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Wounds: decontamination and healing[1]

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Contents

Abstract

Metal ion–ligand interactions which are pivotal to the wound healing and wound decontamination processes require therapeutic encouragement at concentrations of species which are at the limits of laboratory analysis. The general principles involved and some recent progress are described.

Keywords: Wounds; Healing; Decontamination; Metals

1. Introduction

The term "wound" is usually associated with damage to the skin which, in itself, is by far the largest organ of the human body, sometimes accounting for up to $\frac{1}{6}$th the weight of an individual. However, in a broader sense, the term "wound" may be

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applied to damaged bones or other skeletal tissue such as nails, to internal wounds and even to damage to the teeth.

All of these areas are heavily dependent on the coordination chemistry of the metal ions involved in the teeth or bone (and their remineralization) or, indeed, in the enzymes controlling the regeneration of skin tissue back to its original shape and strength [1–3].

Coordination complexes are a determining feature of the threat from contaminating metals which enter a wound and then react with naturally occurring biochemicals or preferably with the new generation of lavage ligands which are now being developed in order to decontaminate wounds before deeper penetration of tissue by the offending metal [1]. The art of the coordination chemist is to analyse the concentrations and structures of such complexes in these highly complex environments without disturbing labile equilibria and then to optimize desirable features to aid the therapy.

2. Wounds

There is a wide variety of wounds encountered ranging from abrasions (grazes), lacerations or tears, penetrating wounds such as may be caused by knives or missiles, bites, surgical wounds, and burns and chemical injuries such as those caused by electrical or by radiation energy sources. Interestingly the damage caused by a source of heat or radiation is very temperature dependent, 70 °C causing epidermal necrosis within 1 s, whereas 45 °C requires an exposure time in excess of 6 h in order to induce damage to the tissues; similarly α, β, γ, UV and visible radiation sources, energy for energy, have profoundly differing effects on the skin.

Ulcers have also been subdivided into different types, i.e. decubitus ulcers often called bed sores or pressure sores, leg ulcers which may be venous, ischaemic or traumatic, ulcers associated with systemic infections, ulcers arising from radiotherapy, and ulcers arising from malignant disease.

Chelating ligands such as histamine or serotonin are usually liberated as a consequence of injury. These will have a noticeable affect on metal ion ligand concentrations and species involved in healing. Furthermore, the pH and the p_{O_2} can assist or detract from wound healing.

The majority of wounds heal uneventfully but there is increasing expenditure on complex wounds where the healing may be delayed because of infection, because of the presence of foreign bodies, or because it is near an outlet from the body, such as a sinus.

Wound dressings play an important role in the management of these different types of wounds. Furthermore, the increasing use of wound cleansing agents and bactericides can markedly influence the progress of repair. Infecting organisms may be present (as many as 100000 per gram of tissue [4]) and foreign bodies, if not removed from the wound, can give rise to chronic inflammatory responses which delay wound healing.

Wound dressings, in earlier days, have invoked cobwebs, plant leaves, animal

excreta, animal fat, honey, and other agents. The gauze currently widely used in hospitals was invented almost a century ago as a mosquito netting for soldiers' tents. The Gamgee bandage was developed in 1880 and was impregnated with iodine, phenol, or paraffin; it is still widely used today.

However, Winter in 1962 researched occlusive dressings and showed that a dressing which keeps the wound moist can increase the rate of epidermal resurfacing by some 40% [5]. In the untreated state, wounds tend to dehydrate and to produce a hard scar. This is a particularly difficult process to reverse when one considers metal ions since all cations involved in wound healing tend to hydrolyse and to precipitate at the pH of wound exudate unless they are firmly complexed in order to remain in solution. It is exceedingly difficult to redissolve such precipitates [6].

The volume of fluid involved in wounds can be impressively large. For example, ulcers, skin donor sites, and some burns can produce more than 5 litres of exudate per square metre of wound per day. This may be more than the total contents of fluid in the blood stream. Thus, the maintenance of the correct isotonic pressure within wounds and wound exudate is critically important to any metal complexing reactions which occur therein.

