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ELECTRICAL STIMULATION AND OSTEOGENESIS

by

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S T A T E M E N T

This thesis contains no material which has been accepted for the award of any other degree or diploma in any University. To the best of my knowledge it does not contain any material previously published or written by another person except when due reference is made in the text and appendices.

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2. D.C. Paterson, T.M. Hillier, R.F. Carter, J. Ludbrook, G.M. Maxwell, J.P. Savage
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5. P.C. Collins, D.C. Paterson, B. Vernon-Roberts, D. Pfeiffer
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6. R.J. O'Reilly, D.J. Cook, R.D. Gaffney, K.R. Angel, D.C. Paterson
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1979 - 1980

Bone growth and impedance, their relationship during electrical stimulation

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CONTENTS

SUMMARY

While electrical stimulation of nonunion of the tibia was first reported by Hartshorne (1841), Lente (1850) and Garrett (1861), interest in the electrical and electro-mechanical properties of bone has only occurred over the past 25 years.

In 1955, the Japanese workers Yasuda, Noguchi and Sata described stress-generated piezoelectric potentials in bone and demonstrated that a one microampere direct current, administered for three weeks, produced new bone growth in rabbit femora. In the United States of America, Bassett and Becker and then Shamos and Lavine, and Friedenberg and Brighton independently reported that (1) bone when stressed developed an electric potential, piezoelectricity, (2) areas under compression became negatively charged and, (3) when an electric current was passed through live bone, new bone formed at the negative electrode.

Much animal work with electrical stimulation followed during the 1960s and interest in its use in human clinical situations has followed. Friedenberg and Brighton in 1971 first reported successful healing of nonunion of the medial malleolus by a semi-invasive technique. Bassett, meanwhile, was evaluating and developing a non-invasive technique using pulsing electromagnetic fields. Dwyer in Sydney,

Australia was using a totally implanted stimulator for long standing ununited fractures of long bones and failed posterior spinal fusions. Many surgeons and workers remained sceptics. Clearly this new device had to be used responsibly or the same fate as befell electrical stimulation in the 19th century might occur. It was considered that, before the implanted bone growth stimulator Osteostim S12 was widely used, its ability to produce osteogenesis in at least delayed union of the tibia in adult dogs should be established.

This thesis describes research, both basic and clinical, with the Osteostim since 1973. It details a sequence of animal and clinical work from the development of a successful model of delayed union of the tibia in dogs (Chapter 2), to the study of the effect of an electrical bone growth stimulator utilising that model (Chapter 3), and the clinical trial in Australia utilising electrical stimulation as a means of treating delayed union and nonunion of bone and congenital pseudarthrosis of the tibia in childhood (Chapters 4 and 5). There follows further studies in animals designed to elucidate the effects of varying current levels of electrical stimulation (Chapter 6), and relationship between bone formation and impedance of electrical current flow (Chapter 7). Finally, the study investigated and designed a titanium cathode for use in implant surgery (Chapter 8).

The findings of this sequence of experimental and clinical studies are summarised below.

A consistently successful model of delayed union of the tibia was eventually developed and was used to determine the effect of the Osteostim in a controlled double blind trial using active and inactive generators. Independent qualitative assessments were made by radiography, gamma imaging, clinical assessment and histopathology. Statistically, there was a significant association between the active stimulator and superiority of bone healing ($p \leq 0.02$). The conclusion was that this commercially available direct current stimulator produced significant osteogenesis at four weeks in the experimental model.

As a result, a controlled clinical trial was carried out in Australia from 1976-1978. Strict criteria were used for case selection for this trial. Two surgical techniques were developed and used in all cases. Fracture healing both clinically and radiologically was achieved in 72 of 84 patients (86%). Further, union was achieved in 83% after previous failure with one or more cancellous bone graft operations and in 86% of chronically infected tibial nonunions. These results compared more than favourably with other standard forms of treatment and had similar success rates to the other techniques of electrical stimulation. Similar successes followed its use in ununited fractures of the scaphoid and failed posterior

spinal fusions. An attempt was also made to assess the ability of serial nuclear scan studies, using technetium 99m methylene diphosphonate, to differentiate between normal and delayed union following fracture of the tibia. This study did not reveal any significant difference.

Perhaps the most spectacular clinical success in the clinical trial has been with congenital pseudarthrosis of the tibia. A surgical technique of management was developed. It has been reported that there were 6 successes out of 7 cases. These results are superior to other reports especially when it is realized that the incidence of amputation in the literature varies from 11% to 40%.

Different current levels have been used experimentally and clinically. No attempt has been made to ascertain the optimum current level in a situation of delayed healing of a long bone and many authors have expressed concern about this. A modified model of delayed union of the tibia of adult dogs was developed. Histological, nuclear scan and biochemical assays established in a preliminary study that bone activity had largely subsided after 4-6 weeks and that the maximum histological difference between normal unstimulated and stimulated bone healing occurred after three weeks stimulation. While many studies have confirmed that a current level of 20μA produced significant

new bone, this study subsequently failed to detect any difference in bone formation with a 20 μA current let alone detect any difference between different current levels. The model, despite a preliminary study, proved to be unsatisfactory. However, the biochemical assays of serum calcium, phosphorus and alkaline phosphatase showed a pattern of responses normally seen in trauma.

A further study was designed to firstly test the hypothesis that, as a result of bone growth stimulation in the vicinity of a titanium cathode, there would be a temporal relationship between bone formation and the impedance to current flow to the cathode and secondly, to evaluate both quantitatively and qualitatively the use of titanium as a cathode. The study revealed that the impedance to current flow to an electrically stimulated titanium cathode did not change appreciably over a 12 week measurement period. Quantitative assessments established that osteogenesis significantly resulted from electrical stimulation using a titanium cathode and that no adverse reactions were observed to the titanium.

After nearly two decades of experience with total joint arthroplasties, many complications have become apparent, particularly loosening of the implant/ methylmethacrylate junction. Increasing efforts are being made to design implant prostheses, particularly porous coated prostheses to enable living bone to be in

direct permanent contact with large areas of the surface of the implant, thereby anchoring the prosthesis to the bony cortex. It would be a major advance to avoid the use of cement and, even more so, if bone formation could be enhanced by electrical stimulation.

A preliminary study has been carried out in adult dogs and sheep to try and determine the aperture size for maximum bone growth, both extramedullary and intramedullary. Variable amounts of bone grew into the apertures in titanium metal plates placed on the cortical surface of the femur but significant bone grew around and into a titanium mesh placed in the intramedullary cavity of the upper femur. A titanium mesh cathode can now be designed and incorporated around the stem of a porous coated prosthesis. Future research will try and determine if there is any significant advantage in electrically stimulating such porous coated prostheses.

Electrical stimulation clearly augments osteogenesis and is potentially an important advance in orthopaedic surgery. In addition to possible use in replacement joint surgery, there is evidence of beneficial effects in the treatment of osteomyelitis, healing of skin ulcers and wounds, and of articular cartilage regeneration.

The long term effects of electrical stimulation are not known. Many questions remain unanswered. Its future use is exciting if it is used responsibly and with care.

SIGNIFICANT CONTRIBUTIONS OF THIS THESIS

1. A detailed review of the literature on electrical stimulation of bone growth and fracture healing has been carried out.
2. A consistently successful animal model of nonunion of the tibia has been developed.
3. A controlled double blind trial, where independent observers did not know the coding of the stimulators and did not collaborate with each other, has evaluated the use of a direct current bone growth stimulator in such an animal model.
4. A multi-centred research programme using a totally implanted bone growth stimulator - Osteostim - for delayed union and nonunion of long bones was carried out in Australia. A technique for insertion of the implanted bone growth stimulator was devised and has been used internationally. Evidence has been presented to indicate the wide variety of situations in which this Osteostim can be used safely and successfully. Its use as a means of treatment for delayed union and nonunion in adults has been established.
5. A technique for treating congenital pseudarthrosis of the tibia with direct current stimulation has been developed.

6. No significant difference in the pattern of uptake of bone-seeking traces using technetium-99m-methylene diphosphonate was found between normal healing and delayed or nonunion of the tibia in humans.
7. The model of delayed union of the tibia in adult dogs was re-evaluated quantitatively and qualitatively. The use of titanium as a cathode material was evaluated and titanium proved to be an inert and effective cathode material.
8. The impedance to current flow to an electrically stimulated cathode was evaluated and no relationship was found between bone formation and impedance to current flow in the region of the cathode.
9. An intramedullary titanium mesh was designed to surround the porous surface coating of the intramedullary stem of a metal implant. As a result, active electrical stimulation can be successfully applied to such an implant successfully and this potentially is a major advance in orthopaedic surgery.

CHAPTER 1

HISTORICAL REVIEW

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CHAPTER 1

HISTORICAL REVIEW

1. INTRODUCTION

Cochran [84] has said: "Accelerating the healing of fractures by artificial stimulation of osteogenesis is an exciting prospect. Great benefits would accrue to orthopaedic patients if the processes of bone healing could be brought under the command of the surgeon, permitting the formation of bone on demand in order to aid in the repair of fractures, nonunions and other skeletal defects ...

Formation of bone can be stimulated by artificial application of electrical energy under appropriate experimental conditions. Although considerable development of procedures is still required, practical clinical applications are foreseen ... Under carefully controlled conditions, relatively early trials might be appropriate in established cases of nonunions and in other bone defects that fail to respond to vigorous courses of standard treatment ...

Whatever the application of this remarkable technology, one fact must be kept in mind. Bone produced by electrical stimulation has been created artificially. Once formed, the bone must be maintained by continuance of the appropriate stimulus, either artificially or naturally, from physiological mechanical stresses. Otherwise the

new bone probably will be resorbed by normal processes of remodelling in accordance with Wolff's law".

2. EARLY EXPERIENCE WITH ELECTRICAL STIMULATION

It was Becker [44] who noted that Galvani in his work "Commentarius" in 1791 [115] reported a number of observations clearly relating electricity to the nerve muscle preparation which he interpreted as evidence for intrinsic "animal electricity". A major scientific debate developed in the mid 19th century when, in 1861, the "Bernstein" hypothesis [47] of a travelling wave of deep polarization in the nerve membrane became the accepted scientific thinking. Throughout this period of intense debate, clinicians of all sorts were enthusiastically applying "galvanic"(DC) and "faradic" (AC) currents to a wide variety of patients.

So far as can be ascertained, electricity was first used to heal fractures by a Mr. Birch, one of the surgeons of St. Thomas's Hospital, London. This was reported in 1841 by Dr. Edward Hartshorne [87, 131] in his monogram "On the Causes and Treatment of Pseudarthrosis and Especially of That Form of It Sometimes Called Supernumerary Joint". Hartshorne refers to the treatment of tibial nonunion using "shocks of electric fluid passed daily through the space between the ends of the bones" for six weeks.

Lente [169] presented a series of case reports concerning the use of electricity to cure nonunions and pseudarthrosis. Lente observed "It is a mode of treatment, moreover, which

is not likely to be adapted by the physicians in ordinary practice or by one in the habit of performing surgical operations of importance. Electricity by the ordinary galvanic apparatus is of easy application, not very painful and in no way dangerous. It is therefore one which I think should always precede the other means. But to be at all efficient, it must be applied in connection with acupuncturation. It appears to have little or no effect when the poles of battery are applied merely to the soft parts on either side of the fracture, as the current does not appear to reach the bone at all. This is especially true in cases of the thigh where the muscular covering of the bone is so thick".

In 1853, in the British publication "The Medical Times and Gazette", the caption to an item read "Galvanism to the ununited fracture". The item stated "A case occurred some months ago, at York County Hospital, in which, under the care of Mr. Holl, the House Surgeon, galvanism was employed for the production of union in an ununited fracture. Mr. Holl introduced a needle from each side of the limb into the interspace between the bones and then passed a continuous galvanised current through. The operation was repeated every day for a fortnight, and a cure ultimately resulted. The fracture was of the leg, very movable and had existed more than a year".

In 1861, the technique had progressed to the point that Dr. A.C. Garrett, a Fellow of the Massachusetts Medical Society of Boston, published a compendium of

"Electrophysiology and Electrotherapeutics" [117] dealing with a wide range of clinical conditions and reported good results in nonunions he treated with the whole electrical stimulation procedure. His treatment for pseudarthroses was the application of direct current through gold needles, insulated except at the tips which were inserted into the site.

Gayda [118] in 1912 first described the electrical potentials generated when bone is loaded. However, apart from a report of the effect of electrolysis on bone by Walter in 1941 [273], no scientific attention was directed towards electrical stimulation and bone healing until the work of Yasuda and his colleagues in Japan in the mid 1950s.

3. INITIAL EXPERIMENTAL WORK

Initially, Yasuda [291] in a series of experiments, firstly fixed one end of a long bone and suspended a weight from the other and this tended to bend the bone (Fig. 1.1). He found that the concave or compressed side of the metaphysis became electronegative and the convex or tension side became electropositive (Fig. 1.2). Furthermore, this occurred in both fresh bone and also in dead bone that had been boiled in saline. In a further experiment, Yasuda [292] continuously applied a 1 microampere electric current for three weeks to the femur of a live rabbit using vitallium needle electrodes. He found that a ridge of callus formed between the electrodes and that more bone formed at the cathode than at the anode (Fig. 1.3).

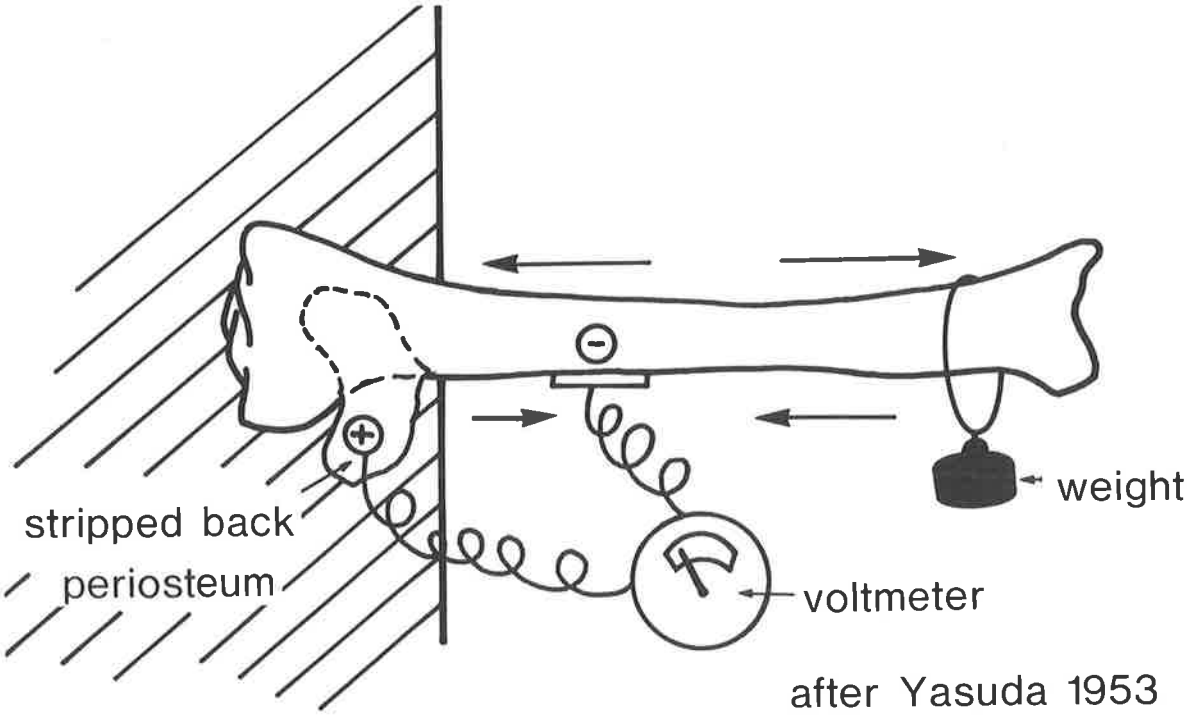


Fig. 1.1 An electrical charge associated with bending bone

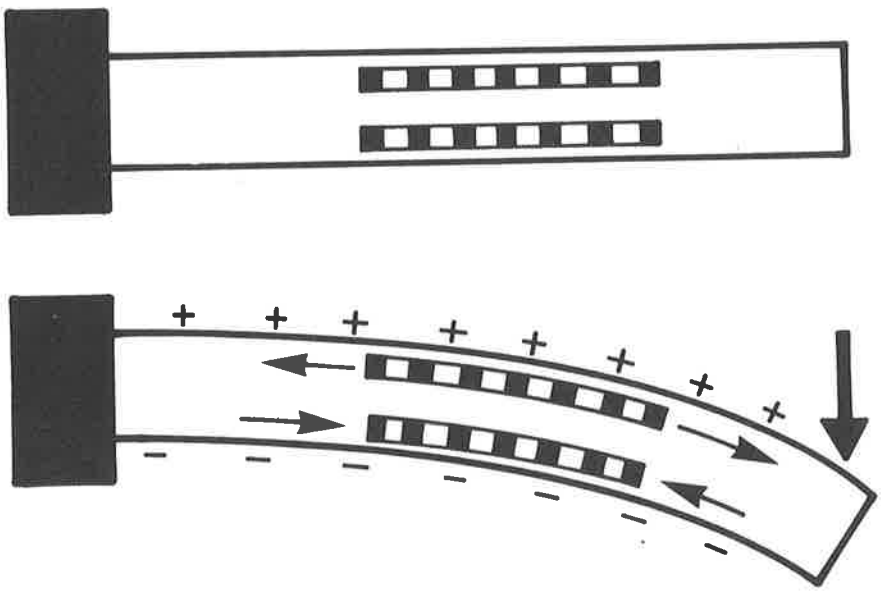
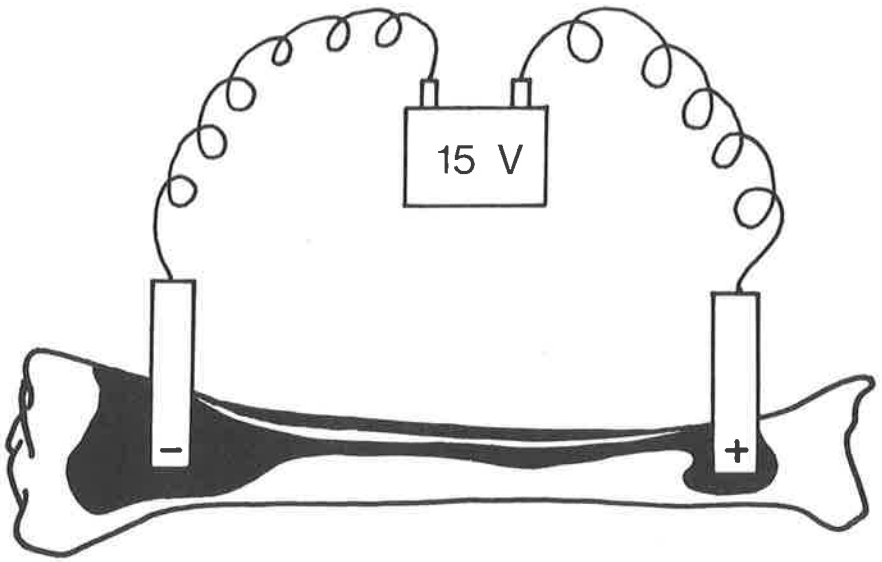


Fig. 1.2 A schematic diagram of a piece of bone under tensile and compressive loading



after Yasuda 1955

Fig. 1.3 A ridge of callus formed between two electrodes, more bone formed at the cathode than at the anode

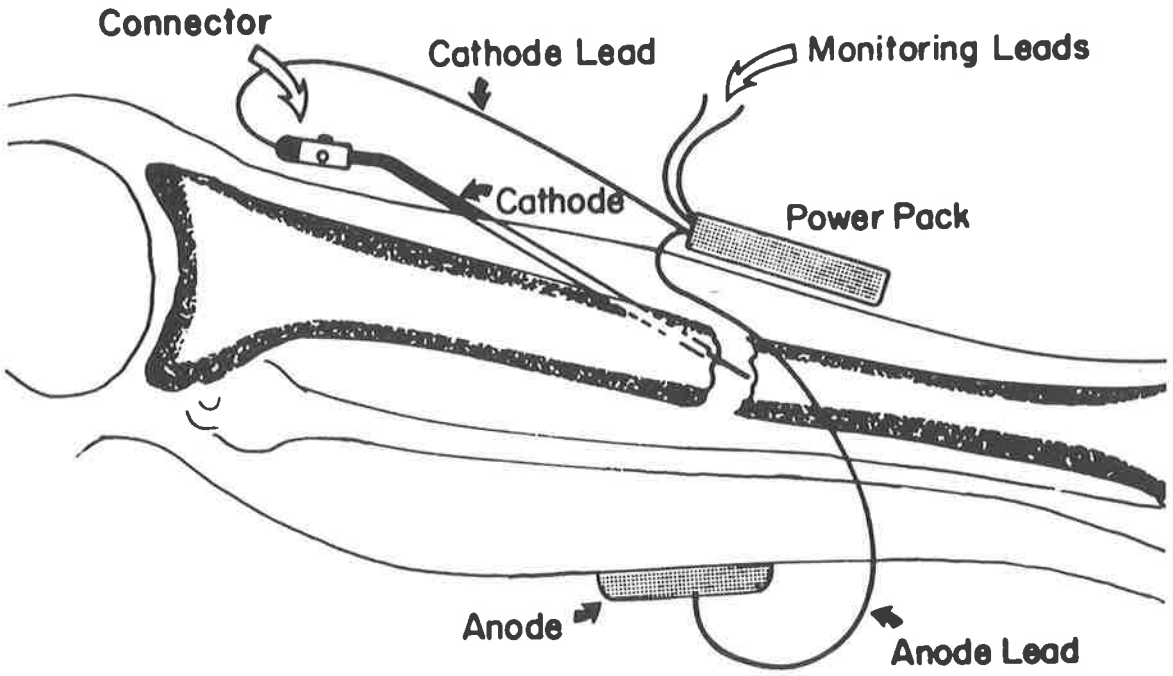


Fig. 1.4 The semi-invasive technique of Brighton

4. THE BIOELECTRIC BEHAVIOUR OF BONE

(a) Piezoelectricity

The bioelectric behaviour of bone was first reported by Fukada and Yasuda [113] when they interpreted the phenomenon as a classic piezoelectric effect. Piezoelectricity is simply electricity resulting from pressure on crystals. It consists of the generation of a pulse of electrical current by the mechanical deformation of a solid crystal having an asymmetric lattice and it is dependent on the rate and magnitude of deformation. Iida [141] and Fukada and Yasuda [113] were able to extend their original observations on stress-generated piezoelectric potentials and showed that it was the collagen portion of the bone matrix rather than the mineral apatite that was responsible for the effect.

At the same time as the Japanese workers were producing their results, and quite independently, Bassett and Becker [17] in the late 1950s and Shamos and Lavine [233, 234] in the early 60s were undertaking similar experiments in the United States. They observed the production of electrical pulses from bone subjected to bending rather than compressional stress. Cochran [84] subsequently observed that these effects were present in the smallest structural unit of bone and consequently each osteocyte was subjected to strong electrical influences.

Friedenberg and Brighton [105] began studies on living non-stressed bone in 1961 and reported another kind of electrical potential in bone. They found that bone in an unloaded condition had a bioelectric or steady-state potential which was dependent on cellular viability and they showed that areas of active bone growth and repair were electronegative when compared to less active areas, the metaphysis being electronegative to the epiphysis.

It should be remembered that bone has two main components. A low modulus, organic matrix of fibrous protein and gelatinous ground substance and a high modulus, inorganic mineral phase. While there are small amounts of sodium, magnesium and carbonate present in the mineral phase, bone can be viewed simply as a collagenous protein matrix impregnated with crystals of hydroxyapatite.

Other workers [32, 33, 34, 35] investigating the origin of the stress-generated potentials established that semi-conduction properties were present for both the collagen and hydroxyapatite of the bone matrix with the formation of a specific type of solid state rectification device, PN junction diode by the organisation between the two in normal bone. Electricity theoretically could be generated by stress or bending of collagen fibres themselves or a stress of the collagen/hydroxyapatite interface.

Shamos and Lavine [234] concluded that stress-induced potentials in bone were basically of a piezoelectric nature and they did not find any merit in the proposed semi-conductor mechanism which was due to assumed changes between the organic and inorganic phases. Further, they [159, 235] found that a number of soft tissues, for example skin, also exhibited piezoelectricity and the effect appeared to be associated with orientated fibrous proteins such as collagen. They further hypothesized that piezoelectricity may be a universal property of all living tissues and was probably a significant physiological phenomenon.

Bassett et al [18, 20] considered that, under the influence of low level direct electric currents, bone formation depended on the polarity of the applied current and then, utilizing a completely implanted direct current generator, they observed that bone growth was limited to the area of the cathode. This has subsequently been confirmed by many workers [108, 109, 161, 207, 287,] but some reports have been equivocal [88, 106, 193, 198]. Becker [35] postulated that the piezoelectric effect was limited only to control of bone growth in response to mechanical stress, and that fracture healing was controlled by another system. Bassett [19] considered that the bioelectric potentials exhibited in bone were physiologically significant and were probably

involved in a negative feedback control system to control bone architecture. Cochran [83] did not find any significant difference between the potential patterns of dead and living bone in response to mechanical stress. However, Marino and Becker [183] subsequently showed that the measurable electric potentials from a stressed, whole human femur, exhibited a pattern that would have resulted in appositional bone growth and resorption in accordance with the known concepts of Wolff's law.

Many years ago in 1892, the German Anatomist, Wolff, [289] published his most famous work "The law of bone transformation". The most simple and direct quotes of his law are; "the form of bone being given, bone elements place or displace themselves in the direction of functional pressure and increase or decrease their mass to reflect the amount of functional pressure" or "every change in the ... function of a bone is followed by certain definite changes ... internal architecture and external conformation in accordance with mathematical laws".

By the mid 70s, most authors based their reasoning for the use of electricity upon the piezoelectric property of the bone matrix itself and, in particular, the collagen. [184] It was Bassett [27] who considered that the collagen molecule became stretched out as it deformed producing a charge from the shearing stresses on the intra- and intermolecular bond.

(b) Streaming potentials

Another source of charge in bone is the extramolecular charge separation which comes primarily from "streaming potentials" which are produced by vascular flow and the movement of extra cellular fluid through the extra cellular matrix [27, 100]. It differs from piezoelectricity in a small way - mechanical force produces structural deformation and this produces a charge or piezoelectricity; while in "streaming potentials" a hydraulic force is used to produce ionic motion and as the ions of charged cell membranes move across the surface of the fixed charge, they have an electrostatic propulsion. *In vivo*, there are a variety of sources of electrical charge and the cell finally sees a total bioelectrical response from all these many different forces - gravity, piezoelectric potentials, streaming potentials, muscle potentials.

Therefore, it has been supposed that mechanical force, electrical charges and cell response are inter-related and all are linked together in a negative feedback control system where an extrinsic force acts on the skeleton to produce an electric charge which directs cellular activity producing a structural response which is appropriate to resist the force. Yasuda [293] stated that it may be possible for electrical current alone to initiate bone proliferation without mechanical stimuli and he showed that both

the type and direction of callus could be controlled by an electrical current and that an electrode could lead to callus formation.

(c) The origin of stress-generated potentials

The origin of stress-generated electrical potentials is still in dispute but is thought to result in part from the piezoelectric mechanism in which the crystalline structure of collagen is the generating unit, and in part from "streaming potentials" which result from the squeezing of electrolytes through the canaliculae of bone. Bassett [17] originally postulated that these collagen-generated electrical phenomena affect bone cells and were responsible for the ability of bone to remodel itself in accordance with Wolff's law, in response to altered mechanical demands by some feedback control system. In addition, however, bone is subjected to other types of electrical influence from "streaming potentials" to action potentials from the nerves that enter bones and from the surrounding muscles. The significance of these influences is unknown. It may be that bone behaves as a transducer of the conversion of mechanical into electrical energy and the magnitude of the latter is proportional to the mechanical stress applied.

In summary, many authors had shown that (1) bone when stressed, developed an electrical potential, piezoelectricity, which was proportional to the applied stress, (2) areas of bone under compression became negatively charged whereas those areas under tension became positively charged, [19, 256,] (3) when an electric current was passed through live bone, new bone formation was stimulated at the negative electrode. [18]

5. ELECTRICAL STIMULATION AND REGENERATION

Becker, [46] in 1981, stated that "Despite its unique structure and its now proven specific electronic properties, bone is still a tissue within an intact organism and there would appear to be no compelling reason to consider its healing properties to be different from the remainder of the body tissues or to have them subject to a different "set" of control. From a biological point of view, fracture healing appears to be the last vestige of regenerative growth available in any component fashion to man ... Concurrent with the investigations on electrical osteogenesis, a major change in the direction of research on regeneration also occurred".

Indeed, it was Becker [31] in 1961 who first indicated that electrical currents were involved in regeneration and postulated that the negative current of injury might be the cellular stimulus producing the blastema of

regenerative healing. Becker and Murray [36] considered the processes occurring at the cellular level in bone regeneration in amphibians. The authors were primarily interested in identifying the factors inducing and regulating the cellular processes of fracture healing. One of their significant findings was that the blastema was not derived solely from periosteum but was more directly the result of the fracture haematoma and, more specifically, nucleated red cells were found to be involved in dedifferentiation. They stated that this cellular activity had all the characteristics of a regenerative healing process with "the callus" of the orthopaedic surgeon being the "blastema" of the biologist. Becker [42] stated that the growth process following electrical osteogenesis was characterized by direct osteogenesis from the periosteum and by the appearance of a mass of primitive cells in the medullary cavity, which subsequently underwent mitosis followed by a differentiation into cartilage and bone. With electrical osteogenesis, intramedullary blastema formation is very important. Biologically, then, electrical osteogenesis is the electrical stimulation of a normal regenerative growth process.

Becker and Spadaro [38] stimulated partial limb regeneration in rats by the application of appropriate low magnitude negative currents to the amputation stump. They concluded that regeneration, like fracture healing, was a two phase process in which the initial phase of cellular stimulation was driven by the electrical factors,

and the second phase of growth and redifferentiation was controlled by completely unknown factors. Becker [46] has concluded that "The growth response of bone to direct current electricity is then not a process unique to bone, but is one to be viewed in the broad concept of regenerative healing in general, in which it is only one of the tissues capable of being formed by the primitive blastema ... It would therefore appear to be technically incorrect to ascribe the growth response of bone to direct current to the piezoelectric properties of bone matrix, and in any clinical situation in which electrical currents are introduced into a bone, it would be erroneous to believe that bone was the only tissue capable of responding to them".

Consequently, there is still doubt as to the origin or process by which electrical potentials are generated. The general consensus is that three factors are involved. (1) Stress induced bioelectric potentials are the result of both the piezoelectric effects of collagen and streaming potentials due to fluid flow in the canaliculae. (2) When a fracture heals, the first step involves the formation of reparative tissue called a blastema (initial soft callus) which is an accumulation of primitive undifferentiated cells at the trauma site. It is now believed that a large proportion of these undifferentiated cells actually result from dedifferentiation of nucleated red cells in the fracture haematoma [36, 37] and once formed, the blastema

subsequently undergoes mitotic activity. (3) Finally, bone exhibits an unloaded or static electrical potential in vivo. These potentials along the bone exhibit specific patterns that are altered when a fracture occurs and the bone ends become highly electro-positive. However, the potentials return to normal once bone healing has occurred [18, 107].

6. CAUSATIVE MECHANISMS IN CURRENT INDUCED OSTEOGENESIS

While the mechanisms operative in current-induced osteogenesis are unknown [112], possible causative mechanisms in the enhancement of new bone growth under the influence of electrical stimulation can be considered. It was Yasuda [292] who initially believed that osteogenesis was produced by mechanical, chemical or electrical irritation. Other mechanisms have been postulated since his original work.

(a) Cellular effect

Bassett [20] postulated originally that these electrical phenomena could affect bone cells. Since then, others [27, 38, 112] have postulated that very small currents lead to cellular differentiation or perhaps dedifferentiation of blood cells to produce a primitive cell, followed by redifferentiation into cartilage and then bone cells. They also considered that direct current produced dedifferentiation of marrow and endosteal cells to produce osteoblasts in close proximity to the cathode.

Lavine and his co-workers [161, 165] were intrigued at what happened at the cellular and ultrastructural levels and reported, with electrical stimulation, an increase in the number of mitochondria which became atypical and swollen and released an electron lucid substance into the extra cellular matrix.

Bassett [18] considered that the degree of osteogenesis was associated with an increase in the mitotic rate of differentiation of young mesenchymal cells and osteoblasts. Brighton [63] postulated that an electric field had a direct effect on the bone or cartilage cells and, as a result, various enzyme systems might bring about specific physiological responses of the bone or cartilage cells.

Others [23, 26, 136] considered that electrical stimulation influenced the microenvironment of the osseus cells and subsequently produced bone healing. Janssen [146] suggested that stimulation of bone cells was related to depolarization of the normal potential difference and considered that this explained bone formation in normal fracture healing.

(b) Collagen

Some [20, 33] have demonstrated that collagen fibres became orientated in an electrical field and considered that such orientation led to a spatial arrangement which enhanced calcification.

Clearly, an important factor in electrical osteogenesis is the action of electricity on the formation, alignment or mineralization of collagen.

(c) Local tissue oxygen tension

Brighton [61, 62] indicated that the known effects of direct current on the microenvironment of the cells was to lower the local tissue oxygen tension which was favourable to bone formation. They suggested a strong possibility of an electrochemical component to the mechanism of electrical osteogenesis.

Others [49, 67, 86, 135, 249, 263] have all considered that at least part of the osteogenic effect related to the prevailing oxygen tension at the tissue level. Friedenberg, Brighton and their co-workers [58, 112] have postulated that the very low oxygen tension may also induce pluripotential cells to differentiate into chondroblasts or osteoblasts.

Brighton and Friedenberg [60] considered, however, that if a lower oxygen tension was a factor, other mechanisms must be operating and electromagnetically induced currents would need a further mode of action as no such oxygen decrease occurs with this type of electrical stimulation.

(d) pH in the vicinity of the cathode

Many [27, 49, 57, 62, 86, 125, 263, 290] have shown that the pH in the vicinity of the cathode increases. The pH at the bone/cartilage junction in the growth

plate, that is in the zone of hypertrophic cells, is alkaline and alkalinity in the vicinity of the cathode enhances the activity of the osteoblasts and calcification.

Black [49] found an increase in pH within a sphere radius of approximately 0.5 cm while Hamblen [125] noted that osteoblasts contained large amounts of the enzyme alkaline phosphatase that will only work in alkaline conditions.

(e) Epiphyseal plate mitochondria

Brighton [58], Friedenberg [112] postulated that epiphyseal-mitochondria released calcium in low oxygen tensions to initiate the calcification process and that alkalinity in the vicinity of the cathode induced calcification. Lavine [165] showed an increase in the mitochondria resulting from electrical stimulation.

(f) Calcium

Jahn [145] suggested that a negative pole would attract calcium ions, even though they were not particularly mobile, and the positive pole would attract chloride ions, which would in turn displace the phosphate ions towards the negative pole.

Lavine et al [161] believed the transmission of signals from one cell to the next was accomplished by a combination of chemical and electrical means.

This transmission was a highly specialised function mediated through a complex of biological physical factors. They contended that the local changes may be effected through the action of calcium ions as it was known that the association of bound calcium could be induced electrically and that calcium ion had a profound effect on cellular and enzyme functions. Others [22, 26, 27, 66, 185, 290, 296] have noticed differential ionic accumulation of calcium around the cathode and have considered that this may be one of the mechanisms by which specific biological effects, particularly cell division, were produced. Bassett [28] suggested that pulsed electromagnetic fields produced an increase in the calcium content of experimental chondrocytes and, as a result, calcification of a fibro-cartilage was an important step preceding osteogenesis.

(g) Other mechanisms

Zichner [296] found significant hyperaemia associated with electrical stimulation, while Connolly [85] noted increased osteogenesis in the presence of infection.

(h) Summary

Clearly, any or all of these factors may be involved in osteogenesis following electrical stimulation. All forms of applying or inducing electricity may have as a common denominator the same basic cellular mechanism of action. All methods

may "trigger" intercellular nucleotides to lead to either cellular differentiation or proliferation. Clearly, a low oxygen tension and an increase in pH are favourable to bone formation and, as these changes occur around the cathode during electrical stimulation, they must be important factors in osteogenesis.

Stan [254], Hassler [132], Becker [36] concluded that bone needs only the appropriate "triggering" stimulus. They believe that electrical stimulation enhanced the nutrition of osteocytes and suggested that the accumulation of calcium ions at the cathode produced mesenchymal cells which differentiated into osteoblasts. Hassler [133] later was of the opinion that the electric current was not acting as a "triggering" impetus and that electrical augmentation could only increase the healing rate by a finite percentage.

Becker [41, 44] considered that electrical stimulation "re-starts" activity of the cell population - a process which is identical to the normal healing process of a fracture. He considered that the end result in all was the stimulation of the endosteal marrow cell population.

While there is abundant evidence that lowering the local tissue oxygen tension and raising the pH in the vicinity of the cathode are conducive to bone formation, Brighton [69] believed that more direct effects of

electricity on the cell, especially at the level of the cell membrane, may play a role that is far more significant than the oxygen and pH effects.

7. TYPE AND SIZE OF CURRENT USED

The majority of studies that have investigated the effect of electricity on bone have dealt with direct current. It has been found that, with direct current stimulation of osteogenesis, resistance builds up rapidly between electrodes when they are inserted into tissues. As a result, there is a decrease in current and, if a constant current is to be maintained, the power source must contain a transistorized control circuit so that as the resistance increases the voltage will increase and the current will remain constant.

(a) Direct current

Most early investigators [18, 106, 161, 164] used a DC stimulator with the battery connected in series with a resistor. In such a circuit, the current applied was difficult to control because of polarization effects by body fluid and a drop in battery voltage with time. Constant current sources were first used in the 1970s [96, 100, 109, 112] and consisted of transistor circuits supplied from hearing aid batteries.

Using a constant current source, electrically induced osteogenesis exhibits a typical dose - response curve. It has been shown [69, 108] that using

a stainless steel cathode, current levels of less than 5 microamperes produce no bone formation; current levels of 5-20 microamperes are associated with increasing amounts of bone formation while current levels of more than 30 microamperes are associated with increasing cellular necrosis.

Others [85, 107, 112, 189, 264, 265, 287] have all concluded that the maximum osteogenesis occurred when 20 microamperes constant current was used. Pawluk and Bassett [207], however, found osteogenesis around the cathode when using a 3-4 microampere current.

Bone destruction around the anode has been observed by many workers [18, 69, 96, 106, 108] and Brighton [69] has said that varying amounts of cellular necrosis may occur in the vicinity of the anode depending on the metallic composition of the anode, the surface area of the anode, and the current amplitude. He reported that cellular necrosis at the stainless steel anode increased in amount as the current amplitude increased and decreased in amount as the surface area of the anode increased. He further stated that the amount of necrosis occurring around an implanted stainless steel anode at current levels that were osteogenic was tolerable in laboratory animals but not in patients.

The location of the cathode [69, 109, 132, 249] within the osteotomy, and therefore within the site of nonunion, has been shown to be the most effective cathode/electrode placement for enhancing osteogenesis.

(b) Pulsed current

Some [83, 170, 171, 173, 254, 287] have suggested that monophasic pulsed currents of low frequency and short duty cycle, that is, little ratio between pulse width and period, can stimulate a strong osteogenesis.

(c) Pulsed voltage

Herbst [136] found that new bone formation was observed around both the anode and the cathode with this type of electrical stimulation though more bone was present around the cathode.

(d) Alternating current

Iida [141] and others [21, 287] found osteogenesis was produced by a symmetric AC current i.e. by an alternating current containing a direct current component. However, Brighton [69] was of the opinion that, to date, alternating currents had not been shown to be capable of producing significant amounts of bone formation. Spadaro [249] found that a DC current was as good as or better than an AC pulsed current.

(e) Electromagnetic field stimulation

In his preliminary studies, Bassett [21] found that osteogenesis is produced by asymmetric AC only, that is, by AC containing a DC component.

Bassett [24] used constant and pulsed capacitively coupled electric fields in their initial studies on rabbits and found an increasing rate of repair of fibular osteotomies. Bassett [22, 23] and his co-workers subsequently found stimulation with an inductively coupled-electromagnetic-field was more promising. They considered [22] that "the major effects of electromagnetic-field stimulation were exerted on the architectural and maturation aspects of the reparative process; that is, the healing process was accelerated".

Kraus and Lechner [156, 157] used a similar technique to Bassett, the difference being that the external alternating magnetic field acted upon specially implanted pick-up coils. In these coils, attached to the insulated screws of the osteosynthesis plate serving as electrodes, an alternating current was induced by the magnetic field variations.

Spadaro [247] has drawn attention to a problem inherent in the implanted electrode, direct current, stimulation technique that has been largely ignored. This refers to the composition of the electrode. The concept that a metal clinically inert in normal practice would be similarly inert when it was passing

electrical current *in vivo* is not correct. Spadaro has shown that there were major electrochemical differences among electrodes of different materials even when operating at the same potential.

Different metals exhibit different dose-response curves at the cathode. Brighton [69] has said that optimum bone growth occurs at a lower current amplitude (5-8 microamperes) with a platinum cathode than with a stainless steel. Becker and Spadaro [45] have shown that optimum bone growth with a silver cathode occurs in the 0.1-1.1 microampere range.

It is clear that osteogenesis can be induced by different types of electrical stimulation. However, Becker and others [41, 46] have stressed that the currents and voltages used are much higher than those measurable in nature and the question of the optimum type and magnitude of electrical stimulation must be kept open. While no major undesirable side effects have been reported with the various types of electrical stimulation, a very real concern [45, 46, 84] would be the stimulation of an unsuspected pre-existing malignant lesion in any tissue in the treatment area. While laboratory investigations and animal experimentation clearly demonstrate the growth-stimulating action of minute electrical currents on many tissues including bone, there is evident disagreement as to the optimal type of current and method of its administration. The great importance of the concept and its implications for future treatment requires that present clinical applications be made with great care and deliberation [46].

8. ELECTRICALLY INDUCED OSTEOGENESIS IN EXPERIMENTAL ANIMALS

The observation that new bone formation occurred around the negative electrode and cathode was confirmed *in vivo* in experimental animals by many investigators during the 1960s, [17, 18, 20, 88, 106, 108, 109, 112, 113, 141, 160, 161, 172, 193, 198, 207, 215, 233, 234, 249, 276, 277, 287, 292]. They have either inserted electrodes into the medullary cavity of intact long bones or stimulated osteogenesis in fresh fractures or freshly osteotomised long bones. Some [88, 106, 193, 198] were equivocal that osteogenesis could be stimulated by means of continuous direct current. Others [18, 106, 108, 215] observed that bone destruction occurred around the anode.

Use in the human clinical situation of nonunion of fractures, congenital pseudarthroses, bone defects and posterior spinal fusion has inevitably followed. While Cieszinsky [82] using the application of surface electrodes to an extremity, reported the first successful treatment of 13 patients with these conditions, it was Friedenberg and Brighton [110] who first reported a successful case of healing of nonunion by inserting the cathode electrode into the site of nonunion of the medial malleolus. Others [59, 62, 149, 156, 162, 163] have used such a semi-invasive technique (Fig. 1.4). Dwyer and others [72, 96, 97] reported a totally invasive method of electrical stimulation, while experience in humans using inductively coupled electromagnetic fields has been reported by Bassett [23, 25] (Fig. 1.5) and Kraus [157] (Fig. 1.6).

