest that possibility.



(A) (B)

Figure 5.41 Antiphospholipid syndrome.

This condition belongs to the group of microthrombotic diseases, and is often seen in the presence of the lupus anticoagulant and anticardiolipin antibodies. The syndrome can include severe systemic symptoms and spontaneous abortions. This Caucasian man had extensive livedo reticularis and very painful ulcers (Panel **A**). Panel **B** illustrates an ankle ulceration which, upon biopsy, showed fibrin thrombi within dermal vessels and with a slight perivascular lymphocytic infiltrate. In the past, we have found that these patients do not respond well to anabolic steroids, which are otherwise helpful in the setting of fibrin thrombi and cryofibrinogenemia. He was treated with systemic immunosuppressive agents.



Figure 5.42 Antiphospholipid syndrome and severe systemic involvement.

Many patients with this condition have systemic disease, and the present recommendation is to treat them with warfarin to prevent complications from clotting. This 20-year-old man had a history of myocardial infarction, deep vein thrombosis, and pulmonary embolism. A nonhealing ulcer was present on his right second toe. Workup showed high levels of anticardiolipin antibodies. Despite treatment with warfarin, the ulcer did not heal. He was treated with repeated applications of cultured epidermal allografts. This treatment, combined with azathioprine at a dose of 100 mg a day, was successful in leading to complete wound closure.



Figure 5.43 A rheumatoid ulcer/no vasculitis.

Ulcers developing in the setting of rheumatoid arthritis can be due to a number of causes, such as vasculitis, pyoderma gangrenosum, cryofibrinogenemia, cryoglobulinemia, and the antiphospholipid syndrome. Many ulcers, however, are difficult to classify. The one shown here falls in the latter category. There was no clinical or histological evidence of vasculitis, and serum and blood studies failed to show cryoglobulins, cryofibrinogen, or anticardiolipin antibodies. We have found that many of these difficult–to-classify ulcers in the setting of rheumatoid arthritis, as the one shown here, have an angular configuration or an undulating border. They prove difficult to treat, even with optimal wound care and potent systemic immunosuppressive agents. Often, palliative therapy is indicated to control pain and discomfort.



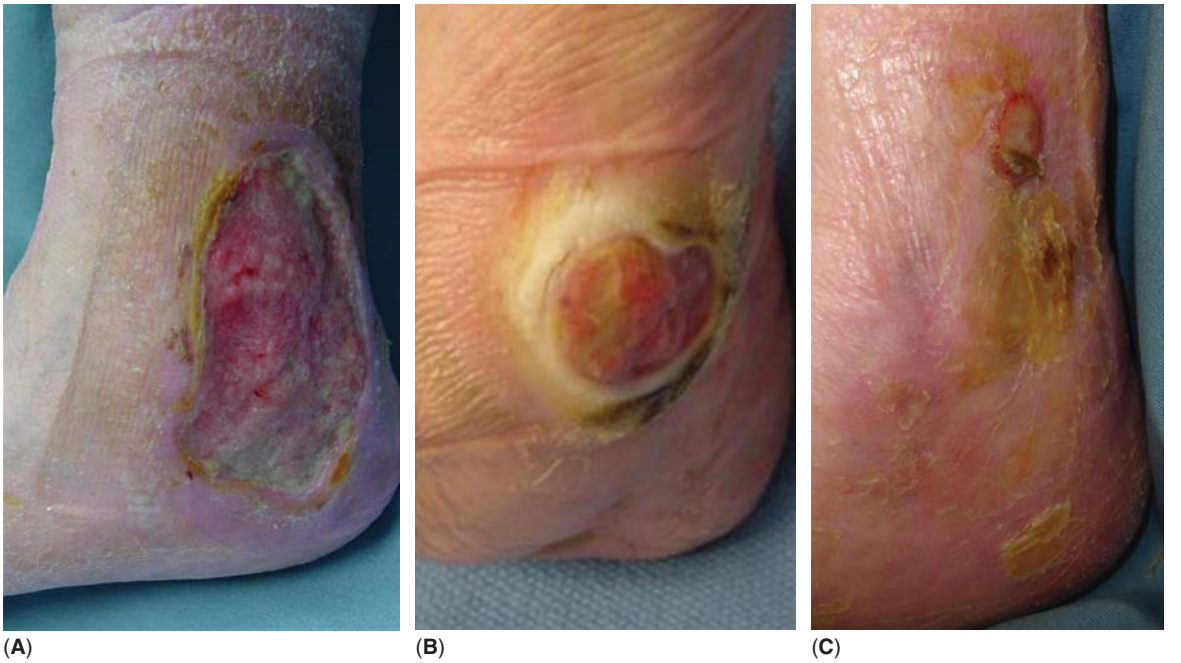
Figure 5.44 A rheumatoid ulcer/vasculitis.

This 62-year-old woman had a long history of rheumatoid arthritis, which had been treated with systemic corticosteroids, plaquenil, and methotrexate. She developed painful ulcers on her left leg. A biopsy showed histological changes of leukocytoclastic vasculitis. Treatment with an increased dose of prednisone, combined with cyclophosphamide, as well as improving wound bed preparation by the application of moisture-retentive dressings, was successful in causing painless debridement and healing the ulcers over the course of several months.



Figure 5.45 A rheumatoid ulcer and pressure.

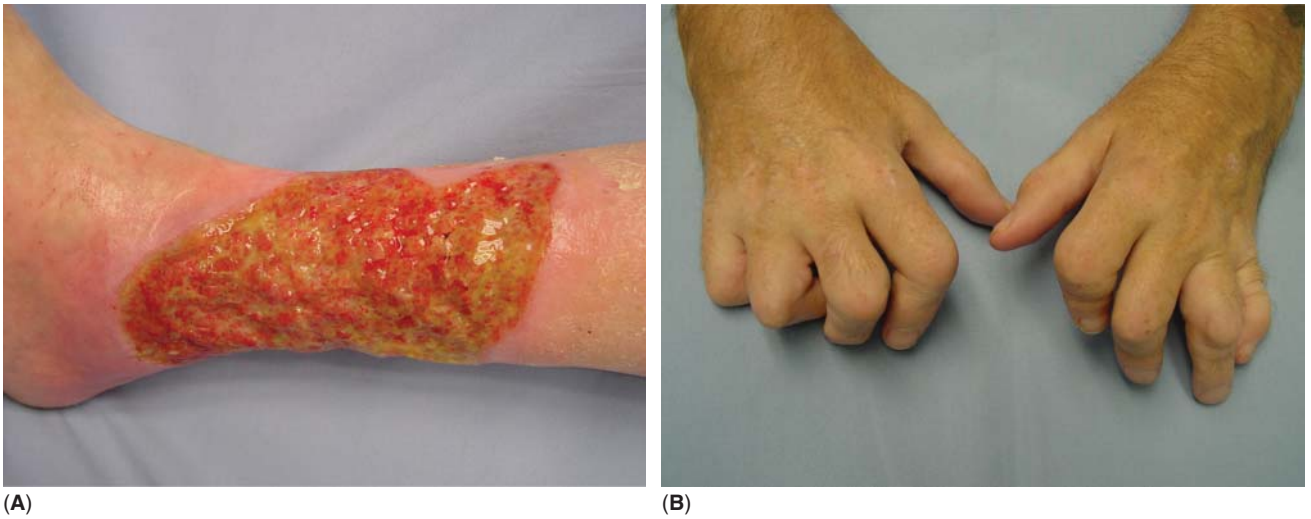
This wheelchair-bound elderly woman with incapacitating rheumatoid arthritis has had recurrent ulcers over the medial malleolus. She has severe knee and ankle deformities and has been on low doses of systemic corticosteroids for years. Because of extensive edema of the lower leg and nonhealing rheumatoid ulcers on her calf, we applied a four-layer compression bandage from her toes to below the knee. The area around the ulcer was padded extensively with a wool wrap to fill in the concave areas around the malleolus and avoid excessive pressure over the ulcer. She would be a good candidate for a Scotch cast boot or a contact cast.



(**A**) (**B**) (**C**)

Figure 5.46 An ulcer in a patient with rheumatoid arthritis.

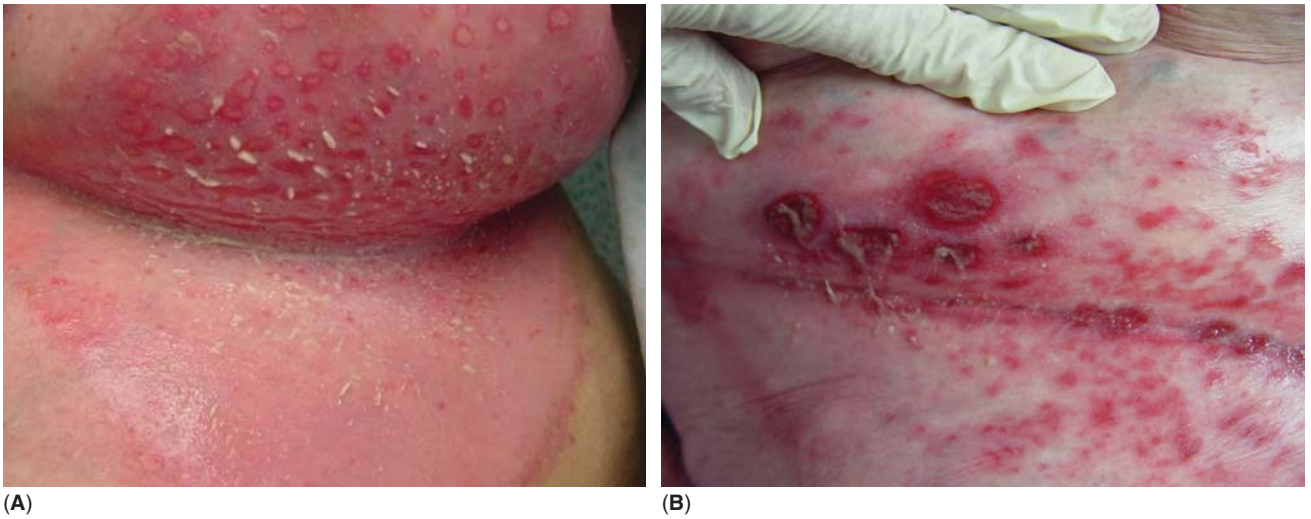
This 70-year-old woman with a long-standing history of rheumatoid arthritis had severe joint deformity and a nonhealing ulcer on the lateral aspect of her left ankle (Panel **A**). Panel **B** shows marked improvement with a low pressure tubular compression bandage. Her clinical course and a complete closure of the wound required several months. The sudden bacterial colonization and deterioration of the wound bed also required repeated use of cadexomer iodine. These steps improved her wound bed preparation and led to progressive healing (Panel **C**). One can still see the brown material of cadexomer iodine in Panel **C**.



(**A**) (**B**)

Figure 5.47 Leg ulcers in a patient with severe psoriatic arthritis.

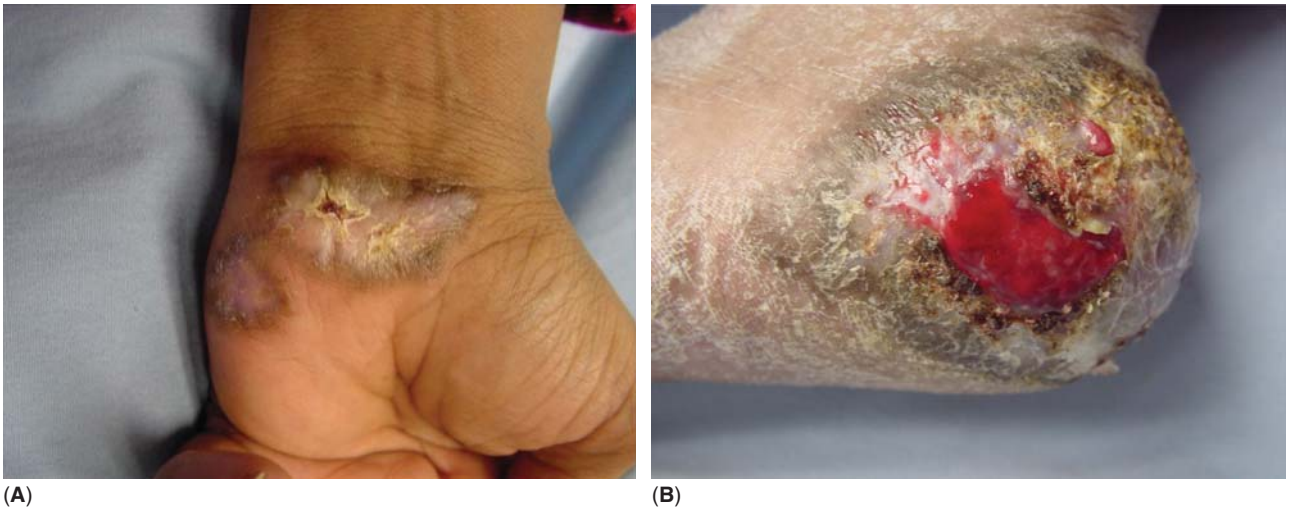
This patient had severe psoriatic arthritis (the seronegative rheumatoid variant) and developed multiple leg ulcers (Panel **A**) that proved refractory to several treatment modalities, including compression therapy to lessen the edema. No doubt, our failure to heal the ulcer was also due to substantial noncompliance and several other systemic complications that prevented us from using certain promising treatments. He had active hepatitis C infection, which worried us about using immunosuppression. Still, after appropriate consultation with his rheumatologist, we began treatment with a TNF-α antagonist. There was definite improvement but, once again, he did not keep up with the treatment. The case highlights the difficulties one faces when treating difficult conditions that require the patient to be fully compliant with therapeutic approaches.



(**A**) (**B**)

Figure 5.48 Inverse psoriasis with recurrent ulcerations.

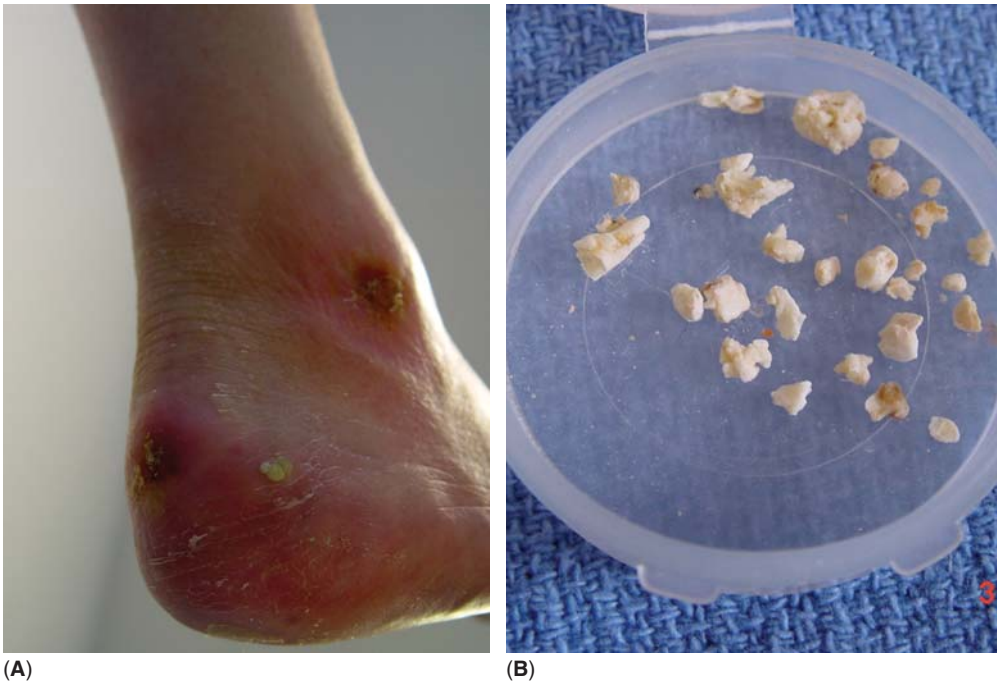
These patients have psoriasis mainly occurring in the body folds, rather than the more common and typical presentation on the extensor surfaces. The morphology of these lesions is different from plaque psoriasis in that the lesions are mostly patches without scaling. There are several reasons why inverse psoriasis ulcerates. Because of the occlusion (under the breast; Panel **A**), candidiasis is common. Patients with psoriasis treated extensively with acitretin may develop epidermal atrophy that further promotes the development of ulceration and the presence of candidiasis (Panel **B**).



(**A**) (**B**)

Figure 5.49 Chronic discoid lupus erythematosus.

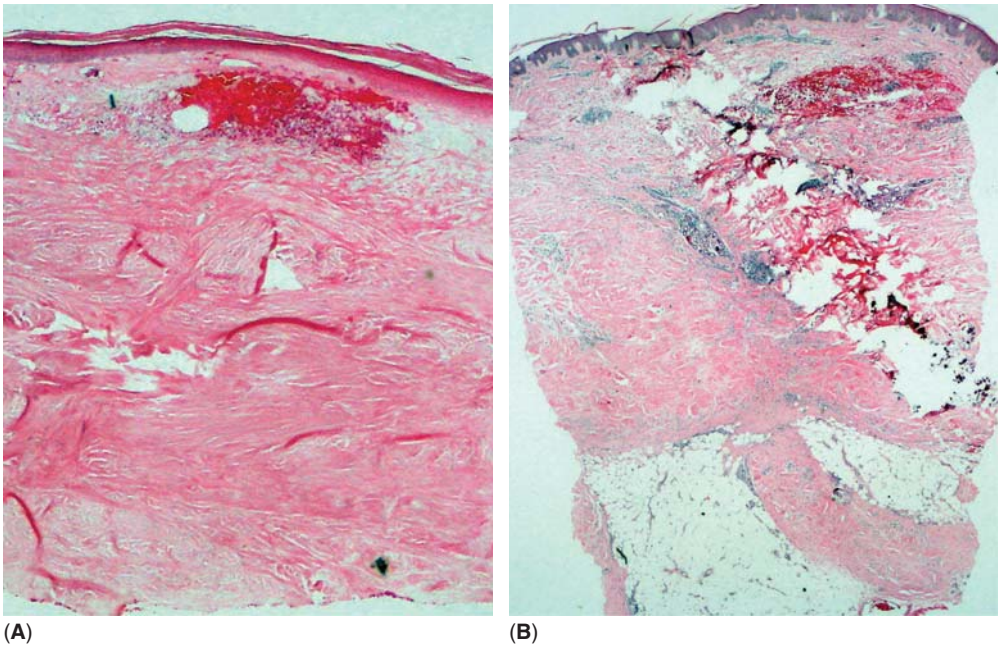
This patient had chronic discoid lupus erythematosus and would develop recurrent ulcerations in areas prone to trauma, such as the heel. The rest of her skin showed multiple areas of atrophy, hyper- and hypopigmentation that are typically seen in discoid lupus erythematosus (hand; Panel **A**). The ulcers healed with the application of bioengineered skin; however, there would be recurrence of the ulcers (heel, Panel **B**). Standard therapy for discoid lupus includes broad spectrum sunscreens, topical corticosteroids, and antimalarial agents. Dapsone and retinoids can be helpful.



(**A**) (**B**)

Figure 5.50a Calcinosis in a patient with systemic sclerosis (scleroderma).

Calcinosis of the skin (calcinosis cutis) is a common finding in patients with systemic sclerosis, although it's more common in the subset having CREST syndrome. This patient, however, had diffuse systemic sclerosis, which is associated with a worse prognosis. Calcium deposits can develop over the elbows, fingertips, and trochanteric areas. The skin overlying the calcium deposits becomes inflamed and painful (Panel **A**); symptoms may resolve once the calcium is extruded. Panel **B** shows the appearance of the extruded calcium deposits brought in by the patient. We have occasionally used low-dose warfarin (in doses not enough to affect coagulation) to decrease the inflammatory component and pain associated with calcinosis cutis.



(**A**) (**B**)

Figure 5.50b Calcinosis in a patient with systemic sclerosis (scleroderma)/histology.

These photomicrographs illustrate some of the changes observed in scleroderma. There are thick hyalinized collagen bundles in the papillary and reticular dermis (Panel **A**). In Panel **B** one can appreciate the "square" shaped biopsy specimen that is the result of the rigid and fibrotic skin. The blue staining material in Panel **B** represents calcium deposition.



Figure 5.51 A decreased oral aperture and furrowing of the lips in systemic sclerosis (scleroderma).

Upon walking into the examining room to evaluate an ulceration, the clinician must pay attention to the overall appearance of the patient and subtle clues. Patients with systemic sclerosis develop thickening and hardening of the skin. Here we can see the thinning of the lips and a small oral aperture (inset). In addition, there are furrows around the mouth that may be distressing to the patients. Note also the subtle telengiectasia on the lips, which is another common physical finding. Patients with systemic sclerosis (both the diffuse and limited form) may have serious and life-threatening systemic complications, affecting especially the lungs, GI tract, heart, and kidneys. The patients need to be monitored frequently for the development of systemic involvement. Digital ulcers may occur in up to 50% of patients with extensive disease.



Figure 5.52 Scleroderma ulcers (scleroderma).

This 48-year-old man with the CREST variant of systemic sclerosis (scleroderma) has had numerous digital ulcerations that have resulted in autoamputation in several digits. The ulceration on his right thumb has been present for several months and is being treated with cadexomer iodine, which has helped with the exudate and has led to considerable healing. On his palm, one can see the typical matted (flat) telangiectasias that are more common with the CREST syndrome subset of systemic sclerosis. Patients with systemic sclerosis develop early vascular damage, such as intimal proliferation. Because of the obstructive nature of the vascular lesions, patients do not respond well to vasodilators unless there is a substantial component of vascular spasm. Systemic sclerosis is up to 15 times more common in women than men, but men generally have a worse prognosis and clinical course.

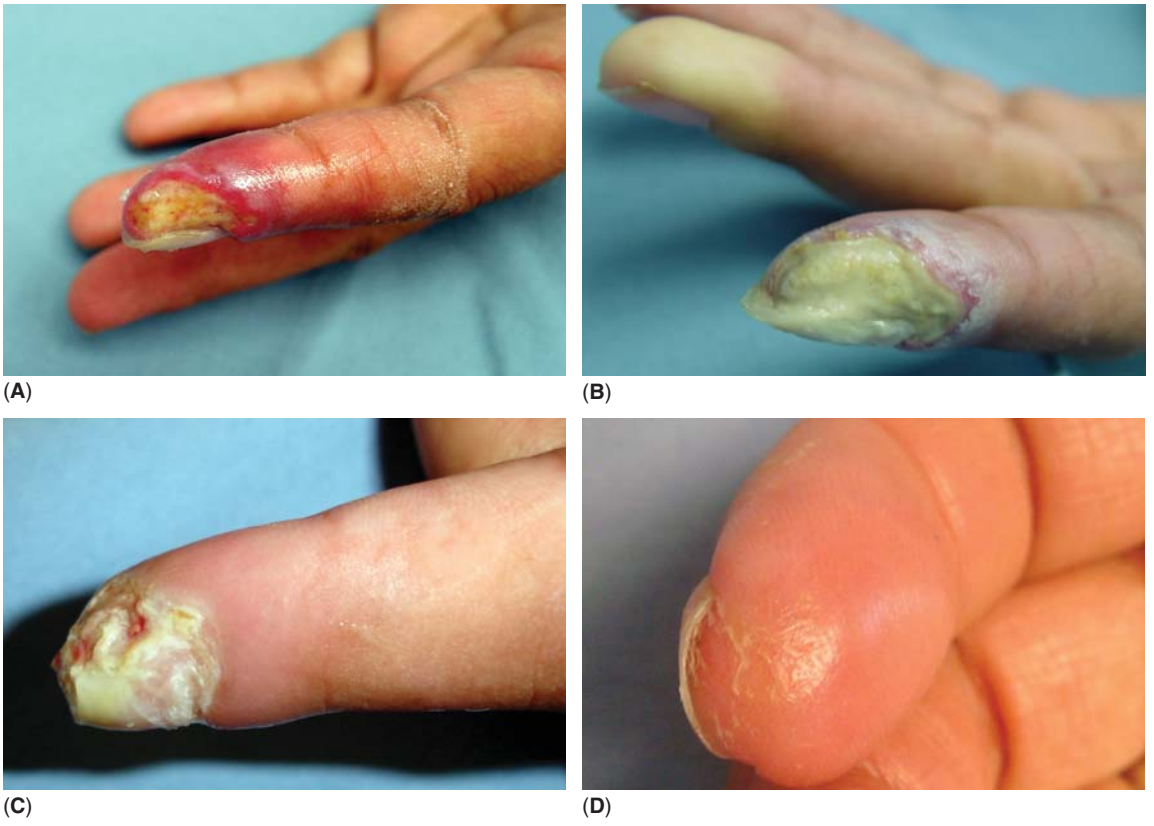


Figure 5.53 Examples of digital ulcers in systemic sclerosis (scleroderma).

Digital ulcers are a cause of great morbidity in these patients. Panels **A**–**D** show some challenging clinical situations. It is our view that digital ulcers in these patients should be evaluated by MRI before embarking on any intervention; osteomyelitis and septic arthritis can be difficult to detect clinically. It should be noted that ulcers on the fingertips are likely due to poor vascular supply, and that the digital blood vessels are obstructed and do not respond well to vasodilators. Still, some systemic vasodilator therapy is worthwhile, particularly with calcium channel blockers and sildanefil. Care must be taken not to lower the blood pressure to the point that vascular flow is adversely affected. Bone seems to be exposed in Panel **A**. Systemic antibiotics may be needed for several weeks, but the possibility of amputation is high. The finger in Panel **B** needs to be surgically debrided to evaluate the presence of bone involvement. If the bone is not involved, enzymatic debridement could be initiated. A similar situation is present in Panel **C**. Of course, in all of these three cases one would be wise to obtain an MRI at baseline. Panel **D** shows the typical indentation (pitting scars) present on the pulp of the finger in many patients with systemic sclerosis. It is probably due to ischemia and collapse of the underlying tissues.



Figure 5.54 Systemic sclerosis (scleroderma) digital ulcers/ partial healing.

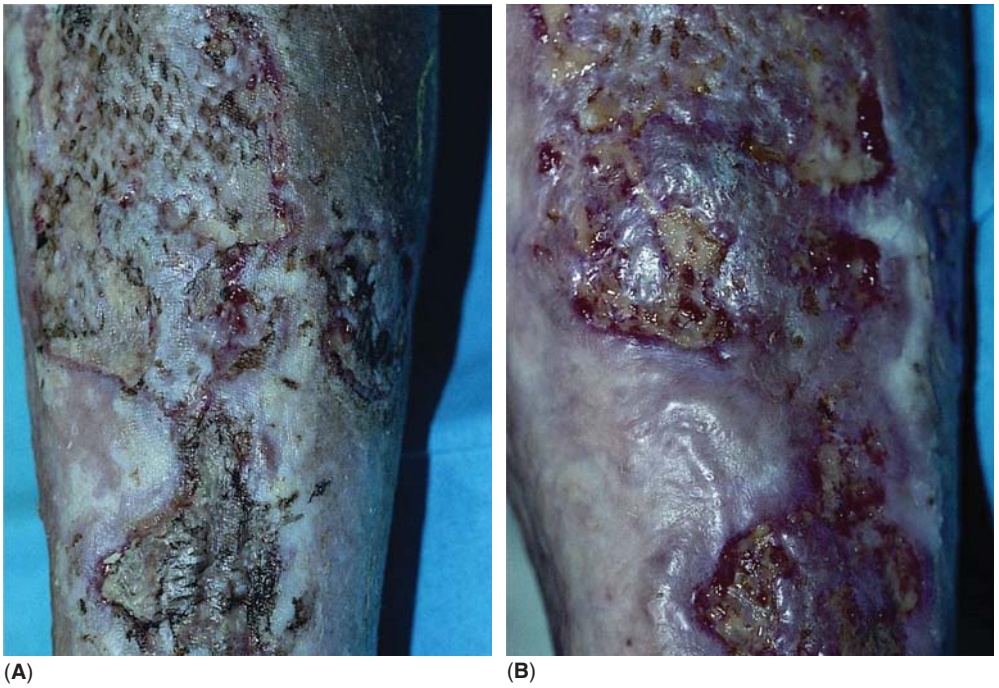
She also has systemic sclerosis and persistent digital ulcers. The thumb ulceration seen here was treated with a hydrogel, which led to pain control, painless debridement, and stimulation of granulation tissue. Her clinical course was complicated by frequent bouts of ulcer infection. It is often difficult to tell whether a sudden worsening of these digital ulcers is due to infection or ischemia. If antibiotics need to be used, they probably have to be administered for prolonged periods of time, because of the vascular deficit and fibrosis, as well as poor intestinal absorption. We typically administer systemic antibiotics for at least 2 weeks.



(**A**) (**B**)

Figure 5.55 A recalcitrant leg ulcer in a patient with advanced systemic sclerosis (scleroderma).

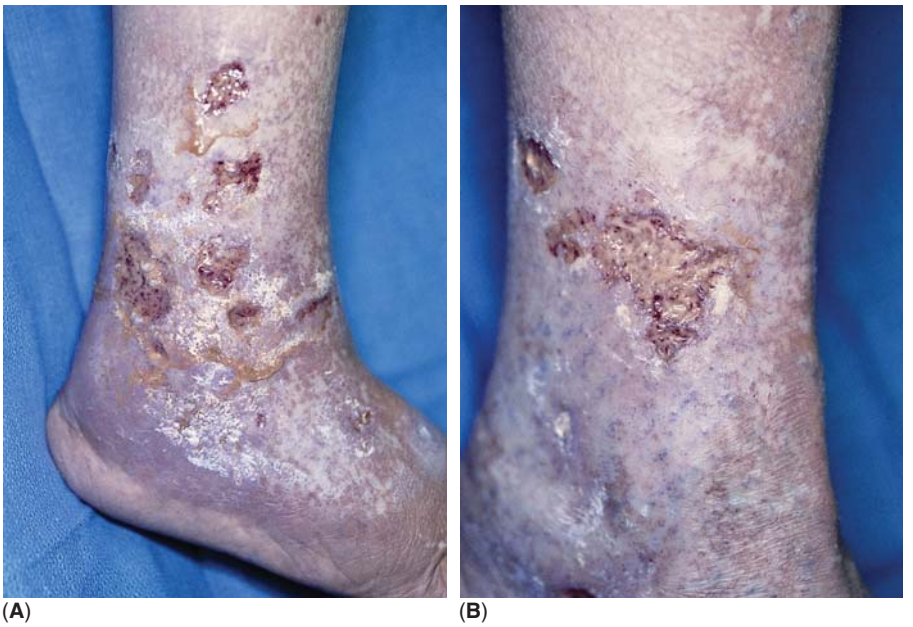
This patient has had systemic sclerosis for more than 15 years. Her leg ulcer (Panel **A**) did not improve significantly over 2 years (Panel **B**). It is true that the granulation tissue and wound bed would improve, but epithelialization would not take place. Several biopsies showed no evidence of malignancy. Treatment with moisture-retentive wound dressings and bioengineered skin did not lead to resurfacing of the ulcer. In such cases, the goals of treatment are patient's comfort and facilitating daily activities. The patient was treated with foam dressings and mild compression. Multiple factors in systemic sclerosis contributed to her inability to heal: immobility due to contractures, extremely poor nutrition from dysphagia and poor absorption, and decreased blood flow due to vascular intimal hyperplasia. She was treated with hyperalimentation but finally succumbed to her disease.



(**A**) (**B**)

Figure 5.56 Calcinosis and ulcers/follow-up.

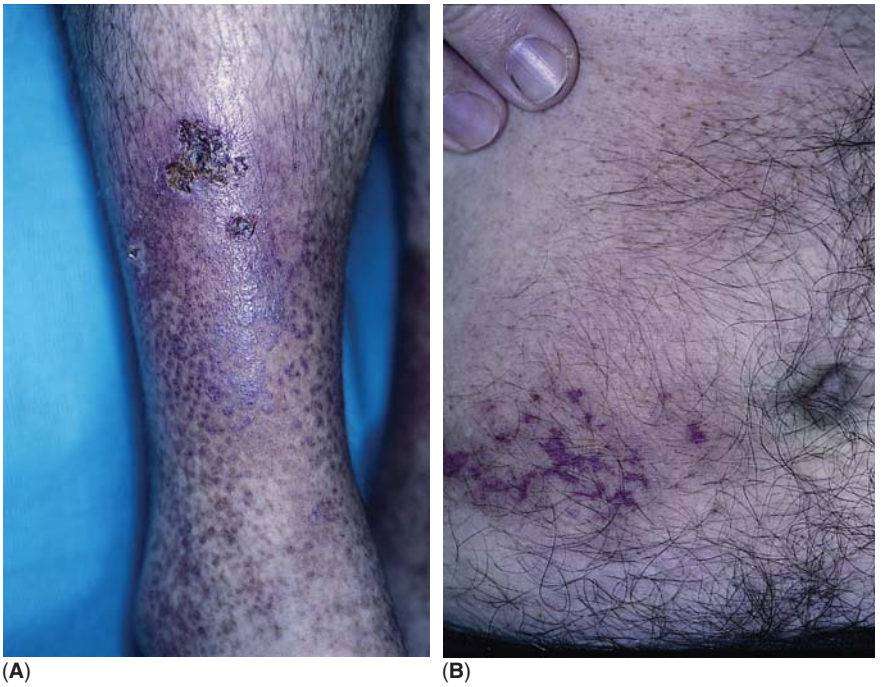
This middle-aged woman had classical CREST syndrome, which represents a subgroup of patients with systemic sclerosis (scleroderma). Her main clinical problem was these extensive ulcerations on the lower extremities, which were literally filled with calcium deposits. Various wound care approaches were tried with minimal results, including the use of hydrocolloids and hydrogels. Panel **A** shows the wound a week after autologous split-thickness skin grafting. The graft did not take but was able to stimulate ulcer healing; there is better granulation tissue and some re-epithelialization (Panel **B**). With all that calcinosis, it is highly unlikely that she would heal.



(**A**) (**B**)

Figure 5.57 Multiple leg ulcers.

The etiology of these ulcerations was not clear. There are areas of atrophie blanche (Panel **A**). Histologically, fibrin thrombi were present in the dermal vessels, suggesting cryofibrinogenemia or the antiphospholipid syndrome. These patients generally need to be hospitalized for local wound care, whirlpool, leg elevation, and intensive treatment with antibiotics. The skin surrounding the ulcers is white and studded with tiny blood vessels, as in atrophie blanche (Panel **B**). The term atrophie blanche is purely descriptive and does not tell us about the etiology of the ulcers. Atrophie blanche is seen not only in venous and arterial diseases, but also in vasculitis, cryofibrinogenemia, and other conditions characterized by thrombosis of dermal blood vessels.



(**A**) (**B**)

Figure 5.58 Cryofibrinogenemia with a widespread skin involvement.

This 44-year-old man has purpura and painful ulcerations, with areas of livedo reticularis (Panel **A**). A number of diagnoses were considered, including cryofibrinogenemia, cryoglobulinemia, vasculitis, Waldenstrom's macroglobulinemia, and the antiphospholipid syndrome. His plasma was positive for cryofibrinogen, and biopsies of the purple areas showed fibrin thrombi within dermal blood vessels. This suggested that his cutaneous findings were most likely due to cyrofibrinogenemia. He also had cutaneous abdominal areas of breakdown (Panel **B**). The ulcers were angular in shape, a finding we have often observed in other inflammatory conditions and when small cutaneous blood vessels are occluded. He responded dramatically to anabolic steroids; we presently use danazol. Surprisingly, patients with cryofibrinogenemia (unlike cryoglobulinemia) do not consistently experience worsening of their symptoms upon cold exposure.



Figure 5.59 Cryofibrinogenemia.

These dramatic leg ulcerations developed within a few weeks in an 87-year-old man with many medical problems, including severe congestive heart failure. By plasma measurements of cryofibrinogen and by histology, we made the diagnosis of cryofibrinogenemic ulceration. We wanted to treat him with anabolic steroids but these agents can cause sodium retention that can greatly worsen congestive heart failure. We decided to hospitalize him and treat him with anabolic steroids in a controlled setting where he could be closely monitored. His pain disappeared quickly with stanozol. We would now treat him with danazol, because stanozolol is no longer available. That systemic treatment and local wound care with surgical debridement and slow-release antiseptics (cadexomer iodine) led to the healing of the ulcer.



Figure 5.60 An example of cryofibrinogenemia treated with danazol.