The oxygen pressure and the pH of wounds are also pivotal [7]. A five-fold increase in the oxygen released from oxyhaemoglobin can be produced by a drop of 0.9 pH units since an alkaline environment stabilizes the coordination complex oxyhaemoglobin. Thus, maintaining a wound nearer to pH 6 rather than pH 7 has many benefits. However, purists will argue that a relatively healthy non-infected wound in its early stages of healing benefits from a relatively impermeable dressing which produces a hypoxic environment. Nevertheless, for the later stages of healing a swap to an oxygen permeable dressing facilitates and encourages epithelial growth.

Of the 500 dressings listed as generic, proprietary or trade names in a recent compilation [3], many involve alginates which were first brought to the clinic in the 1880s by Stanford [8]. The order of 20 000 tons of such material is used annually in the manufacture of dressings and the ability of calcium alginate fibre to be spun was noted 100 years ago by a patent in 1898, although it was the 1930s before it was developed for wound treatment [9]. Even though a small amount of the sodium or calcium salts of alginic acid could well be absorbed, there is histological evidence that it rapidly becomes degraded and harmless. One of the great advantages of calcium alginate dressings is that the woven material becomes gel-like when the coordinate-bonded calcium ions are exchanged for ionically bonded sodium ions and this jelly follows the contours of the wound and keeps it moist. Thus, there is now no doubt that calcium alginate dressings actively contribute to the healing process [10].

The use of wound cleansing agents is particularly interesting to coordination chemists. Hypochlorite solutions have been used for over 200 years and up to 2 l of solution per day were at one time introduced into necrotic wounds in order to encourage healing and cleansing.

Hydrogen peroxide solution (6%) is another commonly used desloughing agent. Proflavine is an acridine derivative which is a mild bacteriostat against Gram-positive bacteria [11]. Cetrimide is a quaternary ammonium compound which has

both Gram-positive and some Gram-negative bacteriostatic effects [12]. It is also a useful detergent which helps in the sloughing-off process.

Chlorhexidine is also active against both Gram-positive and Gram-negative bacteria and is usually administered by diluting by up to 30 times a 1.5% weight per volume solution as chlorhexidine gluconate and 15% cetrimide.

There is also a wide variety of cleansing lotions involving benzoic acid, malic acid, salicylic acid, and propylene glycol. Potassium permanganate also acts as a mild disinfectant and has deodorizing properties.

Thus, against this background of the presence of numerous naturally occurring and administered ligands, the clinician attempts to achieve the right coordination chemistry in order to maximize the wound healing processes.

3. Bioinorganic chemistry

The human body consists of approximately 50 elements, some 24 or so being regarded as essential or highly beneficial [2]. The total elemental composition of the human body is reflected in Table 1 [3]. It can be seen that some 70% of an adult human body is water and an even greater amount of an infant's body mass. Not surprisingly, therefore, the biochemistry of the human body is one of aqueous chemistry, there being the order of 10^{15} cells which separate these tiny aqueous compartments from other cells.

Table 1
The approximate composition of an adult with a mass of 70 kg

Main group non-metals		Main group metals		Transition series metals	
Element	Mass (g)	Element	Mass (g)	Element	Mass (g)
Hydrogen	7000	Lithium	0.0007	**Titanium**	0.01
Carbon	12600	Boron	0.01	**Vanadium**	0.02
Nitrogen	2100	Sodium	105	**Chromium**	0.005
Oxygen	45500	Potassium	140	**Manganese**	0.02
Silicon	1.4	Caesium	0.0015	**Iron**	4.2
Phosphorus	700	**Zinc**	2.3	**Cobalt**	0.0007
Sulfur	175	Arsenic	0.014	**Nickel**	0.01
Fluorine	0.8	Selenium	0.02	**Copper**	0.11
Chlorine	105	**Tin**	0.03	**Molybdenum**	0.005
Bromine	0.2	**Lead**	0.08		
Iodine	0.013	**Cadmium**	0.03		
		Magnesium	35		
		Calcium	1050		
		Strontium	0.14		

Metals having biochemistries which use coordination compounds as pivotal species are shown in bold print. Electron donor atoms involved in these biocoordination complexes are shown in italics. In addition to this list of essential elements, there will be the order of 20 contaminating elements present in low concentrations, e.g. about 0.1 g Al per adult [3].