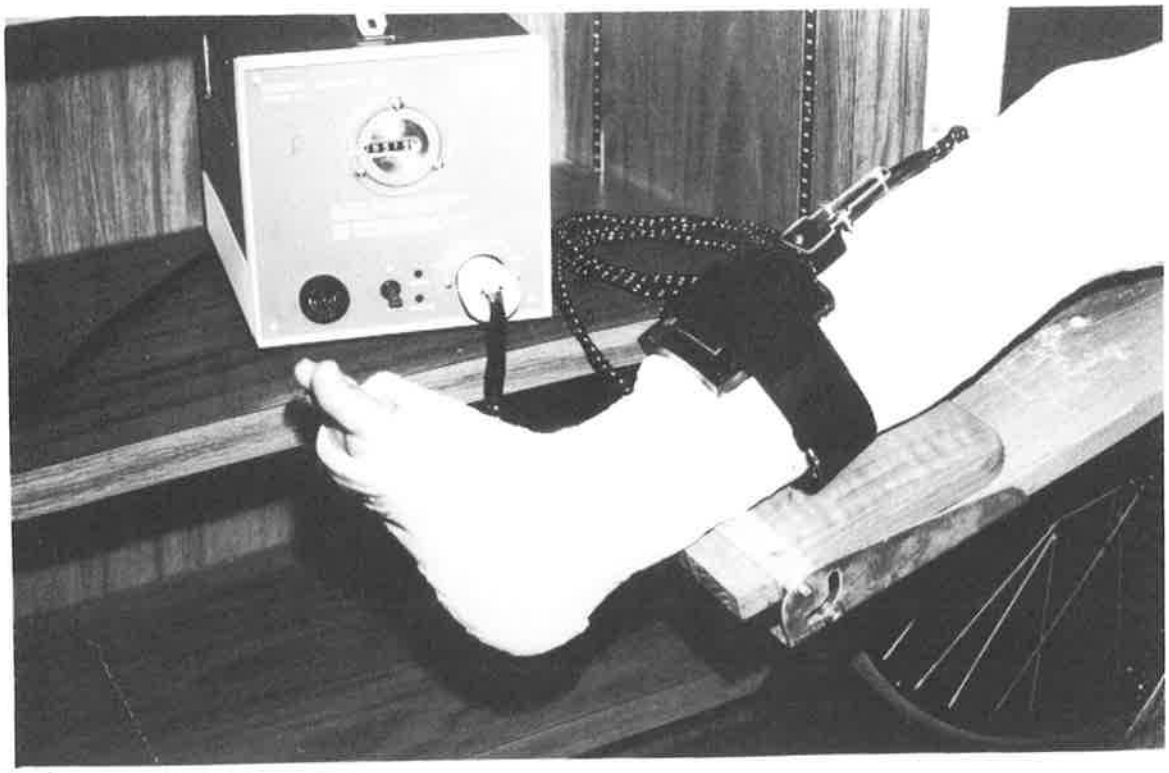


Fig. 1.5 The non-invasive technique of Bassett

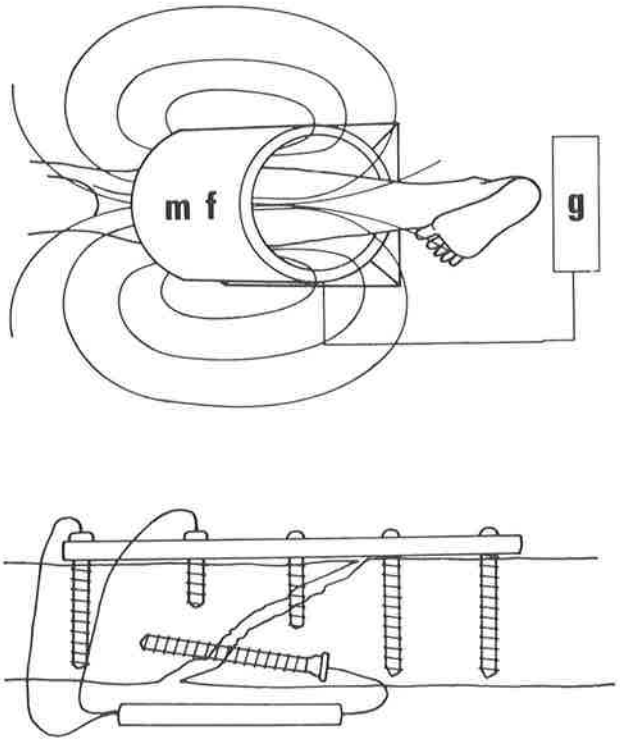


Fig. 1.6 The non-invasive technique of Kraus and Lechner

Many [38, 84, 178, 198, 221] stressed that additional investigations were required before extensive human trials could be justified as many questions remained unanswered and complications could range from destruction of bone to neoplastic changes. By the early 1970s, no conclusive clinical trials had been published and the only justification for use of electrical stimulation in humans was based on these animal experiments and a series of case reports.

No experiments had been performed in animal models of nonunion of fractures. It was considered essential to show that a bone growth stimulator would, in fact, produce osteogenesis in at least delayed union of the tibia of adult dogs before such clinical application in humans could be advised.

9. SUMMARY

A detailed review of the history of electrical stimulation of osteogenesis has been carried out.

The nature of potentials found in bone and the theories for their origin have been indicated.

The mechanisms of action and the type of electrical currents used have been discussed.

A review of the literature of electrically induced osteogenesis in experimental animals indicated that insufficient research had been carried out to justify extensive clinical use of an implanted bone growth stimulator.

This is where this research programme started. Its contribution to this new and challenging field of work will be described.

CHAPTER 2

A MODEL OF DELAYED UNION OF THE TIBIA IN ADULT DOGS

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1. INTRODUCTION

In order to determine whether a bone growth stimulator would be effective in delayed union and nonunion of fractures in humans, it was essential to evaluate this in a similar situation in animals.

So far as could be ascertained, no previous work had established a satisfactory and reproducible experimental model of nonunion of a long bone. This was a necessary prerequisite before a controlled double blind trial in adult dogs could be developed and carried out.

2. MATERIALS AND METHODS

(a) Initial attempts to produce a model

(i) Initially, 1.5-2 cm of the midshaft of the tibia and its surrounding periosteum were removed from the legs of adult dogs (Fig. 2.1). Efforts were made to maintain the gap created with 2 threaded stainless steel pins inserted transversely above and below the defect and secured by an external apparatus. Initially, slats of acrylic were bolted to the threaded pins in the belief that this would allow good radiological assessments. However, the acrylic slats broke very easily and were replaced with 5-ply wooden slats which were bolted and wired (Fig. 2.2) to the threaded pins.

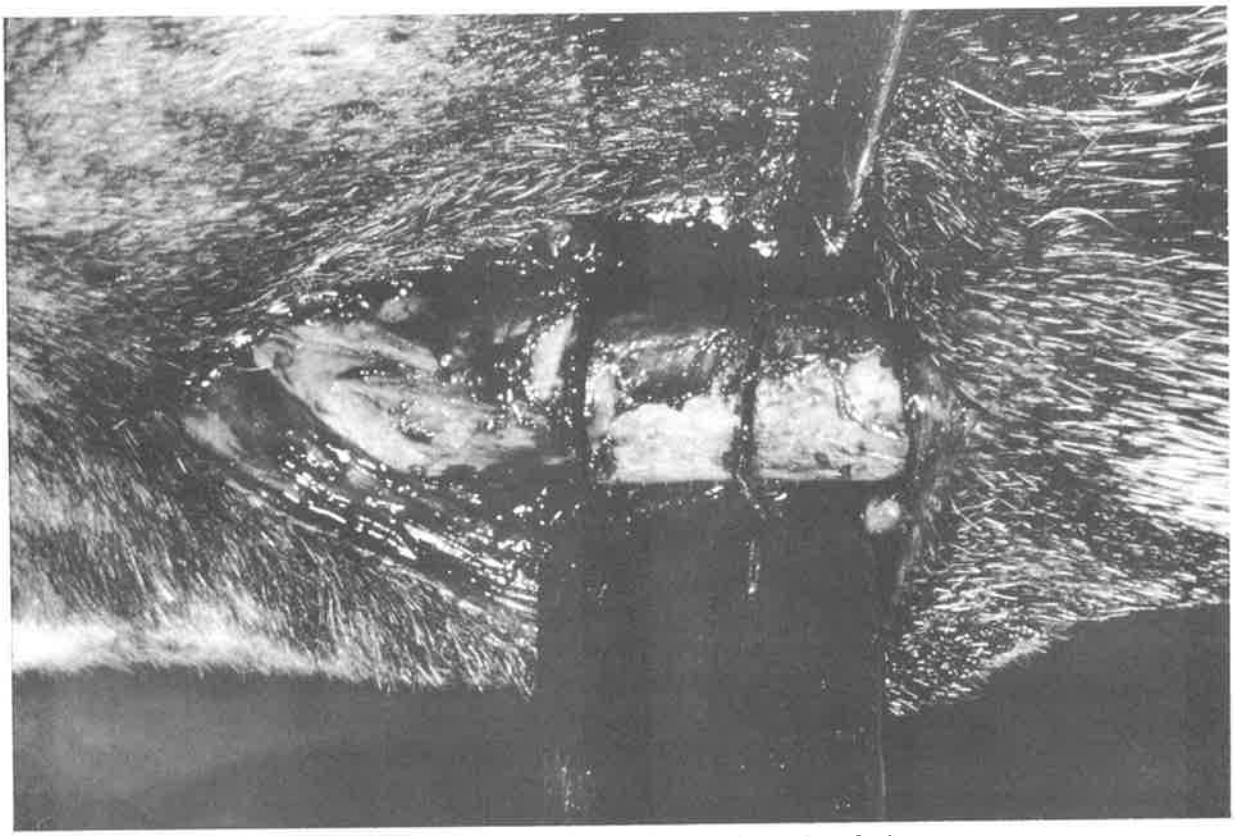

Fig. 2.1 Excision of 1.5 cm of the midshaft of the tibia together with its surrounding periosteum

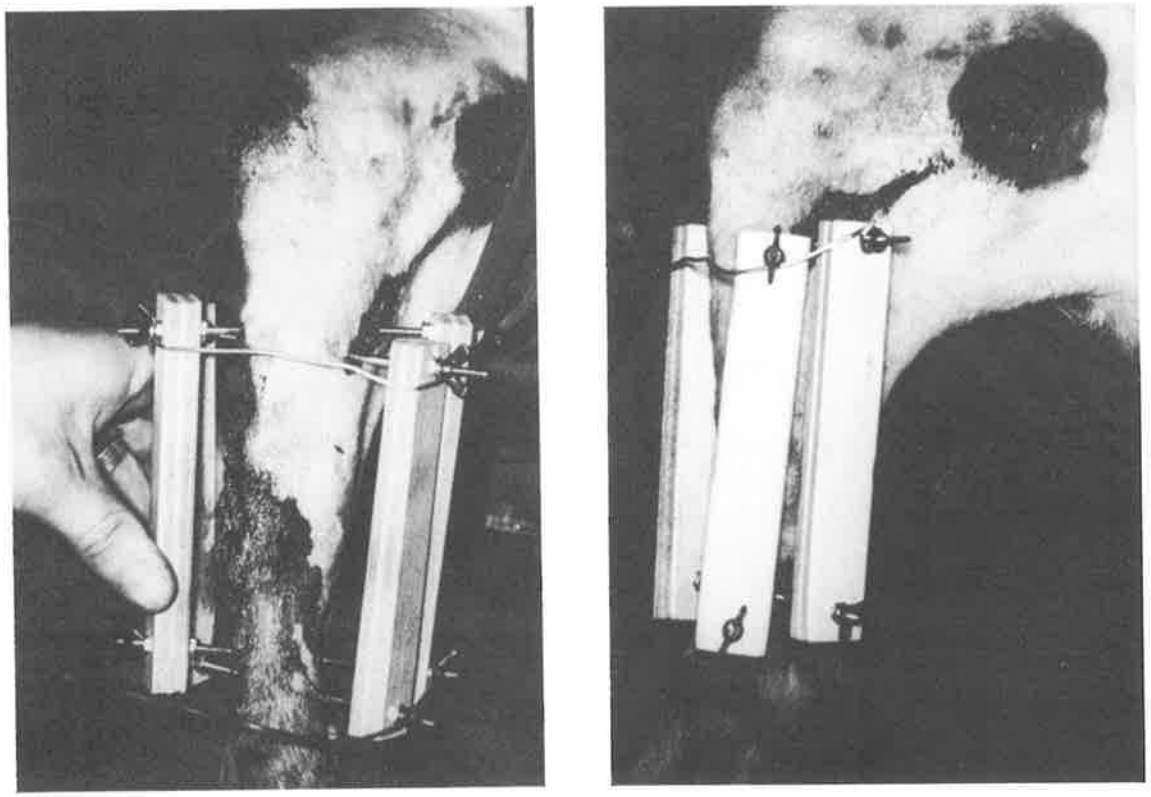

Fig. 2.2 External fixation using four threaded stainless steel pins to which 5-ply wooden slats were bolted and wired

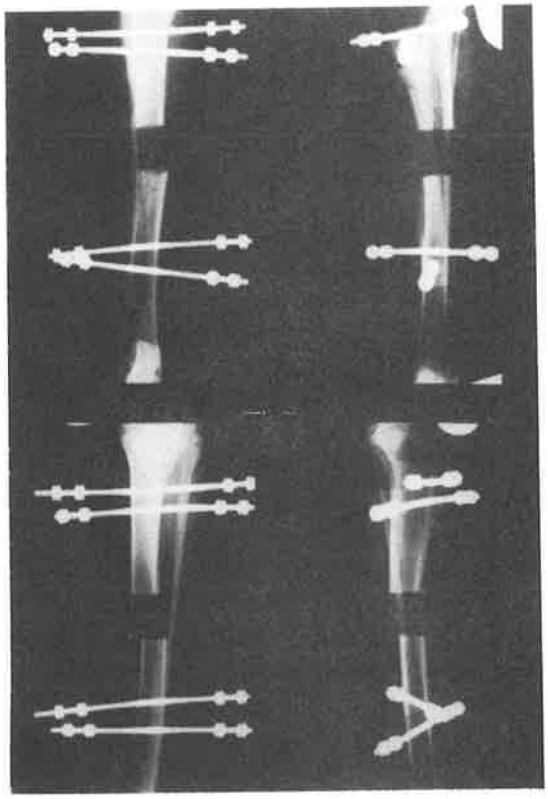

Fig. 2.3 A radiograph of the gap maintained in both hind legs

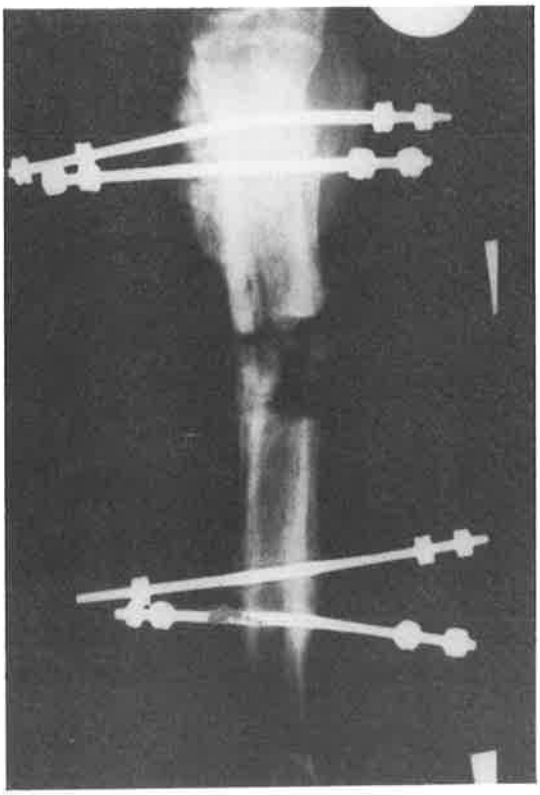

Fig. 2.4 A radiograph showing callus formation despite maintenance of the gap created

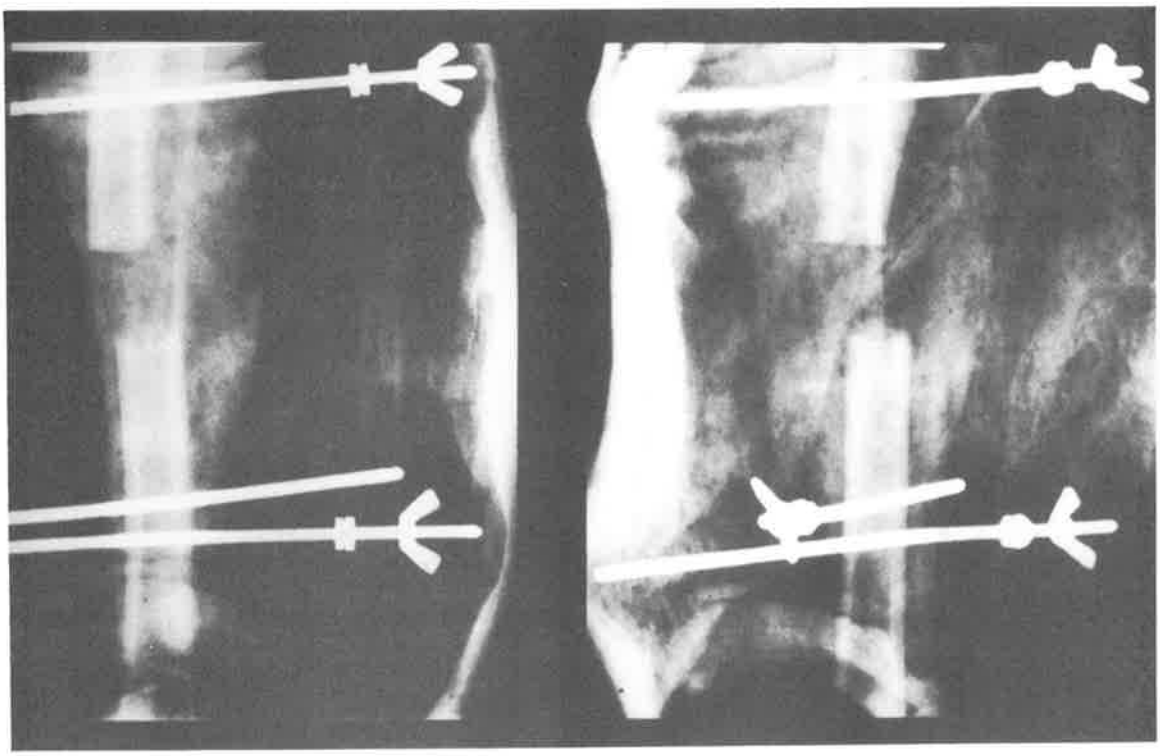

Fig. 2.5 Radiograph of the gap maintained by the external apparatus

In order to provide a control, both legs were operated on together despite the advice of veterinary surgeons who were of the opinion that adult dogs would not tolerate such surgery on both legs (Fig. 2.3). Three of the first 5 dogs died during the immediate post-operative period thereby supporting their views. One dog (Fig. 2.4) survived but went on to solid union despite maintenance of the gap created. Another dog survived, the gap was maintained (Fig. 2.5) and 4 weeks later no evidence of union had occurred radiologically (Fig. 2.6). As a consequence, this technique proved very unsatisfactory and unreliable.

(ii) As silicone elastomer (Silastic*) was used to prevent the recurrence of bone formation in the surgical condition of craniostenosis, it was decided to try to maintain the gap with blocks of this Silastic (Fig. 2.7). Again 4 transverse threaded stainless steel pins were inserted and immobilisation was obtained by bolting 2 wooden slats to opposite pins (Fig. 2.8) after which the threaded pins and wooden slats were incorporated in plaster (Fig. 2.9). Again, operations were carried out on both legs and it was quite clear that adult dogs would not tolerate such a surgical insult. Following many operative attempts, it became apparent that bone soon bridged a gap of up to 2 cm when the tibia was removed sub-periosteally and, more importantly, removal of less than 1 cm and

* Manufactured by Dow Corning Corp. Medical Products,U.S.A.

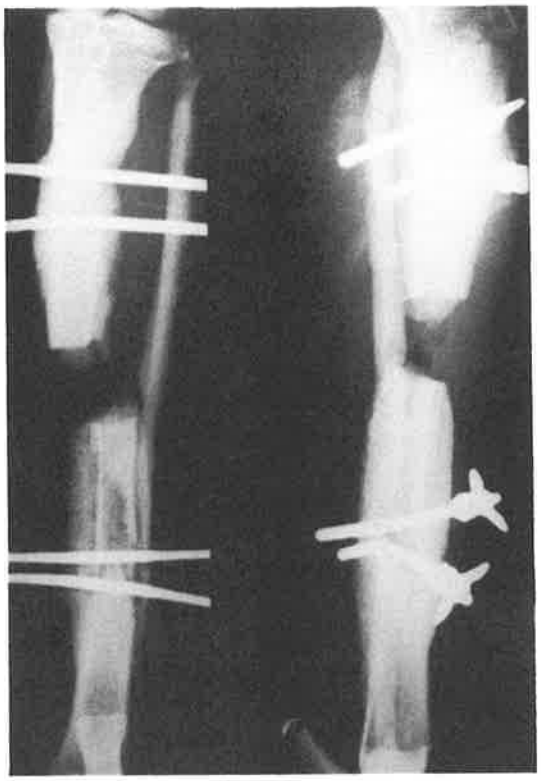

Fig. 2.6 No evidence of union four weeks later and the gap was still maintained

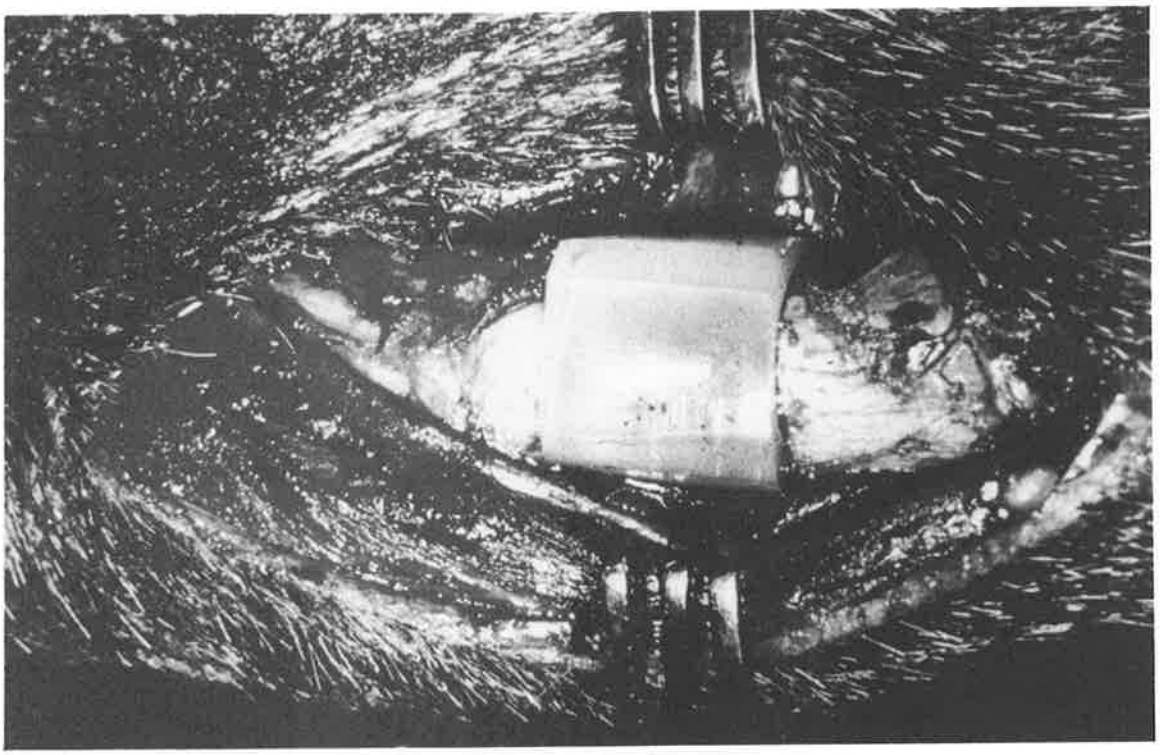

Fig. 2.7 Insertion of a block of silicone elastoma in the gap created by removal of 1.5 cm of the tibia

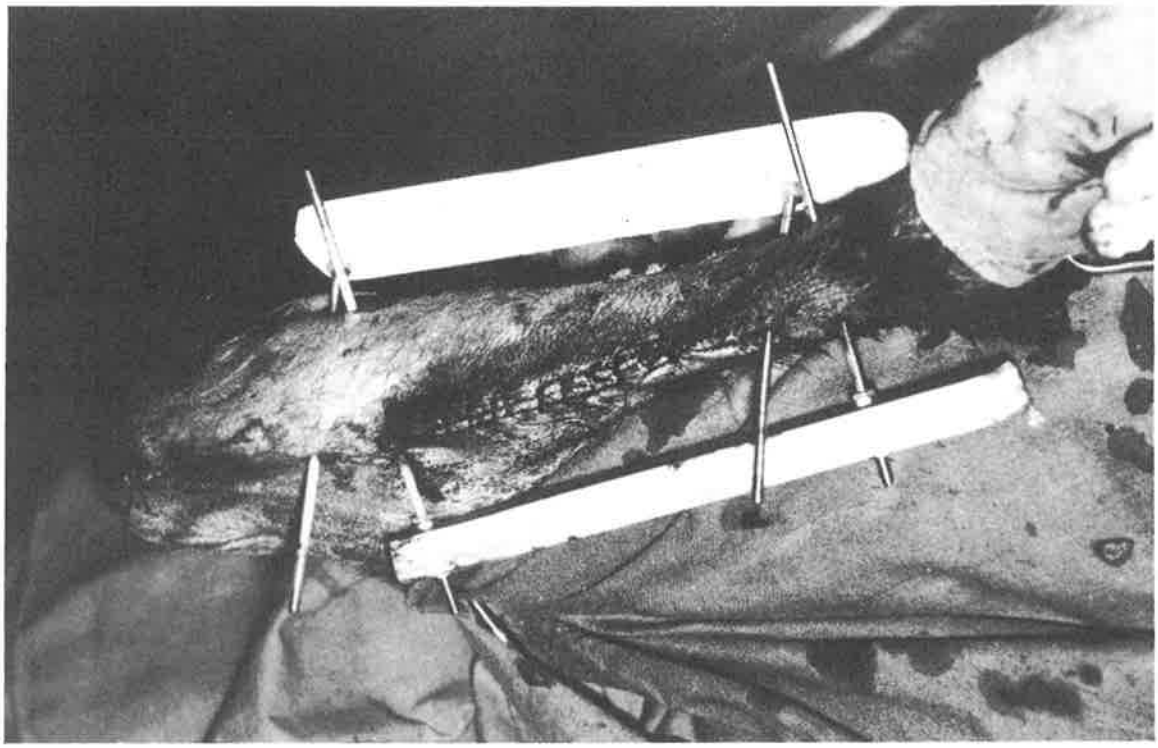

Fig. 2.8 The external apparatus maintaining the silastic in the gap between the tibial fragments

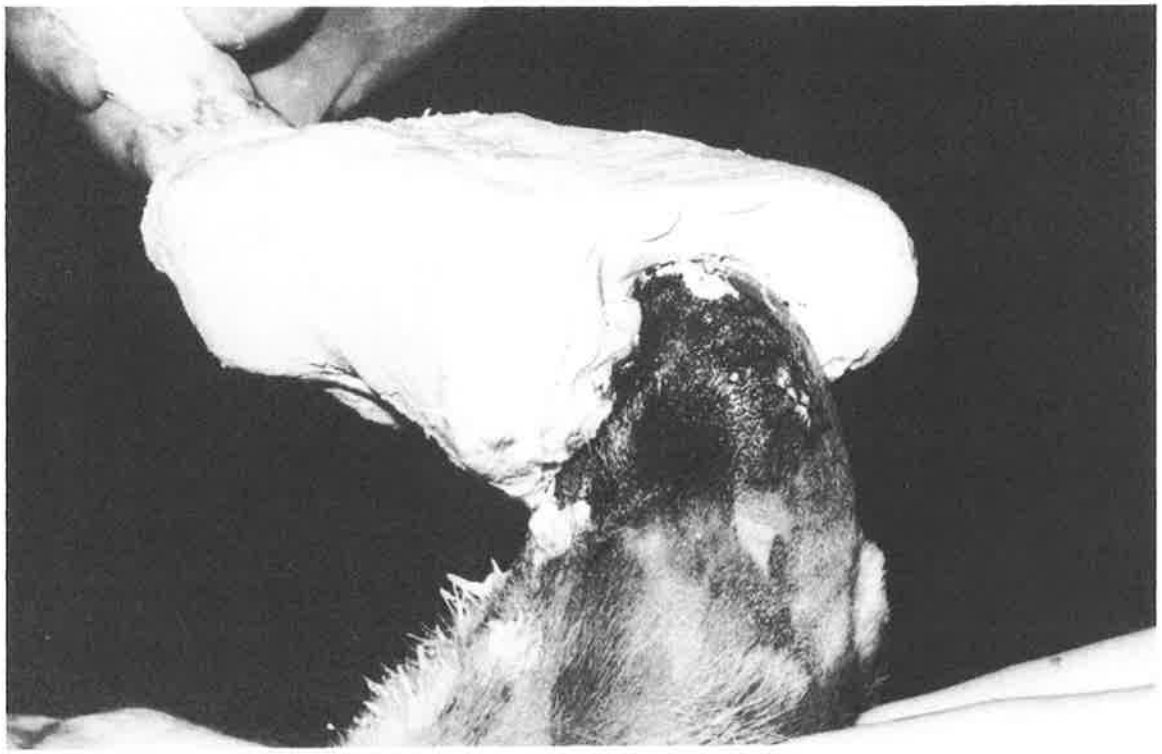

Fig. 2.9 Incorporation of the threaded pins and wooden slats in plaster

more than 2.5 cm of bone extraperiosteally produced union and complete nonunion respectively.

(iii) Finally, extraperiosteal excision of approximately 1.5 cm of bone produced the most significant delay in union though it was difficult to maintain this constant gap with an external apparatus.

Many unsuccessful methods were tried to maintain this gap in the midshaft of the tibia and yet allow the dogs to be active. Eventually, a model of pseudarthrosis of the tibia described by King [154] (Fig. 2.10) in which the divided bone ends were covered with a stainless steel cap and maintained in position with an intramedullary rod was modified and used. It was accepted that only one leg at a time could be operated upon in adult dogs and the defect of 1.5 cm was maintained with a block of Silastic which was held in place with an intramedullary rod. (Fig. 2.11).

(b) Definitive model of delayed union of the tibia

The midshaft of the tibia was exposed extra-periosteally (Fig. 2.12) and 1.5 cm of the midshaft of the tibia together with all its periosteum was removed extraperiosteally with an oscillating saw.

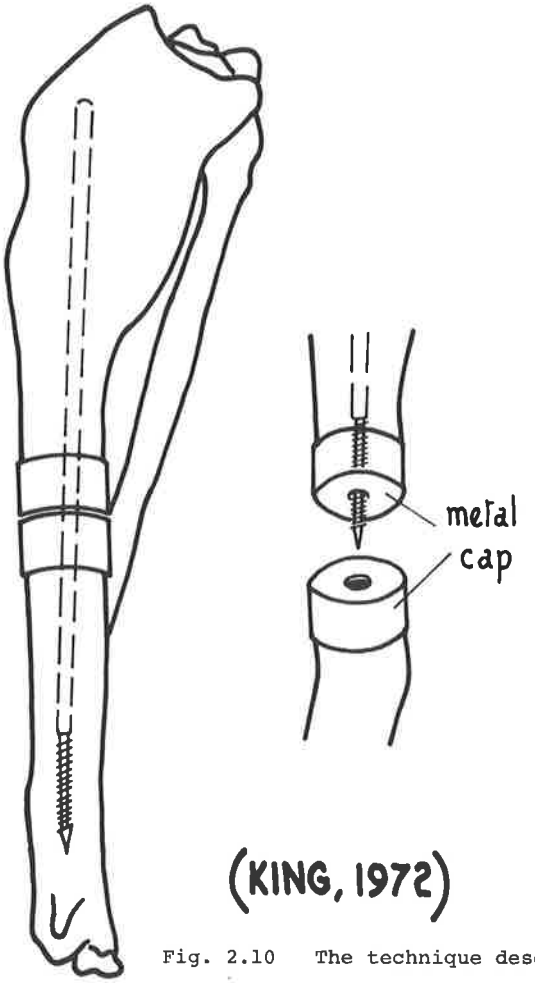

Fig. 2.10 The technique described by King

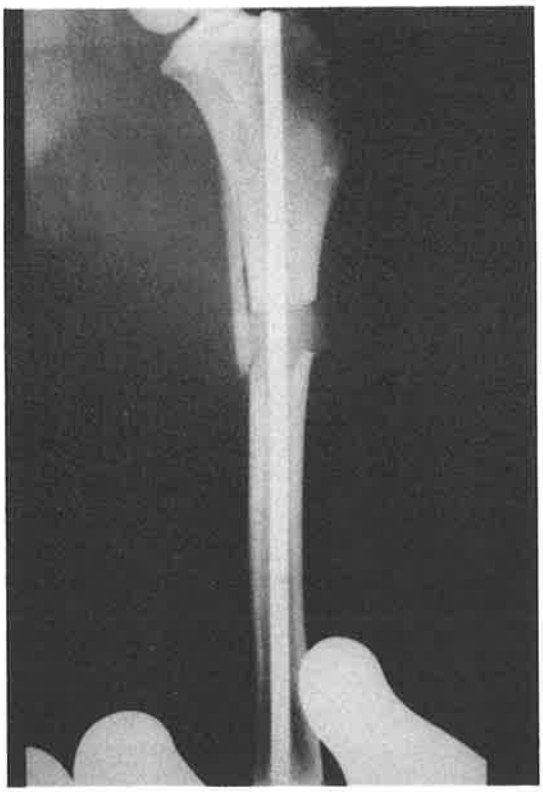

Fig. 2.11 An intramedullary rod providing stability to the tibia and maintaining the silastic block in the gap

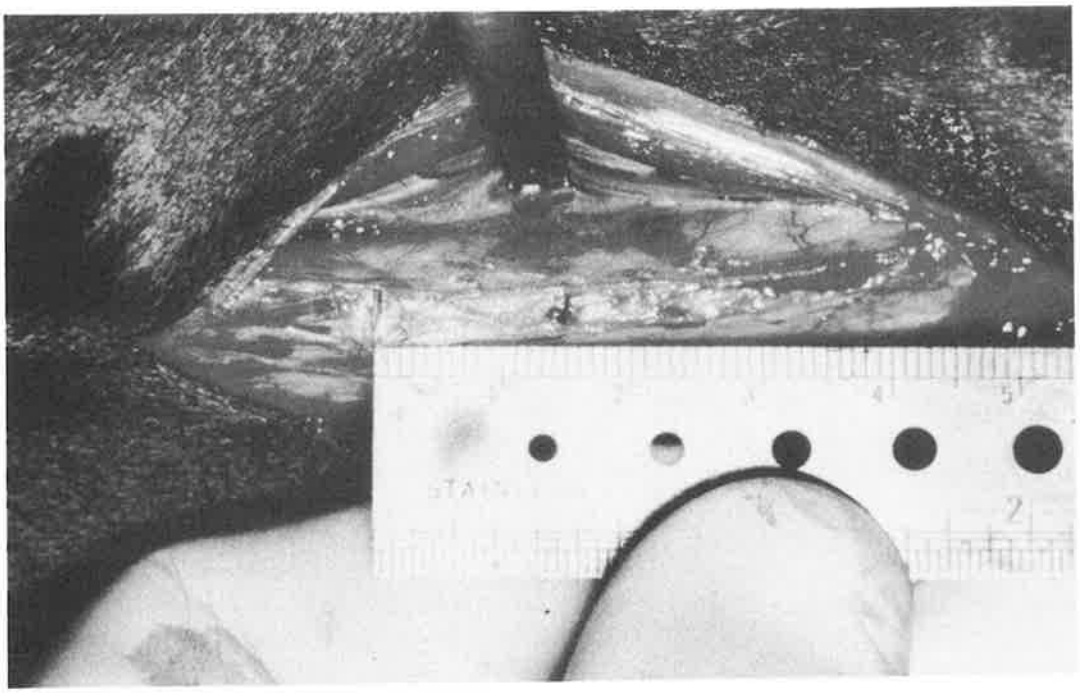

Fig. 2.12 Excision of 1.5 cm of the midshaft of the tibia together with its periosteum

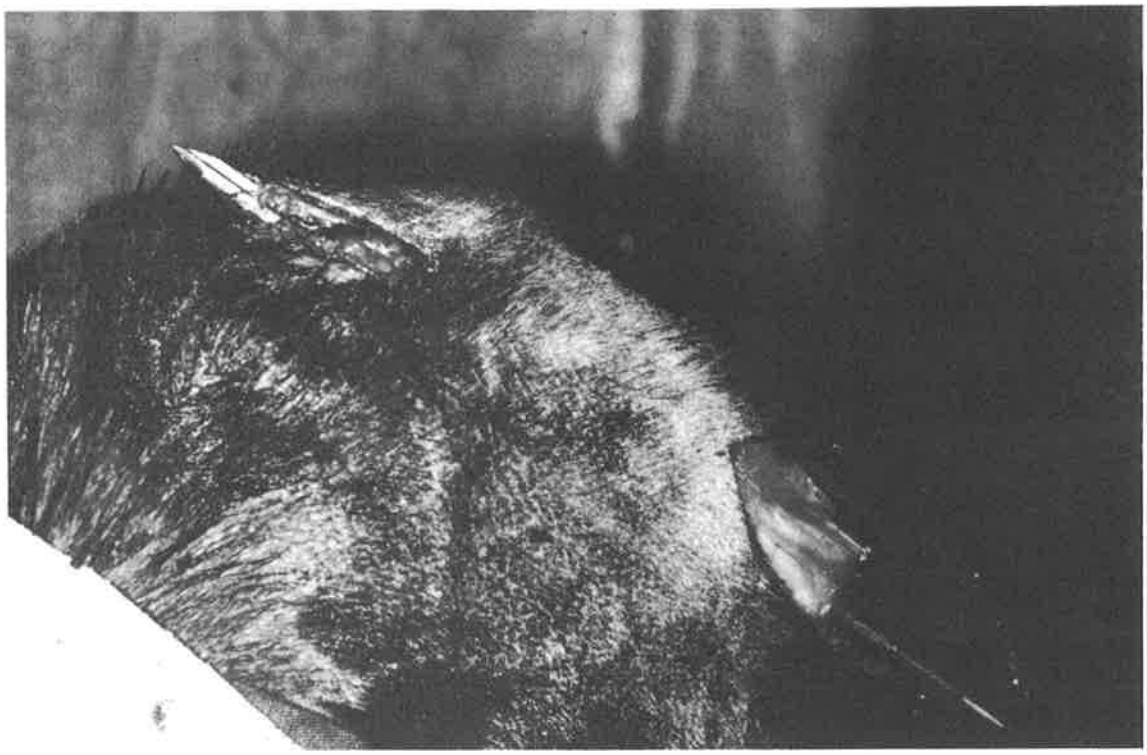

Fig. 2.13 An introducer being passed into the upper fragment into the intercondylar space of the knee joint

An introducer was passed into the upper fragment and exposed in the intercondylar space of the knee joint (Fig. 2.13). An intramedullary rod, threaded at both ends and 4-7 mm in diameter, was passed down the upper fragment to the area of the excised bone. The gap was maintained by inserting a block of hard Silastic - a medical grade of silicone elastomer - which was slightly larger than the block of bone excised (Fig. 2.14). This was maintained in place by passing the intramedullary rod into the lower fragment and its position was determined by an image intensifier (Fig. 2.15). A plaster cast was applied from the thigh to the foot to allow wound healing after which the dog was allowed to be fully active for a minimum of 8 weeks.

Subsequently, the intramedullary rod was removed after exposing its upper end and the silicone block was approached through the previous incision. The surrounding fibrous tissue was carefully incised, the silicone block was removed and the degree of delayed union was evaluated (Fig. 2.16).

