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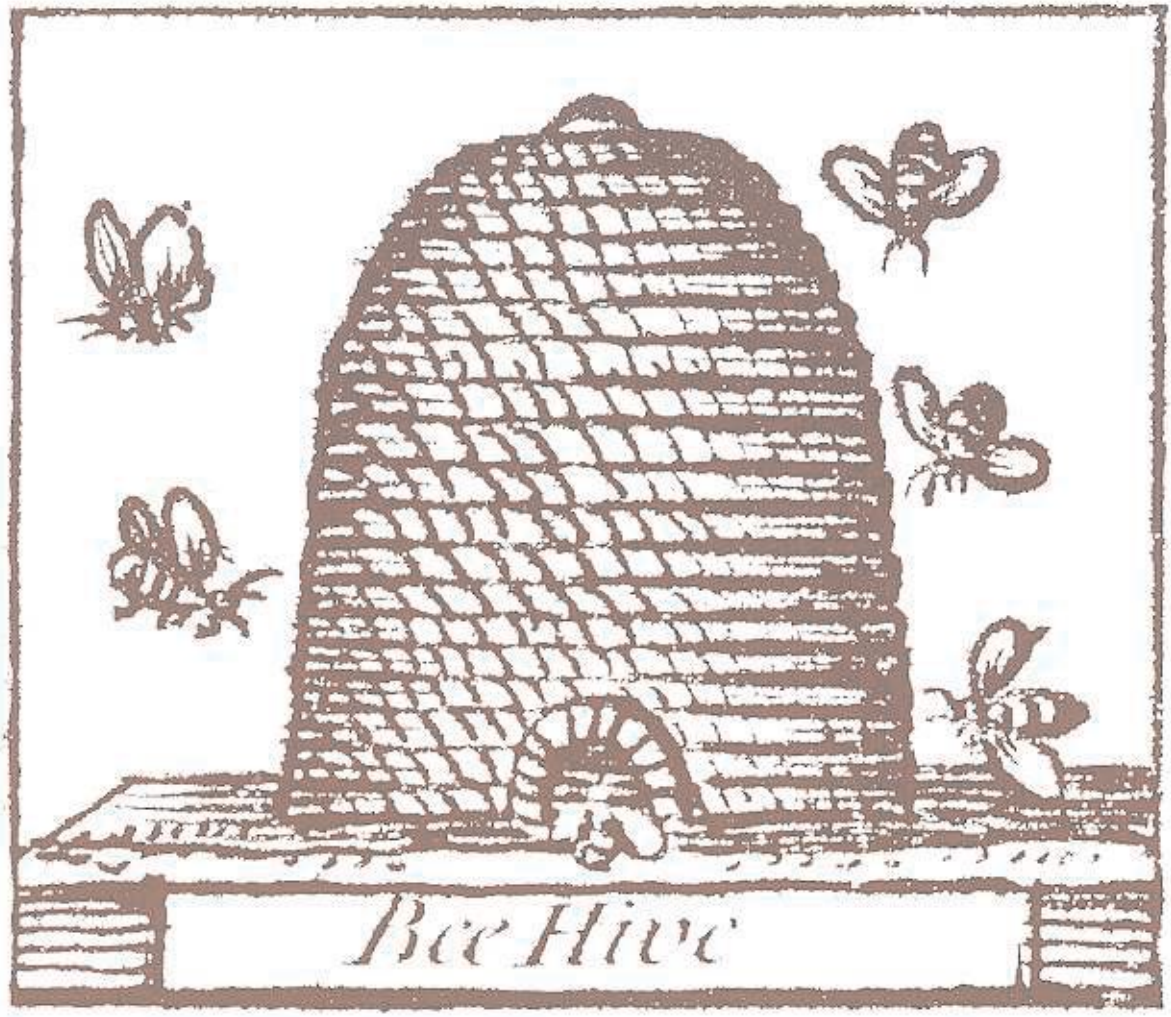

HONEY DRESSINGS
Why do some cavity wounds heal without scarring?

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Why do some cavity wounds treated with honey or sugar paste heal without scarring?

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As well as having antimicrobial properties, honey and sugar paste are associated with scarless healing in some cavity wounds. This article uses evidence to suggest why these products can modify excessive collagen production to prevent scarring

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Honey[1] and sugar[2] or sugar paste[3] have been used to treat wounds for many years. Physicians working for the medical aid agency Médecins Sans Frontières have saved limbs by applying sugar to wounds.[4] There are disadvantages to using honey or sugar, but these can be overcome:

•The 'burning' sensation[5] frequently experienced when honey or sugar is applied to the wound bed may be relieved by first applying a thin film of lignocaine gel[6]

•Adding a material such as sterculia,[7] povidone or hypromellose will stop honey from seeping out of cavity wounds. Such materials give honey visco-elastic properties. The addition of one of these adhesive hydropolymers to honey or sugar paste also appears to prevent hypergranulation and scarring.[8] This article explains how this may occur.

