Bioelectric Stimulation, Electric Fields and the Current of Injury: Have We Been Overlooking One of the Most Important Coordinators of the Wound Healing Process?

Editorial Summary

This article presents a critical examination of bioelectric stimulation, electric fields, and the current of injury as potentially overlooked yet fundamental coordinators in wound healing. It elucidates the physiological basis of bioelectricity in cellular processes and its implications for clinical wound management. The review explores the role of membrane potentials, transepithelial potentials, and bioelectric signalling in modulating key cellular behaviors crucial to healing, including proliferation, migration, and differentiation. It introduces the concept of the "skin battery" and how its disruption generates a "current of injury," which initiates and sustains the healing cascade. Compelling evidence suggests that compromised bioelectric processes may underlie impaired healing in recalcitrant wounds, particularly in geriatric and diabetic populations. The article critically evaluates the efficacy of exogenous electrical stimulation therapy (EST), citing meta-analyses demonstrating significant improvements in healing rates for hard-to-heal wounds. While acknowledging the limitations of earlier EST devices, the authors highlight recent advancements in microcurrent technology that offer more practical and integrable solutions for clinical application. They posit that incorporating bioelectric-based therapies could potentially address the increasing prevalence of chronic wounds more effectively than conventional approaches focused solely on biochemical mediators. This comprehensive review advocates for a paradigm shift in wound care strategies, urging clinicians to consider bioelectric factors as essential components in the multifaceted approach to wound healing.

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Introduction

Delve into any Wound Management textbook and you will learn all about the biochemical basis of wound healing - the complex interplay between growth factors, cytokines, proteases, cell membrane receptors and so on, which drive the wound healing process. However, scientists are becoming clearer that while these factors are indeed important stimulators, a much more fundamental coordinator of healing behaviours that is triggered by wounding is not even mentioned in most wound management texts.[1] We are referring to bioelectricity.

Imagine that the growth factors and cytokines are the musicians in an orchestra, then bioelectricity is the conductor, making sure they are all co-ordinated and working in harmony to restore skin back to pre-wounded state.

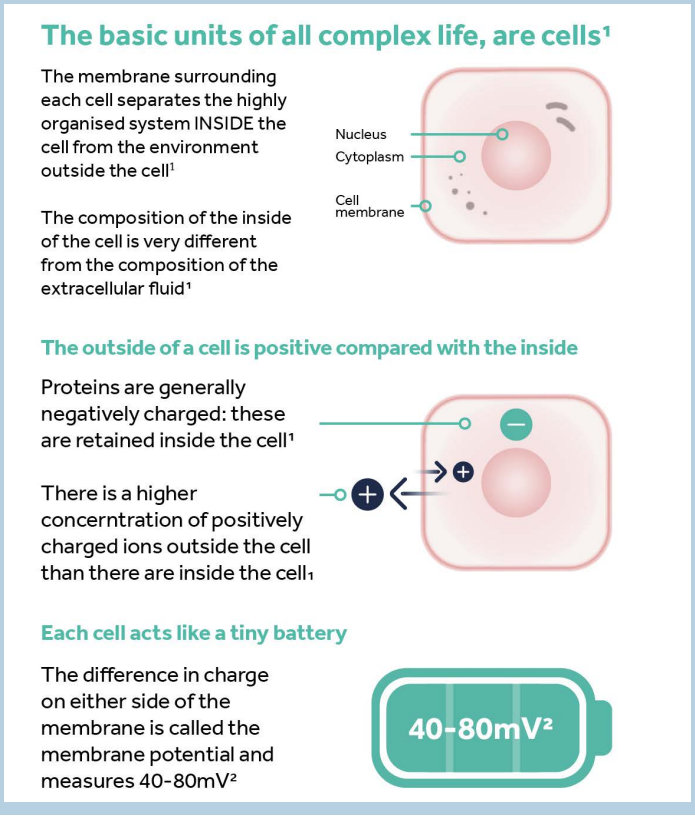
The purpose of this document is to describe the physiological basis of bioelectricity and to explain the fundamental importance of bioelectrical fields and currents in the wound healing process.

