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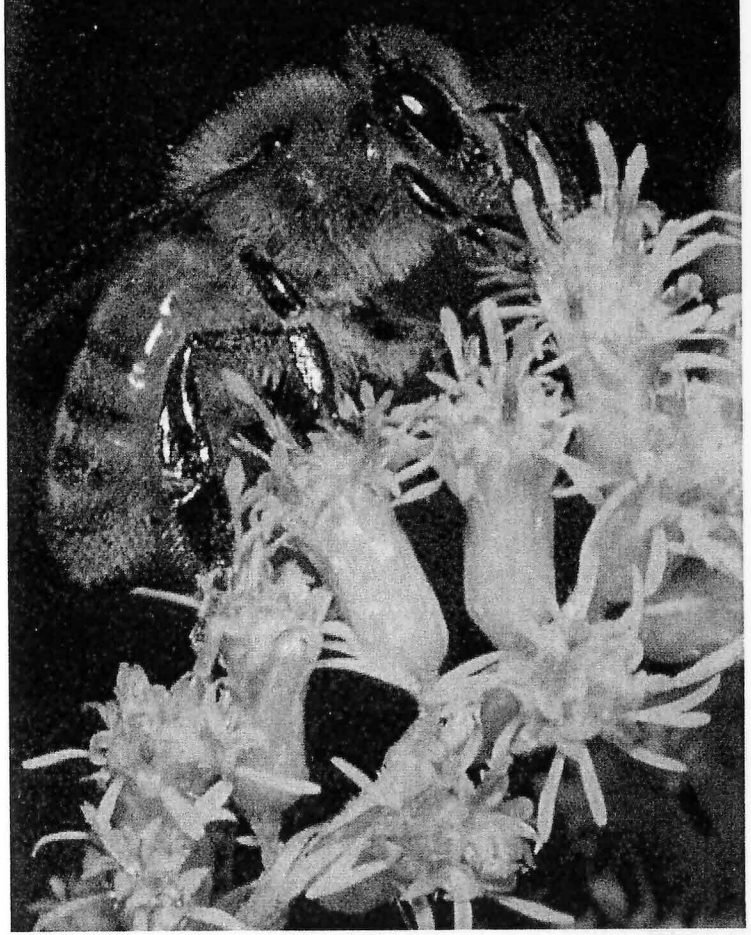
WHY HONEY IS EFFECTIVE AS A MEDICINE

by

Peter Molan



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Why honey is effective as a medicine. I. Its use in modern medicine

PETER C MOLAN

Honey has been used as a medicine for thousands of years and its curative properties are well documented. However, modern medicine turned its back on honey and it is only now, with the advent of multi-resistant bacteria, that the antibiotic properties of honey are being rediscovered.

Introduction

The usage of honey as a medicine is referred to in the most ancient written records[1]. Honey was prescribed by the physicians of many ancient races of people for a wide variety of ailments. Its ancient use as a wound dressing has been described by Beck & Smedley[2], Majno[3] and by Forrest[4]. The ancient Egyptians, Assyrians, Chinese, Greeks and Romans all used honey, in combination with other herbs and on its own, to treat wounds and diseases of the gut[5]. The Muslim prophet Mohammed recommended the use of honey for the treatment of diarrhoea[6]. Aristotle (350 BC) wrote of honey being a salve for wounds and sore eyes[7]. In ancient times honey from Attica had a special reputation as a curative substance for eye disorders[2]. Dioscorides (c. 50 AD) wrote of honey being 'good for sunburn and spots on the face' and 'for all rotten and hollow ulcers'. He also wrote that 'honey heals inflammation of the throat and tonsils, and cures coughs' and 'mollifies the prepuce so that it can be pulled back over the bared glans penis'.

Honey has continued as a medicine into present day folk-medicine. In India lotus honey is said to be a panacea for eye diseases[8]. The use of honey for coughs and sore throats has also continued into the traditional medicine of modern times[2]. Other examples of current day usage of honey in folk-medicine are: as a traditional therapy for infected leg ulcers in Ghana[9]; for earache in Nigeria[10]; in Mali for the topical treatment of measles, and in the eyes in measles to prevent corneal scarring[11]. Honey also has a traditional folklore usage for the treatment of gastric ulcers[12].

There has been a renaissance in the use of honey as a medicine in more recent times. In outlining the resurgence of its usage in modern professional medicine, Zumla & Lulat in 1989[5] referred to honey as 'a remedy rediscovered', and expressed the opinion, 'the therapeutic potential of uncontaminated, pure honey is grossly underutilized. It is widely available in most communities and although the mechanism of action of several of its properties remains obscure and needs further investigation, the time has now come for conventional medicine to lift the blinds off this 'traditional remedy' and

Note: this article reports information, but does not constitute medical advice on the usage of honey

give it its due recognition.' Possibly the increasing interest in the use of alternative therapies is the result of the development of antibiotic resistance in bacteria becoming a major problem[13]; or because people are experiencing the sometimes severe side-effects of many pharmaceuticals[14]which in the currently prevailing ambience of 'chemophobia' may be sufficient to give rise to an aversion to all synthetic drugs[15].

There is a tendency for some practitioners to dismiss out of hand any suggestion that treatment with honey is worthy of consideration as a remedy in modern medicine. An editorial in *Archives of Internal Medicine* assigned honey to the category of 'worthless but harmless substances'[16]. Other medical professionals have clearly shown that they are unaware of the research that has demonstrated the rational explanations for the therapeutic effects of honey[17,18]. Many are not even aware that honey has an antibacterial activity beyond the osmotic effect of its sugar content[18–25], yet there have been numerous microbiological studies that have shown that in many honeys there are other components present with a much more potent antibacterial effect[26].

The ancient physicians who prescribed honey for various ailments would have had no knowledge of the principles involved in its medicinal action, just an empirical knowledge gained from its effective usage. But modern physicians generally require there to be a rational explanation for its medicinal action before a traditional, or 'complementary', medicine is given any consideration. Much has been written on the subject outside the professional medical and scientific literature, but many people, especially medical professionals, treat such reports with scepticism, especially since much of the popular literature claims honey to be almost a panacea. The more convincing professional reports are scattered through a very wide range of journals, and some of the explanations for the medicinal effects of honey are to be found in articles unrelated to honey. Hence this review was undertaken to bring together the evidence that supports the use of honey as a medicine.

The first part of this review will cover the therapeutic effects that have been observed when honey is used as a medicine, and the data from observations, experiments and clinical trials that constitutes the evidence honey is an effective medicine. The second part (the science underlying its effects) will explain the various therapeutic effects of honey.

Treatment of wounds

The medical literature on treating wounds with honey has been reviewed recently in specialist wound-care journals, with a focus on the medical evidence[27] and with a focus on the clinical aspects[28]. Here the focus is on the therapeutic effects observed when honey is used as a wound dressing, which will have their mechanism explained later. In the numerous reports in the medical literature on the use of honey as a wound dressing the types of wounds on which honey has been successfully used are very varied (see box).

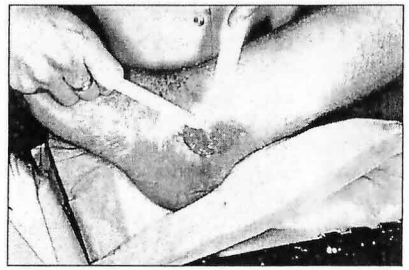
Of particular note are the successful uses of honey to treat Fournier's gangrene[36,64,65], a rapidly spreading infection that is usually managed by aggressive surgical removal of infected tissue, and wounds from surgery for cancer of the vulva[54,56–58], which are difficult to treat because they are in a position where it is difficult to prevent infection occurring. But the therapeutic effects of the honey that have been observed are common to all of these different types of wounds.

Rapid healing

In several reports the rapidity of healing seen with honey dressings is noted. One report[66] refers to wounds becoming closed in a spectacular fashion in 90% of cases, sometimes in a few days. Another[40] refers to healing being surprisingly rapid, especially for first and second degree burns. Hejase[65] has also noted the rapid healing changes when honey is applied to Fournier's gangrene. Blomfield[29] is of the opinion that honey promotes healing of ulcers and burns better than any other local application used before. Clinical observations made are that open wounds heal faster[34,56] and are ready faster for closure by stitching[34] when dressed with honey (than when dressed conventionally). It has been noted that dressing wounds with honey makes the wound bed suitable early for skin-grafting[41], and gives prompt 'taking' of the skin grafts[33,35].

