The biology of fracture healing: optimising outcome

David R Marsh and **Gang Li**

Trauma Research Group. Musgrave Park Hospital, The Queen's University of Belfast, Belfast, UK

Optimising the results of fracture treatment requires a holistic view of both patients and treatment. The nature of the patient determines the priority targets for outcome, which differ widely between the elderly and the young, and between the victims of high and low energy trauma. The efficacy of treatment depends on the overall process of care and rehabilitation as well as the strategy adopted to achieve bone healing.

The rational basis for fracture treatment is the interaction between three elements. (i) the cell biology of bone regeneration, (ii) the revascularisation of devitalised bone and soft tissue adjacent to the fracture; and (iii) the mechanical environment of the fracture

The development of systems for early fracture stabilisation has been an advance. However, narrow thinking centred only on the restoration of mechanical integrity leads to poor strategy – the aim is to optimise the environment for bone healing Future advances may come from the adjuvant use of molecular stimuli to bone regeneration.

The business of restoring function to a patient who has had a fracture requires the surgeon to handle a heady mix of mechanical and biological issues. In real life, it also requires considerable input of time into practice organisation, given the large numbers of patients and the almost universal inadequacy of resource, if each individual patient is to receive timely and appropriate intervention.

There is a perception, not least among fracture surgeons themselves, that the mechanical issues have been over-emphasised in the past. The bonesetter's art consisted basically of providing anatomical realignment and external support for as long as nature then took to restore internal structural competence by bone healing. This was slow and unkind to soft tissues, particularly neighbouring joints, so the development of materials, biomechanical understanding and surgical technique launched a swing towards invasive interventions aimed at immediate restoration of internal structural integrity. The principles of AO treatment, drummed into a generation of orthopaedic trainees, were anatomical open reduction, rigid internal fixation and early rehabilitation of soft tissues without external splintage.

Correspondence to Prof David R Marsh, Department of Trauma and Orthopaedics, Musgrave Park Hospital, The Queen's University of Belfast, Belfast BT9 7JB, UK

But the scale of invasion required to achieve these aims brought a steady trickle of serious problems – most notably infected non-unions, sometimes in cases which surgeons knew they could safely have treated by simpler methods. Furthermore, there was increasing realisation that the abolition of interfragmentary motion implied a commitment to primary cortical union as the only route for healing and a closure of the natural routes of callus formation. From various directions, less invasive alternatives were developed: functional bracing, external fixation (including the remarkable Ilizarov circular fixator developed in the USSR, which invades the bone only with fine wires) and closed intramedullary nailing. The AO philosophy was modified, for high energy fractures, to 'biological fixation', meaning the application of plates as an internal splint with less surgical exposure and less emphasis on exact anatomical restoration and rigidity of fixation. The change has been from rigidity to stability, not abolishing interfragmentary motion but controlling it. Scientifically, the question changed from the 'biomechanical' – how do we construct a device strong enough to restore structural competence to this fractured bone? It became a question of 'biological mechanics' – what mechanical environment will best encourage the healing of this fracture?

Now the science is taking another step, further in the direction from mechanics to biology. If the mechanical environment influences bone regeneration and hence fracture healing, how, at a cellular level, does it do so? – what molecular signals produce the response? If we know the signals, can we deliver them in the form of recombinant growth factors and hurry the cellular response down the right path? The evolution has been first to use nature, then to ignore her, then to remember her, and now to outdo her. The cynic, who felt that philosophies of fixation were overly driven by the manufacturers of implants, now needs to keep a wary eye on the biotechnology companies.

Given this historical context, an orientation to an optimal future for fracture treatment requires the following: (i) a definition of what optimal treatment means and a way of measuring the extent to which it is achieved; (ii) a review of what we know about the natural healing process that we want to harness or improve upon; and (iii) analysis of how to apply the above to clinical practice.

What is optimal fracture treatment?

The challenges presented by a fracture depend to some extent on the overall nature of the patient and the injury. Three archetypal patients would be as follows:

The frail old lady with fractured neck of femur

A patient teetering on the brink of independent existence with several

co-morbidities. The fracture is really a symptom of her general condition and probably took little force to produce. The priorities are to get her out of bed as soon as possible, to treat her medically and to connect her with appropriate support services to allow a successful discharge.