Healing environment

Before the wound-healing process can begin, the wound bed must have similar properties to those in the extracellular matrix.[9,10] Whalen and Zetter[11] stated that 'angiogenesis is dependent on the deposition of the vascular extracellular matrix and that modulation of this matrix can be used to regulate the angiogenic process'. Hollander et al.[12] emphasised this when they stated that 'the association of hyaluronic acid with collagen and fibrin creates an environment that encourages cell migration and proliferation'. This allows angio-genic factors released from platelets[13-15] to exert their effects.

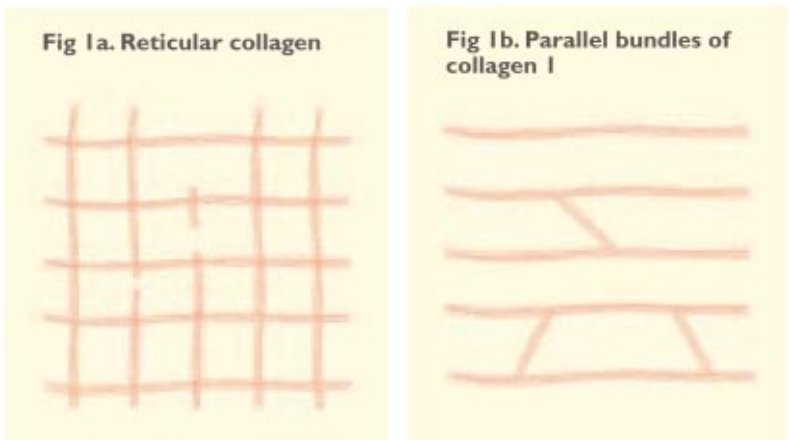
It is generally recognised that excessive amounts of collagen are present in scar tissue.[16,17] However, foetal wounds heal without scar formation.[18] It should follow that the wound bed in the adult would need to have similar physical conditions to the wound bed of the foetus for healing to occur without scarring.

Whitby and Ferguson[19] found that the dermal matrix of healed wounds in foetal rabbits contained a reticular (net-like) collagenous pattern, whereas in postnatal wounds there were large parallel (rope-like) bundles of collagen, some orientated perpendicular to the wound surface (Fig 1). They concluded that scarless foetal wound healing reflected the organisation of collagen rather than the lack of collagen in the wound matrix.

Mast et al.,[18] however, found that the extracellular matrix of foetal wounds is rich in hyaluronic acid and lacks excessive collagen. Weigel et al.[20] stated that this rich matrix reacts with fibrin to form an initial scaffold through which cells involved in wound healing may migrate into the wound site. As a result, foetal wounds have unique features of tissue repair: rapid healing, no scarring, no acute inflammation and minimal fibroblast proliferation.

Hyaluronic acid (hyaluronan)

Hyaluronic acid is classified as a glycosaminoglycan (GAG) with a molecular weight of 2-8 million Daltons.[21] It can absorb up to 3000 times its weight of water[22] by hydrogen bonding. This accounts for its visco-elastic properties, which give it 'a protective, shock-absorbing and structure-stabilising role in connective tissue'.[23]



Hyaluronic acid consists of disaccharide chains made from modifications of the monosaccharide glucose called glucuronic acid and N-acetyl glucosamine.[12,18,24]

Up to 40% glucose is found in honey and 50% occurs in sucrose (sugar). It could be argued, therefore, that the glucose in honey or derived from sugar could be converted into hyaluronic acid at the wound surface.

One possible way in which this may occur is given by Stryer[25] who showed that hyaluronic acid was formed from repeating disaccharide units.

A more probable explanation is that thickened honey, or sugar paste with suitable visco-elastic properties, could form an extracellular matrix that promotes wound healing.

Formation of an extracellular matrix that inhibits scarring

It would appear that, in order to create an environment that encourages scar-free wound healing, the extracellular wound matrix should contain either hyaluronic acid or a substance that physically resembles it. This would have a high molecular weight and combine with water by hydrogen bonding.

Substances such as the cellulose-derived hydrogels (for example, carmellose sodium and hypromellose) and polyvinylpyrrolidones (such as povidone)[26] would seem ideal substitutes. However, these do not have an antimicrobial effect that keeps the wound sterile. Both honey and sugar can be added to the hydrogels to maintain sterility at the wound surface, provided their water activities (vapour pressure of material: vapour pressure of water) are below 0.86[26,27] Both honey and sugar are compatible with the wound matrix[1,8] and add to the viscosity of the visco-elastic gels to produce an environment that may be physically similar to that of the foetal wound described by Weigel et al.[20]

Assuming Mast et al.[18] were referring to the initial stages of foetal wound healing when claiming that the extracellular matrix lacks excessive collagen, it follows that Whitby and Ferguson's[19] assertion that the matrices of rabbit foetal wounds contain a reticular pattern of collagen is correct. This is because it may be assumed that collagen is not produced in the initial stages of foetal wound healing -- when Mast et al. appear to have undertaken their research. However, collagen is created in a reticular (net) pattern soon after this. This pattern may be similar to the mesh-like scaffold of collagen IV. In contrast, collagen I occurs only as parallel filaments.[28]

The filaments (chains) of collagen I form a triple helix which are joined by hydrogen bonding between amino (NH) hydrogens of glycyl (-$NHCH_2CO$-) residues in one chain with a carbonyl (CO) oxygen in an adjacent chain.