Let's start with the basics; the membrane potential in cell biology

All higher organisms, including humans, are organised into organs, the basic units of which are cells. The membrane enveloping each cell separates the highly organised system inside the cell from the environment outside the cell and the composition of the fluid inside the cell is very different from the composition of the extracellular fluid. One key difference is that the levels of electrolytes, for example $Ca2^{+}$, Na^{+}, K^{+}, Cl^{-} ions, vary between the inside and outside of the cells.

Under normal conditions, more positively charged electrolytes (predominantly Na^{+} and K^{+} ions) are found outside the cell than inside the cell. In addition, proteins are generally negatively charged and these are retained inside the cell. The overall effect is that the cytoplasm inside the cell has an electrically negative charge compared with the surrounding extracellular fluid. The difference in this electrical charge on either side of the membrane is called the membrane potential and measures 40-80mV.[2] Essentially, there is a potential difference between the inside and the outside of the cell meaning that each cell can act as a tiny battery that stores 'bioelectricity' (Figure 1).

Figure 1: Membrane potential. All living cells, including human cells, have a different composition inside and outside their cell membranes. Differences in the concentration of charged molecules (like ions and proteins) between the inside and the outside of the cell generates a membrane potential. This is in effect a difference in electrical charge on either side of the cell membrane, which allows each cell to act as a tiny battery.



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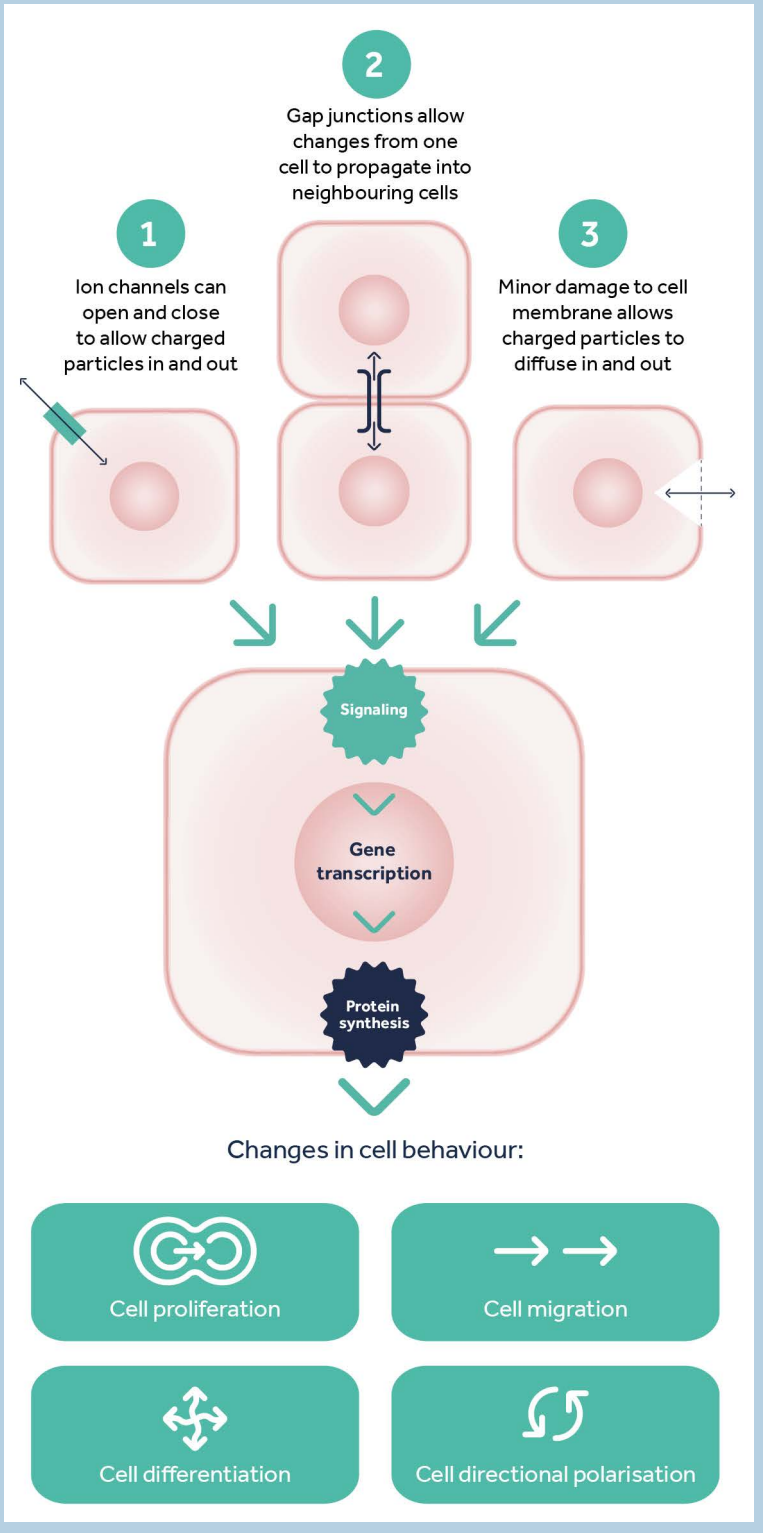
How bioelectric signalling works

