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Invited Review

Models of wound healing: an emphasis on clinical studies

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Abstract: Background: The healing of wounds has always provided challenges for the medical community whether chronic or acute. Understanding the processes which enable wounds to heal is primarily carried out by the use of models, *in vitro*, animal and human. It is generally accepted that the use of human models offers the best opportunity to understand the factors that influence wound healing as well as to evaluate efficacy of treatments applied to wounds.
Objectives: The objective of this article is to provide an overview of the different methodologies that are currently used to experimentally induce wounds of various depths in human volunteers and examines the information that may be gained from them.
Methods: There is a number of human volunteer healing models available varying in their invasiveness to reflect the different possible depth levels of wounds.
Results: Currently available wound healing models include sequential tape stripping, suction blister, abrasion, laser, dermatome, and biopsy techniques. The various techniques can be utilized to induce wounds of variable depth, from removing solely the stratum corneum barrier, the epidermis to even split-thickness or full thickness wounds.
Conclusion: Depending on the study objective, a number of models exist to study wound healing in humans. These models provide efficient and reliable results to evaluate treatment modalities.

Key words: wound healing – review – *in vivo* – human volunteer – clinical study

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IN VITRO studies and animal models have provided useful information for many breakthroughs and medical advances. However, these are not always appropriate and in many cases are inadequate for discovering the actual pathology responsible. While animal models are suitable for many skin disorders and diseases, they do have their limitations when wound healing is being investigated. The complex biological pathway that occurs during wound healing is not always mirrored in animal models and human models need to be considered. In the case of chronic wound pathology, human models are not always good predictors but they do provide a good understanding of acute wound pathology. Because of the difficulty in obtaining suitable volunteers with chronic wounds and incorporating them into a study, human acute wound models provide the best opportunity to understand the wound healing process and the performance of different products that assist and promote wound healing.

This paper evaluates the different wound healing models and discusses the potential for these models to be suitable predictors of wound healing.

Background

Wound healing is a complex and dynamic process consisting of four overlapping phases that happen in a precise and regulated manner, consisting of hemostasis, inflammation, proliferation, and maturation (1, 2). However in contrast, some wounds fail to follow this process resulting in chronic, non-healing wounds such as venous leg ulcers and diabetic foot ulcers. The global impact of either acute (traumatic or surgical) or chronic wounds is huge in terms of the economic costs which runs into millions of

Euros (3). It has been estimated that wounds account for almost 4% of total health system costs, and that this proportion is increasing (4).

Even minor wounds are costly to treat and time-consuming in terms of Accident and Emergency clinician time and resources. Interestingly, there is a significant increase in the so-called 'ambulatory surgery' defined as the diagnostic and surgical intervention in which overnight hospital stay is not required. Innovations in technologies (e.g. in wound care) that enable healthcare professionals to execute a large number of minimally invasive surgical procedures in a single day have propelled this market in Europe. As such research into the treatment of wounds that might be treated in this environment is a key focus. Research has for the most part relied upon the use of models to simulate the wound healing. This is because the complexity of healing of either acute or chronic wounds requires methods that can aid in dissection and identification of mechanisms within this process. Furthermore, if care is not taken and appropriate treatment undertaken and wound dressing used, then these wounds may develop infections which can have a significant impact upon the patient and cost of treatment.

The burden of wounds (both acute and chronic) has increased over the past decades in parallel with ever-increasing populations and the increased requirement for surgical procedures, so too has scientific and medical interest and research in this area. The primary focus of this research has been on areas that might alleviate the burden and aid in the healing process. The seminal work of Winter (5) is probably the single most important discovery that led to the hypothesis that a moist environment is beneficial to the healing process. It has since been recognized that this is one of the most important aspects in relation to treatment of either acute or chronic wounds. From that time, research into wound healing has grown exponentially and there has been significant progress into the development of what are now known as Advanced Wound care products.

Models of Wound Healing

In order that wound care research may be undertaken a variety of models have been developed. These include *in silico*, *in vitro*, *in vivo*, human volunteer, and pure clinical models, with advantages and disadvantages of all. These models have been important in that they have allowed many different aspects of the healing process to be dissected and defined. So that today knowledge of healing and non-healing is far advanced from that of Winter many decades ago. In the development process of wound care products, human testing is often preceded and/or complemented by *in vitro* or preclinical studies. The most frequently used models will be described below. These will be discussed briefly but with an emphasis on human models of wound healing.

In vitro models of wound healing

Laboratory-based tests (*in vitro* assays) are used regularly to provide evidence in support of wound care products such as wound dressings. These assays are also used as tools to help differentiate one product from another. A number of *in vitro* assays are commonly used:

- Cell proliferation assay: a test to determine if the number of cells in a test culture is growing when in the presence (or absence) of a test substance (e.g. chemical, material, etc.)
- Cell cytotoxicity assay: a test to determine if cells are killed by the presence of a test substance
- Cell viability assay: a test to determine if cells are able to maintain viability (i.e. remain alive) when exposed to a test substance

With these laboratory studies, scientists are potentially able to assess a large number of test substances quickly and under controlled conditions, with the assays providing data on how these test materials affect cells. However, with regard to wound dressings, there is little consideration of how relevant these laboratory results are when they are used in support of how these dressings will affect tissues in the clinical setting. When clinicians are presented with laboratory data in support of wound dressings and their clinical impact, questions such as

- How relevant are these *in vitro* assays to the clinical situation?
- Does the assay accurately represent a 'mode of action' that would be present in the patient?