The young male with a high energy tibial shaft fracture

A young breadwinner, developing a career, is suddenly faced with the possibility of losing his leg, or a long and dominating struggle to keep it. Associated injuries may initially be centre-stage and divert attention from the leg but, if he survives them, it will be the leg injury that holds him back for many months. The soft tissue damage in the leg may be more significant than the bone injury itself and will profoundly interfere with fracture healing. If salvage is appropriate, the top priority is to achieve fracture union, dodging the drastic complications to which he is prone.

The amateur sportsperson's isolated low energy fracture

Closed spiral fractures of long bones, non-comminuted intra-articular fractures; such are the nuisances befalling people whose priorities lie elsewhere, and who would like them to remain so. Such a person needs to be out of action for the shortest possible time and to achieve a functional result that amounts to normality. What they need least, however, is a serious complication of an injury which had every potential to heal uneventfully, due to invasive treatment designed to produce a rapid result.

The important outcome issues in fracture management are illustrated by the above cases. First, do no harm; avoid serious complications. Second, assurance of healing; achieving union when damage to the tissues makes this difficult. Third, the speed of fracture healing. Fourth, rehabilitation of soft tissues, function of the whole limb and the whole patient. To these must be added cost-effectiveness, for choices must always be made and they may differ between centres depending on expertise and resources.

Table 1 depicts how the priorities may differ between patient groups, as represented by the above cases. While many would disagree with some of the judgements in it, most would accept the principle that the challenges involved in achieving optimal results depend on the context.

Table 1 Relative priority of the key outcomes in different types of patient

Type of fracture	Avoid complications	Assurance of healing	Speed of healing	Rehabilitation and holistic care
Elderly fractured neck of femur	++	+	+	+++
High energy long bone fracture	++	+++	+	++
Low energy isolated fracture	+++	+	++	+

How should outcomes be measured?

Progress in optimising results depends on the ability to measure the outcomes described above. This requires not only reliable instruments, but also effective audit processes and scientific study designs, which allow surgeons and their colleagues to obtain the necessary data and react to it. These are expensive undertakings but, unfortunately, the demand for clinical governance, which implies their use, has nowhere been accompanied by the necessary funding up to now. The main reason for the expense is that incomplete data are worse than no data; specifically, outcome data are uninterpretable without data describing severity of injury and co-morbidity. Furthermore, missing cases are quite likely to be the very ones most important to know about. Therefore, addressing even simple questions requires the sort of data-set that takes many person-hours to collate. When treatment hypotheses are under test, the discernment of a clear signal from the noise of individual variation requires large numbers, often across several centres.

The result is that even well organised centres can only take on a few questions, if the answers are to be reliable. Real progress depends on resisting demands for everybody to monitor everything, focusing resources and sharing information.

Complications

A distinction has to be drawn between complications of the injury and complications of the treatment. Sometimes this is difficult; compartment syndrome may be established at the time of presentation, or it may be allowed to develop or even precipitated in the course of treatment. Complications will only be found if they are looked for: late reviews of nailed tibial fractures reveal a high incidence of pain at the entry site which interferes with kneeling[1]; this does not seem a problem when patients are discharged at a relatively early stage. In some patient groups (such as the first archetype above), general complications – pressure sores, chest and urinary infection, thromboembolism – may be of more significance than complications local to the fracture.

However, the main focus is on bad things happening at the fracture site, which occur as a direct result of, or at least are not prevented by, the treatment selected for the fracture. Generally these are encompassed in the phrase 'non-union, malunion and infection'. Non-union is discussed below. Malunion is easy enough to describe in terms of angulation and translation in three planes (including shortening) for long bones and loss of congruity in intra-articular fractures. However, there is very little secure knowledge about the clinical significance of degrees of malunion in different contexts. Research in this area is a priority, since we may be undertaking some invasive surgical procedures for no real benefit.