This patient was a bus driver with a history of recurrent and painful ulcers on his foot (Panel **A**). Initially, the patient was treated for the presumptive diagnosis of pyoderma gangrenosum. However, he did not respond to high doses of prednisone and actually worsened (Panel **B**). He insisted on working, even though we were concerned about his use of this dominant foot while driving his bus. His plasma levels of cryofibrinogen were elevated. In spite of the biopsy not showing the classical findings of dermal fibrin thrombi, we decided to treat him for the possibility of a cryofibrinogenemic ulcer. His ulcer healed in 2 months with danazol treatment (Panels **C** and **D**). His ulcer has not recurred for at least a year. (copyrighted, V. Falanga, 2009).



Figure 5.61 Cryoglobulinemia.

The extensive necrosis and microlivedo pattern shown here should always raise the suspicion of ulcerations due to obstruction of small blood vessels. In this case, the underlying condition was cryoglobulinemia. However, a similar presentation would be seen with other conditions where microthrombi are present in the dermis (i.e., cryofibrinogenemia, antiphospholipid syndrome). Such patients often need therapy with immunosuppressive agents. Concomitant hepatitis C infection should always be excluded.



Figure 5.62 An unusual case of cryoglobulinemia.

The punched out ulcers in this 74-year-old woman suggested a number of possibilities, including vasculitis, infection, and factitial disease. Because of the sudden onset of her ulcers, she was admitted to the hospital. Workup showed that she had cryoglobulinemia. She died shortly thereafter because of numerous medical problems. She would have been treated with immunosuppressive drugs, paying close attention to her systemic complications. Painless debridement with hydrocolloid or other moisture-retentive dressings would have improved the wound bed.



Figure 5.63 An example of calciphylaxis and approach to treatment.

This 61-year-old woman developed erythematous, painful patches on her legs. There were areas of microlivedo. The larger ulcer developed after a small punch biopsy, which was initially interpreted by another group as representing a small-vessel vasculitis (Panel **A**). Blood work was negative for perinuclear antineutrophil cytoplasmic antibodies (P-ANCA), cytoplasmic antineutrophil cytoplasmic antibodies (C-ANCA), cryoglobulinemia, and cryofibrinogenemia. We decided to perform a larger excisional biopsy of the ulcer margin. The histology now showed calciphylaxis, but the patient did not have renal failure, hyperparathyroidism, or an elevated calcium-phosphate product, which have been said to be classical for calciphylaxis. The patient did not show much improvement on systemic corticosteroids and was admitted to the hospital for intravenous antibiotics, debridement, and bioengineered skin application (Panel **B**) to achieve proper wound bed preparation. The use of bioengineered skin helped her pain significantly. She healed in 3 months (Panel **C**) and remained healed for more than a year (Panel **D**). Copyrighted, V. Falanga, 2009.

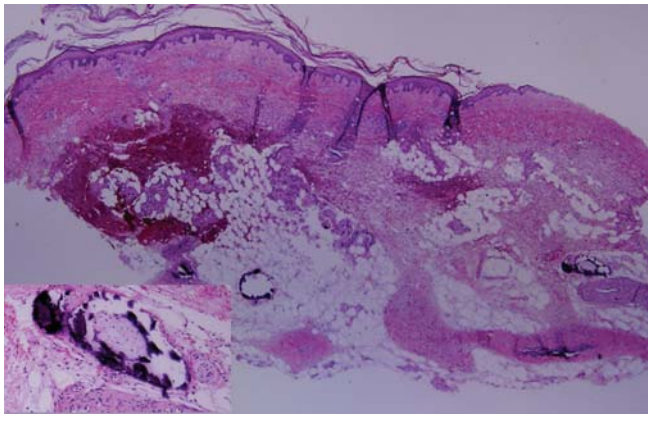


Figure 5.64 Calciphylaxis: Histologic findings.

This photomicrograph shows prominent calcification within some of the dermal vessels (inset), as well as diffuse calcification within the septae of the subcutaneous tissue and deep dermis. The calcium deposition is easily seen on H&E sections. Copyrighted, V. Falanga, 2009.

6 Neoplasms and ulcers

Skin cancers are the most common form of malignancy. Moreover, contiguous extensions or metastases generally take place from lungs, breast, lymphomas, and leukemias (particularly myelomonocytic). Certain conditions have to be present, however, for the development of ulcerations in the setting of malignancies in the skin. For the most part, this has to do with the size of the tumor or whether the cancer arises within pre-existing ulcerations. Neoplasms are highly dependent on angiogenesis and blood supply for continued and stable growth. Generally, it is when growth exceeds vascular supply that ulcers occur within a neoplasm. In other situations, neoplasms develop within ulcers, such as the typical occurrence of basal cell or squamous cell carcinoma in non-healing skin ulcers. A history of ionizing irradiation predisposes patients to the development of primary cutaneous malignancies at the site of radiation, even decades later. Malignant processes, primarily from the skin, from underlying tissues, or from metastases may ulcerate in older or fragile skin.

The diagnosis of neoplasia in ulcers can be difficult, especially when the clinical picture is that of a leg ulcer. For example, basal cell carcinoma (BCC) can present as granulation tissue-like material within venous ulcers, and is often associated with intermittent episodes of look-alike or actual re-epithelialization. It is generally good practice to biopsy leg ulcers that have failed to heal. The timing of the biopsy is uncertain, however. Some clinicians suggest biopsying leg ulcers that have not shown evidence of healing for a period of 2–3 months. This is not unreasonable, but one must remain flexible about this. For example, a sampling problem exists; one biopsy does not necessarily exclude the presence of cancer. Moreover, as we have just stated, intermittent episodes of re-epithelialization can occur within a malignant process. The location of the ulceration is also important. Thus, an ulcerated lesion in areas other than the leg will immediately suggest the possibility of cancer, and a biopsy should be preformed at the start of the evaluation. Another pitfall regarding biopsies of tumors is that a small shave or punch biopsy of the edge of the wound can often be uninterpretable because of the associated inflammatory process and thus completely miss the tumor. If the clinical situation demands it (i.e., unclear diagnosis and failure to heal), one needs to perform an excisional biopsy that goes at least 1–2 cm beyond the wound's margins, into seemingly normal or intact skin. We have found this is particularly true with lymphomas. Occasionally, the tumor is at the base of the wound. This situation arises in cases of recurrent cancers. Indeed, histologic findings of fibrosis or sclerosis can mislead the clinician into thinking that only a scar is present; the fibrosis may simply be a reaction to the tumor and a deeper biopsy will reveal the true malignant histologic findings.

Ulcerated tumors can be very exudative and foul-smelling, features that can contribute to a substantial management problem. This clinical picture is not uncommon with breast carcinomas and with certain lymphomas. In end-stage cancer, and when the ulcerated lesions are extensive, the goal is to provide comfort to the patient and make wound management easier. Antiseptics, which are generally avoided for fear of inhibiting healing, can be helpful in this particular situation. Certain topical antibiotics, such as metronidazole, can also decrease the bacterial burden and improve odor control.

Clinical points

- Nonhealing ulcers with exuberant granulation tissue should be biopsied to exclude basal cell carcinoma.
- Malignancies within ulcers arise more commonly with prior ionizing radiation to the area, or even extensive sun exposure over a long period of time.
- Intermittent re-epithelialization in nonhealing wounds should raise the suspicion of an underlying malignancy.
- Cutaneous lymphomas are often purple in color and ulcerate as they enlarge. Therefore, any ulceration surrounded by purple skin should be viewed with suspicion.
- Unusual streaks of hyperpigmentation of the lower extremity may represent Kaposi sarcoma. This is true also with diffuse hyperpigmentation of the leg, which might resemble venous disease.
- Kaposi sarcoma is strongly associated with herpes virus type 8 infection.
- Squamous cell carcinoma can arise in chronic wounds and scars. It is quite common and behaves very aggressively in patients with epidermolysis bullosa, a genetic blistering disease.
- Tumors infiltrating the skin can block lymphatic channels and cause a clinical picture of cutaneous edema. The edema separates the skin pores, giving the appearance of an orange peel (or peau d'orange).
- The diagnosis of lymphomas and other tumors within ulcers can be missed when the biopsy is small and only involves the inflammatory areas of the ulcer. When indicated, the biopsy should extend well beyond the ulcer's edge.
- Myelomonocytic leukemia commonly involves the skin.
- Ovarian tumors can metastasize to the umbilicus. This is not common, but represents a classical presentation.
- In spite of the presence of an incurable cancer in the skin, the basic principles of wound care still apply in terms of controlling pain, discomfort, exudate, and edema.
- Surgical removal of metastases to the skin should be considered in the context of reducing the tumor burden and making the ulceration easier to manage.

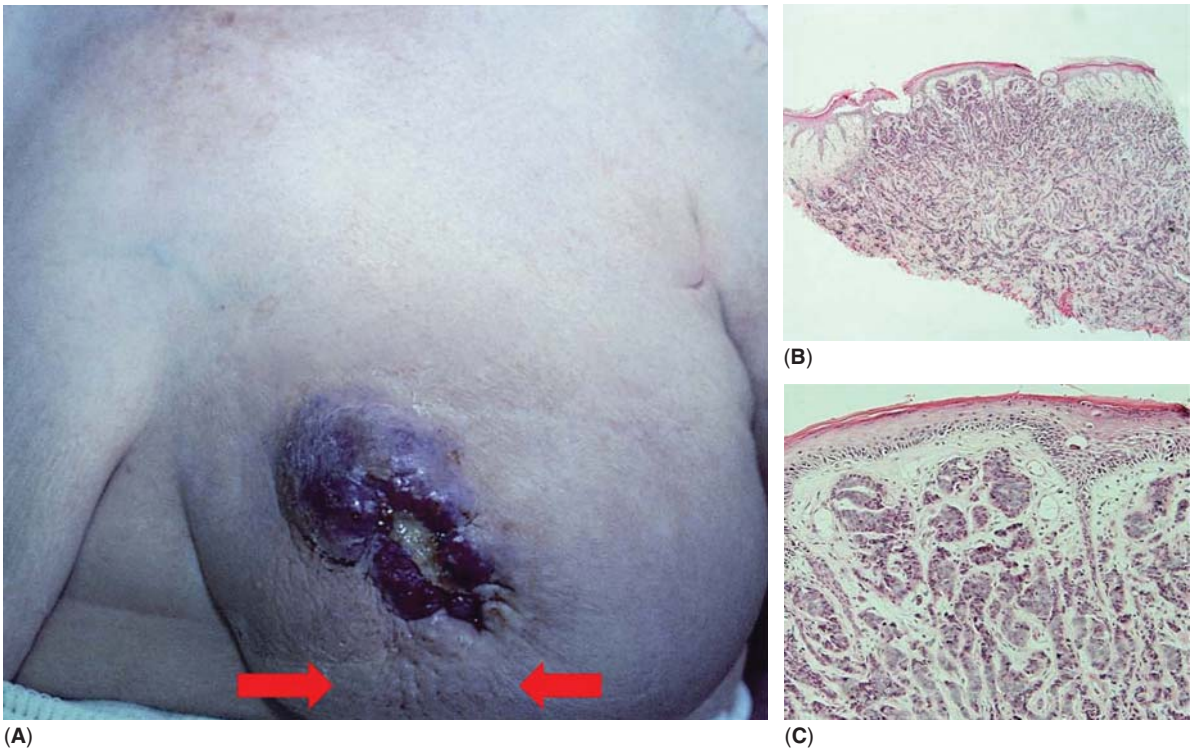


Figure 6.1 Breast carcinoma.

The patient has breast carcinoma extending to the overlying skin (Panel **A**). The lesions are typically quite hard and may assume this purple appearance. Ulceration is a common complication when the tumor reaches a certain size, thus outstripping its blood supply. In the photomicrographs at different magnifications in Panels **B** and **C** we see pleomorphic cells, a glandular-like infiltrate completely filling the dermis. The tumor infiltrating the skin also blocks the lymphatic channels, which may explain in part the dermal and subcutaneous edema. One other clue to lymphatic obstruction within the tumor is the clinically visible separation of hair follicles from one another, which gives the clinical appearance of what is called "peau d'orange" (red arrows in Panel **A**).



Figure 6.2 Rectal carcinoma extending to the overlying and surrounding skin.

This photo shows an extensive local extension of recurrent rectal carcinoma, practically involving the whole buttocks area. The entire perineum is infiltrated by tumor cells and, probably because of the concomitant presence of inflammation, the area is quite tender. The pain is unbearable, and the patient needs to be made more comfortable with potent narcotics. The region immediately adjacent to the anus is ulcerated and weeping. The approaches to manage this wound might include gel dressings to the ulcerated area, powerful systemic narcotics, and a pressure-relieving surface. Here, too, one can see areas of peau d'orange, which suggest infiltration and obstruction of the lymphatic channels by the tumor.



Figure 6.3 Ovarian cancer.

The patient had advanced ovarian cancer. The purple, ulcerated nodules seen in the photograph represent extension of the tumor to the abdominal wall and skin. Involvement of the skin within the umbilicus (so-called Sister Mary Joseph nodule) is a well-described clinical feature of metastatic ovarian cancer. The nodule on the right may indeed represent the involved umbilicus.



Figure 6.4 An adnexal skin tumor masquerading as an ulcerated lesion on the plantar surface.

This young man had a nonhealing ulcerated lesion on his plantar surface for about a year. The ulcer would occasionally re-epithelialize, only to break down again. He was then referred to us. When we saw him, we thought this ulcer could represent a nonmelanotic melanoma or an appendegeal tumor. Indeed, a biopsy of the lesion seen in the photograph showed the typical histological findings of syringocystadenoma papilliferum, which is a benign skin tumor and more commonly observed on the scalp. The lesion was then completely excised. This case underscores the need for biopsy, especially when the location of the ulcer is atypical for common types of ulcerations, such as those due to venous insufficiency or diabetes.



(**A**) (**B**)

Figure 6.5a Basal cell carcinoma of the leg initially thought to be a traumatic wound.

This elderly woman has atrophic and fragile skin. She developed an ulcer on her shin (Panel **A**) which was first attributed to trauma. However, the ulcer failed to heal after several months. Upon our close evaluation of the wound bed we noted areas with a "pearly surface" (Panel **B**). This appearance and lack of healing suggest a skin cancer, particularly a basal cell carcinoma.

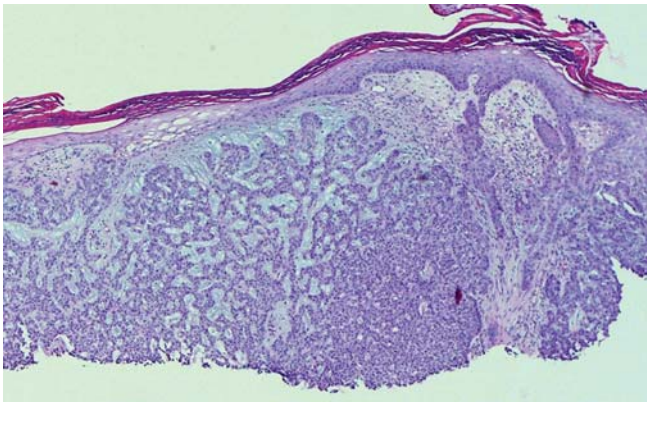


Figure 6.5b Basal cell carcinoma of the leg initially thought to be a traumatic wound/histology.

A biopsy of an area adjacent to the ulcer showed typical findings of basal cell carcinoma (BCC). One can see strands and masses of basaloid cells that originate from the overlying epidermis. BCC is the most common type of skin cancer. Timely and proper removal is curative, but a delay in diagnosis and certain anatomic locations (including the leg) have a worse prognosis.

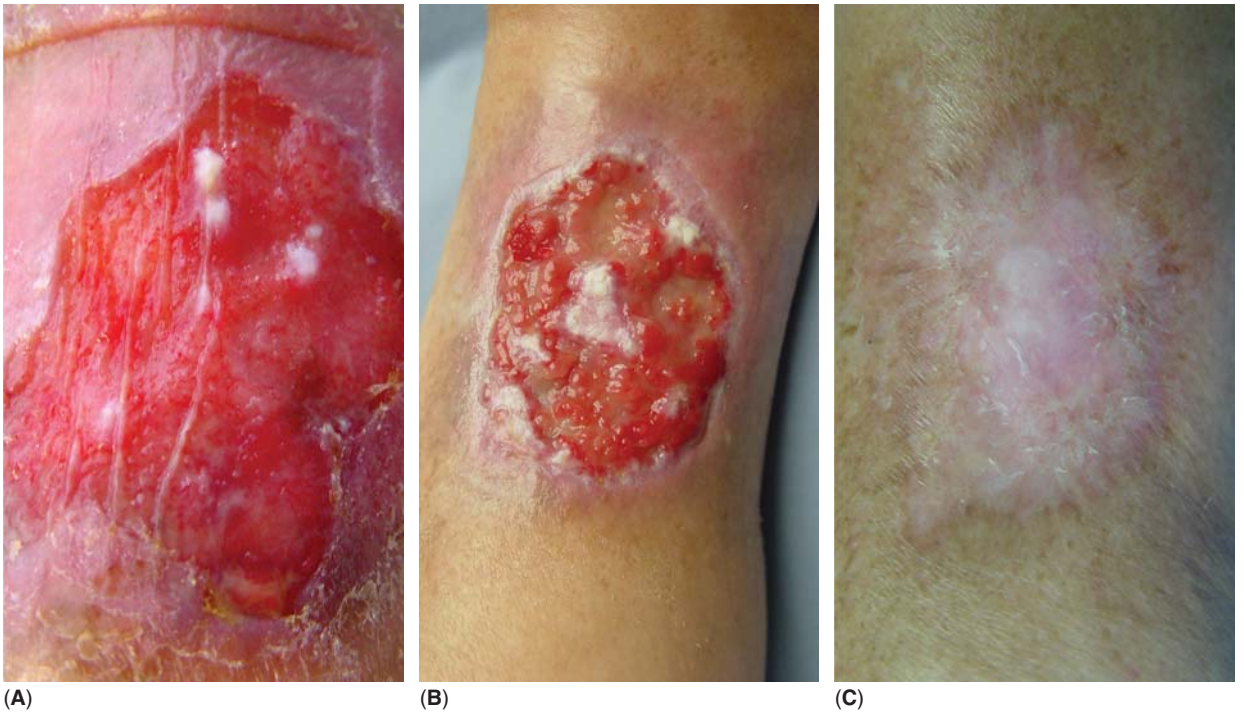


Figure 6.6 Basal cell carcinoma of the leg masquerading as a granulating wound.

Quite frequently, basal cell carcinoma can present as wounds showing almost optimal granulation tissue (Panel **A**). Clues to the diagnosis are failure to heal, a rolled border that seems to spill onto the surrounding skin, and intermittent (not connected) areas within the "granulation tissue" that seem to represent epithelium and attempts at healing. The patient was treated with Mohs micrographic surgery to ensure complete removal of the tumor. Panel **B** shows the wound 2 months after surgery. Complete closure was achieved with secondary intention several months later (Panel **C**).

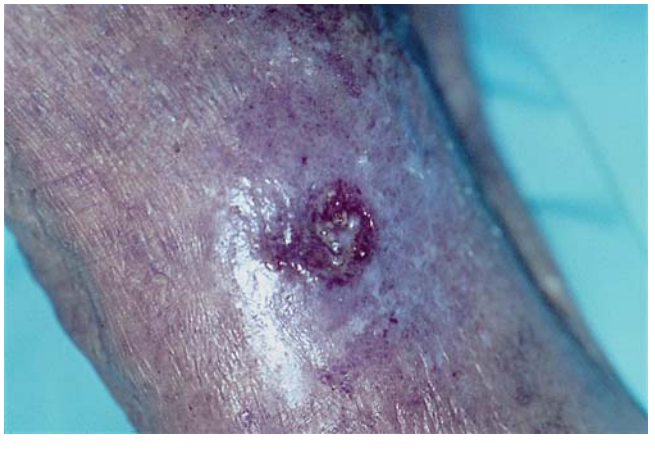


Figure 6.7 Basal cell carcinoma as a nonhealing ulcer of the leg.

This could easily be mistaken for a venous ulcer, given the surrounding hyperpigmentation and the lack of specific features pointing to a tumor. However, the ulcer did not heal with compression bandages and was therefore biopsied. The histology showed a basal cell carcinoma. Management options for this ulcerated tumor include excision or Mohs micrographic surgery. Some people will consider cryosurgery or even the use of imiquimod (to destroy the tumor by inflammation) but, in our opinion, the treatment of this ulcerated cancer should be more definitive. We will stay away from the use of radiation because we have encountered a number of patients who have actinic damage on the leg and develop additional skin cancers after radiation.



Figure 6.8 Ulcerated basal cell carcinomas in venous insufficiency.

In this case, too, one might think of venous ulcers. In addition to hyperpigmentation, the patient's leg has the shape of an inverted "champagne bottle," so typical of lipodermatosclerosis and venous disease. The two wounds on the shin are confusing because of their shape, location, and seemingly good granulation tissue with little or no healing. However, biopsies of these margins and the "granulation tissue" in the wound bed showed a basal cell carcinoma. If the clinician is not extra vigilant and suspicious, this patient will typically be treated with compression bandages and followed for wound closure. However, one must keep a high degree of suspicion and always consider biopsies of these lesions when healing is only partial and is not sustained.



Figure 6.9 Basal cell carcinoma mimicking granulation tissue.

This lesion (red, ulcerated plaque) on the leg is another example of how a basal cell carcinoma (BCC) can present as "granulation tissue." However, it is not granulation tissue histologically but represents a BCC. Note again how the presumed granulation tissue seems to spill onto the surrounding skin. That is quite typical of BCCs.



Figure 6.10 Ulcerated basal cell carcinoma of the cheek.

The patient had a "bump" on her cheek for at least 2 years. Over the last several months, it became necrotic and ulcerated. One can see areas of scarring inferiorly. The cancer was diagnosed by biopsy, and was treated by excision and a cutaneous flap.



Figure 6.11 Large basal cell carcinoma with squamous cell differentiation.

This 62-year-old man presented with a large cutaneous and verrucous mass on his right shoulder that kept ulcerating and consisted of multiple nodules. We performed biopsies that were diagnostic of basal cell carcinoma (BCC) but with squamous cell differentiation; the latter feature is associated with a worse prognosis. It was unclear how long (probably years) this dramatic mass had been present, but in our experience the failure to seek medical attention is due to severe denial or psychological/psychiatric problems. The patient underwent wide excision and reconstruction with a latissimus dorsi flap and with an autologous split thickness skin graft. The patient also received radiation therapy to the area. While BCCs rarely metastasize, they can be locally infiltrative. However, when reaching a large size, as in this case, the tumor has a much higher chance of metastazising. Large size and specific locations (eyelid, nasal labial folds, etc.) are associated with a greater frequency of metastases.

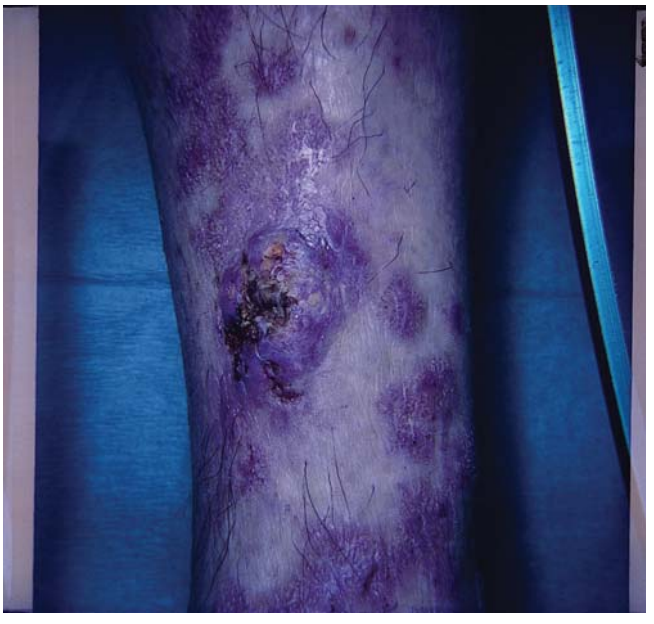


Figure 6.12 Ulcerated squamous cell carcinoma of the leg.

This elderly woman had numerous nodules and plaques on her leg. The anteriorly located and ulcerated nodule was initially thought to represent a keratinous cyst, which some people still call sebaceous cyst. However, the histology showed that this was a squamous cell carcinoma. Unlike basal cell carcinomas, squamous cell carcinomas have a greater potential for spreading and metastasizing. In our experience, squamous cell carcinomas of the leg commonly masquerade as ulcerated cysts. She had received radiation therapy to her leg decades earlier, which would predispose her to the development of squamous cell carcinoma. The other nodules were also found to represent squamous cell carcinomas. The management of these cancers would include excision and/or Mohs micrographic surgery; further radiation therapy should be avoided.



Figure 6.13 Squamous cell carcinoma.

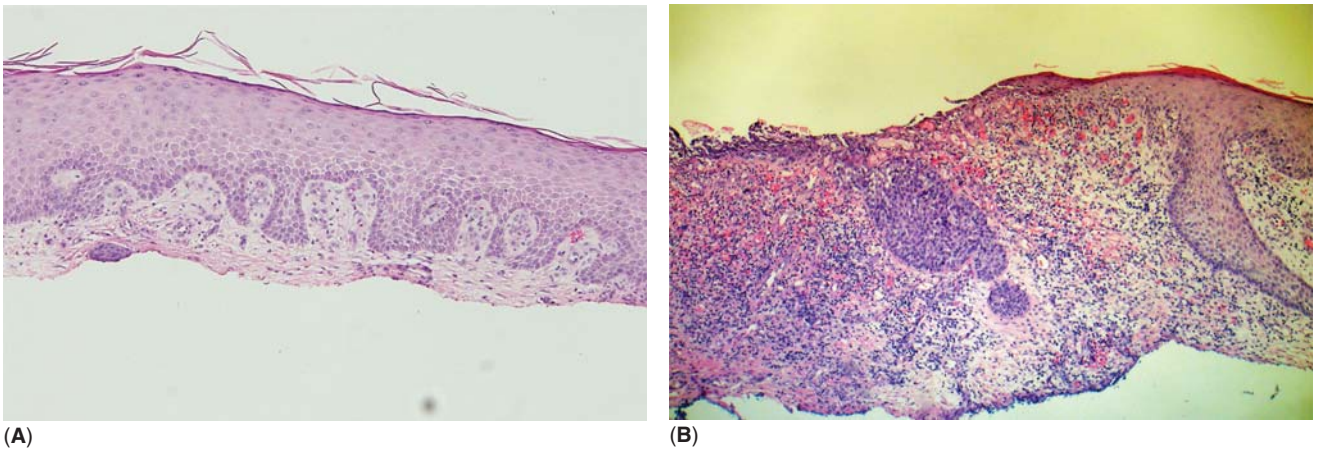
This man had received political asylum after escaping from a Central American totalitarian country. While in prison there, he had received a bayonet injury to both legs more than 20 years earlier. The wound never healed and he refused further treatment. Several years later, the wound began to enlarge and showed increasing amounts of exudate and necrosis. Multiple biopsies confirmed the clinical suspicion that this represented a squamous cell carcinoma. It was poorly differentiated, pointing to an unfavorable prognosis. The patient vehemently refused amputation and was treated for a while with surgical debridement, occlusive dressings, and Mohs micrographic surgery to decrease the tumor burden. However, the cancer extended to the bone and osteomyelitis became evident. He eventually agreed to leg amputation. However, a few years later he died from metastatic squamous cell carcinoma, most likely from this leg cancer.



Figure 6.14a Ulcerated squamous cell carcinoma and diagnostic difficulty.

This ulcerated shin plaque was present for more than 5 years. When he was referred to us, we suspected a malignant process, such as amelanotic melanoma, basal or squamous cell carcinoma, or an appendegeal skin tumor. With the lack of scaling, squamous cell carcinoma would not be at the top of the differential diagnosis. We decided to perform a shave biopsy.

While generally superficial, a shave biopsy samples a larger area of the lesion of interest. The histology was nonspecific and showed no evidence of squamous cell carcinoma. However, we were still suspicious and did not accept the negative findings, especially after we analyzed the histological slides ourselves (Figure 6.14b). A larger, excisional biopsy was done and that specimen did show an invasive squamous cell carcinoma. The patient underwent Mohs micrographic surgery, which should be curative. This particular case illustrates the importance of correlating the clinical findings and impression with histological findings. Persistence is needed when a tumor is suspected.



(**A**) (**B**)

Figure 6.14b Ulcerated squamous cell carcinoma and diagnostic difficulty/histology.

Panel **A** shows the histology of the initial shave biopsy. The pathology report stated that there was no frank evidence of a malignant process. However, our own review of the histology made us suspicious and eager to perform a more extensive biopsy. For example, in our opinion the histology seen in Panel **A** shows atypical cells at the dermo–epidermal junction and superficial dermis. Moreover, there is a relative lack of normal progression of epidermal differentiation from the basal layer to the stratum corneum. Panel **B** shows the histology from the second and more extensive biopsy. The presence of a moderately differentiated squamous cell carcinoma is obvious in this photomicrograph. The lessons in this case are the following: (i) squamous cell carcinomas do not always show extensive scales; (ii) a shave biopsy, which is more superficial, may obviously miss the tumor. Therefore, the clinical assessment needs to be correlated with the histology; (iii) we had the experience ourselves of evaluating the histology, but a similar conclusion about the shave biopsy may have been achieved by consulting more closely with a dermatopathologist or requesting another opinion about the histology.



Figure 6.15a Superficial spreading melanoma.

Melanomas generally ulcerate only when they get to a certain size and are of the nodular type; ulceration is associated with a worse prognosis. The pigmented lesions shown here are biopsy-proven superficial spreading melanomas. When excised at this stage, a chance for cure is high.

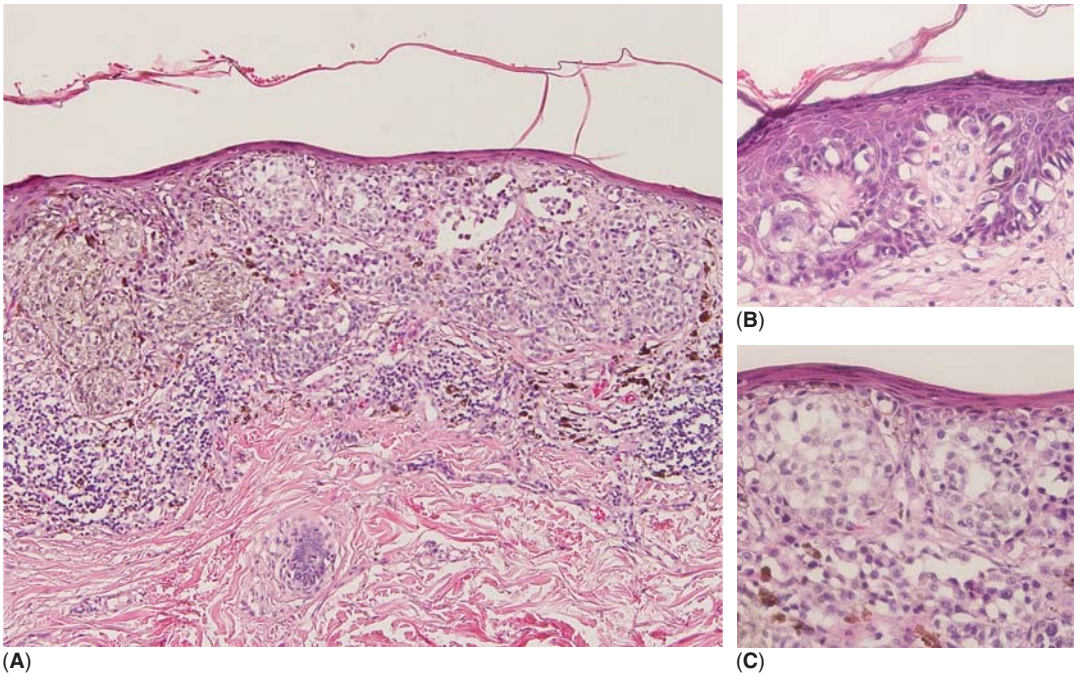


Figure 6.15b Superficial spreading melanoma/histology.

These are photomicrographs of superficial spreading melanoma at different levels of magnification. Panel **A** shows a superficial spreading melanoma with a vertical growth phase. Panels **B** and **C** show nests of melanoma cells at the dermal–epidermal junction and within the epidermis, where one can see atypical epithelioid cells. In these particular illustrations there are no obvious mitotic figures, but one should look for them during a definitive histopathologic evaluation, because both mitotic figures and histologic evidence of ulceration portend a poor prognosis.

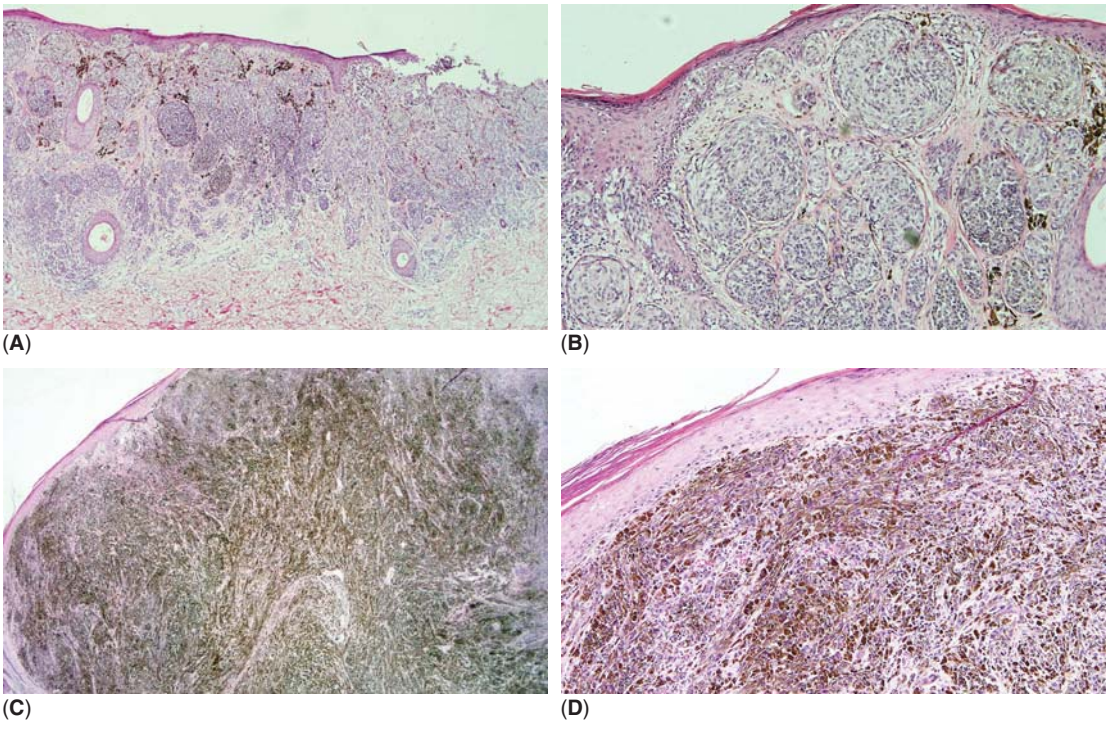


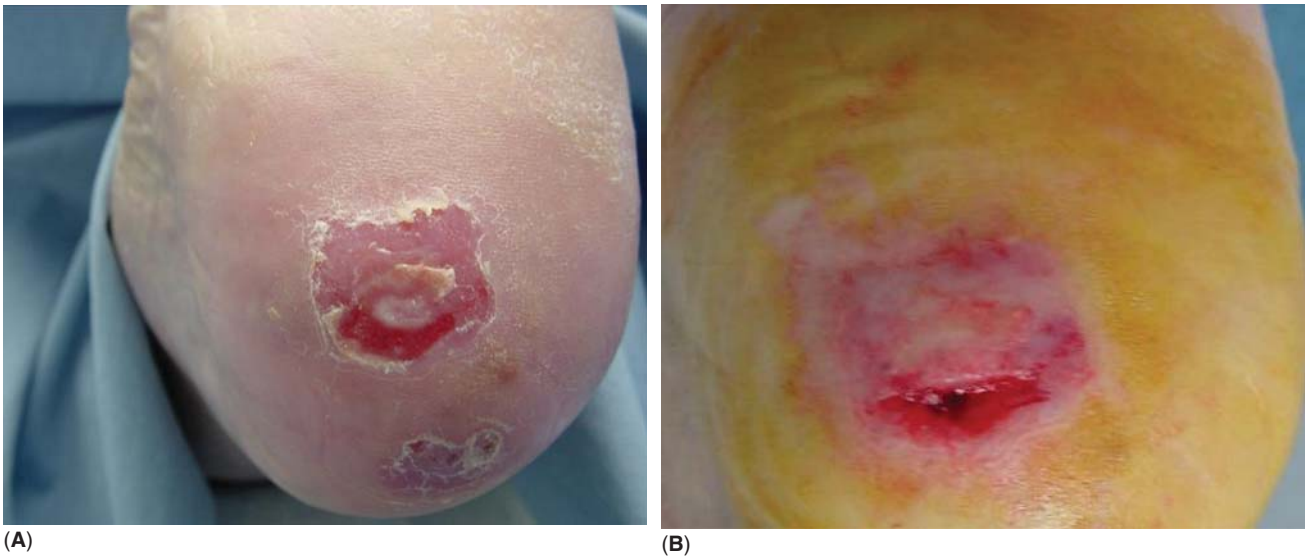
Figure 6.15c Superficial spreading melanoma with a vertical growth phase/nodular melanoma/histology.