- How useful are the results for decision-making?

It is generally accepted that results from *in vitro* studies are not good indicators of how the materials being tested will affect biological processes in the patient. That is, for wound dressings, *in vitro* test results on proliferation, cytotoxicity, and viability are unlikely to reflect the effect of these dressings on tissues of the wound healing process. This is because these laboratory tests are unable to recreate the interaction of the wound/peri-wound tissue and any wound dressing.

Animal models of wound healing

Various aspects of wound healing can be investigated in a reproducible, controlled environment by using animal models. Although animal wound repair can never be a direct and true reflection of human wound healing and its clinical challenges, these models are essential to basic research and development in this area.

Acute wound healing is the simplest to replicate in animal models, e.g. incisional, excisional, full thickness, and burn models have been developed in a variety of animals. However, the anatomy and physiology of the skin has a significant effect on the pathophysiology of healing. Rodents represent excellent preclinical models for the basis of wound healing studies because of their availability, low cost, and ease of handling. However, wound healing in rodent models is fundamentally different to that in humans. This is because the major mechanism of wound closure is contraction, whereas in humans re-epithelialization and granulation tissue formation are the main means of healing (6, 7). In addition, the porcine cutaneous wound healing model is frequently used as a model for human cutaneous wound healing (8). This is because anatomically and physiologically, pig skin is more similar to human skin (9).

Recently, the Wound Healing Society (WHS) has sponsored a half-day preconference symposium on preclinical models of wound healing at the 2012 annual meeting in Atlanta. They identified that pig models of wound healing provide major advantages over other animal models. But as the majority of wound healing research is done in rodents and *in vitro*, the low concordance rate is a significant impediment to research that will have any clinical impact. Furthermore, in order to generate clinically relevant experimental data, hypothesis generation should begin, or at least involve human wound tissue samples. And that once a hypothesis has been formulated and confirmed using human samples, identification of these same mechanisms in animals represents a valid approach that could be used for more in-depth investigations and experimental manipulations not feasible with humans. In conclusion, it was strongly encouraged that all wound researchers involve human wound tissue validation studies to make their animal and cell biology studies more translationally and clinically significant.

This piece of work has highlighted the importance of using humans as the preliminary basis of research rather than *in vitro* or *in vivo*.

Human models of wound healing: Using humans as the basis of a wound healing model makes good sense in that the pathology and physiology of healing (in acute wounds) is identical to that found in the patient. There are a number of wound models that can be inflicted upon a human volunteer to provide accurate and representative research tools. A review of such models is presented here.

Partial thickness: A partial thickness injury is limited to the epidermis and superficial dermis, with no damage to the dermal blood vessels. Healing occurs by regeneration of other tissues. There are a number of methods.

Tape stripping. The simplest partial thickness injury of the skin involves removal of stratum corneum with adhesive tape. In this model of wounding, the epidermal compartment is generally left intact. However, due to removal of stratum corneum layers, the permeability of the skin is temporarily compromised that can be measured using transepidermal water loss (10). Although this is a minor injury and very superficial, it is sufficiently damaging to activate the processes of epidermal repair inducing increased epidermal proliferations and hyperplasia. It is important to note that this type of wound is variable and depends on various methodological factors, i.e. adhesiveness of the tape, pressure exerted when applying the tape onto the skin, velocity and direction of tape removal, and most importantly number of tape strips. Whenever employing this model, all of these factors have to be standardized (11).

Although the tape stripping model has been used to mainly investigate skin barrier function, it has also been used successfully in a number of studies investigating the beneficial effects of treatment on a wound. For example in an early study in human volunteers, it was investigated whether occlusion modulated epidermal proliferation following removal of the stratum corneum by tape stripping. Epidermal proliferation was assessed, using a multiparameter approach, by measuring ornithine decarboxylase activity, keratin 16 expression, and DNA synthesis (12). More recently this model has been used to evaluate the beneficial effects of aloe vera and vitamin E on experimental wounds. The results obtained show that bioadhesive films containing vitamin E acetate and aloe vera could be an innovative therapeutic system for the treatment of burns (13). Additionally, the model has been used to investigate more academic research objectives such as whether acute pain can speed skin barrier recovery in healthy men and women. The results of this study showed that acute pain can affect immune-related processes and may speed recovery from dermal abrasions, although pain is likely to impair recovery from more severe wounds (14).

This model has been developed further to evaluate the effect of wound dressing adhesive on the skin barrier, whereby the wound dressings actually cause disruption to the skin that can be measured in a number of different ways (e.g. TEWL). This was first done by Dykes et al. (15), who used a human volunteer model to quantify the stratum corneum removal and peel force of dressing removal by different adhesive dressings. This model in relation to evaluation of wound dressing causing disruption to the skin barrier was further developed (in terms of more accurate and quantitative methodology for skin damage evaluation) by Waring et al. (16), and has proved extremely useful in differentiating wound dressings in terms of the damage that they cause.