Type of wounds treated succesfully with honey

- abrasions[29,30]
- amputations[30–32]
- abscesses[33–35]
- bed sores (pressure sores, decubitus ulcers)[24,29,31,34,36–38]
- burns[29,30,33,36,39–48]
- burst abdominal wounds following caesarean delivery[49]
- cancrum[36]
- cervical ulcers[23]
- chilblains[50]
- cracked nipples[23]
- cuts[29]
- diabetic foot ulcers[25,33,34] and other diabetic ulcers[33,36,51]
- a fistula[32]
- foot ulcers in lepers[25]
- infected wounds arising from trauma[20,34,36,41,51]
- large septic wounds[52]
- leg ulcers[50,51,53]
- malignant ulcers[36]
- sickle cell ulcers[36]
- skin ulcers[25,29,36,50]
- surgical wounds[32–34,41,54–62]
- tropical ulcers[36]
- wounds to the abdominal wall and perineum[54]
- varicose ulcers[34,51,57,63]



Liquid honey being spread on a skin ulcer.

These clinical observations are in line with the findings from comparative clinical trials and studies on wounds on experimental animals. In one case a patient with multiple ulcers on both legs had one leg dressed with honey and the other treated conventionally (with fibrinolysin and calcium alginate dressing): the ulcers on the leg treated with honey healed much more rapidly[53]. In another case a patient with a long abdominal wound that had become infected following surgery had one end of the wound dressed with honey and the other end dressed with Debrisan (a modern hydrocolloid wound dressing material): it took 16 days with the Debrisan to reach the stage of regrowth of skin over the healing wound achieved after 8 days with the honey. For treatment of burst abdominal wounds following caesarean delivery, the period of hospitalization required was 2–7 days (mean 4.5) for a group of 15 patients whose wounds were dressed with honey and closed with adhesive tape, compared with 9–18 days (mean 11.5) for the comparative group (19 patients) whose wounds were cleaned with antiseptic and restitched[49].

Stronger evidence is provided from the statistically significant results from randomized controlled clinical trials. A trial comparing honey-impregnated gauze with a commonly used polyurethane film dressing (OpSite) as a cover for partial thickness burns in two groups of 46 patients found faster healing with the honey (means 10.8 *vs.* 15.3 days)[44]. Similarly, another trial comparing honey-impregnated gauze with amniotic membrane (a well-established material used as a temporary 'skin') as a cover for partial thickness burns in groups of 40 and 24 patients, respectively, found the burns treated with honey healed faster (means 9.4 *vs.* 17.5 days)[45]. A trial comparing honey with boiled potato-peel dressings (another established material used as a temporary 'skin') as a cover for partial thickness burns in two groups of 50 patients found faster healing with the honey (means 10.4 *vs.* 16.2 days)[46]. A trial comparing honey with silver sulfadiazine, the most commonly used burn dressing, as a cover for partial thickness burns in two groups of 52 patients also found faster healing with the honey: 87% of those treated with honey healed within 15 days compared with 10% of those treated with silver sulfadiazine[43]. A similar trial with two groups of 25 patients found that satisfactory regrowth of skin over the burn had occurred in 84% of those treated with honey by one week, 100% by three weeks, whereas with silver sulfadiazine it had occurred in only 72% of those treated with silver sulfadiazine by one week and 84% by three weeks[47]. A trial comparing honey with saline dressings in the treatment of pressure ulcers (bed sores) in two groups of 20 patients found faster healing with the honey (means 8.2 *vs.* 9.9 days)[38].

Controlled trials have also been carried out on the treatment of wounds on animals, with microscopic examination of the wound tissues confirming the directly observed faster rates of healing with honey. In a trial comparing honey with silver sulfadiazine on deep burns on the skin of pigs, complete regrowth of skin over the burns was achieved within 21 days with honey, whereas it took 28–35 days with silver sulfadiazine[67]. A sugar solution was also compared in this trial: this gave the same rate of healing as the honey, but microscopic examination of the tissues showed a better quality of healing with the honey, and cellular evidence of a more advanced state of healing. In a study comparing honey with sugar solution on superficial burns on the skin of rats, healing was seen by microscopic examination of the tissues to be more active and advanced with honey than with the sugar solution[40]. The time taken for complete repair of the wound was significantly less with honey than with no treatment. A study on full-thickness skin wounds on buffalo calves found that honey gave a faster rate of healing than did the antibacterial nitrofurazone and the petroleum jelly control[68]. A study on full-thickness skin wounds on rabbits found that honey gave a faster rate of healing than the untreated control wounds[69].

Other studies on animals have compared honey with saline, a standard moist dressing for wounds. In a study on infected full-thickness skin wounds on buffalo calves, honey gave the fastest rate of healing compared with ampicillin ointment and saline[70]. A study on deep skin wounds on mice found that the regrowth of tissue was significantly greater, and the area of the wound significantly smaller, in those treated with honey compared with those treated with saline[56]. Another study, on rats, found a statistically significant increase in the rate of healing with floral honey compared with saline, but not with honey from sugar-fed bees[71,72].

Stimulation of the healing process

Some wounds, termed chronic wounds, may go for long periods, sometimes for

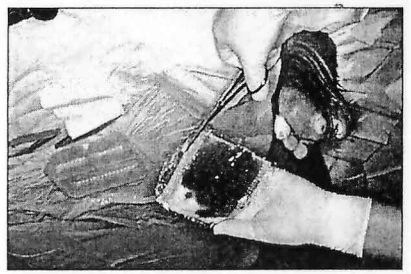
years, without the healing process taking place. Leg ulcers and diabetic ulcers are common examples of this type of wound. Honey has been found to be effective in starting the healing process in non-healing ulcers[24,31,35,36,41,51,63], some of which had been present for a median time of one year[51], or had been treated for up to two years[36], or had shown no healing over more than five years despite usual measures including skin grafts[53]. Honey has also been used successfully on chronic foot ulcers in lepers and diabetic foot ulcers[25].

Honey has a very low failure rate: in reports of at least 143 chronic wounds treated with honey[24,25,31,33,34,36,38,51,53,57,62] there was only one failure in one report (a Buruli ulcer: treatment with honey was discontinued after 2 weeks because the ulcer was rapidly increasing in size)[36] and six in another (where the quantity of honey applied was very small)[51]. Over all of the other reports covered in a review of the literature[27], with more than 470 cases treated with honey, there were only five cases where successful healing was not achieved: in one report two were attributed to the poor general quality of the patients who were suffering from immunodepression, one was withdrawn from treatment with honey because of a painful reaction to the honey, and one burn remained stationary after a good initial response[41]; in another it was an ulcer complicated by the presence of varicose veins[50].

Clearance of infection

Many of the authors reporting the use of honey as a dressing on infected wounds attribute its effectiveness at least partly to its antibacterial properties[5,9,19,33,36,39,41,43–47,49,53,55–58,62,64,67,70,73]. Honey is reported to be very effective in cleaning up infected wounds[20,33,35,41,54,57,58,60]. Its action is effective even in treating Fournier's gangrene, a form of necrotizing fasciitis which is a rapidly spreading erupting infection that is usually treated by aggressive surgical removal of tissue that has died as a result of the infection, which otherwise would support the growth of bacteria. Honey stops the advance of the infection without the need to remove dead tissue[64,65].

Honey is effective in clearing infection in wounds where other treatments have failed. One report gave the results of treating with honey dressings 47 patients with wounds and ulcers which had been treated for one month to two years with conventional therapy (including antibiotics) with no signs of healing, or the wounds were increasing in size[36]. The wounds were of a wide variety of causes. Microbiological examination of swabs from the wounds showed that the wounds with bacteria present became sterile within one week and the others remained sterile. The outcomes were reported as 'showed remarkable improvement following topical application of honey'. A similar report gave the results of treatment with honey dressings of 40 patients, half of which had been treated with 'the usual topical measures' (another antiseptic) which had failed[41]. The wounds were large and of a wide variety of causes. The number of species of bacteria isolated from the wounds dropped from 48 to 14 after two weeks of treatment. Of the 33 patients treated only with honey dressings, 29 were healed successfully, with good quality healing, in an average time of 5–6 weeks.