3. RESULTS

A situation of delayed union was accepted only when (1) fibrous tissue surrounded the silicone block, (2) soft tissue covered the bone ends and (3) there was mobility between the bone fragments. True "nonunion", a situation

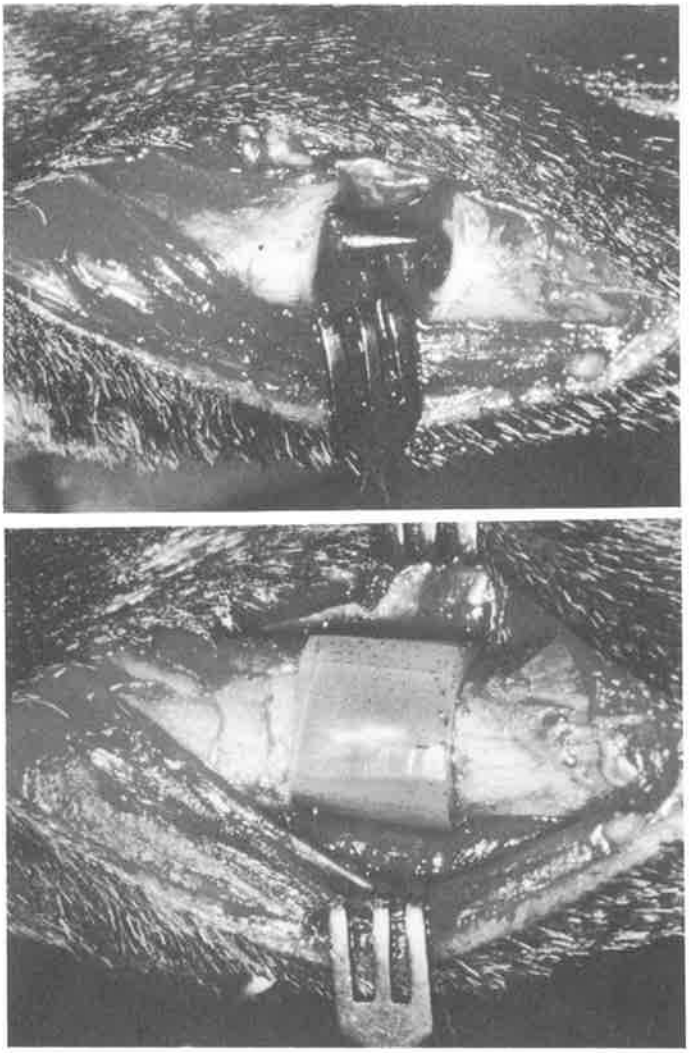

Fig. 2.14 An intramedullary rod is passed (above) down the proximal fragment and (below) through the block of silastic

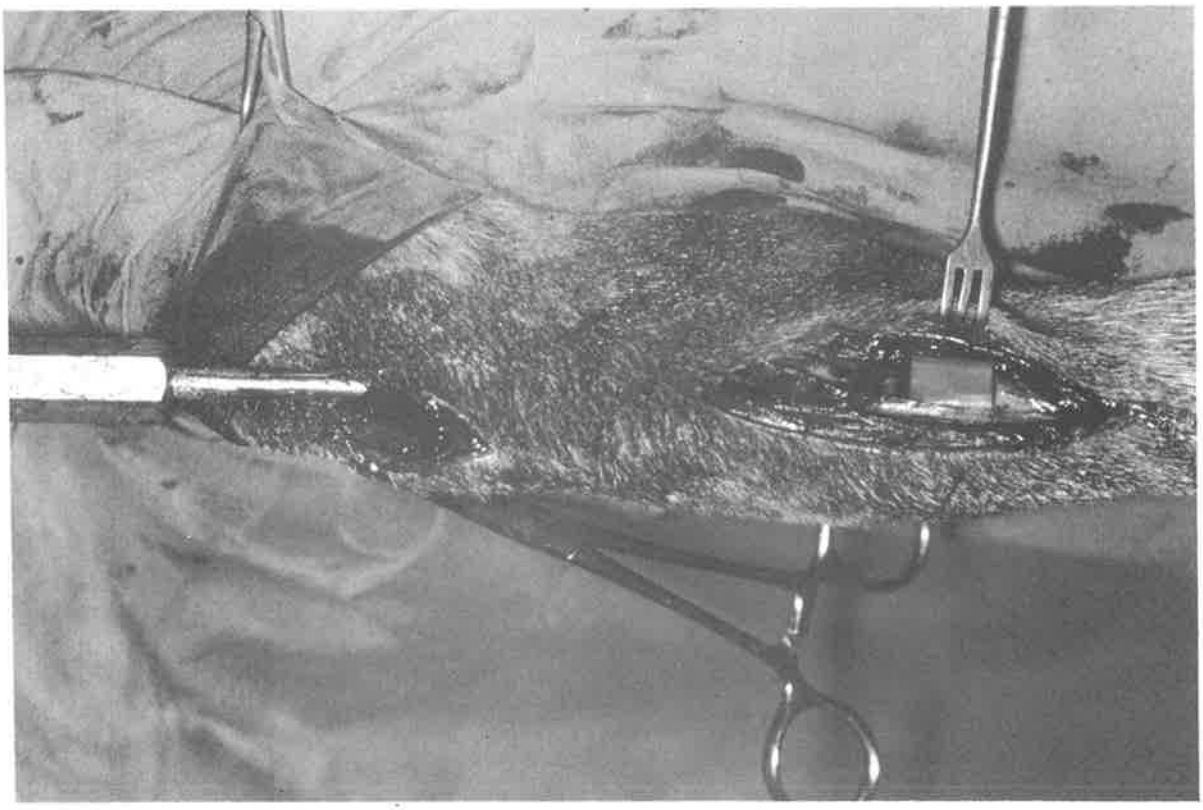

Fig. 2.15 The intramedullary rod is passed into the distal fragment

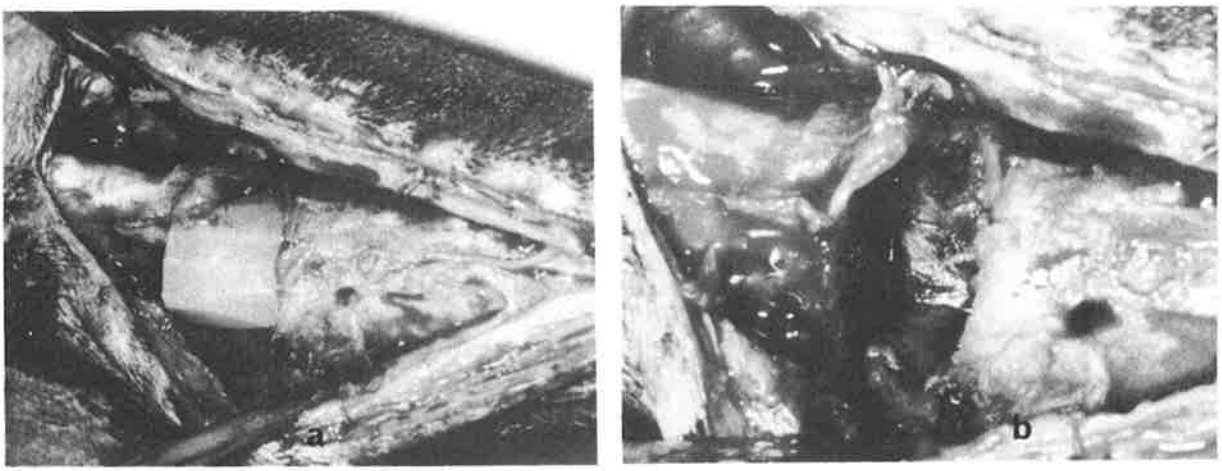

Fig. 2.16 (a) Exposure of the defect site

(b) Removal of the silastic block

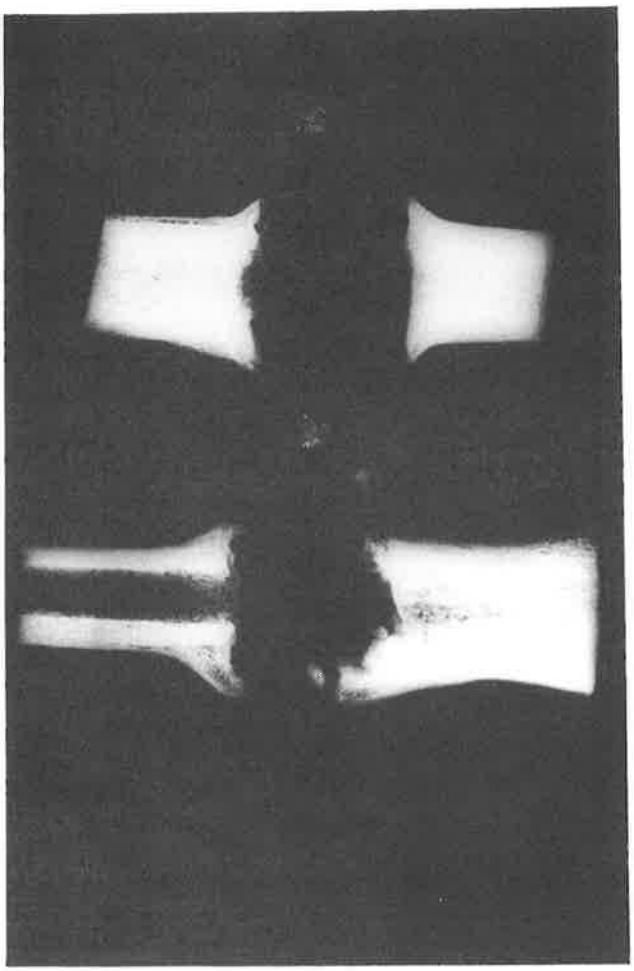

Fig. 2.17 Radiographs of specimens (a) after the silastic block removed and (b) showing no bone between the bone ends after four weeks

in which the reparative processes have come to a complete standstill [73], would have involved maintenance of the dogs for many months and, of necessity, would have avoided many of the factors that are responsible for the development of nonunion in humans.

To confirm the state of delayed union, several dogs were allowed to be active for a further 4 weeks after the silicone block had been removed. Assessment at that time found (1) persistent mobility of the bone ends detected by physical examination, (2) the gap was maintained, (3) absence of any intact bony bridge between the bone ends by radiography (Fig.2.17), (4) insignificant uptake of technetium 99m polyphosphate across the gap (Fig. 2.18), (5) the gap was filled with fibrous tissue macroscopically (Fig. 2.19) and using the modified Movat pentachrome technique of Russell [226], fibrous tissue predominated between the bone ends with minimal evidence of cartilage or bone formation (Fig. 2.20) and (6) microscopically, there was evidence of fibrous tissue in the gap adjacent to the bone ends with lack of any bridging bone or cartilage (Fig. 2.21).

This evidence was reproduced consistently and this model of delayed union of the tibia was suitable for future experimental work with the bone growth stimulator.

Contrary to the views of other experimenters, it was considered that a mixed animal population of adult mongrels, greyhounds and beagles was appropriate. It is interesting

Fig. 2.18 Insignificant uptake of the radionuclide across the gap after four weeks

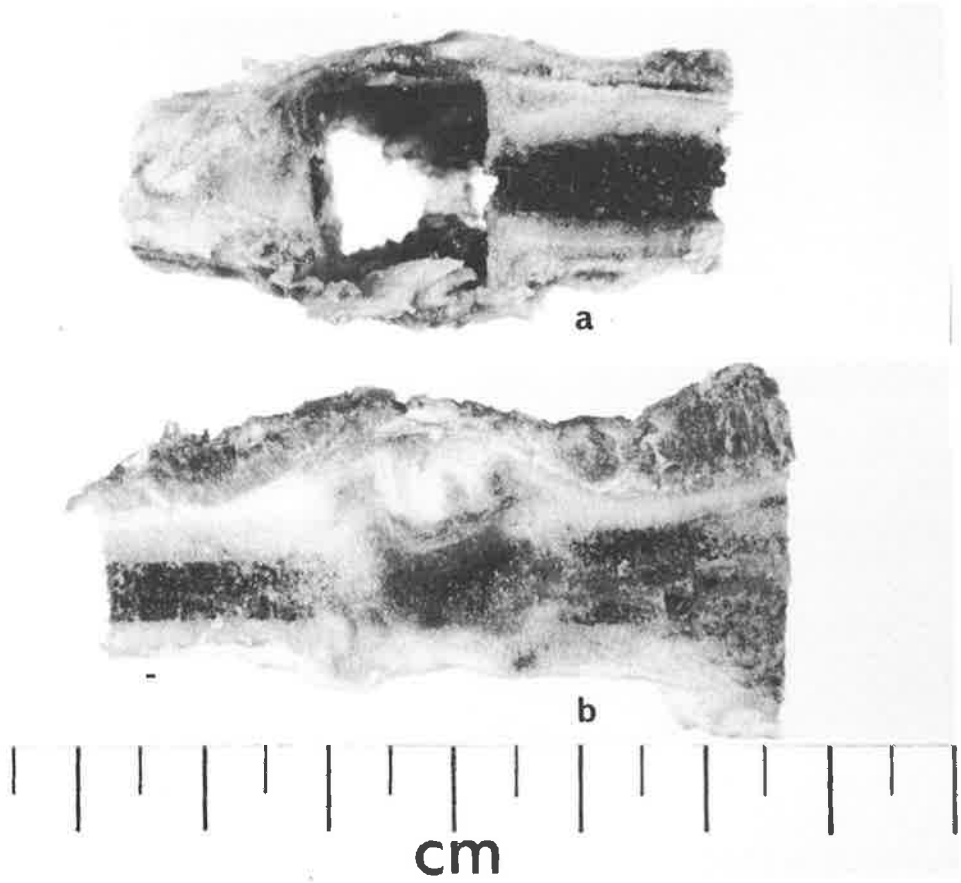

Fig. 2.19 (a) The specimen after the silastic block has been removed

(b) Four weeks later where fibrous tissue occupies the space between the bone ends

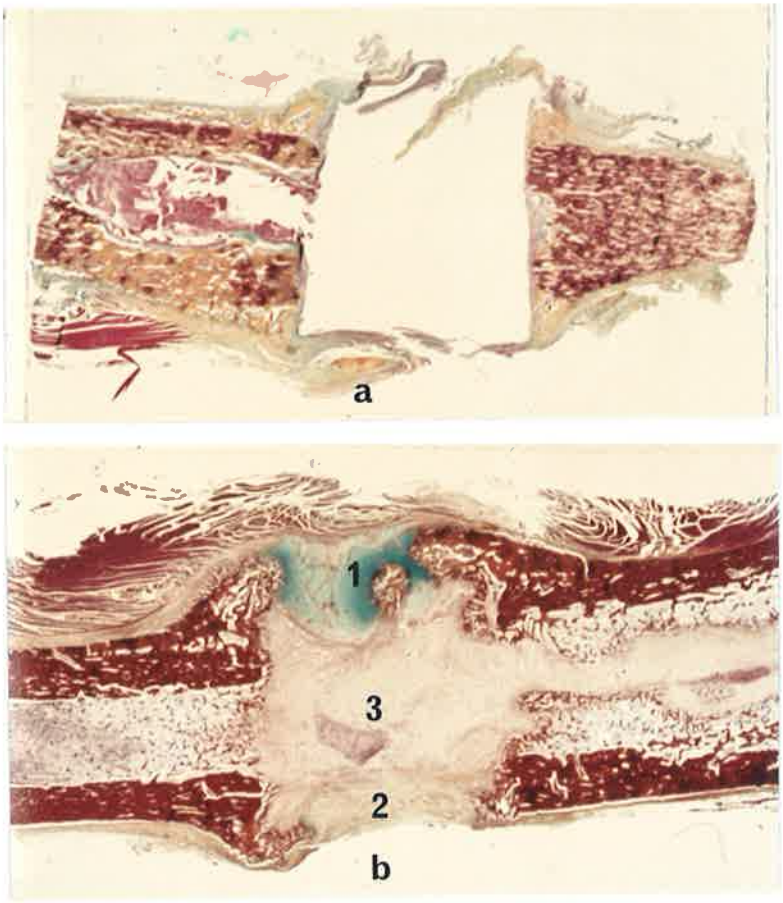

Fig. 2.20 Modified Movat pentachrome stains of section (a) after the silicone block had been removed and (b) four weeks later showing; (1) cartilage (green), (2) bone (pale brown), (3) in the centre, fibrous tissue (pale yellow)

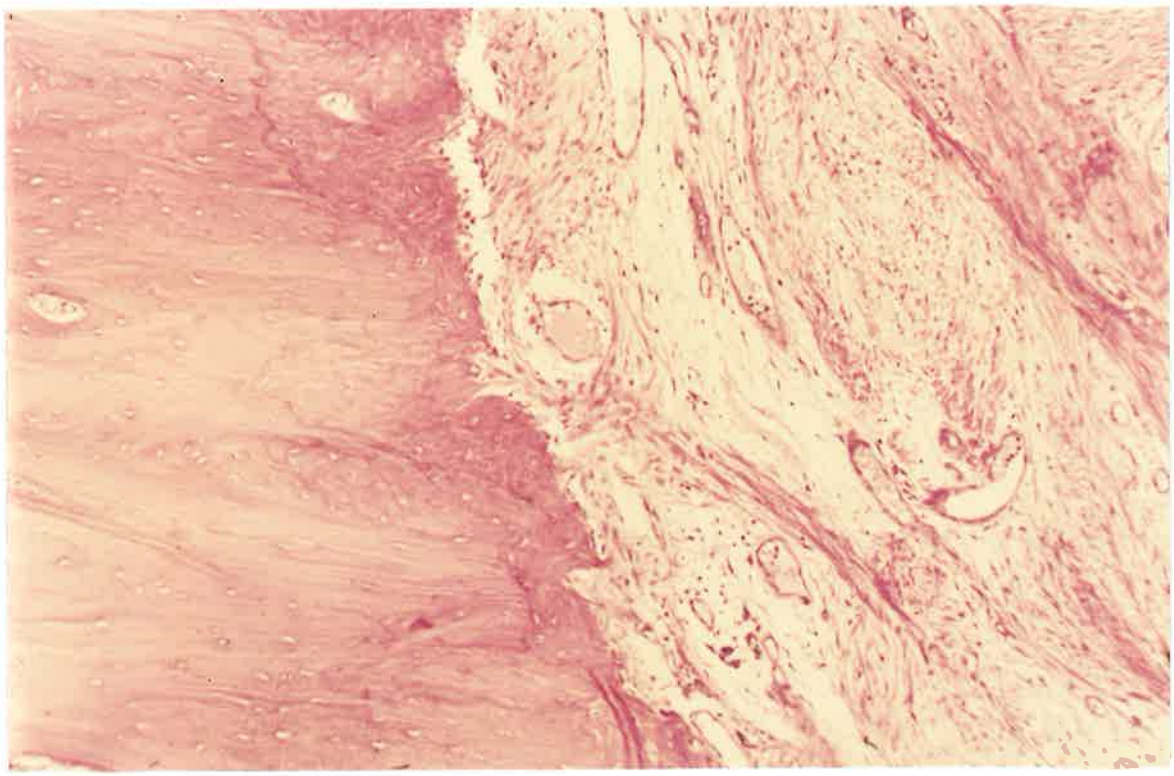

Fig. 2.21 H & E sections showing fibrous tissue (right) adjoining inactive lamellar bone (left)

to report that beagles showed a very much higher survival rate, and produced the best model of delayed union. Of the 69 dogs, it can be seen (Table I) that 50 survived and were healthy at 8 weeks, and of these only 2 were subsequently discarded. All remaining 48 dogs satisfied the criteria given above for delayed union of the tibia.

4. DISCUSSION

The initial attempts to produce delayed healing of the experimental tibia were unsuccessful because an attempt was made to operate on both hind legs. Such a model would have allowed a within-animal comparison in any future experimental work. The chance finding that the extra-periosteal excision of 1.5 cm of bone produced significant delay in bone healing across the defect has since been confirmed by others. Davis et al [91] attempted the model of Robinson [217] and Zadek and Robinson [295] and found none of their 44 dogs could bridge the 3 cm gap produced and advised a gap length of 1-2 cm. Harris et al [130] also came to the same conclusion.

A modification of the model described by King [154] allowed a consistently successful model of delayed union of the tibia to be achieved. The model incorporated two of the important factors that lead to delayed union in human fractures, namely (1) interposition of soft tissues and (2) distraction of the bone ends.

The ideal experimental model for investigating fracture healing should be reproducible, applicable to the human adult, have a relatively sharp end point between union and nonunion, have freedom from prolonged immobilisation and have the ability for each animal to serve as its own control. This model was able to fulfil all except the last criteria.

The model did include important requirements for the consistent production of delayed union of long bones in adult dogs. Extraperiosteal removal of approximately 1.5 cm of bone, maintenance of the gap with an inert synthetic material like Teflon [207] or Silastic together with an intramedullary rod allowed weight bearing by the dogs and provided a stable model suitable for future comparative studies. The dogs tolerated this surgery in one hind leg very well.

5. SUMMARY

A model of delayed union in the tibia of adult dogs was developed and achieved in 48 out of 50 dogs or a 96% success rate. On the basis of these findings, these 48 dogs were used to evaluate the value of a bone growth stimulator.

TABLE I

DETAILS OF DOGS USED IN PRODUCTION OF EXPERIMENTAL DELAYED UNION AND IN ASSESSMENT OF EFFECT OF A BONE GROWTH STIMULATOR

	Mongrels	Greyhounds	Beagles	Total
TOTAL DOGS OPERATED ON	14	37	18	69
Dogs subsequently destroyed:				
wound breakdown	1	9	0	10
pulmonary infection	0	4	0	4
uncontrolled haemorrhage	1	2	0	3
failure of intramedullary fixation	0	2	0	2
REMAINING DOGS HEALTHY AT 8 WEEKS	12	20	18	50
Dogs subsequently destroyed:				
pulmonary infection	0	1	0	1
solid fusion	0	1	0	1
REMAINING DOGS WITH SUCCESSFUL DELAYED UNION	12	18	18	48
Dogs subsequently died or destroyed:				
fulminating infection	1	0	0	1
fatal anorexia	1	0	0	1
displaced anode	0	1	0	1
TOTAL DOGS SURVIVING FOR ASSESSMENT OF STIMULATOR EFFECT	10	16	18	44 (22 pairs)

CHAPTER 3

THE EFFECT OF AN ELECTRICAL BONE GROWTH STIMULATOR IN EXPERIMENTAL DELAYED UNION OF THE DOG TIBIA

CHAPTER 3

THE EFFECT OF AN ELECTRICAL BONE GROWTH STIMULATOR IN EXPERIMENTAL DELAYED UNION OF THE DOG TIBIA

1. INTRODUCTION

It has been stated previously that the only justification for use of electrical stimulation in humans in the early 70s was based on *in vivo* animal experiments by many investigators. However, all this work had involved insertion of the electrodes into the medullary cavity of intact long bones or at the site of fresh fractures or freshly osteotomised long bones. In addition, there were a series of clinical case reports. It was considered essential to show that a bone stimulator would, in fact, produce osteogenesis in at least delayed union of the tibia of adult dogs before such clinical application in humans was appropriate.

A controlled double blind trial using one hind leg of an adult dog was established.

2. MATERIALS AND METHODS

(a) Bone growth stimulator

An implantable direct current bone growth stimulator was used * (Fig. 3.1). This stimulator consisted of three elements; (a) a battery power source with a generator life of 12 weeks (b) an

* Telectronics Pty. Ltd.,Sydney, Australia

Fig. 3.1 An implantable direct current bone growth stimulator

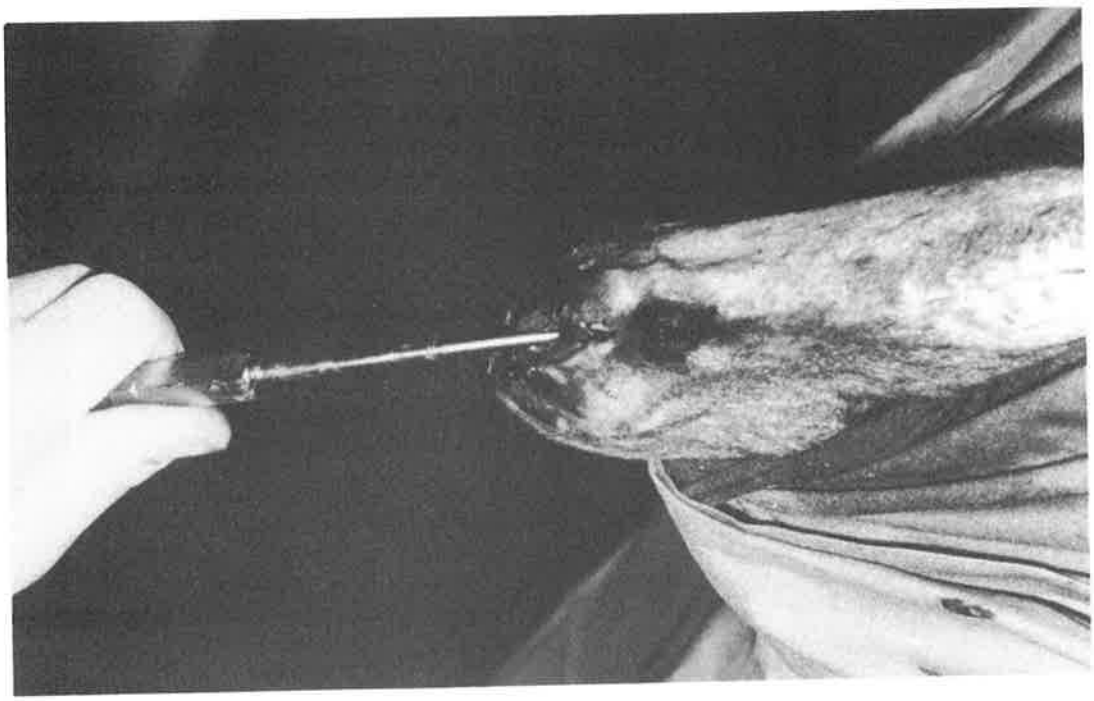

Fig. 3.2 Removal of the intramedullary rod

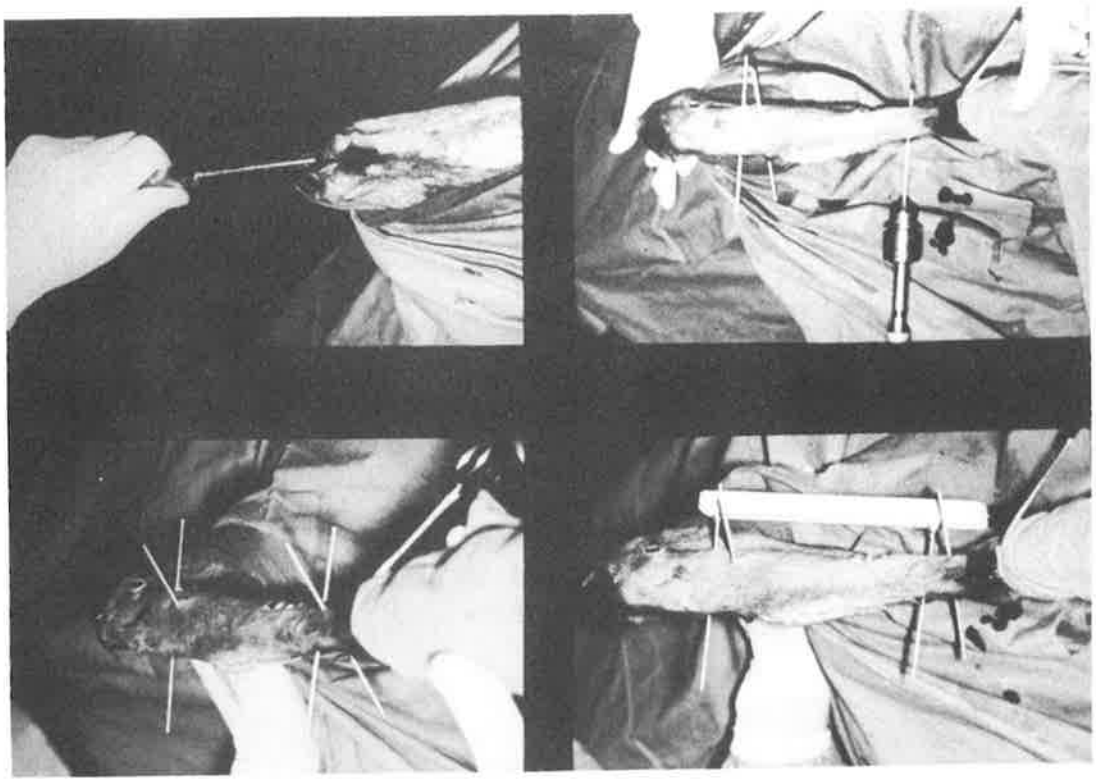

Fig. 3.3 Insertion of crossed Steinmann pins and fixation of the pins with 5-ply wooden slats

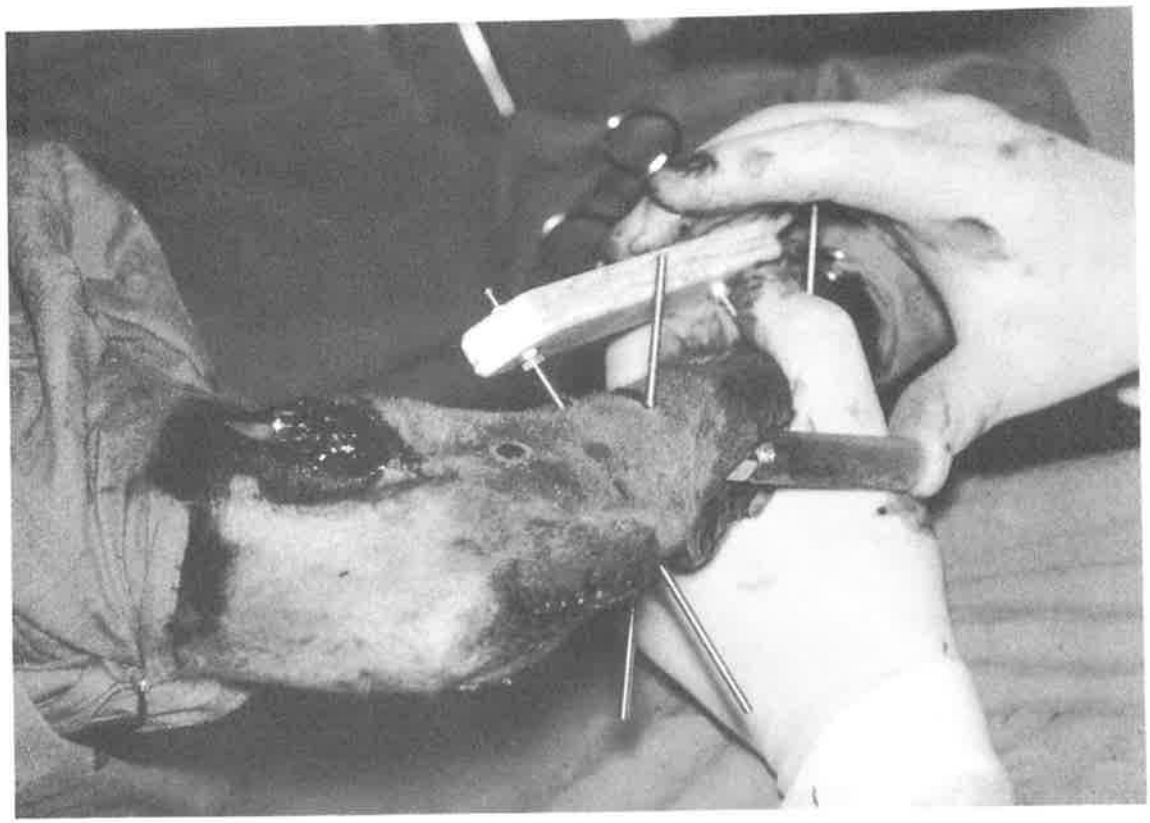

Fig. 3.4 Preparation of the pouch in the lateral hamstring area for the bone stimulator and passing a special trocar and cannula into the area

stimulator pack and using a special trocar and cannula (Fig. 3.4), the electrodes were passed retrogradely into the defect area avoiding any damage to the anodes themselves (Fig. 3.5). The generator unit was placed in the pouch in the lateral hamstring area (Fig. 3.6 (a) & (b)).

A technique for insertion of the bone growth stimulator was developed (Fig. 3.7). The two anodes were inserted tightly into the cortex with their tips extending into the medullary cavity 1.5 cm above and below the defect. The surface area of the insulated tip of each anode was approximately 40 sq. mm. The cathode was made into a helix and inserted into the defect area (Fig. 3.8). A plaster cylinder was applied around the hind leg to fix the external apparatus and to allow the dog to be fully active and weight bearing for the next four weeks when the animals were killed.

(c) Double blind trial to evaluate the use of a bone growth stimulator

The controlled double blind trial was established by pairing the 48 dogs in which delayed union had been established according to their variety and weight.

Pairs of pre-packed, sterilised and coded bone growth stimulators were inserted. One of each pair was active and the other inactive but totally indistinguishable from each other both by external

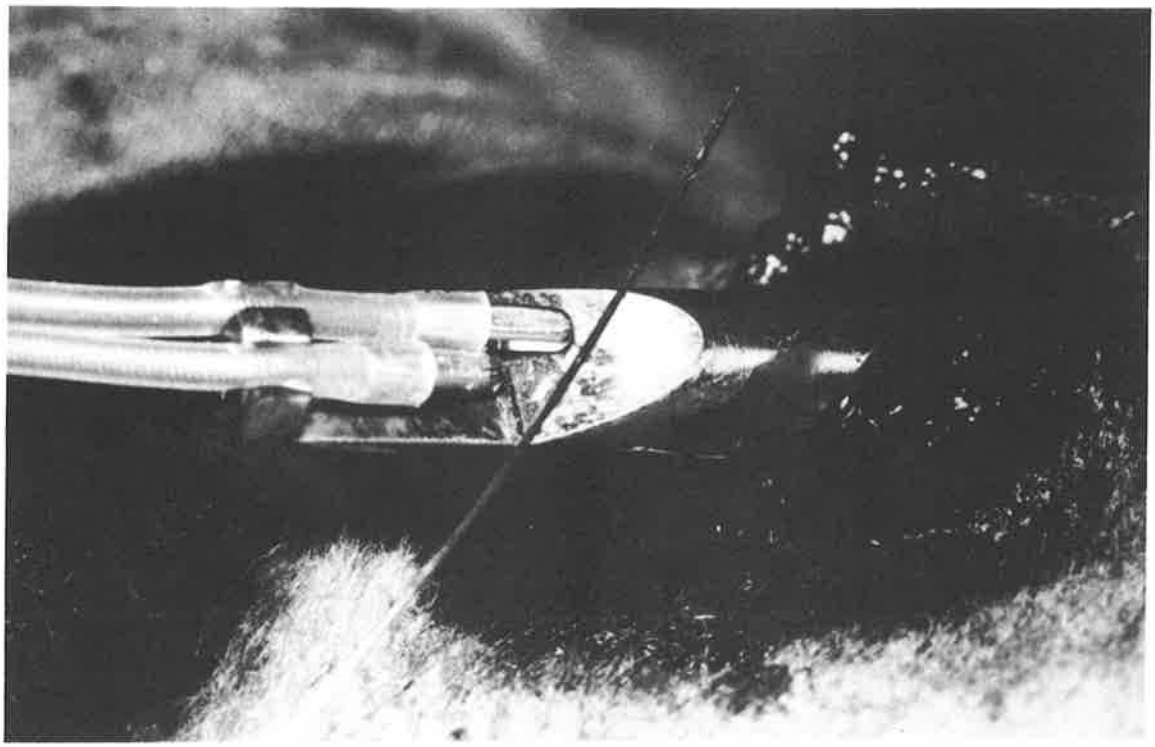

Fig. 3.5 The special instrument used to pass the anodes into the defect area without any damage

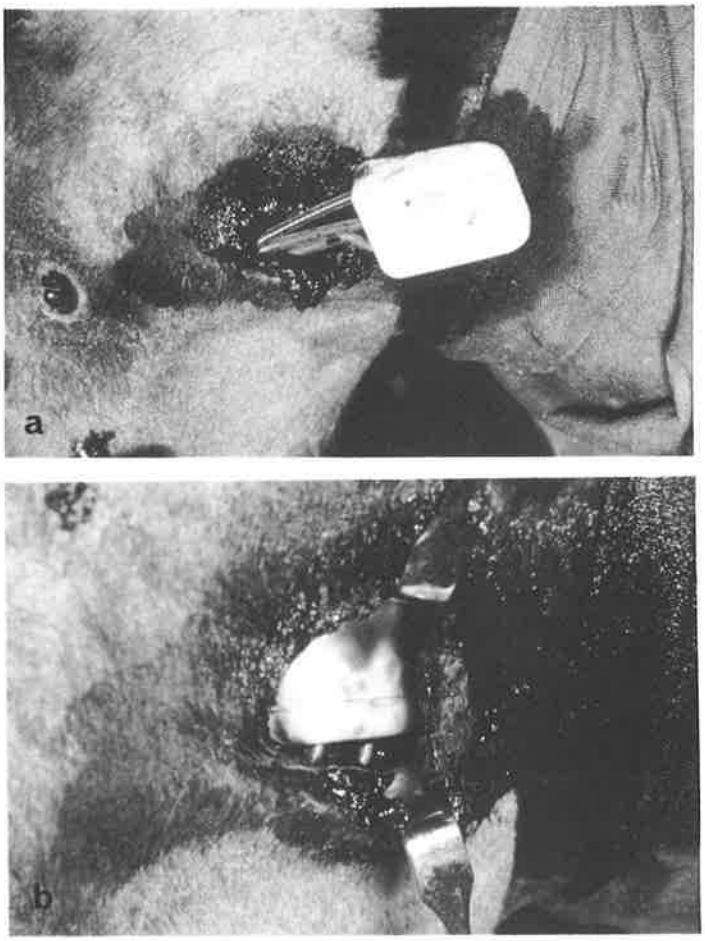

Fig. 3.6 (a) The electrodes passed retrogradely into the defect area

(b) The generator unit placed in the pouch in the lateral hamstring area

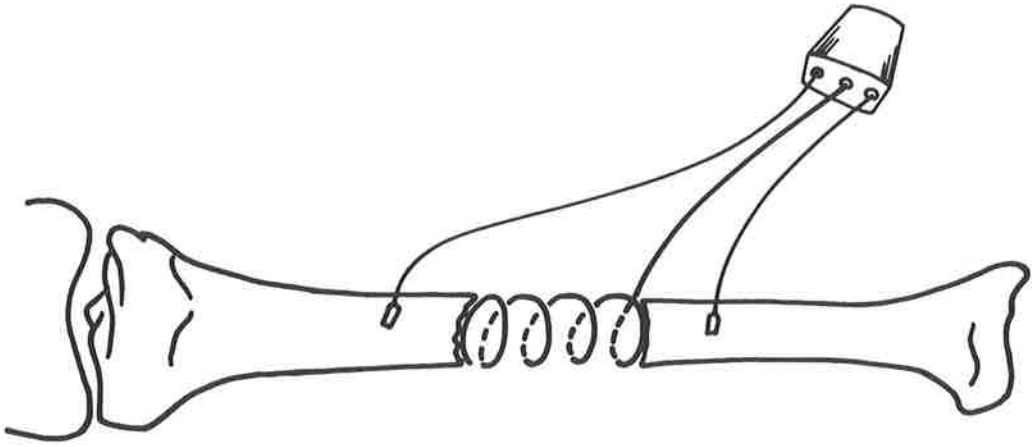

Fig. 3.7 A technique for insertion of the bone growth stimulator

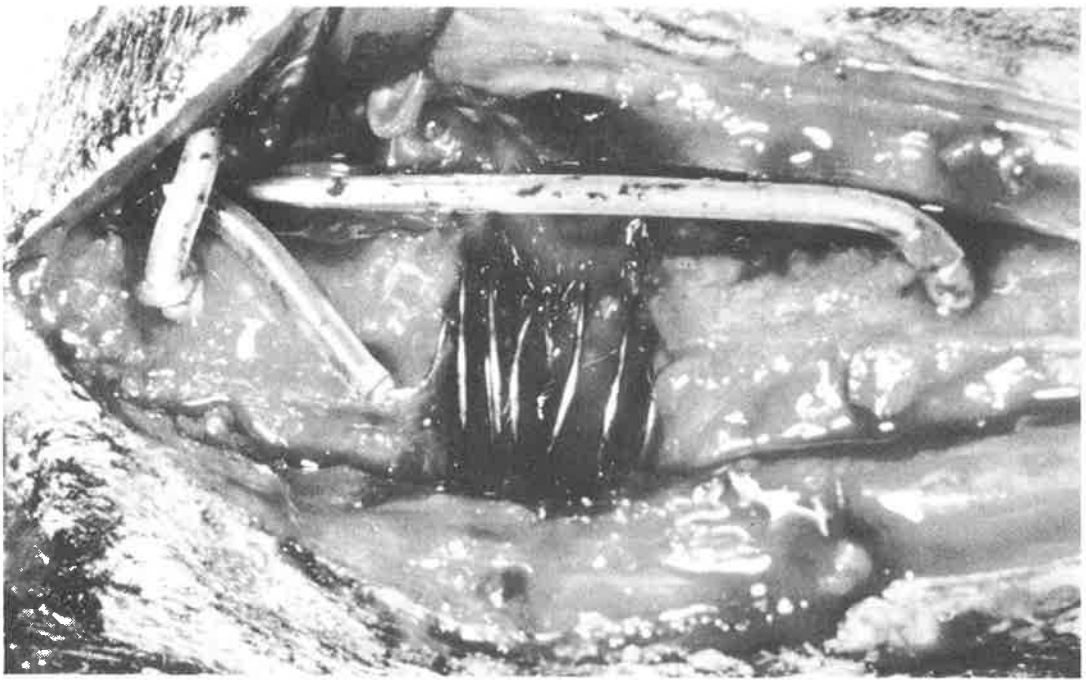

Fig. 3.8 Insertion of the cathode and two anodes into the area of delayed union

electronic circuit supplying a constant current of 20 microamperes for load variations from 0-1 x 10^5 ohms and (c) a single stainless steel cathodic electrode carrying the sum current of two platinum anodes. For biocompatibility and environmental protection the unit was assembled in epoxy resin with a methyl methacrylate case.

(b) Technique

A block of Silastic was inserted into a 1.5 cm defect in the midshaft of the tibia of adult dogs and maintained by an intramedullary rod. The dog was allowed to be fully active for a minimum of eight weeks. The intramedullary rod was removed after exposing its upper end (Fig. 3.2) and the silicone block was approached through the previous incision by gently incising the surrounding fibrous tissues. Once established delayed union of the tibia had been confirmed, the silicone block was replaced in order to maintain a consistent gap between the bone ends. Two threaded stainless steel pins were inserted, under direct vision, transversely above and below the defect area (Fig. 3.3) and secured by 5-ply wooden slats in order to maintain the gap after which the silicone block was removed thereby ensuring that a constant gap area was maintained in all dogs. A pouch was made in the lateral hamstring area for the

appearance and by radiography. All units were factory tested before despatch and were further checked at implant and explant by an independent electronic engineer.

Independent observers were chosen to assess and compare the amount of bone formation in each pair of dogs at the end of 4 weeks of electrical stimulation by four different methods - radiography, gamma imaging, clinical assessment and histology.

At the conclusion of the whole experiment, details of the bone growth stimulator code numbers, the current at implant and explant, and the results of all independent assessments were forwarded to an independent assessor who was the only person to know which dog of a pair had an active stimulator. It was considered that bias on the part of any of the experimenters was thereby eliminated.

(i) Radiography

Radiographs were taken in two planes at 2 and 4 weeks. These ensured that the electrodes remained in place during the trial but the method was discarded as a means of assessment before the code was broken because it was usually not possible to distinguish the members of a pair as regards union (Figs. 3.9, 3.10).