The four Panels (**A–D**) shown here represent photomicrographs of a more invasive type of melanoma. The histology indicates a much more invasive tumor with very dramatic nests at the dermal–epidermal junction and with lots of pigment. The mitotic figures indicate a worse prognosis. Sometimes, melanoma cells can be spindle shaped (not the case here) and, in the absence of pigment, can be confused with other types of tumors such as squamous cell carcinoma. Special stains and immunostaining, including S-100, Melan-A, MART-1, and HMB-45 can be helpful in these situations. However, here the histologic pattern with nesting is more typical of melanoma.



Figure 6.16 Metastatic melanoma to the skin.

Melanomas commonly metastasize to the brain, lungs, and liver. In some unusual cases, as in this 67-year-old woman with a dramatic presentation on her leg, the melanoma metastasized to the skin. Over the last few years since she was diagnosed as having melanoma, she keeps getting recurrent and deep tumors, which require extensive excision down to muscle. Here one sees the result of a large excision on the lower part of her leg. The underlying muscle is clearly visible. The wound will require removal of residual melanoma and grafting.



(A) (B)

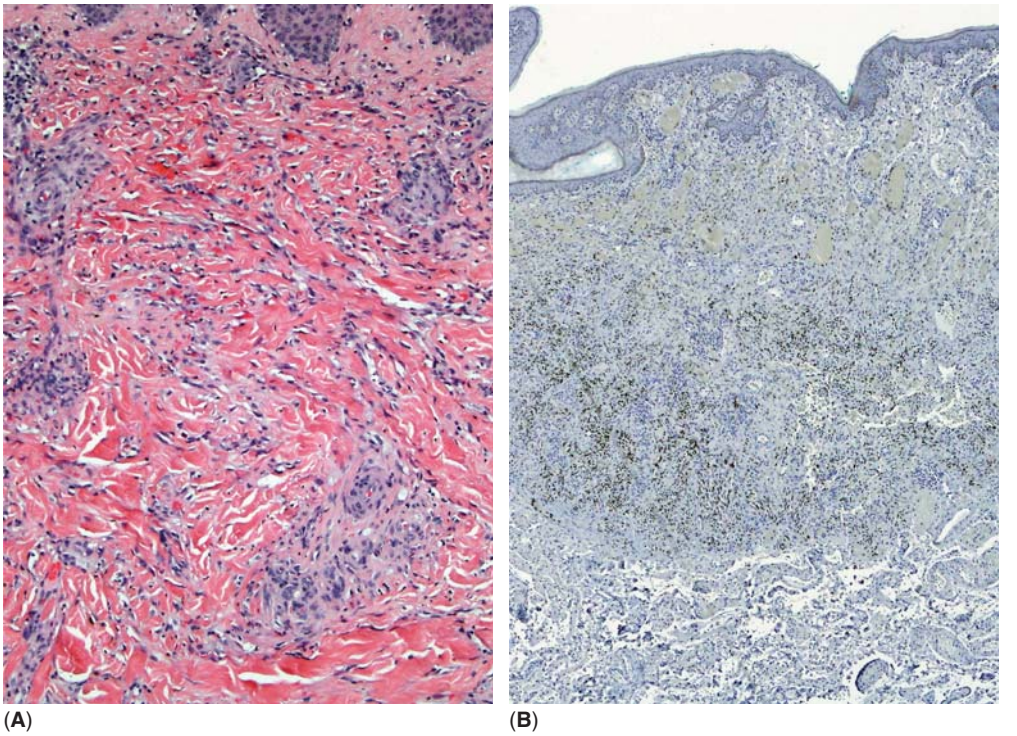
Figure 6.17 Amelanotic melanoma.

This elderly woman with psoriasis presented with a 4-month history of a scaly eroded plantar plaque that was partially responsive to topical corticosteroids (Panel **A**), prescribed by another physician. The wound did not heal, and the patient was then referred to us. Because of its solitary nature, red color within the lesion, and unusual location, we performed a biopsy to rule out a tumor. Panel **B** shows an overhead photograph indicating the site of the biopsy within the red component of the lesion. This biopsy showed an amelanotic melanoma, and special staining with S-100 and immunostaining with MART-1 confirmed the diagnosis. Extensive surgical excision, regional lymph node analysis, and interferon therapy were performed. She remained tumor free after 7 years.



Figure 6.18a Patch stage Kaposi sarcoma.

These purple flat and raised areas (macules and plaques) on this swollen foot are quite typical of Kaposi sarcoma, a vascular-associated cancer. This presentation could also be consistent with vasculitis and other infiltrative vascular tumors. In this case, the patient was of Mediterranean ethnic origin, and thus more likely to develop this life-threatening condition; metastases to the lungs and gastrointestinal tract are common. This type of cancer is associated with infection with human herpes virus type-8, and is therefore also seen in other immunosuppressed states including organ transplantation. He did not have evidence of infection with the human immunodeficiency virus (HIV), which is another common clinical setting for the development of this cancer. In some cases the hyperpigmentation associated with this tumor may be confused with that observed with venous insufficiency, and the clinician must be careful not to commit that diagnostic error. Occasionally, one has to biopsy the involved hyperpigmented skin to make this differentiation.



(**A**) (**B**)

Figure 6.18b Patch stage Kaposi sarcoma/histology.

Panel **A** shows uniformly atypical spindled cells infiltrating the papillary dermis and forming the typical slit-like vascular channels. These findings strongly suggest the diagnosis of Kaposi sarcoma. Panel **B** shows positive immunostaining for herpes virus-8, which is consistent with that diagnosis. Some mitotic figures are present as well.



Figure 6.19a Kaposi sarcoma and AIDS.

This 29-year-old man suffering from AIDS presented with these ulcerations on the lower leg and with very hard skin involving most of the leg (Panel **A**). Biopsy showed Kaposi sarcoma. This represented a more advanced stage of Kaposi sarcoma. On biopsy we found slit-like vascular channels, extensive hemorrhage, and atypical and bizarre spindle cells. The prognosis is poor.



Figure 6.19b Kaposi sarcoma and AIDS/chest involvement.

The patient also had large nodules on his chest. Some of them were linear in shape (left side of his chest), which is rather characteristic of Kaposi sarcoma occurring in homosexual patients with AIDS.



Figure 6.20 Non-Hodgkin's lymphoma.

These large tumors ulcerated and developed sinus tracts between them. As with other lymphomas, the purple color of the plaques and nodules is very helpful in pointing to the diagnosis.



Figure 6.21a Large cell lymphoma in a child.

This child was found to have a $CD30^-$ and $CD4^+$ lymphoma involving the entire thigh and lower abdomen. The tumors have ulcerated and become a difficult management problem because of the bloody exudate. Foam dressings and compression bandages can be used here to help absorb exudate and protect the area from trauma. He is unlikely to tolerate negative pressure treatment, due to the large size of this cancer. In this particular case, there is no obvious evidence of bacterial colonization and no odor from the thigh cancer. Otherwise, one can achieve some control of the exudate and odor with the use of Dakin's solution.

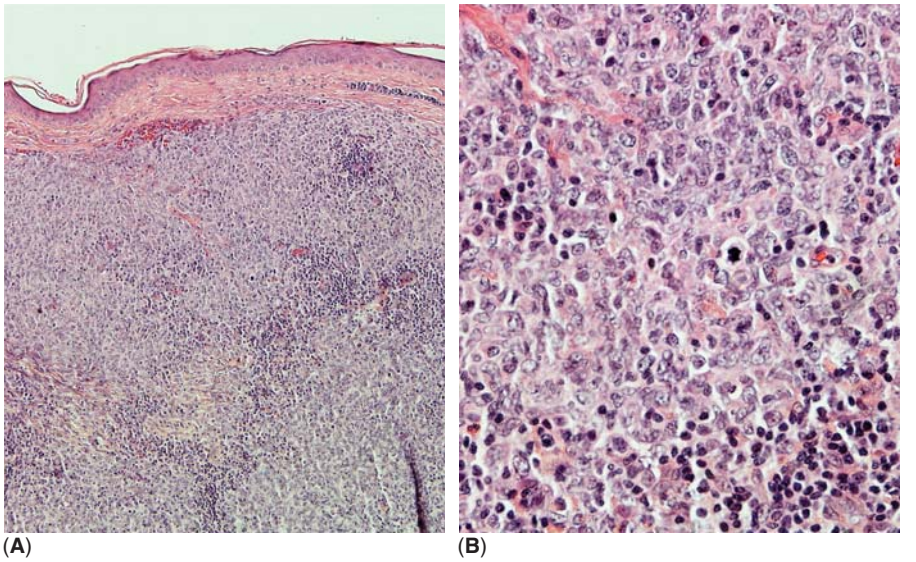


Figure 6.21b Large cell lymphoma in a child/histology.

Panels **A** and **B** are representative micrographs at different magnifications of this type of lymphoma. On H&E we see large, highly atypical cells (i.e., different sizes, nuclei, shape, and color). The cells are hyperproliferative and are exhibiting mitosis and apoptosis in different areas of the tumor.



Figure 6.22 Necrobiotic xanthogranuloma in multiple myeloma.

This necrobiotic xanthogranuloma was present in a patient with multiple myeloma. They are associated with paraproteinemia, and are actually more common on the face, particularly the eyelids. The histology is diagnostic or at least highly suggestive. These yellow-brown or red-brown plaques and nodules can appear as isolated or as multiple lesions. No satisfactory treatment is available, but intravenous immunoglobulin therapy appears to be promising. In this case, she was thought to have an infection at first, until a biopsy was obtained. From a wound management standpoint, removal of the necrotic areas is desirable. This could be achieved surgically, followed by negative pressure for a while. Bioengineered skin could be used to stimulate epidermal migration and closure. The leg is edematous, and therefore compression bandages might be helpful. This case illustrates that, in spite of the unusual etiology, certain basic wound care principles are helpful.



Figure 6.23 Cutaneous T-cell lymphoma and isolated tumors.

The cutaneous tumors in this adult were mostly about his ankle. A larger tumor became ulcerated, probably because it outstripped its blood supply. In spite of the presence of this cancer, one can see strands of epithelium running across the wound. This is also commonly observed in ulcers containing basal cell carcinomas. Therefore, partial and intermittent re-epithelialization should not fool the clinician into thinking that a cancer is not present. The patient was managed by the use of both excision and radiation. Foam dressings for the ulcerated tumor proved useful.

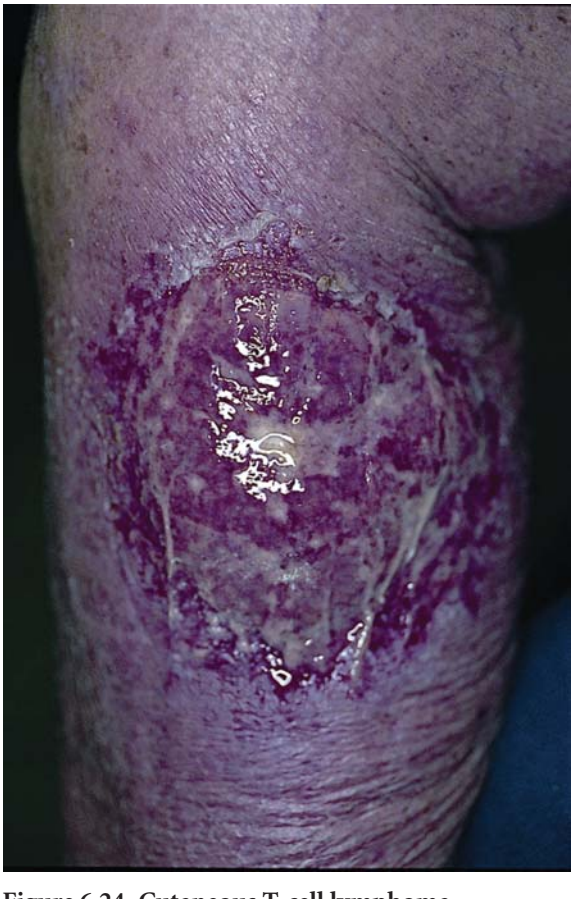


Figure 6.24 Cutaneous T-cell lymphoma.

This painful ulcerated tumor on the lower leg developed rapidly (within weeks) in this patient with pre-existing cutaneous T-cell lymphoma. Bacterial colonization was managed with the topical use of silver sulfadiazine and, subsequently, with slow release silver antiseptics. Once the infection or wound colonization is controlled, one can manage these lesions with occlusive dressings, such as films. She was eventually treated with electron beam therapy, which healed this ulcerated tumor.



Figure 6.25a Cutaneous T-cell lymphoma and ulceration.

The patient was 68 years old and had cutaneous T-cell lymphoma that was diagnosed 30 years earlier. Over the last few years, she began to have cutaneous nodules and tumors. This particular one has ulcerated. It was treated with radiation therapy and local wound care consisting of foam dressings, with eventual complete closure. During her clinical course, and due to bacterial colonization of the wound bed, she was treated with cadexomer iodine dressings.

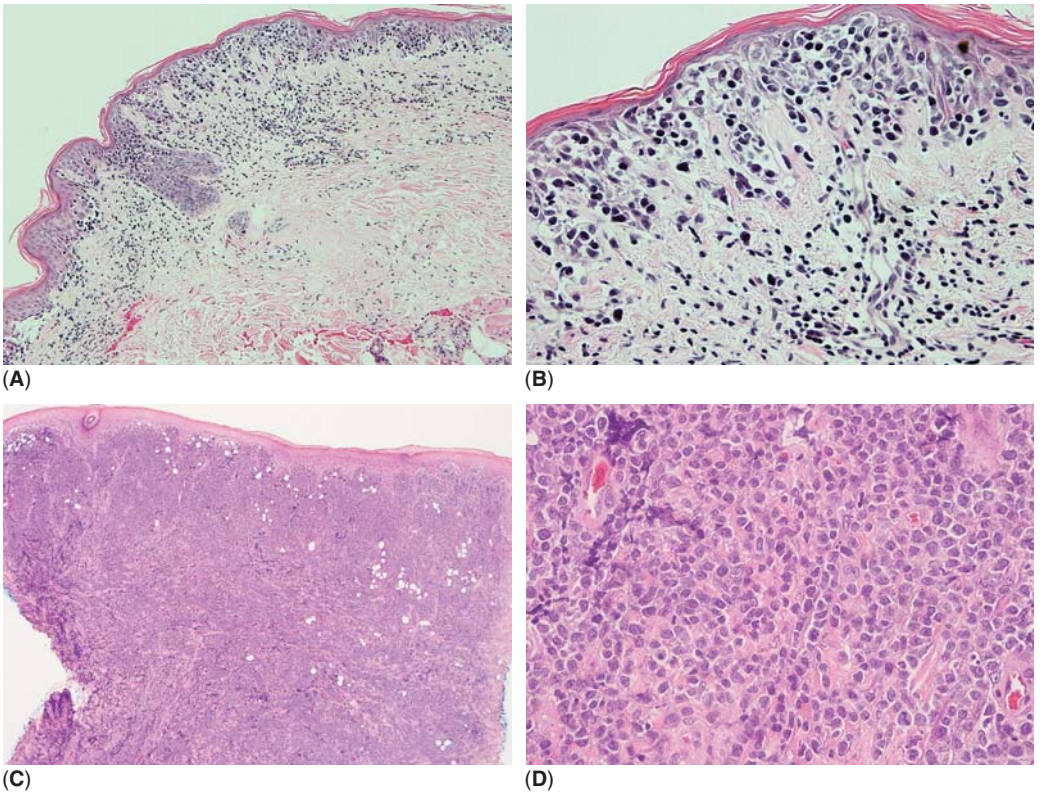
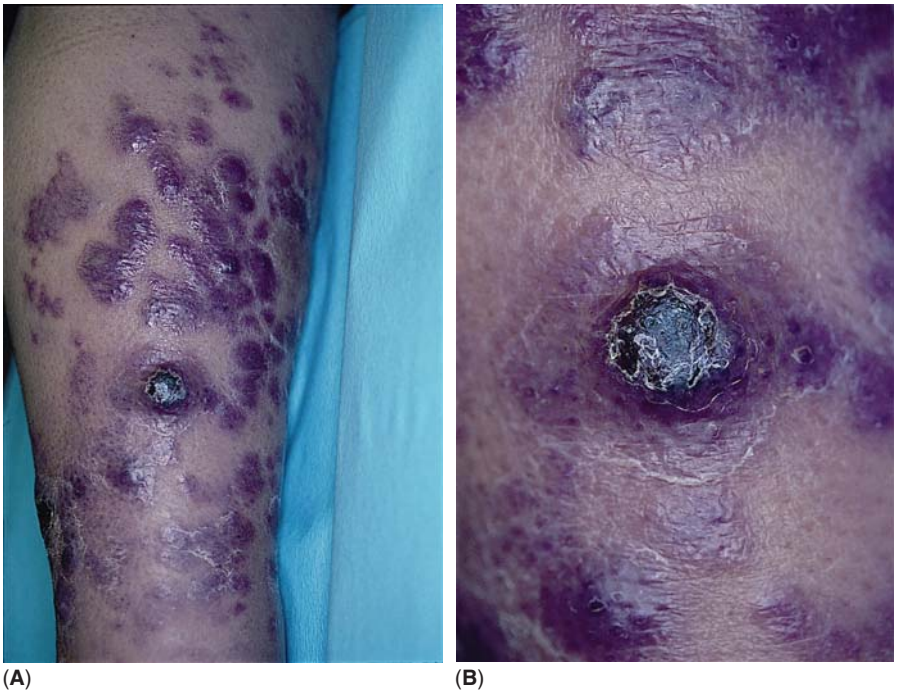


Figure 6.25b Cutaneous T-cell lymphoma and ulceration/histology.

The four photomicrographs (Panels **A–D**) show H&E sections of different fields of the tumor and at different magnification. The four panels also illustrate different presentations and stages of cutaneous T-cell lymphoma. Panels **A** and **B** indicate bizarre and large cells in the papillary dermis that are starting to infiltrate the reticular dermis. There is no separation of the infiltrate from the epidermis (a space known as Grenz zone), which points to a worse prognosis. Both Panels **A** and **B** (larger magnification) show the presence of atypical and bizarre cells infiltrating the epidermis (epidermotropism). Panels **C** and **D** represent photomicrographs at different levels of magnification. This is a truly infiltrative tumor stage process, with progression to the subcutaneous tissue. There are several mitotic figures evident in Panel **D**.



(**A**) (**B**)

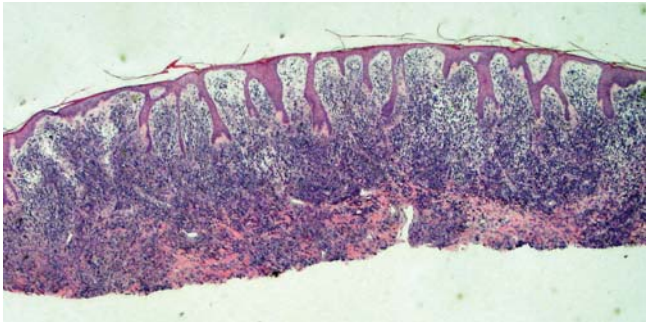
Figure 6.26 B-cell lymphoma.

This 80-year-old man from South America was thought to have Kaposi sarcoma, pseudoangiosarcoma, or lymphoma. He had numerous purple nodules and plaques, and a necrotic crusted wound on the shin (Panels **A** and **B**). At this point we also considered bacillary angiomatosis, which is caused by *Bartonella henselae* or *B. quintana*, because of the typical scaling (collarette of scales) around some of the nodules (Panel **B**). The collarette of scales is a distinguishing clinical feature from Kaposi sarcoma, which can look similar. Upon our histological evaluation of biopsies, he was initially thought to have tumor stage cutaneous T-cell lymphoma. However, further evaluation including gene rearrangement studies showed that this was a B-cell lymphoma. This patient was eventually treated with electron beam therapy. Topical treatment with nitrogen mustard and systemic therapy with retinoids did not help the ulceration, but he was managed with a gel dressing because of pain.

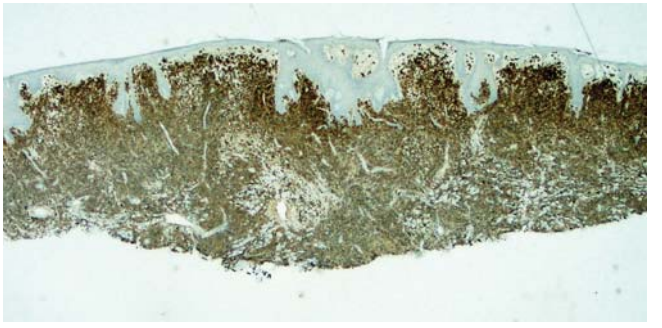


Figure 6.27a B-cell lymphoma resembling exuberant granulation tissue.

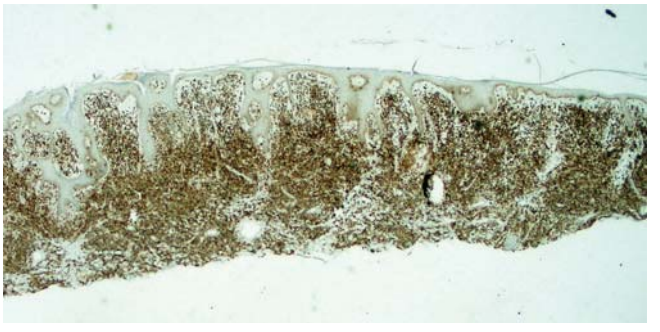
This middle-aged woman had an ulcer on the medial aspect of her leg that was initially thought to represent a venous ulcer with exuberant granulation tissue. The intense purple color of the lesions, the exuberant growth within the ulcer, and the clinical absence of true venous insufficiency findings should lead one to suspect a lymphoma. Biopsy and molecular studies showed that it was a B-cell lymphoma. Another clinical possibility would have been a basal cell carcinoma, squamous cell carcinoma, or amelanotic melanoma. While she was going through the diagnostic studies, the ulcer was managed with compression bandages and foam dressings.



(**A**)



(**B**)



(**C**)

Figure 6.27b B-cell lymphoma resembling exuberant granulation tissue/histology and use of immunostaining.

In these 3 photomicrographs (Panels **A**–**C**) we can observe a large B-cell lymphoma. Panel **A** represents an H&E section, while Panels **B** and **C** represent immunostaining with CD20 and Bcl 2, respectively. Overall, the tumor is composed of large, round, blue cells (in Panel **A**) infiltrating the entire dermis with relative sparing of the upper papillary dermis. The findings support a diagnosis of diffuse large B-cell lymphoma.

7 Practical points

We find it necessary to emphasize that the title of this section does not imply that the previous ones were not "practical" and merely theoretical in content. Nevertheless, there are some aspects of wound management that are essential elements of wound care and are common to many different types of ulcers. Hence, these "points" are described in this section.

Many advances have taken place in the last few years with regard to actual wound care, regardless of wound etiology. There are extensive reviews and guides on the subject of wound dressings and other approaches (see the Bibliography), but it may be useful to provide a brief summary here. The clinical photographs in this section will give some clues and advise on the practical aspects or "points" of wound care. There are now hundreds of different brands of wound dressings. Learning about these dressings may at first seem a daunting task. However, based on composition, transparency, and adherence properties, there are only a finite number of dressing categories from which to choose. In this section, we describe the use of transparent films, foams, hydrogels, hydrofibers, hydrocolloids, slow-release antiseptics dressings, and alginates. Some dressings are created by combinations. For example, an island dressing has a central absorbent portion surrounded by an adhesive component.

Films are generally composed of polyurethane and are adhesive and transparent. They are ideal for erosions or shallow ulcers and are not able to absorb substantial amounts of exudate. They are usually used as a primary dressing (i.e., directly in contact with the wound). However, they can also be used as a secondary dressing to keep other dressings in place. Foam dressings are also generally composed of polyurethane. Unlike films, they are mostly nonadhesive and are not transparent. They can absorb substantial amounts of exudate and thus can be used for deeper and moderately exudative wounds. We often tell our trainees that, when in doubt, foam dressings are probably applicable to most acute and chronic wounds. Hydrocolloids are a third major category of wound dressings. They are composed, for the most part, of carboxymethylcellulose. They adhere to the skin surrounding the wound and "melt" into the wound. In addition to having some absorptive properties, they seem to be particularly useful in causing painless debridement. They can "seal" the wound and prevent the entry of bacteria. Hydrogels are made of polyethylene and up to 90% or more water. Most products in this category are not adhesive but some new products have an adhesive border. We have used hydrogels very successfully in the management of painful ulcers and in the treatment of ulcers surrounded by substantial dermatitis. It should also be noted that hydrogels, besides being available as a sheet (the traditional form), are also available in an amorphous form. Hydrogels, because of their high water content, can actually hydrate thick eschars in the wound bed. A disadvantage might be some maceration of the surrounding tissues. Alginate dressings are derived from seaweed. They are ideal for highly exudative wounds. It should be kept in mind that the field of wound dressings evolves very quickly. For example, in the last few years, new categories of active dressings have emerged, as well as a greater variety of dressings such as collagens, hydrofibers, superabsorbents, and hydropolymers. Clinicians now make greater use of negative pressure devices to handle and remove large quantities of exudate from wounds. It will be challenging to determine when and under what clinical circumstances negative pressure works best. Hydrosurgery is now a reality and can achieve effective debridement of wounds. We are still very much in favor of slow-release antiseptics, such as silver and iodine. They have a definite role in the management of exudative wounds with a high bacterial burden.

There is more to wound care than just dressings, however. Over the last decade, we pioneered and popularized the concept of "Wound Bed Preparation." The concept was born out of our realization that existing guidelines and approaches had not caught up with the increasing scientific evidence and with ways to optimize the wound bed. Interestingly, we became more aware of this gap between science and clinical practice when advanced wound healing agents, such as topically applied recombinant growth factors and living skin constructs became available for treatment of difficult to heal wounds. Basically, we observed that these exciting and advanced therapies were not working as well as they should. We therefore focused on ways to enhance the "preparation" of the wound bed, including more timely use of debridement to remove non-viable tissue and phenotypically altered resident cells, decreasing the bacterial burden, decreasing the exudate, etc. The idea was and remains that proper attention to the wound would result in acceleration of the endogenous process of wound healing. Moreover, the advanced therapies themselves became ways to enhance wound bed prepartion. Wound care preparation has to do with providing the ideal microenvironment to the wound, optimizing wound closure, and addressing all the needs of the patient. All of these aspects have to be taken into account. Thus, in two patients with identical wounds, management may be different because of the clinical and patient-specific circumstances. We hope that this section will highlight some of these points and provide a useful perspective.

Clinical points

- Compression bandages require patient compliance. Although elastic multilayered compression provides the fastest way to control edema, compromises often need to be made so that the patient is willing to continue with the compression bandages.
- Tubular compression bandages do not deliver high pressures, but seem to be well tolerated by the patient.
- Occasionally, the heel may be spared when applying compression and to increase patient compliance.

- Negative pressure is indicated in very exudative or deep wounds.
- Hydrosurgery has emerged as an effective way to debride large wounds in the operating room. There has been considerable progress in this instrumentation.
- In all circumstances, the principles of wound bed preparation must be adhered to. Therefore, the approach to wound care must not be step-wise, but rather involve all approaches that can improve the wound bed and stimulate healing.
- It is wise to have a wide variety of dressing types available and be willing to experiment to find the best one for each individual clinical situation.
- Keeping close at hand a list showing the different types of dressings available and their properties is useful.
- The package insert for each new dressing must be read carefully. Some dressings have one side that is absorbent and one side (away from the wound) which is not water permeable.
- When applying a hydrogel sheet dressing, one must be careful to remove the thin film from the side that will be in contact with the wound. The outer film can be left on to keep the dressing from drying out.
- For a heavily exudating wound with an offensive odor, a foam dressing with an activated carbon layer is useful for absorbing wound odor. An alternative approach is to use topical metronidazole. The latter may be placed within the dressing, to decrease bacterial colonization.
- Patients need to be informed about the possible odor and the rather extensive and pus-like wound fluid that accumulates under hydrocolloid dressings.
- Although each type of occlusive dressing comes with certain recommendations concerning how long it can stay on the wound, in general it is best not to remove the dressing until leakage of the wound fluid occurs. Premature removal of the dressing leads to disruption of re-epithelializing tissue.
- Compression bandages should be applied from the toes to below the knee and should fully enclose the heel. However, "heel sparing" can be useful in patients with combined venous and arterial disease.
- Rigid compression bandages (e.g., Unna boot) are probably not effective in nonambulatory patients. In these patients, elastic bandages are preferred.
- It is wise to be as specific as possible when instructing patients about leg elevation for venous insufficiency. The expression "toes above nose" seems to deliver the message in a more explicit way.
- A stocking butler should be kept in the office in order to demonstrate how useful it can be in applying stockings.
- In order to facilitate compliance with dressings and bandages, it is best to give patients a handout listing the addresses of several local pharmacies or suppliers that carry the harder-to-find items.
- Hydrocolloid dressings are best for painless wound debridement, while calcium alginate dressings and foams are good for highly exudative wounds.
- Adhesive dressings should be used with caution in patients (especially the elderly) with very fragile skin.
- Cadexomer iodine is an ideal agent for exudative and contaminated wounds. It is best to change the dressing daily, both for effectiveness and because dried cadexomer iodine is more difficult to remove.
- Multilayered bandages are ideal in patients whose legs have an "inverted bowling pin" appearance and where other types of bandages tend to slip down.
- One simple way to avoid injury to the leg when removing a leg bandage is to pull the outer wrap away from the leg while cutting it.
- Ulcer pain can often be managed with the use of occlusive or moisture-retentive dressings alone.
- An effective way to minimize pain during debridement is to apply a combination of lidocaine/prilocaine cream to the ulcer for 30–45 minutes before the procedure.
- Film dressings are ideal for controlling the intense pain of fissures of the hands, as in patients with severe dermatitis or psoriasis. There are now polymer sprays that will cover the wound with an invisible film.
- Dermatitis of the leg is often best controlled by the use of hydrogels.



Figure 7.1 Leg edema.

The entire leg became quite edematous when the patient failed to wear the elastic stockings that had been prescribed for the treatment of venous disease. Compliance with the use of stockings is a serious problem. Although she has varicosities (medial aspect of her ankle), the "tubular" configuration of the swelling is also suggestive of concomitant lymphedema. The combination of venous and lymphatic disease is probably in the 20% range.



Figure 7.2 Edema and blistering.

Blisters can develop in the setting of severe leg edema. Because such blisters can lead to chronic ulcers, it is important to establish compression therapy immediately. Another clinical consideration here would be streptococcal or staphylococcal infection, which can present as blisters. The scaling on the lateral aspect of the ankle could represent a dermatophyte infection.



Figure 7.3 An unusually shaped leg.

On legs with small ankle circumference and very large calves ("champagne bottle" or "inverted bowling pin" shaped legs), it is difficult for a short-stretch bandage (i.e., Unna boot) to stay in place and also difficult to get the appropriate distribution of compression. This patient requires a different method of applying compression, one which takes into account this abnormal leg shape. Multi-layered elastic bandages will be more beneficial, because one of the layers is meant to fill in the concave areas of the leg and compensate for the abnormal leg shape. Still, leg shape remains a challenge, because bandages tend to slip down.



Figure 7.4 Multilayered compression bandages.

These compression systems have become very popular world-wide. They are comprised of a primary dressing, the nature of which can vary (i.e., a foam, a nylon membrane), and three to four additional bandages. High resting and working pressures develop under these compression bandages. There is evidence that the high pressures achieved by these bandages are more effective in achieving wound closure. However, the subject is still quite controversial.



Figure 7.5a Four-layer bandaging/primary dressing.

The primary dressing is applied over the wound. It is generally nonadherent and nonabsorbent. Some clinicians prefer to use a hydrocolloid as the primary dressing, to keep a moist wound environment. A number of dressings can be used for this purpose and their choice is dictated by the characteristics of the wound (i.e., exudative, need for debridement, etc.). If the ulcer is highly exudative, a foam dressing or a calcium alginate material could be used as the primary dressing.



Figure 7.5b Four-layer bandaging/first layer.

The first layer, made of cotton-type material (as under orthopedic casts) protects the leg and can be applied to fill in the concave areas of the leg, thus preparing for proper compression. This inflexible material is applied in a spiral fashion with a 50% overlap.



Figure 7.5c Multilayered compression bandages/second layer.

The second noncompressive layer is also applied in a spiral fashion with a 50% overlap. It is nonadherent and does not stretch very much. It holds the previous layer nicely in place and keeps it smooth. Notice how the toes are kept uncovered and how the bandage extends to just below the knee.



(**A**) (**B**)

Figure 7.5d Multilayered compression bandages/third layer.

This compressive layer (Panel **A**) is applied in a figure-of-eight pattern, which tends to prevent slippage. The close-up (Panel **B**) clearly shows that the bandage has been applied by wrapping in a downward and upward motion consecutively. In some types of bandages, such as this one, lines are present over the material in order to stretch it in a consistent way and to achieve a consistent amount of compression.



Figure 7.5e Multilayered compression bandages/fourth and final layer.

The fourth and final layer is also a compression bandage that is applied in a spiral fashion (not in a figure-of-eight pattern) with generally a 50% overlap. These compression systems are usually replaced once or twice a week, depending on the medical needs, including the amount of exudate.



Figure 7.6 Venous ulcer and supplemental pressure.

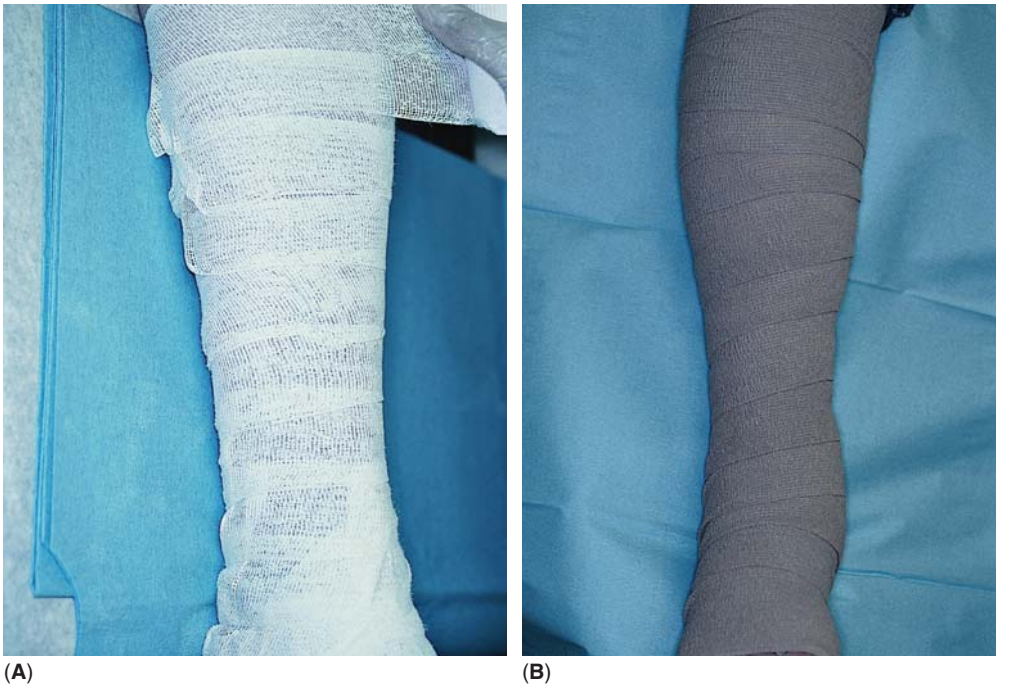
An easy way to circumvent the problem of not being able to apply proper compression to concave areas of the leg is to use extra gauze or foam dressings over the ulcer before compression is applied. We call this localized supplemental pressure.



(**A**) (**B**)

Figure 7.7 Example of localized supplemental pressure using foam.

We use localized supplemental pressure when the ulcer is not healing, irrespective of its location. This 59-year-old woman has a venous ulcer that has not developed good granulation tissue and is not healing (Panel **A**). Frequent surgical debridements have been required. Panel **B** shows the application of a foam dressing insert directly over the wound (extra gauze or foam can be added), which will be followed by the application of compression bandages.