The membrane potential has a purpose; when something happens to disrupt it, this drives a movement of electrically charged ions, which then stimulate the cell to change its cellular processes and behaviours. We most often think about this happening in the context of nerve cells being stimulated to fire off a nerve impulse, but in reality these kinds of events happen in all cells in the human body.

Disruption to the membrane potential can happen in at least three different ways. Firstly, ion channels in the membrane can open, allowing ions to flood in or out, changing the charge across the cell membrane. Secondly, structures called gap junctions that connect neighbouring cells can open or close, either transmitting or blocking changes from one cell into its neighbours. Thirdly, minor physical damage to an individual cell's membrane can allow diffusion of molecules from the inside or outside of the cell (Figure 2).[2]

Figure 2: How disrupting the membrane potential can drive bioelectric signalling. Bioelectric signalling can be initiated in 3 main ways, all of which can result in signalling events inside the cell which trigger gene transcription, protein synthesis and essentially activate a range of cell behaviours.



"The electrical properties of epithelia are hardly ever mentioned in textbooks. Yet these properties are very important for organ function." [1]

In all of these scenarios, the membrane potential of the cell is suddenly changed by a movement of charged ions and proteins across the cell membrane. This change can trigger a wide variety of cellular responses and is collectively termed bioelectric signalling. When the membrane potential is disrupted, and the biochemical composition of the cytoplasm changes, receptors inside the cells respond to these changes by initiating gene expression and the synthesis of proteins through gene transcription and translation. Such cell activation can change the behaviour of a cell. Some changes triggered by bioelectric signalling include: cell proliferation, cell migration, cell differentiation and cell directional polarisation, among others. These are all cellular behaviours that are important drivers of the healing process.[2]

Transepithelial potential and the 'skin battery'

In the previous section we described how bioelectricity is created by the potential difference between different compartments, for example inside and outside the cell. But bioelectricity can also be observed across different compartments of tissue for example the outermost (apical) and innermost (basolateral) surfaces of epithelial tissues. Transepithelial potential has been measured in skin, gut epithelia, kidney and cornea.[3]

In the skin, the transdermal potential is commonly referred to as the 'skin battery'. Intact skin has a transdermal potential of 15 to 50mV with the inside being positively charged relative to the outside (Figure 3A).[4,5] The transepidermal potential is generated in the keratinocyte layers of the epithelium because of a net movement of sodium ions (Na+, positively charged) from the apical side of the cell (the outermost edge) through the cell, to the basolateral (innermost) edge.[1,4,6] All cells have sodium channels, potassium channels and sodium-potassium pumps, and in most cells these structures are randomly positioned around the perimeter of the cell. However, in keratinocytes that make up the epidermis, they are polarised with most sodium channels being localized to the apical (outermost) membrane, most potassium channels being found in the basolateral membrane (innermost layer of keratinocytes) and most sodium-potassium pumps also localised along the basal side where they pump sodium ions out of the cell in the direction of the dermis.[1,4,6]

The positioning of the sodium ions themselves is in constant flux; once they have been removed from the cell at the basolateral side, they try to diffuse down their concentration gradient towards the apical edge, however gap junctions that tightly bind keratinocytes to their neighbours, prevent free diffusion.[6] The positively charged ions at the basolateral side are not able to diffuse away which leads to there being a trans-epidermal potential (Figure 3B).