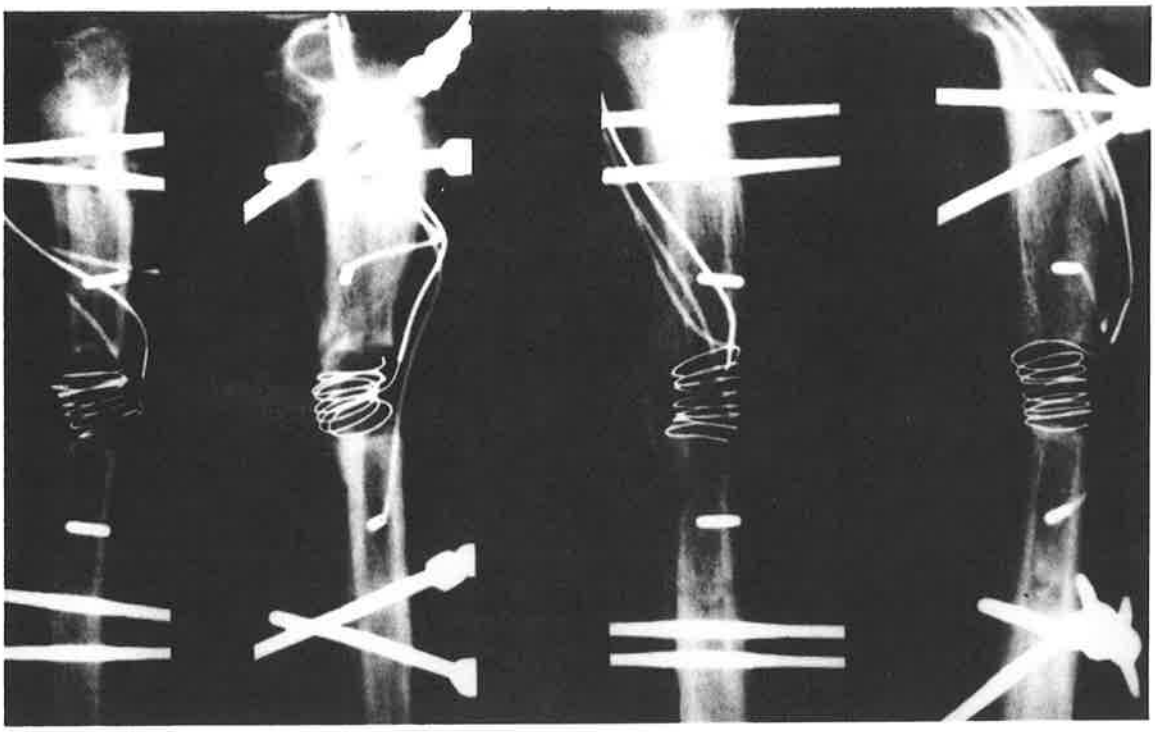

Fig. 3.9 Radiograph showing little difference between an inactive (left) and active (right) stimulator

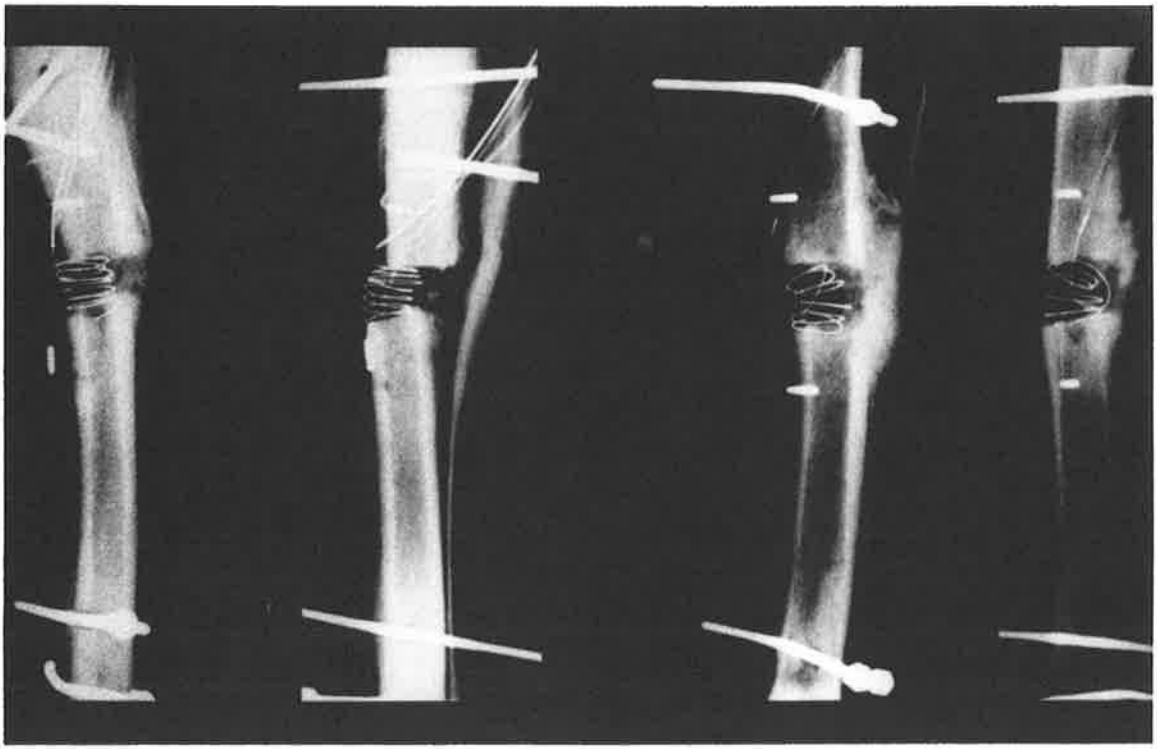

Fig. 3.10 Radiographs showing little bone with an inactive (left) and considerable bone formation with an active (right) stimulator

(ii) Gamma imaging

This was carried out at 2 and 4 weeks using technetium 99m polyphosphate injected intravenously. At the completion of the study, a comparison of the scan films with an initial radiograph allowed the area of "the gap" to be accurately localised and the scan films were then scrutinized in pairs to determine whether there was an appreciable difference in the degree of uptake of the radiopharmaceutical within the gap. It was considered that an increased uptake in "the gap" was an indication of new bone formation. The scanner used did not allow quantitation of the uptake of the radionuclide, hence it was only possible to determine visually in which of a pair the gamma uptake was the greater. This was performed at 2 and 4 weeks (Fig. 3.11).

(iii) Clinical assessment

The animals were killed at four weeks. Initially, a modified Instron press was tested as a means for determining the extent of union but this proved unsatisfactory as it interfered with subsequent histological studies. Crude clinical assessment of union proved adequate and the degree of movement in a given pair of hind legs was assessed by two workers independently. The results were graded from 1 to 4 as follows:- 1 = no union, 2 = mobility, 3 = some movement, 4 = firmly united.

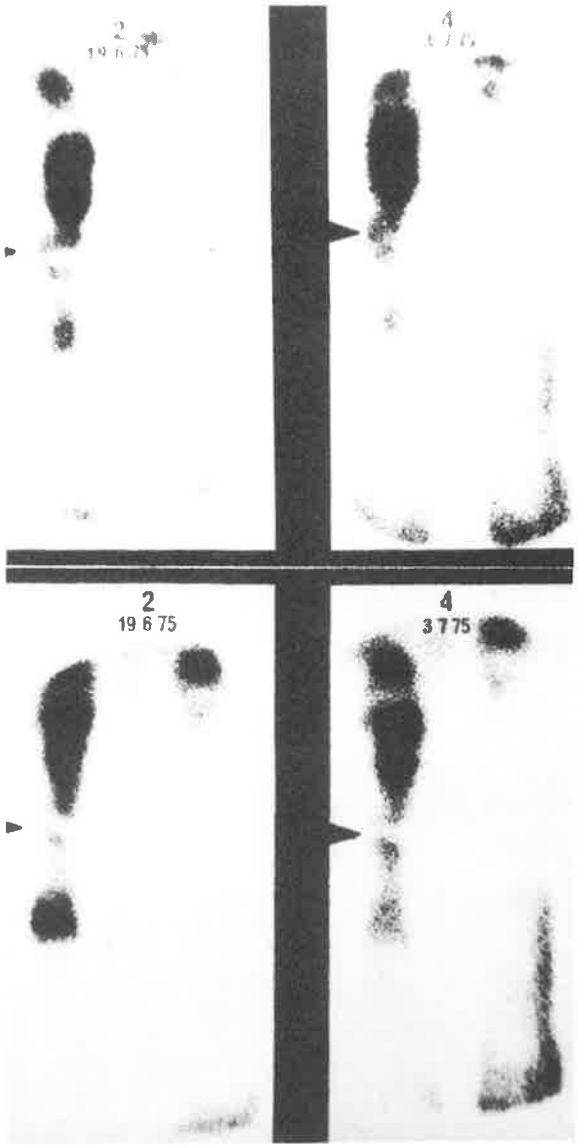

Fig. 3.11 Radionuclide images of a dog pair. The upper two images were interpreted to show a marked increase of activity within the gap between two and four weeks stimulation. The lower two images show no such increase

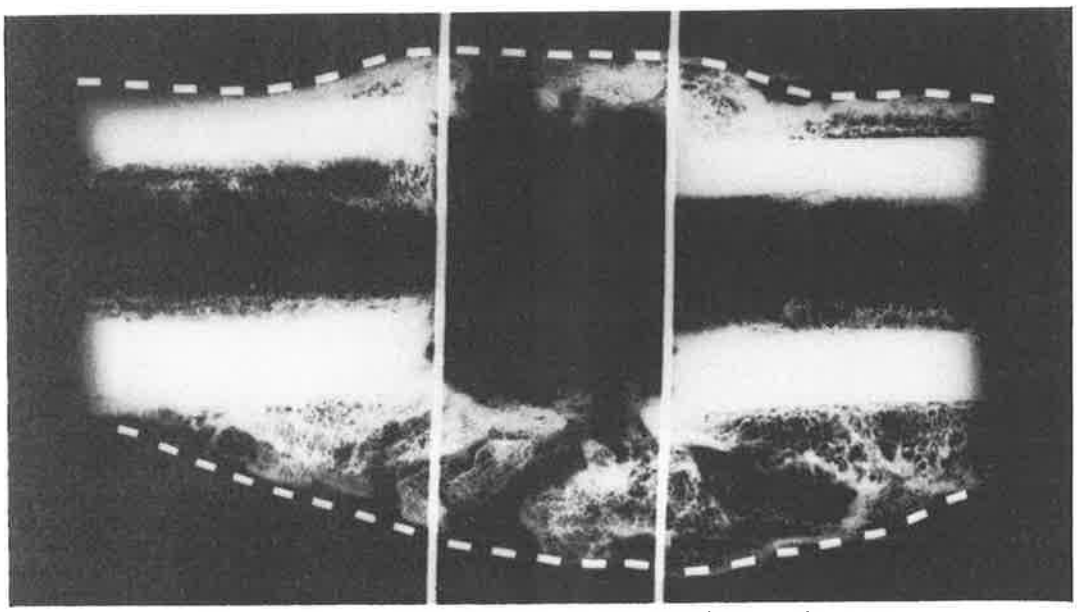

Fig. 3.12 A radiograph of the specimen. The area bounded by the solid and broken lines was regarded as the defect site for the histologic and microscopic estimations

The independent results were summed to enable a judgement to be made that clinical healing was sounder in one of a pair than the other or that there was no difference.

(iv) Histology and Microradiology

Sagittal sections, 0.5 μ in thickness, were obtained from the middle of the bone and radiographs of them were taken. The sections were decalcified and stained with (a) haemotoxylin and eosin and (b) the modified Movat [226] pentachrome technique where new bone stained a pale brown, cartilage green and fibrous connective tissue a pale yellow. Sections were then assessed in random order to determine the nature of the general tissue reaction and type of bone formation, and the degree and type of any inflammation or other abnormality present.

Two macroscopic methods of evaluation were used. (1) The percentage of the area of the defect in which the radiodensity was that of bone or calcification (Fig. 3.12) and (2) the percentage of the defect area occupied by pale brown staining tissue (Fig. 3.13) were estimated. A very close relationship was found between the percentage of bone seen by radiology and histology and this justified the decision to take a central sagittal section of 0.5 μ thickness instead of multiple sections of the whole defect.

Fig. 3.13 Modified Movat pentachrome stain of a sagittal section showing (1) cartilage (green) (2) bone (pale brown) (3) fibrous tissue (pale yellow) in the defect site

Fig. 3.14 Modified Movat pentachrome stain of a dog pair. (Left) Considerable cartilage and bone formation associated with an active stimulator, (right) the gap filled with fibrous tissue and an inactive stimulator

The percentage of these two macroscopic methods were averaged to give a numerical score for each animal. On this basis, the judgement was made as to which animal of a pair showed the greater degree of bone healing (Fig. 3.14).

(v) Summary

As indicated, and prior to breaking the code, the radiological assessment was discarded but the other three assessments were suitable for use as separate evaluations of the degree of bony union. All the results were forwarded to an independent assessor.

3. RESULTS

Forty-eight dogs entered this trial and 4 dogs were excluded (Table I). This left 22 pairs (5 pairs of mongrels, 8 pairs of greyhounds and 9 pairs of beagles) to be assessed independently by gamma imaging, clinical union and histology.

All active stimulators had a current of at least 20 microamperes at implant. Five of the active stimulators were found to be defective at explant, one was weakly active, while 4 were inactive of which 2 were associated with increased osteogenesis and 2 with decreased osteogenesis in a given pair. It was not possible to ascertain if the units were damaged during removal and these dogs were not discarded from the trial as the units were known to be active at time of implant. The remaining 17 stimulators

retained a current of more than 20 microamperes.

Non-parametric methods of data anaylsis [236] were used to test the significance of the results for bone healing of each individual parameter separately and all three together. To the results of assessment by each individual criterion, the sign test (2-sided) was applied to determine whether the outcome could have occurred by chance. The results of all three independent assessments were then combined by giving each animal a numerical score of + 1 for each criterion by which it was judged to show superior healing to its pair, - 1 for each criterion by which it was judged to be inferior and 0 when no difference could be determined. Maximum or minimum scores possible for an individual animal were therefore + or - 3. The numerical scores of the 22 pairs of animals were then paired by the Wilcoxon matched pairs sign rank sum test.

The detailed results are shown in Tables II& III.

By the criterion of clinical assessment of mobility at the defect site, the active stimulator was associated with superior healing in 15 pairs, inferior in 5 and no difference was discernible in 2 ($p = 0.042$).

By the criterion of technetium 99m polyphosphate uptake, the active stimulator was associated with superior healing in 17 pairs and inferior in 5 ($p = 0.016$).

By the microscopic criteria, the active electrode was associated with superior healing in 13 pairs, inferior in 8 and no difference discernible in 1 ($p = 0.384$).

When all three criteria were taken into account, there was a clear-cut positive association between the active stimulator and superiority of healing ($n = 21$; $T_{-} = 48$; $p < 0.02$).

The histologic examinations revealed normal bone healing by endomembranous ossification (Fig. 3.15) with new bone arising from fibrous tissue, and by endochondral ossification (Fig. 3.16) with new bone arising from columns of cartilage cells. Inflammatory changes were infrequent and were not associated with impaired osteogenesis. There was no evidence of dysplastic or neoplastic tissue reaction in either the bone or the surrounding soft tissues.

4. DISCUSSION

While the origin of the stress-generated electric potentials and the exact mechanism of action of electricity in bone are still in dispute, these results show that osteogenesis can be produced around the negative electrode by electrical stimulation in a model of well-established delayed union of the tibia of adult dogs to a highly significant degree.

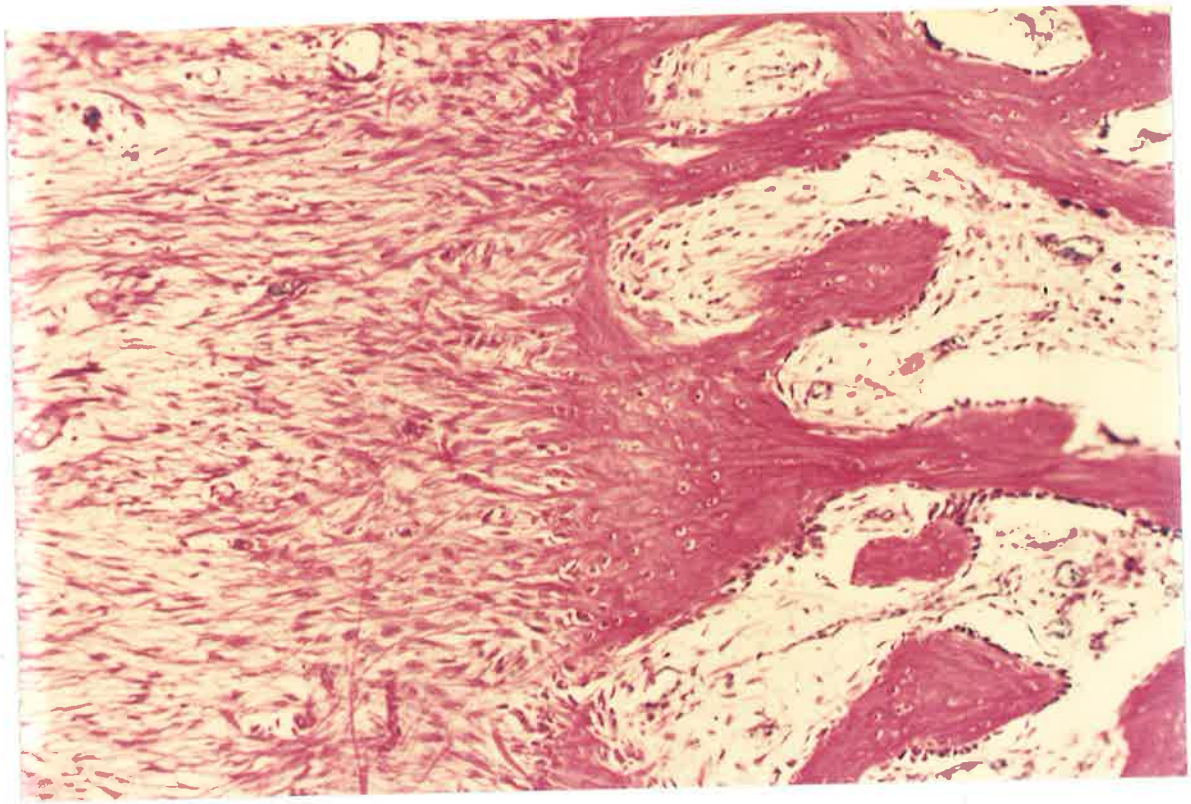

Fig. 3.15 H and E section showing new bone arising from fibrous tissue (left) - endomembranous ossification

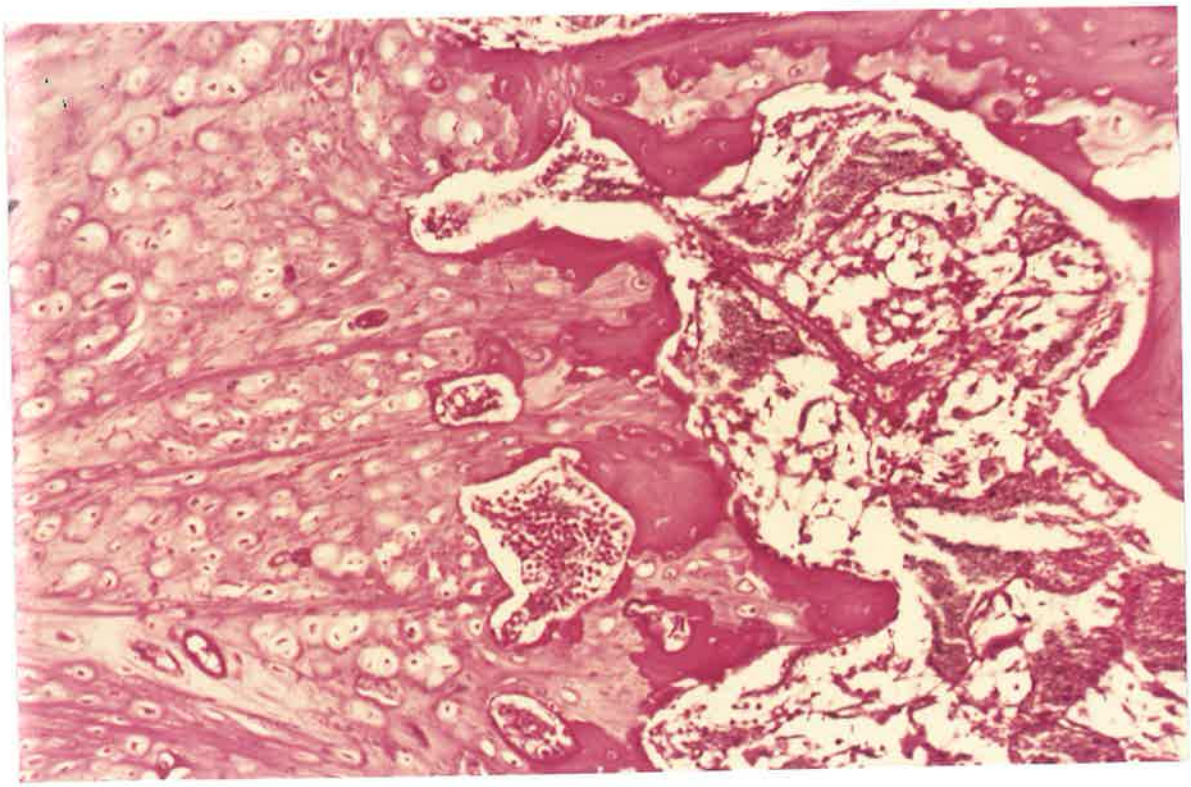

Fig. 3.16 H and E section showing new bone arising from columns of cartilage cells (left) - endochondral ossification

The controlled double blind trial has revealed definite results with clinical assessment and gamma imaging. The crude clinical assessment of union proved adequate. Gamma imaging may have been more precise if numerical quantitation of gamma imaging had been possible at that time. The results from the microscopic examinations did not correlate particularly well with the other two criteria and this may be because only a single sagittal section was studied. The reason for using the three independent methods was because it was difficult to select a single criterion in which one could accurately judge the degree of bone repair.

Those dogs where the stimulators were inactive at explant were also included as it was not known how long electrical stimulation was required to produce osteogenesis and all the active batteries had a current of 20 microamperes or more at implant. It should also be pointed out that the first two pairs (Table II) were the only pairs to produce negative results in all three assessments, and there was some question of misidentification of these animals; in any event they were included in the trial before the code was broken. It is suggested that the design of this study was such as to minimize the likelihood of demonstrating increased osteogenesis with active electrical stimulation rather than the reverse, and yet the results have shown for the first time the association of superior osteogenesis with an active stimulator after an arbitrary period of four weeks in an animal model analogous with

the clinical condition of delayed bone union in man.

The exact mechanism of bone uptake of the radionuclide technetium 99m polyphosphate still remains uncertain. One view [153, 223, 224] has been that the increase in the skeletal uptake is caused predominantly by affinity of the tracer for the non-ossified organic matrix rather than a crystal surface. Another view [148] is that they react through the phosphorus group by absorption on to the calcium of hydroxyapatite in bone. More recently, Garcia et al [116] have regarded the osteogenic process as the major, if not the sole factor, responsible for uptake of the radionuclide. The combination of increased blood supply, and increased metabolic activity occurring in the bone at the time are probably important dual factors. Gamma imaging is a very precise, accurate and early method of assessing new bone formation and has become an important indicator of the rate and amount of bone healing.

It was important to note, in view of the comments in the literature at that time [18, 84, 178, 198] that the histologic examination did not reveal, at least in the short term, any evidence of dysplastic or neoplastic changes.

Many other fundamental questions such as the mechanism of electrically induced osteogenesis, the optimum field density, the size and placement of the cathode and anode, and the size, type and amount of current to be used remain unanswered and require further experimental work.

By the mid 70s, it was important to ascertain the clinical role of electrical stimulation and the results of this work justified the use of electrical stimulation in the human situation. Here, at best 80% of animals derived a significant increase in osteogenesis and attempts were made to remove any variables except an active or inactive stimulator. It was stressed then [84, 198, 221] that electrical stimulation should be used cautiously in humans until the results of controlled clinical trials were known and that continued further experimental work was necessary to determine many of the unanswered questions.

5. SUMMARY

This controlled double blind trial, where independent observers did not know the coding of the stimulators and did not collaborate with each other, evaluated the use of a direct current bone growth stimulator in an animal model of delayed bone healing of the tibia. The conclusion reached was that this commercially available direct current stimulator produced a significant acceleration of bone healing at four weeks in the experimental model used. There was no evidence of inflammatory or neoplastic changes.

Many questions remained unanswered but the results were sufficient to encourage a controlled clinical trial in situations of disturbed bone healing in humans. Electrical stimulation was apparently safe and appeared to significantly augment bone formation. As a result, a controlled clinical trial was carried out in major medical centres in Australia.

TABLE I

DETAILS OF DOGS USED IN PRODUCTION OF EXPERIMENTAL DELAYED UNION AND IN ASSESSMENT OF EFFECT OF A BONE GROWTH STIMULATOR

	Mongrels	Greyhounds	Beagles	Total
TOTAL DOGS OPERATED ON	14	37	18	69
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wound breakdown	1	9	0	10
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REMAINING DOGS WITH SUCCESSFUL DELAYED UNION	12	18	18	48
Dogs subsequently died or destroyed:				
fulminating infection	1	0	0	1
fatal anorexia	1	0	0	1
displaced anode	0	1	0	1
TOTAL DOGS SURVIVING FOR ASSESSMENT OF STIMULATOR EFFECT	10	16	18	44 (22 pairs)

TABLE II

	Active stimulator			Inactive stimulator		
Pair	Clinical union	Gamma activity	Histologic appearance	Clinical union	Gamma activity	Histologic appearance
1	50	-	50	100	+	87.5
2	25	-	25	100	+	50
3	75	+	30	25	-	15
4	100	+	70	50	-	35
5	25	-	5	25	+	22.5
6	75	+	60	25	-	40
7	100	+	50	60	-	40
8	25	+	7.5	25	-	22.5
9	100	+	7.5	25	-	50
10	75	+	10	25	-	27
11	75	+	17.5	25	-	7.5
12	75	-	30	25	+	7.5
13	100	+	15	25	-	7.5
14	100	+	10	25	-	0
15	60	-	25	100	+	30
16	25	+	5	100	-	50
17	25	+	20	100	-	60
18	100	+	35	25	-	5
19	100	+	40	25	-	30
20	100	+	25	25	-	25
21	100	+	50	50	-	35
22	75	+	45	25	-	35

The detailed results were obtained as follows:-

Clinical union was graded 1 - 4: 1 = no union, 2 = mobile
3 = some movement, 4 = united

Gamma activity - the amount of uptake in a given pair was estimated at 2 and 4 weeks, differences being recorded as + or - (a quantitative assessment was not available at the time)

Histopathology - the percentage of union by radiograph and the percentage of bone by histology were summated and divided.
the results of clinical union and histopathology were expressed as a percentage.

TABLE III

CRITERIA FOR BONE HEALING

Pair	Clinical Union	Gamma Activity	Histologic Appearance
1	-	-	-
2	-	-	-
3	+	+	+
4	+	+	+
5	+) -)	-	-
6	+	+	+
7	+	+	+
8	+) -)	+	-
9	+	+	+
10	+	+	-
11	+	+	-
12	+	+	+
13	+	-	+
14	+	+	+
15	-	-	+) -)
16	-	+	-
17	-	+	-
18	+	+	+
19	+	+	+
20	+	+	+
21	+	+	+
22	+	+	+

Scores for each of the three individual criteria of bone healing for the animal of each pair with the active electrode. Scores have been assigned depending on whether healing was judged superior (+) or inferior (-) to that in the paired animal with the inactive electrode by the independent "blind" observer. Significance of the difference between animals with active versus inactive electrodes was calculated by the sign test for individual criteria and by the Wilcoxon matched-pairs sign rank sum test for all three criteria.

CHAPTER 4

TREATMENT OF DELAYED UNION AND NONUNION OF LONG BONES WITH AN IMPLANTED DIRECT CURRENT STIMULATOR

CHAPTER 4

TREATMENT OF DELAYED UNION AND NONUNION OF LONG BONES WITH AN IMPLANTED DIRECT CURRENT STIMULATOR

1. INTRODUCTION

The use of electricity to promote healing in cases of difficult nonunion dates back over 160 years [131]. Despite much research [246] no one has been able to describe precisely the mechanism by which small electric currents are able to influence the formation of bone. There has been adequate evidence to show that practical use may be made of the phenomenon [23, 26, 29, 30, 41, 45, 62, 63, 67, 68, 96, 110, 142, 149, 150, 156, 162, 163, 189, 297].

Reports in the literature have described semi-invasive [59, 62, 63, 65, 67, 68, 110, 149, 156, 162, 163] and non-invasive techniques [23, 25, 26, 29, 30, 156, 157, 167]. The use of the Osteostim in Australia was withheld until there was sufficient justification of its use from animal experimentation [202, 203]. As a result a clinical trial was organised and controlled by the author. The use of the Osteostim was restricted to those cases and surgeons participating in this controlled trial. The self-powered, self-contained and implanted bone growth stimulator was first used by the late Alan Dwyer in 1969 for failed posterior spinal fusions and success with this technique was subsequently reported [72, 96, 97] for both failed posterior spinal fusions and fractures with established nonunion.

The first implantable stimulator for ununited fractures of long bones was successfully inserted by Dwyer in Australia in 1972. A 22-year-old man sustained a severe compound fracture of the tibia and fibula. Two previous attempts to achieve union with cancellous bone grafts had failed. Seventeen months after the accident a bone growth stimulator was inserted. The cathode was attached to a stainless steel suture used to hold the two bone fragments in apposition and an anode was placed in the medullary cavity in both the proximal and distal fragments. Eleven weeks later, union was present (Fig. 4.1).

The first personal clinical experience with this stimulator was the successful union of a pseudarthrosis of the midshaft of the tibia in a 7-year-old child who had severe manifestations of neurofibromatosis. This pseudarthrosis [205] followed tibia leg lengthening by the Anderson technique [10] as a treatment for congenital shortening of one leg.

Despite much experimental work and increasing reports in the literature of clinical use in humans, there remained in the mid 70s scepticism in Australia and elsewhere regarding the value and use of electrical stimulation in orthopaedic surgery.

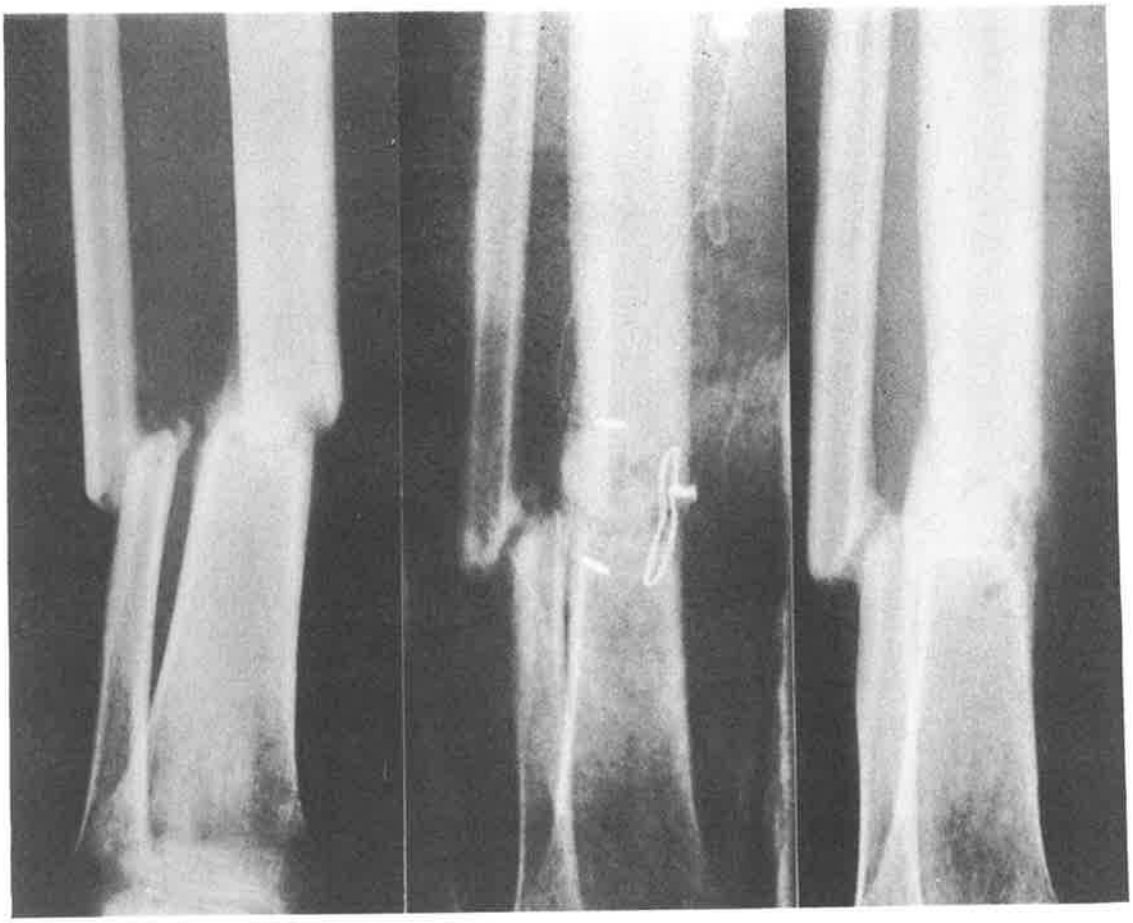


Fig. 4.1 A 22 year old man with a severe compound fracture of the tibia which remained ununited 17 months later. The cathode of a bone growth stimulator was attached to a stainless steel suture and 11 weeks later union was present

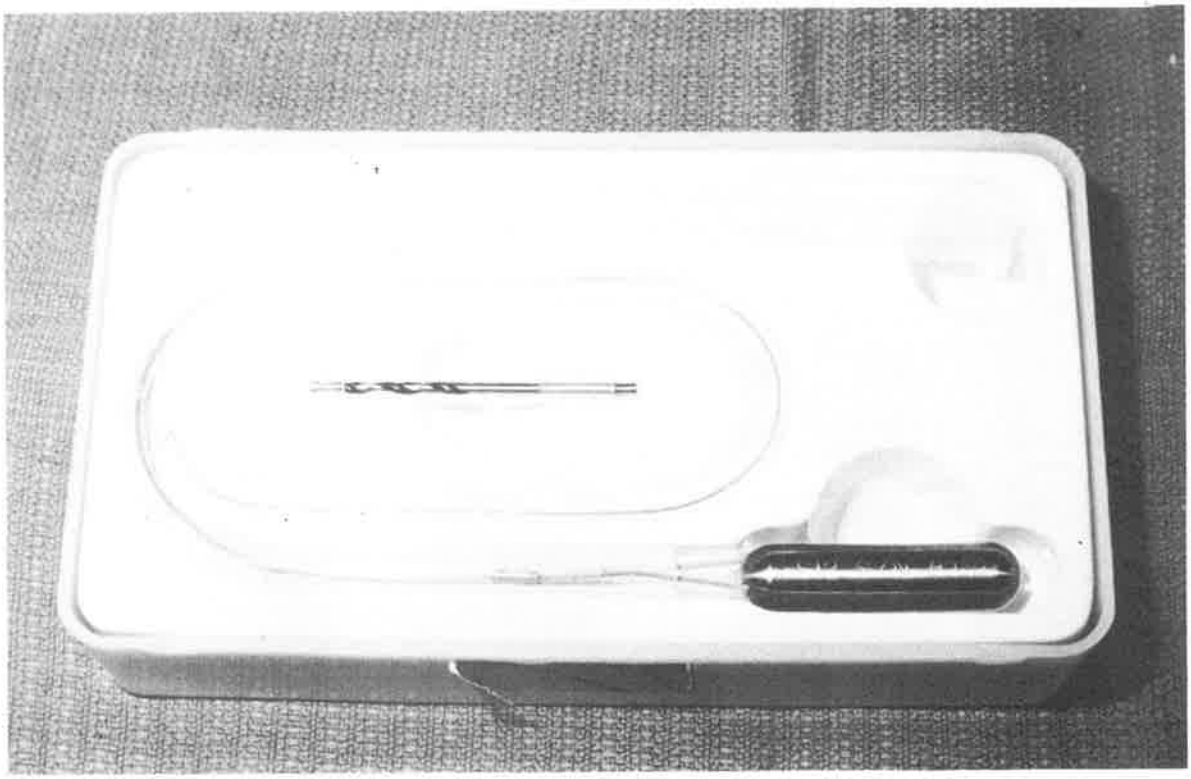


Fig. 4.2 Implanted direct current bone growth stimulator - Osteostim S12

2. MATERIALS AND METHODS

(a) The bone growth stimulator

The totally implanted direct current bone growth stimulator, Osteostim S12 * (Fig. 4.2) consisted of three elements: (1) an electronic assembly, consisting of two zinc/silver oxide cells, series-connected to produce three volts which were coupled to the active electrodes via a transistorized constant current regulator. The latter produced a constant current output of 20 microamperes regardless of bone tissue resistance changes over the range of 0-100,000 ohms. The operating life of the assembly is 22-26 weeks post implant; (2) a single titanium cathode which was designed to be incorporated in the fracture site; (3) a single platinum anode which was placed in the soft tissues adjacent to the generator.

Initially, for biocompatibility and environmental protection, the generator was encapsulated in epoxy resin with a methyl methacrylate case. This was later changed to a pure titanium capsule since fibrous tissue reaction to this material is minimal [101, 190, 210, 283, 284, 294] and it further ensured good long-term protection of the battery and electronics. A stainless steel cathode was originally used. The cathode was changed to a pure titanium wire when it was shown firstly that the cathode helix became firmly embedded in new

* Telectronics Pty. Ltd., Sydney, Australia

bone, making removal of the wire difficult and, indeed, undesirable; and secondly, that titanium produced an even growth of bone along the entire length of the cathode [187].

(b) The clinical trial in Australia 1976 - 1978

A prospective non-randomised and open clinical trial was held in Australia from 1976 to 1978 to evaluate if electrical stimulation was, at least, as effective in healing ununited fractures as other accepted surgical procedures. This was considered a responsible attitude in view of the scepticism towards electrical stimulation and osteogenesis that existed amongst surgeons. A randomised clinical trial was not considered for medical and ethical reasons.

This trial was entirely organised by the author. Thirty orthopaedic surgeons in major teaching hospitals were invited to participate in the trial and all the details and techniques used were personally explained to them throughout the country. A protocol form in triplicate (Appendix D) was prepared and was completed for each case by the responsible surgeon and returned to the author for evaluation. The author was personally involved in 60 cases treated at the Royal Adelaide and Adelaide Children's Hospitals. Orthopaedic surgeons at the Mater and Princess Alexandria Hospitals, Brisbane; the Prince of Wales and St. George's Hospitals, Sydney; the Alfred Hospital, Melbourne; and the Queen Elizabeth

Hospital, Adelaide took part in this trial and carried out the surgery on the remaining cases, under supervision initially.

Strict criteria were used for case selection in the clinical trial and included clinical, radiological, and nuclear scan evidence of at least delayed union of fractures of long bones not less than 16 weeks from the initial injury. Furthermore, surgical confirmation of lack of union at the time of the implant surgery was mandatory.

Certain definitions were essential. Nonunion [73, 191, 267] is a specific term referring to a situation where bone healing has ceased, where the fracture is mobile clinically and where well-defined radiologic features are present. Delayed union is more difficult to define, but it is a situation where the possibility of bone healing still persists, even though clinically and radiologically the fracture is ununited.

As a result, delayed union was defined for the purposes of this clinical trial as being present when the fracture had failed to unite within six months [222], and that nonunion was present when the fracture had not united within 12 months, and, further, that it was the individual surgeon who had to determine whether a fracture had delayed or nonunion in the "grey" period of 6-12 months. Bone union was defined [8, 143, 244] as the time when it was considered safe either clinically

or radiologically, or both, to remove all plaster immobilisation and allow full weight-bearing.

(c) Technique for insertion of the bone growth stimulator

(i) Long bones

Two techniques were used (Fig. 4.3). In some cases the cathode could be threaded across the fracture site through small drill holes to form a figure-8. In the majority of cases, however, the cathode was placed across the fracture site coiled in the form of a helix; the single platinum anode was positioned in the soft tissues adjacent to the generator and 8-10 cm from the cathode.

An operation was required but it should be emphasized that this was a small operation and the simple techniques allowed for great variation of the surgeon's technical skills. However, the simple technical details needed to be adhered to.

In the preferred technique, the nonunion of the long bone was exposed by a direct approach and a cortical defect was created by removing approximately 2-3 cm x 1 cm of cortical bone making sure that the nonunion was in the centre for the defect so created. It was important to curette the sclerotic bone or fibrous tissue from the medullary cavity so that continuity across the fracture site could be ensured [44, 204] (Fig. 4.4).

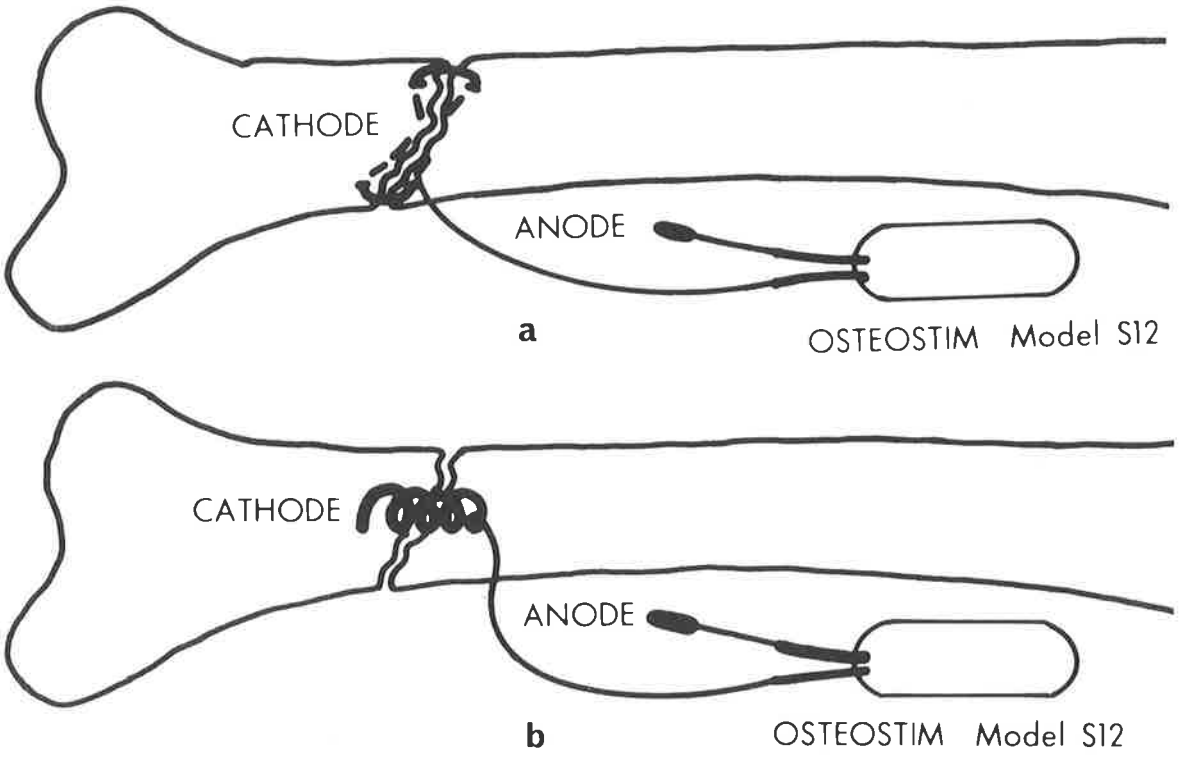


Fig. 4.3 Techniques of insertion of bone growth stimulator. The cathode may be; (a) threaded across the fracture site to form a figure-of-eight, or (b) coiled into the form of a helix

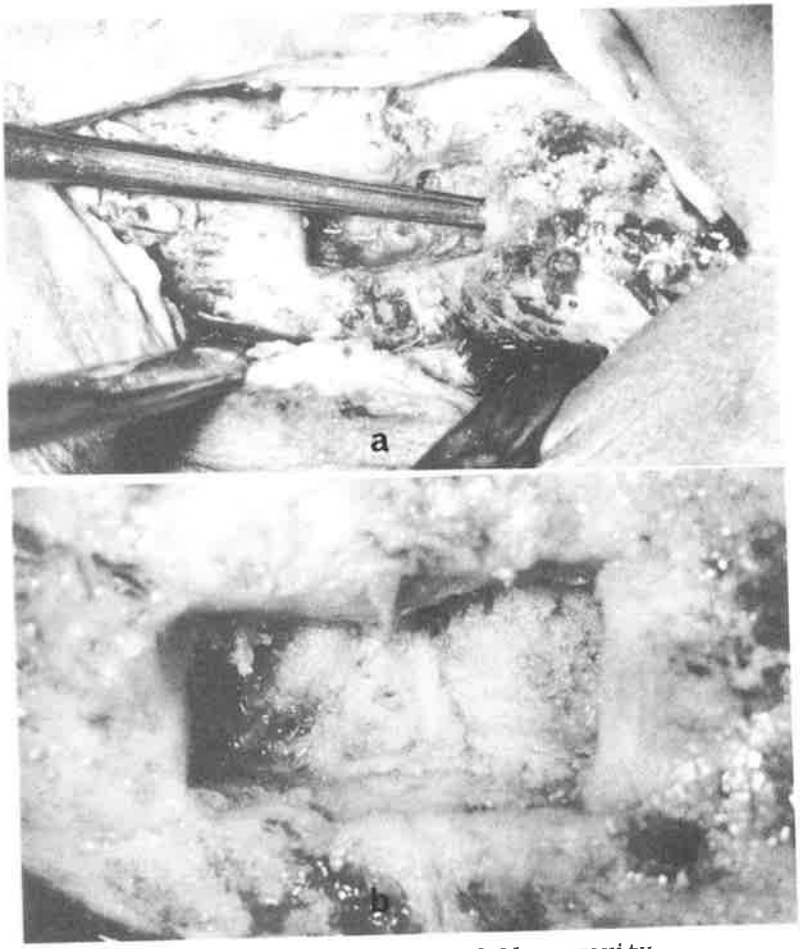


Fig. 4.4 (a) Curettage of the medullary cavity

(b) Cortical bone defect approximately 2 x 1 cm with a fracture line in the centre of the defect

The generator with its incorporated platinum anode must be deep to the deep fascia. In most instances an appropriate soft tissue space was found through the single incision but, in the case of the tibia, it might be more appropriate to make a separate incision in the calf and place the generator in the intermuscular plane between the gastrocnemius and soleus muscles (Fig. 4.5).