A honey-impregnated dressing pad being prepared for application to a diabetic foot ulcer.

Another report described honey being used on nine infants with large, open, infected surgical wounds that failed to heal with conventional treatment of at least 14 days of intravenous antibiotic and cleaning the wound with antiseptic[60]. Before treatment with honey the wounds were still open, oozing pus, and bacteria were present. A marked improvement was seen in the appearance of the wounds in all of the infants after five days of treatment with honey. The wounds were closed, clean and sterile in all infants after 21 days of application of honey.

The speed with which wounds dressed with honey become clear of infection is remarkable. Wounds have been reported to become sterile in 3–6 days[52,58], 7 days[36,49,64] or 7–10 days[55]. But, possibly because of differences between honeys in their antibacterial activity, there have been findings of slower clearance of infection: there have been reports of bacteria still present in wounds after 2 weeks[41,53], 3 weeks[47,60,62], and 5 weeks[35].

Dressing infected wounds with honey gives a clean clear base that allows early grafting[41], and gives prompt graft taking[33,35]. By cleaning up the wounds it also allows the wound boundaries to be more clearly defined to facilitate surgical procedures[36,41].This is of particular advantage in the case of diabetic and malignant ulcers where surgery is often required[36].

Perhaps the most important role for honey in wound care will prove to be in the treatment of wounds infected with antibiotic-resistant bacteria. Honey has been shown to be effective in laboratory testing against MRSA (multi-resistant *Staphylococcus aureus*)[74], and has been found to be effective in clearing up wounds infected with multi-resistant bacteria[35].

Cleansing action on wounds

Several authors have reported the cleansing effect of honey on wounds[29,33,35,41,57,59,62]. The standard procedure for the treatment of wounds is to surgically remove any dead tissue (i.e. debride the wound) which would serve to support the growth of infecting bacteria. Otherwise these would produce toxins which would kill more surrounding tissue. Debridement is a painful procedure that usually requires anaesthesia of some sort. Honey has a debriding effect on wounds so that surgical debridement is unnecessary[36,43,44,46,64,65] or a minimum of surgical debridement is required[58]. Dead tissue separates easily from the wound bed after honey has been applied to a wound[31,36,57]. The dry crust formed on the surface of a wound is also removed by the application of honey[31], and no dry scab forms on burns dressed with honey[47]. It has also been noted that dirt is removed with the bandage when honey is used as a dressing, leaving a clean wound[30].

Infected wounds can be malodorous, especially those infected with anaerobic bacteria. This can be distressing for those who have to treat the wounds, and even more so for the patient, who cannot move away from the smell and who may find it embarrassing. Honey has been reported to give rapid deodorization of offensively smelling wounds[36,43,44,49,54,64,65].

Stimulation of tissue regeneration

When a wound heals, the dead or damaged tissue is replaced by the growth of new connective tissue and a new outer layer of skin (epithelium) spreads over the surface of the wound. The new connective tissue grows in a granular fashion (around newly formed blood vessels), hence is termed granulation. Many have reported that honey promotes the formation of clean healthy granulation

tissue[31,33,35,36,47,50,52,55,58,59,62,64] and growth of epithelium over the wound[36,45,47,50,64,65]. Thus it helps skin regenerate, making plastic surgery unnecessary[47,54,58,64,65]. It has also been reported that dressing wounds with honey gives little or no scarring[64].

These clinical observations of stimulation of tissue growth have been corroborated by microscopic examination of wound tissues in studies of the effect of honey on wound healing in animals, where there has been clear evidence seen of stimulation of tissue growth[40,56,67–70]. These studies have also shown a stimulation of the synthesis of collagen, the protein responsible for giving the strength to skin and to scar tissue[68,75]. The formation of other connective tissue components is also stimulated[76], and there is improvement of the strength of collagen[75] and of the healed wounds[69]. The stimulation of the development of new blood vessels in the bed of wounds has also been observed[68,70].

Reduction of inflammation

The inflammation of surrounding tissues that results from infection of a wound, or directly from the damage to tissues caused by burns, is the major cause of the pain and discomfort associated with wounds. The process of inflammation involves blood capillaries opening up and allowing plasma from the blood to flow out into the surrounding tissues. This causes swelling of the tissues (oedema), the pressure giving rise to damage and discomfort in the healing area. It also causes plasma to exude from open wounds, sometimes in large quantities. Honey has been reported to reduce inflammation[40,47,50], oedema[36,46,62,64,65] and exudation[36,40,64,65]. This would account for the soothing effect observed when honey is applied to wounds[21,30,40,44] and the reduction of pain from burns[40,44]. In some cases there is a rapid diminution of local pain[50].

The anti-inflammatory effect of honey has also been observed by microscopic examination of wound tissues in studies of the effect of honey on wound healing in animals, where reduction in the number of white blood cells involved in inflammation could be seen[40,67–72]. The reduction in inflammation seen when honey is applied to wounds must be a direct anti-inflammatory effect, not just a result of removing inflammation-causing bacteria: the anti-inflammatory effects of honey were seen in animal studies where there was no infection involved[40,67–70].

Comfort of honey dressings

Honey generally causes no pain on dressing[54,57] or causes only momentary stinging[30,41,57], is non-irritating[46,57–59], and does not cause allergic reaction[33,36,41,45,49]. In several of the reports of honey being used on wounds the authors have observed that honey has no harmful effects on tissues[33,36,46,49,57]. Over all the reports of honey being used on wounds, with a total of more than 600 cases, there have been no reports of any harmful effects of honey on tissues. Nor have any adverse effects been noted in any of the studies in which honey has been applied to wounds on animals[56,67,70,71,75,76]. These studies have included microscopic examination of the wound tissues[56,67,70,72]. However, there have been two cases where the pain persisted for 15 minutes[51] and in two cases where the pain was such that the application of honey could not be tolerated[41,51].

The pain or discomfort usually associated with changing dressings is minimized when honey dressings are used, which are easy to apply and remove[29,33,35]. There is no difficulty removing dressings[44] because there is no adhesion to cause damage to the exposed regrowing tissues on the surface of wounds[38,47,54,57]. Also there is no bleeding when removing dressings[44]. Any honey left on the surface of the wound is easily

Honey dressings do not adhere to wounds, so can be removed without pain or damage to the tissues.

removed by simple bathing[20], unlike with many other dressing materials which have to be wiped off or forcefully washed off.

Gastroenteritis

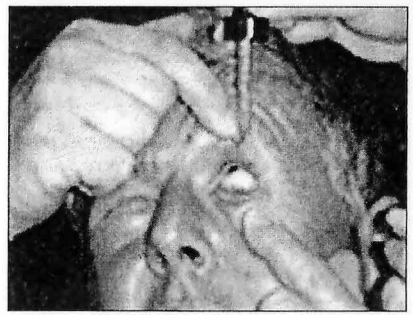
The Holy Hadith records the Muslim prophet Mohammed instructing a man afflicted with diarrhoea to take honey[6]. The Roman physician Celsus, (*c.* 25 AD) used honey as a cure for diarrhoea[77]. Dosage with water and honey is also used by many veterinarians for treatment of diarrhoea in small animals[78], and dosage with an 8% (vol./vol.) solution of honey has been reported to be effective for the treatment of chronic diarrhoea in a horse[78]. Honey has been used at a concentration of 5% (vol./vol.) in place of glucose in a rehydration fluid (solution of electrolytes) in a clinical trial conducted on 169 infants and children admitted into hospital with gastroenteritis[79]. The patients were randomly assigned into two groups, the control group being treated with the standard rehydration therapy (2% wt/vol. glucose in a solution of electrolytes). Testing showed that in each group there were 18 patients with bacterial diarrhoea. The treatment with honey gave a statistically significant reduction in the duration of the diarrhoea (58 h *cf.* 93 h), and gave no increase in the duration of non-bacterial diarrhoea.

Peptic ulcers and gastritis

Honey has a traditional folklore usage for the treatment of peptic ulcers[12]. Also there are numerous reports of oral dosage of honey being successfully used in modern times to treat upper gastrointestinal dyspepsia, including gastritis, duodenitis and ulceration, particularly in Russia and Arabic countries[80–86].