Figure 3: How transdermal potential is generated in human skin. Figure 3A. Human skin is electrically charged with a relatively positive charge on the basolateral side of the epidermis (next to the dermis). This electrical charge has led to the skin being described as a battery. Figure 3B represents a layer of within the epithelium. Sodium channels on the apical side of the keratinocytes pump sodium into the cell. Sodium-potassium pumps situated on the basolateral side of the cell then eject the sodium from the cell. The sodium is not able to diffuse back to the apical side of the cell because it is blocked by the presence of tight junctions that tightly link keratinocytes to their neighbours and forms an impermeable barrier. Therefore, the basolateral side has a higher concentration of sodium ions and their positive charge generates a transmembrane potential that is positive on the basolateral side and negative on the apical side.

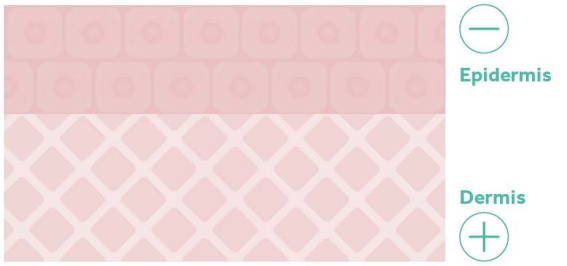


Figure 3A

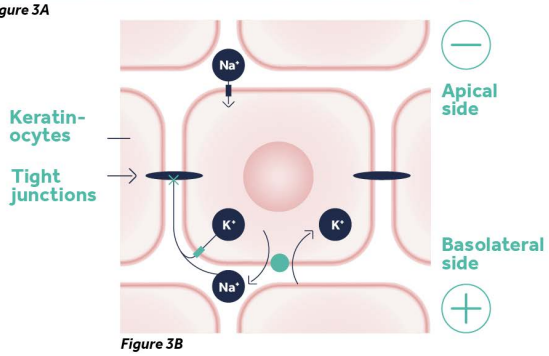


Figure 3B

Tight junctions prevent diffusion from the basolateral to the apical side of the epidermis. This means that the basolateral side remains electrically positive compared to the apical side.

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The 'current of injury'

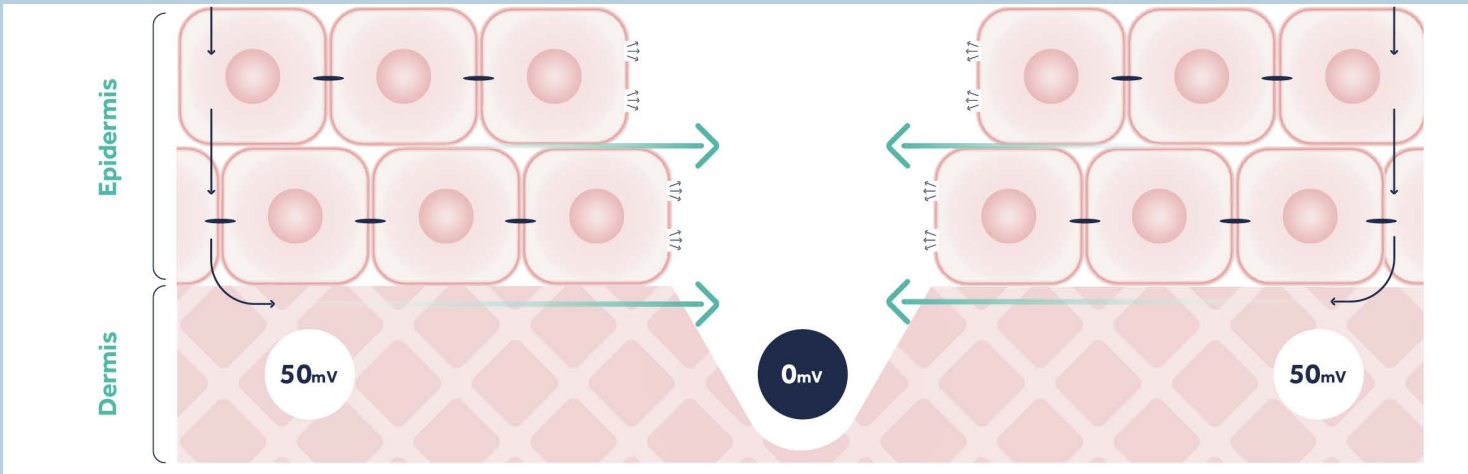
While intact skin acts as a battery of potential bioelectrical energy, what happens when the skin is wounded? Scientists have known the answer to this question for well over a century, since, in 1843, the scientist Dubois-Reymond first used a galvanometer on his own cut finger and identified that wounds had a measurable electric current.[5] This has since been named the 'current of injury'.