Our cellular evolution having occurred on the surface of the earth and, especially, on beaches washed by ancient oceans is reflected in the elemental composition of our bodies which is mainly that of the lighter elements of the periodic table. However, in geochemical terms, more recent mining of heavier elements from deeper down both in the periodic table and in the earth's crust, and the production by nuclear industry of radioactive isotopes of elements, means that the biochemistry of the human body, when contaminated, is discouraged by the presence of such intruding newer elements. Frequently, the route through which such troublesome elements penetrate into the human body is through the skin, which has evolved to be an exceedingly efficient barrier to outside environment influences for most of the time. Thus, the contamination of the skin by heavy or radioactive elements and, also, by irritating organic ligands is a matter of some concern to healthcare scientists.

4. Speciation and bioavailability

The chemical speciation of an element defines the oxidation state, concentration, and composition of each of the species of the element present in a given chemical sample. Unfortunately, in sophisticated environments such as biological tissue, the exact analysis of all the species present is still beyond the realm of the most sophisticated analytical equipment. However, recent improvements to analytical methodology which can take the analyses down to parts per billion and also means of extrapolating beyond such limits by using computer simulation has meant a growing interest in the links between chemical speciation and biological effects.

It is now widely recognized that biological parameters, such as health, are not directly correlatable with the total amounts of the element present. Changing the species of the element can markedly influence its reactivity by factors of hundreds of thousands. For example, some 200 g of barium sulphate can be swallowed quite safely as an X-ray contrasting agent, whereas merely changing the anion to give barium chloride produces a serious risk of overdosing at levels as low as 20 mg [13–16].

Similarly, when a low molecular mass species is overall electrically neutral, it is usually sufficiently lipophilic to penetrate through a lipid protein cell membrane and to flow with the concentration gradient in order to permit, for example, the metal complex to travel from the small intestine through the epithelial hairs lining that organ into the capillaries which, in turn, feed the bloodstream. This is a common route for bioavailability of metal complexes arising from intake of food and drink.

Similarly, when such low molecular mass complexes in blood plasma are charged, either positive or negative, they may be excreted through the kidneys. Such renal desalination mechanisms enable byproducts to be removed from the blood and the blood pressure to be maintained at a constant isotonic level.

Finally, blood plasma complexes which are electrically net neutral may be re-excreted into the intestine via the bile duct or can even pass through the blood–brain barrier into the cerebrospinal fluid whence they may re-equilibriate and influence the nervous system.

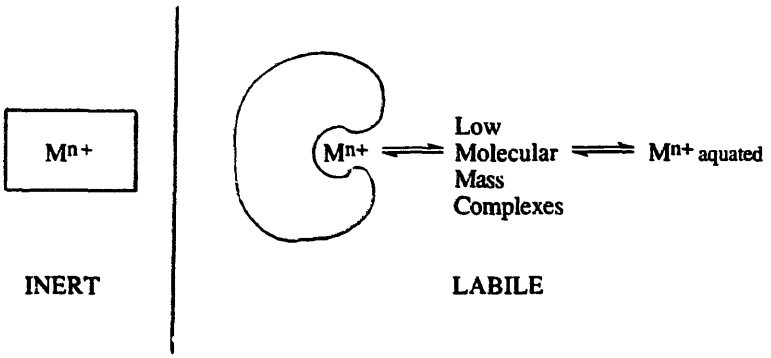

Fig. 1. Schematic representation of the four broad classes of metal species in humans. The "inert" form may be a metalloprotein or a solid structure such as calcium hydroxy apatite (bone and tooth). The labile forms shown are a metal ion-apoenzeme protein, low molecular mass complexes, and hydrated metal ions.

All metal ions found in vivo tend to fall into four broad categories. First, some of the metal ion may be associated with a relatively inert species, such as a metalloprotein, from which it is almost impossible to remove the metal without destroying the whole structure (Fig. 1). Alternatively, this category might include such metals as calcium which is deposited in bones and teeth.

Secondly, there are three categories of metal complex which are in a considerably more labile state of equilibrium. These include metal complexed reversibly to metalloprotein which acts as a circulating buffer for the metal ion and this, in turn, is an equilibrium with low molecular mass metal complexes formed by biological ligands such as amino acid anions etc., and finally there will be a fairly low concentration of the aquated metal ion. These last three species are at equilibrium such that an increase in the total metal present leads to an across-the-board increase in all three. Conversely, the circulating pool of labile protein metal complexes is the source of metal liberated whenever a ligand is administered as part of a decontamination or lavage procedure [13,16,17].