A clinical trial has been reported[84] in which 45 patients with dyspepsia were given no medication other than 30 ml of honey before meals three times daily. After treatment with honey the number of patients passing blood (from peptic ulcers) in their faeces had decreased from 37 to four; the number of patients with dyspepsia had decreased from 41 to eight; the number of patients with gastritis or duodenitis seen on endoscopy had decreased from 24 to 15; the number of patients with a duodenal ulcer seen on endoscopy had decreased from seven to two. The healing effect of honey on gastric ulcers has also been shown in a trial carried out on rats with ulcers caused by aspirin[12]. After 3 days of treatment the control group of 10 rats (given saline) had 15 ulcers whereas the group of 10 rats given honey from sugar-fed bees had eight ulcers, and the group of 10 rats given floral honey had three ulcers: the differences between these numbers were statistically significant. In a similar study[87] the gastric ulcers in the rats were caused by indomethacin, another non-steroidal anti-inflammatory drug (NSAID), which is like aspirin in its action. The healing rate achieved with the honey in this study was 70%, measured as the number of ulcers in the honey-treated group compared with an untreated control group.

Other studies with rats have shown that honey also has a preventative action, protecting the stomach from ulceration by



Honey being used as eye drops for conjunctivitis.

substances which commonly cause peptic ulcers in people: an NSAID (indomethacin)[88], and alcohol[88–91].

Ophthalmology

In ancient times honey from Attica had a special reputation as a curative substance for eye disorders[2]. Aristotle wrote in 350 BC in section 627a 3 of *Historia Animalium*[7] that 'White honey.... is good as a salve for sore eyes'. In India lotus honey in more recent times (1945) was said to be a panacea for eye diseases[8]. Honey is also a traditional therapy in Mali for measles, it being put in the eyes to prevent scarring of the cornea which occurs in this infection[11].

Meier has referred to honey being used to treat eyes discharging pus[92]. Sarma, an ophthalmic surgeon at Rangaraya Medical College, India, has been treating bacterial corneal ulcers with honey[93]. The use of honey to treat blepharitis (inflammation of the eye-lids), catarrhal conjunctivitis, and keratitis (inflammation of the cornea) has also been reported[94]: good results in general were obtained, with remission in more than 60% of the cases. Another report has described the use of honey in place of petroleum jelly in a 3% sulfidine eye ointment for the treatment of three cases of keratitis[95]: significant improvement in one case and complete restoration of vision in the other two cases resulted from the treatment with honey, yet there had been no effect when treated with the 3% sulfidine in petroleum jelly. This same paper reported the successful treatment with the honey ointment of 28 patients with various ailments of the cornea, successful in all cases; also the effective treatment with honey of syphilitic keratitis, corneal ulcers, injuries to the cornea, and lime burns of the cornea. It also described a case where a lime burn of the cornea was treated with pure honey, with half-vision being restored in 12 days; and reported that several cases of scrofulous keratitis had responded to treatment with pure honey. Mozherenkov & Prokof'eva have reviewed the use of honey in ophthalmology in Russia[96]. Anti-inflammatory, antibacterial and antifungal actions are seen, the honey being applied to the eye under the lower eyelid. It has been used for chemical and thermal burns to the eye, conjunctivitis, and infections of the cornea, being applied undiluted or as a 20–50% solution in water.

The results have been reported of treating 102 patients with a variety of ophthalmological disorders not responding to conventional treatment, such as keratitis, conjunctivitis and blepharitis[97]. The honey was applied under the lower eyelid as an eye ointment would be applied. Improvement was seen in 85% of the cases, with no deterioration seen in any of the other 15%. There was reported a transient stinging sensation and redness of the eye soon after putting honey in the eye, but never enough to stop the treatment in the 102 cases in the trial. A similar reaction was reported by one of the other authors describing the use of honey in ophthalmology[95].

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Why honey is effective as a medicine

2. The scientific explanation of its effects

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The effectiveness of honey as a therapeutic agent has been unequivocally demonstrated in the literature reviewed in Part 1 of this article published in 1999, but the biochemical explanation of these effects is more hypothetical. However, a rational explanation can be seen when one looks at the scientific literature outside that on honey. Some of the components of honey are substances known to have physiological actions that would explain many of its therapeutic effects. In addition, research on honey has shown directly that it has physiological actions that would give therapeutic effects.

Therapeutic properties of honey

Antibacterial activity

The large volume of published literature from laboratory studies that has established that honey has significant antibacterial activity has been comprehensively reviewed[92,93]. Since then there have been many other studies reported[5,14,15,24,37,38,40,51,53,55,67,104,110,122,144,145]. But much of the published work establishing the sensitivity of bacteria to honey has unfortunately not taken into account the marked variation in potency of different honeys. However, some studies have used honeys with median levels of activity so that the sensitivity of various species of bacteria to typical honeys could be determined. In one of these studies[150] the non-peroxide antibacterial activity of a typical manuka (*Leptospermum scoparium*) honey was tested against seven major wound-infecting species of bacteria in comparison with a typical honey with activity due to hydrogen peroxide. The MIC (minimum inhibitory concentration) of honey was found to range from 1.8% to 10.8% (v/v), i.e. the honey had sufficient antibacterial potency to still be able to stop bacterial growth if diluted at least nine times, and up to 56 times for *Staphylococcus aureus*, the most common wound pathogen. In another study of the same honeys against 20 isolates of *Pseudomonas* from infected wounds[37], the mean MIC was found to be 6.9% (v/v) (range 5.5% to 8.7%) for the manuka honey and 7.1% (v/v) (range 5.8% to 9.0%) for the other honey. A similar study with a range of clinical isolates of *S. aureus*[38] found the MIC to be between 2% and 3% (v/v) for the manuka honey and 3% and 4% (v/v) for the other honey.

Note: this article reports information, but does not constitute medical advice on the usage of honey

There is also clinical evidence for the antibacterial activity of honey being sufficient to achieve a therapeutic effect. In a clinical trial of honey for the treatment of diarrhoea it was found that administering honey halved the duration of diarrhoea caused by bacterial infection[64]. There are also reports of infected wounds dressed with honey becoming sterile in 3–6 days[25,31], 7 days[49,50,108] or 7–10 days[17], and the advance of infection through tissues halted[50,70]. Also it has been reported that honey provides a protective barrier that prevents wounds from becoming infected[20,49,91,128,129], and thus protects patients in hospital from cross-infection[55]. The clinical significance of the antibacterial activity of honey can be seen in reports of honey being effective on wounds not responding to conventional therapy with antibiotics and antiseptics[47,49,66,74,101,141,143,152] and a wound infected with the antibiotic-resistant MRSA (methicillin-resistant *Staphylococcus aureus*)[48].

The antibacterial activity of honey is very important therapeutically, especially in situations where the body's immune response is insufficient to clear infection. Bacteria often produce protein-digesting enzymes, which can be very destructive to tissues[135] and can destroy the protein growth factors that are produced by the body to stimulate the regeneration of damaged tissues in the healing process[112]. Furthermore, some bacteria produce toxins that kill tissue cells[43]. Additional damage is often caused by bacteria carrying antigens that stimulate a prolonged inflammatory immune response which gives excessive production of free radicals that are very damaging to tissues[61] (as discussed below). Bacteria in wounds can also consume oxygen and thus make the level of oxygen available to the wound tissues drop to a point where tissue growth is impaired[123]. The consequences of bacterial infection, avoided by administering honey to clear infection, are: non-healing of wounds; increase in size of wounds and development of ulcers and abscesses; failure of skin grafts; inflammation, causing swelling and pain.

Because of the large variation in antibacterial activity of honey, not all honey is likely to have the same therapeutic effect. Physicians in past millennia were aware of this, at least from practical experience, and specified particular types of honey be used to treat particular ailments. Dioscorides (*c.* 50 AD) stated that a pale yellow honey from Attica was the best, being 'good for all rotten and hollow ulcers'[62]. Aristotle (384–322 BC), discussing differences in honeys, referred to pale honey being 'good as a salve for sore eyes and wounds'[16]. There is a similar awareness in present-day folk medicine: the strawberry tree (*Arbutus unedo*) honey of Sardinia is valued for its therapeutic properties[57]; in India, lotus (*Nelumbium sceciosum*) honey is said to be a panacea for eye diseases[59]; honey from the Jirdin valley of Yemen is highly valued in Dubai for its therapeutic properties[1]; and manuka honey in New Zealand has a long-standing reputation for its antiseptic properties.