Wounding the epithelial sheet creates a hole that breaches the high electrical resistance established by the tight junctions between the cells, and this short-circuits the epithelium, in the local vicinity of the wound. The transdermal potential therefore drops to zero at the wound. However, because normal ion transport continues in unwounded epithelial cells beyond the wound edge, the transcutaneous potential difference remains at normal values around 2mm back from the wound.[6] It is this gradient of electrical potential, 0 mV at the short-circuited wound bed, 15-50 mV a short distance away in unwounded tissue, that establishes a laterally oriented electrical field and drives a steady bioelectric flow of current (Figure 4). This is termed the 'current of injury' and, in healthy individuals, is around 140mV per mm .[4-6]

All cells in tissue at the edge of the wound are exposed to this current of injury which stimulates their activity for several days after wounding. In normal wound healing, this wound-induced electrical field persists until the migrating epithelium reseals the wound and re-establishes tight junctions which create a uniformly high electrical resistance, at which point the wound-induced electrical field drops to zero and the transcutaneous potential, the skin battery, is restored.[4-6]

So, as the wound heals, the current of injury progressively reduces. The current of injury will also gradually decrease if the wound is left open to dry.[7] Maintaining a moist wound environment has been recognised for decades as being vital for healing. Given that electrolytes are soluble and need fluid to diffuse, it is highly likely that moist wound healing is essential for the current of injury to exist. Seeing moist wound healing in the context of the movement of electrolytes and the current of injury, provides a new way

Figure 4: The 'current of injury'. On wounding, there is an immediate, collapse of the transepithelial potential at the site of the wound (to 0mV) caused by loss of an intact epithelium. In adjacent unwounded areas, the ion transport properties of the epithelium remain intact and Na+ continues to be transported inwards towards the basolateral side of the epithelium (narrow black arrows) and prevented from diffusing to the apical side by the presence of intact gap junctions. However, there is no barrier to prevent ions from nearby unaffected areas to flow laterally towards the centre of the wound (blue arrows). This uncontrolled movement of ions towards the centre of the wound can be measured at around 50mV and is known as the current of injury. Adapted from Tyler et al (2017).[2]



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of appreciating this basic tenet of wound management.