The benefits of this model are that it is quick and simple to use, relatively painless, and allows evaluation of a component (re-epithelialization) of acute wound healing. The disadvantages are that only a limited component of wound healing is evaluated and that this model bears no relevance to deeper wound pathology.

Blister model. This method was originally developed to measure drug concentrations in various parts of the skin (17) but has soon been employed to study wound healing as well. A blister is formed as a result of the separation of the epidermis and dermis, at the basal membrane between the lamina lucida and the lamina densa. The blister cavity is filled with tissue fluid or interstitial fluid (18). As early as the 1960s, it was identified that for research purposes, there was need for a technique by which epidermis could be separated from the dermis by purely mechanical forces avoiding chemical or thermal damage. 'The suction blister' model was developed that involved application of a constant negative pressure of 300 mm Hg for a period of 3–4 h. This resulted in a split in the basal membrane and hence a neat separation between epidermis and dermis. After excision of the blister roof, clean wounds are obtained that heal without scarring (Fig. 1).

Various forms of mechanical suction devices can be used to cause blisters in human volunteers (19–21). Blisters can also be induced with a variety of chemical or biological vesicants (22) or with heat (23). The blister model has been used for some time to look at various components of wound healing in clinical studies. Parameters for healing include measurement of transepidermal water loss and determination of wound area by quantitative image analysis (Fig. 2).

Krawczyk and Wilgram (24) employed this model to evaluate the synthesis of keratinosomes during epidermal wound healing. Experimental suction blister wounds offer advantages over uncontrolled patient conditions in that they are well-standardized and controlled for a wide range of clinical acute wound healing studies (19). The blister model has been used as a research tool to investigate the kinetics of healing, particularly in relation to keratinocyte migration, proliferation, and differentiation in acute wound healing (19, 25) and the long-term course of epidermal regeneration (19, 26). More importantly this model has been identified as a useful research tool to help elucidate the mechanisms for potential development of treatments for human skin disorders and impaired healing, including chronic ulcers (27). In addition, a suction blister model on healthy volunteers has been used to evaluate the kinetics of physiological skin flora after treatment with water-filtered infrared-A radiation (wIRA) and to show the beneficial effects