Boosting the immune system

As well as having a direct antibacterial action, honey may clear infection through stimulating the body's immune system to fight infection. It has been reported that honey stimulates B-lymphocytes and T-lymphocytes in cell culture to multiply, and activates neutrophils[2]. It has also been reported[76] that honey stimulates monocytes in cell culture to release the cytokines TNF-α, IL-1 and IL-6, the cell 'messengers' that activate the many facets of the immune response to infection. In addition to its stimulation of these leucocytes, honey provides a supply of glucose which is essential for the 'respiratory burst' in macrophages that produces hydrogen peroxide, the dominant

component of their bacteria-destroying activity[117]. Furthermore it provides substrates for glycolysis, which is the major mechanism for energy production in the macrophages, and thus allows them to function in damaged tissues and exudates where the oxygen supply is often poor[117]. The acidity of honey may also assist in the bacteria-destroying action of macrophages, as an acid pH inside the phagocytotic vacuole is involved in killing ingested bacteria[117].

Anti-inflammatory action

The anti-inflammatory properties of honey have been well established. It has been observed clinically that when honey is applied to wounds it visibly reduces inflammation[30,132,154]. It has also been observed to reduce oedema around wounds[46,49,50,131] and exudation from wounds,[30,49,50,70] both of which result from inflammation. Pain is another feature of inflammation, and honey has been observed to be soothing when applied to wounds[30,81,129,154,155]. A histological study of biopsy samples from wounds has also shown that there are fewer of the leucocytes associated with inflammation present in the wound tissues[132]. What is responsible for these observations is a direct anti-inflammatory effect, not a secondary effect resulting from the antibacterial action removing inflammation-causing bacteria: the anti-inflammatory effects of honey have been demonstrated in histological studies of wounds in animals where there was no infection involved[30,52,63,77,105,113]. A direct demonstration of the anti-inflammatory properties of honey, where honey decreased the stiffness of inflamed wrist joints of guinea pigs, has also been reported[35].

The anti-inflammatory action of honey is potentially very important therapeutically, as the consequences of inflammation can be major. Although inflammation is a vital part of the normal response to infection or injury, when it is excessive or prolonged it can prevent healing or even cause further damage. Some of the 'messengers' produced by the leucocytes involved in inflammation to regulate the activity of surrounding cells are prostaglandins which cause the painful symptoms of inflammation. Others cause blood vessels to dilate and the walls of the capillaries to open up, so plasma flows out to cause swelling in the surrounding tissues. The pressure building up from this restricts the flow of blood through the capillaries[32], thus starving the tissues of the oxygen and nutrients that are vital for the cells to fight infection and multiply to repair damage. The swelling also increases the distance for diffusion from the capillaries to the cells[126]. The opening up of capillaries also causes exudation of serum from wounds and exudation of serum into the gut in gut infections, both of which can lead to malnutrition if they continue for a pronged period. But the most serious consequence of excessive inflammation is the production of reactive oxygen species (free radicals) in the tissues[56]. These arise through a series of reactions that are initiated by the production of superoxide by certain leucocytes that are stimulated to do so as part of the inflammatory process[115]. Free radicals can be extremely damaging as they are very reactive and can break down the lipids, proteins and nucleic acids that are the essential components of the functioning of all cells[36], so their continued production can lead to localized erosion of body tissues. The anti-inflammatory action of honey has been found in a clinical trial to prevent partial-thickness burns from converting to full-thickness burns which would have needed plastic surgery[132], a characteristic of burns, where there is much inflammation.

The free radicals formed in inflammation are also involved in stimulating the activity of the fibroblasts[34], which is the basis of the body's repair process, normally triggered by the inflammation that follows injury. These are the cells which are responsible for producing the connective tissue, including the collagen fibres of scar tissue, and in situations where there is prolonged inflammation their over-stimulation can lead to 'proud flesh' and fibrosis, an excessive production of collagen fibres[100]. The reduction in keloids and scarring that is a feature of the dressing of wounds with honey[50,128,130], and the cosmetically good results obtained[47], are probably due to the antiinflammatory action of honey.

Thus, there are significant benefits to be derived from therapeutic use of anti-inflammatory substances. However, the pharmaceutical ones have serious limitations: corticosteroids suppress tissue growth and suppress the immune response[27], and the non-steroidal anti-inflammatory drugs are harmful to cells, especially in the stomach[26]. But honey has an anti-inflammatory action free from adverse side effects (see below).

Antioxidant activity

Honey has been found to have a significant antioxidant content[60], measured as the capacity of honey to scavenge free radicals. The antioxidant activity of honey has also been demonstrated as inhibition of chemiluminescence in a xanthine-xanthine oxidase-luminol system that works via generation of superoxide radicals[12]. This antioxidant activity may be at least partly what is responsible for the anti-inflammatory action of honey, as oxygen free radicals are involved in various aspects of inflammation, such as further recruitment of leucocytes that initiate further inflammation[44,56]. (The application of antioxidants to burns has been shown to reduce inflammation[136].) But even if the antioxidants in honey do not directly suppress the inflammatory process they can be expected, by scavenging free radicals, to reduce the amount of damage that would otherwise have resulted from these.

As well as scavenging free radicals to neutralize them after they have been formed, honey has the potential to exert an antioxidant action by a completely different mechanism, inhibition of the formation of free radicals in the first place. The superoxide that is first formed in inflammation is relatively unreactive, and is converted to hydrogen peroxide which is much less reactive, but from this is generated the extremely reactive peroxide radical[39]. This formation of the oxidant peroxide radical is catalysed by metal ions such as iron and copper, and sequestering of these metal ions in complexes with organic molecules is an important antioxidant defence system[65]. Flavonoids and other polyphenols, common constituents of honey, will do this[42].

Stimulation of cell growth

It has been observed clinically that when honey is used as a wound dressing it gives rapid healing of wounds[20,21,30]. It has been reported by many clinicians that honey promotes the formation of clean healthy granulation tissue (the clusters of fibroblasts around new capillary beds that is the regenerating connective tissue)[17,25,31,46,49,50,55,74,132,143]. It has also been reported that honey hastens epithelialization of the wound (coverage with a new outer layer of skin)[49,50,70,130,132], making skin grafting unnecessary[31,50,70,91,132]. This growth-stimulating property of honey has been confirmed histologically in many studies of wounds in animals[20,30,63,85,113], as has a stimulation of the synthesis of collagen fibres[134] and other connective tissue components[133], and improvement of the strength of collagen[134]. It has also been observed histologically in studies of wounds in animals that honey stimulates the development of

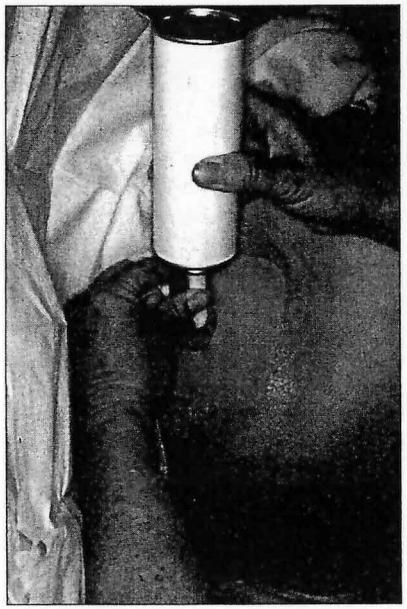

FIG. 1. Honey is harmless to tissues so can safely be used to fill deep abscesses. A prototype pressurized delivery system for doing this is illustrated.

new capillary beds[63,85], which is the rate-limiting factor in the formation of granulation tissue[123]. It is likely that it is the stimulation of cell growth by honey that is responsible for the 'kick-starting' of the healing process observed in chronic wounds which have remained non-healing for long periods[22,49,66,127,152].