(**A**) (**B**)

Figure 7.8 Short-stretch compression treatment/Unna boot.

This bandage (Unna boot) might be considered a short-stretch bandage, although that is not entirely correct because it is quite rigid. It is generally applied with a 50% spiral overlap. Interestingly, we have recently started to apply it in a figure-of-eight fashion, which allows a more even distribution of the bandage. The Unna boot, which is still quite commonly used in the United States, is a largely inelastic bandage that works best in ambulatory patients, because its mechanism of action has to do with the pressing of the leg against the semi-rigid structure of the bandage. The Unna boot, with or without an additional elastic bandage, is still favored in the United States, while many European clinicians prefer more elastic compression bandages. Panel **B** shows the application of the elastic compression over this primary "short stretch" bandage. Compression bandages are traditionally applied from the base of the toes, including the heel, to just below the knee. Interestingly, some clinicians have recently suggested that exclusion of the heel from bandaging may be advantageous; presumably, this allows a safer use of compression in patients with concomitant arterial disease and may improve ankle motion and calf muscle pump action.



Figure 7.9 A scissor injury upon dressing removal.

This patient presented to us with an injury to her ulcer that occurred during the removal of the short-stretch bandage. The injury is seen here as a horizontal cut at the inferior margin of the wound. Extreme care must be used upon dressing removal.

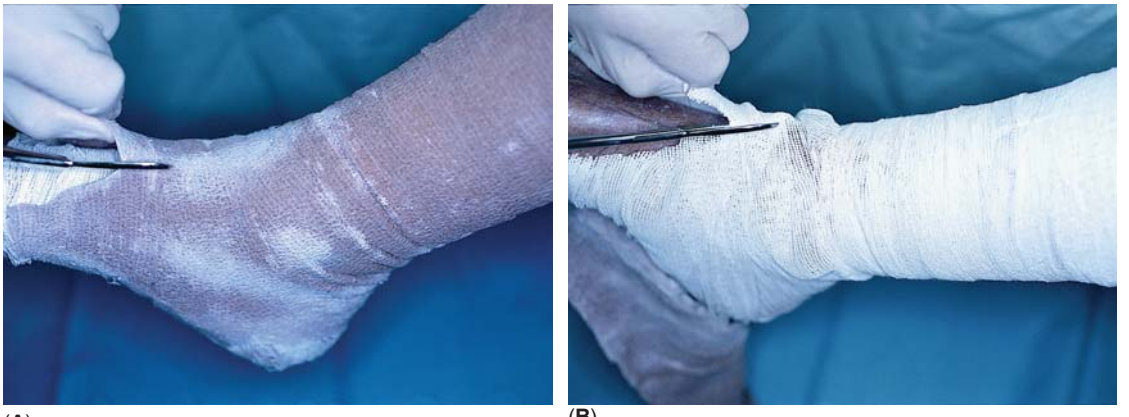


Figure 7.10 Avoiding scissor injuries upon dressing removal.

One simple way to avoid injury to the leg when removing a leg bandage is to pull up the outer wrap and the scissor in the process of cutting the bandage (Panel **A**). The same procedure is used with the inner wrap (Panel **B**), pulling the bandage up and away from the leg and cutting it with blunt nosed, bandage scissors. We recommend using the thumb to get under the dressing and to pull it away from the underlying layers and skin.

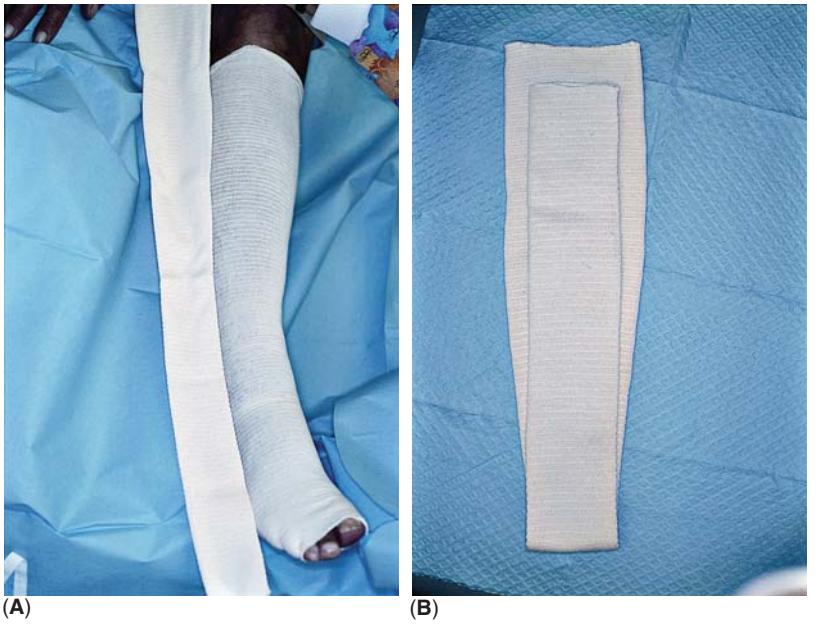


Figure 7.11 Shaped support bandages.

Shaped support bandages (Panel **A**) can be used as a primary compression bandage or for short-term use while patients are healed and waiting for their graded stockings. The bandage shown in Panel **A** comes as individually wrapped. Unlike regular tube gauze, this is specifically made smaller at the ankle and larger at the calf area to produce graduated compression. Panel **B** shows a similar bandage superimposed on the bandage illustrated in Panel **A**. This type of bandage comes as a large roll that needs to be cut according to the diameter at the ankle, calf, and the length of the leg. Admittedly, these types of bandages produce less resting and working pressures, and some clinicians and other experts would disagree with their use. However, their advantages include greater compliance, ease of use, and ability to change primary dressings for daily topical treatment or dressing changes. We have evidence that they are indeed effective in reducing leg edema and contribute to wound healing; published literature also supports that. These bandages are clearly a compromise in terms of therapeutic sub-bandage pressures, but the reality is that clinical circumstances, including patient compliance, often dictate this approach.

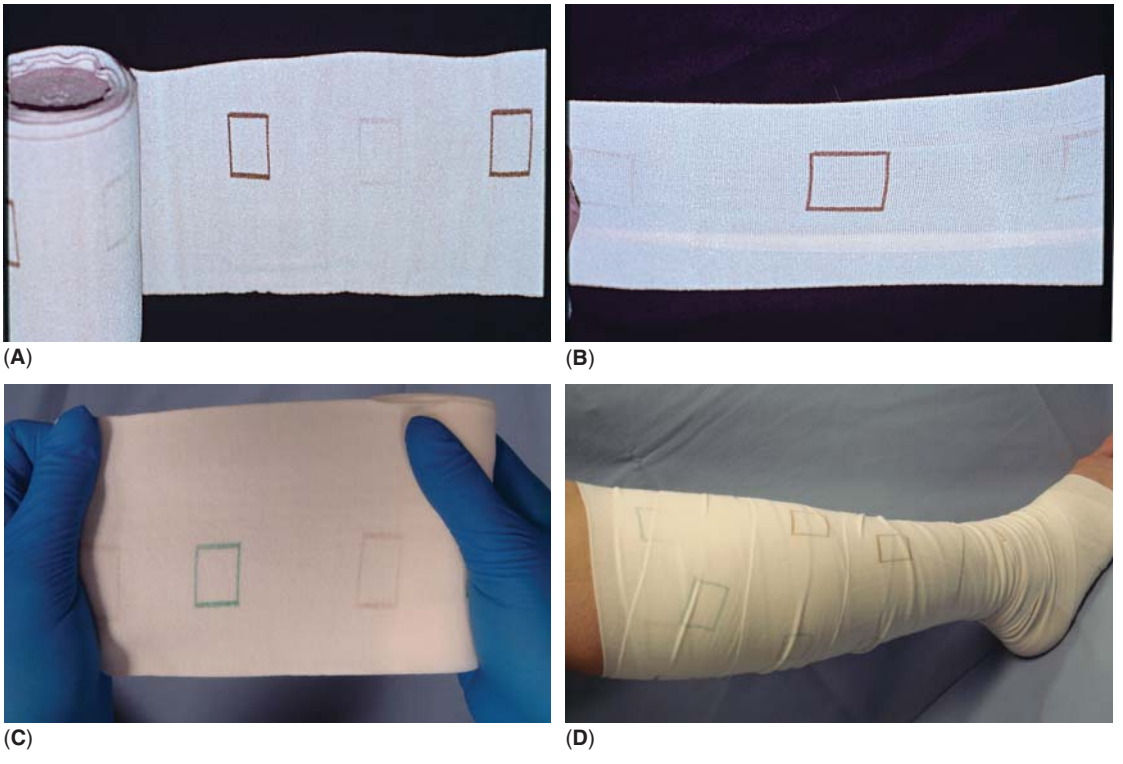


Figure 7.12 Regulating the amount of compression.

There are a variety of bandages that are useful and effective in the treatment of venous ulcers. Some allow the clinician to more accurately determine the amount of pressure being applied. Panels **A–D** are meant to be examples. Panel **A** shows an elastic bandage with rectangles on its surface before being applied, and which (when stretched to the appropriate tension) become squares (Panel **B**). Panels **C** and **D** show a different type of bandage that has greater flexibility in terms of the amount of pressure applied with stretching. For example, using color coding on the rectangles, one can apply a differential amount of pressure when the baseline rectangle becomes a square (Panel **C**). Panel **D** shows the bandage in place with a higher (brown square) amount of pressure being delivered. The very existence of these types of bandages points to the fact that it is challenging to be consistent in applying a bandage and maintain similar amounts of tension.



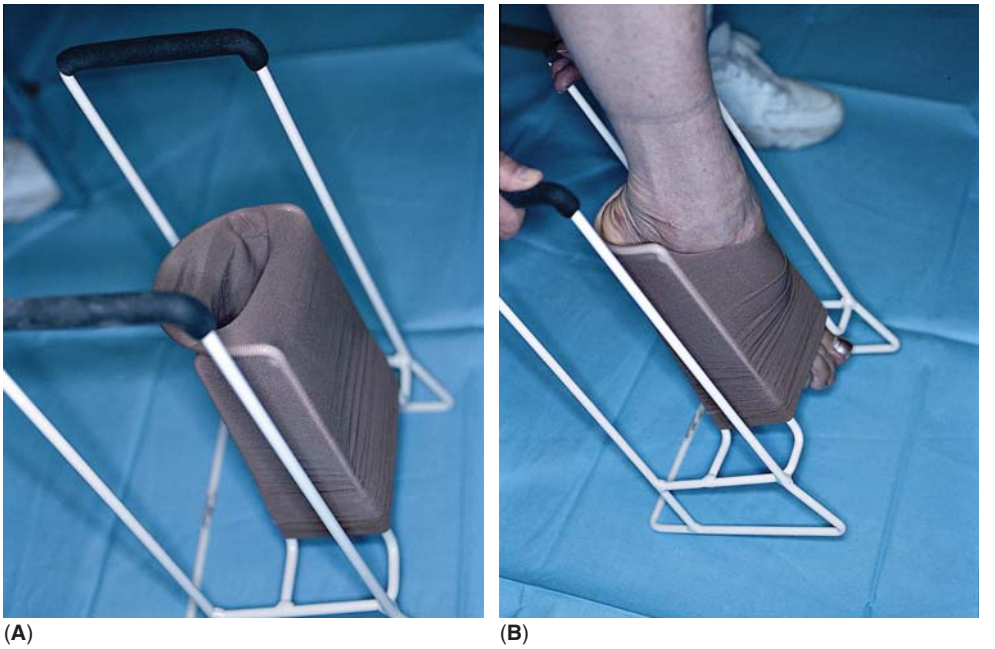
Figure 7.13 Facilitating the application of elastic stockings/sleeve.

It is generally thought that elastic stockings can help prevent ulcer recurrence; however, venous ulcer recurrence (possibly related to patient compliance) is still at 21% at year 1 and 30% at year 5. Stockings do have the advantage of being less bulky than compression wraps. The major difficulty with compression stockings is the daily application by the patients themselves; some devices have been developed to facilitate the process of application. Here we see a smooth and slippery sleeve (*left*) over which the stocking (*right*) can be slided for easier application. However, removal of the stockings remains difficult, especially for the elderly or disabled.



Figure 7.14 Facilitating the application of elastic stockings/ use of the "butler."

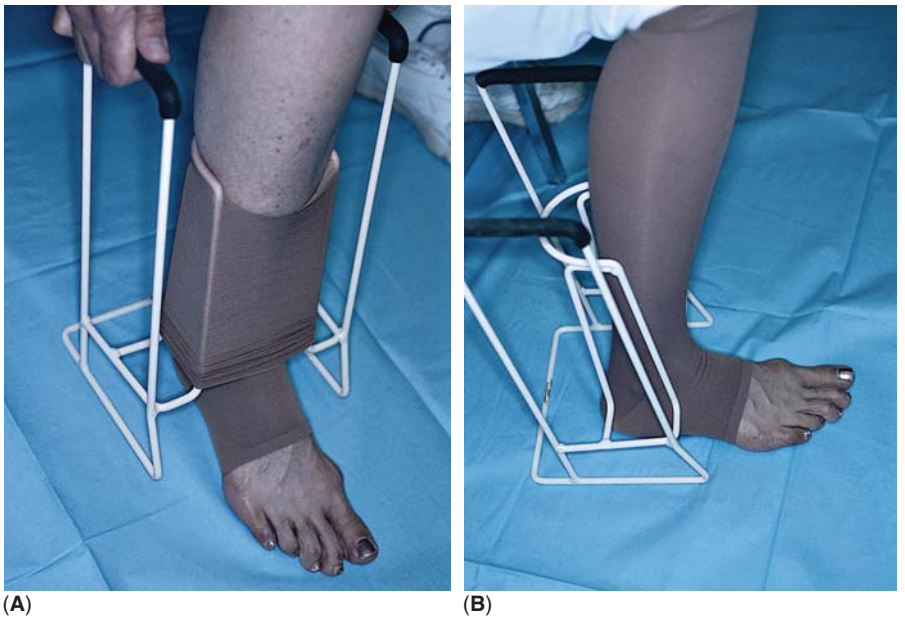
There are different types of devices that can facilitate the application of stockings. Ironically, it is the patients who need stockings the most who have difficulty with putting them on: the elderly, the obese, the patients with limited mobility and arthritis, etc. A butler device (shown here) or a stocking donner/ caddy can facilitate the application of stockings, mainly for people with limited strength or ability to bend down and stretch the stocking over the foot. The next sequence shows the use of the "butler" in more detail.



(**A**) (**B**)

Figure 7.15a Application of compression stockings with a "butler" device.

Panel **A** shows the standing "butler" in place so that the patient can grab the side bars and insert his/her foot into the stocking that has been placed over the metal frame. The "butler" can be used in an upright or horizontal position, but the latter is more practical. Panel **B** shows the patient in a sitting position and applying stockings to her legs by grabbing the side bars of the "butler" and pushing the foot through.



(**A**) (**B**)

Figure 7.15b Application of compression stockings with a "butler" device/completion.

Panel **A** shows the foot and leg sliding into the device with relative ease. Panel **B** shows the stocking in place. A minor adjustment may be needed at times for optimizing the application. There are other ways to facilitate the application of stockings. For example, there are gloves with rubber dots that can also aid in the application and removal of stockings. In our opinion, while these devices can be quite helpful, there is no substitute for a caregiver who helps the patient put on the elastic stockings. We say this because the removal of the elastic stockings at night can also be extremely challenging.



Figure 7.16 Stockings with posterior zippers.

The incorporation of zippers in the back of a stocking can also facilitate their application. In our opinion, the use of this type of stocking is more applicable to patients with considerable strength and dexterity, which are desirable for getting the foot into the stocking and then to close the zipper. In this particular case, the stocking may be larger than what is required or may need to be pulled up further.

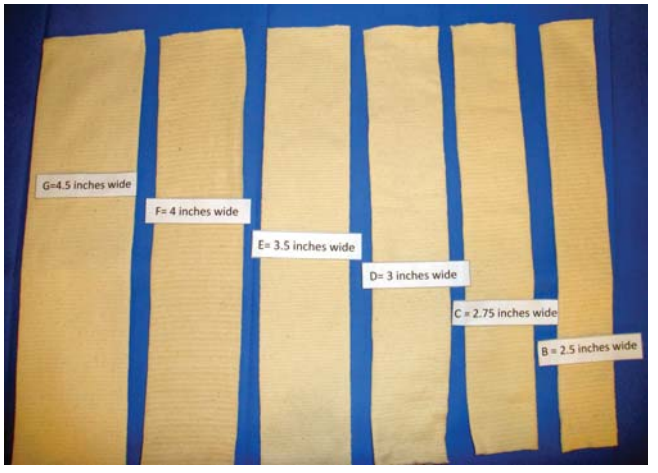


Figure 7.17a Tubular compression bandages.

There are different sizes of tubular elastic support bandages. These may be used in more than one layer (doubled up) to increase the resting and ambulatory pressures. While these bandages provide less pressure than shaped tubular devices, compression stockings, and multilayered bandaging, we find them to be useful because patients often cannot tolerate higher compression due to arterial insufficiency, pain and tenderness, or difficulty in application. Also, both in the clinic and in research trials, a certain topical medication may need to be applied daily or even twice a day.

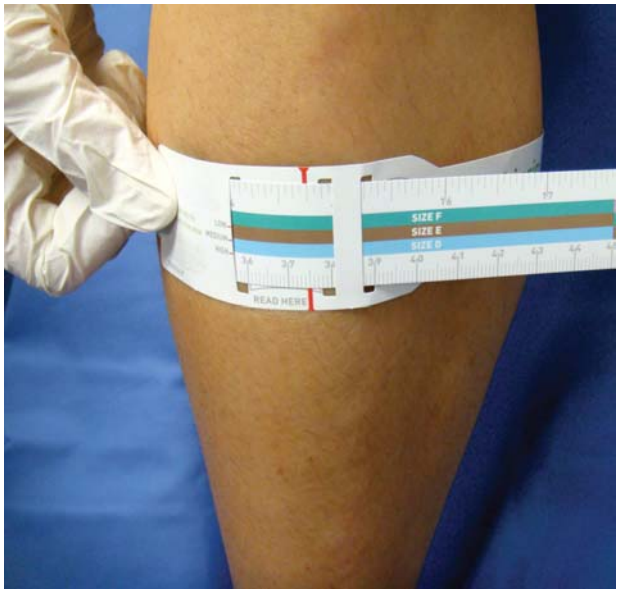


Figure 7.17b Tubular compression bandages/measurement for size.

To select the proper size of bandages to be used, the measuring tape is placed around the widest part of the leg. The next step is to match the amount of desired pressure (low, medium, high) with the size of the stocking that would be required.



Figure 7.18 Difficult-to-treat legs with compression bandages and stockings.

There are patients in whom the application of compression bandages or stockings is either difficult or impractical, or virtually impossible. This is because of the shape of the legs or the presence of lymphatic disease. In fact, this particular patient with combined venous and lymphatic disease is an example of these difficulties. Note the verrucous changes in the leg, which are typical of concomitant lymphedema. Such patients are candidates for compression pumps or the use of velcro-based compression bandages.



Figure 7.19 Sequential graded pumps.

These devices can be very helpful in removing edema and managing lymphedematous legs, particularly in children and in adults who are able to use them easily. It has also been stated that pumps can help heal wounds by removing edema, but variables related to frequency of use have not been worked out in detail. The pumps for treatment of edema in leg ulcers have to be sequential in the inflation of the different compartments and in providing graded pressures.



Figure 7.20 Pedal edema.

The photograph shows pitting edema (indentation with external pressure) of the dorsum of the foot. Pedal edema can result from inadequate compression. It is important to apply compression bandages starting at the toes.



Figure 7.21 Technical failure of the use of compression.

This patient presented to us with a short stretch bandage (Unna boot) that apparently did not stay in place for several reasons. We also thought he had bilateral cellulitis. What can also happen is that compression reduces the baseline edema and the short stretch bandage becomes loose. Moreover, it seems that the bandage was not applied all the way to the knee; anchoring the bandage above the calf muscles keeps it from slipping down. An additional reason for failure of this bandage is the inverted "champagne bottle" leg shape that is common in venous disease. The patient needs immediate hospitalization. The occlusive dressing applied to the left leg will probably be contraindicated in the setting of cellulitis.



Figure 7.22 Importance of properly applied compression.

This is another example of a compression bandage applied too far below the knee. Indeed, one can easily appreciate the increased edema on the upper part of the leg, above the bandage. The increased edema of the upper part of the leg may lead to the development of blisters, difficulty in optimal graded pressure application, and deformity of the leg. Also, it appears that the upper portion of the bandage is cutting into the skin, and causing erosions and cellulitis.



Figure 7.23 Difficult-to-compress legs.

This is another example of a patient in whom the application of compression bandages or stockings is very challenging or virtually impossible. The goal of a gradual decrease of compression from the ankle to below the knee will be very difficult to accomplish. The use of padding materials to normalize the shape of the leg may be attempted, as well as the use of multilayered bandages made for leg circumferences greater than 30 cm. Cellulitis is present and the patient can benefit from hospitalization. One must also immediately exclude the possibility of thrombophlebitis, especially in the left leg.



(**A**)

(**B**)

(**C**)

Figure 7.24 Management of dermatitis (irritant or allergic).

The surrounding skin of chronic wounds, especially those caused by venous disease, is frequently complicated by scaling, redness, warmth, and other signs that, collectively, we call dermatitis. Not infrequently, it may become difficult to distinguish dermatitis from cellulitis. In our experience, topical antibiotics and emollients are the most common reasons for dermatitis. In treating this complication, we try to avoid other topical agents and advise discontinuing all topical medications. In some cases, we prefer to use films, hydrocolloids, or hydrogels to treat the dermatitis. Dermatitis can present in many ways. Panel **A** shows a dermatitis over a leg stump (below the knee), which prevented the patient from using his prosthesis. We excluded a dermatophyte infection and also biopsied the scaly area to rule out a squamous cell carcinoma. A hydrogel will be helpful in the management. Panel **B** shows a severe dermatitis on the dorsum of the foot and between the toes. The patient had onychomycosis, but the dermatitis was not due to a dermatophyte infection. Reluctantly, we did have to use a topical corticosteroid ointment. The use of ointments, which contain less chemicals and possibly sensitizing ingredients, is preferable to the use of creams. Panel **C** shows yet another example where we would use a hydrogel to control the severe leg dermatitis occurring in the setting of venous insufficiency. In severe and unresponsive cases of dermatitis, after ensuring that no infection is present, we may choose to use systemic corticosteroids for a short period of time.

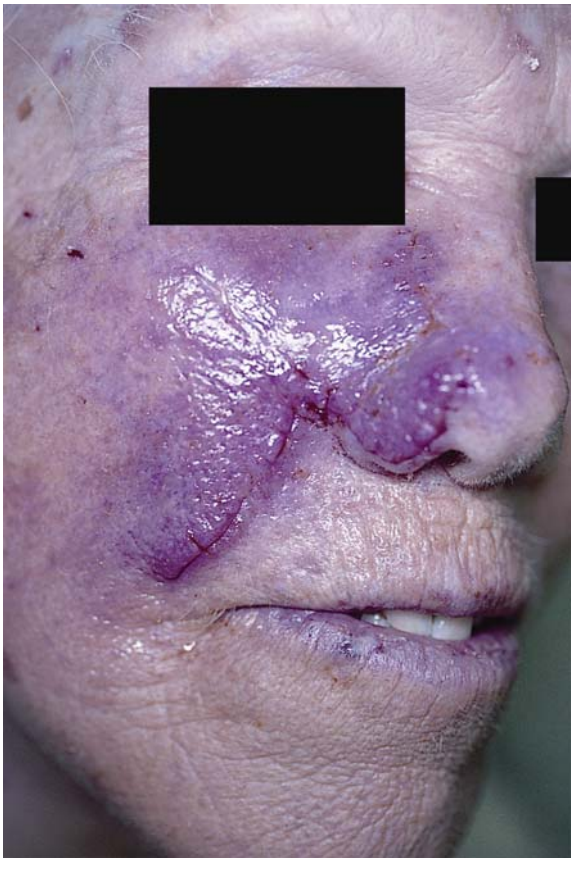


Figure 7.25 Contact dermatitis after surgery.

She had a basal cell carcinoma removed from her cheek, and the resulting defect was repaired with a flap. After having used bacitracin ointment for several days, she returned with the involved area being red and slightly warm. There was no fever, tenderness, or pus. We thought that most likely she had developed an allergic contact dermatitis to bacitracin. However, in spite of the absence of key clinical findings, we could not exclude a concomitant infection. Therefore, as is commonly done, she was treated with systemic antibiotics and the topical agent was stopped. The problem resolved nicely within a few days. She was patch tested for bacitracin, and the testing was positive.



Figure 7.26 Leg dermatitis at the site of saphenous vein harvesting.

This middle-aged man had a cardiac bypass operation for which the saphenous vein was harvested. A few months later, he developed this persistent dermatitis along the course of the incision on the medial aspect of the leg. Dermatitis after harvesting of the saphenous vein is a reported complication of this procedure. Avoidance of topical agents, which could be sensitizing and aggravate the dermatitis, is important. Graded compression stockings are the treatment of choice.

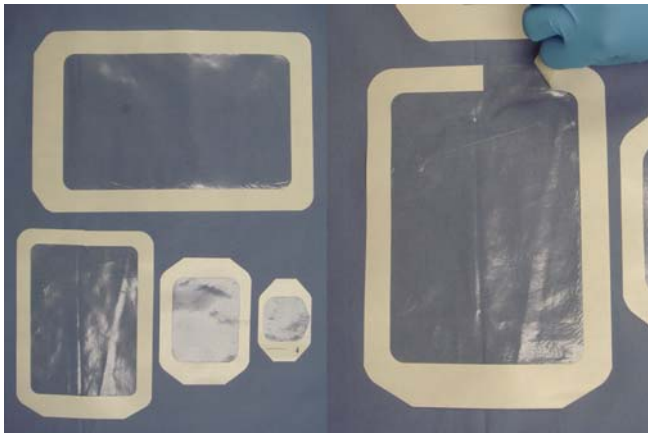


Figure 7.27 Film dressings.

These polyurethane dressings are generally transparent and adhere to the skin surrounding the ulceration. They are very good for shallow wounds with little exudate. Only a handful are shown in this photograph, and each brand will have its own specific advantages or special indications. They also vary in terms of permeability.



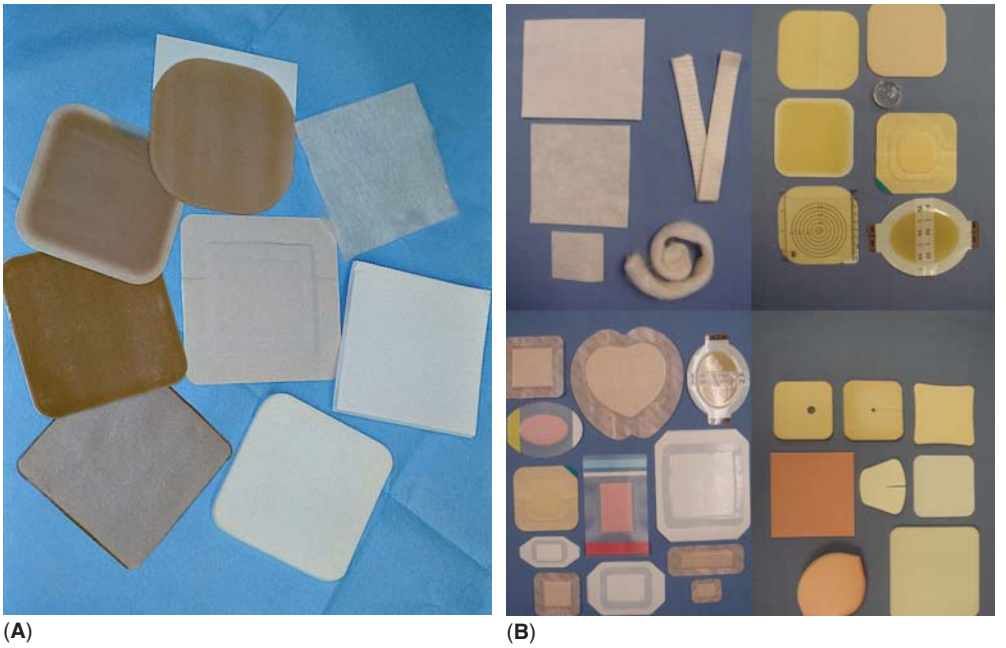
Figure 7.28 Gel dressings.

These nonadherent semi-transparent dressings are made of polyethylene and consist of large (greater than 90–95%) amounts of water. If marketed as being sterile, they require irradiation. Generally, on either side is a polyurethane film. One removes the film side that will be in contact with the wound. By keeping the upper film on the dressing, one avoids excessive drying of the polyethylene portion. Gels are capable of providing moisture to the wound and help in the debridement of eschars. In our experience, they are also excellent for the treatment of dermatitis. Hydrogels provide a soothing relief from pain, and can be kept refrigerated to give a cooling effect when applied to the skin.



Figure 7.29 Examples of dressings/gels.

This photograph shows several types of gel materials that can be used to fill the wound, and provide an absorptive function and, in some cases, debridement and wound stimulatory effects.



(**A**) (**B**)

Figure 7.30 Examples of dressings/absorptive wound dressings.

There are dressings that are able to handle considerable amounts of exudate (Panels **A** and **B**). The photograph shows a small sample of hydrocolloids, foams, and calcium alginate. There are many variations of these dressings, and they keep evolving. Although there is substantial experimental evidence that moisture-retensive dressings are capable of accelerating the healing of partial thickness wounds, there is no absolute evidence that they achieve complete wound closure in full thickness wounds. However, they are very useful in pain relief, autolytic debridement, and stimulation of granulation tissue. Hydrocolloids can also block bacteria from entering the wound bed.

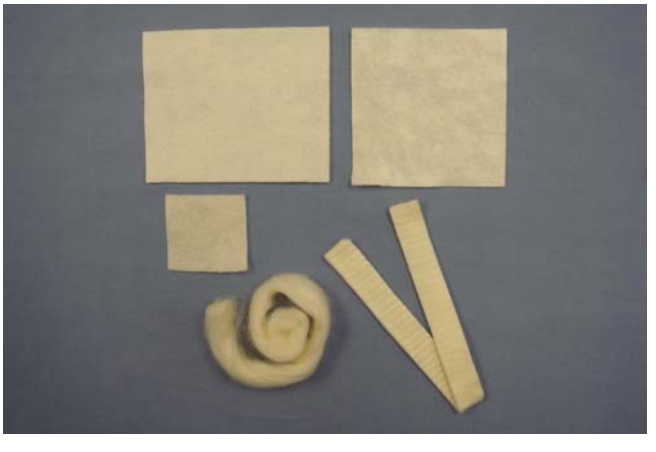


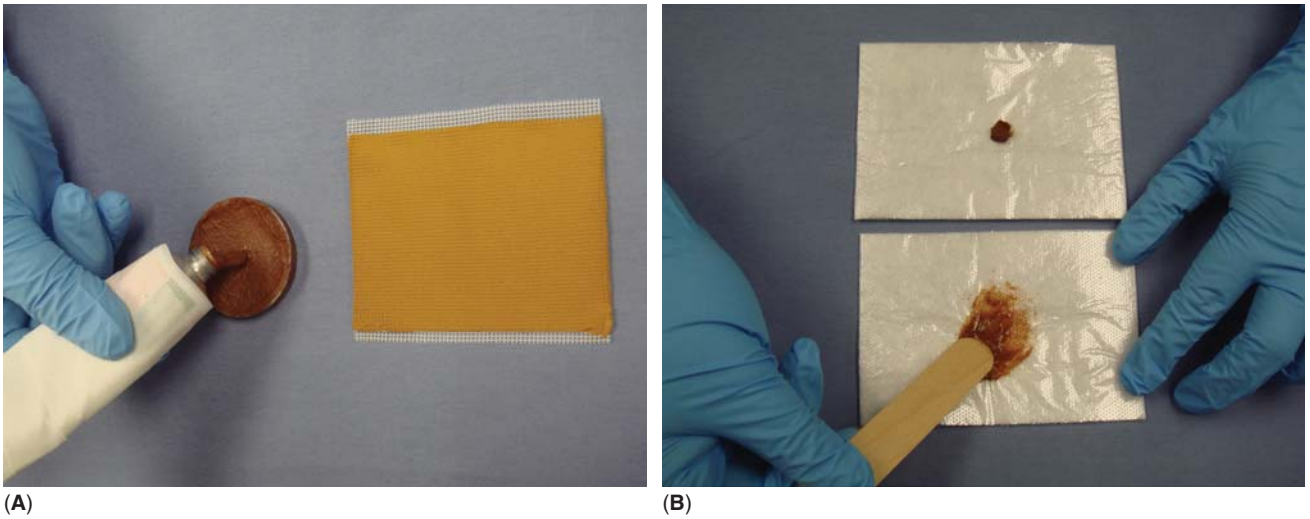
Figure 7.31 Calcium alginate.

These dressings are extremely useful for highly exudative wounds. As shown here, there are several different types to fit the clinical needs, that is, sheets and ropes for large wounds, draining sinuses, etc. The calcium in the dressing is exchanged for sodium, which is present in the wound exudate. Antimicrobial agents, such as silver, are incorporated in some versions of the calcium alginate dressings.



Figure 7.32 Various wound dressings that deliver silver to the wound.

Silver dressings come in several concentrations of this antimicrobial, different forms and sizes of the sheets, and in different materials such as foams, calcium alginates, and hydrofibers. These dressings can provide a sustained release of silver (even in nanoparticle technology) to the wounds, and are able to absorb exudate. In relatively dry wounds, silver dressings may be moistened with sterile water to facilitate transfer of silver into the wound bed. Silver dressings are generally well tolerated by patients, and allergic contact dermatitis to silver is rare. The dressing material into which silver is incorporated consists of single/multiple and combinations of rayon, polyester, and polyethylene. Silver delivery to the wound can take place within minutes of the application.



(**A**) (**B**)

Figure 7.33 Cadexomer iodine dressings.

Shown here are two types of iodine-containing dressings. In a cadexomer (microbeads) vehicle, cadexomer iodine is available as a sheet (right side of Panel **A**) or as an ointment (Panel **B**). The sheet form of this dressing has the advantage of not containing polypropylene glycol and thus is less irritating. The ointment form in Panel **B**, which can generally be applied to other support dressings, does contain polypropylene glycol and can be quite irritating and cause burning on application. For this reason, the cadexomer iodine ointment must be applied very sparingly to the wound. These dressings are used in exudative wounds and exchange iodine for wound exudate. One gram of the cadexomer iodine can absorb up to 6 g of fluid. The dressings facilitate autolytic debridement. A relative contraindication for use is allergy to iodine, the presence of severe thyroid disease, or the concomitant systemic use of lithium.



Figure 7.34 Methylene blue dressing.

This is a foam dressing containing methylene blue and gentian violet. When using this dressing it is necessary to hydrate the foam to the extent that it is damp prior to application.

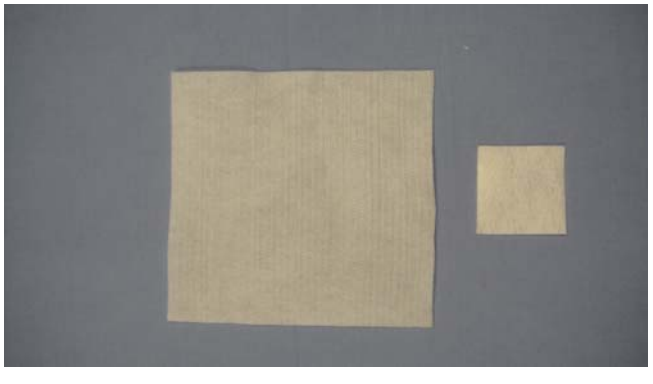


Figure 7.35 Hydrofiber dressings.

This is an example of a hydrofiber dressing. It is a moisture-retentive dressing consisting of soft nonwoven sodium carboxymethylcellulose fibers. The dressing turns into a gel upon contact with wound fluid. Absorption of wound exudate occurs by vertical absorption and thus the dressing is able to wick away the fluid and prevent maceration of the surrounding skin. In addition, removal of the saturated dressing is generally associated with very little pain. Silver has been incorporated into these types of dressings as well.



Figure 7.36 Other absorbent dressings.

As an example, the four types of dressings shown here can be used as either primary or secondary dressings. All of them are absorbent and minimally adherent. These dressings are ideal for use in leg ulcers and under compression bandages when there are several days between dressing changes.