Infection in bone is difficult to eradicate. Even microscopic fragments of dead bone act as a nidus, larger sequestra and metallic implants render antibiotic therapy ineffectual. Hence the need for thorough cleansing and ruthless resection of devitalised tissue at the initial surgery of an open fracture. Insufficient rigour in performing this step, or the inadvertent introduction of hospital organisms at or around the time of surgery, represent perhaps the most important complication of fracture treatment.

Assurance of healing

An aseptic non-union in a limb with stable soft tissue cover may be a reasonable half-way stage in the treatment of an injury which could easily have resulted in limb loss or established osteomyelitis, and is often retrievable by secondary surgery, with an acceptable final result. Nonetheless, primary union is preferable and, in the vast majority of cases, the failure to achieve it means that a wrong healing strategy was followed, or a good strategy was incorrectly applied.

Systematic evaluation of union rates requires definitions of delayed union and non-union. Some workers use definitions based purely on time elapsed since injury, but a more meaningful definition of delayed union is based on whether the fracture heals before the periosteal response ceases and of non-union on the establishment of radiographic sclerosis across the medullary cavity in the absence of healing[2]. In comparing treatments on the basis of their non-union rate, it is particularly crucial to be sure that severity of injury is taken into account, since the non-union rate in high energy injuries is much higher, irrespective of treatment method.

Speed of healing

The term 'union' is used to describe an end-point of fracture healing – the point at which the injured bone has regained enough strength and stiffness to function as a weight-bearing structure without external support. The definition of such an end-point[2], in what is in fact a gradual process, is naturally problematic, but an objective approach is possible when a mechanical property such as bending stiffness (which is a good predictor of breaking strength) can be measured – as in externally-fixed or conservatively treated tibial shaft fractures[3]. This is impossible when the fracture has been mechanically bypassed by a nail or plate, when we are thrown back on radiological imaging as the only window into the healing process. Despite attempts to devise standard scoring systems[4], and the elaborate quantitation possible in geometrically consistent experimental osteotomies[5], there is currently no radiological method of quantifying healing applicable to human fractures with metalwork *in situ*.

Given a quantitative radiological or mechanical measure, there are two ways to use it. One is to record the time taken to reach a defined point of 'union' — this would be the measure most consonant with clinical decision-making. The other is to express the rate of bone regeneration, or mechanical reconstitution, as a function of time – this would potentially yield more information of interest to researchers. However, most current reports define the point of union by reference to the decision-making of the clinicians treating the patients – this always needs to be considered critically in evaluating their conclusions.

Functional assessment

Recent years have seen recognition by many fracture surgeons of the necessity to look beyond the specific issue of bone healing and restoration of normal bony anatomy in assessing the outcome of fracture treatment. The bone may heal well, but the limb or the whole patient remain functionally poor. There is increasing acceptance of the validity of generic scoring systems such as the Short Form-36 health status questionnaire in the post-trauma patient. However, there is a fear that such generic scores may not adequately reflect the specifically musculoskeletal disability resulting from trauma. The Musculoskeletal Function Assessment questionnaire[6] is said to be more sensitive. Whether the increased complexity of such a questionnaire, and its inability to allow comparison with disability arising from dysfunction in other body systems, will be outweighed by its greater sensitivity has not yet been established.

Finally, it must be emphasised that the most powerful determinant of outcome is the severity of the presenting injury. Measurements of any of the above outcomes, analysed in isolation from indices of injury severity, are completely meaningless. Furthermore, in the case of functional and generic measures, outcome is determined by the combination of all the injuries resulting from a given accident plus any co-morbidities unrelated to the accident. Complex and tedious though it may be, the only valid judgements about treatment efficacy are those which take these facts fully into account.

How do fractures heal?

The striking feature of fracture healing, compared to healing in other tissues, is that repair is by first class bone, not scar tissue. Regeneration is a better descriptor than repair. This is linked to the capacity for remodeling which intact bone possesses. As knowledge deepens, the description progresses from the morphological to an understanding of gene expression and intercellular signalling.

Classic fracture healing concepts

The healing of a long bone fracture has traditionally been described in four phases. This picture has evolved mainly from observations on low energy fractures with a well-preserved soft-tissue envelope, so it can only be taken as a starting point.