5. Essential element supply and recommended daily amounts

Normally, only a fraction of metals taken in through the oral route becomes sufficiently biodegraded from the polymers in diet to give soluble low molecular mass net-neutral species that pass through to the blood stream and thence the tissues. Taking into account such relative bioavailabilities and differences between intake and uptake of metals, tables of recommended daily amounts have been compiled for various countries (Table 2). It must be recognized, however, that there is a wide range of requirements even for comparable adults of similar age and these levels broaden even further to account for children, teenagers and those in later years of life.

Naturally, when a wound occurs, most of these metals are necessary to support the healing processes and a deficiency in this circulating fundamental supply route can be reflected in slow or non-healing.

Table 2
Recommended daily amounts of mineral intakes for a 70 kg adult by either the oral, in which case uptake is only a fraction of intake, or the intravenous (uptake = intake) routes

Element	Recommended daily amounts (mg)	
	Oral	Intravenous
Calcium	800	280–560
Chromium	0.05–0.20	0.05–0.12
Copper	1.9–2.8	1.9–5.1
Fluorine	1.5–3.9	0.93
Iodine	0.15	0.13–0.89
Iron	10.0–18.1	1.2–2.3
Manganese	2.5–5.0	0.3–1.9
Molybdenum	0.14–0.48	0.019
Phosphorus	770	430–2170
Selenium	0.047–0.20	0.012–0.039
Zinc	15	3.2–13.8

A more direct route to producing nutritional components at their correct levels is that of total parenteral nutrition (TPN) in which "intake" equals "uptake". This is an efficient means of providing all nutritional requirements for seriously ill patients. It supplies a mixture of carbohydrates, fats, nitrogen (as amino acids) electrolytes, trace elements and vitamins so that a positive nutritional status is achieved. This type of patient support is particularly useful in injuries and wounds such as wasting disease, burns, trauma, prolonged ileus and cancer. Approximately 5% of hospital patients require parenteral nutritional support in some form. The benefits of such support in terms of wound healing are obvious to clinicians. A major problem is that TPN requires the patient to be hospitalized which is not only disruptive to lifestyle but also expensive and time consuming [18].

The main thrust of balanced TPN is to add all chemicals into the blood in a form such that their free equilibrium buffered states are as close as possible to those encountered in the blood plasma; this produces minimal disruption and reduces side effects. There are six fundamental components of TPN regimes as shown in Table 3. Many of these interact and hundreds of different regimens and sets of data have been published concerning desirable and undesirable reactions of such agents. Nowadays, modern computer methods and speciation programs such as PARSAFE [19] attempt to accommodate all formation constants, solubility products and other interaction constants as well as checking that the patient receives nutritional sufficiency for all the items listed in the table.

Incompatibility problems, for example, exceeding solubility products and producing precipitates which cause thrombosis or cause line blockages, high charge density complexes which destroy the soya oil emulsion which is the core of the energy input from TPN, interactions between metal ions and sugars, such as might occur in the Maillard reaction, etc., are all checked out by the computer and a safety margin of at least a factor of 10 is used lest the mixing of these solutions (a process known as

Table 3
Fundamental components of total parenteral nutrition fluids which, with the exception of specially selected drugs, are required by healing wounds [18]

Energy	Minerals
Amino acids	Electrolytes
Glucose	Trace elements
Soya protein	Impurities
Phospholipids	
Glycerol	Vitamins
	Water
Nitrogen	
Amino acids	Drugs
	Anticoagulants

compounding) is not instantaneous and complete. One of the ingredients to such compounding is a mixture of metal ions embracing all of those necessary for an hospitalized adult. This mixture will be referred to later in this review.

There are still some problems to be tackled in TPN such as the solubility of additives and precipitation occurring during shelf storage, longer-term stability and the presence of metal complexes, side effects caused by impurities in bulk agents such as glucose, the knock-on effects of administering drugs through TPN fluids and the slow kinetics of some precipitation reactions.