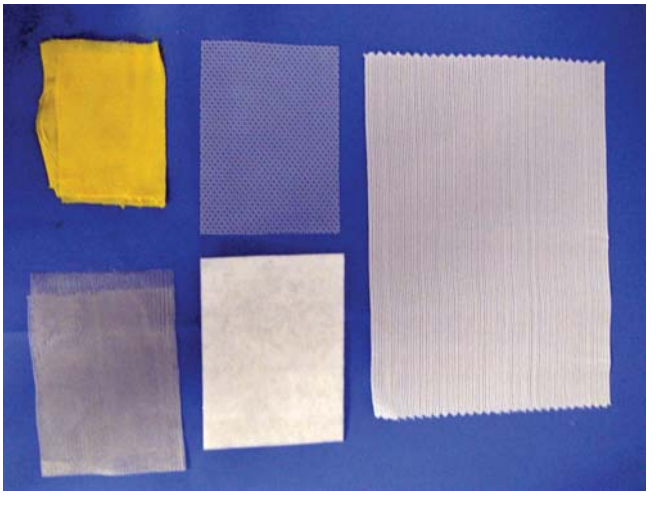


Figure 7.37 Wound contact (primary) dressings.

These are all examples of primary dressings. Going horizontally from top to bottom, the left upper dressing is a meshed gauze impregnated with petrolatum and 3% bismuth. The upper middle dressing is a soft fenestrated, net-like silicone dressing, which allows wound fluid to escape and decreases the need for painful dressing changes. The large dressing on the right is a nonadherent knitted viscose rayon material that allows free passage of exudate. The left lower dressing is a soft sterile cellulose material impregnated with ionic silver. The bottom middle dressing is a thin cotton nonadherent pad. While these dressings and others are labeled as being "non adherent," they still adhere to the exudative wound and commonly cause dressing removal injury to the thin migrating epithelium.

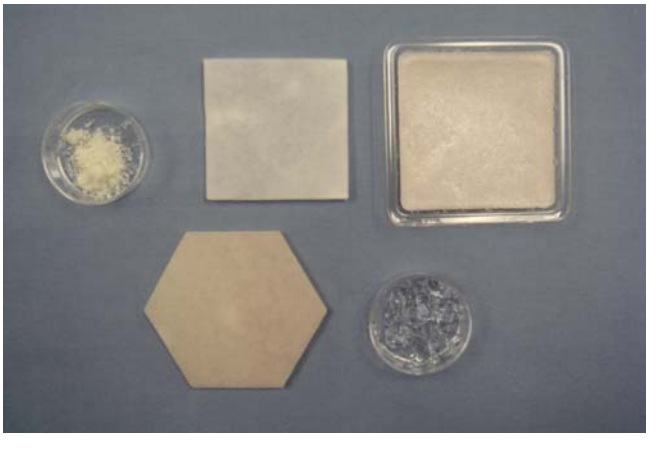


Figure 7.38 Protease modulating dressings.

These dressings are used to control wound exudate and theoretically help healing by binding proteases and matrix metalloproteinases that are elevated in chronic wounds. They are frequently composed of collagen, cellulose, or superabsorbent polymers.



(**A**) (**B**)

Figure 7.39 A collagen-alginate dressing/application.

Panel **A** shows a collagen-alginate combination dressing being used in this difficult to heal venous and lymphatic ulcer that has been present for many months. The nodular or pebble-like skin appearance on the middle portion of the leg strongly suggests a lymphatic component. The linear, horizontal, and hypopigmented scar above the wound suggests a history of trauma, possibly related to scissor-induced injury from dressing removal. Panel **B** shows how this particular dressing is being saturated with sterile water prior to application, in order to allow for easier calcium alginate and sodium exchange.



Figure 7.40 Securing a hydrocolloid dressing in place.

It is extremely useful to hold down the dressing and its borders when applying a hydrocolloid dressing. Sometimes, it is helpful for the clinician to keep his or her hand over the dressing for almost a minute; this helps in warming the material and securing it to the wound. Rounding the edges of the dressing with scissors prior to application makes it less likely that the originally sharper edges of the dressing will be stuck onto the secondary dressing and come off unintentionally upon dressing removal.

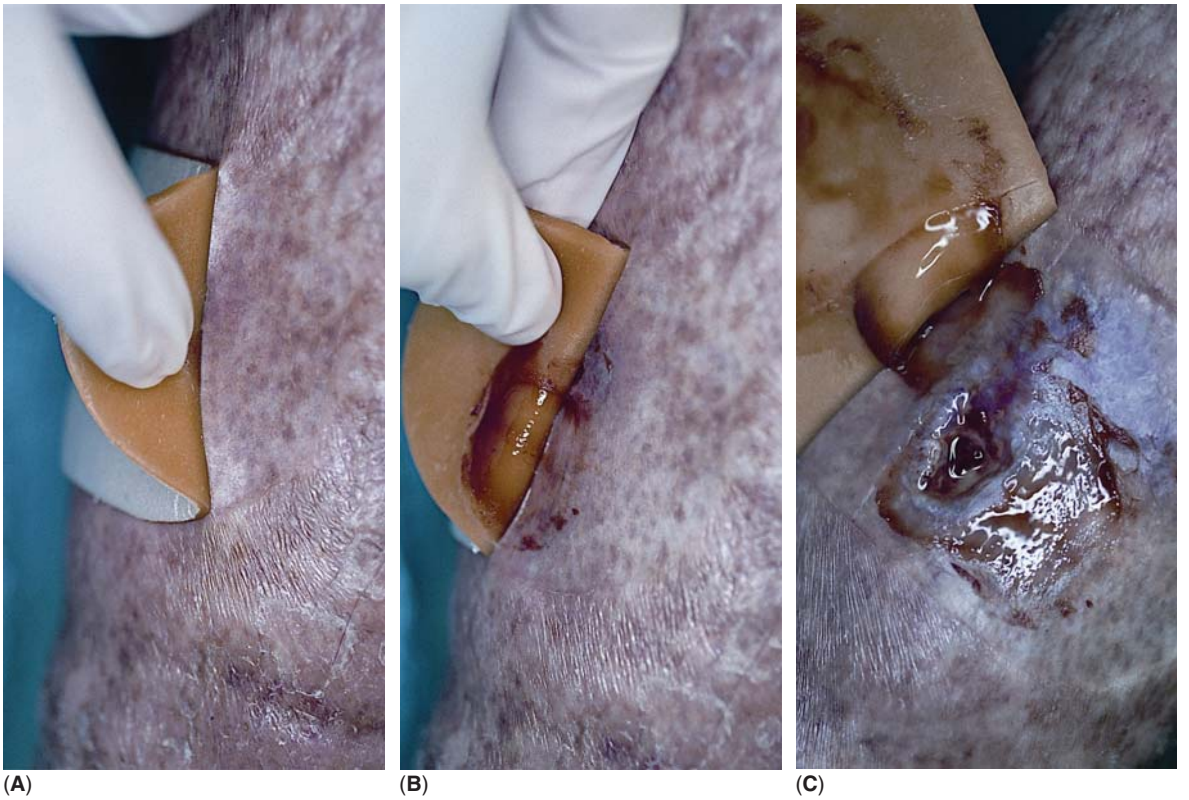


Figure 7.41 Removal of a hydrocolloid dressing.

During dressing removal and in order to minimize tissue injury, there is a natural tendency to roll back the dressing very close to the wound, as shown in these three panels. However, it appears that (lifting the dressing by its edge in a way that is almost perpendicular to the wound Panels **A** and **B**) leads to less trauma upon removal. As shown in these sequential photographs of dressing removal (particularly, Panels **B** and **C**) hydrocolloids generate a sero-sanguinous exudate and melt into the wound. In fact, there is histological evidence that hydrocolloid material can be detected in wound bed macrophages.

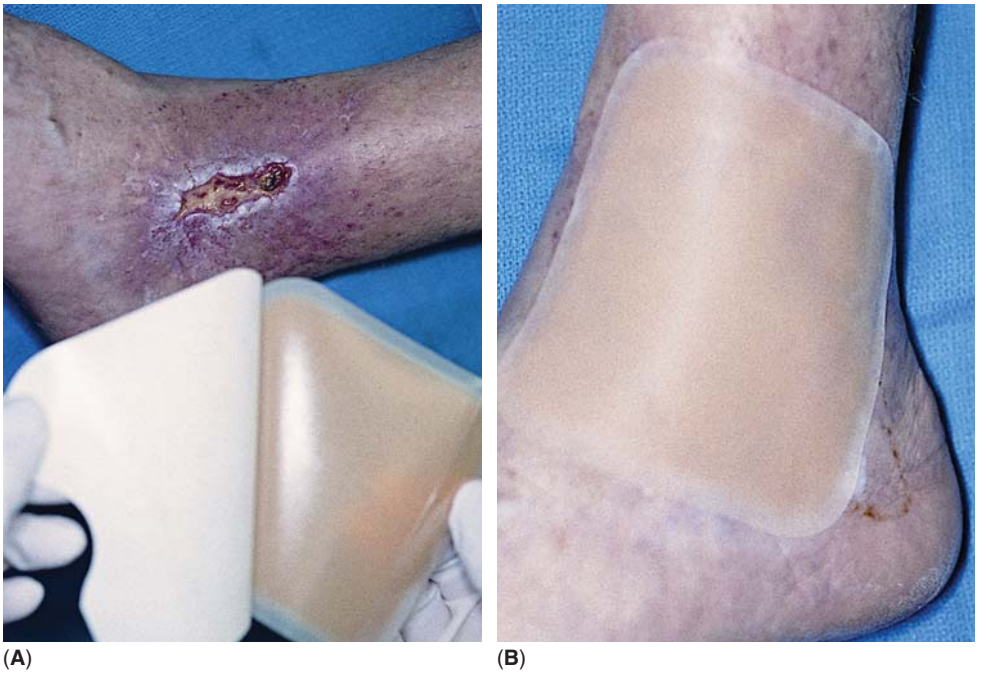


Figure 7.42 Application of hydrocolloid dressings.

Panel **A** shows how the white backing of the dressing is removed and discarded and the tacky (adherent) side of the hydrocolloid is about to be applied to this venous ulcer. Panel **B** emphasizes that a generous border of the dressing is needed around the wound to achieve adequate adherence and containment of exudate.



Figure 7.43 Proper hydrocolloid removal.

Depending on whether the patient is ambulatory or not, it is wise to have a rather extensive border of the dressing on the side that is most dependent, in order to minimize leakage of exudate and dressing removals. These four panels show the appearance and removal of a thin hydrocolloid dressing 3 days after it was applied to a venous ulcer. Panel **A** shows that the patient has been mostly in a recumbent position, for the exudate is tracking down posteriorly. As mentioned earlier, the best way to remove these adherent dressings and minimize damage to the healing structures is to lift up the dressing as a sheet and not to roll it back (Panel **B**). It seems anti-intuitive, but it has been shown to generate less damage to the wound. This movement is slowly continued throughout the process of dressing removal (Panel **C**). At the end, once the nonulcerated skin has been reached, the dressing can be slowly rolled back (Panel **D**).

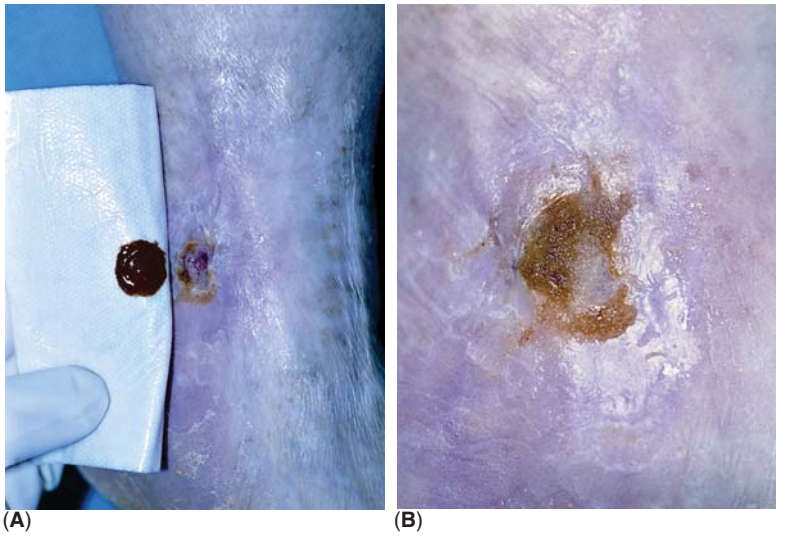


Figure 7.44 Cadexomer iodine application.

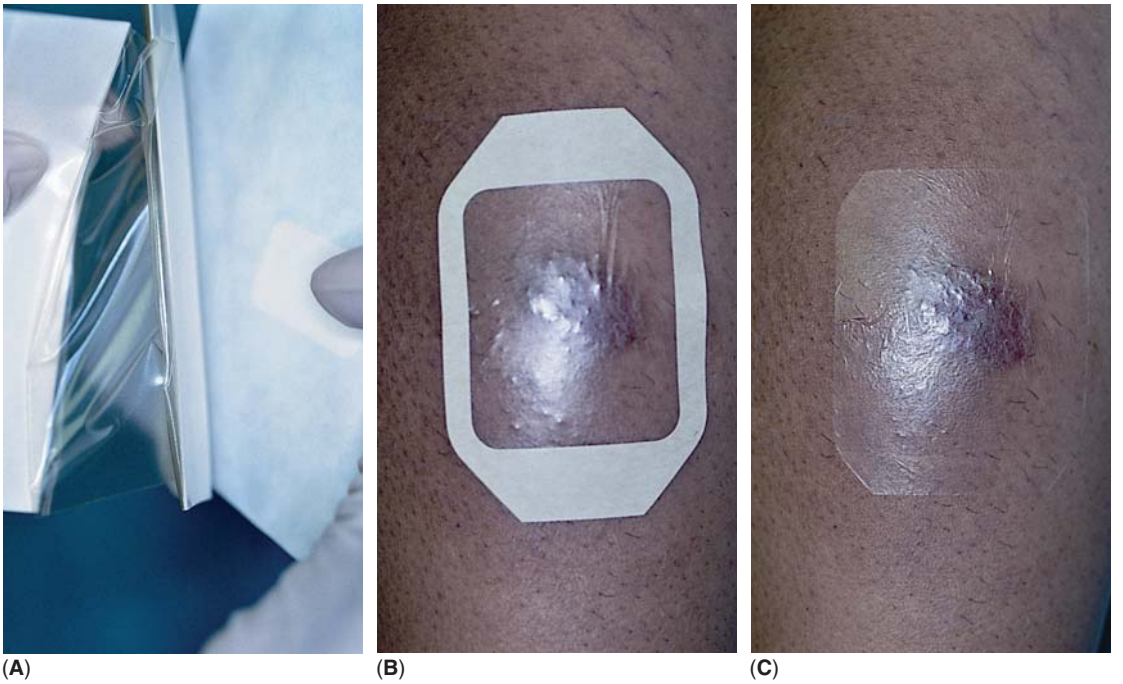
When indicated, there are several nonsurgical ways to debride wounds and stimulate granulation tissue, besides the use of moisture-retentive dressings. Here we have used cadexomer iodine ointment. This preparation consists of 0.9% iodine incorporated into cadexomer beads. When this agent is applied to an exudative wound, the iodine within the microscopic beads is slowly exchanged for wound fluid and released into the wound. Cadexomer iodine ointment is usually applied by spreading a very thin layer of it on a minimally adherent dressing (Panel **A**). Only enough cadexomer iodine to cover the wound area should be used. The iodine is slowly released into the exudative wound, and the ointment becomes a light brown color as shown here (Panel **B**). This is a signal for removal of the material and, if needed, a new application. From a practical standpoint, it is probably easier to instruct the patient or the visiting nurse to remove cadexomer iodine and reapply it daily, rather than waiting for this change in color. Also, we have found that dried cadexomer iodine is more difficult to remove.



(**A**) (**B**)

Figure 7.45 Cadexomer iodine removal.

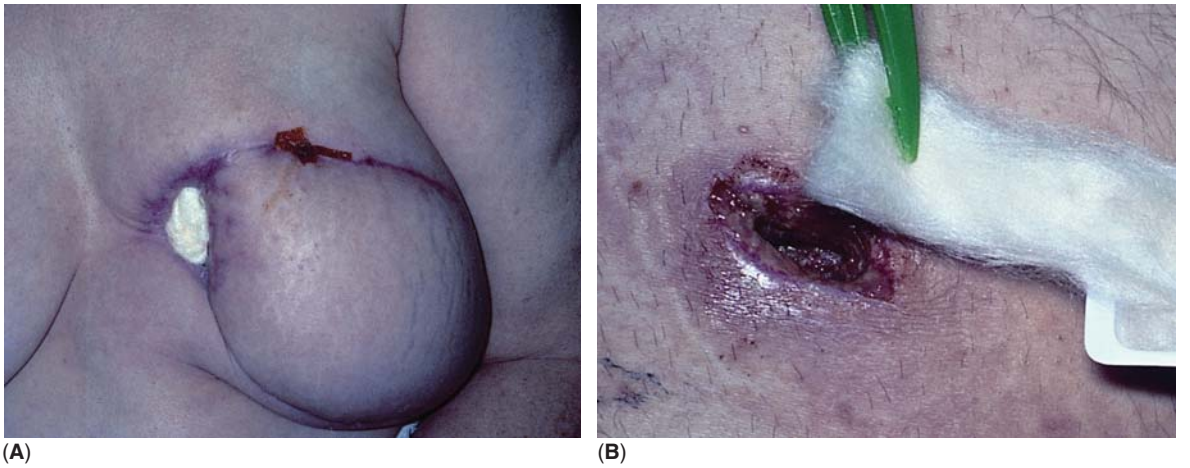
Panel **A** shows an example where cadexomer iodine was applied improperly by also being applied to the surrounding skin. What happens is that the material hardens on nonulcerated skin and becomes difficult to remove. Irrigating the material with saline is the first step in making removal of the ointment a little easier. Panel **B** shows that saline irrigation and soaking of the involved areas with saline for a prolonged period of time helps in the process of removal.



(**A**) (**B**) (**C**)

Figure 7.46 Application of a film dressing.

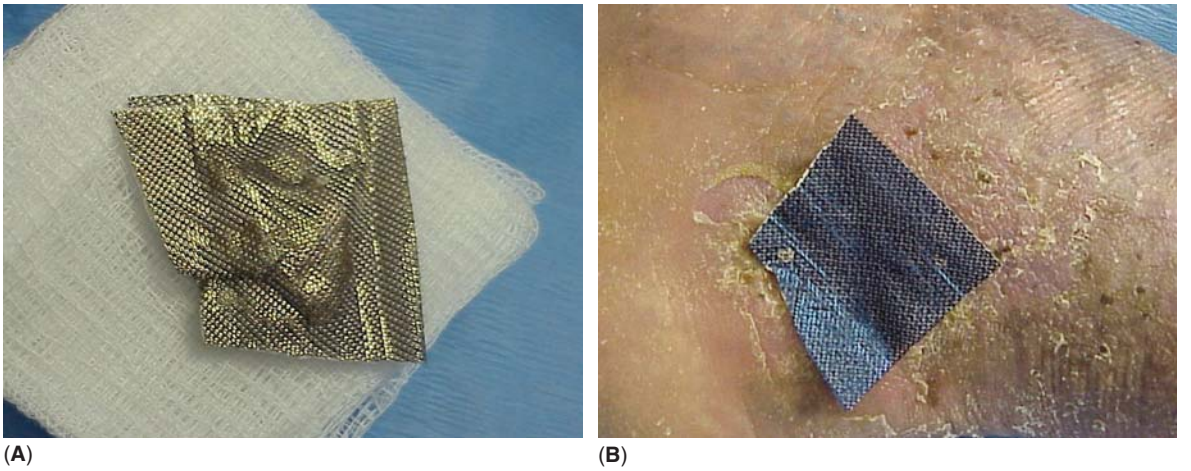
One must avoid self-adherence of the film dressing when removing its support backing. This backing keeps the dressing stable during application and is removed gradually during the application process. Here one sees that a portion of the film has adhered to itself (Panel **A**). One can free up the film that has become stuck to itself, but this is highly dependent on the film brand being used. Panel **B** shows that film dressings can be applied to the wound with the frame still present around them. The frame provides support during the application process and can be peeled off easily once the dressing is in place (Panel **C**).



(**A**) (**B**)

Figure 7.47 Calcium alginate packing.

Panel **A** shows the material inserted into a breast post-operative wound sinus to absorb drainage. As shown in Panel **B** and in a different patient, even deeper wounds can be packed with alginate, either as a sheet or rope configuration.



(**A**) (**B**)

Figure 7.48 Use of a silver-delivery dressing.

Dressings capable of delivering silver for its antimicrobial properties come in different and often complex configurations. They can consist of polyester, rayon, polyethylene, and combinations. The silver component is generally coated on one side of the dressing. When wounds are dry, the dressing needs to be saturated with sterile water for effective delivery of the silver. Panel **A** shows one such dressing over a layer of gauze and which has already been saturated with sterile water and is ready for application. Panel **B** illustrates how these dressings can be cut to conform more easily to the size of the wound.

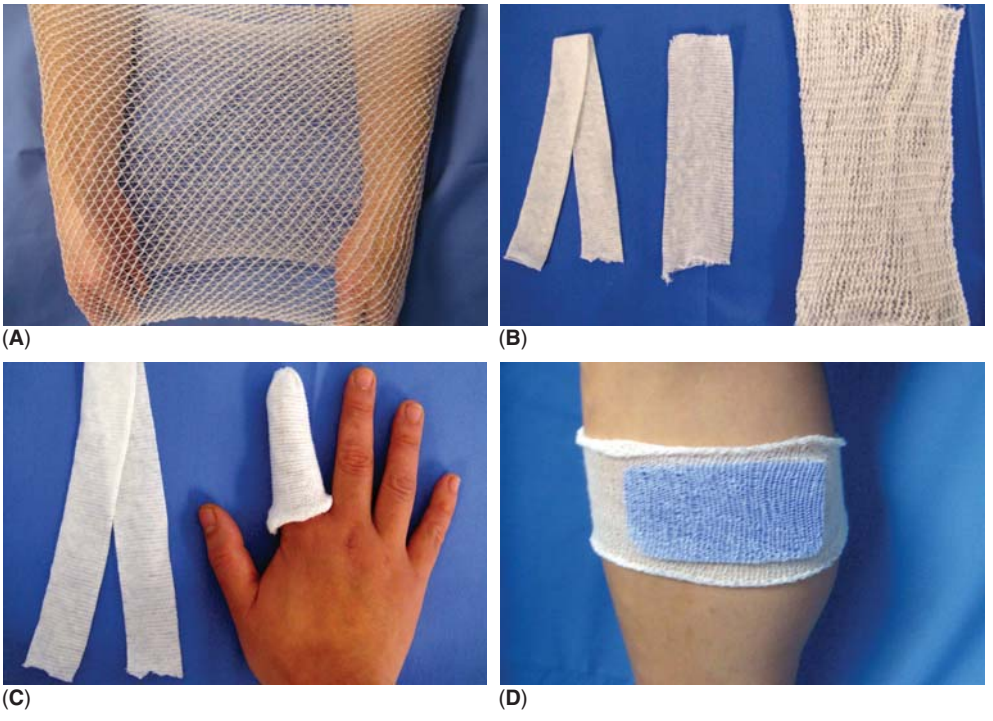


Figure 7.49 Keeping primary/secondary dressings in place.

Several stretchable, tubular, and net-like materials are available to hold primary and secondary dressings in place without the need for adhesive bandages. They can indeed be quite stretchable, which is indicated in Panel **A**. This stretchability is shown in Panel **A** by placing normal upper extremities within one of these bandages. They can also come in different widths and sizes (Panel **B**). These bandages are quite helpful for digits (Panel **C**) as well as securing primary dressings on the leg and larger wounds (Panel **D**).

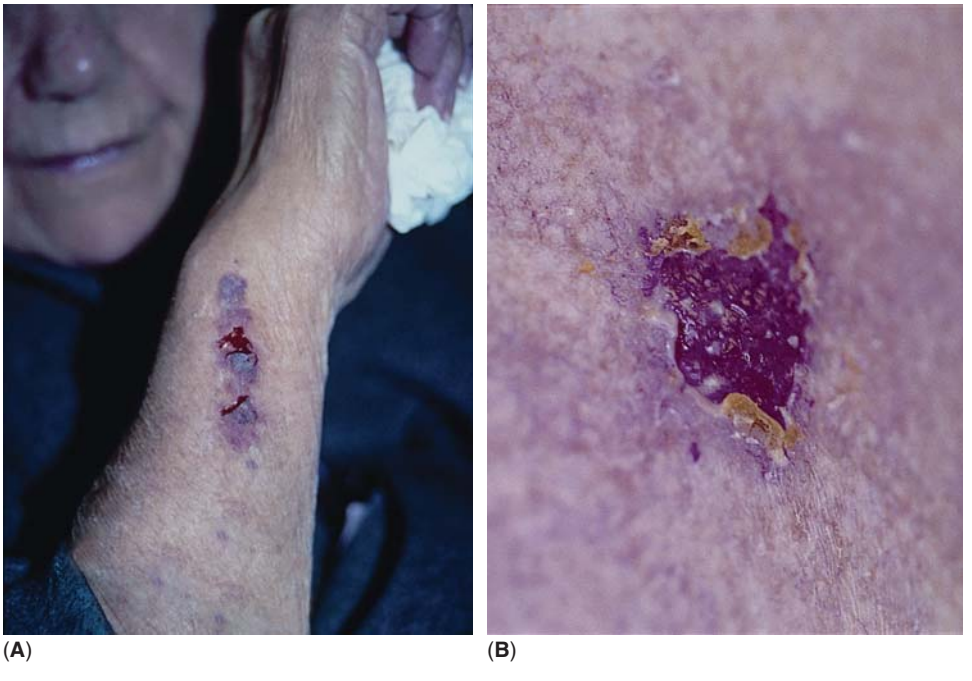


Figure 7.50 Choosing a wound dressing/fragile skin.

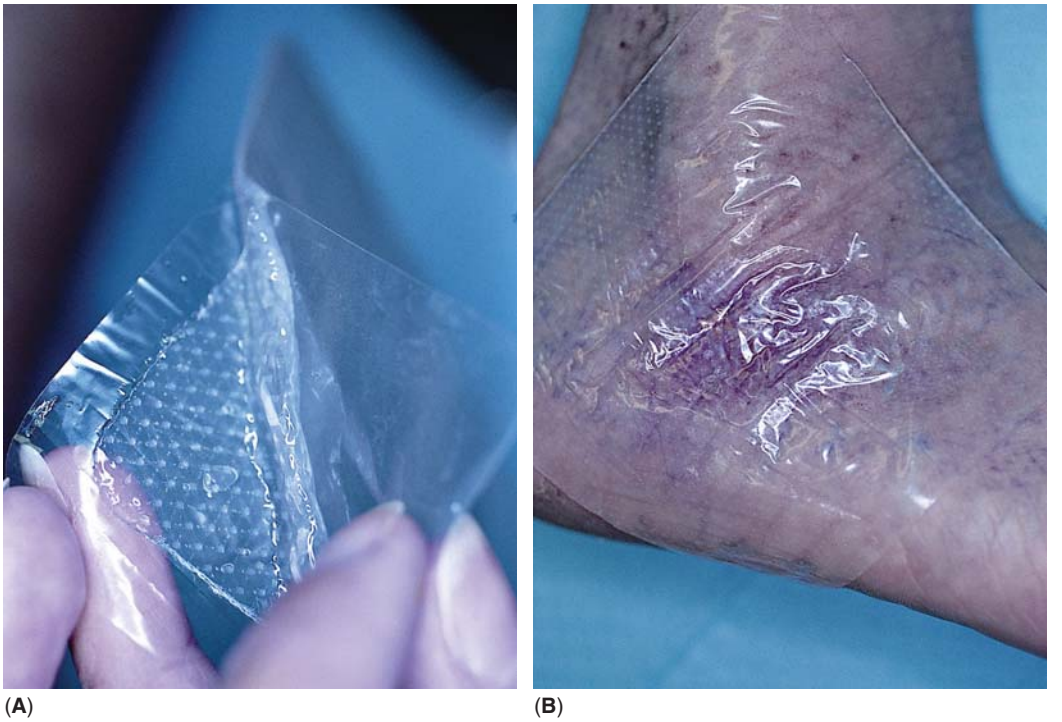
The skin in the elderly or in patients on corticosteroids (including inhaled preparations for asthma) is very fragile and tears easily (Panel **A**). Some clinicians like to use adherent film dressings for these wounds and emphasize that the dressings may remain in place until healing has occurred. We disagree with this approach because removal of the adherent dressing will inevitably remove the fragile surrounding skin and create a new wound. The same argument applies to other delicate conditions, such as blistering from pemphigus vulgaris (Panel **B**). We prefer the use of film spray dressings, which commonly consist of polymers, and which protect the wound for up to 24 hours. Some of these polymer spray dressings do not sting, and so are preferable. A net-like bandage described earlier could then be used as a secondary dressing.



(**A**) (**B**)

Figure 7.51 Choosing a wound dressing/blistering conditions.

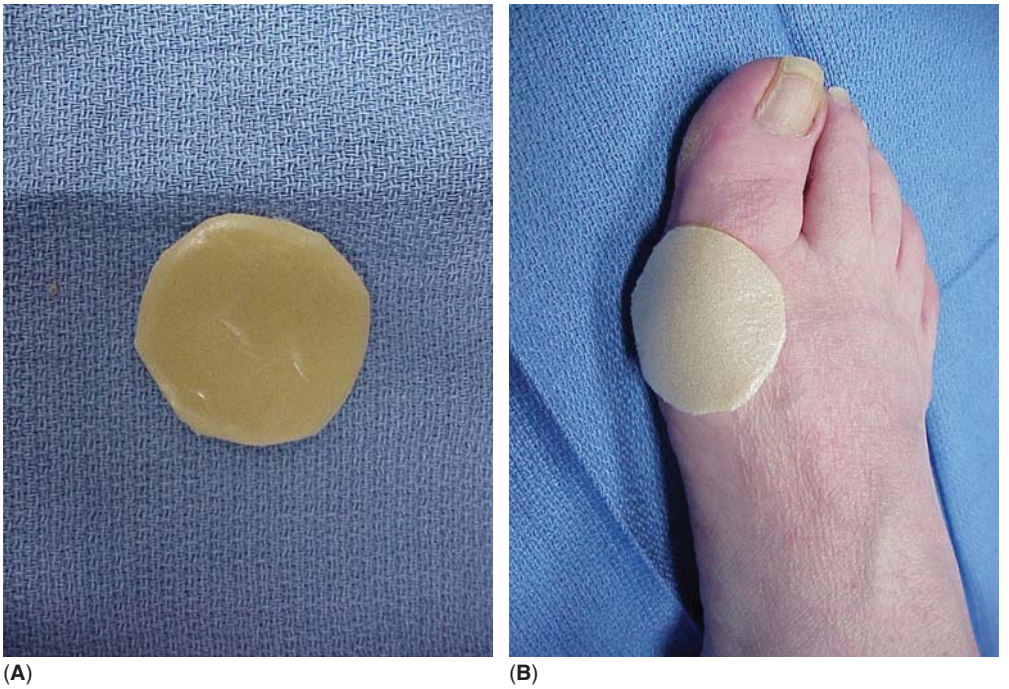
Panel **A** shows a blister from pemphigus vulgaris. The blistering is caused by antibodies to certain components of the skin (desmoglein 1 and 3). The condition mainly affects the oral mucosa, and can be life-threatening. The toe blister in Panel **A** was very painful and difficult to manage. This area would rub against his shoe and needed a bandage system that would stay in place. Panel **B** illustrates a film dressing with an island of nonadherent material in its center. Here one can see the application, after which the backing is removed from the island dressing and stays in place (Panel **B**).



(**A**) (**B**)

Figure 7.52 Choosing a wound dressing/relieving pain.

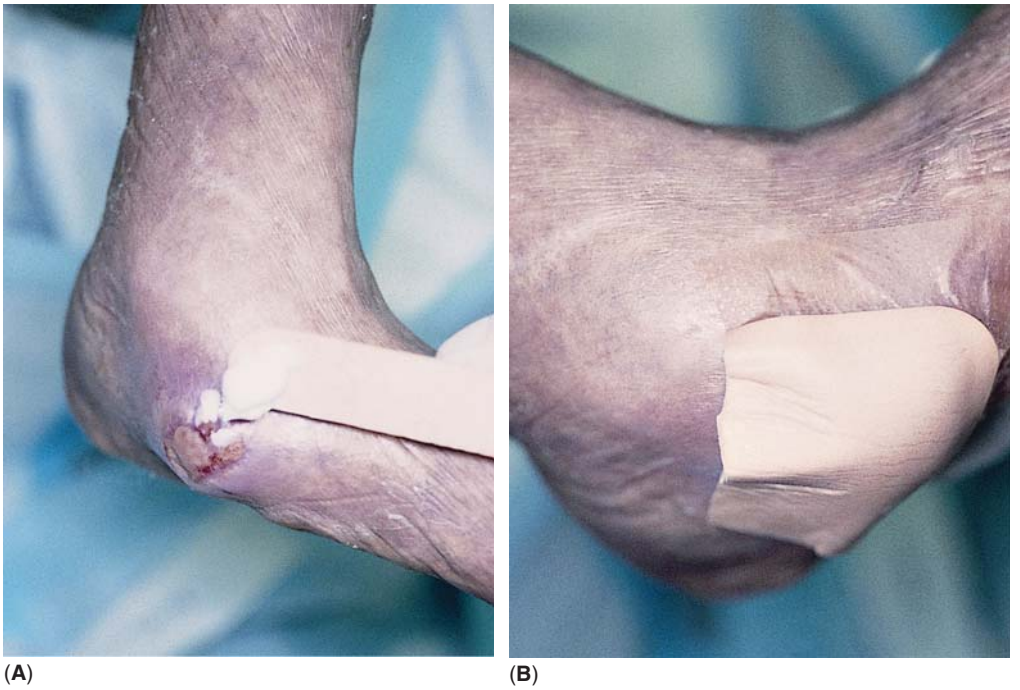
This illustrates the application of a hydrogel dressing (Panels **A** and **B**). Panel **A** shows the polyurethane covering on one side (which will be in contact with the wound bed) being removed. It is easy to minimize the clinical significance of the shallow wound seen in Panel **B**. However, such small wounds (in this case from livedoid vasculitis) are very painful. The vasculitic component is suggested by the purple areas and hyperpigmentation. Gel dressings can be quite effective in relieving pain in these types of ulcers. Panel **B** shows the coverage of the wound with the hydrogel dressing. At this point the outer polyurethane film has not been removed yet and may remain in place to prevent drying of the gel dressing.



(**A**) (**B**)

Figure 7.53 Choosing a wound dressing/pliability.

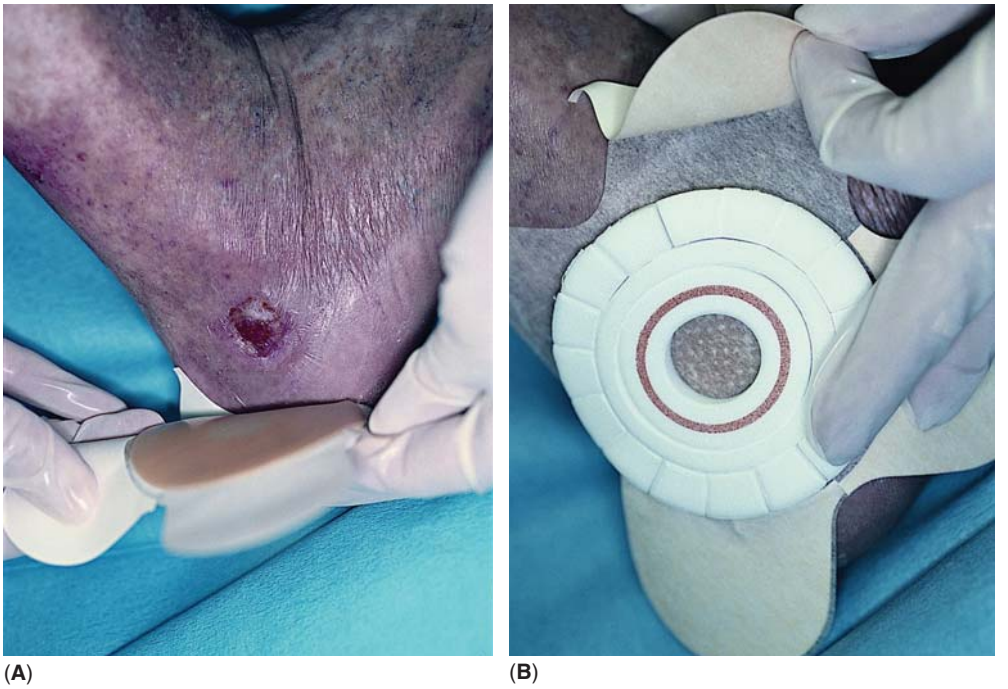
Hydrocolloid dressings adhere to the skin and, when cut to size (Panel **A**), can be ideal for contoured surfaces. Panel **B** illustrates how the dressing can be applied to the erosion that has developed in this woman who kept using ill-fitting shoes. Although manufacturers of hydrocolloids will officially state that the dressing can stay in place for up to a week, in situations such as the one shown in Panel **B** we would advise the patient not to remove the dressing until it is no longer completely adherent to the wound. This tends to prevent reinjury from dressing removal.