The cathode was formed into a helix commencing at the junction of the bare titanium cathode with the insulated coating and it was then placed across the defect securing it in place by putting one loop of the helix into each medullary cavity. It must be placed centrally across the nonunion site so the field of electrical influence was centrally placed within the fracture site [204] (Fig. 4.6). If a metallic implant was present, the cathode could be placed in the same way provided a sliver of bone, usually taken from the iliac crest, was placed between it and the metal. The bone prevented contact between the two metals which would have dissipated the current over a large area and resulted in little or no effect. After wound closure, the fracture was immobilised in the usual way for the particular fracture.

A constant observation has been the minimal amount of post-operative pain associated with insertion of the Osteostim alone. In the absence of any post-operative complications, the patient has remained in hospital for a few days only. If the fracture was stable, as was

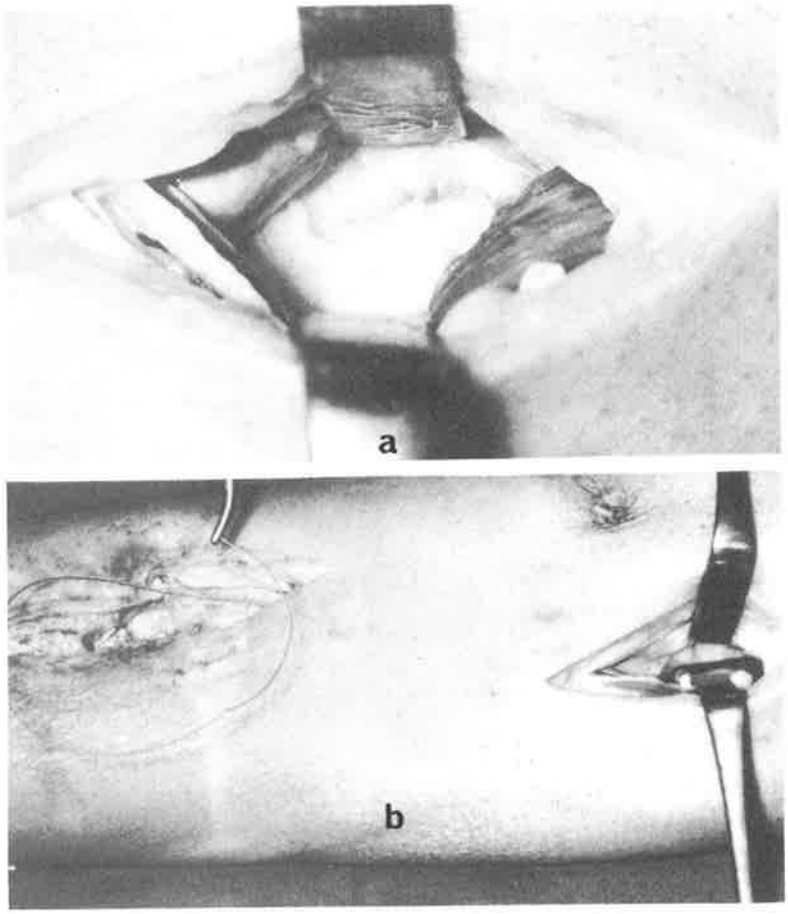


Fig. 4.5 (a) Intermuscular space in the calf between gastrocnemius and soleus

(b) The cathode and anode are placed in the intermuscular space and the cathode is passed subcutaneously into the fracture site

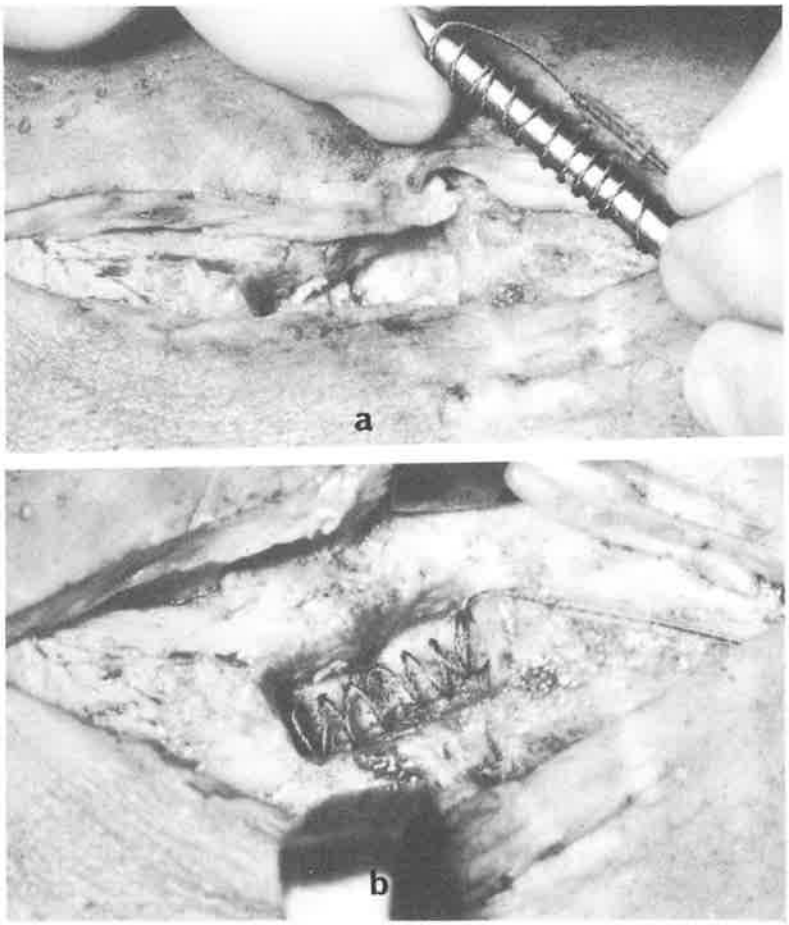


Fig. 4.6

(a) The cathode is wound into a tight helix

(b) The cathode placed across the defect site

the case with most long standing nonunions of the tibia and once wound healing had occurred, weight bearing was encouraged using a walking heel attached to the plaster. The implanted generator, anode and as much as possible of the cathode were simply removed at the end of approximately six months under either general or local anaesthesia - a minor procedure. Patient co-operation was not required after insertion of the Osteostim as the case was treated in the usual way for the particular fracture.

A typical example (Fig. 4.7) is a 46-year-old male who sustained a compound fracture of the tibia and fibula in a vehicle accident. After two failed Phemister cancellous grafts over two years, an Osteostim was inserted. The tibia was clinically united 14 weeks later and radiologically consolidated at six months.

(ii) Scaphoid

The Osteostim was just as applicable to ununited fractures of the scaphoid.

The technique involved a volar exposure of the scaphoid. A defect was created gently and both proximal and distal fragments of the scaphoid were curetted. Stability was achieved by taking a small cortical graft from the lower end of the radius and placing it across the nonunion site to fix the proximal and distal fragments. The Osteostim was then inserted across the defect in

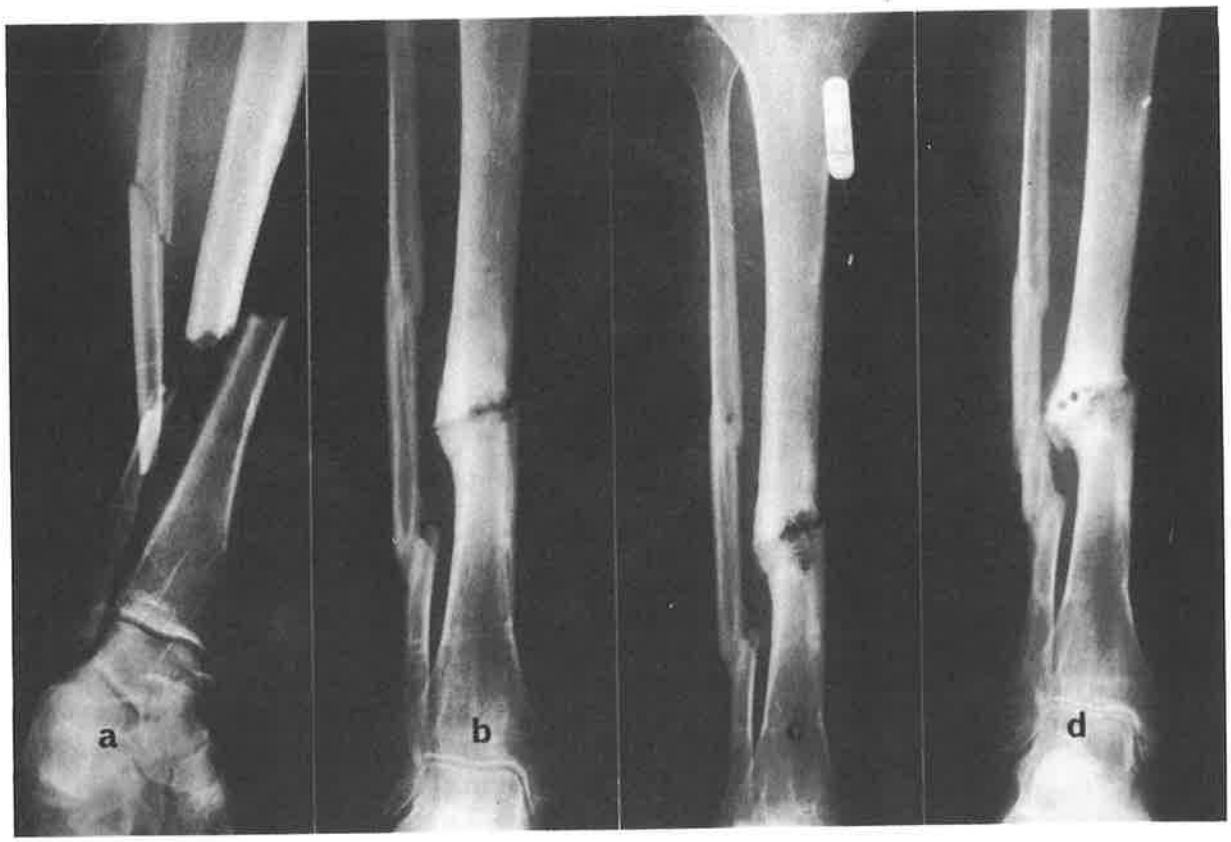


Fig. 4.7 (a) A 46 year old man with a compound fracture of the tibia and fibula

(b) Ununited tibia after two Phemister cancellous grafts

(c) Insertion of the Osteostim - note the accurate placement of the cathode

(d) The tibia consolidated radiologically six months later

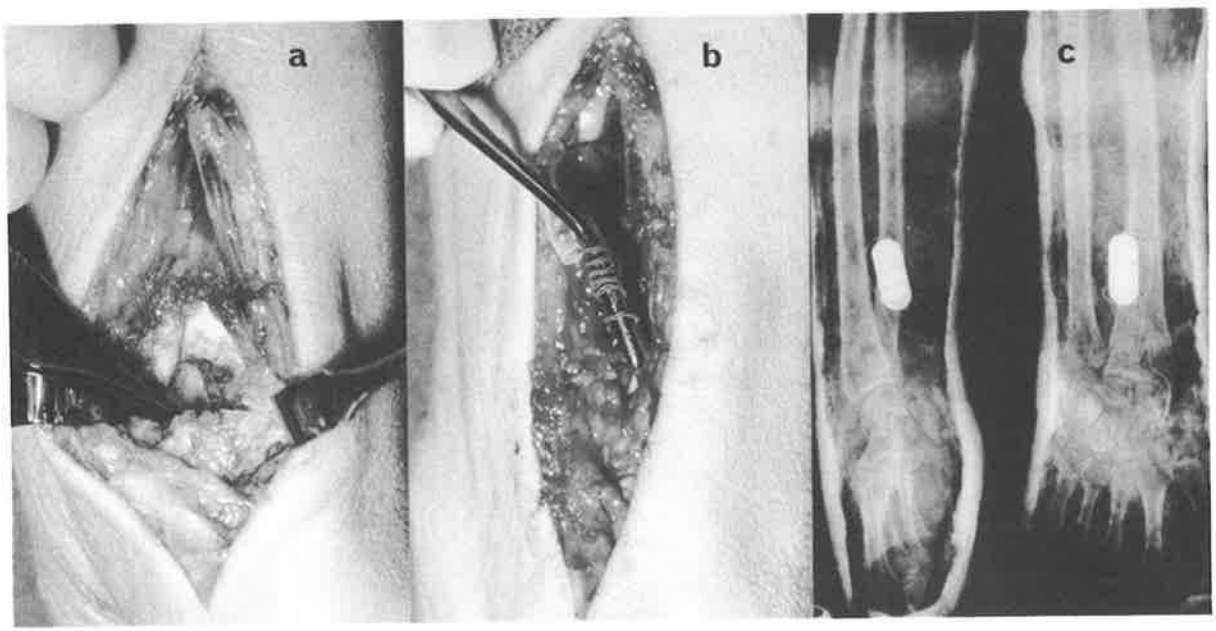


Fig. 4.8 (a) Volar approach to the scaphoid, a defect is created in both fragments which are stabilized by a small cortical graft taken from the lower end of the radius

(b) A small tight helix is made and inserted into the defect

(c) A radiograph showing the helix in place in the scaphoid and the generator lying on the interosseous membrane

the same way as previously described and the helix was made very much smaller, using only part of the titanium cathode. The generator was placed along the anterior surface of the interosseous membrane. The ununited scaphoid was treated in plaster of Paris in the usual way (Fig. 4.8).

3. RESULTS

An Australia wide clinical trial was held from 1976-1978.

(a) Long bones

(i) 84 patients with delayed union and nonunion of long bone fractures were treated. There were 47 patients with delayed union fractures and 37 patients with nonunion fractures. 72 fractures involved the tibia, predominantly the middle and lower thirds (Table I). There were 64 male patients and 20 female patients. The age range was from 5-81 years with a mean age of 30 years. There was no relation in the success rate between age and sex but there was a marked difference in the success rate of different bones.

(ii) Overall result

Fracture healing, clinically and radiologically was achieved in 72 of 84 patients (86%).

(iii) Time from injury

The 84 cases varied widely in their degree of difficulty since the time from injury to the implant operation varied from 3 months to 7½ years, with an average time of 10 months. (Fig. 4.9). For 60% of

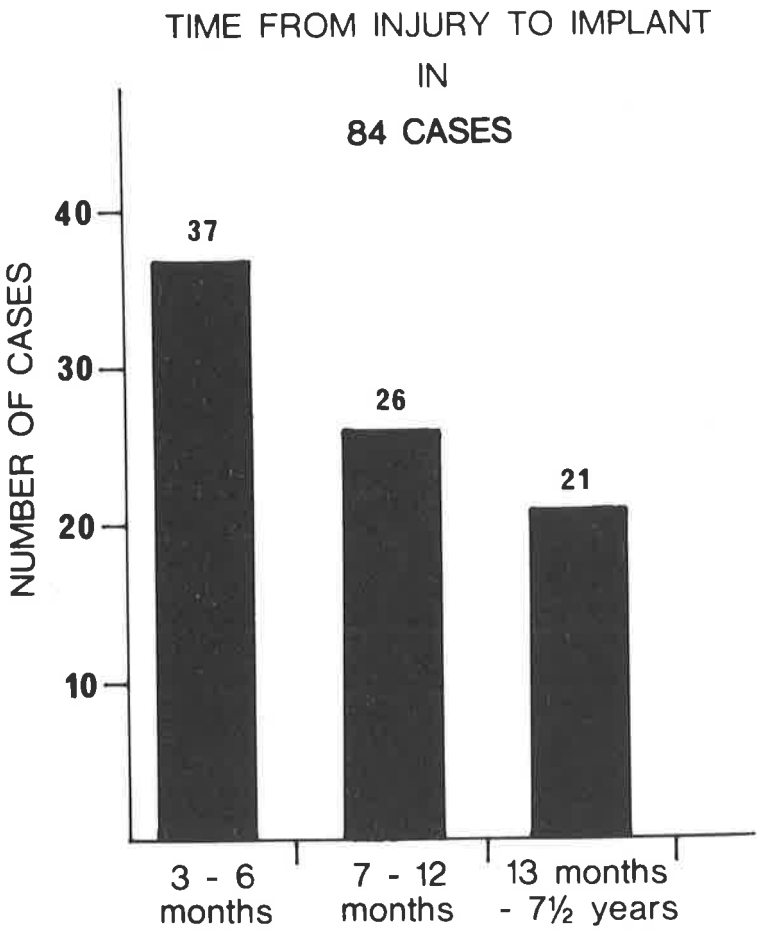


Fig. 4.9 Time from injury to implant in 84 cases

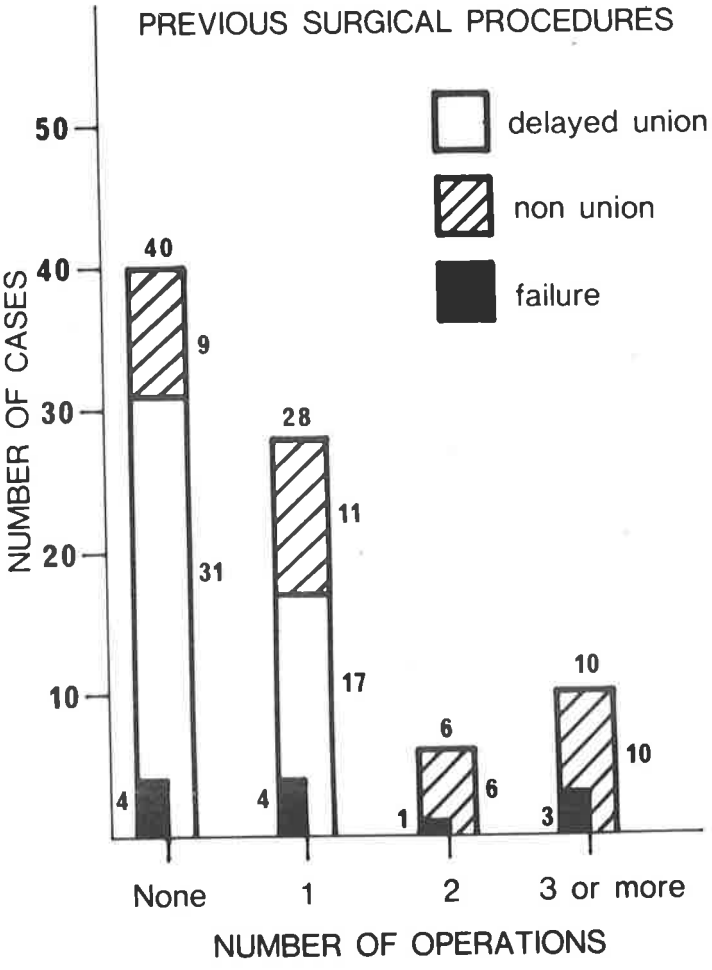


Fig. 4.10 Previous surgical procedures

the patients, more than six months had elapsed from the time of injury; indeed, this method of treatment was used for the first 45 patients only when confirmed nonunion of fractures was present or when other methods of treatment had failed.

(iv) Time to achieve union

In the 72 patients who were successfully treated, the time to achieve union ranged from 12 to 36 weeks with an average of 16 weeks (SD 3.14).

(v) Previous operations

44 patients had one or more operations, consisting of various types of bone grafting procedures and internal fixation, after the initial treatment to achieve union. Fractures in 36 of these patients united after electrical stimulation. Ten patients had three or more previous operations, and union was achieved in seven of these patients (Fig. 4.10).

It is significant that 12 of the unsuccessful previous operations consisted of cancellous bone grafts, and that 10 of these (83%) went on to union after electrical stimulation.

(vi) Compound and infected fractures

Many of the fractures were initially compound, and 15 had infection present at the time of electrical stimulation. Of these, 13 fractures united with good wound healing and the infection subsided. Only two fractures failed to unite when the implant was inserted

in the presence of infection. It is important to stress that the bone growth stimulator was inserted through an anterior approach in all patients treated for tibial fractures.

(vii) Failures

Failures have occurred in 12 cases (14%) Table II. The majority affected the lower third of the tibia and have been attributed to (a) inadequate plaster immobilisation before union had consolidated and experience has shown that once union has started to occur after electrical stimulation, the fracture may still take at least the usual time for consolidation; (b) faulty technique especially incorrect placement of the cathode centrally across the nonunion site (Fig. 4.11); (c) premature removal of the implant which now has an active life of six months; (d) nonunion and a chronic discharge which has been present for too long and no method, including electrical stimulation, was able to recommence osteogenesis (Fig. 4.12); (e) finally, it is agreed [69] that any gap larger than one half the diameter of the bone at the level of the nonunion does not contain enough responsive cells to form bone when stimulated by electricity.

(viii) Complications of the bone growth stimulator

These have generally been minor. Soft tissue reaction was observed around the generator in earlier models. All wounds have healed and there has been no instance of infection occurring around the cathode wound as a direct result of the operative procedure itself.

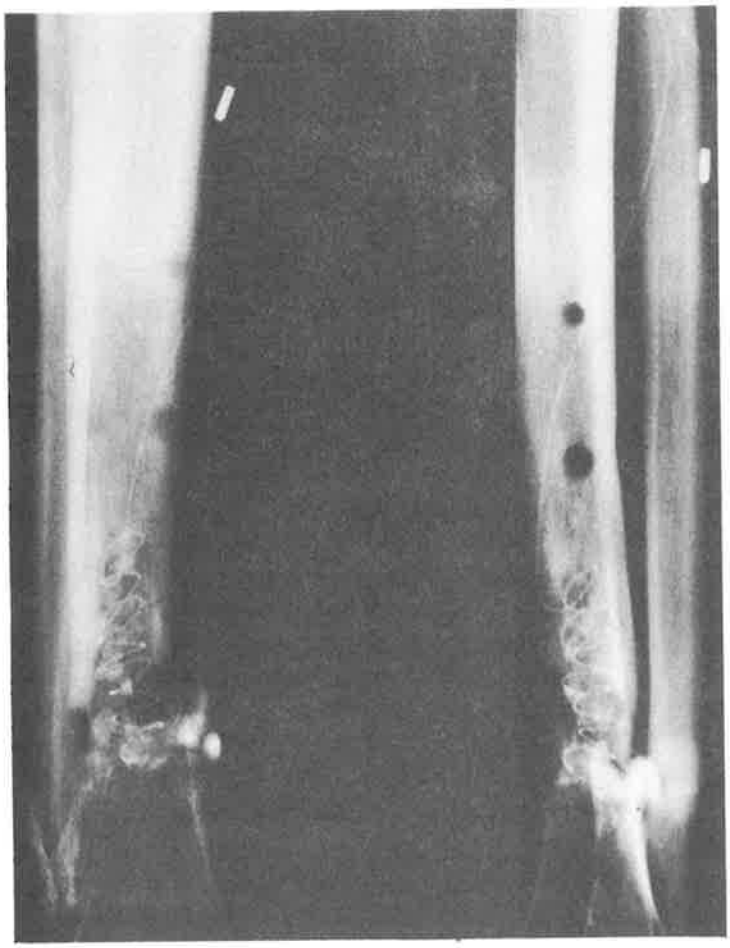


Fig. 4.11 Incorrect placement of the cathode - almost entirely placed in the proximal fragment

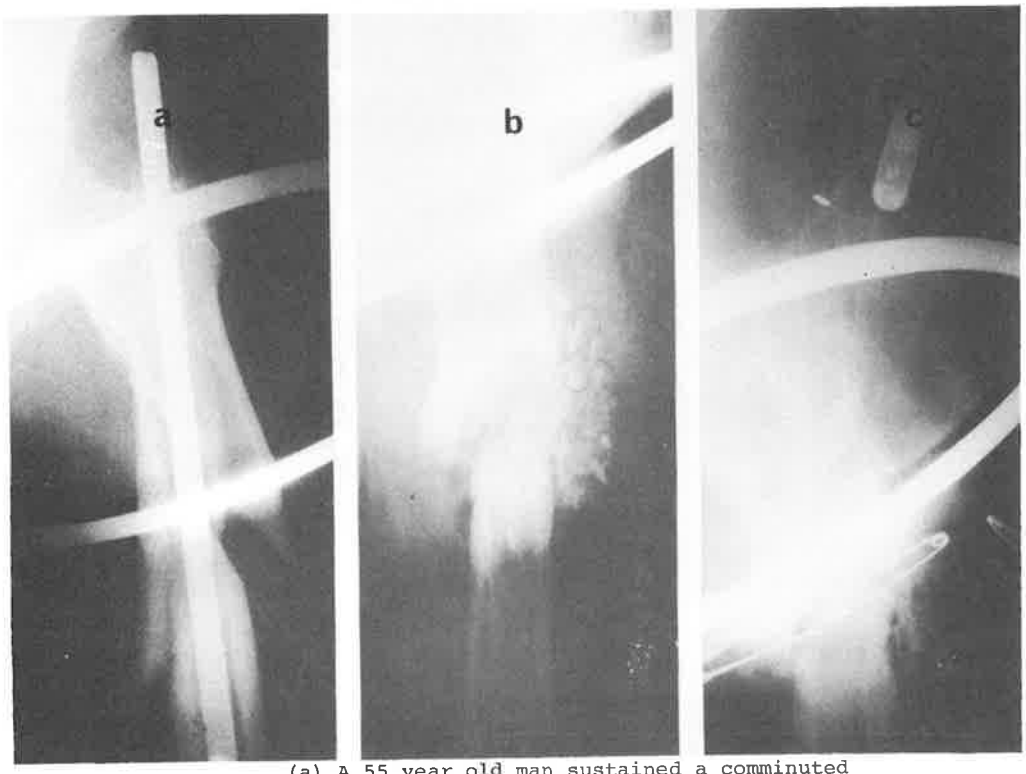


Fig. 4.12

(a) A 55 year old man sustained a comminuted spiral fracture of the shaft of the femur

(b) 5 years later, after several varieties of internal fixation with cancellous bone grafting operations, he had 11.25 cm of shortening, an ununited fracture of the upper end of the femur and a large gap between the bone ends

(c) Electric stimulation and further cancellous bone grafting failed to achieve union

The cathode wire has broken in four instances, and in all the generator was not placed beneath the deep fascia. Despite this, these fractures all united.

(ix) Phemister cancellous grafting plus electrical stimulation

Phemister cancellous grafting was used in conjunction with bone growth stimulation in 11 patients. In 8 patients, previous operations had failed to achieve union, and it was considered that every effort was necessary if electrical stimulation was to succeed. Cancellous grafting was added in three other instances at the direction of the surgeon involved.

(x) Second bone growth stimulator

Five patients had a second stimulator inserted to achieve union. These cases were judged to have insufficient consolidation at the fracture site after 4-6 months of electrical stimulation and a second stimulator was inserted. However, the fractures of three of these patients may well have united if the electric stimulator had remained implanted for the currently recommended 24 weeks, since the first stimulator had been removed at 16 weeks, and union became apparent 4-8 weeks after insertion of the second stimulator.

(b) Ununited fractures of the scaphoid

There have been 10 successes out of 13 cases. Failures have been associated with either a severe transcaphoid perilunar fracture dislocation or ununited fractures through a small proximal pole of the scaphoid.

4. FURTHER CLINICAL EXPERIENCE WITH THE OSTEOSTIM

(i) Australia 1976 - 1978

As a result of the clinical trial, the Osteostim has been used widely in Australia.

The technique has been successfully used in all long bones of both upper and lower limbs. It has achieved union where cancellous grafting has failed in a pathological fracture of the tibia with Paget's disease and in failed arthrodesis of the ankle, knee and hindfoot. In addition, to its use for ununited fractures of the scaphoid, this simple technique may also be used as the primary treatment once radiographs illustrate that the scaphoid fracture is not uniting.

By the end of 1981, 283 cases had completed treatment in Australia. The cases in which the Osteostim was used after the trial ended have not been subjected to the same critical analysis as the Osteostim has been freely available for use in Australia and its use has been based on the individual surgeon's judgement. However, information has been directly sought from the involved surgeons and the data suggests an overall success rate of 88%.

(ii) The United States of America 1980 - 1981

The Australian experience [204] formed the basis of approval by the United States Food and Drug Authority for use of the Osteostim in the United States in 1980.

As a result, the same techniques and the same criteria for the use of the Osteostim have been used in that country. It is important and significant to note that the overall success rate and the success when used after failed Phemister bone graft and in the presence of chronic infection are the same as the Australian experience (Tables III, IV, V).

These comparable results would therefore confirm that this is a simple surgical technique that can be reproduced by a wide variety of surgeons in different countries.

(iii) Failed posterior fusion of the lumbar spine

The totally implantable bone growth stimulator was first used in 1969 for failed posterior spinal fusions [96, 97]. This stimulator had four cathodes for insertion into four apophyseal joints and together had a constant current of 20 microamperes.

The Osteostim S11 was produced for posterior spinal fusions. The Technique (Fig. 4.13) involves excision of the articular surfaces of the superior and inferior facets of the particular lumbar joint, placement of a small graft between the joint surfaces and passage of the titanium cathode at right angles across the joint. Kane [151,152] has reported a success rate of 91.5% with this technique in posterior spinal fusions in 82 patients of whom 80% had previous surgery.

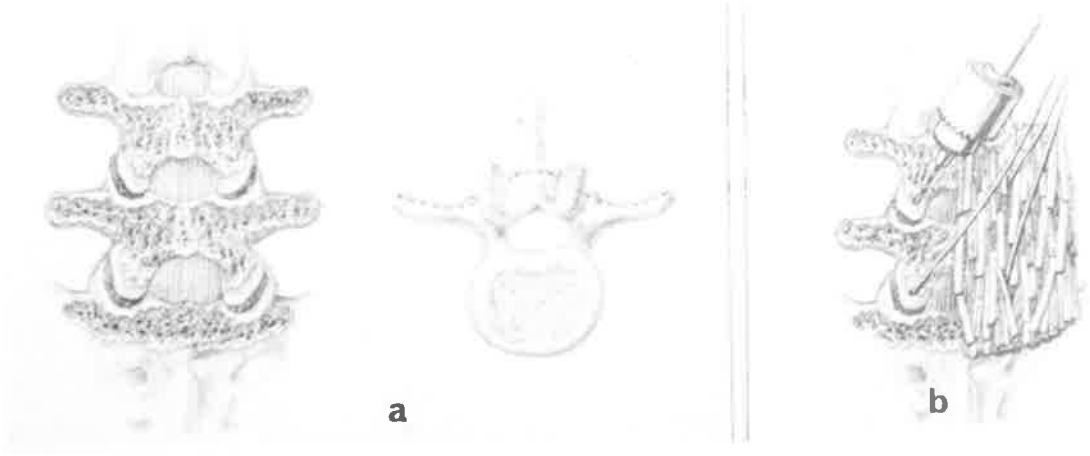


Fig. 4.13 (a) Creation of a large bed of bleeding bone by fish-scaling the cortical bone in the area to be fused including the laminae, the transverse processes and the sacral ala

(b) A 1.6 mm drill bit passes through the facet block complex consisting of the superior and inferior facets of adjacent vertebrae and the intervening bone block. The cathode lead is inserted into the drill hole from the medial to the lateral side

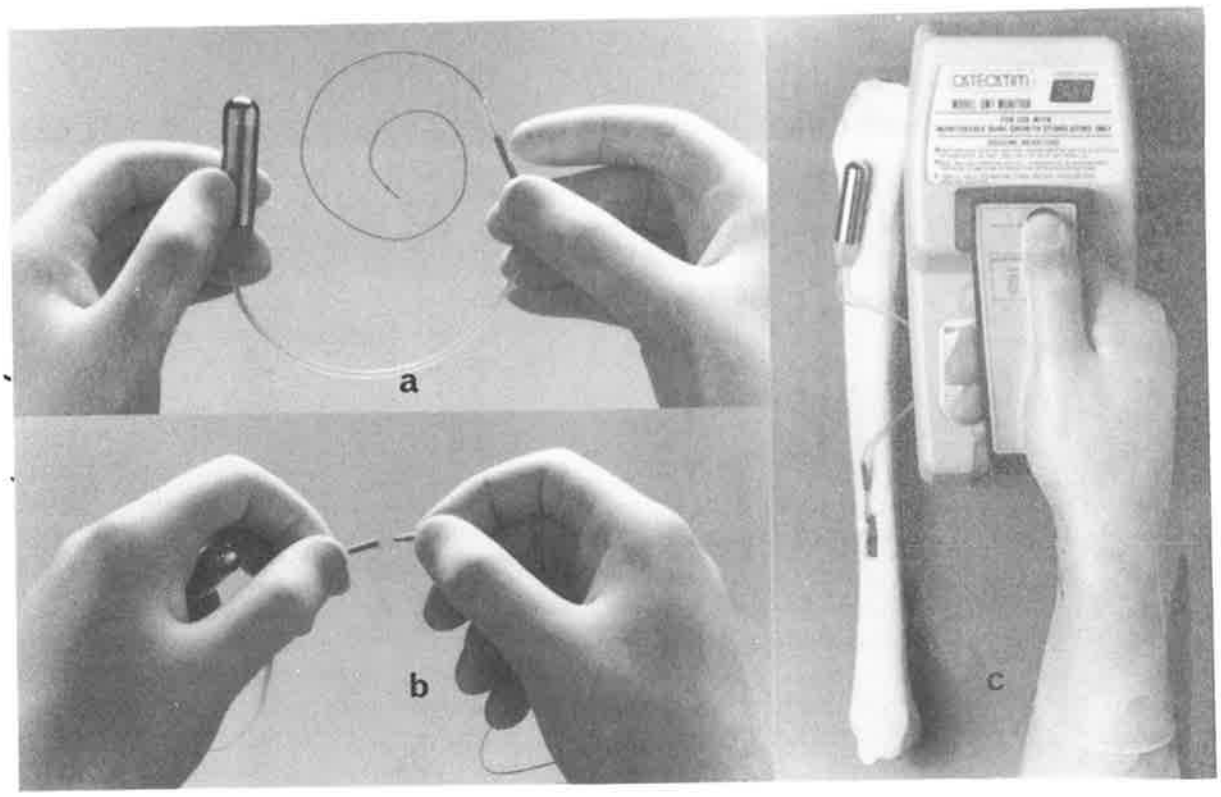


Fig. 4.14 The Osteostim XM12

(a) The hermetically sealed casing incorporating the anode in the platinized hemispherical end of the case

(b) A silicone insulated flexible stainless steel lead which is joined to the titanium cathode by a connector

(c) An external monitor of the current flowing

(iv) Osteostim XM12

The Osteostim has been modified to provide additional capability of external monitoring of the current flowing, measured to the nearest microampere. It also incorporates (Fig. 4.14) an hermetically sealed casing with ceramic feed-through of the cathode lead, thereby enhancing protection of the power source and electronics; it incorporates the anode in the platinised hemispherical end of the case; and it contains a silicone-insulated flexible stainless steel lead that is joined to the titanium cathode by a connector. This last imparts greatly increased fatigue resistance to the lead and simplifies its removal.

The change to titanium for the case material not only affords better protection of the contents against the hostile body environment but also results in only minimal soft tissue reaction. The cathode material was changed from stainless steel to titanium when it was shown that titanium produced an even growth of bone along the entire length of the cathode [186, 187]. Stainless steel, on the other hand, is effective as a cathode material only in the area immediately adjacent to the insulation [64]. Additionally, since some of the cathode usually remains behind when the generator is removed, the choice of the most inert material is desirable.

5. ILLUSTRATIVE CASES OF SUCCESSFUL UNION

Union has been achieved in three difficult instances (a) ununited long bone fractures, (b) ununited fractures of the scaphoid and (c) failed posterior spinal fusions. The following examples will illustrate how effective this method of electrical stimulation has been and its wide range of applications.

(a) Ununited fractures of long bones

Case 1

An 18-year-old male sustained a very severe compound fracture of the lower end of his tibia and fibula. 18 months later, after numerous sequestrectomies and attempts to achieve stability and skin cover, he presented with a completely mobile nonunion of the fracture of the tibia together with a chronic discharge through thin attenuated skin. Amputation had been advised. An Osteostim was inserted and six months later the discharge had ceased and the fracture was almost united. A second Osteostim was inserted - autogenous bone graft was quite impracticable - and the fracture consolidated clinically and radiologically over the next four months. He has returned to work, (Fig. 4.15)

Case 2

A 20-year-old male sustained a severe compound fracture of the lower end of the tibia and fibula which was treated by an intramedullary nail. Two years later the fractured tibia was ununited but

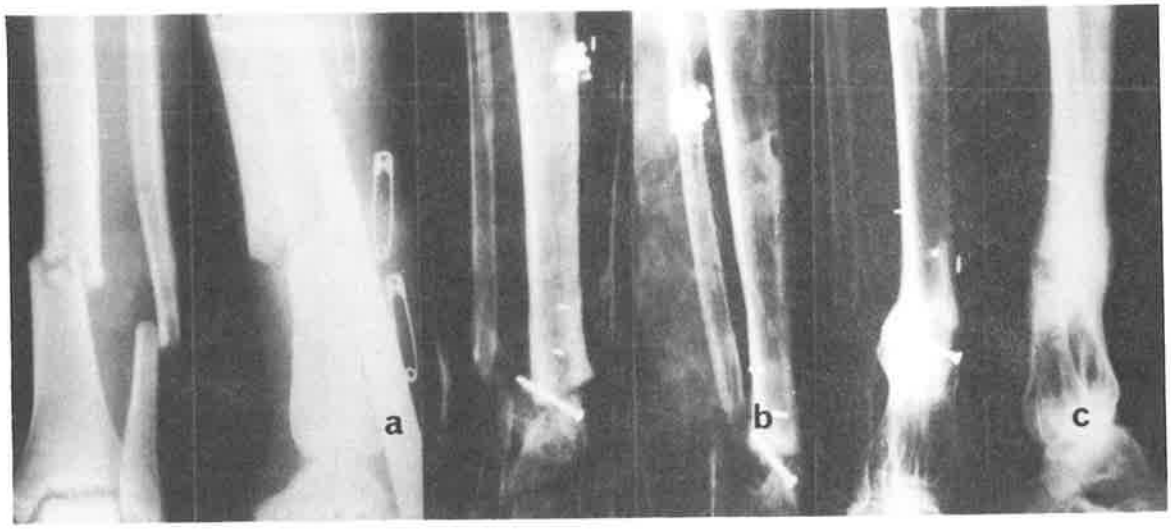


Fig. 4.15 (a) 18 year old male with a very severe compound fracture of the tibia and fibula

(b) 18 months laters, after numerous sequestrectomies, a mobile non union of the tibia together with a chronic discharge was present

(c) Radiologically consolidated 10 months after electrical stimulation

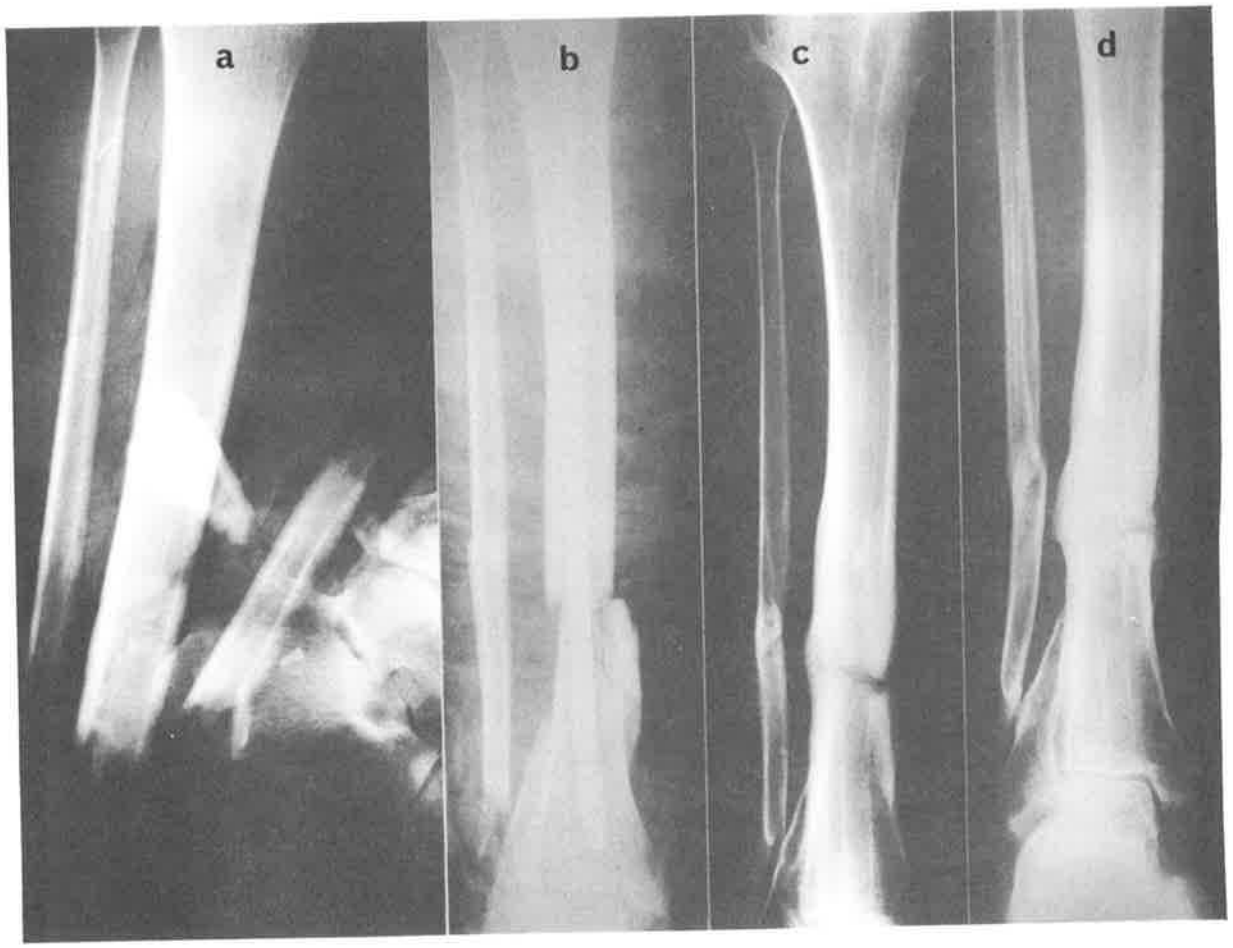


Fig. 4.16 (a) A severe compound fracture of the lower tibia, (b) treated with an intramedullary nail, (c) ununited two years later, (d) united 12 weeks after insertion of the osteostim

was clinically united 12 weeks after insertion of the Osteostim alone (Fig. 4.16).

Case 3

A 64-year-old female sustained a fracture of the upper end of the tibia and fibula in a vehicle accident. Five months later, the fracture was ununited and there was a large bony defect. An Osteostim was inserted and six months later the fracture was radiologically consolidated (Fig. 4.17).