Haematoma formation (inflammation or granulation) phase

Activated platelets release a variety of products, including fibronectin, platelet-derived growth factor (PDGF) and transforming growth factor β (TGF-β), which trigger the influx of inflammatory cells. The subsequent cytokine cascade brings the cells of repair (fibroblasts, endothelial cells and osteoblasts) into the fracture gap.

Soft callus formation (proliferative) phase

This is characterised by the formation of connective tissues, including cartilage, and formation of new capillaries from pre-existing vessels (angiogenesis).

Hard callus formation (maturing or modeling) phase

Leads to woven bone, either directly from mesenchymal tissue (intramembranous) or via an intermediate stage of cartilage (endochondral or chondroid routes). Osteoblasts can form woven bone rapidly, but it is randomly arranged and mechanically weak. Nonetheless, bridging of a fracture by woven bone constitutes 'clinical union'.

Remodeling phase

Woven bone is remodelled into stronger lamellar bone by the orchestrated action of osteoclast bone resorption and osteoblast bone formation.

In terms of extracellular matrix formation[7], type III collagen predominates at the inflammatory stage, followed by type II collagen in the cartilaginous phase and type I collagen production at the ossification and remodeling stages. Type IX collagen and aggrecan expressions coincide with type II collagen expression during chondrogenesis. Type X collagen occurs somewhat later during endochondral ossification, in hypertrophic chondrocytes. Osteonectin is present throughout the healing process and peaks during rapid new bone growth.

Radiologically, or histologically in animal models, fracture gap bridging occurs by three routes:

1 Inter-cortical bridging (primary cortical union), in which the fracture gap is obliterated by normal cortical remodeling under conditions of rigid fixation. This mode of healing is the aim in rigid internal fixation[8].

2 External callus bridging by new bone arising from the periosteum and the soft tissues surrounding the fracture. Small degrees of movement at the fracture stimulate external callus formation[9] . This mode of healing is the aim in functional bracing[10] and IM nailing.

3 Intramedullary bridging by endosteal callus. McKibbin[9] described this as a late event, occurring in delayed union when periosteal bridging had failed. However, Rhinelander[11] described it as a very rapid event in undisplaced fractures, bridging the fracture first.

Modification of natural healing by soft tissue injury and fracture treatment

The above description is subject to considerable modification in the context of greater degrees of damage to bone and the soft tissue envelope by high energy injury. It is also modified by surgical intervention, both because surgery may add to the soft tissue damage and because it affects the mobility between the fracture fragments. The two key determinants of whether a fracture will heal and if so, how, are the blood supply and the mechanical environment — the degree of motion experienced by the fracture ends. These set the conditions for the success or otherwise of the bone cells in regenerating structurally competent tissue. On the other hand, stiffening of the matrix by the osteoblasts' work alters the mechanical environment and creates the stability needed for new capillaries to grow and survive. Understanding this triangular relationship is fundamental to both treatment and research in fractures. It is summarised in Figure 1.

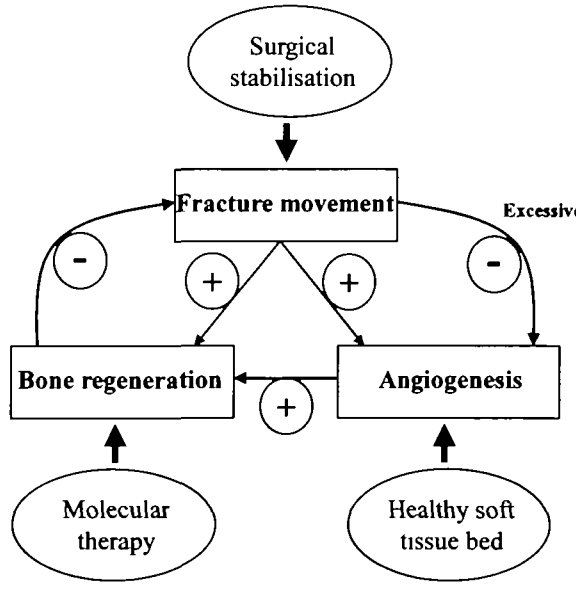

Fig. 1 The triangular relationship at the heart of fracture healing.