(**A**) (**B**)

Figure 7.54 Choosing a wound dressing/bone deformity.

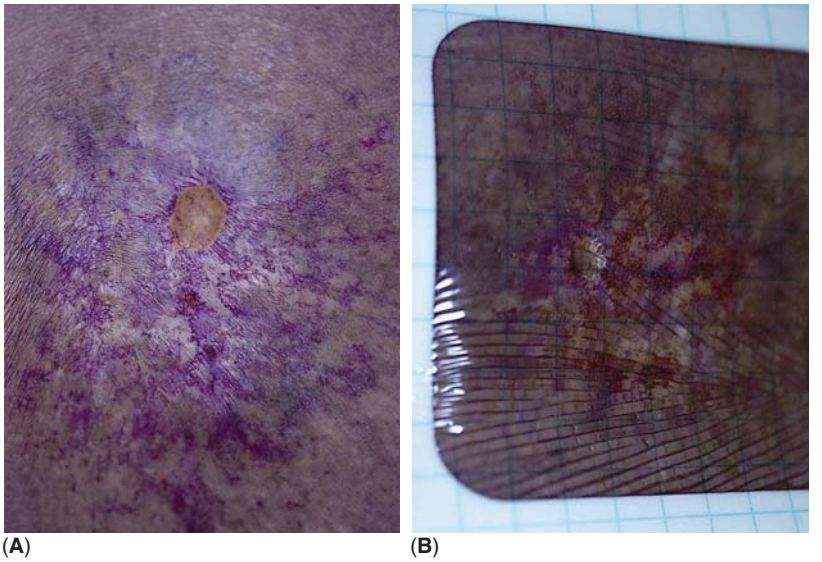
This elderly woman is confined to a wheelchair and is on systemic corticosteroids used for many years for her rheumatoid arthritis. Her foot ulcer was difficult to heal and be kept healed, in large part because of the underlying bone deformity that would become easily traumatized. In this case, the wound was managed with silver sulfadiazine (Panel **A**). Panel **B** shows that a foam island dressing was applied to provide absorption of exudate and to act as a protective barrier. The dressing adheres well to difficult areas, such as this one, its border being a thin flexible film. At other times in her clinical course, we have used wool padding to fill in the areas adjacent to the bony prominence where the ulcer is located. This allowed us to use compression bandages to control the edema.



(**A**) (**B**)

Figure 7.55 Choosing a wound dressing/difficult locations.

At times, the location of the ulcer makes it very difficult to apply certain dressings. A dressing we have found to be helpful in these circumstances is this hydrocolloid dressing with paper tape "wings." Panel **A** shows this dressing being applied to this foot ulcer just above her heel. In Panel **B** the hydrocolloid portion of the dressing is over the ulcer. Rings of foam on the outside act as a protective barrier. One can remove as many of these rings as needed based on the size of the ulcer.



(**A**) (**B**)

Figure 7.56 Choosing a wound dressing/radiation injury.

This man had a liver transplant and required multiple fluoroscopic exams. Although this is not commonly known, repeated or prolonged exposure to fluoroscopy can cause serious radiation injury. This painful wound developed in the midst of the area affected by the radiation. The tissue around the wound is fibrotic and shows telangiectasia (Panel **A**). These types of indurated plaques are commonly mistaken for the morphea variant of localized scleroderma. The ulcer itself has a poor wound bed, even after several attempts at surgical debridement. There were two problems in choosing a dressing for this wound. One is that the wound was on the back, thus a nonadherent dressing would have to be taped in place. The second problem was that tape or strongly adherent dressings could further damage the atrophic surrounding skin. In this case, an island hydrogel was used (Panel **B**) because it has an adherent border that allows easier removal. At the same time, the hydrogel provides pain relief. It is transparent, thus allowing wound inspection without removal. Moreover, the grid on the dressing can be useful for wound measurement.

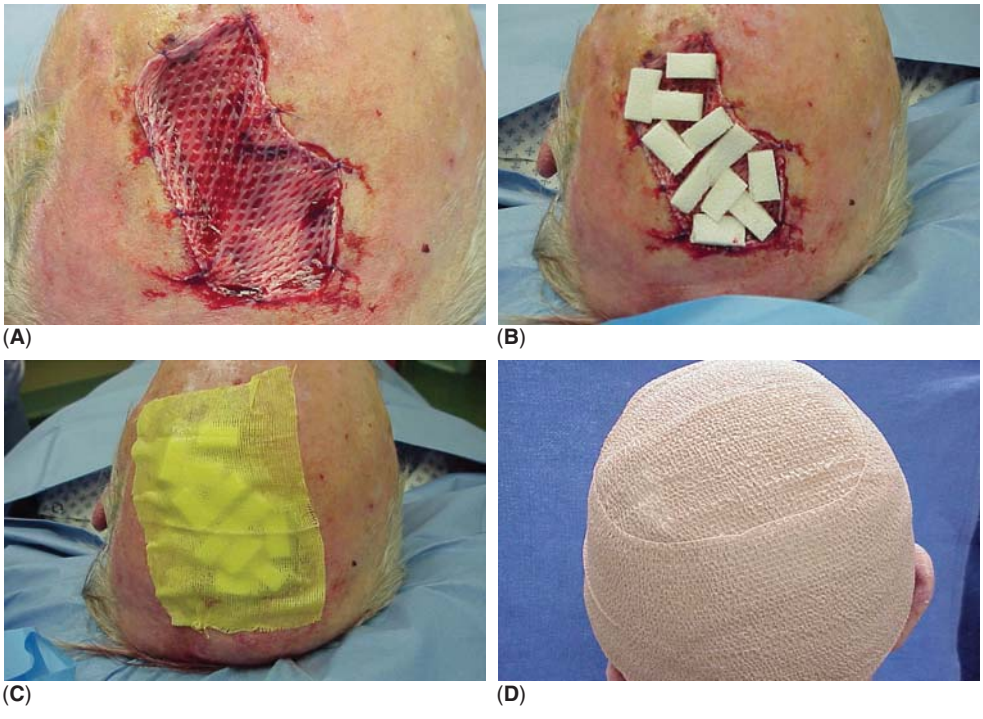


Figure 7.57 Choosing a wound dressing/hemostasis.

A living, bi-layered skin construct was used to cover the surgical scalp defect after the removal of a large squamous cell carcinoma (Panel **A**). The construct was sutured in place. The bioengineered skin has been meshed (ratio 1.5:1) to minimize the formation of a clot that will cause lifting of the construct away from the wound. In addition, we used foam strips of an anti-clotting collagen-based material (Panel **B**) to further control the bleeding. We generally like to use a bismuth/petrolatum impregnated gauze to keep these constructs in place (Panel **C**). A self-adherent bandage will then be placed on the scalp in a way that is similar to what is done after a hair transplantation (Panel **D**).

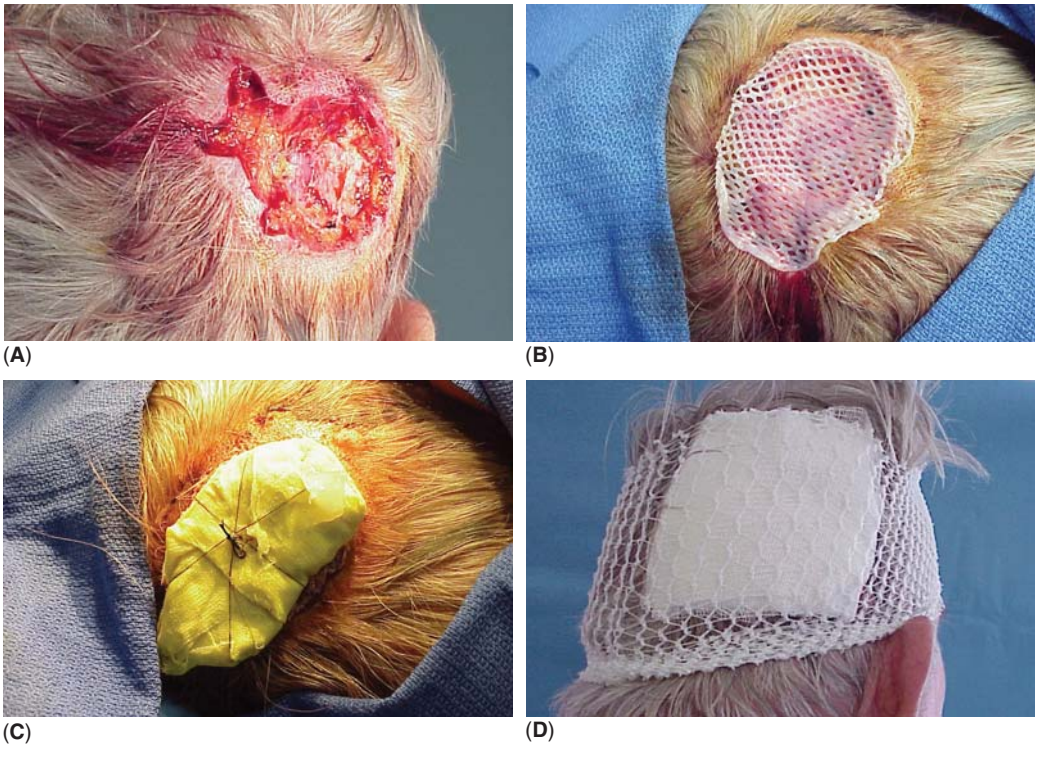


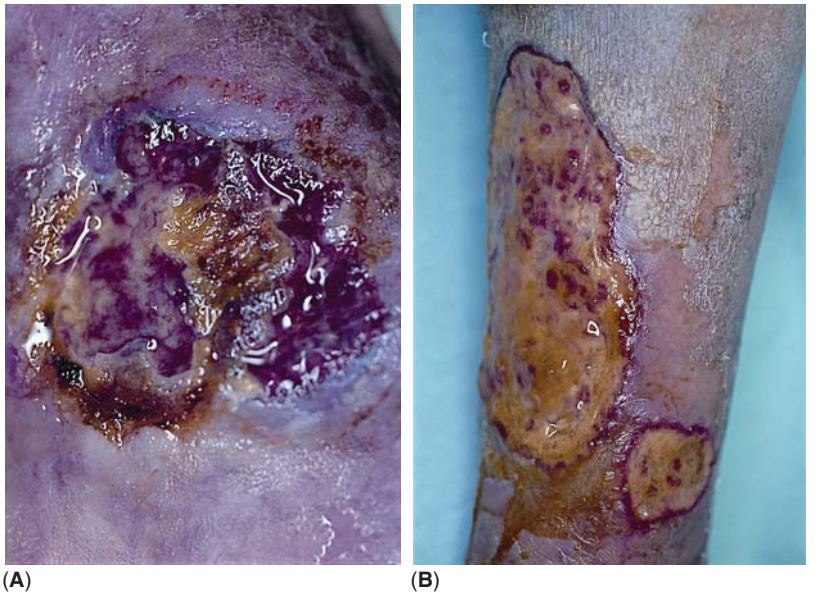
Figure 7.58 Choosing a wound dressing/keeping bioengineered skin in place.

In this other surgical scalp wound (Panel **A**) after removal of a squamous cell carcinoma, bleeding was not the problem, but we chose a different way of keeping bioengineered skin in place (Panels **B** and **C**). Sutures were not required. The bolster shown in Panel **C** was then covered with gauze and a net-like bandage (Panel **D**).



Figure 7.59 Choosing a wound dressing/limitations in highly exudative wounds.

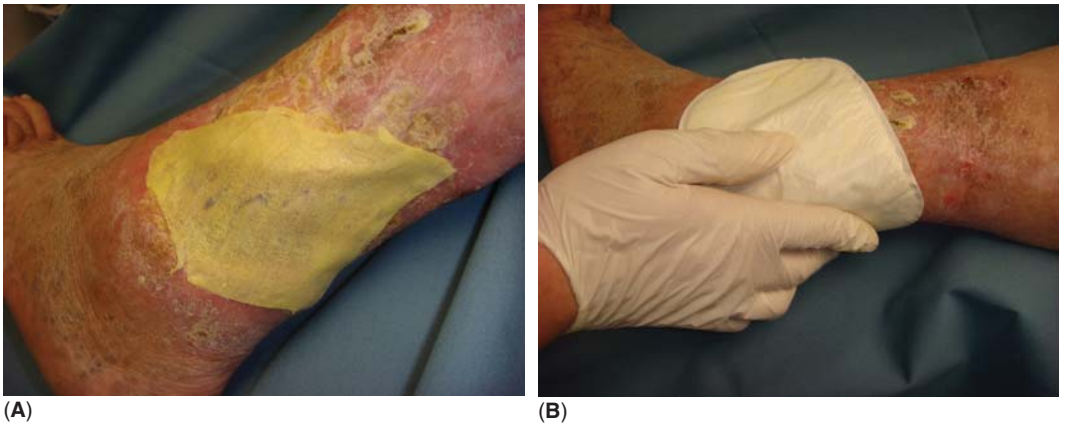
The photograph shows the challenges and consequences of keeping a compression bandage over highly exudative leg wounds. In this case, the bandage has been cut and removed, showing the massive exudate that accumulated underneath. The drainage is often foul smelling, which can be very upsetting to patients and can fool inexperienced clinicians into thinking that the wound is infected. Ways to deal with this problem is to use an absorbent wound dressing, such as foams, hydrocolloids, alginates, and to change the bandages more frequently. Other clinicians have used antimicrobial agents or adsorbent material within the bandages to decrease the bacterial burden and the foul odor.



(**A**) (**B**)

Figure 7.60 Choosing a wound dressing/exudate and purulence.

Highly exudative and/or purulent wounds require a localized approach, because systemic antibiotics are often not effective or indicated. The ankle ulcer shown in Panel **A** is highly exudative and contains a high bacterial burden (colonization). In this case, we will prefer the use of foam, calcium alginate, or a hydrofiber dressing with or without silver. Another possibility would be cadexomer iodine. The extensive ulcerations shown in Panel **B** are not as exudative but probably also contain a very high bacterial burden. Colonization here is more likely than cellulitis, because there is no severe pain or fever and there is not much redness around these ulcers. Extensive surgical debridement in the operating room is an option, perhaps with hydrosurgery. Antimicrobial dressings, containing either silver or iodine, will be helpful.



(**A**) (**B**)

Figure 7.61 Choosing a wound dressing/adressing dry skin in an exudative wound.

Panels **A** and **B** show the use of a primary dressing (bismuth/petrolatum impregnated gauze; Panel **A**) and the use of an absorbent secondary dressing (Panel **B**), respectively. The patient had a large venous ulcer that was complicated by the presence of severe dermatitis.



Figure 7.62 Choosing a wound dressing/the challenge of copious amounts of exudate.

This complex ulcer in a patient with systemic sclerosis (scleroderma) was complicated by marginal arterial flow, calcifications, and frequent bouts of cellulitis. The very copious exudate required the frequent removal of highly absorbent foam dressings.



Figure 7.63 Debridement/hydrosurgical approach.

In the last few years, methods for achieving thorough debridement of wounds with high-powered water devices have improved and progressed substantially. This type of debridement is known as hydrocision/hydrosurgery. It generally still requires general anesthesia and an operating room setting for large wounds. Compared to scalpel/surgical debridement, it has the advantage of accomplishing a very extensive and rapid removal of necrotic tissue even in deep wounds. It shares with surgical debridement the disadvantage of often not distinguishing between viable and nonviable tissue. Panels **A** through **D** show the use of hydrocision in complex wounds precipitated by trauma (Panels **A** and **B**: foot trauma and fractures; Panel **C**: development of compartment syndrome on the leg; Panel **D**: debriding necrotic tissue of a below the knee amputation stump). There are various configurations to the hydrosurgery tip associated with these devices and they all deliver water at very high pressures.



Figure 7.64 Debridement/localized pain control.

This particular topical anesthetic is a mixture of prilocaine and lidocaine. It is useful for pretreatment of the wound prior to either further anesthesia using the injection of lidocaine, or for direct but minor surgical debridement. Panel **A** represents the baseline appearance of a necrotic and painful ulcer from cryofibrinogenemia in a middle-aged male. Because of the pain, he will also scratch and cause further damage to the area. In Panel **B** we see the same wound covered with a generous amount of the topical anesthetic. Achieving optimal anesthesia requires between 30 and 60 minutes and can be accelerated by the use of an occlusive film dressing. Thereafter (Panel **C**), the injection of lidocaine can take place with less pain. Panel **D** shows the surgically debrided wound.

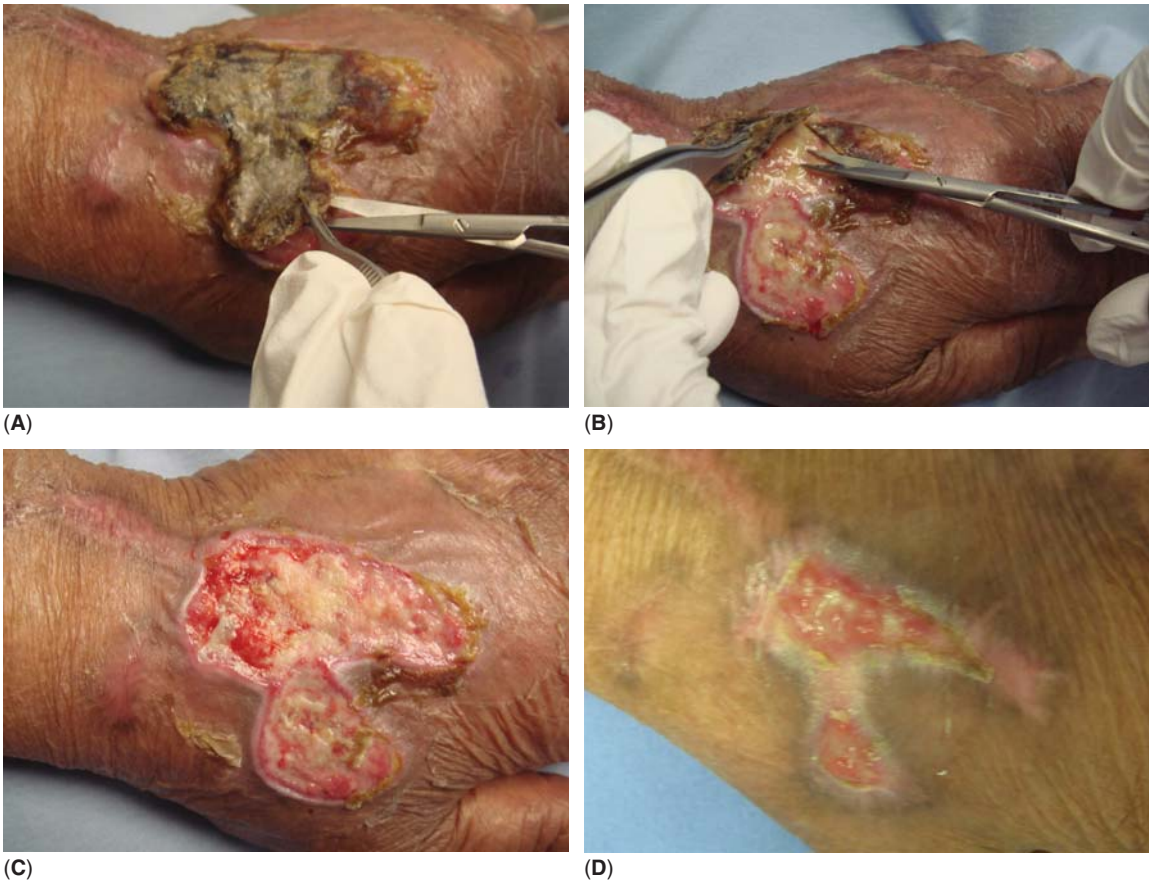


Figure 7.65 Surgical debridement without anesthesia.

Unfortunately, we sometimes see patients with severe neuropathy involving the upper and lower extremities. The only advantage is that in such cases surgical debridement can be accomplished without anesthesia. Panels **A** through **C** in this elderly man with syringomyelia and blistering of the dorsum of the hands show the progression of surgical debridement in one setting. Panel **D** shows a photograph taken several weeks later and illustrating remarkable healing. The light colored skin indicates recently healed portions of the wound. This is because the pigment largely lags behind during the process of re-epithelialization.



Figure 7.66a Debridement/the use of maggots.

Maggot debridement therapy (also known as biodebridement or biosurgery) is the intentional introduction of fly larvae (generally commercially available maggots) into a wound for debridement of necrotic tissue. In the United States, maggot therapy can be prescribed for soft tissue wounds and nonhealing necrotic skin (i.e., postsurgical wounds, venous ulcers, etc). It is approved by the FDA. These fly larvae are placed on wounds and left in place under a cage-like dressing for approximately 2 days. Panel **A** shows a company container with maggots (about 1–2 mm) clinging to the wall and to the bottom. One substantial problem is to ensure that the maggots do not escape and contaminate the clinical setting.

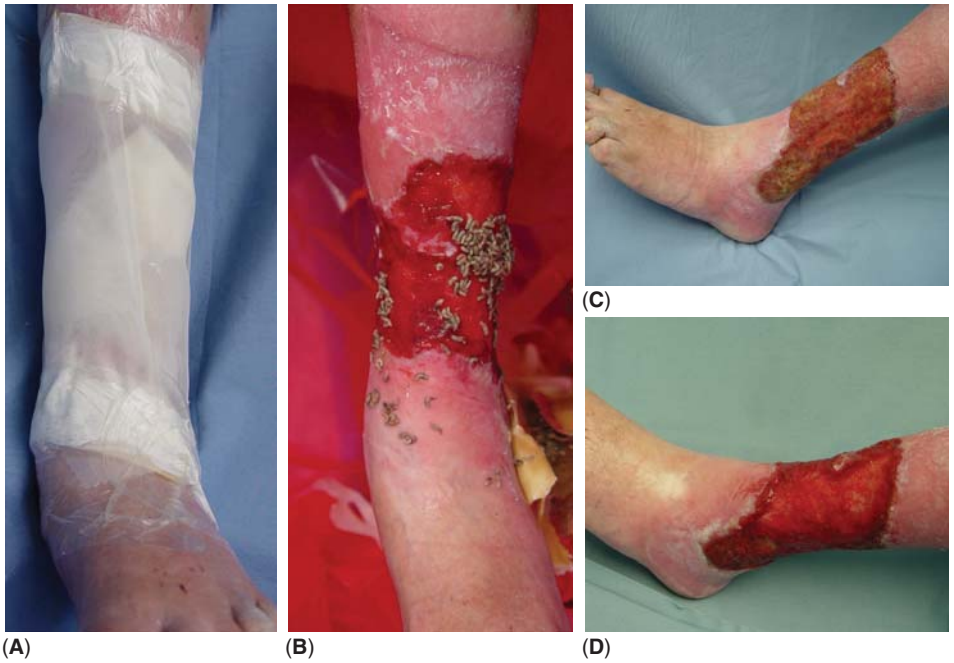


Figure 7.66b Debridement/the use of maggots/dressing for biodebridement.

Panels **A** through **D** illustrate the application of the maggots and the resultant stimulation of granulation tissue free of necrotic material. As mentioned, containment of the larvae and avoiding their escape is critical. Panel **A** shows the application of multiple dressings that create a "cage" for the larvae. Panel **B** shows engorged maggots over an improving wound bed. Since maggots can affect keratin, there has been some increased redness around the wound. It is important to realize that maggots don't have teeth and don't chew the tissue. Rather, they deliver enzymes that break down the wound tissue and they are able to then suck the fluid. Panels **C** and **D** show a progressive improvement of the wound bed in this man with rheumatoid ulcers.

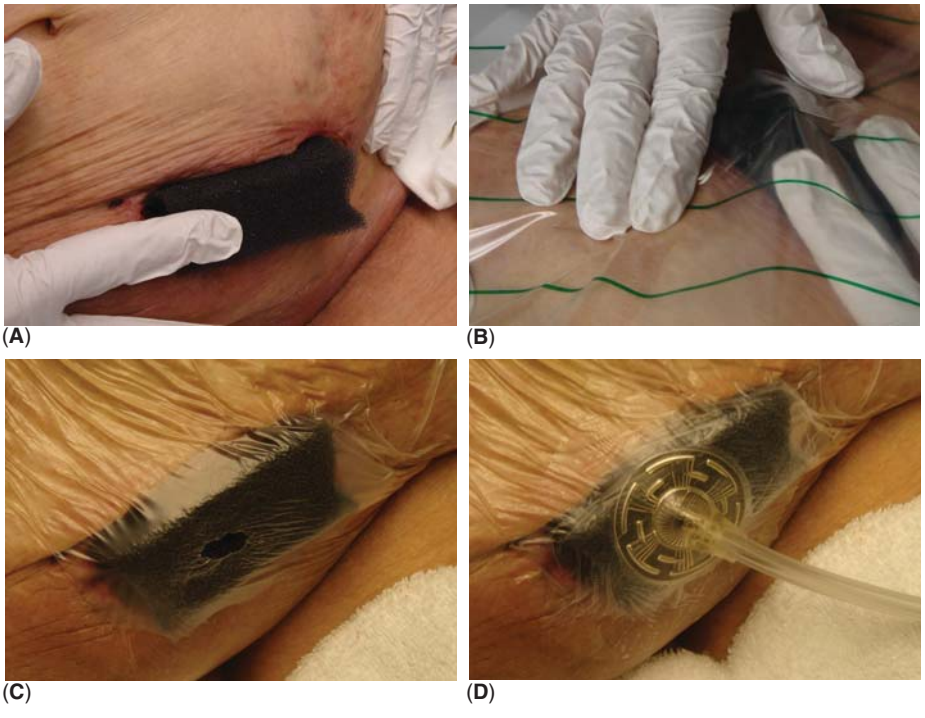
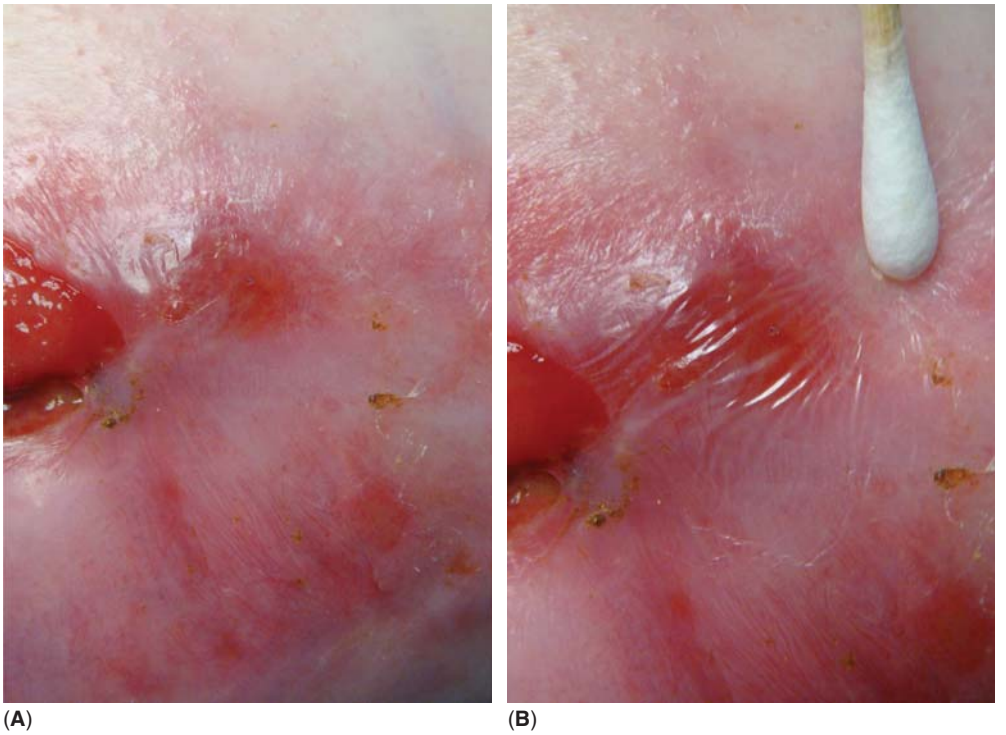


Figure 7.67 Debridement/negative pressure devices.

A number of devices that create negative pressure and are able to remove wound fluid have emerged in the last few years. The general principle is the application of a closed system generally connecting a wound dressing to a tubing mechanism for removing fluid through a negative pressure pump. Panels **A** through **D** illustrate the use of a wound contact foam (Panel **A**), the application of an overlying film dressing (Panels **B** and **C**), and the negative pressure tubing in place (Panel **D**). Negative pressure is now commonly used for acute and chronic wounds. We don't think it is helpful in all cases of chronic wounds but clinical studies are under way to identify prognostic guidelines for the use of these devices. We believe that the mechanism of action is not just simple removal of wound fluid, but may involve other, more biological effects.



(**A**) (**B**)

Figure 7.68 Detection of re-epithelialization/the wrinkle test.

The steps outlined above for wound debridement are aimed at removal of necrotic tissue, improve the wound bed, and achieving wound bed preparation with better granulation tissue. Ultimately, however, the goal is to have the wound resurfaced from epithelium at the edges of the wound or from within the wound. During the re-epithelization process, the new epidermis is thin, very fragile, consisting of only 2–3 keratinocyte layers, and probably without the formation of a stratum corneum, which gives it durability. These features of neoepidermis make it difficult to detect. Moreover, the new and fragile epidermis is commonly stripped unknowingly during dressing removal. Several years ago, we noted that the gentle application of a cotton tipped applicator next to the thin epidermis generates wrinkle-like lines. These "wrinkles" are not seen when only granulation tissue is present. We see here a shallow peristomal erosion with some suggestion of complete re-epithelialization (Panel **A**). A simple test can be done to determine if a wound has re-epithelialized. A sterile cotton-tipped applicator is gently pressed adjacent to the wound to determine whether there are "wrinkles" on the surface. This detects early epidermal resurfacing in a noninvasive way.

8 Other established procedures and experimental issues

We now come to the final section, which describes some established clinical procedures, both diagnostic and therapeutic, as well as information about clinical trials. This section contains clinical information that could have been in any of the previous sections. Rather than being redundant, we have chosen to group these matters in the final section. Among the clinical photographs are basic issues regarding wound bed preparation (with a scoring system), biopsy of wounds, Doppler examination, hyperbaric oxygen therapy, scraping of scaling skin to exclude fungal infection, and harvesting of autologous skin (both under general anesthesia and as pinch grafting performed at the bedside or in the clinic). We show a program (Image J) that is extremely useful for measuring wound size from simple tracing. We then describe some basic matters related to the performance of clinical trials. After all, it seems appropriate to end with clinical trial attempts, because we still have a long way to go for consistently healing difficult chronic wounds. In that context, we describe the steps that are required for initiating a trial, the nomenclature, and rigorous facilities needed by regulatory agencies. We also discuss the necessity for exemptions for investigational new drugs (IND) and investigational devices exemptions (IDE). We end the section by providing an example of a single center experimental approach using autologous cultured bone marrow-derived mesenchymal stem cells. Looking over this and the previous sections, we are fully aware that much still needs to be done to achieve a consistently effective diagnostic and therapeutic approach to nonhealing wounds. Thus, ending with an experimental protocol seems appropriate.

Clinical points

- Wound bed preparation is critical for achieving complete closure of chronic wounds. A scoring system for its different components, as we have begun to develop, might have predictive values and could be done at the bedside.
- It is often important to biopsy wounds to determine their etiology and before embarking on a therapeutic approach. It is also important to exclude malignancy in nonhealing wounds. Although a punch biopsy specimen from the wound margins may be sufficient, we prefer to take excisional biopsies that encompass the wound margin and its wound bed.
- Other areas of the wound bed can be sampled to ensure the absence of a malignancy.
- Any excisional biopsy of a wound must take into account the level of skin hardness (suggesting fibrosis) and edema. For example, areas of lipodermatosclerosis must be biopsied with a high length-to-width ratio, or else the biopsy site will dehisce and become a chronic wound.
- Biopsies of venous ulcers and other chronic wounds tend to heal readily, back to the original margin, and do not result in an overall deterioration of the wound. However, we have noted that it is safer to wait at least 3–4 weeks before biopsying a wound that was complicated by cellulitis.
- Although the vascular laboratory is ideal for obtaining information about the patient's vascular status, a handheld Doppler in the office or the clinic can be quite useful in evaluating new patients and in deciding the initial diagnostic and therapeutic approach.
- Patch testing is extremely useful for determining potential allergens that are complicating the patient's clinical course and preventing healing by causing a contact dermatitis. Even dressing materials and topical corticosteroid preparations can cause an allergic contact dermatitis.
- Patients with venous insufficiency and/or ulceration are peculiarly more likely to develop contact dermatitis. It is wise to use latex-free bandages, if at all possible.
- A Wood's lamp (black light or ultraviolet A) can be used to detect green and red fluorescence indicative of some bacterial colonization/infection.
- Image J program, a powerful software that can be downloaded for free from the National Institutes of Health (NIH) web site, can be used to accurately measure the surface area of wounds from photographs and planimetric tracings.
- Although autologous skin grafting of chronic wounds is more elegantly performed with a dermatome and under general anesthesia (particularly important for large wounds) one should strongly consider the use of pinch grafting to not only replace tissue but to stimulate wound healing in the context of wound bed preparation.
- In order to develop new treatments, we need to perform clinical trials. Clinical experimentation is not easy and has in fact become subject to more regulatory hurdles. Clinical trials involve many safety and regulatory steps, interactions with regulatory bodies (such as the Food and Drug Administration; FDA) and, in developing certain therapies, construction of safe laboratory facilities.

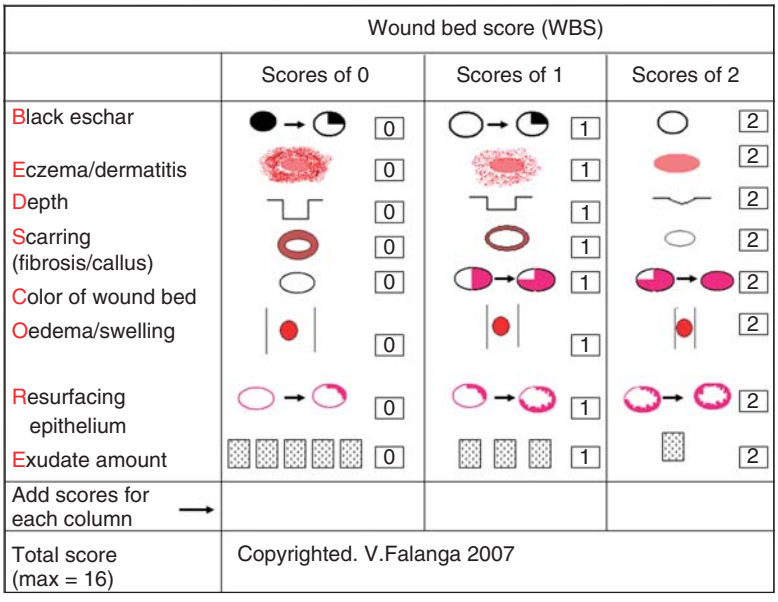
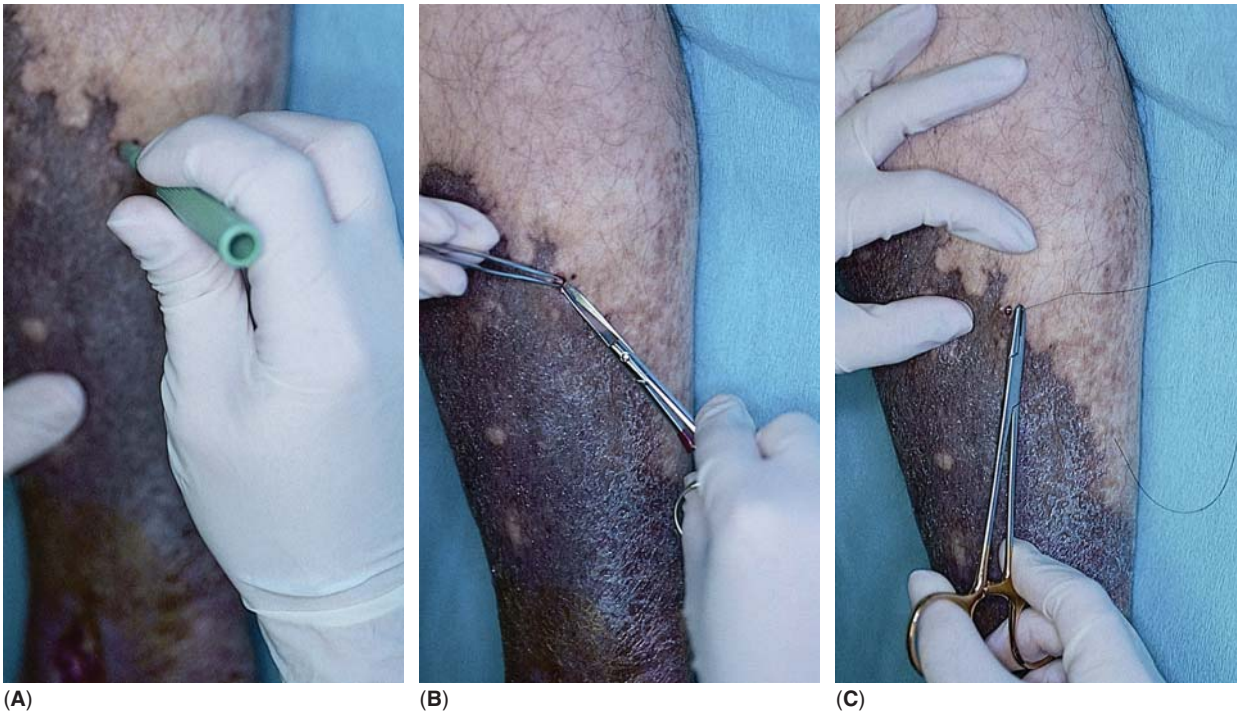


Figure 8.1 Wound bed preparation: a scoring system.