Case 4

A 58-year-old male sustained a double fracture of his tibia in 1973 and the lower fracture remained ununited four years later. After numerous unsuccessful bone grafting procedures, electrical stimulation alone resulted in clinical and radiological union in very atrophic bone eight months later (Fig. 4.18). Attenuated skin cover precluded any bone graft procedure.

Case 5

A 19-year-old female with renal rickets had corrective osteotomies of the lower end of each femur for valgus deformities. The osteotomies had failed to unite after two bone grafting procedures associated with Kuntscher nail fixation. Five and seven years after the initial corrective osteotomies, nonunion was still present. Bone growth stimulation with Phemister grafting achieved union in both legs. (Fig. 4.19).

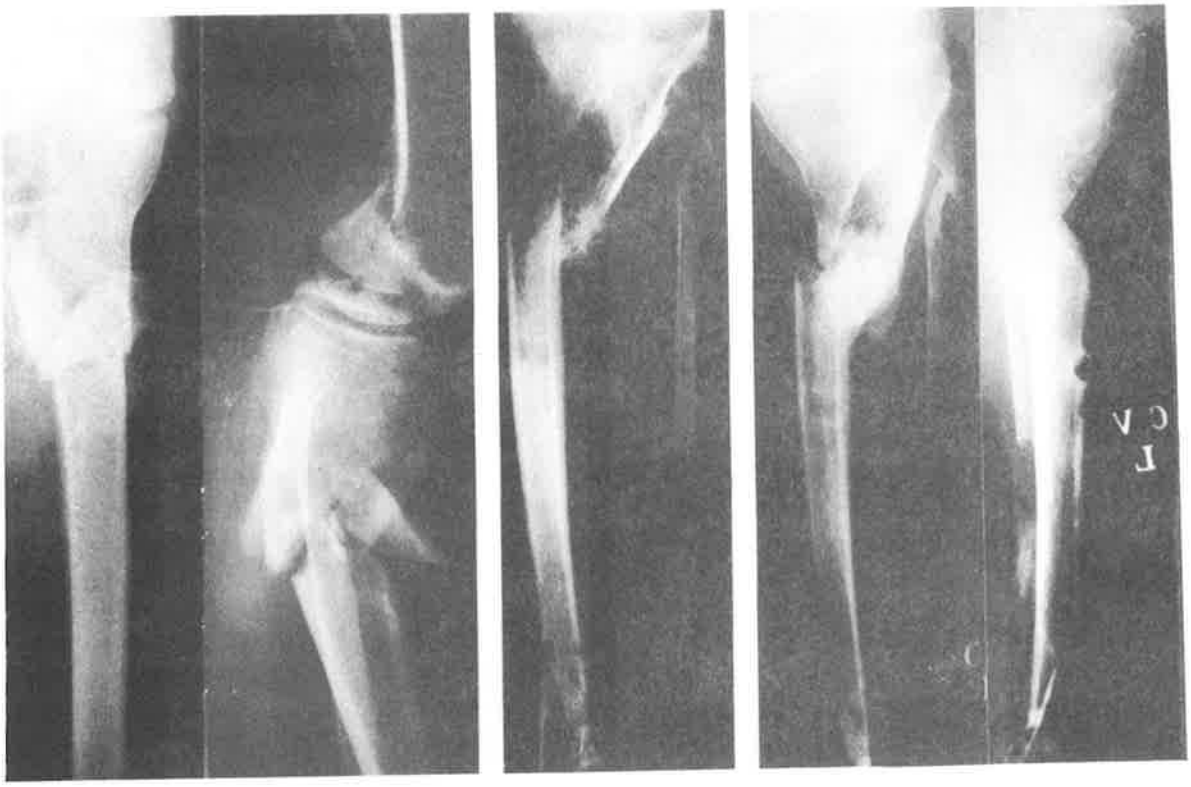


Fig. 4.17 A fractured upper end of tibia, ununited with a large bony defect 5 months later, radiologically consolidated 6 months after electrical stimulation

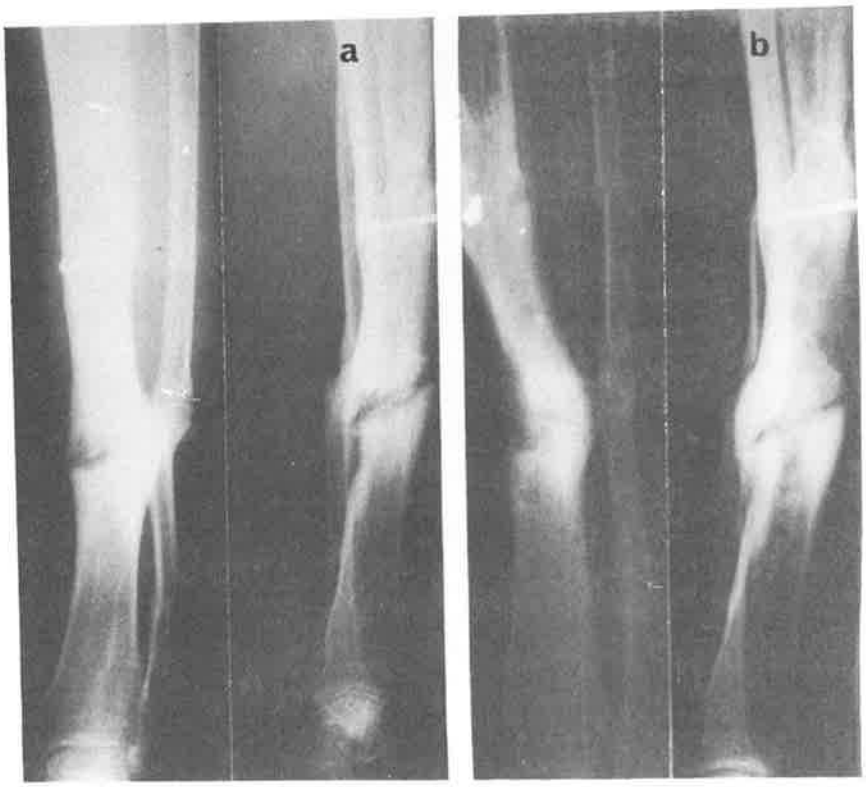


Fig. 4.18 (a) An ununited fracture of the lower end of the tibia four years after the injury and numerous unsuccessful bone grafting operations

(b) Union following electrical stimulation of very atrophic bone

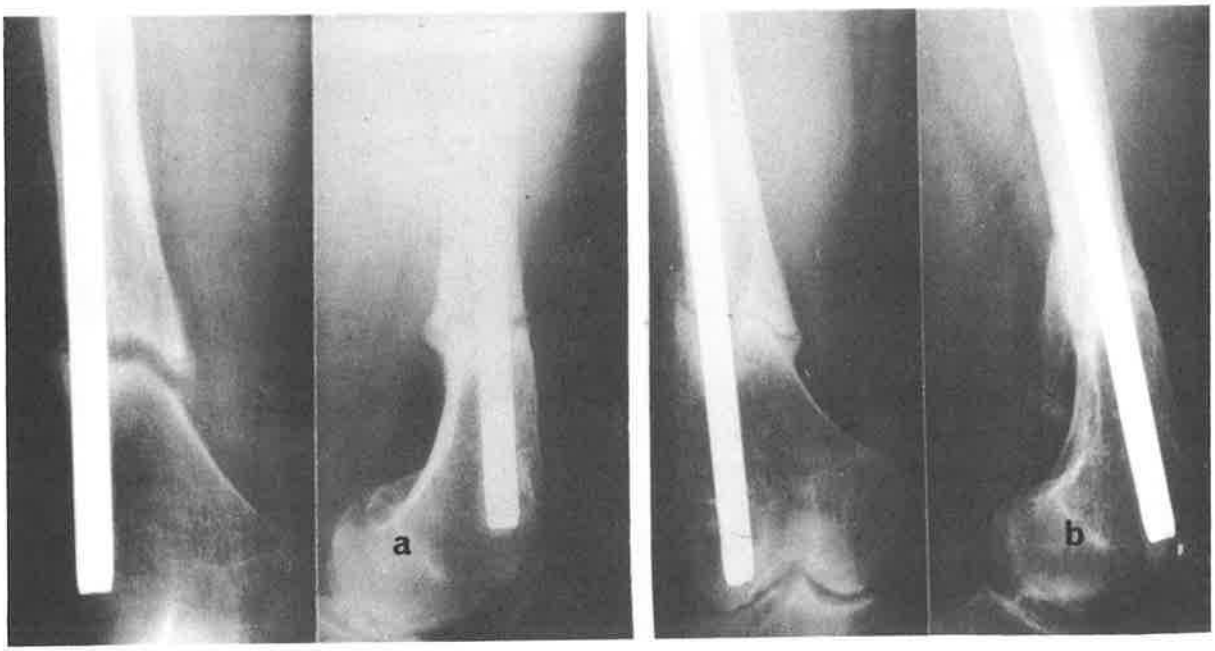


Fig. 4.19 (a) A 19 year old woman with renal rickets had ununited fractures of the lower end of both femora after corrective valgus osteotomies and two previous bone grafting procedures

(b) Union following electrical stimulation and Phemister grafting at 7 years after the initial osteotomy

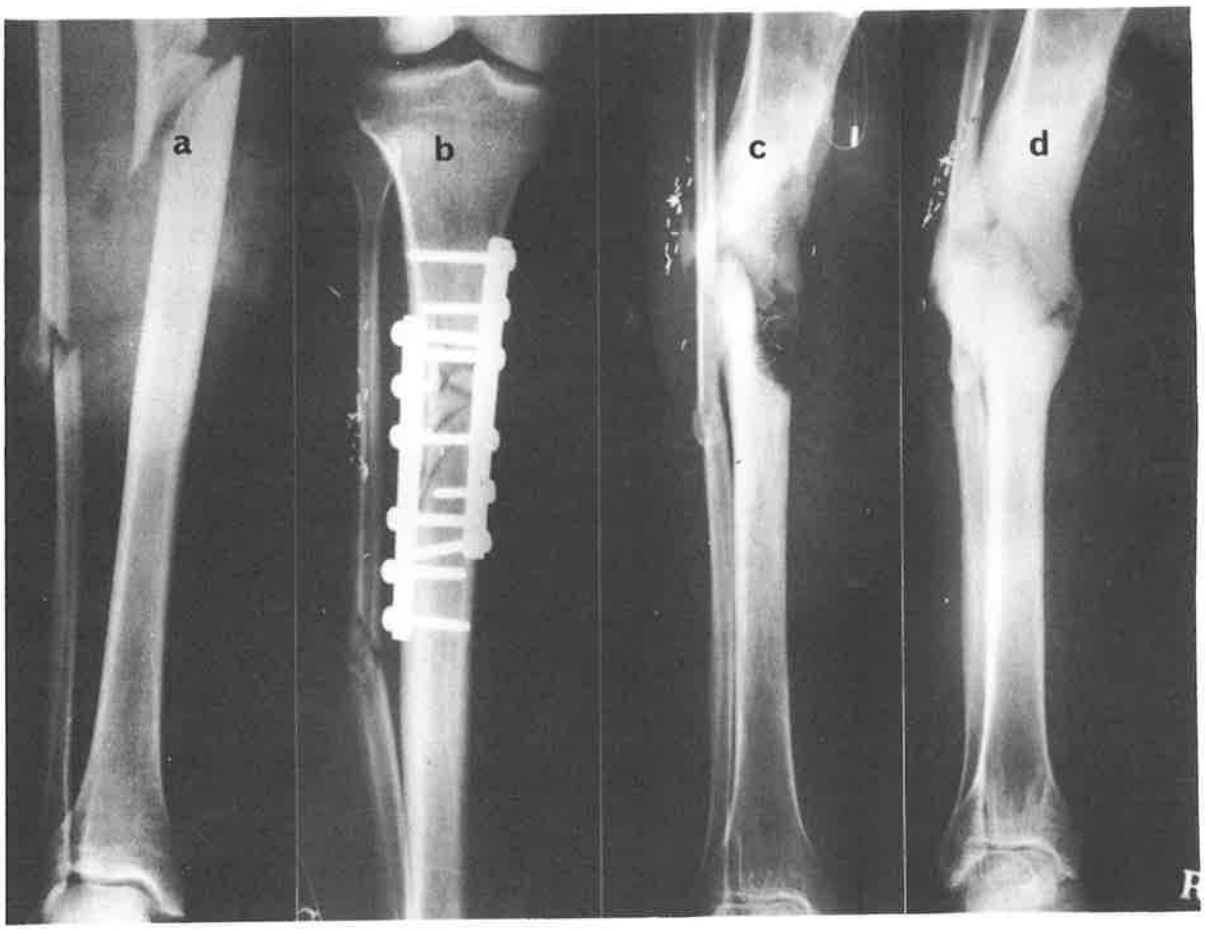


Fig. 4.20

(a) An 18 year old female sustained severe compound fracture of her tibia associated with extensive skin loss

(b) Numerous attempts were made to obtain solid fixation

(c) After two years, there was a mobile non union of the tibia and a profuse chronic discharge

(d) The discharge ceased and union occurred over 9 months with electrical stimulation

Case 6

An 18-year-old female sustained a severe compound fracture of the upper end of her tibia and fibula in a vehicle accident. Numerous attempts to obtain solid internal fixation in order to allow major plastic surgery to cover the extensive skin defect were performed but, at the end of two years, there was a profuse chronic discharge, the fracture was very mobile and amputation was advised. An Osteostim was inserted, this gradually controlled the discharge and over a nine month period, union of the tibia occurred (Fig. 4.20).

Case 7

A 27-year-old male sustained a severe crushing injury to his forearm in an underground coalmine accident. He had a double fracture of his radius and developed a Volkmann's ischaemia that required extensive resection of necrotic forearm skin, muscle and nerve tissue. The forearm was covered with a split-thickness skin graft. The proximal fracture of the radius failed to unite and he developed a chronic discharging osteomyelitis. Twelve months later, when amputation was being considered, a sequestrum was simply removed, a cathode in the form of a helix was placed across the nonunion site and the generator was placed beneath the deep fascia in the forearm. The discharge ceased and the fracture united (Fig. 4.21).

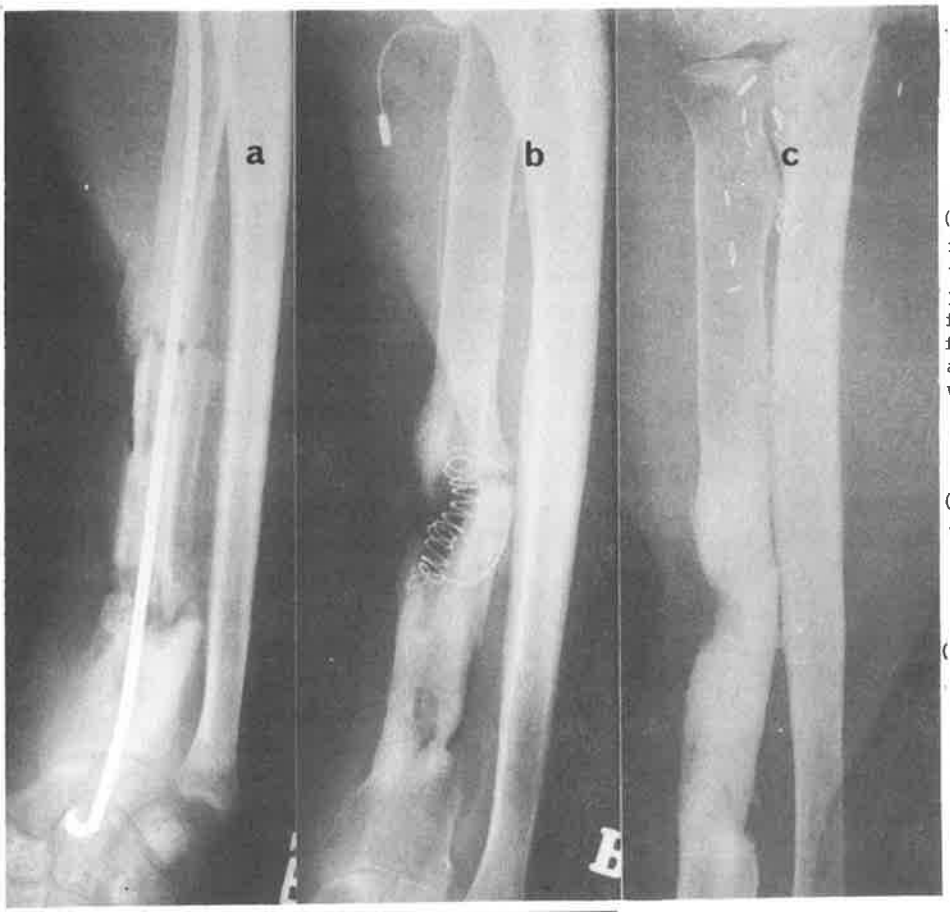


Fig. 4.21

(a) A severe compound fracture of the radius treated with a Rush pin. The proximal fracture of the radius failed to unite and a chronic discharge was present

(b) Insertion of an Osteostim

(c) The discharge ceased and union rapidly occurred

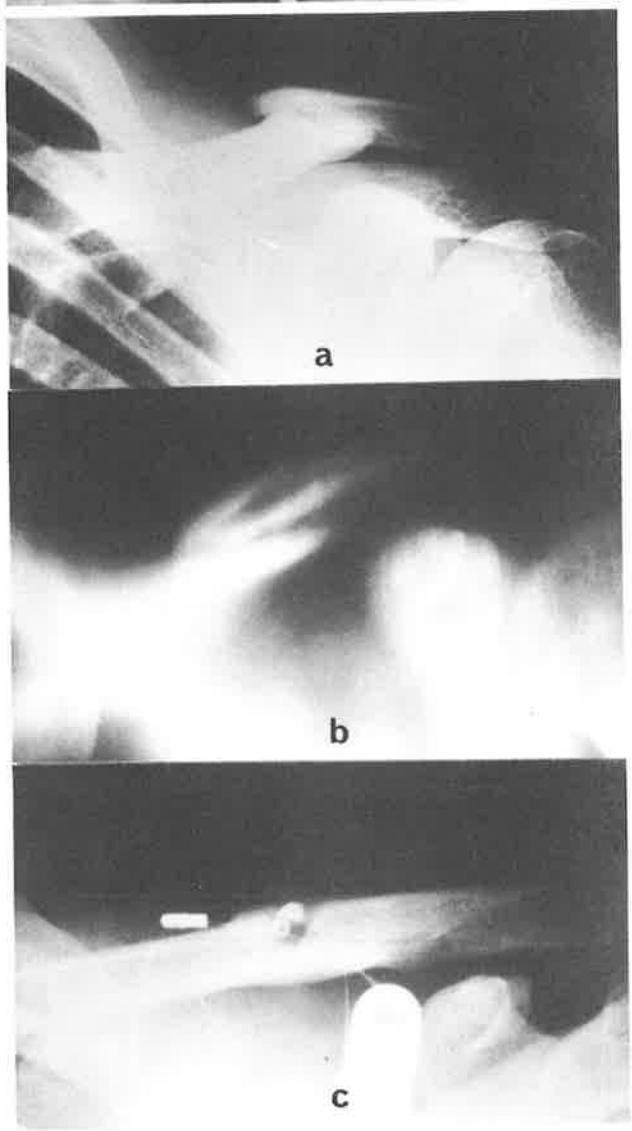


Fig. 4.22

(a) An ununited fractured clavicle

(b) Confirmed by tomogram

(c) United with electrical stimulation

Case 8

A 24-year-old international rugby player sustained a fracture of his clavicle. Nine months later he was still complaining of discomfort and was unable to return to active sport. A tomogram revealed that the fracture was ununited, an Osteostim was inserted and four months later he was playing competitive rugby again (Fig. 4.22).

Case 9

A 66-year-old female had a Charnley type arthrodesis of her knee which was ununited 12 months later. An Osteostim was inserted across the arthrodesis site together with the application of further compression clamps and three months later the arthrodesis was united (Fig. 4.23).

Case 10

A rhabdomyosarcoma of the thigh developed in a 5-year-old boy. He received maximal-dosage radiotherapy for it, and 18 months later his protective caliper was removed. He developed a pathological fracture that went on to nonunion 2 years later. As can be expected, his skin was tissue paper thick and there was an absence of soft tissues at the site of the nonunion of the femur.

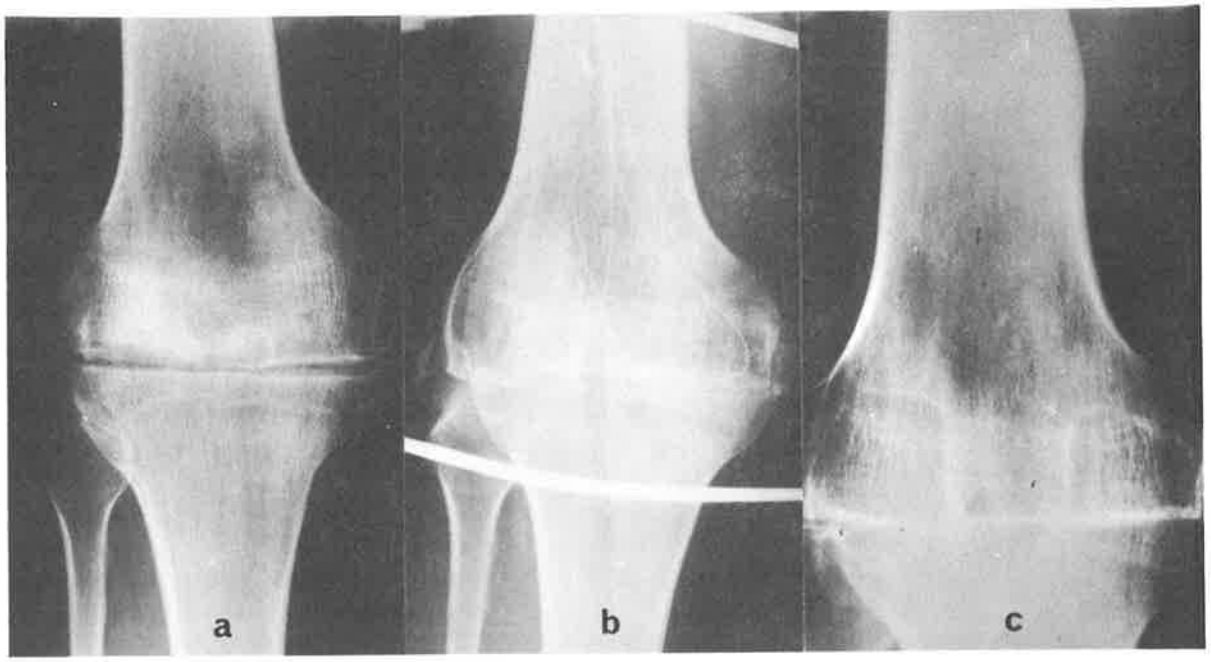


Fig. 4.23 (a) A failed Charnley arthrodesis of the knee

(b) Electrical stimulation with compression clamps

(c) Solid arthrodesis three months later

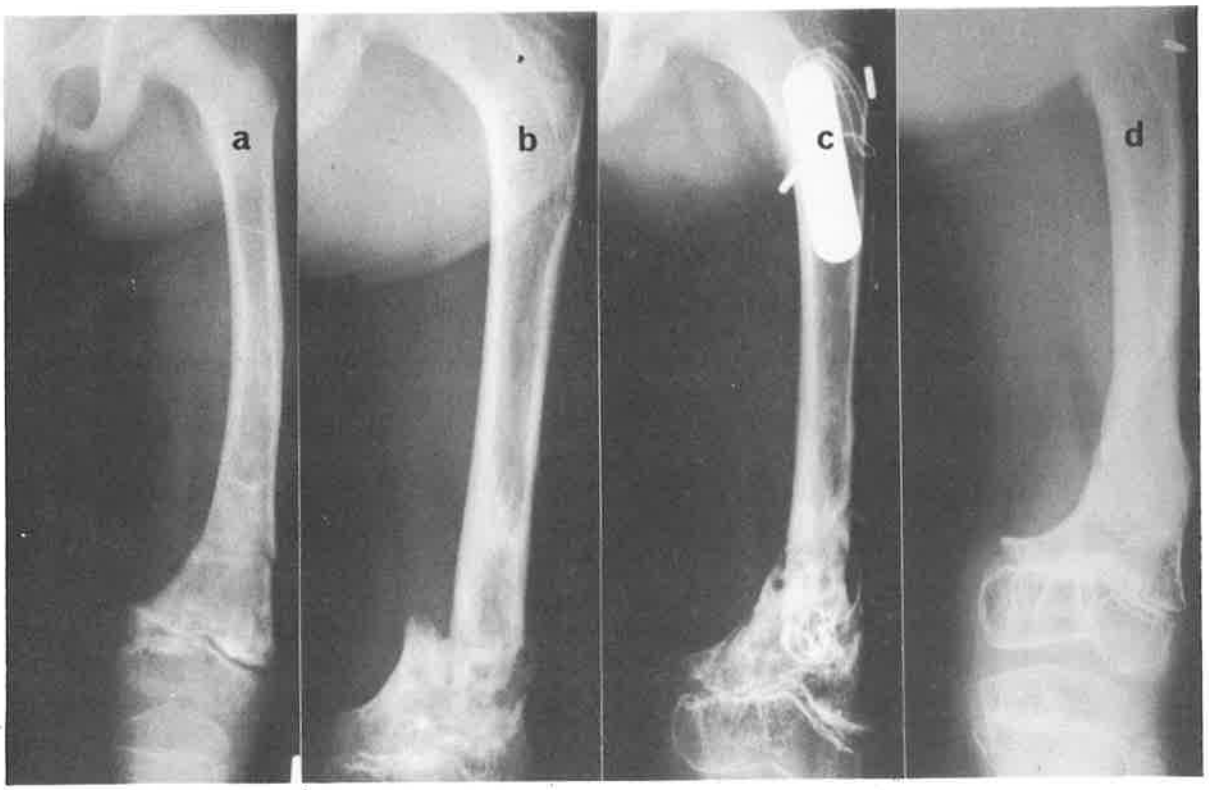


Fig. 4.24 (a) Pathological fracture of the femur in a 5 year old boy following radiotherapy for a rhabdomyosarcoma

(b) An ununited fracture two years later

(c) Insertion of electrical stimulation

(d) Radiological consolidation of the femur 18 months later

An Osteostim was inserted, and the bone at the time was found to be densely sclerotic and avascular. The nonunion became firm at about six months and a further Osteostim was inserted. Twelve months later the bone was clinically and radiologically united. Sclerotic avascular bone developed osteogenic properties without the addition of any cancellous bone graft (Fig. 4.24).

(b) Ununited fracture of the scaphoid

Case 11

A 21-year-old footballer injured his wrist and sustained a fractured scaphoid, which was treated in plaster for three months. Six months later the scaphoid fracture remained ununited. It was then treated by a bone graft and further plaster but remained ununited for 18 months. Three months after the Osteostim was inserted, the fracture was united (Fig. 4.25).

6. DISCUSSION

Hartshorne [131] said in 1841 that "happily fractures in general unite ... and only one case of confirmed supernumerary joint has been known to originate in the wards of the Pennsylvania Hospital in the last 40 years, during which time about 4,000 fractures have been treated here".

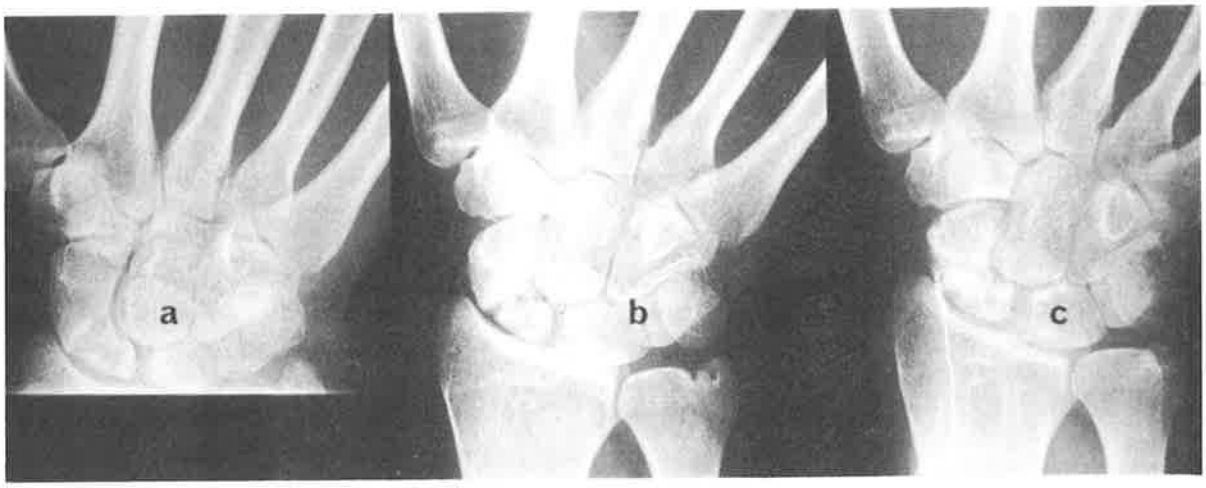


Fig. 4.25 (a) A 21 year old footballer with a fractured scaphoid

(b) 18 months later an ununited scaphoid was present

(c) Union after 3 months of electrical stimulation

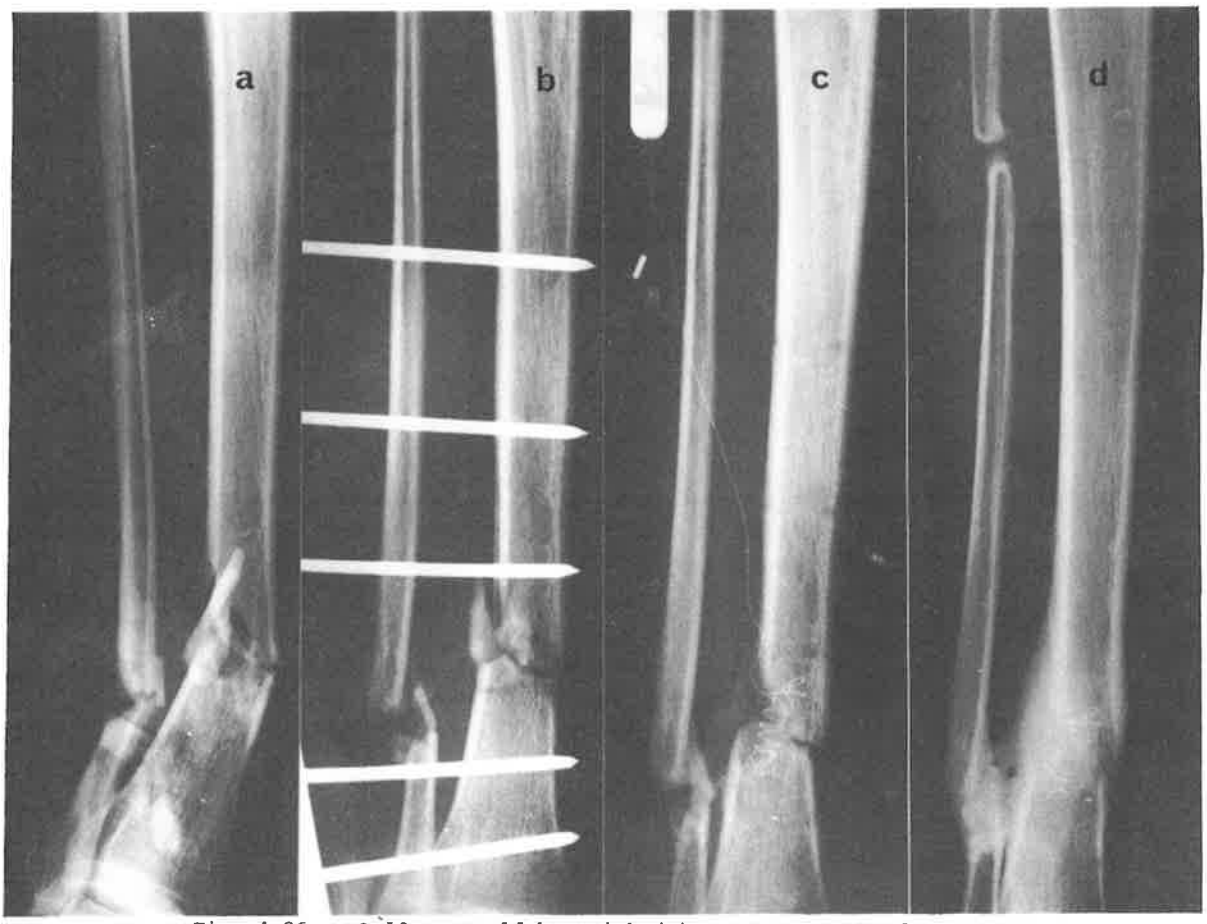


Fig. 4.26 A 19 year old boy with (a) a gross compound fracture of the lower third of the tibia and extensive skin and soft tissue damage, (b) stabilization of the fracture with external fixation, (c) delayed union at 14 weeks and (d) radiologically consolidated six months after electrical stimulation

Clearly, the type of fracture seen then was different to that of today, for many fractures in this series were the result of severe trauma with resulting compound and infected fractures.

Although the overall incidence of delayed-union or nonunion of fractures has previously been estimated at less than 3% for the skeleton as a whole [51], there is clearly a range from 7-39% of tibial fractures developing nonunion [90, 158, 192, 195, 267, 280] very often depending on the nature of the fracture and the type of treatment instituted. Jackson and McNab [143] substantiated that fracture union in the lower third of the tibia was slowed because of the periosteal stripping interfering with the blood supply.

Twenty-five years ago Urist [267] suggested that "the minimum healing time which should elapse before a bone graft procedure or other surgical operation is advised should be 12 months for non-comminuted fractures, 18 months for comminuted fractures with a single wedge fragment, and 24 months for severely comminuted or displaced segmental fractures". Others [143, 195] have expressed strong views against early bone grafting and have stated that at least six months should pass before grafting is attempted. Orthopaedic surgeons today should at all costs endeavour to prevent a fracture developing nonunion and the stability of a fracture should be assessed after three or four months. Definite mobility of the fracture at that time denotes potential delayed union, and treatment should be undertaken without further delay. It may be that such a policy would

result in a number of unnecessary operations, but early treatment of severe tibial fractures will produce better functional results when undertaken within four months of the initial injury than when it is further delayed [76, 244].

Initially, electrical stimulation was used in this series where there was established nonunion or where surgical treatment had failed. As experience was gained, the method was chosen as the preferred operative procedure. It had the advantage of simplicity, low morbidity, a short hospital stay and little post-operative pain. The only ill-effects reported [185] have been tissue reactions or infections associated with anode corrosion, predominantly with stainless steel. In many instances, bone grafting would have been precarious because of poor and inadequate skin cover or in the presence of infection. Two cases illustrate the potential place for electrical stimulation; (a) a 19-year-old boy with a gross compound fracture of the lower third of the tibia and extensive skin and soft-tissue damage required extensive plastic surgery to achieve a full thickness skin cover. At 14 weeks, there was no evidence of bone healing either clinically, radiologically or by nuclear scan. Cancellous bone grafting in this case would have been difficult - as indeed it was in many other cases - because of the precarious skin cover. The fracture united after insertion of the implant alone (Fig. 4.26); (b) a 22-year-old dental student sustained a simple fractured tibia which was well reduced and immobilised in a plaster cast. Sixteen weeks later the fracture was very mobile and, in order to cause minimal

interference with his university studies, electrical stimulation alone was carried out. He resumed his studies after 72 hours and the fracture was united three months later (Fig. 4.27).

The possibility that early intervention may shorten the healing process in fractures developing delayed union has led to a recent interest in the early diagnosis of this state of affairs. Scintigraphy, a sensitive means for detecting an otherwise occult fracture [224] measures the changing patterns in uptake of bone-seeking traces recognised in bone healing. During this clinical trial, 22 patients were studied serially using technetium 99m methylene diphosphonate to assess the ability of serial scintiscanning to differentiate between normal and delayed union following fracture of the tibia. The type of fracture (simple, comminuted or compound) influenced the appearance of the automated computer profile. However, no significant differences in the patterns of change were noted between normal healing and delayed or nonunion [199, 200]. It may be that osteomedullograms may be a helpful investigation in delayed-union and nonunion [123].

It is suggested that the bone growth stimulator may be used in (1) failed previous attempts to achieve bony union, (2) established nonunion (3) delayed union where the orthopedic surgeon considered, from his experience and the nature of the injury, that bone healing was most likely within a reasonable period of time and (4) after tibial

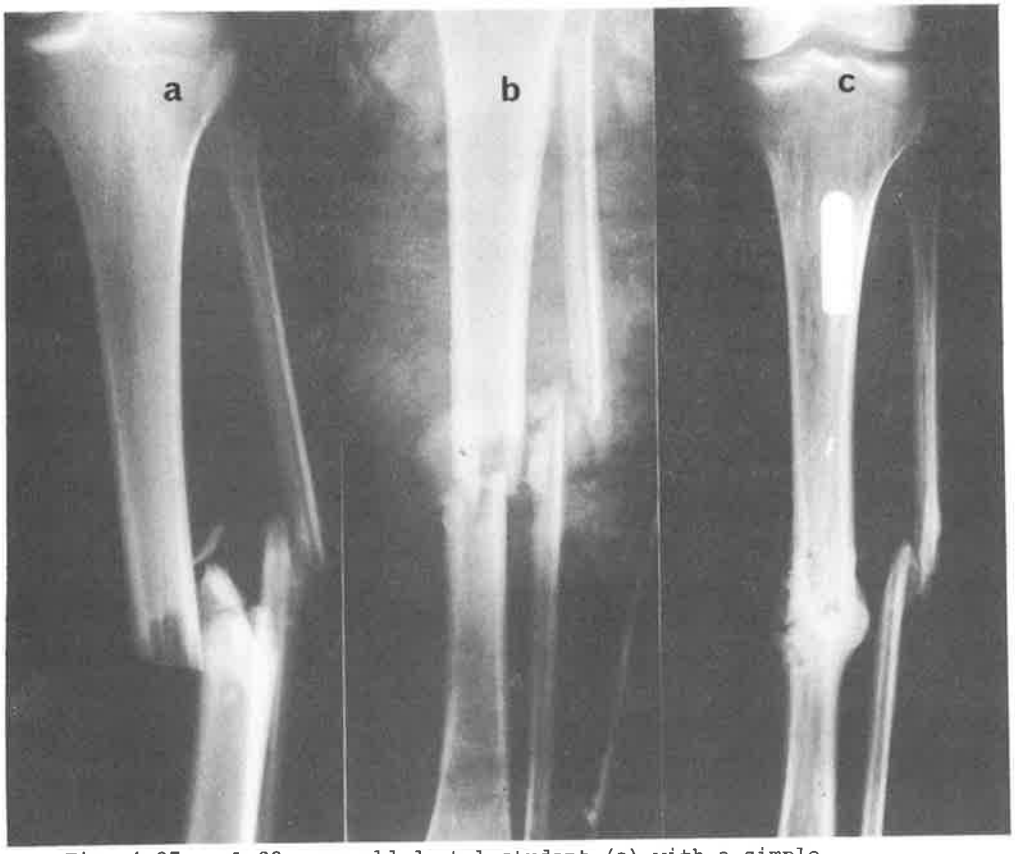


Fig. 4.27 A 22 year old dental student (a) with a simple fractured tibia and fibula, (b) reduced and immobilised in plaster but developed delayed union, (c) united three months after electrical stimulation

lengthening as, while nonunion is rated with the Anderson[10] technique (Fig. 4.28) there is significant evidence of nonunion with the Wagner technique (Fig. 4.29).

The effectiveness of electrical stimulation in producing bone has been shown to be related to the magnitude [108], power [132] and energy production [185] of the current. Also, physiochemic changes at the cathode have been shown to be associated with bone formation [60]. Time is necessary for these changes to occur and in this series 18 patients undergoing electrical stimulation of ununited tibial fractures more than 18 months after their injury, took statistically longer to unite than those patients in whom the implant was inserted 12 months or less after injury [182].

It is important to put the results of these 978 cases treated in Australia and the U.S.A. with electrical stimulation in proper prospective. Although there are definitions for delayed-union and nonunion of fractures, the dividing line must remain imprecise in the majority of cases. Nicoll [195] in his review combined delayed and nonunion and this has been followed in this analysis. Most patients in this clinical trial had either none or one previous operation aimed at achieving union of the fracture. This is in line with common practice today [55] where the surgeon attempts to determine as early as possible when a fracture is not uniting and to initiate treatment to achieve union.