How normal wound healing processes are reliant on the current of injury

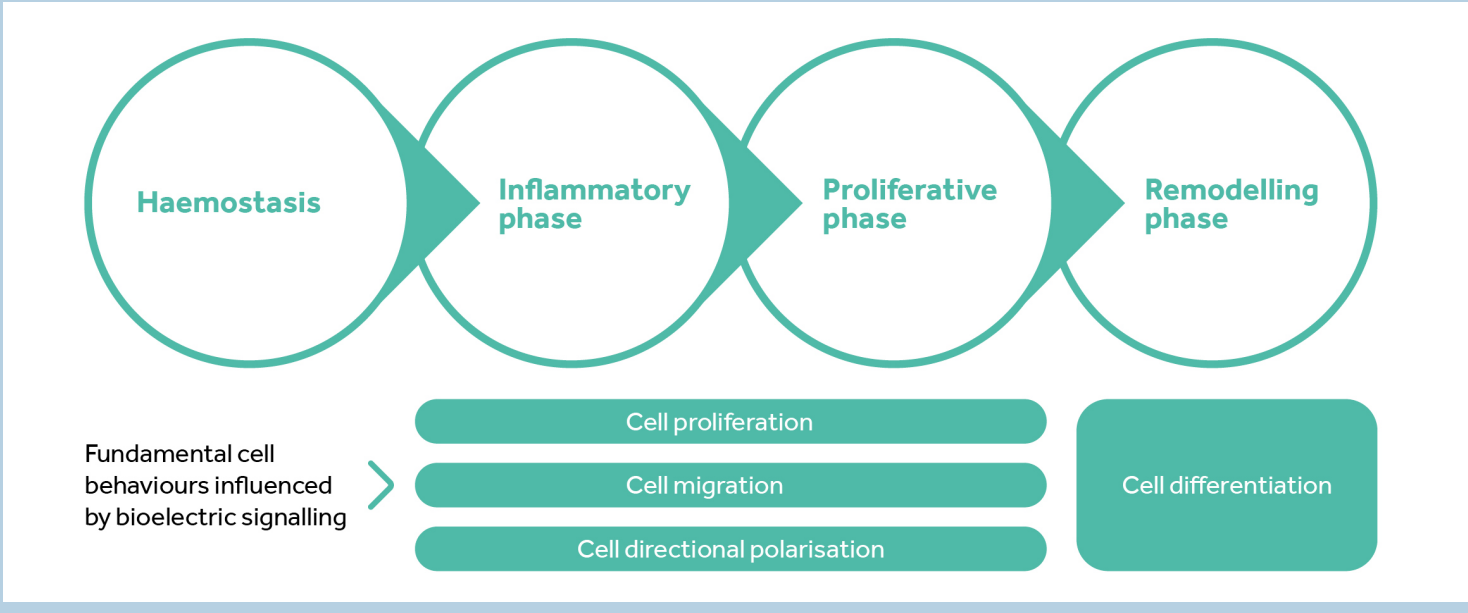
Many of the fundamental cell behaviours essential to the healing process are stimulated by bioelectric signalling, as evidenced in numerous scientific studies (Figure 5):[1,4,6,8,9]

- Proliferation: many cell types need to proliferate for normal wound healing to progress including white blood cells (essential in the inflammatory phase), keratinocytes (for re-epithelialisation), endothelial cells (to make new blood vessels essential for granulation tissue formation) and fibroblasts in the dermis (required to deposit replacement ECM). Bioelectric signalling stimulates proliferation in all of these cell types.[1,6]

- Migration: Bioelectric signalling, through cell directional polarisation, is believed to instruct the newly proliferated cells in which direction to migrate, so, for example, keratinocytes know to migrate towards, not away from the centre of the wound.[1,4,6,9]

- Cell differentiation This process is essential in later stages of healing, in particular during the late proliferative stage and throughout the remodelling phase. New keratinocytes need to differentiate to form the layers of the epidermis. Fibroblasts differentiate during the phases of healing as their role changes. During the early proliferative phase fibroblasts are stimulated to rapidly produce ECM which is deposited quickly to close the wound. During the remodelling phase fibroblasts become differentiated into myofibroblasts, which remodel this newly deposited ECM into tissue more like normal dermis. Electric fields have also been shown to coordinate these cell maturation events.[8]

Figure 5: The cellular processes in wound healing that are reliant on the current of injury.[1,4,6,8]



"Not all wounds heal normally and hard-to-heal wounds which remain unhealed for at least 12-months represents some 30% of all wounds treated annually (UK data)." [11]

Several studies have been conducted where researchers have used drugs to enhance or decrease ion transport, and therefore the current of injury, in wound healing models. They have found a clear association between the current of injury and the rate of healing – the lower the current, the slower the rate of healing.[10] Given that the movement of charged ions is the way in which bioelectricity is 'delivered', these studies also demonstrate the central role of bioelectrical signalling on wound healing events.