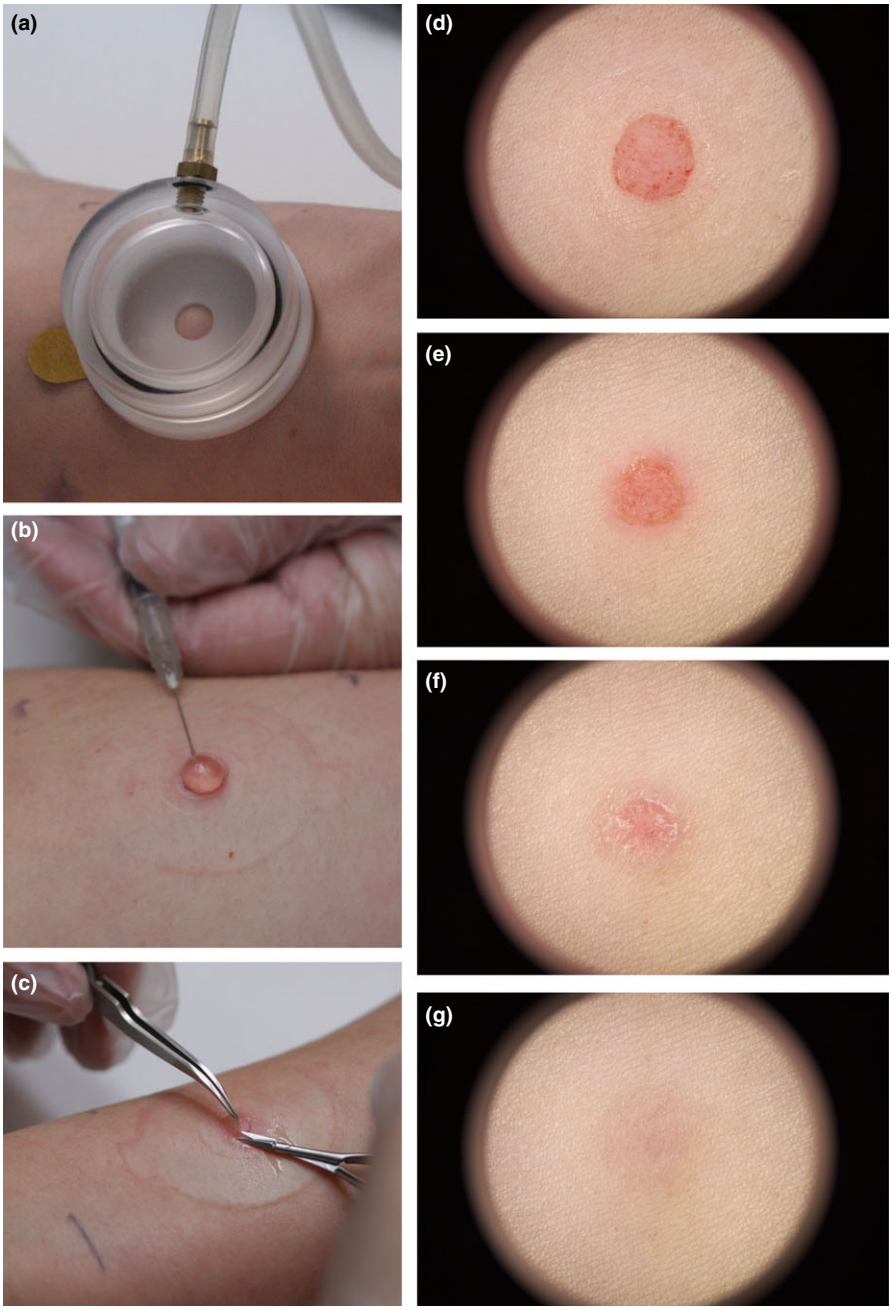

Fig. 1. Suction blister model. (a) Induction of suction blister by applying a vacuum of 300 mm HG for 3–4 h by suction cups with an opening diameter of 4–8 mm. (b) Puncture of a freshly formed blister filled with clear interstitial fluid. (c) Removal of blister roof. (d) Open wound directly after complete removal of blister roof. (e) Partial closure of suction blister wound on day 4. (f) Almost complete healing on day 10. (g) Complete healing on day 26.

of wIRA in the promotion of wound healing (28).

Abrasive wound model: A slightly more invasive wound model was established by our group that induces uniform abrasions and be used to evaluate the healing properties of a variety of wound care products (29). This model consists of inflicting standardized, superficial abrasions by repeatedly abrading skin with a surgical brush until the first signs of uniform glistening and punctuate bleeding are observed. As the epidermal cells are relatively loosely attached to each other, almost the entire epidermis can be removed by this procedure while keeping the basal membrane still intact (Figs 3 and 4).

The abrasive model is therefore resulting in a wound depth comparable to the suction blister model. As the basal membrane remains intact, wounds heal ad integrum without scarring.

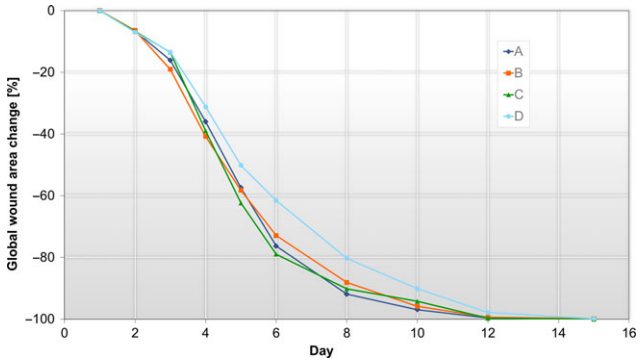

Fig. 2. Healing phase of suction blister wounds. Two weeks after induction of suction blister wounds, there is a complete closure of the wound irrespective of treatment. Between day 4 and day 10 wound areas tend to close faster for sites treated with different topical wound creams (A–C) then for untreated control areas (D). Indicated are means (without error bars for better clarity) of n = 22 volunteers.

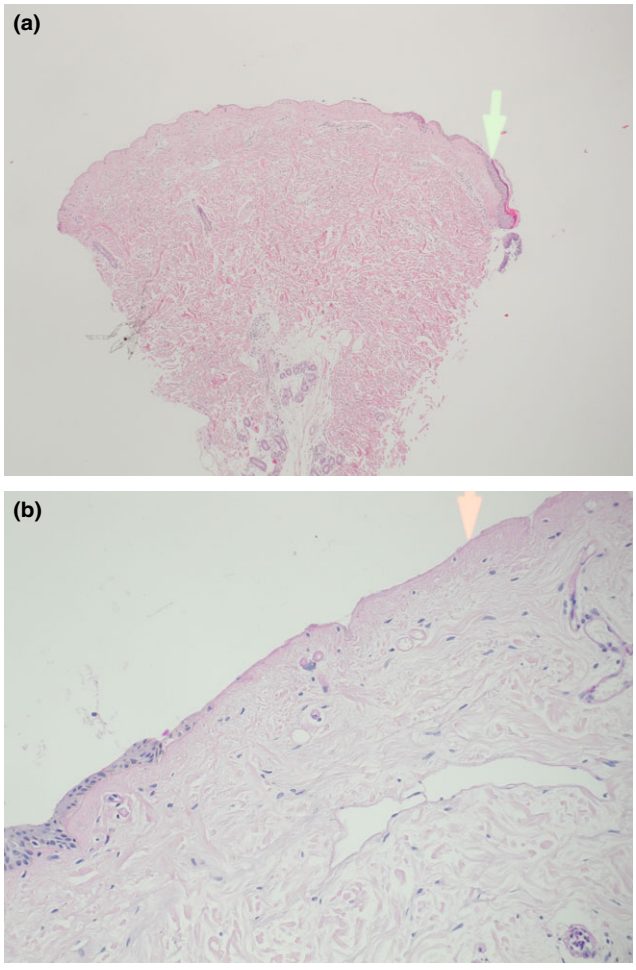

Fig. 3. Histology of a fresh abrasive wound. Complete removal of epidermis in center of wound with a few reminiscent epidermal cells near boarder of wound in H & E stain (a) and clear evidence of intact basal membrane in PAS stain (b).