Harmlessness of honey

The Hippocratic principle of doing no harm to the patient is particularly relevant to the selection of therapeutic agents, as most have untoward side effects. Antibiotics have numerous adverse side effects, and antiseptics are all toxic to some degree to the cells in body tissues and thus slow the healing process[137]. For example, in comparative trials on burns with silver sulfadiazine ointment, an antibacterial agent that is the standard treatment for burns in developed countries, it was found that significantly slower healing rates were achieved with this ointment than with honey[113,128,132]. (Honey also gave a better control of infection than silver sulfadiazine ointment in these trials[128,132].) Honey has no adverse effects other than a stinging sensation experienced by some people when it is applied to open wounds[28,101,152]. A transient stinging sensation and redness of the eye soon after putting honey in the eye, but never enough to stop the treatment, was reported in the 102 cases in a trial of honey for ophthalmological use[54]. Over the thousands of years honey has been used on open wounds and in the eyes it has not gained any reputation for adverse effects, and this is borne out by histological examination of wound tissues that have been treated with honey[20,52,63,113]. In papers describing the application of honey to open wounds it is reported to be soothing[129], to relieve pain[129], be non-irritating[28,31,131], cause no pain on dressing[91], and give no secondary reactions[101]. Although allergy to antibiotics is fairly common, allergy to honey is rare[82]. It may be a reaction to either the pollen or the bee proteins in honey[18,71]. In reports of clinical studies where honey was applied to open wounds of a total of 134 patients it was stated that there were no allergic or adverse reactions[49,55,108,130,141].

Reference has been made to dehydration of tissues if too much honey is applied to an open wound, but it has been stated that the hydration of the tissues is easily restored by saline packs[23,31]. It has also been pointed out that although a piece of flesh removed from the body would dehydrate if exposed to a highly osmotic sugar solution, when blood is circulating in it this replaces from underneath any fluid withdrawn by osmosis[33].

There is a hypothetical risk of infection of wounds resulting from the application of honey, as honey sometimes contains viable spores of Clostridia[98]. However, in none of the more than 470 cases in the many reports published on the clinical usage of honey on open wounds was the honey that was used sterilized[94], yet there are no reports of any type of infection resulting from the application of honey to wounds. If spores germinated, any vegetative cells of Clostridia, being obligate anaerobes, would be unlikely to survive in the presence of the hydrogen peroxide that is generated in diluted honey. But any concern about risk of infection can be overcome by the use of honey that has been treated by gamma-irradiation, which kills Clostridial spores in honey[97,111] without loss of any of the antibacterial activity[97].

There is also a risk of blood glucose levels in diabetics being raised by honey. There is also a hypothetical risk of blood glucose levels in diabetics being raised by honey, through glucose being absorbed from honey across the bed of large wounds, but in cases where this has been checked there has been no sign of this happening (J Betts, personal communication). Where honey is taken by mouth by diabetics for treatment of gastrointestinal infections the risk is greater, but research has shown that honey gives a lower peak of blood glucose than table sugar does because the absorption from the gut is slower[4,78,120].

Mechanisms of action of honey in therapeutic applications

Action of honey as a wound dressing

The report of G Winter in 1962[151], that wounds heal faster if kept moist than if a scab is allowed to form, was the start of what has become the standard modern approach to wound treatment, the prevention of drying out of a wound. The epithelial cells, which spread across the surface of a healing wound to restore the skin cover, need moist conditions to be able to grow. (When there is a dry scab on the surface of a wound the epithelial cells grow across in the moist area beneath it, and thus leave a pitted scar in the skin.) Also, the fibroblasts, functioning as a rudimentary form of muscle cells, need moist conditions to be able to contract and pull the margins of the wound together. A dressing of honey over a wound provides the moist conditions needed for these processes. The amount of free water in honey is very low, such as would be expected to dry out wound tissues. But the osmotic effect draws fluid out from below the honey dressing, and thus creates a layer of fluid that is a dilute solution of honey in plasma or lymph. A secondary benefit of this fluid layer is that there is no sticking of dressings to the surface of wounds when honey is used[28,91,129,132,147]. As well as giving painless dressing changes, this gives faster healing than with dry dressings because there is not the tearing away of the delicate newly re-grown tissues that adhere to the dressing when dry dressings (or even sometimes the modern moist wound healing dressing materials) are used. Combined with the stimulatory effects on tissue regeneration discussed above, this puts honey in the same category as the latest dressings produced by pharmaceutical technology, a bio-active moist wound dressing material.

One problem with using dressings that create a moist environment is that the moist conditions favour growth of bacteria, and for this reason some of the moister products in use are contra-indicated for use on infected wounds. But honey creates a moist environment in which bacterial growth is prevented by the antibacterial activity of the

honey. Furthermore, the antibacterial components of honey, unlike antibiotics, have a high solubility in water and thus can diffuse into the tissues. Honey has also been reported to give rapid deodorisation of offensively smelling wounds[49,50,70,91,108,128,129], whereas malodour is a common feature of the use of pharmaceutical moist dressings on wounds. It is probably more than just the antibacterial action of honey that is involved in removal of malodour: the high glucose levels that the honey provides would be used by the infecting bacteria in preference to amino acids[103] from the serum and dead cells, and thus would give rise to lactic acid instead of ammonia and the amines and sulphur compounds that are the cause of malodour in wounds.

Another advantage of having a moist wound-healing environment is that it allows the protein-digesting enzymes in the wound tissues to work and loosen any scab or pus and dead tissue. The alternative that often is necessary when this autolytic debridement is insufficient to achieve a clean wound bed is to use surgical debridement, as it is important to remove what would otherwise be a good culture medium for bacterial growth[68,126]. A more expensive option is to apply pharmaceutical enzyme preparations, or in some cases maggots that have been especially bred for this purpose. Honey has a very efficient debriding action, such that it is frequently remarked upon in papers reporting on the use of honey in wound treatment[21,28,31,46,49,50,55,70,74,101,128,129,131,143,146]. It has also been noted that dirt is removed with the bandage when honey is used as a dressing, leaving a clean wound[155]. The outflow of lymph caused by the osmotic effect of honey could be expected to help in this clearing of dirt from wounds.

Another beneficial effect that could be expected from the osmotic outflow of lymph caused by honey is increased nutrification of the tissues in healing wounds. Whether caused by trauma or infection, at the site of tissue repair in wounds there are often insufficient functioning blood vessels to supply the cells with the nutrients that they need to grow and multiply. The importance of this is demonstrated by the observation that wounds heal faster if a nutrient mixture is applied to them[80,102,124,142]. The drawing out of lymph would provide a constant flow of nutrients from the functioning blood vessels deeper down. Honey would in addition supply nutrients directly, not just readily metabolisable sugars but also a wide range of amino acids, vitamins and essential minerals[69,149]. The supply of glucose would be of particular importance to the epithelial cells which have to build up an internal store of carbohydrate to provide the energy they need to be able to migrate across the surface of the wound to restore skin cover[123].

The osmotic outflow of lymph induced by honey could also be expected to increase the oxygen supply to the tissues in healing wounds. Because of destruction of the local circulation there are insufficient functioning blood vessels around a wound to supply the cells with oxygen, thus growth of the cells repairing the wound is restricted[73]. Additional oxygenation of wound tissues is also likely to be induced by the acidity of honey, this being one of the two mechanisms proposed[86] to account for the finding that acidification of wounds increases the rate of healing[79,86]. The other mechanism proposed is the conversion of the toxic form of ammonia, NH_3 (produced in wounds by bacterial decomposition of protein), to the non-toxic ionic form, NH_4^+, that is the predominant form in an acidic environment[86]. As an acidulant for wounds, honey has the advantage of having a gentle action because the acidic component of honey, gluconic acid, exists mostly in the form of a neutral lactone that is in a slowly-converting equilibrium with the free acid form.

Action of honey in treating diarrhoea

The shortening of the duration of diarrhoea by administering honey in a clinical trial was attributed to the antibacterial activity of honey[64], which was in line with the finding that in the patients in this trial who had diarrhoea due to a viral infection there was no shortening of the duration by the honey treatment. (It was of significance that the duration of the viral diarrhoea was not increased by the antibacterial activity of honey, as commonly happens with other antibacterial therapy.) But it has also been suggested that the effectiveness of honey in treating diarrhoea may be due to it effecting repair of the intestinal mucosa (the lining of the intestines) damaged by the infection[88]. This suggested mode of action would be in line with the effect of honey in wounds of stimulating the growth of tissues to repair damage. Both of these modes of action could be involved simultaneously, along with a third possibility, that of the anti-inflammatory action of honey reducing the malfunctioning of the mucosa and the loss of serum from the inflamed tissue.