Revascularisation during fracture healing

The fracture ends are devascularised over a variable distance and cannot participate directly in the repair process. They must be bypassed, absorbed and then replaced. This is true even in a low energy fracture – but becomes much more significant in high energy injuries. Angiogenesis is the outgrowth of new capillaries from existing vessels and it depends on well-vascularised tissue on either side of the gap and sufficient mechanical stability to allow new capillaries to survive.

Figure 1 illustrates the two key facts about angiogenesis in fracture healing: (i) angiogenesis leads osteogenesis, new blood vessels cross the fracture gap with new bone close behind[11]; and (ii) the mechanical environment determines the degree and pattern of angiogenesis.

The coupling of angiogenesis and osteogenesis is more than temporal coincidence: pericytes and endothelial cells involved in angiogenesis probably also participate in osteogenesis[12] and the mineralisation of soft (cartilaginous) callus depends on vascular invasion, in fractures as in the embryo. The pattern of bony bridging is set by the pattern of revascularisation, which, in turn, is determined by the mechanical environment. If the fracture is held stable, intramedullary blood vessel bridging can occur – along with rapid union by endosteal callus. If there is movement between the fracture ends this cannot happen, but the magnitude of movement will be less in the soft tissues circumferential to the fracture gap; angiogenesis can occur there and periosteal callus will form. The spindle of stiffening callus progressively stabilises the bone ends, allowing capillary and bony bridging in the centre at a later stage.

Vigorous angiogenesis depends on a good blood supply adjacent to the gap, either in the medullary canal or in the soft tissues surrounding the bone. This is why it is so important to resect devitalised tissue at the time of primary surgery and to have a low threshold for importing fresh vascularised muscle by means of a free flap in high energy injuries with muscle loss. It is also a factor which needs to be weighed alongside the mechanical environment when planning surgical stabilisation of the fracture. Plating impairs periosteal blood supply, intramedullary fixation impairs medullary blood supply, reducing cortical blood flow by 60-70% in the short term. External fixation respects blood supply, especially fine-wire fixators.

Influence of the mechanical environment on fracture healing

Figure 1 illustrates that movement between fracture ends can be stimulatory or inhibitory depending on their magnitude. Although excessive interfragmentary movement prevents the establishment of delicate new capillaries across the gap, small degrees of micromotion have been shown to stimulate blood flow at the fracture site[13]. Micromotion

stimulates periosteal callus and can speed up union[14] but it does not stimulate endosteal callus and excessive motion leads to non-union.

A fracture which is rigidly internally fixed produces no periosteal callus, and heals by a combination of endosteal callus and primary cortical union. An intramedullary nail blocks endosteal healing but allows enough movement to trigger periosteal callus. External fixation, particularly with fine wires in a circular fixator, is least damaging to the medullary blood supply and may provide enough stability to allow rapid endosteal healing without external callus[2]. Functional bracing produces insufficient stability to allow rapid endosteal healing in the majority of fractures, but leaves the muscle envelope undamaged to produce external callus.

Bone-forming cells, growth factors and cytokines

Fractured bones heal by a cascade of cellular events in which mesenchymal cells respond to local or systemic regulators by proliferating, differentiating, and synthesizing extracellular matrix. The origin of bone-forming cells is still controversial, but the evidence suggests that periosteal, endosteal and bone marrow stromal cells are the major contributors. There is also evidence that satellite cells of muscle, pericytes and endothelial cells from blood vessels and some circulating blood cells may be capable of re-differentiating into bone forming cells[15].

At some point in the progression from granulation tissue to hard callus, it is presumed that bone-forming cells become sensitive to mechanical loading and respond to it by increased matrix synthesis. This would be the same mechanism as operates in intact bone in the process of remodeling. The point at which this sensitivity becomes established, and the optimum mechanical stimulus to encourage healing, have not yet been established.