While the removal of epidermal layer is not as clean and partly not as complete as with the latter, the advantage of this model is that the procedure is not only faster but also closer to real-life conditions when inflicting a superficial minor wound. This method has been used in an open-label, randomized, intra-individual comparison pilot study to evaluate the healing properties of polyurethane, hydrocolloid, hydrogel, and two standard wound dressings on healthy volunteers. The results showed that uniform and identical standardized wounds could be created using this abrasive brush technique and that the method reliably detected differences in the performance of wound dressings. Products that enabled a moist wound environment produced better results with an earlier onset of healing and better healing outcomes than those that promote a dry wound environment (Fig. 5).

Topical preparations are a common treatment for superficial acute wounds, which at the least do not interfere with healing and ideally result in enhanced wound healing irrespective of microbial colonization. This model has also more recently been used to evaluate the effects of a topical antimicrobial gel and its vehicle on wound healing (30).

Laser- and microderm abrasion-induced wound models

Lasers namely CO_2 and Er:YAG laser as well as microdermabrasion devices are widely used by dermatologists and cosmetic surgeons for skin resurfacing procedures. Both techniques have been recently also been introduced as wound research tools. The benefit with both techniques is that wounds of various depths can be induced in a highly reproducible way (31). Ferrag and coworkers (32) have utilized an Er:YAG laser at a total fluence of 15 J/cm² and a pulse length of 250 microseconds to induce 1 × 1 cm² wounds. This procedure resulted only in partial removal of the epidermis. Three-dimensional analysis demonstrated that the laser wounds were more superficial than suction blister wounds. Healing time, however, was comparable between laser-induced wounds and suction blister wounds. The cost of these devices might limit a more widespread use.

Split-thickness wounds. A split-thickness injury generally involves the use of a sharp bladed device (e.g. dermatome) that cuts parallel to the skin surface at a defined depth. This will remove 100–1500-micron-thick layer of the epidermis/upper dermis. A significant amount of

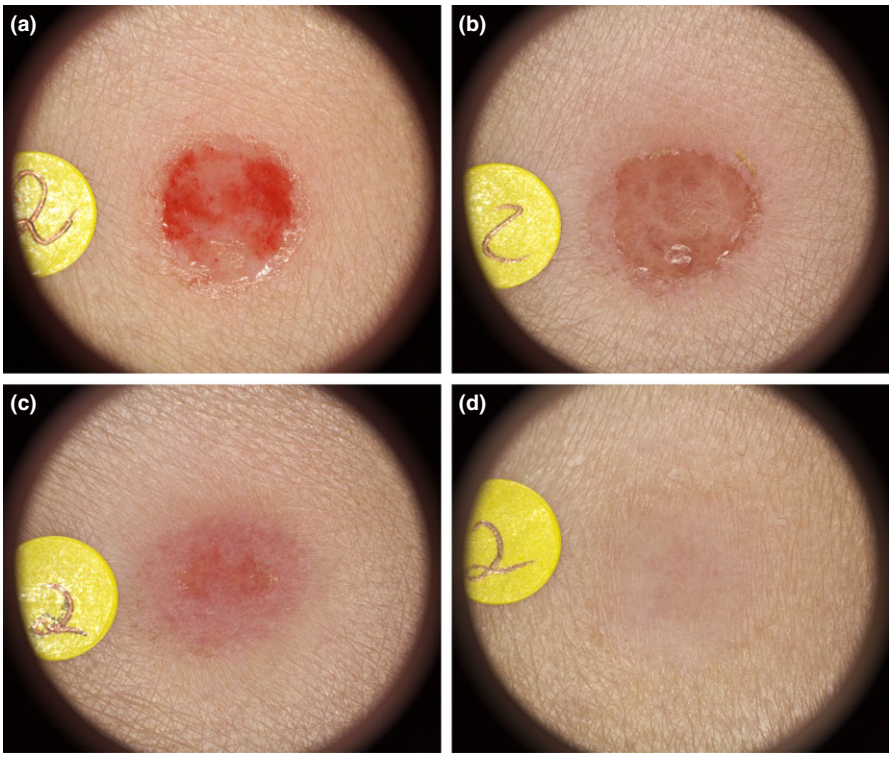

Fig. 4. Abrasive wound model. (a) Freshly formed abrasive wound. (b) Day 3. (c) Day 5. (d) Day 15.

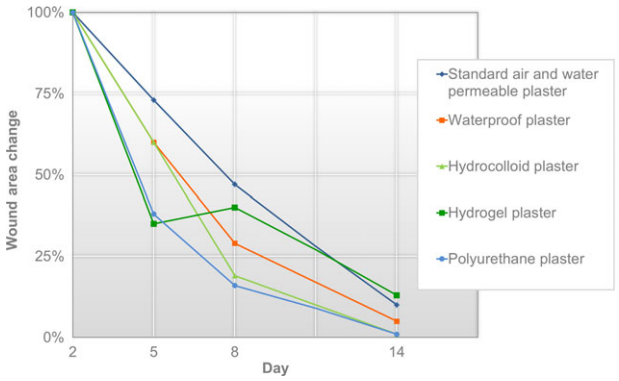

Fig. 5. Healing of abrasive wounds over time following treatment with three different wound dressings. Kinetics of wound area reduction after induction of an abrasive wound. All moist treatments improved healing time as compared with a dry treatment with the greatest improvement delivered by polyurethane product [Data redrawn from Wigger-Alberti et al. (29)].