Wound bed preparation (WBP) is the process by which multiple and critical components of the wound bed are improved to allow healing to proceed unimpeded and in an accelerated fashion. Therefore, the use of a scoring system for WBP will be important for clinical practice and documentation. We have developed such a scoring system based on the following parameters: healing edges (wound edge effect), presence of eschar, greatest wound depth/granulation tissue, amount of exudate, edema, periwound dermatitis, periwound callus and/or fibrosis, and a pink/red wound bed. Please note that, after preliminary scoring in case an eschar is present, the eschar needs to be removed to obtain a final score (i.e., assessment of depth, wound bed color, etc.). Therefore, even after eschar removal, the maximum eschar score remains at 2. Each parameter receives a score from 0 (the worst score) to 2 (the best score), and all the parameter scores are added for a total score. Each wound can have a maximum score of 16 (the best score possible), to a minimum score of 0 (the worst score possible) (Copyrighted *Source*: V. Falanga, 2009).



(**A**) (**B**) (**C**)

Figure 8.2 Biopsies of the wound edges: punch biopsy.

Biopsies and histological evaluations of different areas of wound-associated findings are important to determine the etiology of the underlying process and, in many cases, to exclude the presence of malignancy. The decision to perform a punch versus an excisional biopsy and the choice of where to biopsy are very much dependent on the clinical situation and findings. In this case, the patient had a history of leg ulcers and very dramatic hyperpigmentation. We thought that he most likely had venous insufficiency, but wanted to exclude Kaposi sarcoma. Panels **A** through **C** show the sequential steps of taking a simple punch biopsy of the edge of the hyperpigmentation. In cases where the skin is fibrotic or affected by lipodermatosclerosis, we prefer to suture the punch biopsy defect so that the defect can heal by primary intention and we can minimize the development of a chronic wound.

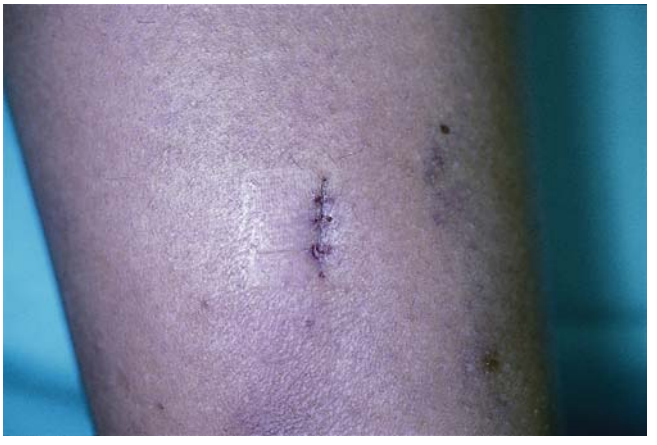


Figure 8.3 An excisional biopsy: primary-intention healing.

In this case, an excisional biopsy was done to obtain a specimen from an area of lipodermatosclerosis. Such biopsies from fibrotic skin need to be very thin and long, so as to allow easy closure without much tension. If this is not done, one often runs the risk of creating an ulcer. As in this case, we supplement the sutures with adhesive strips and delay the removal of the sutures by a few days. When biopsying the leg, we need to make sure that the sutures remain in place for at least 2 weeks.



Figure 8.4a An excisional biopsy and secondary-intention healing.

This 73-year-old woman with pyoderma gangrenosum of the leg was responding favorably to a living bi-layered bioengineered skin construct, both in terms of pain and initiation of healing from the wound margins. The purpose of the biopsy was to determine whether the cells comprising the construct remain detectable in the wound. This and studies in other patients, by using PCR and FISH analysis, have allowed us to conclude that these living constructs do not remain within the wound for more than 4–6 weeks. Therefore, the mechanism of action of bioengineered skin is probably due to the stimulation of wound healing. The area to be biopsied is outlined with sterile blue ink; notice that 3 areas are being sampled: wound bed, wound edge, and the surrounding skin. The rectangular biopsies are our choice when assessing the wound from the histological standpoint or conducting research on cells cultured from the wound.



Figure 8.4b An excisional biopsy and secondary intention healing/immediately after the biopsy.

This photo was taken immediately after the biopsy encompassing the wound bed, the edge, and the surrounding skin. The gray wound bed, which is frequently seen after the application of bioengineered skin, is often mistaken for nonviable tissue and the presence of cellulitis. Clinicians must be aware of this normal appearance of the wound bed after construct application. However, in this typical case one can see areas of exuberant granulation tissue and evidence of epidermal healing from the edges of the wound.



Figure 8.4c An excisional biopsy and secondary intention healing/biopsy site healing.

This photograph was taken a week after the biopsy. It should be noted that biopsies of venous ulcers generally heal up to the original edge. We have recently published a series of patients who underwent biopsies of the wound edge, which also healed up to the original wound edge. Moreover, in that study there was no evidence of deterioration in the overall ulcer and eventual ulcer healing. We should add that this patient gave her informed consent for participation in this approved research study.



Figure 8.5a Obtaining scales for fungal evaluation.

Here is an example of a simple test to check for a fungal infection in this woman with venous insufficiency. Although dermatophyte infections do not directly cause ulceration, they may provide a portal of entry that leads to cellulitis; this is even more common in diabetic patients. Here one must aggressively scrape the scales at the periphery of the ulcer and collect them on a glass slide. The scales will then be treated with 10% potassium hydroxide to detect the microscopic presence of organisms. Cultures for dermatophyte infection (from the scales) can also be obtained at the same time.

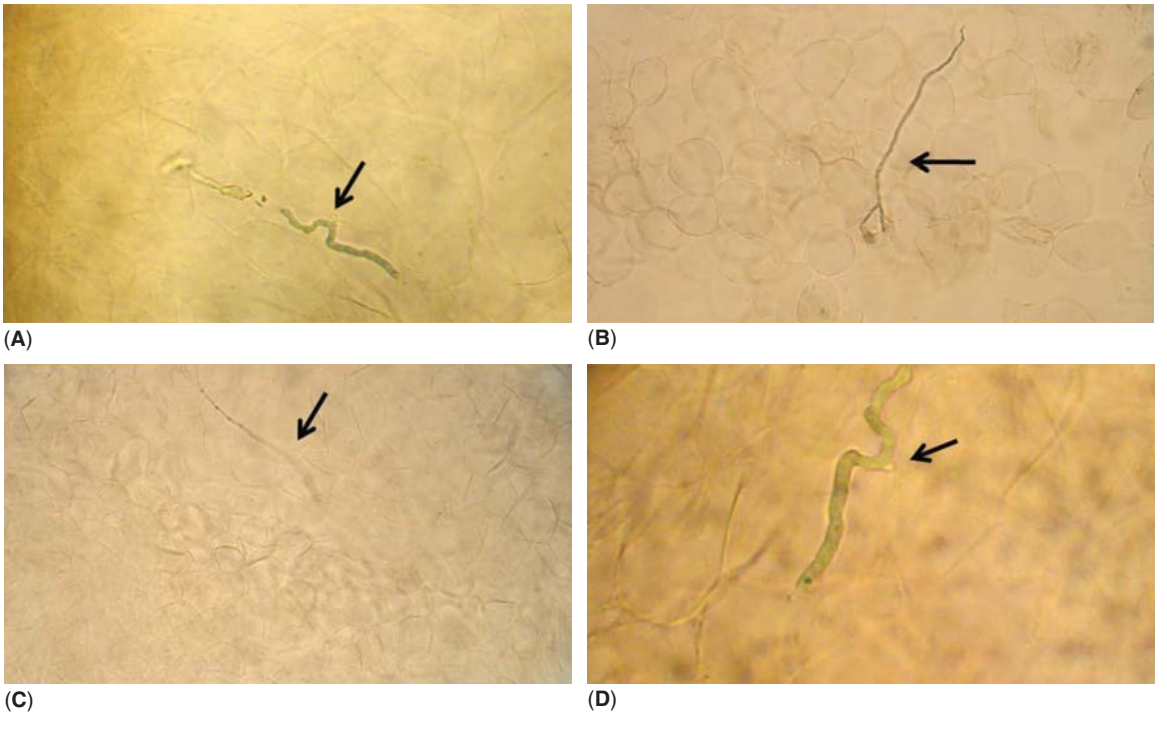


Figure 8.5b Obtaining scales for fungal evaluation/potassium hydroxide mount examination.

These four panels (**A**–**D**) show different microscopic magnifications and in different areas of the collected scrapings. The arrows point to the hyphae and one must note that many similar structures actually represent cell walls, which can be a major cause of confusion. Proper potassium hydroxide mount examination actually requires considerable experience. The hyphae in this case are septate and definitely more consistent with a dermatophyte infection, rather than yeast or other, more unusual fungal organisms.

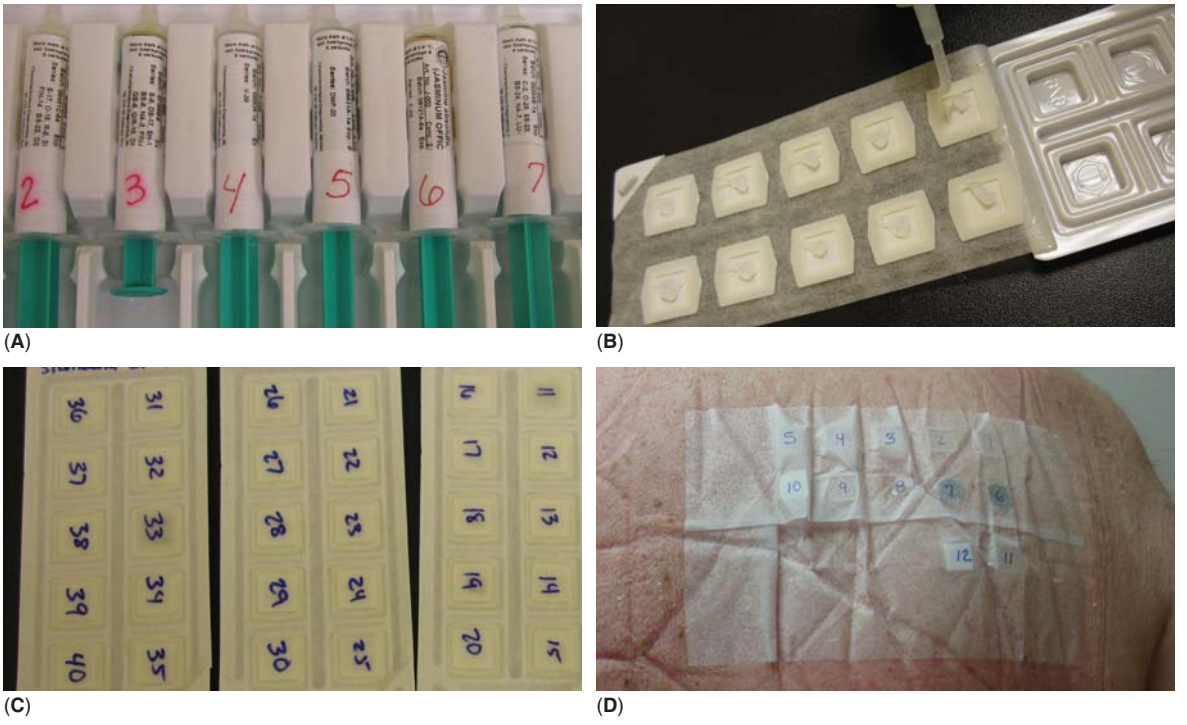


Figure 8.6 Patch testing.

In the management of leg ulcers, particularly those caused by venous insufficiency, the development of dermatitis and allergies to topical agents can be quite challenging. We actually prefer not to apply any topical agents to venous ulcer patients unless absolutely necessary, because these patients are more easily sensitized to topical ingredients and other allergens. Panel **A** shows a small representative sample of the many allergens we evaluate for (over 100) that are in syringes. Some of these allergens are commercially available, while others are prepared within our department. We also use a variety of wound dressings to test patients for allergies. Panel **B** shows the application of specific allergens from the respective syringe to small pads that come in stripes and which will be placed on the patient's skin; we generally perform patch testing on the patient's back (Panel **C**). Panel **C**, showing different strips of allergens, also illustrates how important it is to keep track of the number that identifies the specific allergens. Ultimately, numerous strips are applied in one setting to the patient's back and kept in place with additional tape (Panel **D**). A map of the allergens and their locations is kept as a record to identify subsequent areas of reaction to the allergens. The strips are removed at 48–72 hours, and the skin under each strip is scored for the presence of an inflammatory reaction. These tests tend to be invalid if the patient is on high doses of systemic immunosuppression or if multiple reactions are seen (the so-called "angry back syndrome"), which may represent nonspecific reactions. Hopefully, one or two reactions are identified that will help wound management by having the patient avoid medications containing those allergens. This is a very specialized procedure, and it requires a dedicated effort for assessing allergic contact dermatitis.

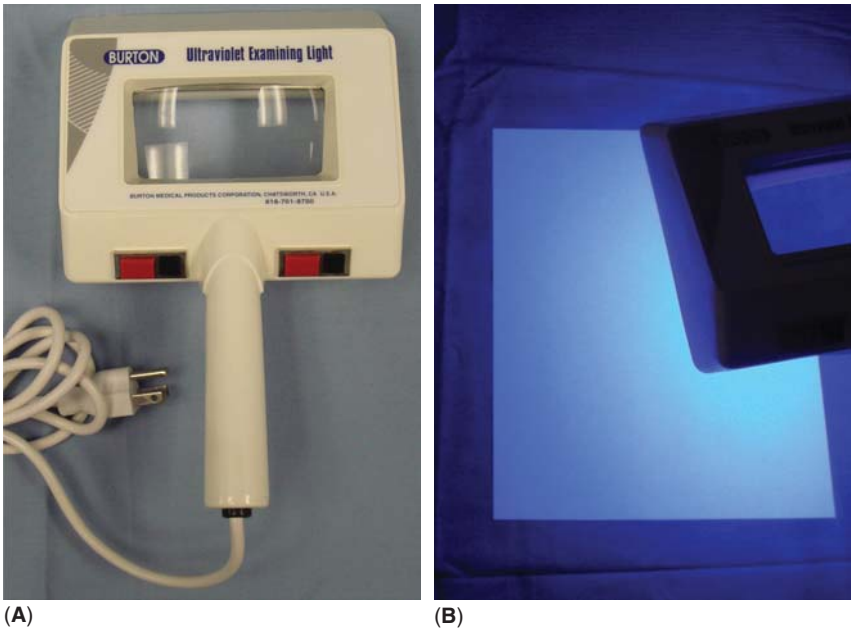
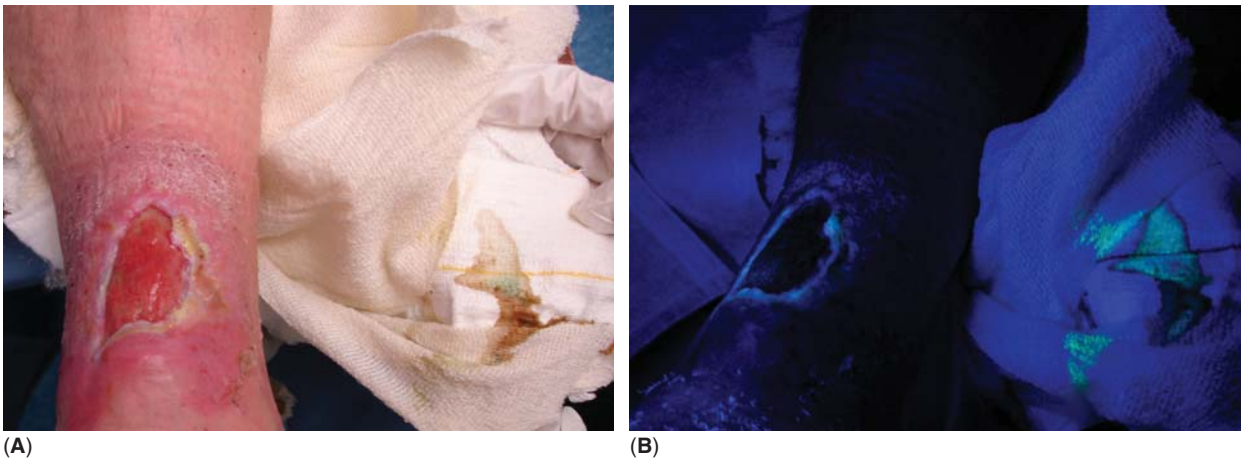


Figure 8.7a Wood's lamp examination.

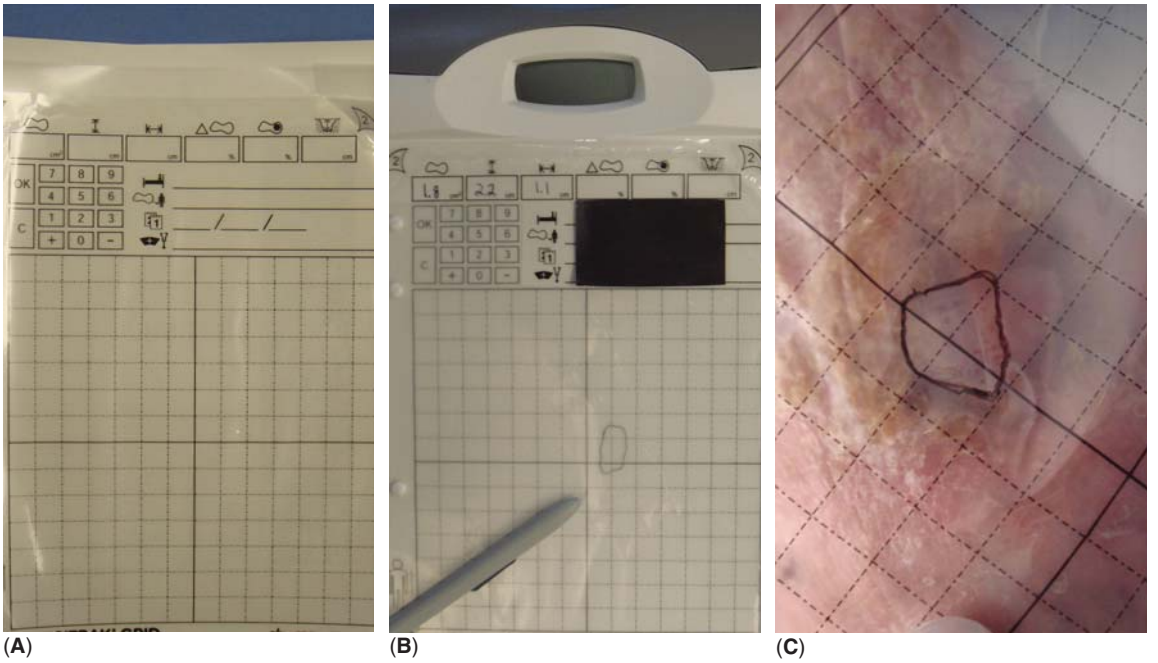
This relatively inexpensive and useful device (Panel **A**), known as a Wood's lamp (black light), transmits ultraviolet-A light and has been used as a diagnostic tool since the 1920s. Panel **B** illustrates the background light one normally sees. The lamp is helpful in determining hyper- or hypopigmentation. For example, accentuation of hyperpigmentation suggests that most of the pigment is in the epidermis. Certain types of bacteria and fungi can be detected by a green or red fluorescence.



(**A**) (**B**)

Figure 8.7b Wood's lamp examination/*Pseudomonas aeruginosa.*

Panel **A** represents a venous ulcer with seemingly good granulation tissue. However, there has been a strikethrough and the bandages show exudate that appears to be green in some areas. Wood's lamp examination indicates green fluorescence of the exudate on the dressings but not within the wound bed (Panel **B**). This is suggestive (not entirely specific) of the presence of *P. aeruginosa*. However, it may also indicate that the threshold level for the detection of the organism within the wound bed has not been reached, and the growth of *P. aeruginosa* has taken place within the dressing. Burn centers can make use of this lamp to identify excessive colonization with *P. aeruginosa*.



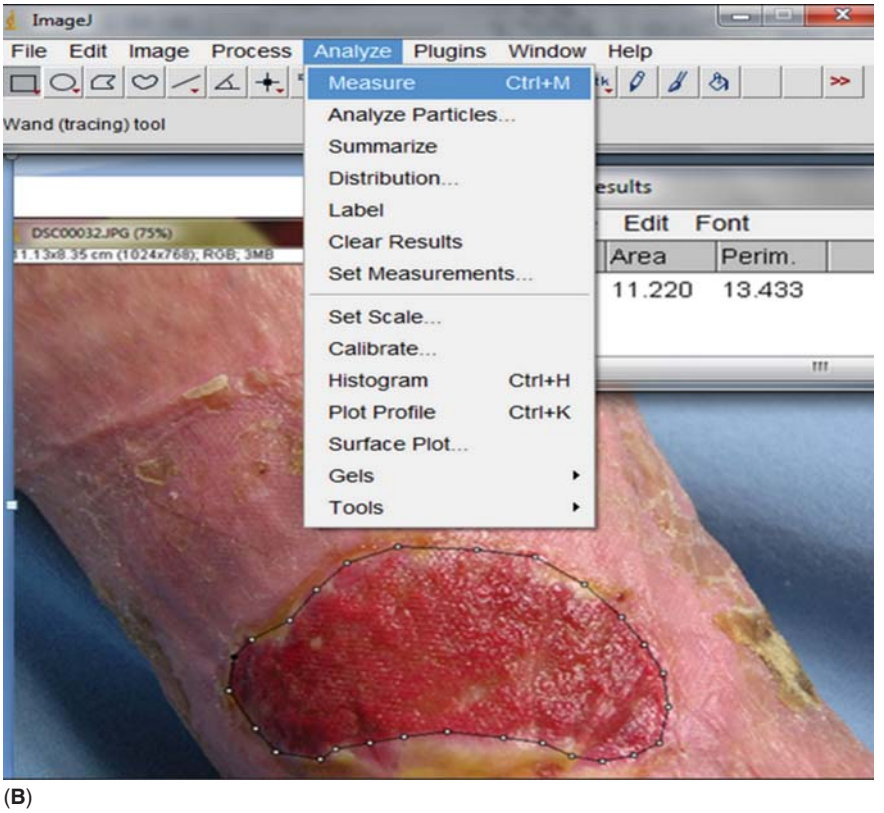
(**A**) (**B**) (**C**)

Figure 8.8 Wound measurement systems.

There are several ways and devices to measure the wound area and perimeter. Some of these methods use digital photography. Other methods, as in this case, rely on planimetry by tracing the wound and computing the tracing on a digital pad. Shown here (Panels **A**–**C**) is an example of a disposable tracing grid system that can be used to measure the wound area. As shown in Panel **A**, this particular product consists of 3 layers: the 2 superficial layers are translucent and the 3rd is a white backing layer. After this backing layer is removed, the 2nd (contact) layer is placed against the wound. Panel **B** shows the contact layer over the pad, ready for measurement by using a specialized retracing pen. The area of the ulcer can now be traced over the top layer, which is ultimately separated from the underlying second contact layer that will be discarded. Panel **C** shows an example of a tracing of a venous ulcer.



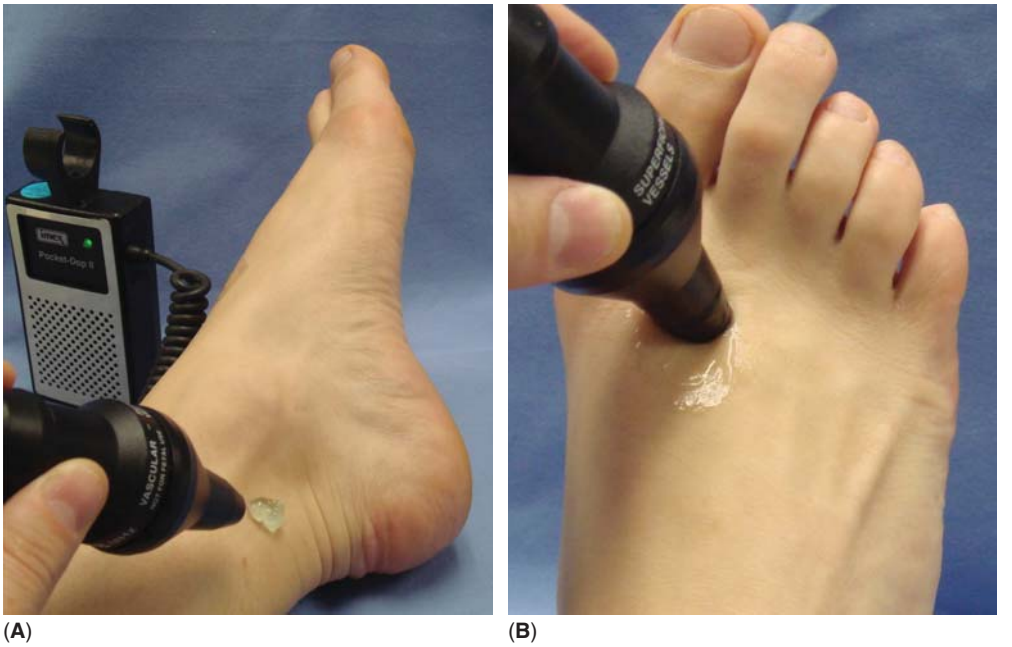
(**A**)



(**B**)

Figure 8.9 Analyzing the wound surface area with the Image J program.

This is a venous ulcer with good granulation tissue, flush with the surrounding skin, and shows early evidence of migrating epidermis from the edges (especially inferiorly.) Here is an example of the use of a computer program (photos show the computer screen) for digital planimetry. The program used here is the powerful Image J program which is available for free and can be downloaded from the National Institutes of Health (NIH) web site. Panel **A** shows the computer screen and the menu when the photograph is uploaded into the Image J program. One can set some parameters, including pixels and the pixel aspect ratio relative to a set scale (centimeters). Panel **B** shows the wound edges outlined and the results in area (11.220 cm^2) and perimeter (13.433 cm).



(**A**) (**B**)

Figure 8.10 A handheld Doppler device to assess vascular flow in the lower extremity.

It is not always possible to detect palpable pedal pulses, and patients are often referred to a specialized vascular laboratory. However, a preliminary assessment is often needed upon first seeing the patient. In that case, a handheld Doppler device may be used to locate and analyze the arterial pulses. A gel or lubricant is applied to the location over the expected pulse, and the handheld Doppler device can be used to magnify the signal and make it audible (Panel **A**). Both the posterior tibialis pulse (Panel **A**) and dorsalis pedis pulse (Panel **B**) need to be evaluated. In a normal situation, the audible signal should indicate a loud sound followed immediately by a lower amplitude sound that corresponds to the dichrotic notch; a dull sound (like hitting a column of blood) without the second sound component may indicate arterial disease. The handheld Doppler can also be used to analyze the venous flow.



Figure 8.11a Ankle–brachial index.

The photograph shows the basic supplies and devices needed to measure the ankle–brachial index. One must be careful in using appropriate sizes for the calf and arm blood pressure cuffs. The stethoscope is not normally needed, because the systolic pressure is detected using the handheld Doppler device. Most lubricants are adequate to make proper contact between the skin the the Doppler sensor.

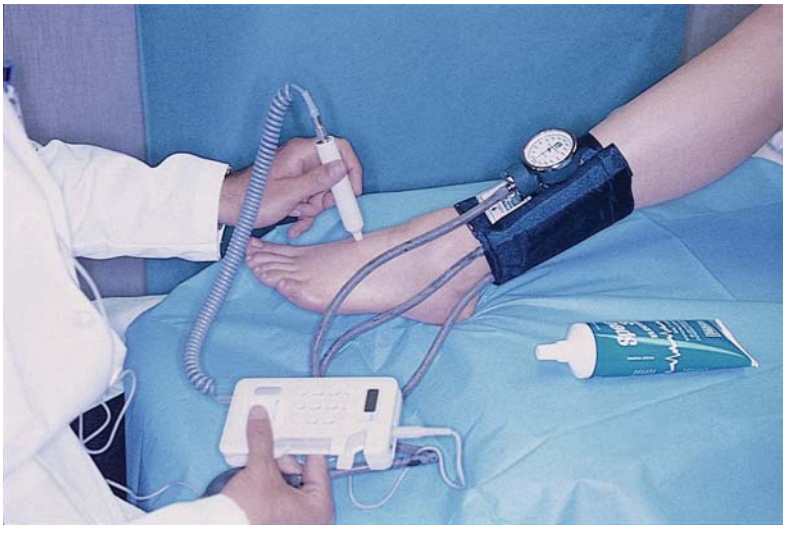


Figure 8.11b Ankle–brachial index.

The vascular laboratory is better equipped to test for arterial insufficiency, venous thrombosis, and venous insufficiency. However, essential components to exclude obvious arterial insufficiency are relatively inexpensive. The basic principle of the ankle–brachial index (ABI) is that the maximal systolic pressure in the foot should be slightly higher than the one measured at the brachial artery, with an ideal ratio of 1.1. An ABI ratio of less than 0.7–0.8 should indicate the need for further investigation. The testing is done with the patient supine, and the handheld Doppler device is used to detect the first systolic signal both at the ankle and the arm. The ABI is not a valid test in patients with diabetes and in other patients with noncompressible arteries. In fact, a high ratio may indicate noncompressible arteries. We rely on the vascular laboratory to measure pulse volume recordings and toe pressures when evaluating patients with diabetes.



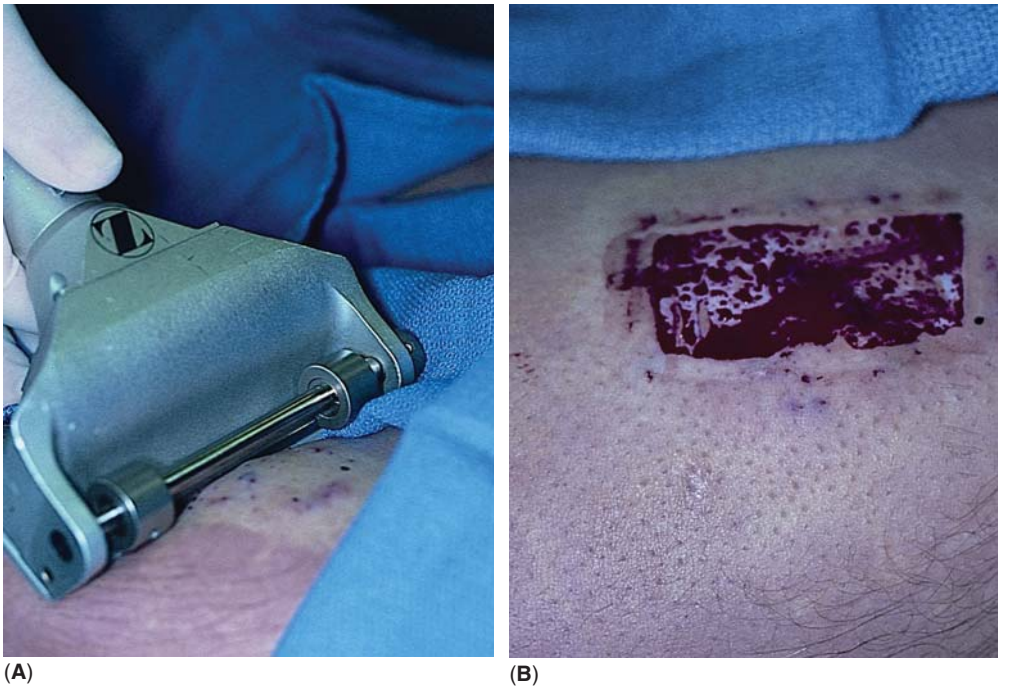
Figure 8.12 Use of a durometer for testing skin hardness.

This device has traditionally been used by engineers to measure the hardness of metals and plastics. We were the first to use it and adapt it for measuring skin hardness in various situations, including lipodermatosclerosis (as in this photograph) and scleroderma. The test is easy and reproducible, but will give falsely elevated readings when the probe is applied directly over bone. It is important to apply the device directly perpendicular to the skin and use gravity to hold it in place. Digital durometers are also readily available now.



Figure 8.13 Transcutaneous oxygen ($TcPO_2$) measurements.

The measurements are made with sensors attached to electrodes, which connect with a central unit. The sensor temperature is usually 42°C, but there has been some controversy as to whether 37°C should be used. At the higher temperature, the dermal vessels are maximally dilated. Multiple measurements can be made at one time. Usually, a control site, such as the infraclavicular area, is chosen to compare readings. In venous disease, the levels of oxygen next to the ulcers can be close to zero, and therefore do not reflect subcutaneous oxygen lavels. However, $TcPO_2$ appears to be much more reliable in arterial disease and in diabetes, where the test actually determines the need for hyperbaric oxygen treatment. $TcPO_2$ levels have also been used to determine the level of amputation.



(**A**) (**B**)

Figure 8.14 Harvesting of split-thickness graft using local anesthesia.

The photograph shows the use of a dermatome to harvest a split-thickness graft from the anterior thigh after local anesthesia (Panel **A**). The healing of the wound created by harvesting a graft (Panel **B**) is accelerated if one uses an occlusive film. The donor site has generally been thought to heal within 8–10 days, but some studies have shown that complete closure takes longer, up to 20 days or so. The healing of the donor site can also be accelerated by the application of bioengineered skin. Acceleration of healing of donor sites is important in many circumstances, for example in burn victims where reharvesting may be necessary.