These structures are further strengthened by the presence of water molecules forming hydrogen bonds between hydroxyproline ($NHCH_2CHOH$ $CH_2CHCOOH$) in one chain and glutamic acid ($COOHCHNH_2CH_2CH_2COOH$) in a neighbouring chain.[29] The hydroxyprolines are critical for triple helix formation and thermal stability of collagen.[40]

Theoretically, if one or more of these hydrogen bonds is linked to a carbonyl oxygen of a glucose or sugar molecule, the typical triple-stranded helical rod structure of collagen type I will not be produced because the saccharide will act as a side chain, to which more saccharides can be added. However, if a sufficient number of these side chains are formed a reticular pattern should occur, in a similar way to the formation of collagen type IV.[28] Therefore, as collagen I forms, side chains of saccharides can be added to produce a reticular pattern.

This theory is supported by the Cortesi et al.[31] who found that, when various mono and di-saccharides were added to gelatin (obtained from the hydrolysis of collagen),[25,32] a cross-linked gelatin network was produced which reduced the rate of gelatin dissolution. Lopez-Diez and Bone[33] have provided further evidence of this interaction. The clearest description of this process is given by Stryer[25] in an illustrated account which shows how saccharides may be incorporated into newly forming collagen at hydroxylysine ($NH_2CH_2CHOHCH_2$ CH_2CHNH_2COOH) and hydroxyproline sections.

Discussion

Thomas[34] stated that 'vitamin C is an essential co-factor for the hydroxylation of proline and lysine prior to their incorporation into collagen and depletion can lead to decreased wound strength' and that it could be argued that patients should be given vitamin C prophylactically. If we accept the hypothesis that saccharides enter the collagen chains at hydroxyproline and hydroxylysine sections to form mesh or net structures, which aid non-scar wound healing, it can be argued that vitamin C is important for the prevention of scars when sugar or honey are applied to wounds.

Middleton and Seal[35] incorporated polyethylene glycol 400 (PEG 400) into sugar pastes to improve their flow properties. Concerns were initially raised about the toxicity of PEG 400,[36] but its widespread use has shown them to be unfounded.[37] However, these pastes did not contain any adhesive hydrogel, with the result that, at the end of granulation, an alginate, hydrocolloid or hydrogel dressing was applied to complete epithelialisation.[38]

Topham[8] found that hypergranulation occurred when some cavity wounds were treated with a sugar paste that did not contain an adhesive hydrogel, but not on wounds treated with a sugar paste containing povidone. These wounds were also scar-free.

Conclusion

There are three ways in which thickened honey and visco-elastic sugar paste may help to reduce scarring:

•Saccharides at the wound surface encourage the production of hyaluronic acid from glucose, simultaneously suppressing the formation of fibre-forming collagens

•The sugar preparations at the wound bed create an environment that enables wound-healing proteoglycans to exert their effects without producing excessive quantities of collagens

•The sugars combine with the polypeptide chains of nascent collagen by covalent or hydrogen bonding at hydroxylysine or hydroxyproline groups. The saccharide attachments to the nascent collagen may result in branching of the triple-stranded helical structure of collagens. This will produce the mesh-like scaffold structure of collagen type IV.

Alternatively scar-free healing may be accomplished by a combination of these methods. Further research will hopefully shed more light on.

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Box 1. Summary of the main findings

There are bundles of collagen strands in scar tissue

Foetal wounds heal without scar formation. Animal studies have shown that the extracellular matrix of foetal wounds is rich in hyaluronic acid and lacks excessive collagen

Collagens that occur in foetal wounds have flexible mesh or net structures. It has been suggested that the presence of sugar or honey may assist the formation of similar structures

Hyaluronic acid consists of disaccharide chains made from modifications of monosaccharide glucose called glucuronic acid and N-acetyl glucosamine. Glucose in honey or derived from sugar may be converted into hyaluronic acid at the wound surface. One possible explanation is that the honey or sugar forms an extracellular matrix that promotes wound healing

Another explanation for the absence of scarring is that, when mixed with cellulose-derived hydrogels (such as carmellose sodium) or polyvinylpyrrolidones (such as povidone), sugar or honey may act as substitutes for hyaluronic acid

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