dermis (reticular) is left with most epidermal appendages (sebaceous and sweat glands, hair follicles) remaining intact and is particularly useful for determining re-epithelialization. An earlier study demonstrates how this model has been used as a valuable research tool to evaluate the effect of age on wound healing in healthy human beings. The results of which showed that elderly volunteers had a significant delay in re-epithelialization (1.9 days), no effect on collagen synthesis, but non-collagenous protein was decreased (33). Although the rapid/normal healing rate in healthy tissues may make it more difficult to determine clear differences among treatment groups, this model has also been used to evaluate specific treatments that may act to aid in the treatment of acute (or chronic wounds). For example, this model has been used to show that the topical application of epidermal growth factor did not significantly affect the healing times between the human epidermal growth factor-treated sites and the silver sulfadiazine cream controls in human volunteers (34). Additionally, a donor site wound model was used to study the importance of temperature (topical radiant heating–TRH) in a wound healing evaluation in human volunteers. The results of which showed that TRH increased local blood flow and lymphocyte (CD3) extravasation and it was concluded that such changes may be beneficial in that it could lead to enhanced local innate immunity within the healing wound environment (35). A recent study involved a biopsy on split-thickness skin graft donor site wounds, before and after harvesting and at days 3 and 7 thereafter, in order to investigate transcriptome during normal human epidermal wound healing. The data

revealed novel genes associated with epidermal wound healing and also provided a fundamental basis for the translational interpretation of data acquired from experimental models (36). During the course of excisional wound healing, granulation tissue growth can be exuberant enough to raise the wound above the plane of the skin. This hypertrophic phase subsides rapidly in animals, but it may be the closest approximation of cutaneous hypertrophic scarring as seen in man.

Full thickness wound models: This model requires the complete removal of epidermis and dermis to the depth of fascial planes or subcutaneous fat and disrupts dermal blood vessels. This can be done using a number of devices to inflict a lesion in a standardized fashion (e.g. including punch biopsy, scalpel, dermatome, and laser). This model offers the advantages of healing involving all of the dermal components and epithelialization from the wound margins. Wound healing involves the synthesis of several types of tissue and scar formation. Bleeding and fluid loss are more extensive in the excisional model, and there is greater susceptibility to infection. Healing rates can be measured macroscopically in relation to total excisional volume (or cross-sectional area), granulation tissue formation, and re-epithelialization. Taking biopsies of the healing tissue allows analysis of chemistry, histology, and cell populations in the wound site in terms of histological organization of connective tissue, angiogenesis, and biochemical content of collagen or proteoglycans.

Punch biopsy wounds are widely used in wound healing research both in animal models and human volunteer studies. These wounds are useful from an experimental perspective in that their size and depth can be precisely controlled. As they involve all the components of the healing process, they provide an excellent research tool and have been used to investigate angiogenesis (37–39), wound contraction, and closure (40, 41). This model has also been used to investigate the effects of new treatments on wound healing. For example, it was shown that topical platelet-derived growth factor limited the role of wound contraction in wound closure and that PDGF-treated wounds close by re-epithelialization and filling in with scar (42).

TABLE 1. Different human wound healing models

Wound model	Depth into skin	Comments
Skin stripping using adhesive tape	Stratum corneum	Simple, yet time-consuming procedure
Suction Blister model	Epidermis A split in the basal membrane produces a clear removal of the epidermis with the dermis remaining 100% intact	The suction blister model utilizes application of a constant negative pressure. This results in a split in the basal membrane and hence a separation between epidermis and dermis. After excision of the blister roof clean wounds are obtained that heal without scarring
Abrasive wound model	Epidermis As the dermis provides heater resistance to the brushing only epidermal cells are removed	This model consists of inflicting standardized, superficial abrasions repeatedly abrading skin with a surgical brush until the first signs of uniform glistening and punctuate bleeding are observed. Useful for differentiating wound dressing properties and semi solid preparations in terms of wound healing, high similarity with real everyday wounds
Laser wounds	Variable depth depending on laser type and energy settings. Lasers can be tuned to induce very superficial, i.e. just upper epidermal layers to deeper wounds, i.e. full epidermis and partially dermis	Costly technique with flexibility in terms of wound depth. Creates wounds with great reproducibility
Microdermabrasion	Variable depth depending on device and device settings	Less expensive than lasers, high investigator skills required
Dermatome	Split-thickness wounds This will remove 100–1500-micron-thick layer of the epidermis/upper dermis	Time-honored technique. High investigator skill required. Invasiveness depends on instrument settings. Typically a significant amount of dermis (reticular) is left with most epidermal appendages (sebaceous and sweat glands, hair follicles) remain intact and is particularly useful for determining re-epithelialization
Biopsy	Full thickness wound model Removal of epidermis and dermis. Depth depends on biopsy technique, i.e. punch vs. scalpel	This model offers the advantages of healing involving all of the dermal components and epithelialization from the wound margins. Because of depth scar formation is inevitable

More recently, it has been used successfully in evaluating the effects of electrical stimulation on various components on healing in volunteers (43, 44). And in the evaluation of new test compounds such as bismuth subgallate/borneol (suile) which was tested against and shown to be superior in terms of healing than bacitracin in a human forearm biopsy model (45).