Growth factors and cytokines are the means by which cells co-ordinate their activities. Regulatory roles for platelet derived growth factor (PDGF), acidic and basic fibroblast growth factors (aFGF, bFGF), and transforming growth factor-β (TGF-β) in the initiation and the development of the fracture callus have been well documented[16]. These growth factors influence the formation of cartilage and intramembranous bone, and are present in osteoblasts and chondrocytes throughout the healing process. Cytokines (such as the interleukins) are also involved in fracture healing. Haematoma may be an important source of cytokine release during early fracture repair and removal of the haematoma some days after fracture is harmful to fracture healing[17].

What are the promising avenues for biological enhancement?

The aim of enhancement may be to accelerate the healing of a fracture which is likely to heal anyway, or to assure the healing of a fracture

which is likely not to heal without powerful encouragement. Generally speaking, the latter aim is of more value to the surgeon and patient, which is relevant when considering the cost-effectiveness of expensive new treatments. The means of enhancement of fracture healing include both the non-invasive delivery of molecular or physical treatment modalities and the invasive local application of osteogenic molecules or cellular materials.

Non-invasive stimulation of fracture healing using systemic drugs is an appealing option for fracture management. L-dopa has been reported to enhance early stage fracture healing in fracture models[18,19], and has proved effective in the treatment of non-unions[20]. L-dopa may stimulate the uptake of sulphur into the cartilage callus and enhance the endochondral ossification process[19]. FGF-like peptides[21], prostaglandins and some natural herbs[22] are also candidates for the systemic enhancement of fracture healing. None are in widespread use as yet.

The most widely used non-invasive techniques currently are the physical modalities of electrical fields and ultrasound. Despite the difficulties of providing valid control groups in clinical studies, there is now a convincing weight of evidence that pulsed electromagnetic fields significantly influence the healing of fresh fractures[23] and may also enhance the healing of tibial fractures with delayed union[24]. Similarly, Heckman[25] reported clinical and radiographic evidence of accelerated healing in 67 human tibial fractures by ultrasound stimulation, and no serious complications were noted. In a rat femoral fracture model[26], low-intensity pulsed ultrasound at 0.5–1.5 MHz accelerates the early stage of fracture healing and this may be due to stimulating earlier synthesis of extracellular matrix proteins in cartilage, possibly by enhancing chondrocyte maturation and endochondral bone formation[27].

The gold standard invasive technique is autologous cancellous bone grafting, which has long been used extensively in orthopaedic and trauma surgery. It delivers at least some living bone producing cells, bone inductive proteins and hydroxyapatite mineral. Its use, however, is hindered by morbidity at the donor site with pain, scarring and risk of infection. Furthermore, the volume required often exceeds what is available. Alternative graft materials have been sought but none yet provide all the qualities of autologous cancellous bone. The use of autologous bone marrow to enhance fracture healing is beneficial. Bone marrow has been shown to contain a population of mesenchymal stem cells that are capable of forming bone, cartilage, and other connective tissues. Connolly and his associates[28] have refined these techniques for clinical application by harvesting autologous bone marrow and then centrifuging and concentrating the osteogenic marrow elements prior to implantation. Methods of culturing autologous mesenchymal stem cells and the ability of cultured autologous mesenchymal stem cells on the

healing of critical-sized segmental defects in animal experimental models have also been reported[29]. Recently, it has been suggested that a collagen matrix of demineralised human bone may be coated with a composite of the patients own bone cells so providing a living autologous graft without the morbidity of bone harvesting[30].

Other attempts to speed bone healing by using osteo-inductive factors such as recombinant growth factors would seem to be a logical therapy. Several growth factors are potentially beneficial for bone and cartilage healing, such as TGF-β, FGF, PDGF and the bone morphogenetic proteins (BMPs). Although there is increasing evidence supporting the use of these growth factors in fracture treatment, the clinical applications have been hampered by the selection of an appropriate carrier, timing of delivery, the optimal dose and the cost. The delivery carrier should be biocompatible, non-reactive and non-toxic either in its initial form or after degradation. Depending on the delivery method, either by implantation or injection, the carrier can be liquid, semisolid or solid. Among them, porous calcium phosphate-based materials are most desirable, since porosity facilitates contact of the protein with tissue fluids and bone forming cells. Such ceramics may also provide a certain degree of mechanical support while bone or cartilage is being formed. However, the long-term effects of the residual calcium phosphate ceramic material on the modeling, remodeling and mechanical properties of the bone need further investigation. The other widely used form of delivery carrier is type I collagen sponge, which has no known toxic or reactive effects, and can be resorbed completely after 1–2 weeks of implantation. The disadvantage of collagen sponge is that it has no mechanical properties and can only be used as an acute delivery carrier. Timing and dose of growth factors are also crucial and studies on these two topics are very limited; a delivery system with a timed-release capability would be advantageous. The ideal delivery system is yet to be developed.