Table 2 shows the recommended daily intakes of micro nutrients by the parenteral route and, in principle, all wound management patients ought to be brought to nutritional balance in respect of these elements [18]. Clearly, for healthy wound healing all of this material should in principle be carried in adequate amounts to the wound tissue via the arterial network. Bearing in mind, however, that many wounds are often at the extremities of the blood distribution system and that blood flow can vary between 60 pints per minute for a healthy adult down to 1 pint per minute for an elderly person having walking difficulties, it would appear to make more sense to apply such nutrients directly to the wound rather than to rely entirely on circulation. It must be stressed, however, that as much nursing care as possible must be directed towards maintaining the circulation and encouraging patient exercise, otherwise a freshly healed wound could tend to go into remission after two or three weeks because of an apparent underlying malnutrition.

6. Wound management and treatment

Of the range of dressings used over hundreds of years, those based on seaweeds in the form of calcium alginate have produced the most remarkable benefits in the management of many wounds to date. Such wounds include leg ulcers, pressure sores and other chronic or bleeding lesions. Ideally, such treatment ought to be implemented in the presence of adequate whole body nutritional balance in order

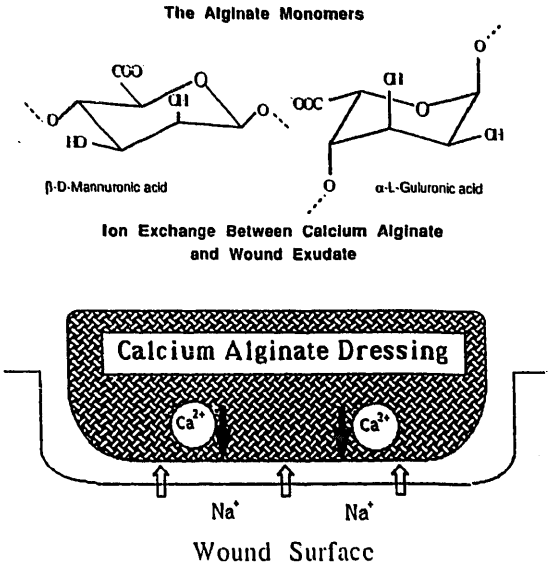

Fig. 2. The binding of Ca^{2+} ions in a cavity formed by two α-L-guluronic acid units in an alginate polymer. The structures of β-D-mannuronic acid and α-L-guluronic acid are also shown.

to optimize effective healing. However, many patients, particularly the elderly, suffer from ailments arising from inadequate circulation but can still benefit from the topical supplementation of essential trace elements to wounds.

There have been several papers quantifying reactions between alginate dressings, metal ions, and wound exudate [1,17]. Alginates are salts of the polysaccharide alginic acid which occurs in the cell walls as well as within intercellular spaces of brown algae. Basically, alginic acid is a co-polymer of 1,4-linked β-D-mannuronic acid (M) and its C-5 epimer of α-L-guluronic acid (G). The monomers are organized into block-like structures which may contain predominantly M or predominantly G residues which chelate with a metal ion. Such structures are polyanionic and form intermolecular ionic bonding to a wide range of cations (Fig. 2). The calcium alginate complex is a solid which can be spun into long fine fibres (called a tow) which is woven into a traditional style gauze-like wound dressing. The calcium ions are coordinated within the alginate block structures rather akin to eggs in an eggbox. It is most useful to note that when these calcium ions are replaced by sodium ions from the wound exudate this white gauze-like dressing becomes a clear gel which moulds to the contour of the wound, not only reducing abrasive irritation of solid against wound tissue but also entrapping moisture and acting as a barrier against invading bacteria. We have been researching the possibility of using such eggbox-like alginate–metal ion complexes as a means of transferring essential trace metals from dressing to wound fluid. In order to quantify the concentration of binding sites and how such sites interact with metal ions the following assumptions were adopted.

(1) A deep binding site consists of two guluronic residues, has a double negative charge, and a molecular mass of 366 Da.

(2) The calcium alginate tow researched, as supplied by BritCair Ltd., was

obtained from seaweed called *Laminaria hyperborea* contained total guluronic:mannuronic acid residues in a ratio of 2:1.

(3) All guluronic acids pair up to form a binding site.