The routine therapy for diarrhoea is simply re-hydrating the body and restoring electrolytes (salts) lost in the diarrhoea, by administering fluid by mouth or intravenously[64]. The World Health Organisation's recommendation for oral re-hydration is to use an electrolyte solution with glucose added[153]. The active absorption of glucose by the intestinal mucosa is a process that is coupled to the uptake of sodium[64], so the glucose aids in the absorption of electrolytes. It also increases the uptake of water[58]. In the clinical trial where honey replaced glucose in the electrolyte solution it was found that it was just as effective as glucose in re-hydrating the patients[64]. Honey has the added advantage of also containing fructose which has the ability to promote additional water uptake with less sodium uptake[58], avoiding the risk of too much sodium being taken up into the circulation[64]. Fructose also promotes the uptake of potassium whereas glucose causes net loss of potassium[58].

Action of honey in treating peptic ulcers and gastritis

The discovery that one of the causes of peptic ulcers and gastritis (inflammation of the stomach lining) was infection with the bacterium *Helicobacter pylori*[45] raised the suggestion that the effectiveness of honey in treating these conditions may be due to its antibacterial activity[5,14]. Testing of clinical specimens of *H. pylori* showed that they were sensitive to the antibacterial activity of honey[5,14], but possibly not sufficiently sensitive to account for the therapeutic effect of honey. The concentration of honey needed to stop the growth of the bacteria in one study[14] was 20%. In the other study[5] the bacteria were not inhibited by a 40% concentration of a honey selected to have a median level of antibacterial activity due to hydrogen peroxide, the common antibacterial component of honey. However, with a manuka honey of a median level of activity due to the unidentified antibacterial component of this type of honey, the concentration of honey needed to completely inhibit the growth of the bacteria was 5%[5]. But a clinical trial using manuka honey with a similar level of activity has found that infection of the stomach with *H. pylori* was not cleared after two weeks of treatment with four-times-daily doses of a tablespoon (c. 25 g) of honey[90]. Although it was concluded from this trial that any effectiveness of honey against peptic ulcers and gastritis is not through an effect on *H. pylori*, this is not a reasonable conclusion when the trial was with only six patients treated, and was with

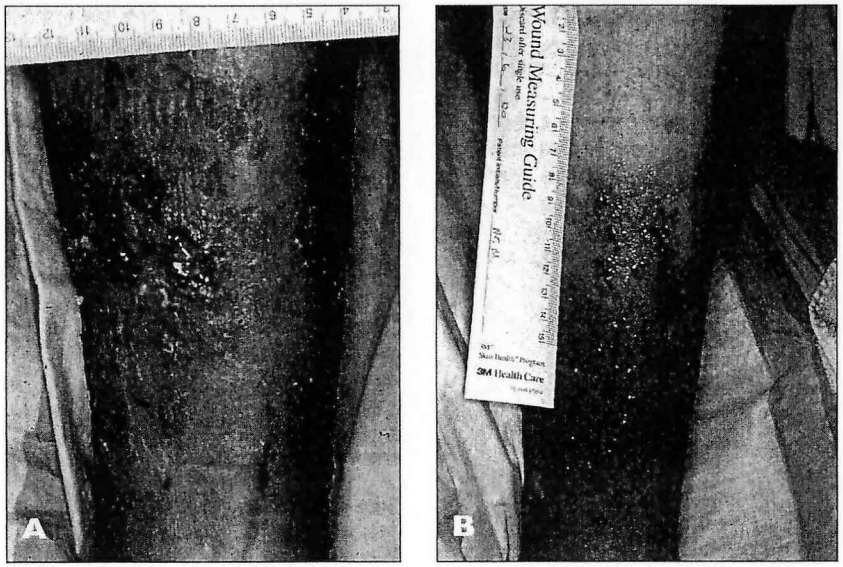

FIG. 2. A case of cellulitis (infection of skin tissues) cleared up by one week of dressing with honey (A: before treatment; B: after).

a single, arbitrarily chosen dose rate which may have been insufficient and may not have been continued long enough to clear the infection. However, it should also be born in mind that this trial was carried out with a honey to which *H. pylori* is very sensitive, whereas in the many reports of successful treatment of peptic ulcers and gastritis cited in Part 1 of this review it was not manuka honey that was used.

Alternative explanations for how honey has a therapeutic effect on gastritis and peptic ulcers have come from a series of studies conducted by Ali and co-workers, who have investigated the influence of honey on various parameters known to be involved in ulceration in the stomach. There are various causes of peptic ulcers, the major ones being aspirin-type anti-inflammatory drugs, alcohol, and stress, which restricts the blood supply to the gastric mucosa (the stomach lining) and leaves it more susceptible to erosion by the stomach contents[26]. Studies of the action of honey on peptic ulcers in rats have shown that it has a dose-dependent effect protecting the stomach from ulceration being caused by alcohol[6,8,9,10,12] and indomethacin (an aspirin-type anti-inflammatory drug)[10]. At the higher dose rates used, there was around an 80% protection from the ulceration caused by alcohol[6,8], but only if the honey was given 30 minutes beforehand and not if given simultaneously. Only in one case[10], with a very high dose rate, was there any protection if the honey was given simultaneously. But honey gave 100% protection from ulceration caused by indomethacin when given simultaneously. (The difference in time frame of protection may reflect the much slower development of ulcers seen with indomethacin than with alcohol[7,8].) There was no protection from either agent if a sugar mixture simulating honey was used in place of honey[8,10], showing that the protection is due to a component of the honey other than the sugars.

Investigation by Ali *et al.* of the mechanisms of these protective effects of honey have given an insight into how honey may work in therapy of gastritis and peptic ulcers. Aspirin-type anti-inflammatory drugs, especially in the presence of acid, enter the cells and block their energy-producing metabolism, thus causing the cells to decrease their protective secretions and become permeable to acid[26]. This leads to shedding of the surface cells and development of erosion of the sub-surface, with bleeding and inflammation[26]. Production of prostaglandins, with a protective function, is inhibited by these drugs, but prostaglandins protect only the sub-surface mucosal tissue, repair of the mucosal surface (epithelial cells) being independent of prostaglandins[26]. The action of alcohol is more complex and less well understood, but also involves inflammation[9,10].

The studies on the effects of honey on ulcers have demonstrated that an influence of honey on prostaglandin production is not involved[6,9], but that honey has a stimulatory effect on the sensory nerves in the stomach that respond to capsaicin (the irritant in chilli pepper)[6]. Stimulation of these nerves causes the release of vasodilatory peptides in the stomach which, mediated by production of nitric oxide, increase the blood supply and thus help protect the gastric mucosa from damage[6,11].

A second mechanism of action has also been identified from these studies that involves the antioxidant properties of honey. Honey has been found to protect or augment the level of non-protein sulfhydryls (substances such as glutathione) in gastric tissue subjected to factors inducing ulceration[6,8,9,13], a class of substances that are part of the body's antioxidant defence system[65], and depletion of which is an indication of oxidative damage to tissues[39]. Oxidative damage to tissues through free radical production occurs in reperfusion injury (injury resulting from the restoration of blood flow to tissues that have been deprived of it). The free radicals are formed by the action of the enzyme xanthine oxidase in the tissues, formed during the period of oxygen starvation, producing superoxide from oxygen when it becomes available again[39]. This type of injury is involved in the formation of peptic ulcers[13], and has been found to be decreased in rat stomachs by dosing with honey 30 minutes before restricting then restoring the circulation[13]. Another study showed that the permeability of the blood vessels in the gastric mucosa developing as a consequence of exposure to alcohol, a feature of inflammation, could be reduced in a dose-dependent manner by pretreatment of the stomach with honey[12]. But none of these findings of an antioxidant effect of honey in the stomach rule out the alternative or additional possibility that it is an antiinflammatory component of honey distinct from the antioxidants that is involved. As mentioned above, oxygen free radicals can initiate further inflammation, and inflammation gives rise to oxygen free radicals, thus giving a self-amplifying inflammatory response[56]. The oxidative damage resulting could be decreased by blocking either the oxygen radicals themselves, or by blocking the inflammatory response that would otherwise be giving rise to more oxygen radicals.

Ali *et al.* have also identified a third mechanism of action of honey in the therapy of peptic ulcers, that of stimulating repair of the damage to the gastric mucosa. Feeding honey to rats with stomach ulcers caused by indomethacin gave 61–70% more healing than in the controls[7]. Observation of the ulcers revealed that the honey caused a decrease in oedema (swelling of the surrounding tissue, a feature of inflammation) and formation of healthy granulation tissue.