Key points for clinical practice

One way to use the biological knowledge that is accruing about fracture healing is to apply it to the selection of surgical technique for individual cases. Knowing the three basic routes by which new bone can bridge the fracture, and the mechanical and vascular requirements for each of them to succeed, analysis of the injury often has clear implications as to what strategies for healing may or may not work. Some examples would be as follows:

In a high energy fracture. Interfragmentary motion is needed for stimulation of external callus. A large volume of cortical bone is likely to be

devascularised. Therefore rigid internal fixation, relying on intercortical union, is inappropriate.

In the presence of severe damage to surrounding soft tissue, where IM nailing is considered the best method of stabilisation. Given that intramedullary fixation is sufficiently flexible to allow external callus, but that formation of the latter depends on a well-vascularised soft tissue bed, this fracture is likely to benefit also from the transfer of fresh vascularised muscle by a plastic surgical procedure.

In severe injury with extensive devascularisation of bone and soft tissue, the task of revascularisation may be judged too much to expect. In this case, non-union can confidently be predicted, despite involvement of plastic surgeons in soft tissue transfer. An early bold decision to excise a segment of dead bone, acutely shorten the leg to allow easier reconstitution of the soft tissue envelope, and subsequently relengthen by distraction osteogenesis, can save the patient many months of grafting treatment which may well fail ultimately.

In most low energy fractures there would be several possible routes to successful healing. Two opposite philosophies would be: (i) closed intramedullary nailing, aimed at healing by external callus – this would be the preferred method in most Western centres; and (ii) closed fixation using fine wires with an Ilizarov fixator, aimed at healing by endosteal callus – Russian Ilizarov surgeons claim incredibly short healing times for tibial fractures treated in this way.

A controlled trial, comparing these two on speed of healing, ease of rehabilitation and incidence of complications, has not so far been done. If the latter method does produce faster healing, it would be important to know this before judging the cost-benefit of expensive biotechnological adjuvant treatments designed to be used in combination with IM nailing.

In conclusion, understanding nature's ways of bridging fractures allows more thoughtful deployment of the current armamentarium of surgical technique and may, in the not too distant future, provide effective biological adjuvant treatments which will improve the outlook for patients with fractures.

References

1 Orfaly R, Keating JF, O'Brien PJ. Knee pain after tibial nailing: does the entry point matter? *J Bone Joint Surg Br* 1995; 77: 976–7

2 Marsh D. Concepts of fracture union, delayed union, and nonunion. *Clin Orthop* 1998, 355: S22–30

3 Richardson JB, Cunningham JL, Goodship AE, O'Connor BT, Kenwright J Measuring stiffness can define healing of tibial fractures. *J Bone Joint Surg Br* 1994, 76 389–94