Conclusion

Breaking down physiological processes into component parts by modeling is an important part of research. Wound healing is a complex process. The use of models (*in vitro*, *in vivo* – animal and human) has enabled extensive research into this area that has significantly enhanced the knowledge of the mechanisms of both acute and chronic healing. In parallel with this knowledge has been the development of new wound treatments and understanding of how advanced wound care may be developed to obtain better patient outcomes. Although *in vitro* and animal models have their place, by far the better models are based on humans that provide physiologically accurate mechanisms on which new treatments may be tested (Table 1).

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References

1. Gosain A, DiPietro LA. Aging and wound healing. World J Surg 2004; 28: 321–326.
2. Mathieu D. Role of hyperbaric oxygen therapy in the management of lower extremity wounds. Int J Low Extrem Wounds 2006; 5: 233–235.
3. Sen CK, Gordillo GM, Roy S, Kirsner R, Lambert L, Hunt TK, Gottrup F, Gurtner GC, Longaker MT. Human skin wounds: a major and snowballing threat to public health and the economy. Wound Repair Regen 2009; 17: 763–771.
4. Drew P, Posnett J, Rusling L. The cost of wound care for a local population in England. Int Wound J 2007; 4: 149–155.
5. Winter GD. Formation of the scab and the rate of epithelization of superficial wounds in the skin of the young domestic pig. Nature 1962; 193: 293–294.
6. Galiano RD, Michaels J, Dobryansky M, Levine JP, Gurtner GC. Quantitative and reproducible murine model of excisional wound healing. Wound Repair Regen 2004; 12: 485–492.
7. Dunn L, Prosser HC, Tan JT, Vanags LZ, Ng MK, Bursill CA. Murine model of wound healing. J Vis Exp 2013; 28: e50265.
8. Seaton M, Hocking A, Gibran NS. Porcine models of cutaneous wound healing. ILAR J 2015; 56: 127–138.
9. Sullivan TP, Eaglstein WH, Davis SC, Mertz P. The pig as a model for human wound healing. Wound Repair Regen 2001; 9: 66–76.
10. Gao Y, Wang X, Chen S, Li S, Liu X. Acute skin barrier disruption with repeated tape stripping: an in vivo model for damage skin barrier. Skin Res Technol 2013; 19: 162–168.
11. Lademann J, Jacobi U, Surber C, Weigmann HY, Fluhr JW. The tape stripping procedure – evaluation of some critical parameters. Eur J Pharm Biopharm 2009; 72: 317–323.
12. van de Kerkhof PC, de Mare S, Arnold WP, van Erp PE. Epidermal regeneration and occlusion. Acta Derm Venereol 1995; 75: 6–8.
13. Pereira GG, Guterres SS, Balducci AG, Colombo P, Sonvico F. Polymeric films loaded with vitamin E and aloe vera for topical application in the treatment of burn wounds. Biomed Res Int 2014; 2014: 641590.
14. Graham JE, Song S, Engeland CG. Acute pain speeds skin barrier recovery in healthy men and women. J Psychosom Res 2012; 73: 452–458.
15. Dykes PJ, Heggie R, Hill SA. Effects of adhesive dressings on the stratum corneum of the skin. J Wound Care 2001; 10: 7–10.
16. Waring M, Bielfeldt S, Mätzold K, Wilhelm KP, Butcher M. An evaluation of the skin stripping of wound dressing adhesives. J Wound Care 2011; 20: 412–422.
17. Kiistala U. Suction blister device for separation of viable epidermis from dermis. J Invest Dermatol 1968; 50: 129–137.
18. Escobar-Chávez JJ, Bonilla-Martínez D, Villegas-González MA, Molina-Trinidad E, Casas-Alancaster N, Revilla-Vázquez AL. Microneedles: a valuable physical enhancer to increase transdermal drug delivery. J Clin Pharmacol 2011; 51: 964–977.
19. Kottner J, Hillmann K, Fimmel S, Seité S, Blume-Peytavi U. Characterisation of epidermal regeneration in vivo: a 60-day follow-up study. J Wound Care 2013; 22: 395–400.
20. Smith TJ, Wilson MA, Young AJ, Montain SJ. A suction blister model reliably assesses skin barrier restoration and immune response. J Immunol Methods 2015; 417: 124–130.
21. Alexis AF, Wilson DC, Todhunter JA, Stiller MJ. Reassessment of the suction blister model of wound healing: introduction of a new higher pressure device. Int J Dermatol 1999; 38: 613–617.
22. Lomash V, Jadhav SE, Vijayaraghavan R, Pant SC. Time course pathogenesis of sulphur mustard-induced skin lesions in mouse model. Int Wound J 2013; 10: 441–454.
23. Hartel M, Illing P, Mercer JB, Lademann J, Daeschlein G, Hoffmann G Therapy of acute wounds with water-filtered infrared-A (wIRA). GMS Krankenhhyg Interdiszip 2007; 2: Doc53.
24. Krawczyk WS, Wilgram GF. Hemidesmosome and desmosome morphogenesis during epidermal wound healing. J Ultrastruct Res 1973; 45: 93–101.