It is of interest that these observations parallel those made with skin ulcers treated with honey (see above). Ali *et al.* have proposed[7] that the stimulation of healing of peptic ulcers is by its stimulation of blood supply[6,11], which is one of the mechanisms that is involved in the healing of skin ulcers (see above). The anti-inflammatory action reducing oedema would be involved in this as well (see above), additional to the direct stimulation through the sensory nerves in the stomach. The stimulatory effect of honey on the growth of epithelial cells (see above) could also be expected to help restore the surface cells of the gastric mucosa, which cannot be helped by prostaglandins.

The role of hydrogen peroxide

Hydrogen peroxide, the principle antibacterial component of honey, is well known as an antibacterial agent, although it has had a chequered history of use as an antiseptic. In its history it has been in then out of favour with the medical profession twice since first coming into use in the late 19th Century. It has been suggested that its ready decomposition in solutions containing traces of catalytic metals such as iron or copper may be the reason why hydrogen peroxide went out of favour as an antiseptic after initially being hailed for its antibacterial and cleansing properties when first introduced[140]. There was an upsurge of interest in its use later when stabilized preparations became available, with good germicidal activity being reported[140], but in more recent times it has again gone out of favour as awareness has developed of the inflammation and damage that are caused to tissues by substances giving rise to oxygen free radicals[65,118,119]. However, the hydrogen peroxide concentration produced in honey activated by dilution is typically around 1 mmol/l[93], about one thousand times less than in the 3% solution that is commonly used as an antiseptic. Also, there is the potential for honey to sequester and inactivate the metal ions which catalyse the formation of oxygen radicals from hydrogen peroxide, and the antioxidant components of honey to mop up any free radicals that may be formed.

Hydrogen peroxide is an effective antimicrobial agent if present at a sufficiently high concentration[116], but at higher concentrations causes cellular and protein damage in tissues by giving rise to oxygen radicals[36,125]. A study of hydrogen peroxide antiseptic has found that there is no bactericidal concentration of hydrogen peroxide that is not toxic to fibroblasts (the cells that repair wounds)[87]. Minimum concentrations reported to be necessary in the culture medium to inhibit bacterial growth range from 0.12 to 5.9 mmol/l[92]. However, it has been reported that a given quantity of hydrogen peroxide is more effective when it is supplied by continuous generation by glucose oxidase than when it is added separately[114], and a study with *Escherichia coli* exposed to a constantly replenished stream of hydrogen peroxide showed that their growth was inhibited by 0.02–0.05 mmol/l hydrogen peroxide, a concentration that was not damaging to fibroblast cells from human skin[75]. A further consideration is that myeloperoxidase, the enzyme that generates bacteria-destroying free radicals from hydrogen peroxide in the phagocytotic vacuoles of the leucocytes[83], is inactivated by hydrogen peroxide levels in excess of 2 mmol/l[3]. Thus, in living tissue where there will be leucocytes active, a better overall antibacterial action may be obtained with low levels of hydrogen peroxide. The action of the enzymes catalase and glutathione peroxidase in tissues will give equilibrium concentrations of hydrogen peroxide that will be lower than the 1 mmol/l found in honey solutions *in vitro*.

But hydrogen peroxide has roles in healing quite separate from any antibacterial action. It has been reported that at levels of 30–100 µmol/l it activates the NF-κB transcription factor in lymphocytes to activate the expression of genes for the immune response[121]. Research on various cell lines in culture is showing that it has a variety of effects in the role of a 'cellular messenger'. A review of the voluminous literature appearing on this topic[29] has pointed out the large amount of evidence for hydrogen peroxide being involved in many cell types in the body as a stimulus for cell multiplication. It acts at various points in the mechanisms of the cells that control the cycle of cell growth and division, most probably by oxidising the proteins involved and thus causing a change in the conformation of the protein molecule. This action has particular relevance in wound healing, where the inflammatory response that is a natural consequence of injury or infection produces hydrogen peroxide, and this serves to stimulate the growth of fibroblasts and epithelial cells to repair the damage[29]. Only where there is excessive inflammation does the hydrogen peroxide rise to levels that instead cause destruction of tissues by killing the cells[29]. Even with these high levels of hydrogen peroxide the cells can be protected by iron-chelating agents which prevent the catalysis by iron of the formation of membrane-damaging free radicals[29]. Without this protection, hydrogen peroxide is toxic to cells at concentrations above 0.1 mmol/l, but only needs to be at levels around one thousandth of this to stimulate cell multiplication[29]. It has been proposed that low concentrations of hydrogen peroxide might be used to stimulate wound healing, rather than the expensive cell growth factors produced by biotechnology for this purpose (the bioactive wound dressings)[29]. But another proposal that hydrogen peroxide could be applied to promote the wound healing process has pointed out that this is feasible only if the concentration could be carefully controlled[34]. It has also been proposed that honey be used in place of recombinant growth factors to provide hydrogen peroxide to stimulate the healing of burns[112]. The application of creams containing hydrogen peroxide to stimulate the development of new capilliaries in wound tissue[139]. It is possibly through the production of hydrogen peroxide in the presence of components protecting the cells from oxidative damage that honey is effective in stimulating the rate of healing, and particularly in kick-starting the healing process in wounds that have remained unhealed for a long time.

Another cell growth factor involved in wound healing is the hormone insulin. Wound healing research has shown that intravenous infusion of insulin or applying it to the surface of a wound stimulates the rate of healing[19,89,109]. This is to be expected, as when insulin is present it binds to the insulin receptor protein molecules on the outside of cells and causes them to change conformation, thus triggering a chain of molecular events in the cell that stimulates the uptake of glucose and amino acids, and promotes anabolic metabolism, giving cell growth. The insulin receptor complexes are activated in the same way by low concentrations of hydrogen peroxide[41,72,84], raising the possibility that this is another mechanism by which honey may stimulate wound healing.

Change in the conformation of protein molecules brought about by oxidation by hydrogen peroxide may account for another feature of honey seen when it is used on wounds, that of enzymic debridement of the wound. Although any moist dressing promotes the removal of pus and dead tissue by allowing the action of protein-digesting enzymes in the wound tissues, this debriding action by honey is remarkable. There are two types of protein-digesting enzyme involved in wound tissues: the matrix

metalloproteases of the connective tissue[99], and the serine proteases produced by the neutrophil leucocytes[138]. The serine proteases are normally inactive because of the presence of an inhibitor, but hydrogen peroxide inactivates the inhibitor, so the protease becomes active[106]. The metalloproteases are normally present in an inactive conformation, but hydrogen peroxide changes the conformation of these and makes them active[107,148].

Conclusions

Although honey has in the past been a standard medicine, most medical practitioners in the present day in developed countries are not aware of that, and consider it to be an 'alternative' or 'complementary' medicine. Although there are some very good indications of its effectiveness in reports published in medical journals, there is evidence from randomized controlled clinical trials only for its use as a dressing for burns. Even where there is evidence of effectiveness there is still a reluctance to use alternative medicines where there is no rational explanation for how they work. Thus, it is unlikely that the further randomized controlled clinical trials necessary to conclusively establish the effectiveness of honey as a medicine, and discover how it compares in performance with modern pharmaceuticals will be carried out. This review of the literature has shown that there are rational explanations for the therapeutic effects of honey. But further research is needed to establish that the possible explanations deduced from other biomedical research findings are in fact what is occurring when honey is used.

In any future research, the large variation in composition of honey needs to be taken into account. There has been a tendency in the past to consider any honey to be representative of all honey, and the consequence of this is seen in the very large differences in findings reported on the sensitivity of bacteria to honey[92,93]. In Part 2 of this review mention was made of the awareness of the ancient physicians, and in present day folk medicine, of particular honeys being the best for particular medical uses, yet no account of this is taken in any of the clinical trials of honey. Considerations in the selection of honey for medical use have been discussed[95], and the point raised that until the importance of the anti-inflammatory and antioxidant components of honey have been established, only the antibacterial activity of honey for use as a medicine can be standardized. In light of the likely importance of all of these components, the need for further research to identify their involvement and their nature is needed, so that honeys can be selected to give the best results when used as a medicine.

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