4 Lane JM, Sandhu HS. Current approaches to experimental bone grafting *Orthop Clin North Am* 1987; 18: 213–25

5 Markel MD, Chao EY. Noninvasive monitoring techniques for quantitative description of callus mineral content and mechanical properties *Clin Orthop* 1993; 293: 37–45
6 Martin DP, Engelberg R, Agel J, Swiontkowski MF. Comparison of the Musculoskeletal Function Assessment questionnaire with the Short Form-36, the Western Ontario and McMaster Universities Osteoarthritis Index, and the Sickness Impact Profile health-status measures *J Bone Joint Surg Am* 1997; 79 1323–35
7 Hiltunen A, Aro HT, Vuorio E Regulation of extracellular matrix genes during fracture healing in mice. *Clin Orthop* 1993, 297. 23–7
8 Muller ME. Internal fixation for fresh fractures and nonunion. *Proc R Soc Med* 1963, 56 455–60
9 McKibbin B The biology of fracture healing in long bones *J Bone Joint Surg Br* 1978; 60· 150–61
10 Sarmiento A, Mullis DL, Latta LL, Tarr RR, Alvarez R. A quantitative comparative analysis of fracture healing under the influence of compression plating vs closed weight-bearing treatment. *Clin Orthop* 1980; 149· 232–9
11 Rhinelander FW. Tibial blood supply in relation to fracture healing. *Clin Orthop* 1974, 105: 34–81
12 Clemens TL. Vasoactive agents and bone metabolism. In: Bilezikian JP, Raisz LG, Rodan GA (Eds) *Principles of Bone Biology*. San Diego, CA Academic Press, 1996; 597–603
13 Wallace AL, Draper ER, Strachan RK, McCarthy ID, Hughes SP. The vascular response to fracture micromovement. *Clin Orthop* 1994, 301: 281–90
14 Kenwright J, Richardson JB, Goodship AE *et al.* Effect of controlled axial micromovement on healing of tibial fractures *Lancet* 1986; ii: 1185–7
15 Caplan AI. Mesenchymal stem cells *J Orthop Res* 1991; 9 641–50
16 Einhorn TA. Enhancement of fracture-healing [see comments] *J Bone Joint Surg Am* 1995; 77: 940–56
17 Grundnes O, Reikeras O The importance of the hematoma for fracture healing in rats. *Acta Orthop Scand* 1993; 64· 340–2
18 Waisman M, Schweppy I. Experimental study on healing of bone fractures using L-dopa. *Clin Orthop* 1979, 142. 244–8
19 Gao TJ [Promoting effect of L-dopa on experimental fracture healing]. *Chung Hua Wai Ko Tsa Chih* 1990; 28: 367-73
20 Pritchett JW L-dopa in the treatment of nonunited fractures. *Clin Orthop* 1990; 255: 293–300
21 Gospodarowicz D, Greenburg G, Birdwell CR Determination of cellular shape by the extracellular matrix and its correlation with the control of cellular growth. *Cancer Res* 1978; 38: 4155–71
22 Yu X, Yang Z, Xu S. [The effect of wumingyi chongji on BMP content in callus]. *Chung Kuo Hsiu Fu Chung Chien Wai Ko Tsa Chih* 1997; 11: 153–6
23 Hadjiargyrou M, McLeod K, Ryaby JP, Rubin C Enhancement of fracture healing by low intensity ultrasound [In Process Citation]. *Clin Orthop* 1998; 355: S216–29
24 Sharrard WJ. A double-blind trial of pulsed electromagnetic fields for delayed union of tibial fractures [see comments]. *J Bone Joint Surg Br* 1990; 72: 347–55
25 Heckman JD, Ryaby JP, McCabe J, Frey JJ, Kilcoyne RF Acceleration of tibial fracture-healing by non-invasive, low-intensity pulsed ultrasound. *J Bone Joint Surg Am* 1994, 76 26–34
26 Wang SJ, Lewallen DG, Bolander ME, Chao EY, Ilstrup DM, Greenleaf JF Low intensity ultrasound treatment increases strength in a rat femoral fracture model. *J Orthop Res* 1994; 12. 40–7
27 Yang KH, Parvizi J, Wang SJ *et al.* Exposure to low-intensity ultrasound increases aggrecan gene expression in a rat femur fracture model *J Orthop Res* 1996; 14 802–9
28 Connolly JF. Injectable bone marrow preparations to stimulate osteogenic repair. *Clin Orthop* 1995, 313: 8–18
29 Bruder SP, Kraus KH, Goldberg VM, Kadiyala S The effect of implants loaded with autologous mesenchymal stem cells on the healing of canine segmental bone defects. *J Bone Joint Surg Am* 1998; 80: 985–96
30 Nolan PC, Nicholas RM, Mulholland BJ, Mollan RA, Wilson DJ. Culture of human osteoblasts on demineralised human bone Possible means of graft enhancement. *J Bone Joint Surg Br* 1992; 74: 284–6