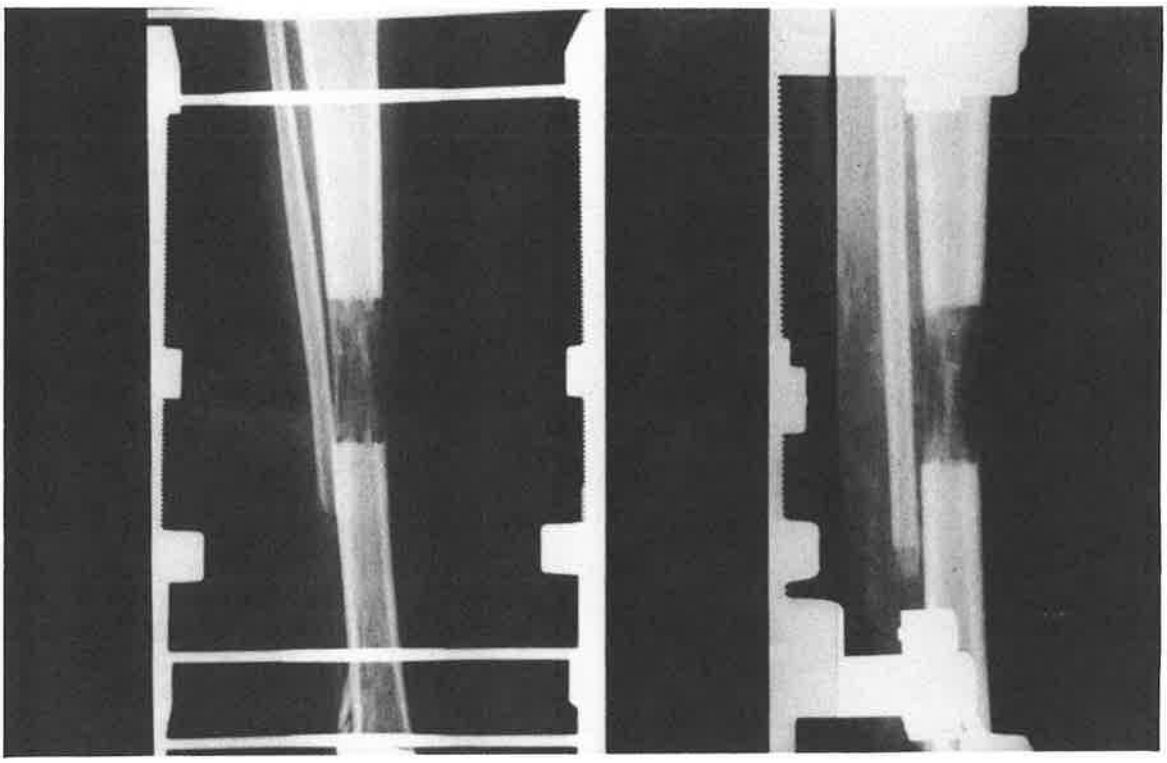


Fig. 4.28 Good bone formation four weeks after tibial lengthening (Anderson technique)

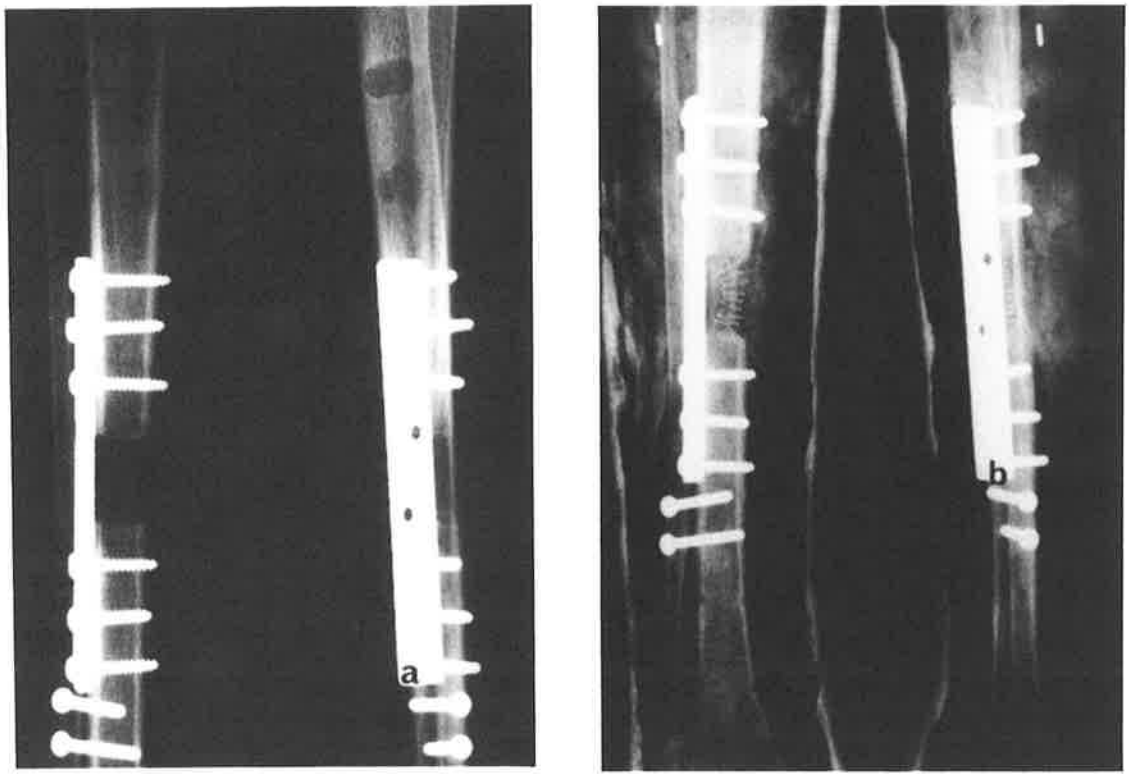


Fig. 4.29 (a) No bridging bone eight weeks after tibial lengthening by the Wagner technique

(b) Union achieved by electrical stimulation

The overall success rate (86%) reported here where the Osteostim has been used to achieve union of long bones compares favourably with those reported using cancellous bone grafts [54, 55] and other methods of electrical stimulation [26, 29, 30, 45, 63, 65, 67, 68, 297]. It is important to note that the success rate of Boyd's series [54, 55] fell to 66% and 69% respectively with a second attempt at cancellous grafting. These figures can be compared with the 83% success rate reported here after previous cancellous grafts had failed.

The results of the tibial fractures in this series have been compared with a comparable group from the literature [8, 54, 92, 104, 143, 192, 218, 219, 220, 229, 244] which were treated successfully by cancellous and cortico-cancellous grafts using techniques described by Phemister [209] and modified by Charnley [76] (Table VI). The overall success rate in this large series was 92% compared to 88% success with tibial fractures reported here. The time from grafting to union was difficult to extract from the literature but, in the comparison group, a mean of 24 weeks (SD 6.89) may be compared with a mean time to union in the reported series of 15 weeks (SD 4.3).

Union and failed Phemister grafts

Eighty-three percent of the cases in this series, that had failed previous Phemister grafting attempts, went to union at an average of 16 weeks after insertion of the

Osteostim. This compares favourably with the results described by Boyd et al [54, 55] in which only a 67.5% success rate was achieved with bone grafting techniques.

Patients often have poor skin cover which necessitates limited cancellous grafting, particularly when limbs have been salvaged following very severe injuries. This usually results in a high failure rate [54]. Electrical stimulation is an alternative treatment for these situations.

Infected nonunions

A chronic discharging wound is not a contraindication to the use of the Osteostim. Boyd [54] believed that infection if present, should be controlled or quiescent for at least six months before grafting. Urist [267] stated that anterior bone graft operations performed after healing of infection were accompanied by recurrence of infection in 20% of cases. Others [8, 54, 56, 92, 104, 218, 219, 229, 244] have all reported failures of Phemister grafts when performed on infected fractures.

Because of the problem of achieving success with anterior bone grafts in the present of persistent infection, often with scarred and attenuated skin cover, many [79, 92, 126, 147, 158, 192, 267] have advocated a postero-lateral approach for bone grafting ununited tibial fractures, a technique first described by Harmon [128]. Using the postero-lateral approach, an average success rate of 86% has been reported and, although it is not strictly comparable because an anterior approach was used, in this series a

success rate of 86% was achieved in Australia, and 82% in the United States.

It is important to stress the difference in the time from treatment to union in the two groups which was 16 weeks (SD 4.9) in the series reported [204] compared with 35 weeks (SD 3.14) in those previously reported with infected nonunions [55, 104, 126, 158, 192, 229]. While there is no significant difference in the success rate of each method of treatment, there is a marked difference between the time for union as determined by full weight-bearing. Even more significant is the fact that one can use the direct approach to the shaft of the tibia and obtain wound healing. Cancellous bone grafting is thereby avoided.

Friedenberg [105] showed that the bioelectric potential in the region of a normally healing fracture is always electronegative and this has been referred to as the "injury" or "healing" potential.[12] Boyd [55] offered the opinion that, in essence, "a bone grafting procedure is a new insult produced by the surgeon in the hope that the response to this second insult will be more favourable than the first". Clearly, any method of fracture treatment aims to stimulate osteogenesis and it may be that the artificial means of stabilizing an electronegative potential in the fracture site, as used here, is only a means of duplicating the "healing" potential for an adequate duration.

7. SUMMARY

There can now be no doubt that electrical stimulation produces osteogenesis and significantly helps to achieve union where impaired bone healing exists.

One method of electrical stimulation is the self-powered, self-contained and totally implantable Osteostim. Examples have been given to show its success in ununited fractures of long bones with or without chronic infection, and ununited fractures of the scaphoid. It has also been successfully used in failed posterior spinal fusions.

The Osteostim is safe, can be used in a wide variety of situations, requires a short simple operation with strict adherence to the operative details, and is associated with insignificant morbidity and a short hospital stay. There are no contraindications, and it can be used in the presence of a chronic discharge. It does not require patient cooperation and it interferes little with the patient's lifestyle. A monitoring device ensures that a direct current constantly flows. The current model, Osteostim XM12, allows for easy removal of the generator and cathode.

Orthopaedic surgeons should no longer be sceptics about the value of electrical stimulation for impaired bone healing. The success so far justifies that the Osteostim should be accepted as a form of treatment in delayed-union and nonunion of bones.

TABLE I

SITE FOR DELAYED AND NONUNION IN LONG BONES

(84 cases)

		Delayed	Nonunion
Tibia	upper 1/3	8	6
	mid 1/3	19	10
	lower 1/3	18	11
Femur	upper 1/2	-	3
	lower 1/2	1	5
Humerus		1	1
Ulna		-	1
		47	37

TABLE II

FAILURES AFTER ELECTRICAL STIMULATION

	Cases	Successful	Failure
TIBIA			
prox 1/3	14	13	1
mid 1/3	29	28	1
lower 1/3	29	22	7
FEMUR			
upper	3	2	1
lower	6	4	2
OTHER	3	3	0
	84	72	12

TABLE III

EXPERIENCE IN THE UNITED STATES OF AMERICA

Bone	Total	Success	Percentage
Tibia	351	305	87
Femur	164	143	87
Humerus	55	40	72
Ulna/Radius	43	39	92
Others	82	64	78
	695	591	85

TABLE IV

ELECTRICAL STIMULATION AND FAILED PHEMISTER GRAFT

(U.S.A. experience 1980-1981)

Success with electrical stimulation	83%
Success with further grafting	67.5%

TABLE V

ELECTRICAL STIMULATION IN THE PRESENCE OF INFECTION

(U.S.A. experience 1980-1981)

Cases associated with chronic infection	94
Union achieved	77
Success	82%

TABLE VI

UNITED TIBIAL FRACTURES TREATED BY PHEMISTER/CHARNLEY TECHNIQUE

		Number of patients who achieved union	Time to achieve union (weeks)	Success rate %
Jackson	(1959)	60	19.6	90
Boyd	(1960)	262	35	92
Forbes	(1961)	27	20	93
Sakellarides	(1964)	73	35	90
Anderson	(1967)	32	18.7	90
Rokkanen	(1967)	19	12	86.4
Rogers	(1968)	16	24	100
Miller	(1969)	21	30	81
Souter	(1969)	47	18.6	96
Rokkanen	(1972)	50	16	96
Dawson	(1978)	23	25	100
	Total =	612	Mean time = 23.6 (S.D. 6.89 weeks)	Average 92

CHAPTER 5

TREATMENT OF CONGENITAL PSEUDARTHROSIS OF THE TIBIA WITH DIRECT CURRENT STIMULATION

CHAPTER 5

TREATMENT OF CONGENITAL PSEUDARTHROSIS OF THE TIBIA WITH DIRECT CURRENT STIMULATION

1. INTRODUCTION

Congenital pseudarthrosis of the tibia has long been recognized as perhaps the most difficult condition in paediatric orthopaedics to treat [127]. However, in recent years electric stimulation has been used [162, 228] and in 1975, McElhannon [179] stated that "electrical stimulation holds considerable promise for the future". The author's first experience with electrical stimulation was in a case of congenital pseudarthrosis of the tibia where previous attempts to achieve union of the tibia had failed and amputation was seriously being considered. Following use with the Osteostim and a further cancellous bone graft, the tibia united.

The aetiology of congenital pseudarthrosis of the tibia remains an enigma. Credit for the first description of this condition is given by Boyd [53] to Hatzoecher in 1708, although it is distinctly possible that Hatzoecher was not referring to the same condition that we recognize today. In 1937, Ducroquet [94] and in 1939, Barber [15] first described the association of congenital bowing, pseudarthrosis (Fig. 5.1) and neurofibromatosis. Aegerter [1] and Jaffe [144] discussed

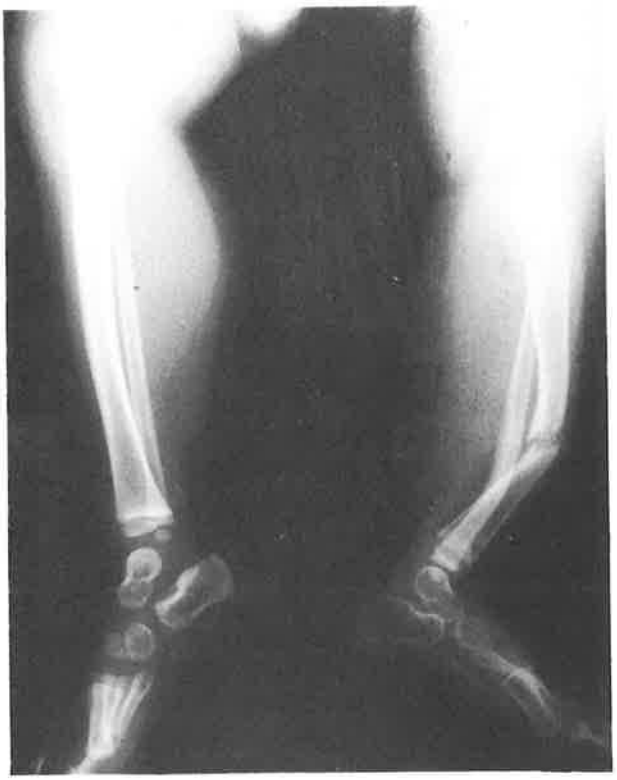


Fig. 5.1 Radiograph of congenital pseudarthrosis of the tibia with a typical anterior bowing at the junction of the middle and lower thirds

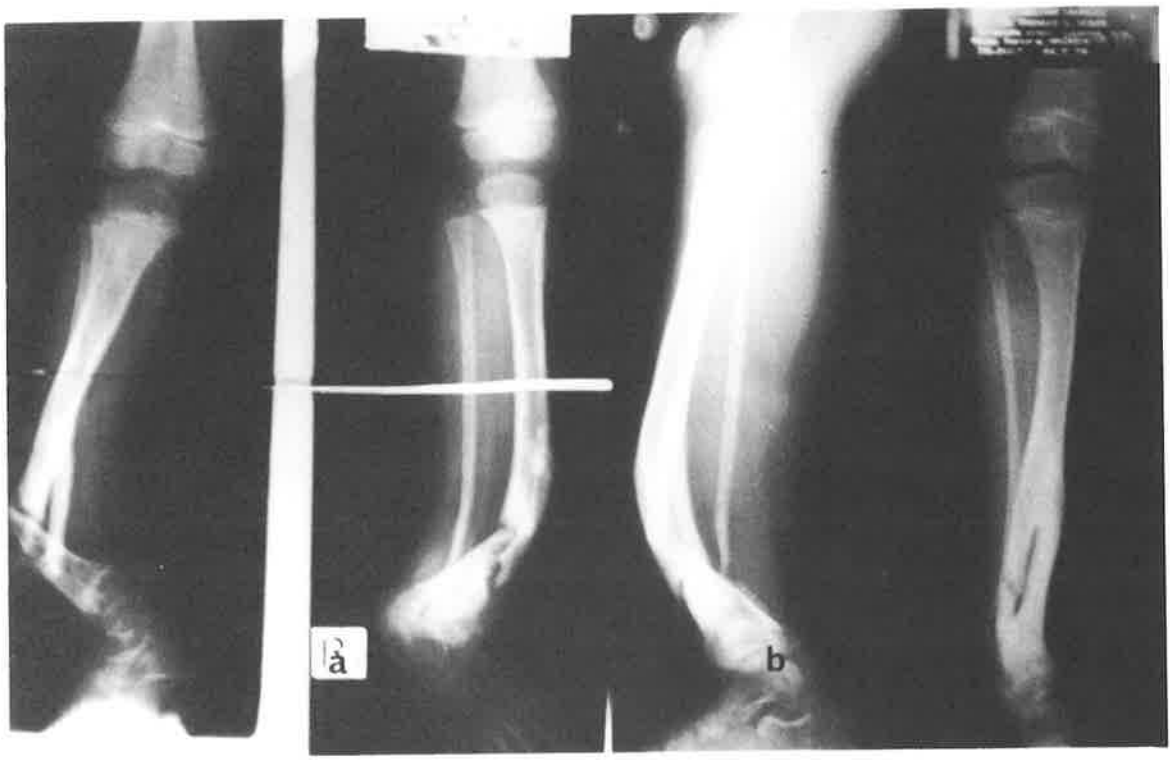


Fig. 5.2 (a) A McFarland cortical bypass graft

(b) Achieved solid union

the pathologic relationships and suggested that pseudarthrosis was not caused by an interosseous neurofibroma.

In spite of improvements in surgical cancellous grafting techniques [76, 209] and more sophisticated bone grafting procedures [52, 75,180, 181, 240, 241] (Figs. 5.2, 5.3, 5.4) authors have remained pessimistic about the eventual outcome of treatment for this condition (Fig. 5.5). Reports [9, 127, 177, 188, 216] continue to show a high incidence of amputation following treatment.

2. MATERIALS AND METHODS

During the clinical trial in Australia with the Osteostim S12 from 1976 to 1978, 5 further patients with 6 pseudarthroses of the tibia received treatment with electrical stimulation. The author was personally involved in the management of these cases. Experience with these and a further 8 cases since the trial was completed has given the author the opportunity to report the results of fourteen cases and fifteen examples of this condition and to propose a regime of treatment.

The same two techniques [204, 206] for insertion of the Osteostim were used and in all except Case 3, cancellous bone graft was added followed by prolonged immobilisation in plaster of Paris. The importance of good correction of the deformity and firm internal fixation was not as apparent in the cases in the clinical trial as in those treated subsequently.

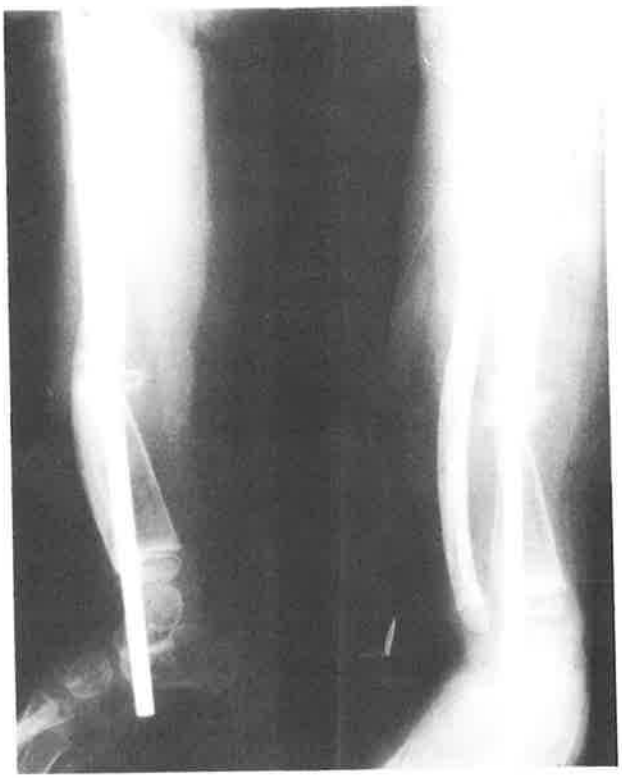
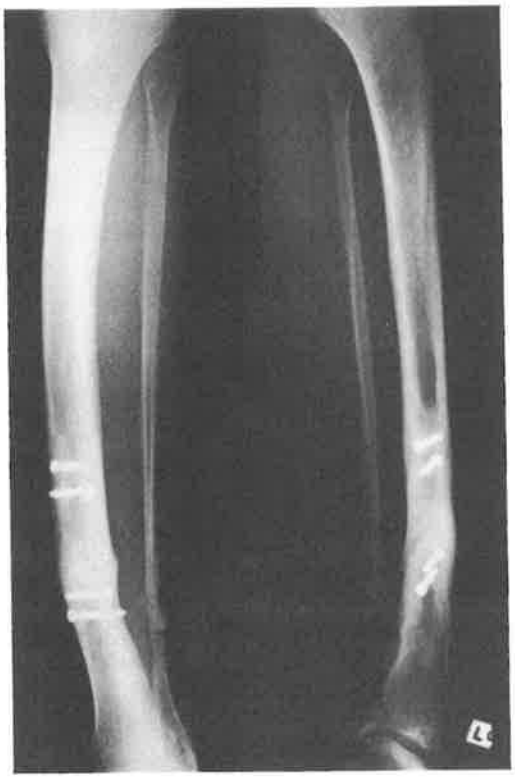


Fig. 5.3 Correction of the deformity and internal fixation with cancellous bone in the defect area (Sofield)

Fig. 5.4 A successful double onlay cortical graft (Boyd)



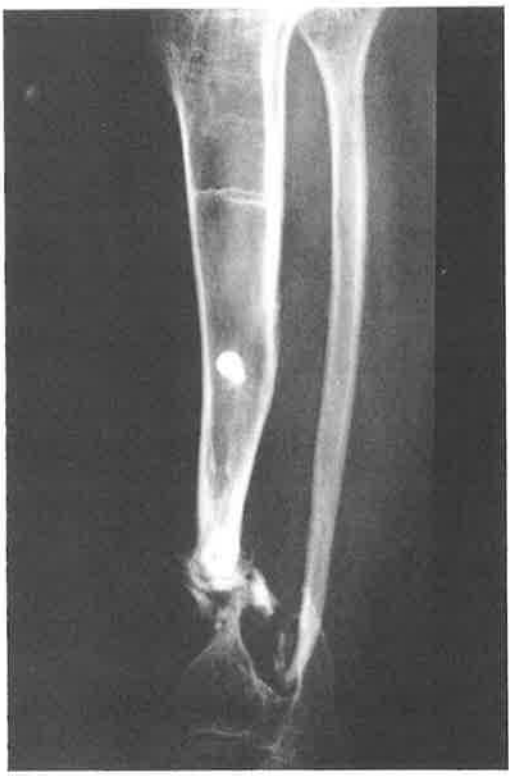


Fig. 5.5 A typical radiograph of congenital pseudarthrosis of the tibia after many unsuccessful operations

The protocol form (Appendix D) was completed in triplicate for all cases by the surgeons involved and they were evaluated by the author. These cases have been considered separate from the Australian clinical trial of treatment of ununited fractures of long bones with the Osteostim.

3. CASE REPORTS

Case 1

A 7-year-old boy had a marked thoracic scoliosis and other manifestations of neurofibromatosis including numerous large cafe-au-lait spots. In addition, he had a congenitally short leg. This was treated by lengthening his tibia by the Anderson technique [2] (Fig. 5.6). Six months later, he had developed a pseudarthrosis of the midshaft of the tibia with tapering of the adjacent bone ends (Fig. 5.7). A cancellous bone grafting procedure failed to achieve union and six months later, a bone growth stimulator was inserted. At that time, the Osteostim * consisted of a stainless steel cathode which was wound around the fibrous tissue and two anodes which were placed in the adjacent bone fragments (Fig. 5.8). The generator was placed subcutaneously in the calf. Cancellous bone graft was, in addition, placed around the extensive area of fibrous tissue. The stimulator was removed after 12 weeks when the tibia was found to be uniting clinically and radiologically. Seven

* Telectronics Pty. Ltd., Sydney, Australia

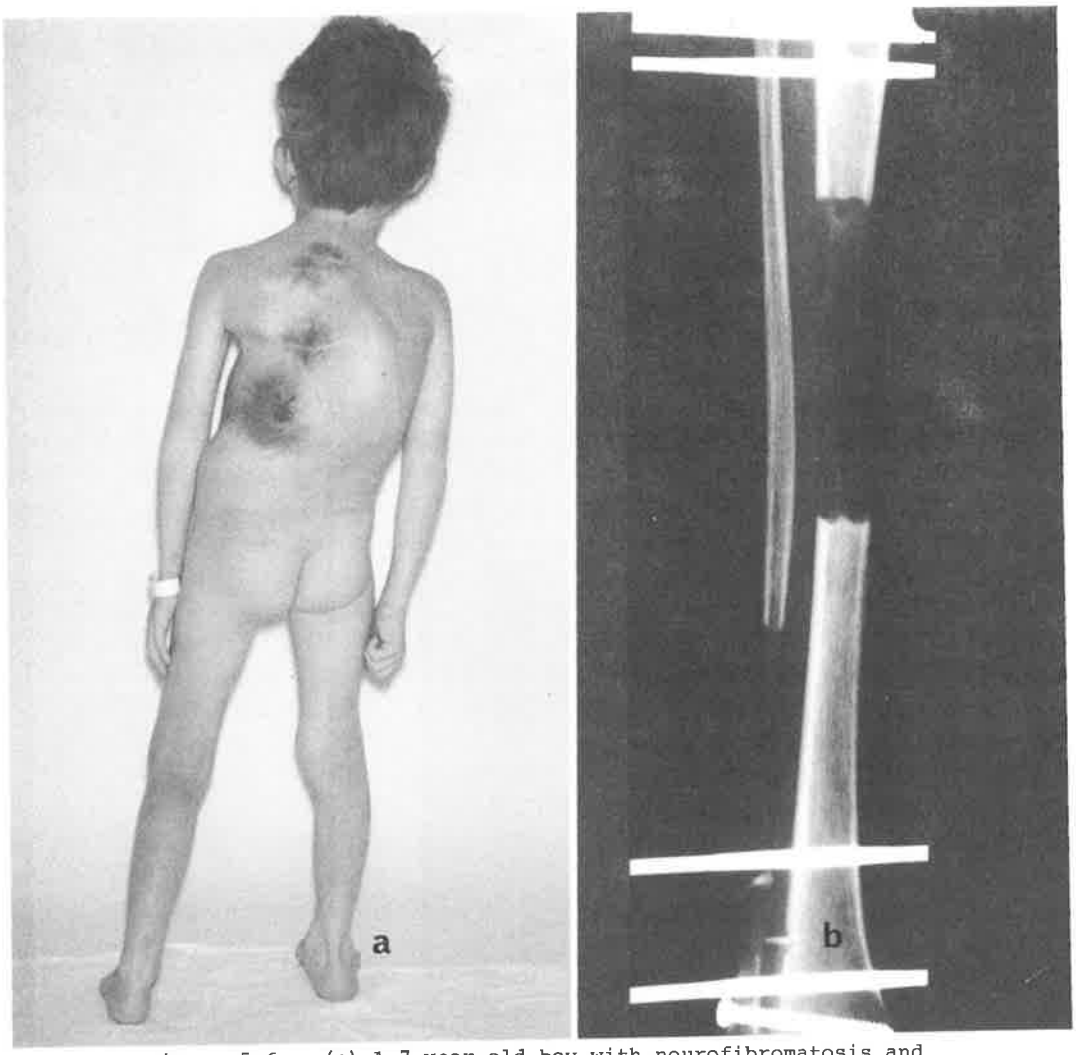


Fig. 5.6 (a) A 7 year old boy with neurofibromatosis and
Case 1 a short right leg. (b) After tibial lengthening

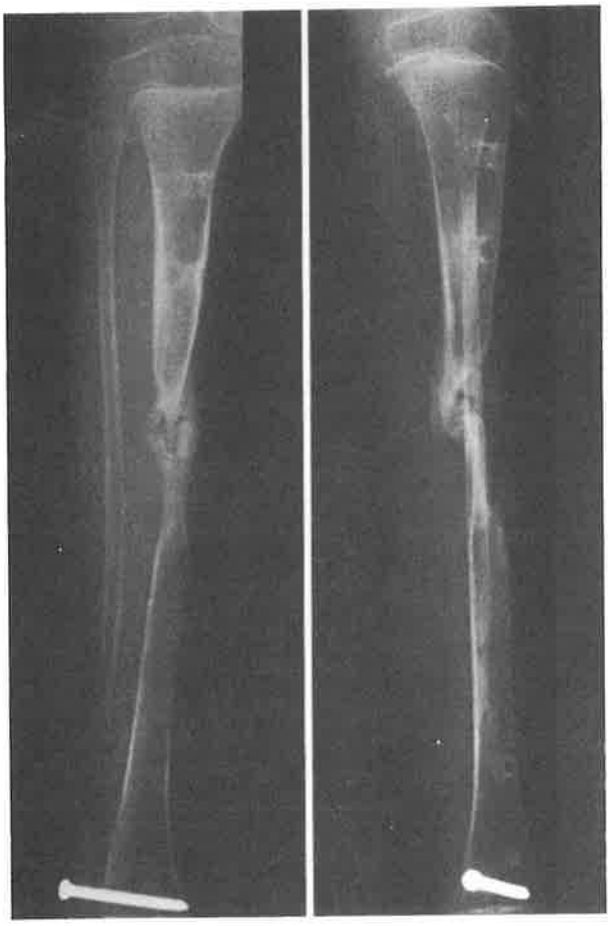


Fig. 5.7
Case 1 Six months later

a pseudarthrosis was present

in the tibia

months later, sufficient consolidation had occurred for the patient to walk in an ischial-bearing caliper which was maintained until the medullary canal had reformed. His tibia remains soundly united 7 years later (Fig. 5.8).

Case 2

At birth, a baby had a deformed left tibia. When he was 8 months old, a below knee orthosis was applied to protect his leg. When he was 11 months old, he fell and sustained a fracture of the tibia at the junction of the middle and upper thirds. This fracture failed to unite and developed a well defined pseudarthrosis of the left tibia which was confirmed radiologically. Cancellous bone grafting was performed unsuccessfully. When the baby was 18 months old, the pseudarthrosis was explored. Internal fixation using an intramedullary rod was performed, and a bone growth stimulator together with cancellous bone graft was inserted. The titanium cathode was made into a helix and placed across the defect site (Fig. 5.9). It should be noted that incomplete correction of the tibial deformity was achieved.

Seven months later, the generator was removed, the tibia was explored and found to have bony union which was confirmed radiologically. The patient's leg has continued to be protected in an ischial-bearing caliper. Consolidation occurred (Fig. 5.10) but, as

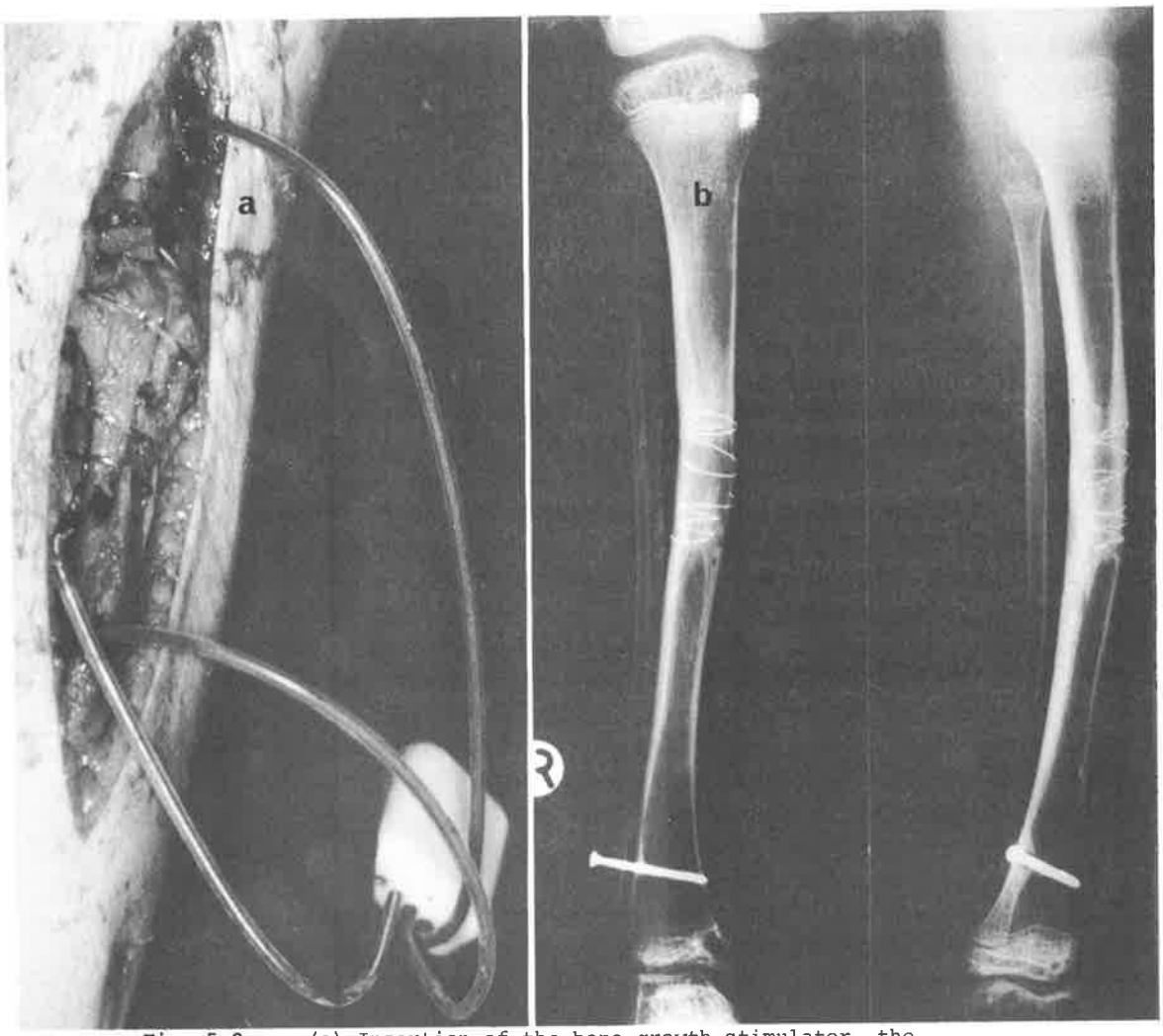


Fig. 5.8 Case 1: (a) Insertion of the bone growth stimulator, the battery and leads were passed subcutaneously into the hamstring area. (b) Solid union of the tibia clinically and radiologically seven years later

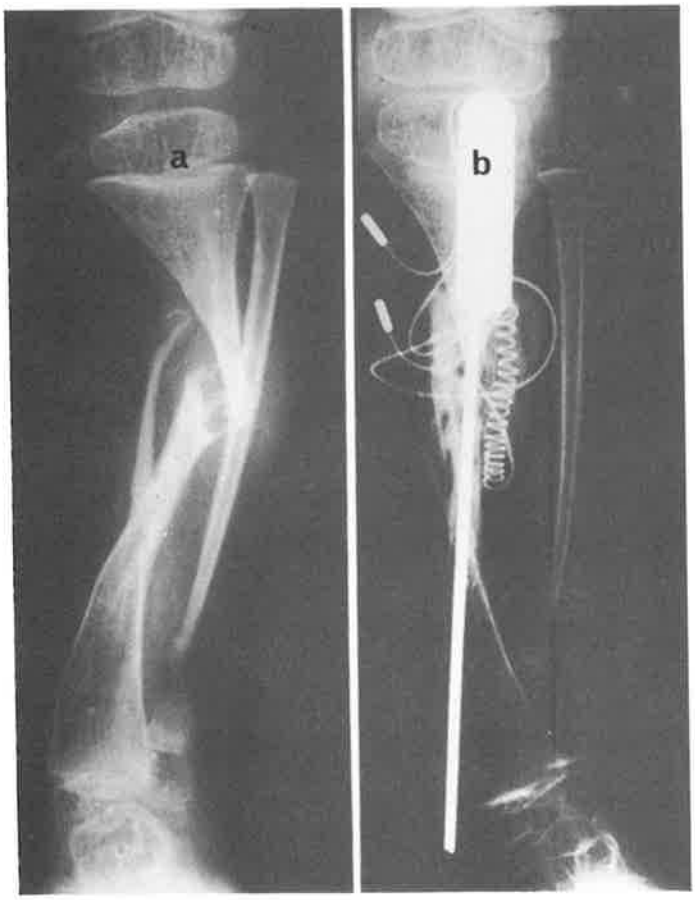


Fig. 5.9
Case 2

(a) Pseudarthrosis of the tibia.

(b) Intramedullary nail fixation with electrical stimulation and cancellous bone grafting

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the intramedullary rod was removed, the tibia has slowly deformed though it has not re-fractured some six years later (Fig. 5.11).

Case 3

A boy was first seen when he was 5½ years old. He had cafe-au-lait spots and 1.5 cm shortening of his left leg with anterolateral bowing of the lower third of the left tibia. Radiographs disclosed the deformity with severe cortical thickening in the region of this bowing without evidence of a fracture of the tibia; however, there was a pseudarthrosis of the fibula. The patient was treated by observation for the next 3 years.

When the boy was 8-years-old, his limp had become more obvious and his leg more painful. Radiographs disclosed a pathologic fracture through the lower shaft of the tibia and, at this time, almost complete obliteration of the medullary cavity. Increased angulation occurred, and 4 months later the fracture was exposed when the tibial fragments were found to be mobile. The cathode of the bone growth stimulator was inserted across the fracture site in the form of a figure-8, as previously described [204, 206]. Sixteen weeks later, the generator was removed, the fracture site was exposed and found to be completely united without any evidence of a fracture line. There was abundant callus formation. The tibia has continued

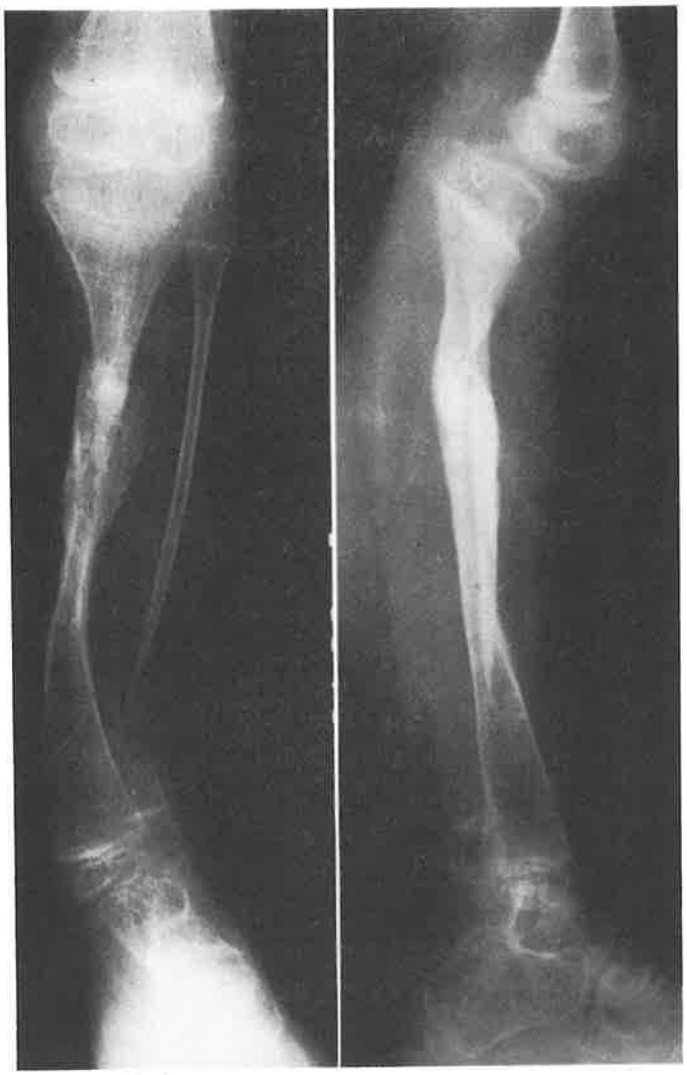

Fig. 5.10 Case 2 Radiological consolidation seven months later

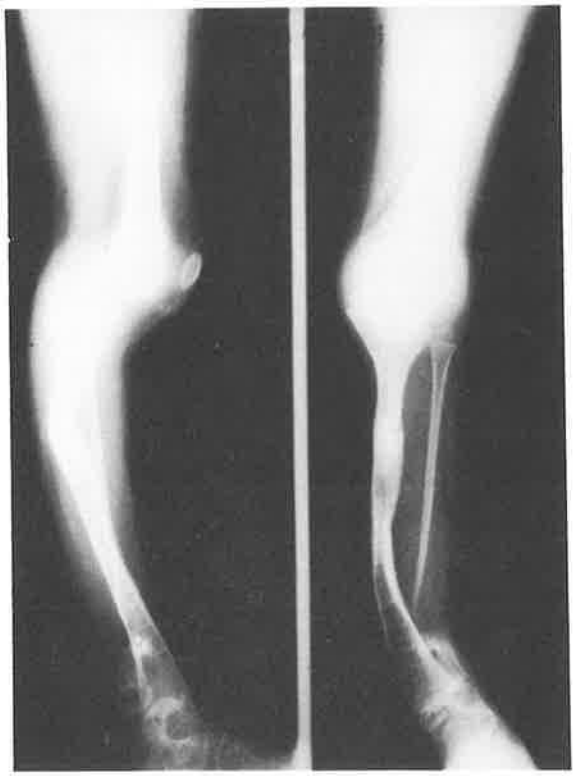

Fig. 5.11 Case 2 The tibia remains united four years later but is slowly angulating

to consolidate whilst being protected in an ischial-bearing caliper (Fig. 5.12). The boy is now 15 years old and his tibia remains well united.

Case 4

A 6-year-old girl was found to have slight anterior bowing at the junction of the middle and lower thirds of her tibia. The anterior bowing increased during the next 18 months. The area of fibrous dysplasia was then removed from both the tibia and fibula. However, the deformity increased and a pseudarthrosis developed.

When the patient was 8 years old, bilateral cortical tibial onlay grafts were performed unsuccessfully and, as a result, the pseudarthrosis recurred together with marked anterior bowing. Twelve months later, the pseudarthrosis was excised; internal fixation was provided with a tibial onlay graft; and a bone growth stimulator was inserted. Six months after this operation, the stimulator and screws were removed; sound union had occurred. During the next 3 years, the patient undertook full activity and was fully weight-bearing in a below knee caliper.