25. Myers SR, Leigh IM, Navsaria H. Epidermal repair results from activation of follicular and epidermal progenitor keratinocytes mediated by a growth factor cascade. Wound Repair Regen 2007; 15: 693–701.
26. Evans ND, Oreffo RO, Healy E, Thurner PJ, Man YH. Epithelial mechanobiology, skin wound healing, and the stem cell niche. J Mech Behav Biomed Mater 2013; 28: 397–409.
27. Martins-Green M. The Yin and Yang of integrin function in re-epithelialization during wound healing. Adv Wound Care (New Rochelle) 2013; 2: 75–80.
28. Daeschlein G, Alborova J, Patzelt A, Kramer A, Lademann J. Kinetics of physiological skin flora in a suction blister wound model on healthy subjects after treatment with water-filtered infrared-A radiation. Skin Pharmacol Physiol 2012; 25: 73–77.
29. Wigger-Alberti W, Kuhlmann M, Ekanayake S, Wilhelm D. Using a novel wound model to investigate the healing properties of products for superficial wounds. J Wound Care 2009; 18: 123–131.
30. Wigger-Alberti W, Stauss-Grabo M, Grigo K, Atiye S, Williams R, Korting HC. Efficacy of a tyrothricin-containing wound gel in an abrasive wound model for superficial wounds. Skin Pharmacol Physiol 2013; 26: 52–56.
31. Lee WR, Shen SC, Kuo-Hsien W, Hu CH, Fang JY. Lasers and microdermabrasion enhance and control topical delivery of vitamin C. J Invest Dermatol 2003; 121: 1118–1125.
32. Ferraq Y, Black DR, Theunis J, Mordon S. Superficial wounding model for epidermal barrier repair studies: comparison of Erbium: YAG laser and the suction blister method. Lasers Surg Med 2012; 44: 525–532.
33. Holt DR, Kirk SJ, Regan MC, Hurson M, Lindblad WJ, Barbul A. Effect of age on wound healing in healthy human beings. Surgery 1992; 112: 293–297.
34. Cohen IK, Crossland MC, Garrett A, Diegelmann RF. Topical application of epidermal growth factor onto partial-thickness wounds in human volunteers does not enhance reepithelialization. Plast Reconstr Surg 1995; 96: 251–254.
35. Khan AA, Banwell PE, Bakker MC, Gillespie PG, McGrouther DA, Roberts AH. Topical radiant heating in wound healing: an experimental study in a donor site wound model. Int Wound J 2004; 1: 233–240.
36. Nuutila K, Siltanen A, Peura M et al. Human skin transcriptome during superficial cutaneous wound healing. Wound Repair Regen 2012; 20: 830–839.
37. Brown NJ, Smyth EA, Cross SS, Reed MW. Angiogenesis induction and regression in human surgical wounds. Wound Repair Regen 2002; 10: 245–251.
38. Lockhart AC, Braun RD, Yu D et al. A clinical model of dermal wound angiogenesis. Wound Repair Regen 2003; 11: 306–313.
39. Ud-Din S, Sebastian A, Giddings P, Colthurst J, Whiteside S, Morris J, Nuccitelli R, Pullar C, Baguneid M, Bayat A. Angiogenesis is induced and wound size is reduced by electrical stimulation in an acute wound healing model in human skin. PLoS ONE 2015; 10: e0124502.
40. De Vries HJ, Zeegelaar JE, Middelkoop E, Gijsbers G, Van MJ, Wildevuur CH, Westerhof W. Reduced wound contraction and scar formation in punch biopsy wounds. Native collagen dermal substitutes. A clinical study. Br J Dermatol 1995; 132: 690–697.
41. Sørensen LT, Toft BG, Rygaard J, Ladelund S, Paddon M, James T, Taylor R, Gottrup F. Effect of smoking, smoking cessation, and nicotine patch on wound dimension, vitamin C, and systemic markers of collagen metabolism. Surgery 2010; 148: 982–990.
42. Ehrlich HP, Freedman BM. Topical platelet-derived growth factor in patients enhances wound closure in the absence of wound contraction. Cytokines Cell Mol Ther 2002; 7: 85–90.
43. Sebastian A, Syed F, Perry D, Balamurugan V, Colthurst J, Chaudhry IH, Bayat A. Acceleration of cutaneous healing by electrical stimulation: degenerate electrical wave form down-regulates inflammation, up-regulates angiogenesis and advances remodeling in temporal punch biopsies in a human volunteer study. Wound Repair Regen 2011; 19: 693–708.
44. Ud-Din S, Perry D, Giddings P, Colthurst J, Zaman K, Cotton S, Whiteside S, Morris J, Bayat A. Electrical stimulation increases blood flow and haemoglobin levels in acute cutaneous wounds without affecting wound closure time: evidenced by non-invasive assessment of temporal biopsy wounds in human volunteers. Exp Dermatol 2012; 21: 758–764.
45. Serena T, Parnall LK, Knox C et al. Bismuth subgallate/borneol (suile) is superior to bacitracin in the human forearm biopsy model for acute wound healing. Adv Skin Wound Care 2007; 20: 485–492.

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