(4) Mannuronic acid residues are not involved in binding.

(5) Binding sites are not formed between guluronic residues from two different polymer chains.

Using such a model, it is possible to quantify the binding between such dressings and a range of metal ions provided that the formation constants are known [20–23]. Two different styles of models were established. In the first instance it was assumed that none of the tow dissolved and that the alginate network acted as an ion exchange resin for releasing calcium ions and taking up trace element or sodium ions as appropriate. In the second respect it was assumed that a small amount of the mannuronic and guluronic acid dissolves in the wound fluid and that these could be considered as simple ligands competing with other ligands for the metal ions present.

The pH of wound exudate is not known for most patients but there is some evidence that it is more acidic than blood plasma and thus our researches covered the pH range from 5.8 to 7.4 [24,25]. The results showed that the portion of alginate dressing which became soluble in wound exudate was insufficient to participate appreciably in metal ion–biochemical ligand interactions prevailing therein. Calcium, as expected, is the metal ion most released by a tow but even then its complexing influence is only of the order of 2%–3% of the overall calcium complexing in the wound exudate.

The work also suggested that transition metal ions could be carried and released by the tow and this led to further laboratory work to quantify this transfer. There is a need to establish the required level of trace elements supplementation to a wound and also the efficacy with which a dressing impregnated with metal ions is capable of satisfying this need. Thus, a total audit of the ability of a dressing to move metal ions into wound tissue was researched [26].

The problems to be tackled are that only an extremely small sample of wound fluid or wound tissue can reasonably be expected to be available. Classically, this is acquired by taking a 2 mm diameter boring into the freshly healing wound tissue (fortunately freshly grown tissue contains very few nerve endings and so this biopsy sampling can be quite painless) which, in principle, can be compared with a similar boring from a healthy part of the patient (after suitable administration of a local anaesthetic).

Another problem is that trace metals from the transition series present in tissue are at levels below those analysable by techniques such as atomic absorption spectrophotometry, without access to a very large amount of sample, which is then digested in acid and concentrated. However, approaches such as potentiometric stripping analysis have now been developed such that they can work on 20 mg samples of skin at levels of copper and zinc of the order off 12 ppb and 33 ppb respectively of dry mass.

We have recently published a report concerning the design of the digestion stage, the calibration and the robustness of this technique which is now available for

studying wounded as well as normal tissue [26]. In principle, such approaches can now be applied to a wide range of trace elements of relevance to wound healing (Fig. 3). Such an approach permits trace element analyses to within 5% at levels of 100 ppb [27]. Such precision is more than adequate for establishing whether newly healed tissue contains sufficient trace elements or whether more administration from a dressing is required. This approach is now available to medical authorities in order to accumulate experience and patient data.

Finally, it must be stressed that the biopsy punch used ought to be considered as a source of possible ultratrace element contamination [28]. Ideally, titanium nitride for coating the stainless steel surgical instruments could well improve the accuracy of such determinations in the future.

We are now in a position to pass trace elements from dressing, suitably impregnated with appropriate species, to wound fluid and to make a total audit of this transference procedure.

Recent work has used two different types of TPN trace element packages (Addamel and Addamel N, the latter lacking calcium and magnesium) as shown in Table 4 to impregnate calcium alginate tow [29]. This tow was then exposed to fluid resembling that of wound fluid (in fact blood plasma was used since the first stage of wound

										Al			S	Cl
Sc	Ti	V	Cr	**Mn**	**Fe**	**Co**	**Ni**	**Cu**	**Zn**	**Ga**	Ge	**As**	**Se**	Br
	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	**Cd**	**In**	**Sn**	**Sb**	Te	I
			W	Re	Os	Ir	Pt	**Au**	**Hg**	**Tl**	**Pb**	**Bi**	Po	
			U	Np	Pu	Eu								

Fig. 3. Metals, shown in bold print may be determined by a potentiometric stripping technique since they form amalgams: detection levels of 0.1 ppb are possible in addition to the concentrations of different oxidation states. Metals shown in light face may be determined by voltammetry at levels of parts per million or above.