There is some evidence that the skin battery and the current of injury are reduced in some people

Not all wounds heal normally and hard-to-heal wounds which remain unhealed for at least 12-months represents some 30% of all wounds treated annually (UK data).[11]

Some of the main risks of hard-to-heal wounds include older age, diabetes, poor nutrition and ischaemia. It has been suggested that older people and those with diabetes have reduced or compromised transepidermal potential and a lower current of injury.[5,12,13] Research in a volunteer study has shown that the current of injury is 48% lower in older people (aged 65+) than in younger people (aged 18-25). There were no differences between male and female. This suggests that the skin battery in older people is less efficient than in younger people.[5] Other studies have shown that the skin battery (in intact skin) is lower in people with diabetes than in age matched controls, also suggesting that the skin battery is less powerful in people with diabetes, than in people with no diabetes.[14] Studies in the cornea, an epithelium that has much in common with the skin and is often used as a model for cutaneous wound healing, have also shown that diabetes reduces the current of injury.[15]

It's thought that having a compromised current of injury makes the wound healing process less efficient – the conductor of the orchestra is not doing the job properly - and this is likely to be one of the reasons why hard-to-heal wounds are more common in these groups of people. More research is needed to fully understand how these factors interplay but it is possible that a compromised current of injury could reasonably be considered a barrier to healing.

In people with compromised skin battery and compromised current of injury, application of EST at physiologically relevant levels may be beneficial

For those people with a hard-to-heal wound, who may have a compromised current of injury, there is a promising treatment to promote healing. Electrical stimulation therapy (EST) is a highly evidenced treatment type in the field of hard-to-heal wounds with numerous meta-analyses of randomised controlled trials (of which 3 are described below).[16-18] The rationale for applying EST is that by replacing the lost endogenous current it can 'normalise' the healing process. Many experts suggest that microcurrent EST may resemble a natural electric field or electric current, enhancing the patient's own endogenous wound healing processes.[2,19]

One key meta-analysis focussed on hard-to-heal wounds treated with microcurrent devices. This meta-analysis found that wounds treated with microcurrent devices alongside standard care, reduced significantly more in size and healed significantly faster.[17] A separate meta-analysis published by the Cochrane group, but focused on pressure ulcers, showed that compared with standard care alone, wounds treated with electrical stimulation wound therapy are almost twice as likely to heal and have a 4.6% increase per week in the rate of wound healing.[20]

Aside from stimulating healing, microcurrent electrical stimulation wound therapy has also been shown to significantly reduce wound pain,

starting after only a few days of treatment.[21] We know that wound pain is often linked with inflammation, so it may be that the effect of microcurrent EST on pain is related to its ability to dampen down macrophage-mediated inflammatory processes.[22]

In the past, EST devices designed for use in wound management were expensive, very large and awkward to use. Also, most of these devices weren't able to be used along-side standard care and this made it difficult to incorporate this potentially beneficial technology into every-day wound care routines. However, a new and innovative device, Accel-Heal Solo, is now available to enable use of this technology in frontline practice.

Conclusion

The burden of hard-to-heal wounds is enormous and is growing,[11] despite the efforts of dedicated clinicians and scientists alike. The current approaches aren't working well enough, and we need to do something different. Over the past several decades, much of the research and innovation in wound management has focussed on understanding and modulating the biochemical mediators of the wound healing process, the growth factors and cytokines, without much success.

However, running in parallel, a compelling body of clinical evidence supporting the use of exogenous EST to promote healing in hard-to-heal wounds has been steadily growing. What scientists now know about the fundamental role of bioelectricity in coordinating the wound healing process, fits perfectly with this body of evidence and underpins the clinical benefit of applying EST to hard-to-heal wounds. Although in the past these EST devices were difficult to adopt in frontline clinical practice, that is no longer the case and innovative new devices that deliver microcurrent EST are now available that are easily incorporated into existing wound care practice and routines. These microcurrent devices are subsensory and inherently safe, and together with the substantial underlying science and evidence base, this should provide clinicians with the confidence to use in their everyday practice.

Of course, what every healthcare professional wants is to help their patients to achieve respite and to recover from their painful, hard-to-heal wounds. We believe that microcurrent EST may help to achieve this goal. In the words of one patient with a painful VLU of 5 months duration, after starting treatment with microcurrent EST* his "leg started to heal and [he] started to get [his] life back".[23] And that is what we want for all our patients!

*Accel-Heal Solo, Accel-Heal Technologies Limited, Hever, Kent, UK.

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