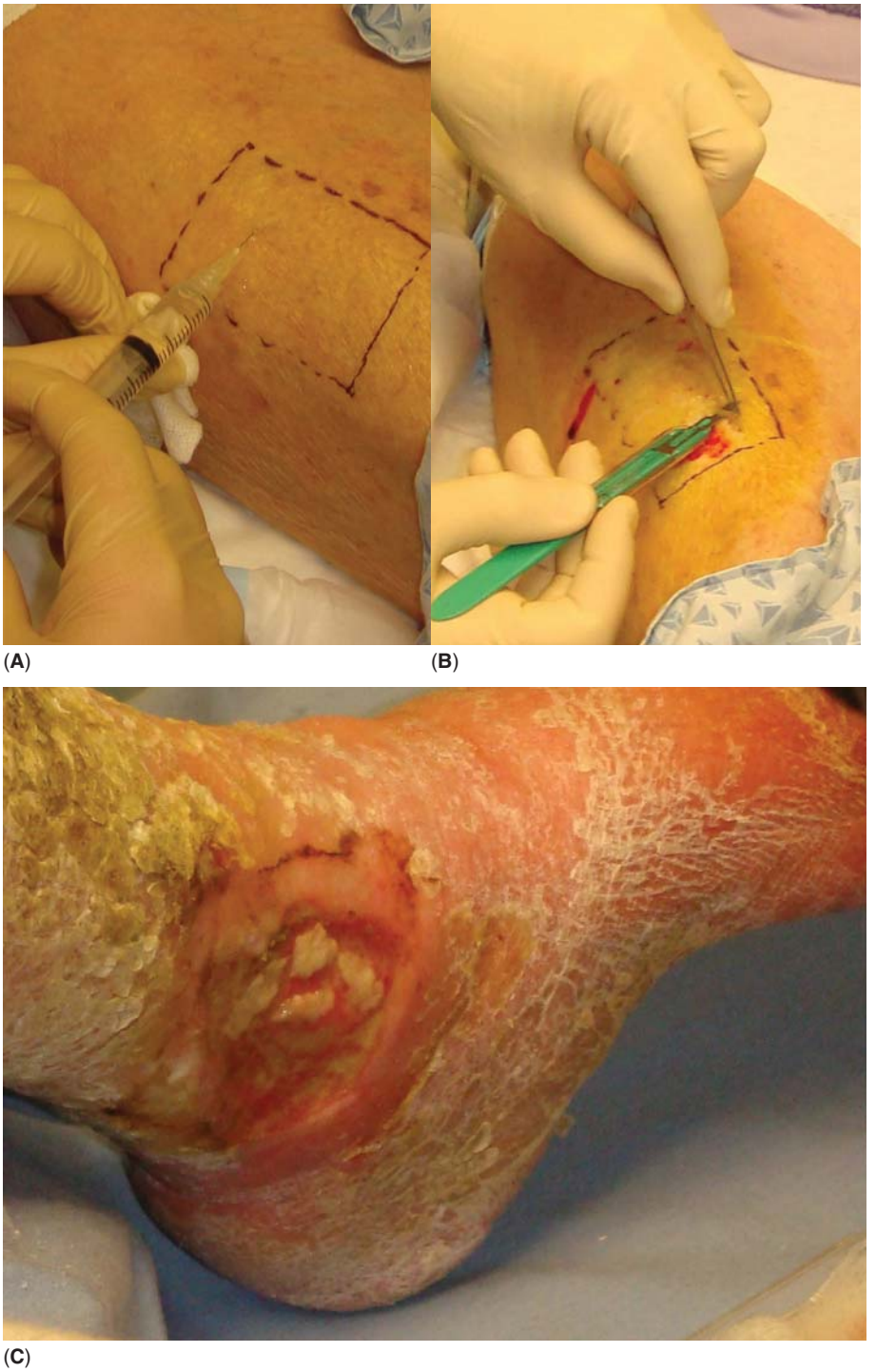


Figure 8.15 Pinch grafting in a patient with multiple wound complications.

The advantage of pinch grafting using local anesthesia is that it can be performed in the outpatient setting and with little morbidity. Panel **A** shows the anterior thigh (donor site) being anesthetized with lidocaine without epinephrine. Panel **B** shows the process of lifting up anesthesized skin with forceps and slicing small strips of skin with a scalpel. Ideally, one would like to have very thin strips of skin without any adipose tissue. The small pinch grafts, whose shape and configuration vary considerably, are then placed on a gauze that has been saturated with normal saline and is in a sterile dish. When harvesting, the very superficial (split-thickness) strips tend to curl; one must be careful to place them immediately on the wet gauze and keep the proper orientation (Panel **C**). Panel **C** shows the skin strips being placed on the wound bed of a venous ulcer. This was a complicated venous ulcer and not ideal necessarily for the procedure. The patient was nonambulatory and had recurrent bouts of cellulitis. We were hoping that the procedure would improve the wound bed at the same time as we were treating the other components of edema and persistent cellulitis. She was also treated with hyperbaric oxygen. Admittedly, pinch grafting is not pretty and produces uneven small grafts that are not as good as dermatome-generated split-thickness grafts. However, the procedure is inexpensive, can be done at the bedside, and can be repeated with less objections from the patient.

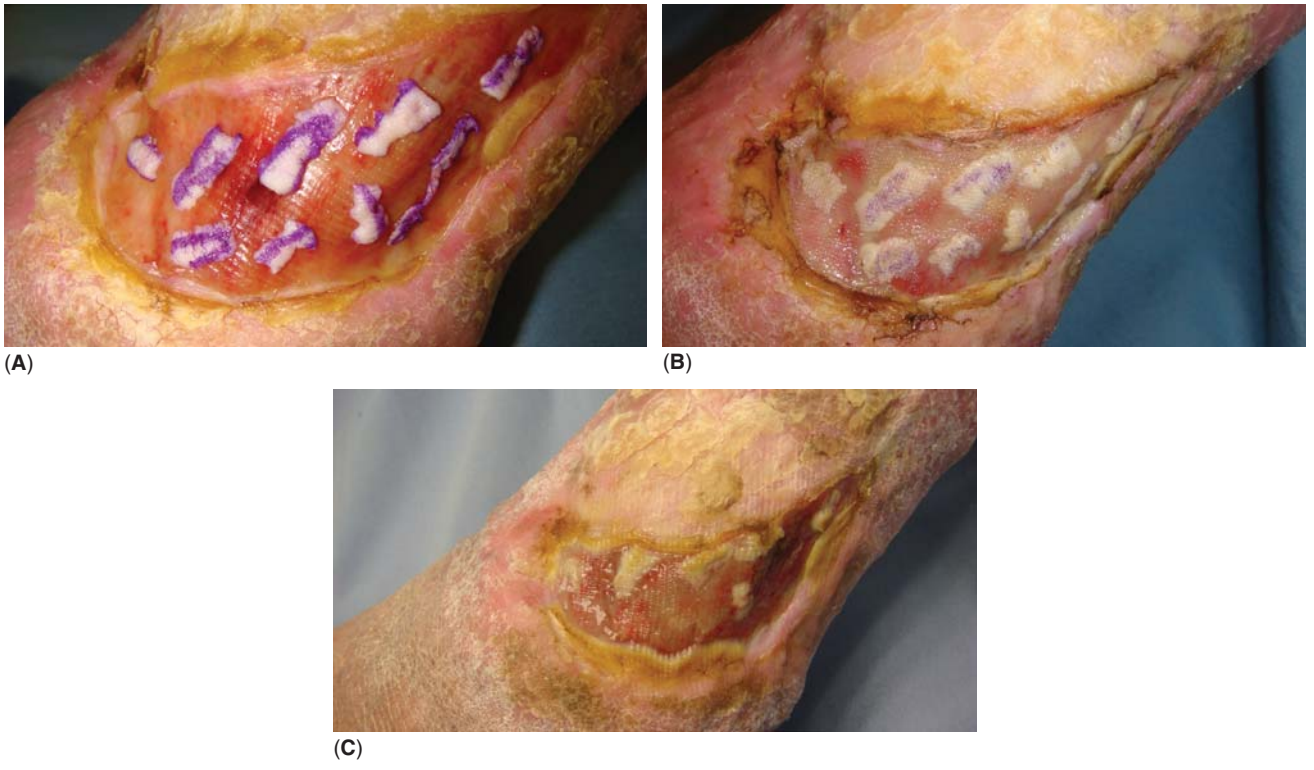


Figure 8.16 Stimulation of the wound edge by pinch grafting.

The general notion is that autologous skin, however it is harvested, acts as a tissue replacement in chronic wounds. This is true in many cases, but in our experience an important value of autologous skin in chronic wounds is its positive pharmacological effect in wound bed preparation and for stimulating granulation tissue and epidermal migration. Therefore, the grafts can take and not persist, but they may still provide a beneficial effect. Panel **A** illustrates a venous ulcer with a reasonable wound bed that already shows some epidermal migration, mainly superiorly. The patient's pinch grafts (taken from her abdominal skin) were applied away from the wound margins. These mini grafts were labeled with ink to determine whether, during follow-up, they would spread and mature as the epidermis underwent differentation and stratum corneum formation (disappearance of the ink). Indeed, in Panel **B** one can now see that a week later the mini grafts have spread beyond the original inked area, with the ink now fading because of differentiation of the grafts. Panel **C**, showing the wound a month later, indicates how most of the grafts are no longer within the wound. However, there has been continued stimulation of the wound edge. Indeed, the edge has not only migrated to make the wound smaller, but is also showing signs of maturation because of its thickness and probable formation of stratum corneum.



Figure 8.17 Harvesting of split-thickness graft using general anesthesia.

Often, pinch grafting is just not adequate, both in terms of inadequate coverage of the wound area and because of considerations of appearance and scarring. In those situations, a dermatome is used to harvest autologous skin from the thigh. Obviously, that approach is more involved, takes longer, and is more expensive. Here we see a dermatome being used on the thigh of a patient under general anesthesia in the operating room. The advantage of the resulting autologous graft is that, when meshed, it is expanded and can cover a larger wound area.

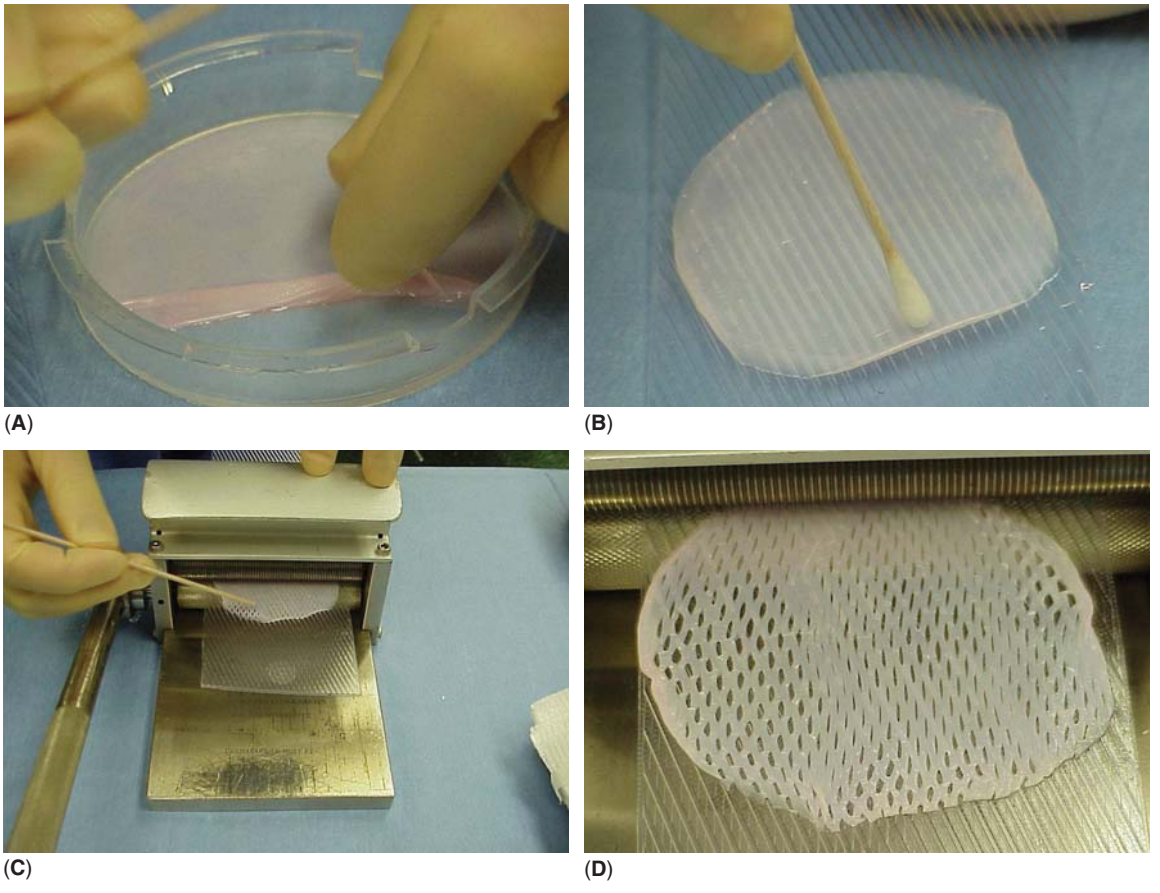


Figure 8.18 Use of a bi-layered bioengineered skin construct.

Although this procedure has been shown in other sections as well, we feel it is important to emphasize its importance and sequence. This type of bi-layered skin construct has been available for the treatment of venous ulcers for several years. In fact, it is approved by the FDA for both venous and diabetic ulcers. It is composed of living keratinocytes and fibroblasts derived from human neonatal foreskin. The keratinocyte sheet is grown over a type I bovine collagen gel that contains the fibroblasts. This product is delivered fresh and living in a transwell that contains special nutrients to keep the cells viable. Here, one sees the removal of the construct from the insert using a cotton-tipped applicator (Panel **A**). The construct is about to be passed through a skin graft mesher before being applied to a venous ulcer (Panels **A** and **B**). Skin graft meshers (Panel **C**) have corresponding carriers that provide varied ratios of meshing. Panel **D** shows the construct meshed at a ratio of 1.5 to 1. Here it is still on the carrier used to pass it through the mesher. Alternatively, instead of meshing, slits or fenestrations can be made in the construct by using a scalpel, which will still allow the wound exudate to escape and not interfere with the adherence of the construct to the wound bed. The clear advantage of meshing is that the construct (7.5 cm in diameter) will expand and be able to cover a larger wound.



Figure 8.19 Bioengineered skin applied to leg ulcers.

This patient was referred to us with a presumptive diagnosis of both venous ulcers and pyoderma gangrenosum. We were somewhat perplexed by the clinical presentation. For example, the inferiorly located ulcer looks traumatic and made us think of a factitial component. Other ulcers were clearly affected by venous insufficiency. Biopsies of several ulcers were nonspecific and did not show a vasculitis. In the end, we used bioengineered skin to try and heal these difficult wounds. Here, one sees the bioengineered skin, meshed at a ratio of 1.5:1, being applied to the superior and larger ulcer. In the original publications, clinicians cut the bioengineered skin to fit within the wound. However, in practical terms, we generally allow the bioengineered skin to extend beyond the wound's margin. The construct may be trimmed down to the preferred size by the clinician.

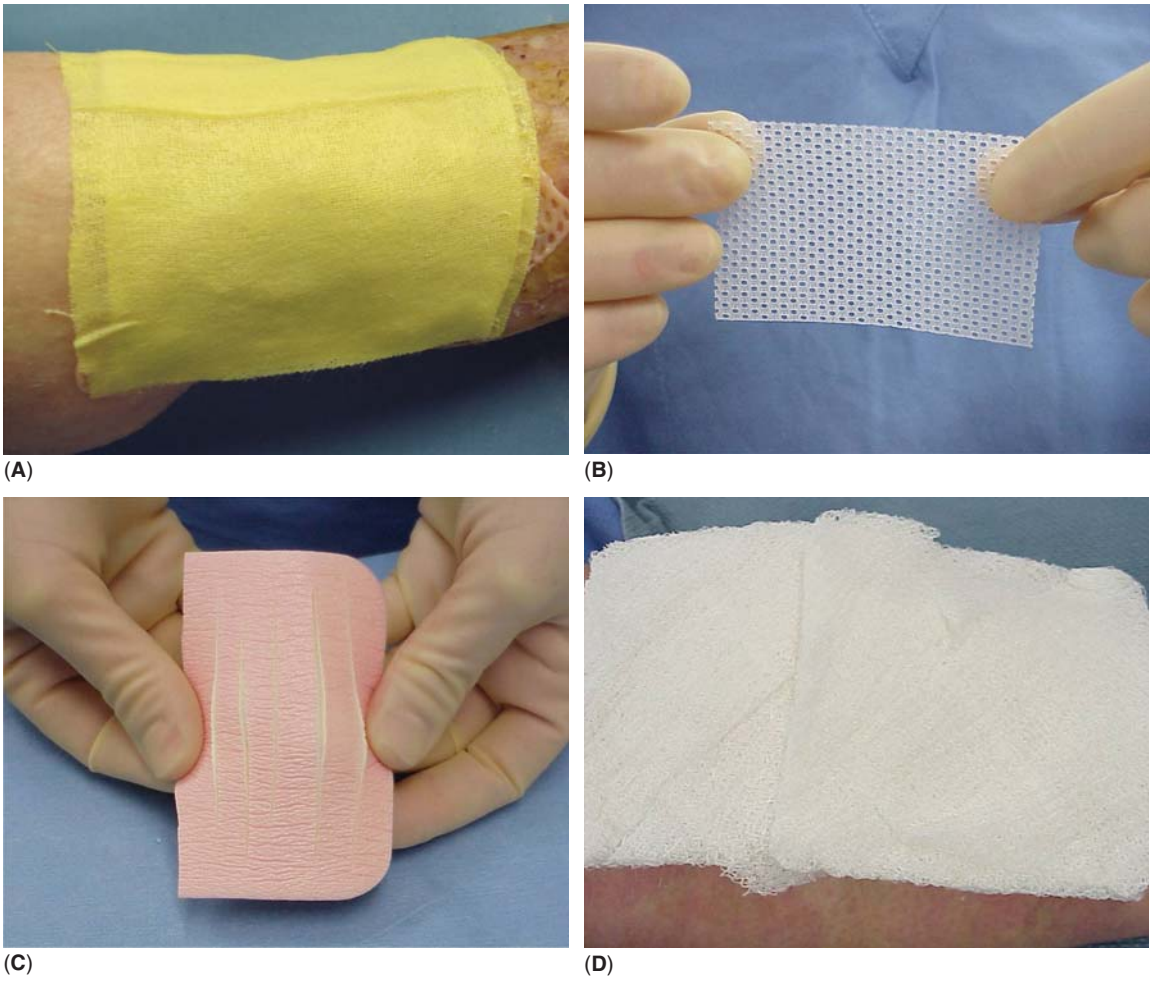


Figure 8.20 Dressings after application of bioengineered skin to a venous ulcer.

Identifying the ideal dressing to be used in wounds treated with bioengineered skin (in this case a bi-layered living construct) has been challenging. Panel **A** shows a primary dressing consisting of a bismuth–petrolatum impregnated gauze, which has the advantage of providing moisture and keeping the construct in place. However, we have used alternatives for both the primary and secondary dressings. Panel **B** shows a silicone-based perforated sheet that can be used as a primary dressing. It tends to adhere to the construct very quickly, and therefore one has to be absolutely certain that it is applied in the proper and desired way; removal and adjustments of the dressing will disrupt the underlying construct. Secondary dressings are meant to collect the exudate so as to minimize bacterial colonization of the construct. Panel **C** shows a foam dressing that is commonly used to treat wounds, and which we frequently use as a primary dressing in chronic wounds. The external (pink) layer is made of polyurethane and is impermeable; it would not allow the escape of wound fluid once this foam becomes saturated. Hence, slits are made into the foam so that fluid can escape in the outer dressings. The outer dressings can be as simple as gauze or other absorbent material (Panel **D**).



(**A**) (**B**)

Figure 8.21 "Psudoinfection" with a bioengineered skin.

Panel **A** shows a venous ulcer that is going to be treated with bioengineered skin. Unlike what is mentioned in the literature, we believe the wound bed need not be red, which actually could signify a substantial bacterial colonization. In fact, we are generally look for a pale to pink wound bed before the application of conventional autografts or bioengineered skin. A living bi-layered bioengineered skin construct was applied to this wound. However, 1 week later, this yellow gel-like material was now evident within the wound bed (Panel **B**). This did not cause concern to us, because we know from our clinical experience and clinical trials that this appearance is not uncommon. In the original clinical trials and prior to FDA approval, clinicians unfamiliar with bioengineered skin often labeled the patient as having an "infection." However, as also indicated by the proceedings at the FDA, such wounds commonly healed just as well or faster. Therefore, we tend to call this "pseudoinfection." We think the gel-like material represents a degenerated and swollen construct. It need not be removed but simply followed closely. Note the inferior erosion, which may have been due to dressing removal. We prefer to keep the construct in place for 2 weeks. Generally, a second application of the construct may be required when, that is after 4–6 weeks, there is a plateau in the initial beneficial effect on the wound bed and epidermal migration.

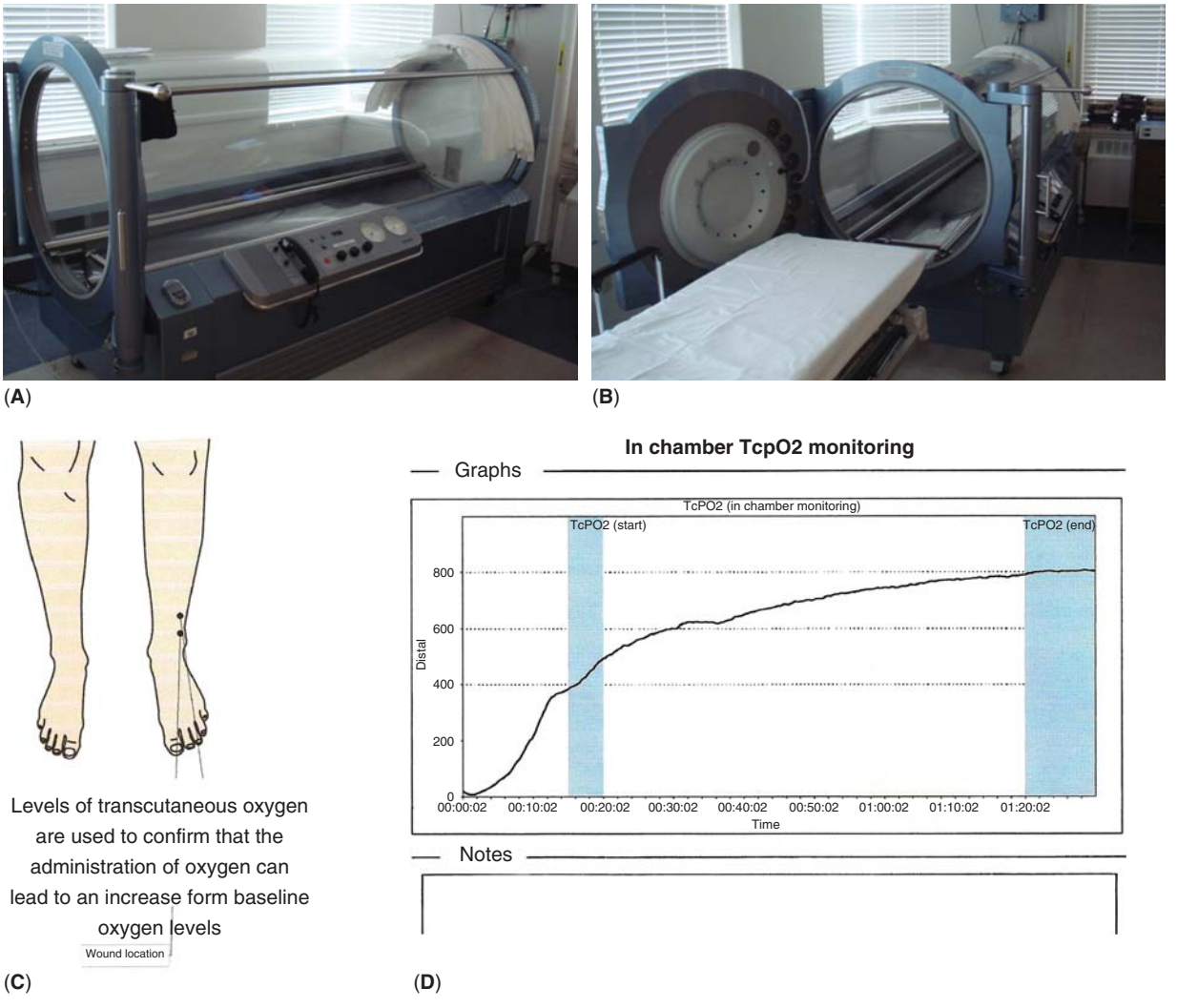


Figure 8.22 Hyperbaric oxygen therapy.

Generally, hyperbaric oxygen therapy (HBOT) is used only after confirmation that the levels of transcutaneous oxygen at the wound site will increase with oxygen administration. HBOT plays a definite role in the treatment of difficult-to-heal wounds. Recently, a number of well-performed clinical trials have shown the effectiveness of this treatment modality. Panels **A** and **B** show a typical mono chamber where the patient is wheeled-in in a supine position. It is wise to have at least 2 chambers in case one is malfunctioning. Panel **C** indicates that proper selection of patients for HBOT is dictated by careful measurements of transcutaneous oxygen pressure ($TcPO_2$) prior to and after the administration of oxygen; patients who are unable to show an increase of oxygen level next to the wound site are generally excluded. Panel **D** shows how, over a period of almost 2 hours, the levels of oxygen at the wound site is increased by HBOT. There are probably multiple mechanisms of action for HBOT, including antimicrobial properties. Vascularization appears to be enhanced by HBOT. One hypothesis we have formulated is that the sudden decrease in oxygen levels after the patient leaves the chamber could be stimulatory to wound cells (including fibroblasts and endothelial cells) and increase the localized production of growth factors or the recruitment of stem cells.

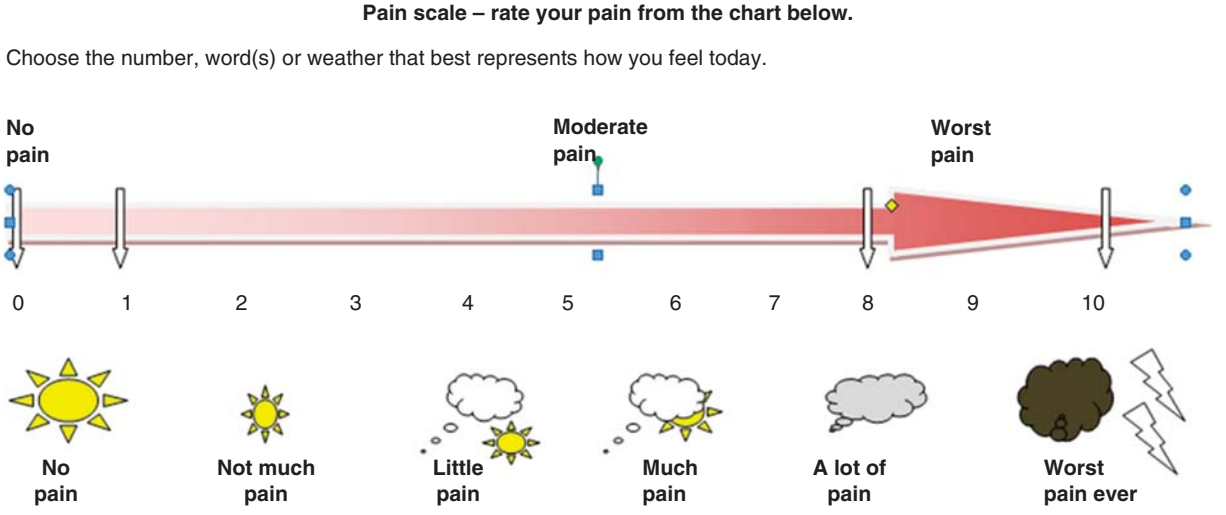


Figure 8.23 Pain scale: documenting pain for both investigational and noninvestigational patients.

This visual scale may be used to document and semiquantitavily assess pain in patients with chronic wounds. It is surprising how reproducible these visual scales are, but investigators often rely on more than one instrument to ask patients about pain or other symptoms. (Copyrighted, P. Carson, 2011)

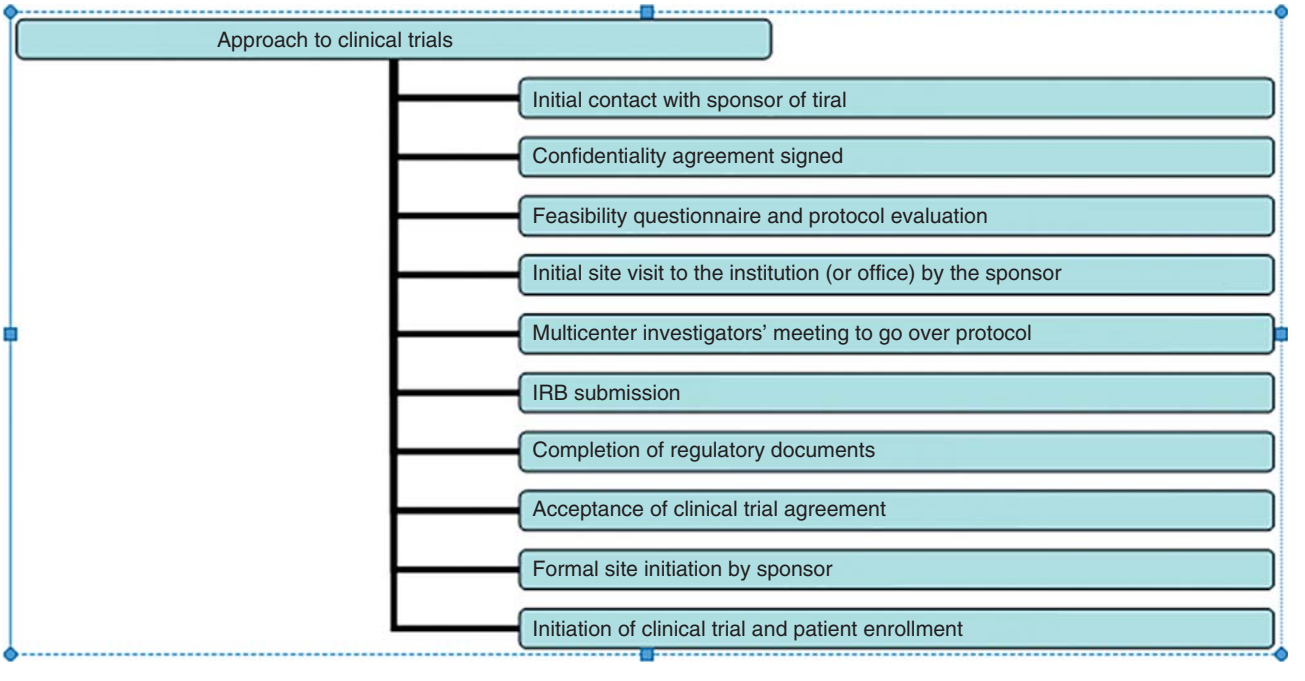


Figure 8.24 A diagram showing the steps required in clinical trials.

Successful healing of difficult wounds does not always take place, or there is recurrence of the ulceration. New therapeutic approaches are always required and desirable. This diagram points to the essential steps that are involved in initiating a clinical trial that is sponsored by a pharmaceutical or device company. The diagram makes the assumption that the drug or device being tested has already gone through the regulatory steps and has been approved for testing by the FDA or other regulatory bodies in other countries. Clinical trials require a team comprising the principal investigator, a clinical coordinator, ancillary personnel, an institutional review board, and proper clinical facilities that make it possible to test the product safely.

1572 Form – Statement of investigator. This is a legal document binding the PI of the study as to the responsibility for the conduct and supervision of the trial at his or her clinical center. This document requires the name and address of the investigator, location of the where the study will be conducted, name and address of any clinical laboratory facilities to be used in the study, name and address of the Institutional Review Board, names of any subinvestigator's and name and code number for the study. The PI is required to sign and date this form.

1571 Form – Investigational New drug Application (IND). This important document must be completed and submitted along with the 1572 form when applying for an IND. It requires the name, address and telephone number of the sponsor, drug name, indication, phase of clinical investigation, study protocol, investigator's brochure, pharmocology and toxicology data, and previous human experience. The sponsor (person who takers responsibility for and initiates the clinical investigation) is required to sign and date this form.

Once all documents are sent, the FDA will have thirty days to respond to the request. No clinical investigations for new indications can be conducted without the approval of the FDA.

Figure 8.25 Initiating a clinical trial at one institution.

Types of investigational new drugs (INDs):

1. **Investigator IND**: This IND is a physician-initiated request to perform an investigation.
2. **Emergency Use IND**: This IND is for the FDA to allow the use of an experimental drug in an emergency circumstance when there is not enough time for submission of an IND. It can also be used for patients who do not meet the criteria of an existing study protocol or if a study protocol does not exist.
3. **Treatment IND**: This IND is submitted for experimental drugs showing promise in clinical testing for serious or immediate life-threatening conditions while the final clinical work is being conducted and the FDA review takes place.

IND Categories:

1. Commercial
2. Research (non-commercial)
3. In case a device is being tested, the process involves a new investigational device exemption (IDE).



Figure 8.26 Good manufacturing practice.

When manipulating cells or other agents in the laboratory before their use on patients, one must adhere to guidelines that ensure the patient's safety (i.e., avoiding contamination) and the validity of the product being tested. Increasingly, a good manufacturing practice (GMP) facility is required for this purpose and for receiving approval from regulatory agencies. Among other requirements, a GMP facility requires an elaborate set of regulations regarding dedicated equipment, protocols, gowning, and specialized laboratories where air intake is being filtered and access is restricted and controlled.

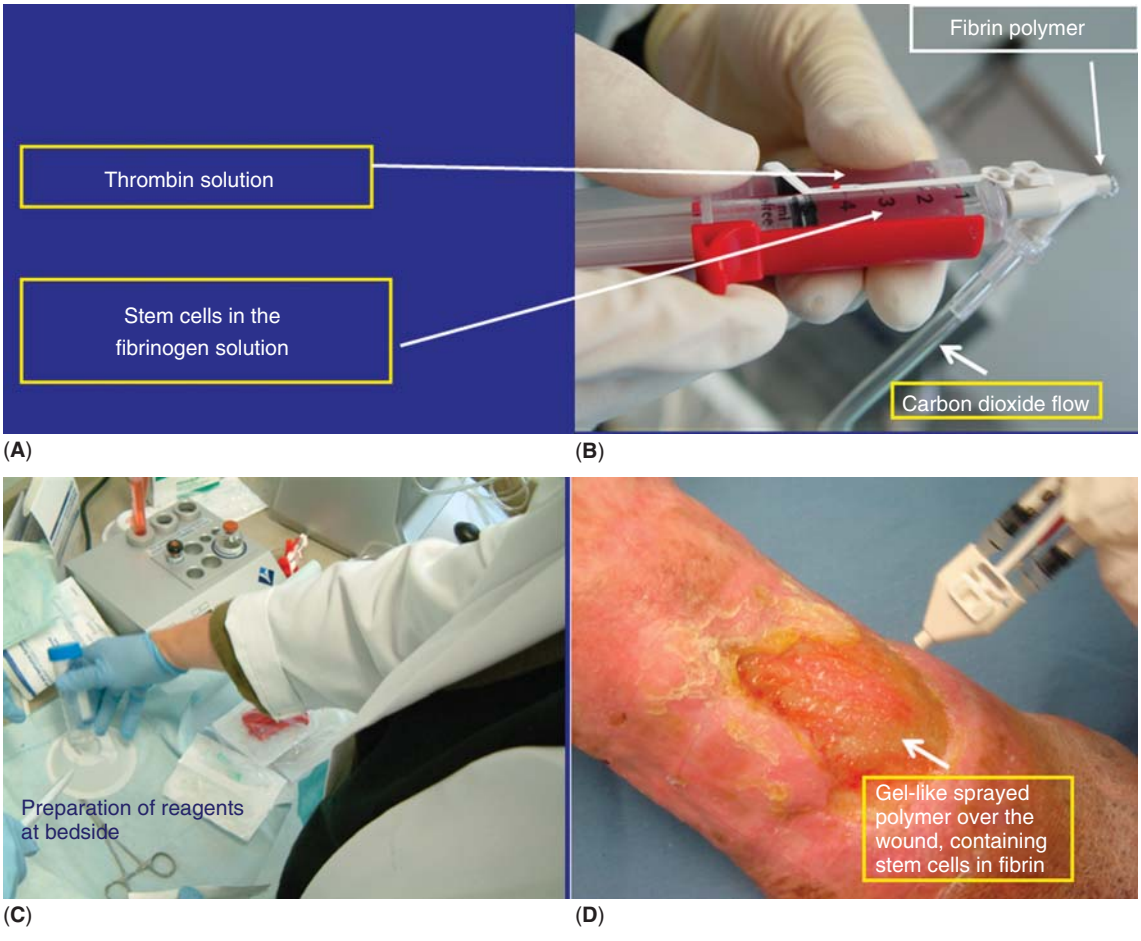


Figure 8.27 Spraying autologous bone marrow-derived cultured mesenchymal stem cells in a nonhealing wound.

The steps we have outlined, including the need for IRB approval, for obtaining and IND, and for constructing a GMP facility culminate in the experimental therapy shown in this photograph (Panels **A–D**). We used a modification of a fibrin preparation that has been used for many years to deliver fibrin and control bleeding. In our case, we wanted to deliver to a non-healing wound the mesenchymal stem cells isolated and cultured (in our GMP facility) from the patient's bone marrow. The fibrin was modified by decreasing the fibrinogen and thrombin concentrations and eliminating the protease inhibitor (Panel **C**). We placed the cells in the fibrinogen solution of the double-barreled syringe (Panel **B**), which has a common plunger. Upon pushing the plunger, and with the aid of the gas flow, fibrinogen mixes with thrombin and polymerizes to a stem-cell-containing fibrin polymer upon exit. Panel **D** shows the fine polymer, gel-like, over the wound.

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