Table 4
A typical trace element supplement (Addamel, Kabi Pharmacia) as added to total parenteral nutrition fluids for an adult [18]

Component	Concentration (mmol dm^{-3})
Calcium(II)	500
Magnesium(II)	150
Iron(II)	5
Zinc(II)	2
Manganese(II)	4
Copper(II)	0.5
Fluoride	5
Chloride	1330
Iodide	0.1

healing exudes fluid analytically similar to plasma) and then to monitor the passage of these trace elements from impregnated wound dressing tow into the wound fluid. The complete audit of such an experiment has shown that up to 85% of transition metals can be transferred from impregnated dressing through to wound fluid. Similarly, the previous paragraphs have shown that it is possible to assess the state of trace elements in such newly healed wound tissue in order to prevent overdosage. Thus, metal complex impregnated alginate dressings seems to be a useful means of topically applying most trace elements which are required by the different stages of wound healing.

7. Wound decontamination

Many of the industrially mined and refined metals pose a hazard to workers in the industry especially if they react with components of wound fluid or with blood to form soluble species. Probably the greatest threat is from the actinide elements and from fission products whose isotopes are radioactive. Such ionizing radiations can seriously damage cells and have even more harmful effects if the metals become deposited in bones. Thus, as soon as a break in the skin is contaminated or, indeed, is suspected of being contaminated, considerable effort is expended to remove such contamination before it reacts and enters into the circulation of the patient [30].

The relationship between speciation and bioavailability of actinide elements has been well reviewed and many conclusions are based on computer simulation of the speciation since it is difficult to work with the analysis of such exceeding low concentrations. At physiological pH values, much of the actinide chemistry is that of the hydroxide, or the even more insoluble oxide, precipitates [31].

Wounds contaminated by radioactive material are rarely simple. Unless the isotopes are extremely soluble, the radioactivity will usually have infiltrated the surrounding tissues and undergone chemical changes which include interactions with proteins and with a wide range of other tissue components. More seriously, particulates may have become dispersed around the wound. The overall result is that the radioactivity cannot be removed by a simple act of copious washing with clean water or with saline solutions.

For several decades ligands have been used for detoxifying tissues and biofluids. More recently, synergistic chelation therapy [32–37] has been administered to eliminate metals from cells and thence via the renal route.

In theory, some of these ligands may be useful as a component of the lavage fluid in order to elute away the radionuclides contaminating a wound. A detailed study involving the chemical speciation produced when a range of ligands based upon carboxylic acids are used to elute the hydroxides and the oxides of plutonium in wounds has shown that for both puncture wounds and for incised wounds (i.e. cuts) diethylenetriaminepentaacetic acid anions, $DTPA^{5-}$, are capable of removing plutonium(IV) from its hydroxide but not from the oxide [31].

The order of decreasing efficacy for eluting plutonium(IV) is DTPA > EDTA > NTA > citrate.

Speciation studies have shown that a minimum of a 100-fold excess of ligand over the plutonium is recommended for effective solubilization. This is supported by the work of Duffield et al. in 1986 involving DTPA and Licam(C) to remove plutonium.

A large amount of the ligand used in lavage becomes complexed to calcium ions and so there may well be a future in co-administering calcium with the ligand.

The solubilization of $Pu(OH)_4$ by all chelating ligands is pH dependent and greater solubilization can be achieved by using mildly acidic lavage fluids (e.g. pH 6.4).

Regrettably, a ligand showing promise for solid PuO_2 removal yet to be identified.

8. Wound decontamination dressings

Ligands can now be chosen specifically to complex metals in a given oxidation state. We have recently reported success in using calixarenes for complexing uranyl ions. One of the advantages of calixarenes is that their metal binding sphere is separate from their outer layer of other reactive groups. This outer layer could well be used to bind to dressings and thus concepts being explored are the use of dressings either impregnated with ligands as in the previous section or containing resins holding the complexing ligand. This work is proceeding [38].

9. Concluding remarks

In the areas of both trace metal supplementation and metal removal from wounds, it is important that as much monitoring data as possible are obtained. This may involve easy-to-use modern techniques such as potentiometric stripping analysis or even radiochemical analysis, if the contaminant is a radioactive isotope. This data can then be used in speciation modelling which will reveal the form in which the contaminant exists or the type of species of essential trace metal that is deficient. Therapy can then be targeted and contingency plans made ahead of need for decontamination [39].

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