At the age of 12, she fell from her bicycle and fractured the same tibia through the upper portion of the middle third; the previous area of pseudarthrosis remained healed. This fracture was treated unsuccessfully with an AO compression plate and screws. Six months

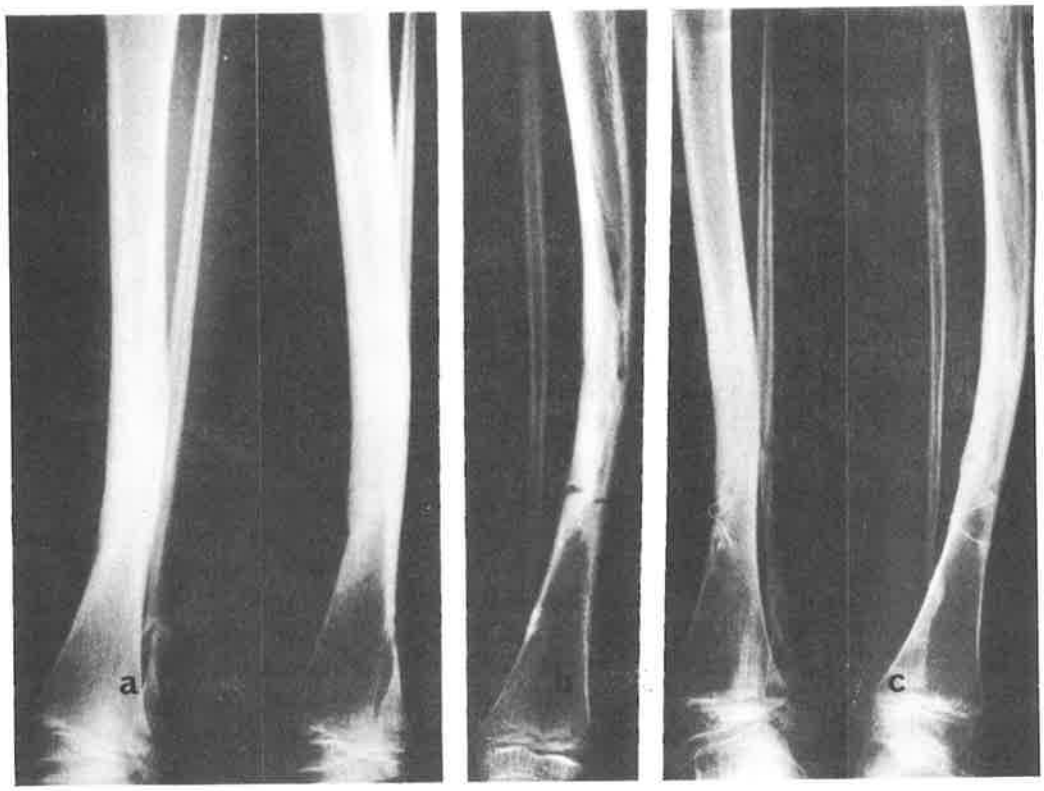

Fig. 5.12
Case 3

(a) Pseudarthrosis of the fibula,
(b) pseudarthrosis of the tibia and fibula, (c) six months after electric stimulation, clinical and radiological union

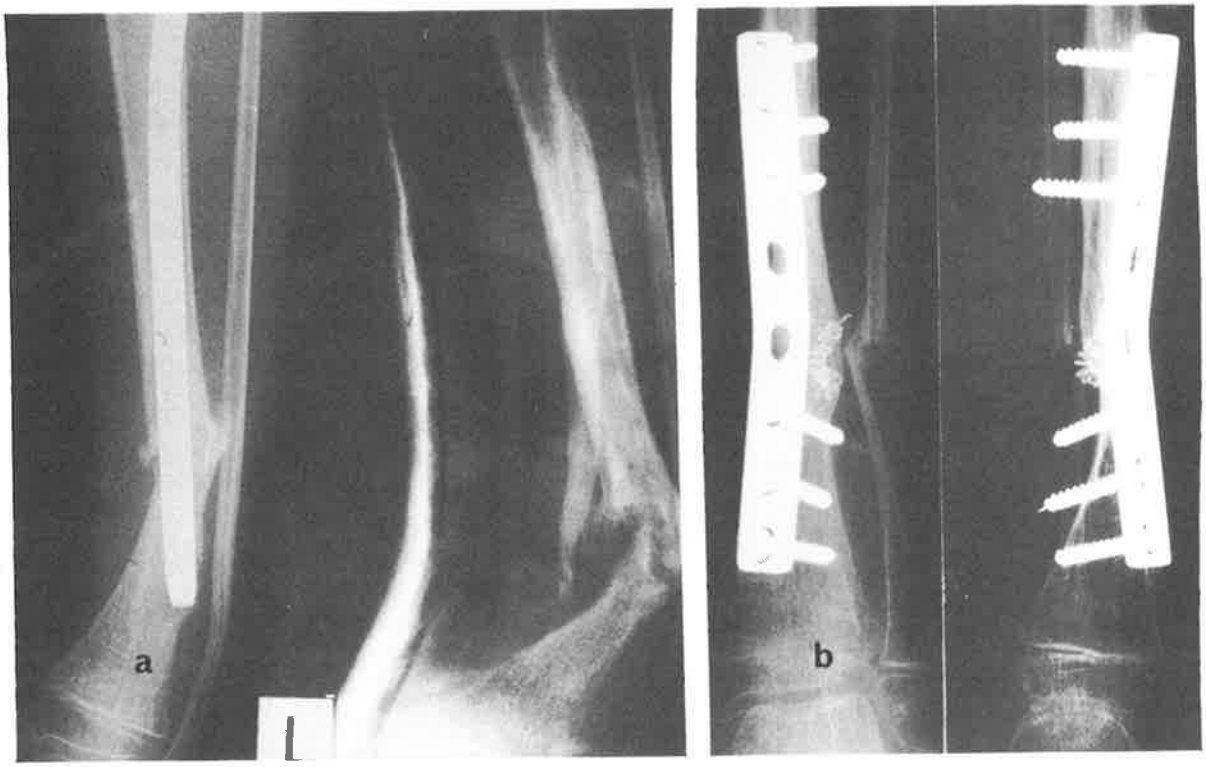

Fig. 5.13
Case 5

(a) Failed attempts to achieve union in a congenital pseudarthrosis

(b) Apparent union four months after AO compression plate fixation and electrical stimulation with cancellous bone graft

later, the area of nonunion was excised, a further tibial onlay graft was applied, and a bone growth stimulator was inserted. Eight months later, the generator was removed. Good union was confirmed radiologically and has remained so for 8 years.

Case 5

A 6-year-old boy sustained a fracture of his tibia following a fall. He was treated in plaster for 5 months, developed nonunion of the tibia and a varus deformity. A diagnosis of congenital pseudarthrosis of the tibia was made.

The patient was subsequently treated with a closed intramedullary nail to the tibia but increasing deformity occurred. Six months later, a periosteal tube graft was performed unsuccessfully and a further periosteal graft was attempted four months later. Nonunion of the tibia persisted.

When the patient was 9 years old, the pseudarthrosis was explored and excised. The deformity was corrected and held with an AO compression plate and screws.

A bone growth stimulator was inserted together with cancellous bone graft. Four months later, the generator was removed when good evidence of union was determined clinically and radiologically (Fig. 5.13).

Eighteen months later he presented with a fractured plate and recurrence of the pseudarthrosis of the tibia which was successfully treated by an intramedullary rod and cancellous bone graft (Fig. 5.14). The leg has been protected in an ischial-bearing caliper.

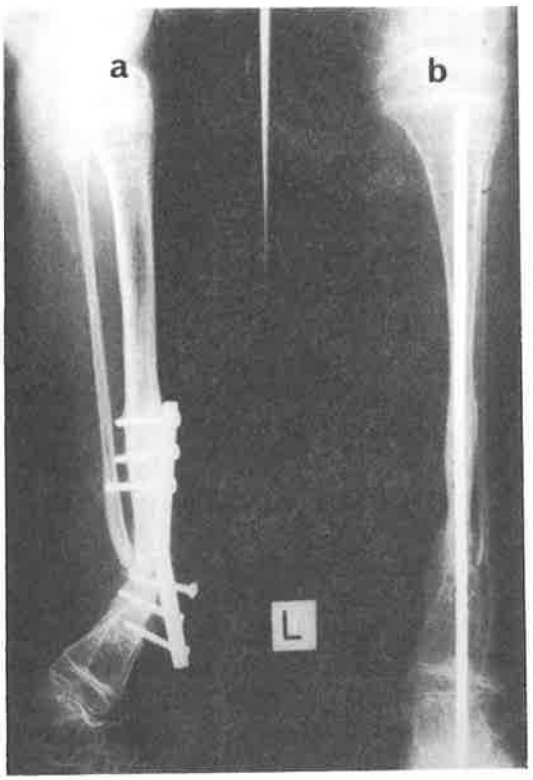

Fig. 5.14 Case 5 (a) 18 months later the plate broke and the pseudarthrosis had recurred; (b) the tibia has united with intramedullary fixation and cancellous bone graft

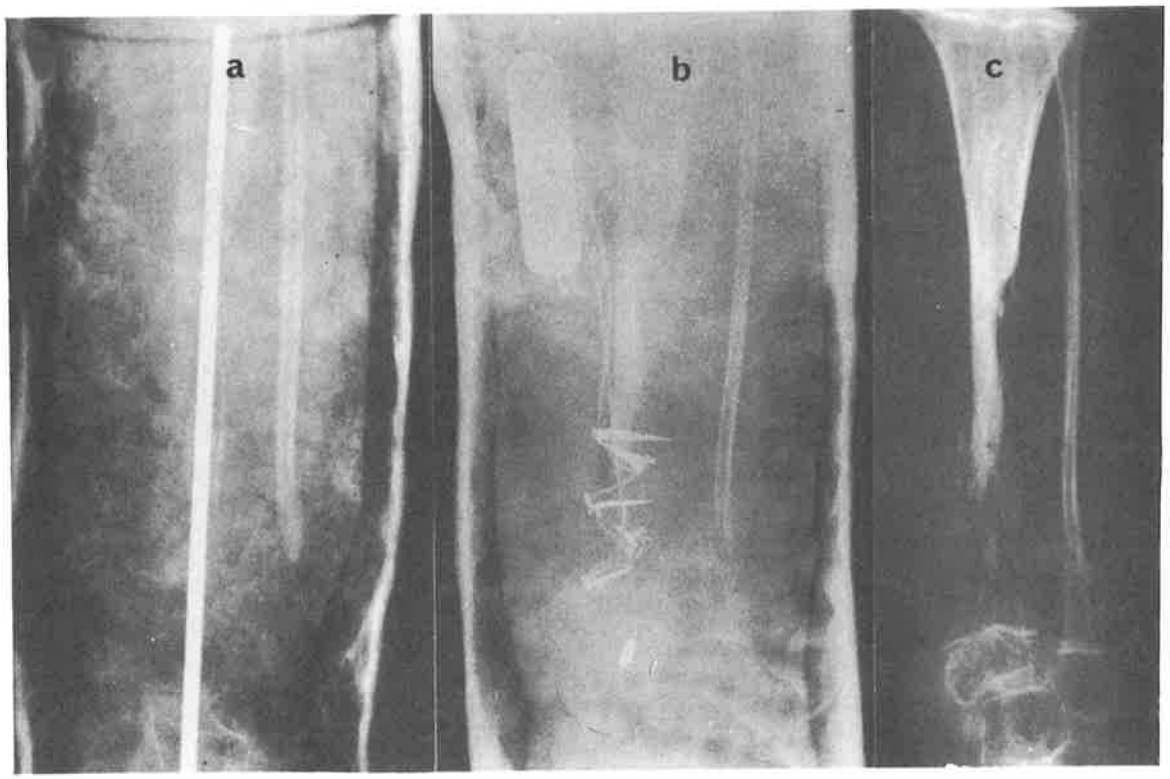

Fig. 5.15 Case 6

(a) An unsuccessful transtarsal intramedullary tibial rodding

(b) Modified electrical stimulation without internal fixation

(c) Failure to induce any osteogenesis

Case 6

A 12 months old baby was found to have bowing and a congenital pseudarthrosis at the junction of middle and lower thirds of his left tibia. By the age of 7, he had many unsuccessful cancellous bone grafting operations and a recent transtarsal intramedullary tibial rodding with additional cancellous grafting. At the time of insertion of the bone growth stimulator and cancellous bone grafting, a large defect existed at the lower end of the left tibia with attenuated sclerotic bone ends (Fig. 5.15). The generator was removed after 3 months, union had failed to occur and the leg was amputated.

The gap was far in excess of that accepted for electrically induced osteogenesis [69] to occur successfully.

4. RESULTS

Six children with pseudarthrosis of the tibia have received treatment with electrical stimulation. In case 4, a second site of pseudarthrosis developed following a separate incidence and it can be included as an additional example of this condition.

Union was achieved in 5 out of 7 cases. It should be noted that case 5 was considered radiologically united for nearly 18 months before further fracture occurred.

The mean time for union was 6 months (SD 1.67). The follow-up was 6 months to 6 years. Except in one case, all patients received cancellous bone grafting in addition to electrical stimulation.

In all cases, the tibia was protected after clinical and radiological union and this should continue until normal bone texture has been restored and skeletal maturity obtained.

5. FURTHER CLINICAL EXPERIENCE

A further 8 cases have had surgical treatment including electrical stimulation for congenital pseudarthrosis of the tibia. The follow-up in two cases is only 8 months but union has occurred and is consolidating. Four other cases are soundly united and two have failed to achieve union.

This indicates that 11 of 15 cases have united with a combination of correction of the deformity, cancellous bone grafting and electrical stimulation.

Case reports

Case 7

An 18-month-old girl had treatment of a pseudarthrosis of the tibia by fragmentation of the tibia, intramedullary rod fixation and cancellous bone graft. This failed to achieve union and 12 months later, an Osteostim alone was applied across the defect but union did not occur.

Three years later she presented with a deformed tibia and a broken intramedullary rod. Her tibia was fixed again with an intramedullary rod, bone graft and electrical stimulation but failed to unite because of inadequate fixation of the tibial fragments and poor placement of the cathode. Twelve months ago she had the deformity of the tibia corrected again, fixation with an AO tibial compression plate, Osteostim and bone graft. Union has not occurred.

Case 8

A 13-year-old boy with neurofibromatosis presented at 18 months of age with a pseudarthrosis of the fibula and anterior bowing of the tibia. His leg was protected in a caliper for many years and, when he was 13 years old, the deformity was corrected by osteotomy of the tibia, plate and screw fixation, bone graft and electrical stimulation.

The wound became infected and six months later, he had the plate and screws removed with further bone graft and electrical stimulation. His tibia has been soundly united for 18 months and is protected in a weight-relieving caliper.

Case 9

A 10-year-old girl with the diagnosis of neurofibromatosis had a deformed tibia all her life (Fig. 5.16) and used a staff for walking.

Radiologically she had a typical congenital pseudarthrosis of the tibia (Fig. 5.17). The defect was treated by correction of the deformity, intramedullary rodding, electrical stimulation and cancellous bone grafting. Union was noted radiologically at 3 months (Fig. 5.18) and the tibia continued to consolidate over the following 9 months.

The intramedullary rod was then removed, and the tibia refractured. The procedure has been repeated and the tibia is again consolidating radiologically (Fig. 5.19).

Case 10

A 21 month old girl with many cafe-au-lait spots presented with a fractured tibia which did not unite. Two years later she had the pseudarthrosis fixed with an intramedullary rod and bone graft but this failed to unite as did a similar procedure two years later.

A further two years later she had further bone graft applied with electrical stimulation. The deformity was not corrected nor was the tibia stabilised. However, the tibia united and is radiologically solid three years later though the tibia, protected in a caliper, is slowly bowing.

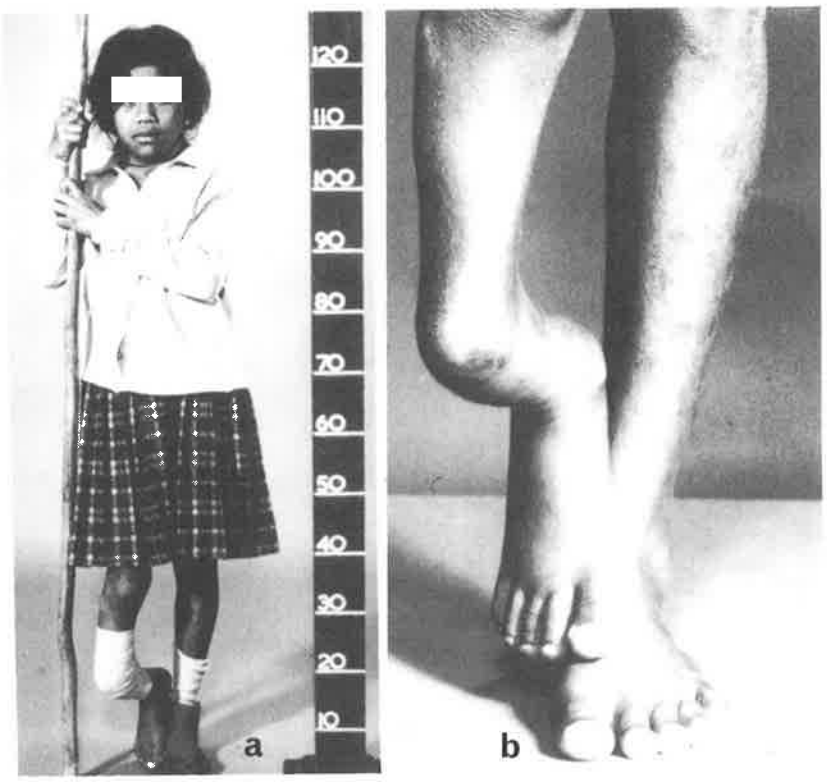

Fig. 5.16 Case 9 (a) & (b) A 10 year old girl with a deformed tibia

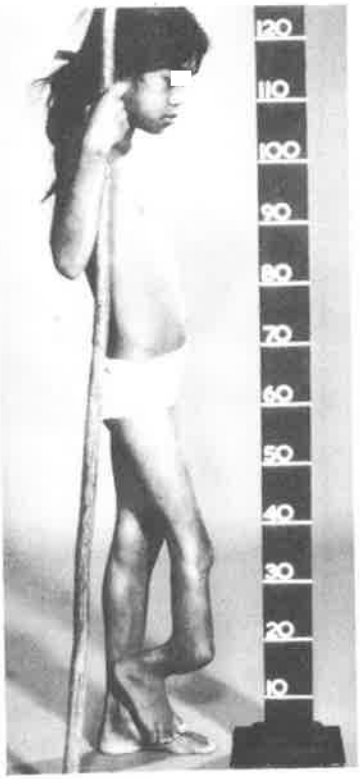

Fig. 5.17 Case 9 The deformed tibia

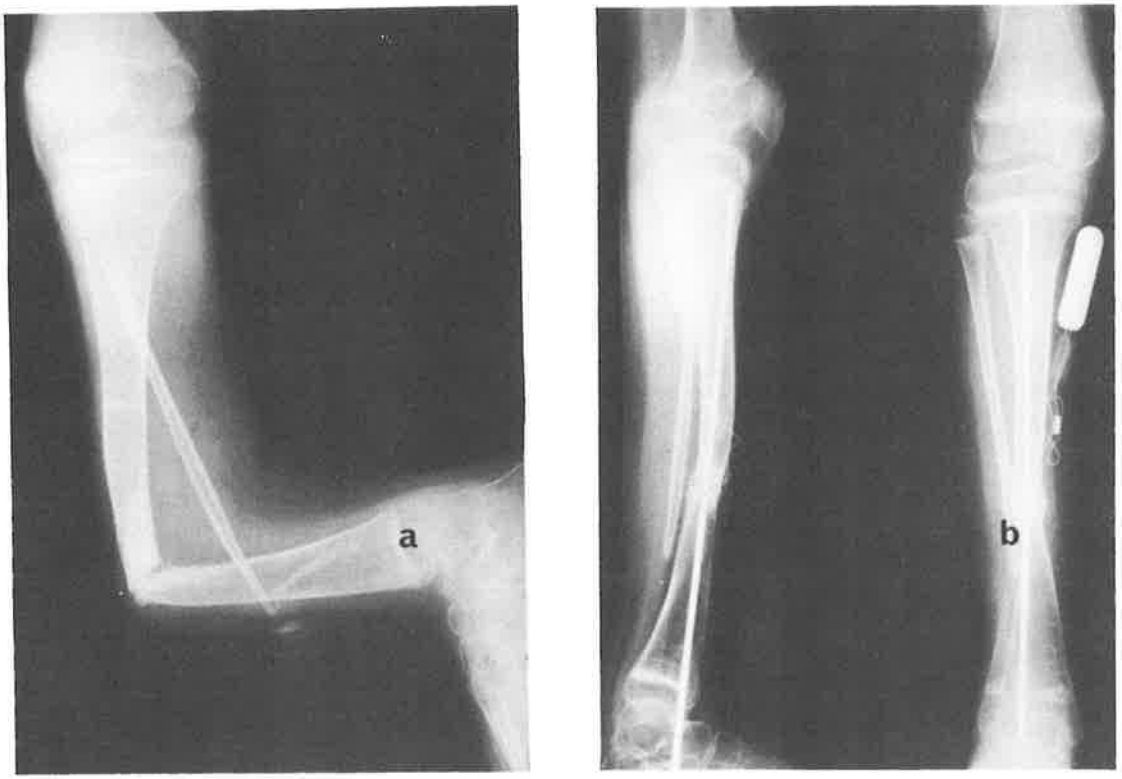

Fig. 5.18 Case 9

(a) Congenital pseudarthrosis of the tibia radiologically

(b) Intramedullary fixation with cancellous bone graft and the Osteostim showing early union three months after surgery

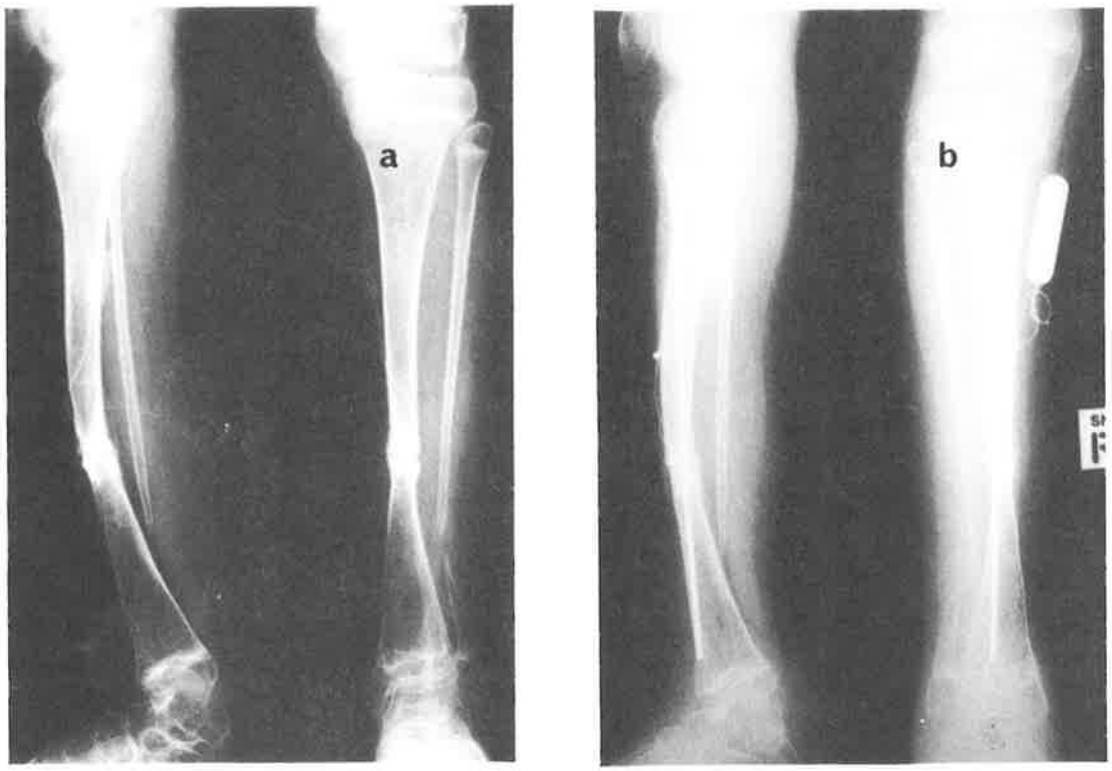

Fig. 5.19
Case 9

(a) Re-fracture of the tibia one month after removal of the intramedullary nail

(b) Union again after further surgery with electrical stimulation

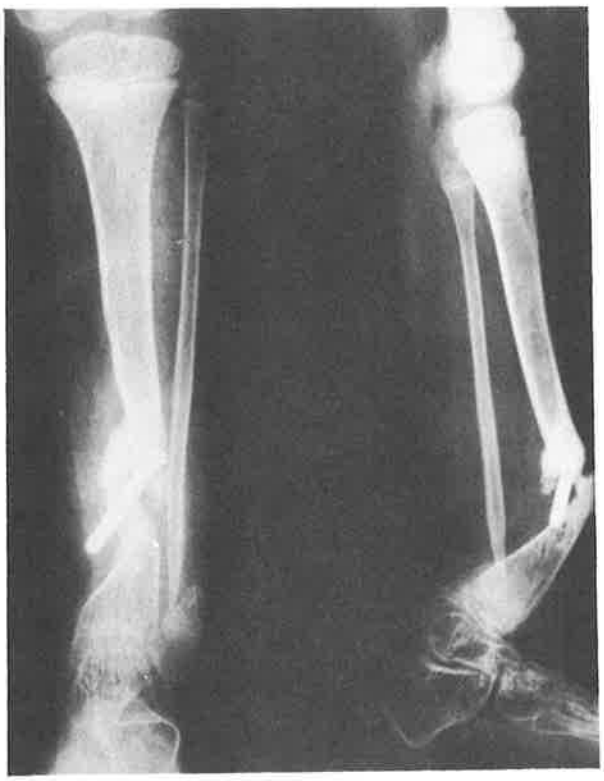

Fig. 5.20
Case 14
A 7 year old girl who presented after eight failed previous operations to achieve union of a congenital pseudarthrosis of the tibia

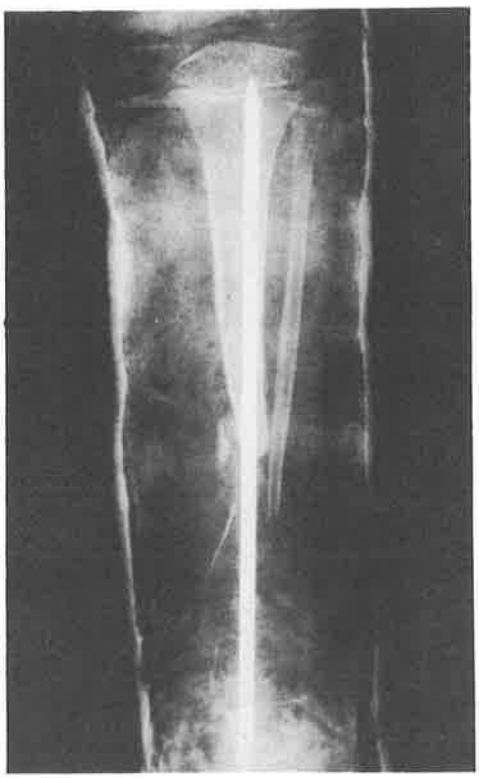

Fig. 5.21
Case 14

The cancellous bone graft has disappeared three months after internal fixation and bone graft

Case 11

A 4-year-old boy with cafe-au-lait spots fell and fractured his tibia. He developed a pseudarthrosis which was protected in a caliper. One year later the deformity was corrected, fixed with an intramedullary rod, cancellous bone graft and electrical stimulation. The tibia is well united.

Case 12

A 6-month-old boy with gross features of neurofibromatosis had a pseudarthrosis at the junction of the upper and middle thirds of the tibia. This was protected in an orthotic appliance.

When he was 2½ years old an Osteostim was inserted across the pseudarthrosis without correcting the deformity or stabilising the tibia. The helix displaced slightly anteriorly but the tibia united.

However, he developed a further lesion at the junction of the middle and lower thirds of the tibia. This difficult deformity has been only partly corrected, inadequately fixed with a small intramedullary rod, bone graft has been applied and an Osteostim inserted with an inadequately placed cathode helix. This has failed to unite.

Case 13

An 11-year-old boy with neurofibromatosis was diagnosed at 4 years of age to have a pseudarthrosis of the tibia. The leg was protected in an orthotic appliance until he was 8 years old when he had an operation consisting of cancellous bone graft and electrical stimulation. His tibia united, refractured three years later and has united again after correction of the deformity with intramedullary rod fixation, bone graft and Osteostim.

Case 14

This 7-year-old girl presented after 8 previous operations to try and achieve union of a congenital pseudarthrosis of the tibia (Fig. 5.20). The deformity was corrected by an intramedullary rod and cancellous bone graft was applied but three months later the graft had disappeared and union was not occurring (Fig. 5.21). Further bone graft and, in addition, electrical stimulation was carried out (Fig. 5.22) and three months later (Fig. 5.23) the tibia was united. Two years later the tibia remains well consolidated and is protected in a weight-relieving caliper.

6. DISCUSSION

Several attempts have been made to classify congenital pseudarthrosis of the tibia [13, 177, 188, 196]. Hardinge [127] reviewing 100 cases, classified them into four groups:

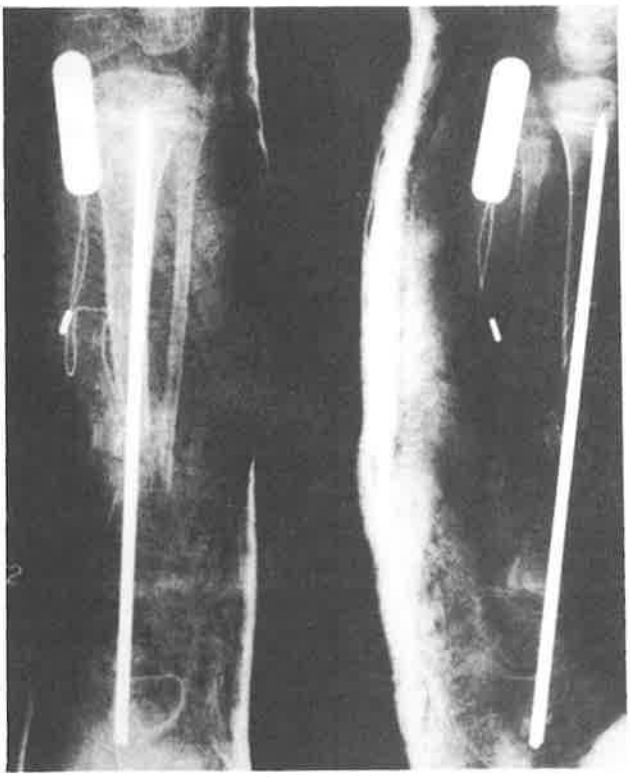

Fig. 5.22
Case 14

A further operation consisted of adding electrical stimulation and further cancellous bone graft

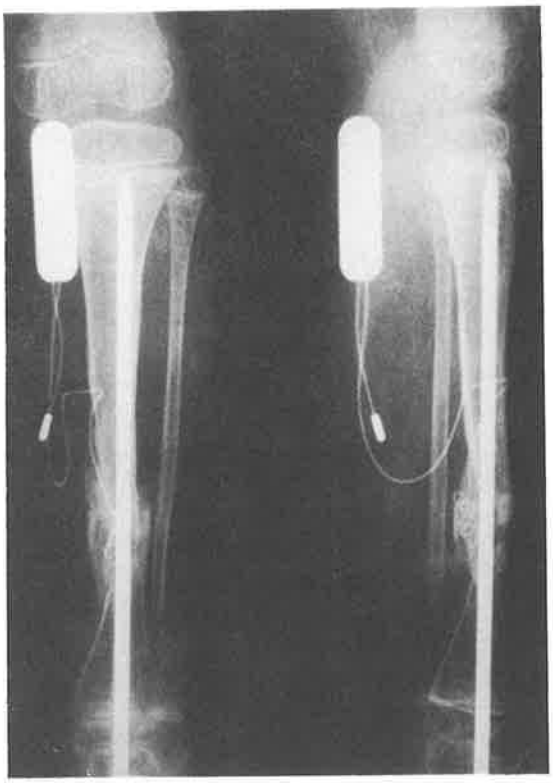

Fig. 5.23
Case 14

The tibia was united three months later

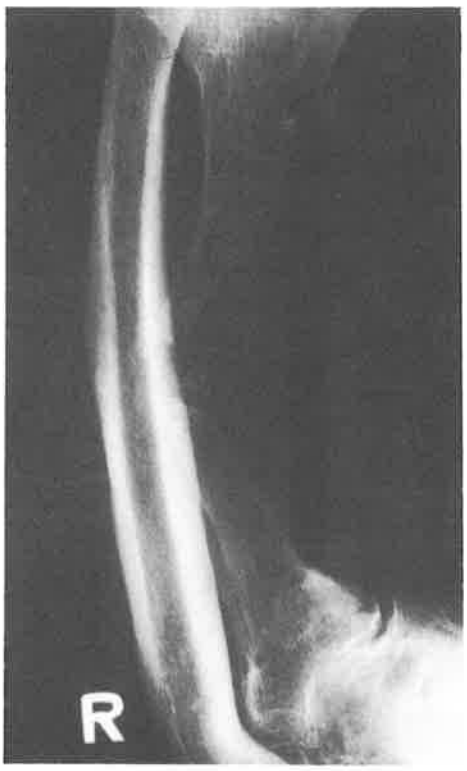

Fig. 5.24 An 80 year old female with an untreated congenital pseudarthrosis of the tibia and marked hypertrophy of the fibula

(a) pseudarthrosis following a spontaneous fracture of a bowed tibia in neurofibromatosis; (b) pseudarthrosis following corrective osteotomy or trauma in congenital anterior bowing of the tibia; (c) pseudarthrosis occurring in a tibia affected by fibrous dysplasia of bone; and (d) pseudarthrosis in childhood (ages 5-12 years) not preceded by bowing and not associated with neurofibromatosis.

Clearly there is an association of congenital pseudarthrosis of the tibia with neurofibromatosis [1, 15, 94, 144, 177, 179, 241]. This has been present in 10 of the 15 cases reported here. It is, however, uncertain if the presence of neurofibromatosis affects the prognosis.

Treatment has always been difficult. Some authors have suggested prophylactic bracing [269], prophylactic surgery [175] and, as previously mentioned, specialised surgical approaches [52, 75, 180, 181, 240, 241]. Although prophylactic treatment has a place, conservative treatment does not help once the pseudarthrosis is established [269] though this may be compatible with surprisingly good function (Fig. 5.24).

The results of surgical treatment, however, vary. Van Nes [269] reported only one amputation in 23 patients. Radiologically confirmed consolidation occurred in 19 of these patients when surgical treatment, consisting of an intramedullary pin and double cortical grafts was delayed until the patients were 5 years old. The reported incidence of amputation varied from 11% to 40% [9, 127, 177, 188, 216, 241]. The time of amputations also varies, since some [241] suggest that amputation should be avoided at all costs while others [188] recommend

early amputation when the prognosis is not good. Hardinge [127], in his large series, stated his belief that one factor common to the success of any operative procedure was the age of the child at the time of surgery. Indeed, he reported that long term union was never obtained below the age of 33 months and that simple grafting procedures were never successful below the age of 6 years and very rarely successful above that age. However, it appears that the age of the child at the time of surgery is not as important as was first believed [170, 188, 241]. Experience with these cases agrees with this latter view.

There can be no doubt, nonetheless, that all involved extremities must be protected to skeletal maturity or to the development of a normal medullary cavity [13, 102, 214, 269].

The use of electrical stimulation for congenital pseudarthrosis of the tibia was first reported in the early 1970s [162, 228]. Subsequently, other authors [23, 26, 29, 62 137, 165, 179] have reported varying success using either semi-invasive or non-invasive techniques. The results with the totally invasive Osteostim are most encouraging.

In the light of experience [205, 206] with these 15 cases, certain procedures appear to be desirable to achieve bony union. The deformity should be corrected by a long intramedullary rod from the heel to the upper part of the tibia (Fig. 5.25), together with electrical stimulation. It is important to ensure that a sliver of cancellous bone separates the intramedullary rod from the helix (Fig. 5.26).

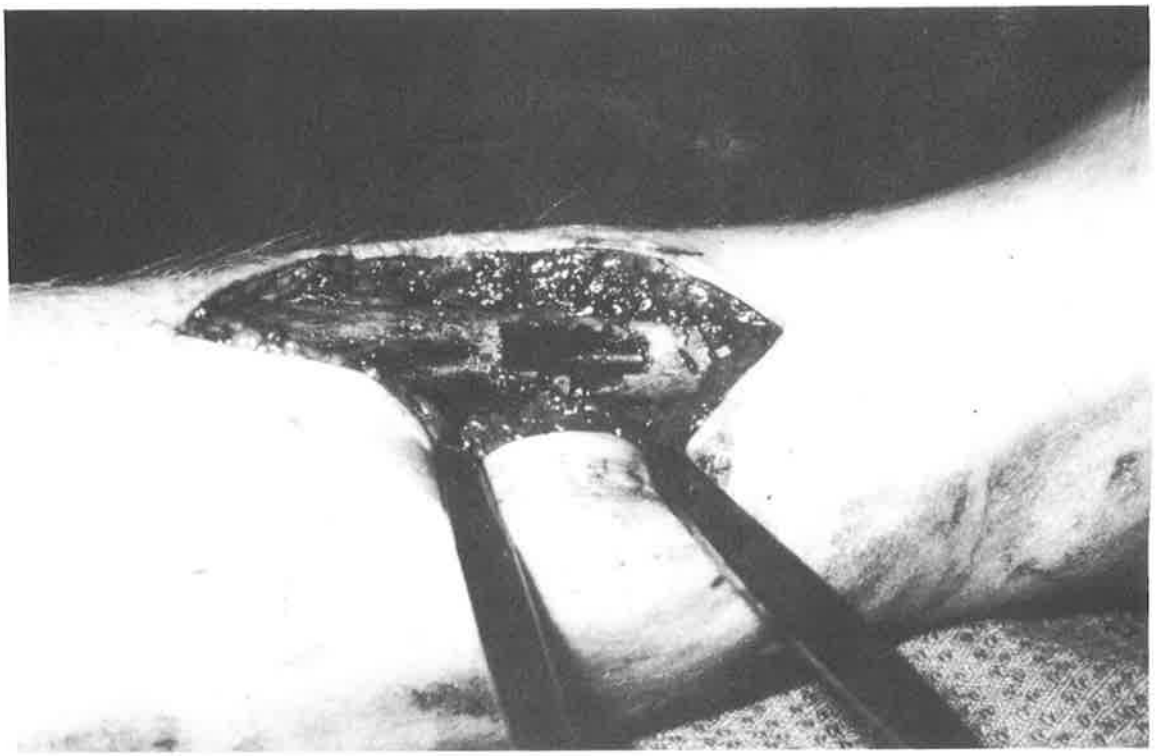

Fig. 5.25 Correction of the tibial deformity and fixation using an intramedullary rod; the defect has been created

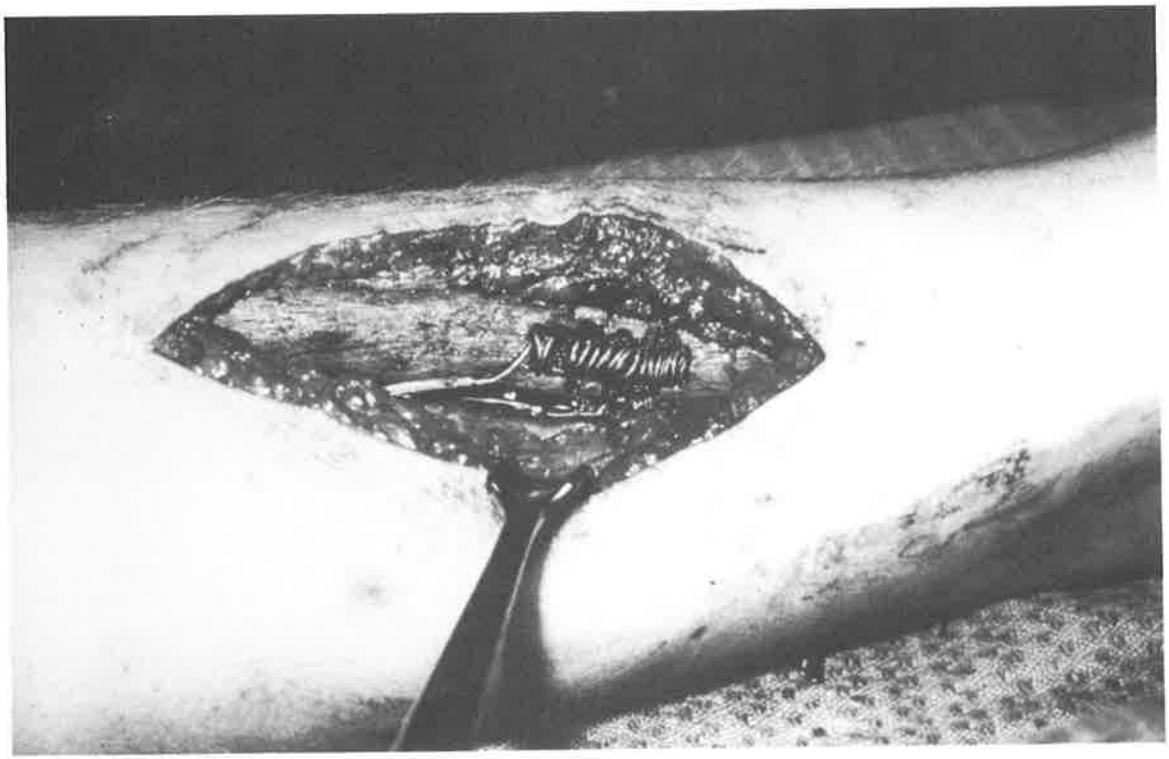

Fig. 5.26 The cathode helix is inserted into the defect and is separated from the underlying intramedullary rod by cancellous bone graft. Further bone graft is placed around the tibia

Where the tibia is extremely thin, the titanium cathode can instead encircle the whole tibia and form a helix. The area should be surrounded by autogenous bone graft, the leg immobilised in a plaster hip spica for at least 6 months followed by long term protection of the leg. The intramedullary rod should not be removed.

7. SUMMARY

Congenital pseudarthrosis of the tibia presents surgeons with one of the most challenging of all orthopaedic problems. The results of various forms of surgical treatment are rarely successful.

The results achieved with an implanted bone growth stimulator when used in conjunction with cancellous bone grafting, complete correction of the tibial deformity and efficient immobilisation of the tibia, are superior to any previous reports. The leg, however, requires long-term protection of the fracture site until skeletal maturity is complete.

This successful approach offers the surgeon an encouraging and alternative approach to congenital pseudarthrosis of the tibia.

CHAPTER 6

EFFECTS OF VARYING CURRENT LEVELS OF ELECTRICAL STIMULATION

CHAPTER 6

THE EFFECT OF VARYING CURRENT LEVELS OF ELECTRICAL STIMULATION

1. INTRODUCTION

Various methods of clinical application of electrical stimulation are available - a totally invasive method [96, 204, 205, 206], a semi-invasive method [62, 63, 68, 110, 162], a totally non-invasive technique [23, 26] and other methods [46, 137, 164, 170, 171, 173, 262, 297] and all have used different current levels as well as different anode and cathode materials.

Fridenberg et al [110] were the first to report healing of an ununited fracture by electrical stimulation in modern times and they used a direct current of 10 microamperes [105] based on their previous analysis of electrical potentials accompanying fracture healing. Subsequently, they [62, 63, 68] used a direct current of 20 microamperes because "10 microamperes produced inadequate electricity".

Yasuda [292] in his original work used 1 microampere to produce osteogenesis in the femur of a rabbit. Subseqeunt workers [18, 106, 108, 161, 207, 293] have used freshly fractured or intact long bones to evaluate current levels of 5-20 microamperes. Friedenberg et al [112] stated that the greatest bone response was related to 20 microamperes and beyond 30 microamperes, osteonecrosis occurred.

Becker [41, 44] believed that the question of optimum magnitude of the electrical current must be kept open and, in 1981, [46] he stated that "there is evident disagreement as to the optimum type and level of current and method of administration." Treharne [264] suggested that direct current was more than twice as effective as either pulsed current or currents pulsed with the same shape as though they were stress-generated.

So far as could be ascertained, no previous research has attempted to compare varying current levels in a situation of delayed healing of a long bone. In previous work [203], we have produced a reliable model of delayed union of the dog tibia which showed statistical difference in bone healing using a 20 microampere direct current. However, this model had inherent technical and sampling problems, the most notable being the necessity to control the experiment by using two animals as it was not possible to insert an active and an inactive stimulator in the one animal. It was considered that these variables might prevent the detection of potentially smaller differences of osteogenesis between different current levels. The aim of the present work, therefore, was to produce a more sensitive and better controlled experimental model that simulated delayed union of a tibia or femur in an adult dog in which varying current strengths could be applied and an assessment made of the most effective order of magnitude of direct current for bone growth stimulation.

2. MATERIALS AND METHODS

A simple and reproducible surgical model in adult dogs was constructed (Fig. 6.1) in which a segment of one cortex of the tibia or femur was removed and this area was prevented from healing for six weeks by the interposition of a block of silicone elastomer (Silastic). The titanium cathode of an implanted bone growth stimulator, Osteostim S12 *, was attached to a special titanium cathode plate which was fixed to the centre of this defect. It was possible to operate on both hind legs and this allowed one leg to act as a control for the other.

Direct current levels of 200 nanoamperes, 2 microamperes, and 20 microamperes were used and assessments were made to evaluate the amount of osteogenesis produced with the varying current levels. A current of 200 microamperes was not used as previous work had shown that this level would lead to tissue necrosis [108, 112] or fibrosis [293] rather than osseous healing.

(a) Delayed union model

In all dogs, general anaesthesia was induced with intravenous pentobarbitone sodium followed by intubation using nitrous oxide, oxygen and halothane. Intramuscular injections of pentazocine were given post-operatively.

* Telectronics Pty. Ltd., Sydney, Australia

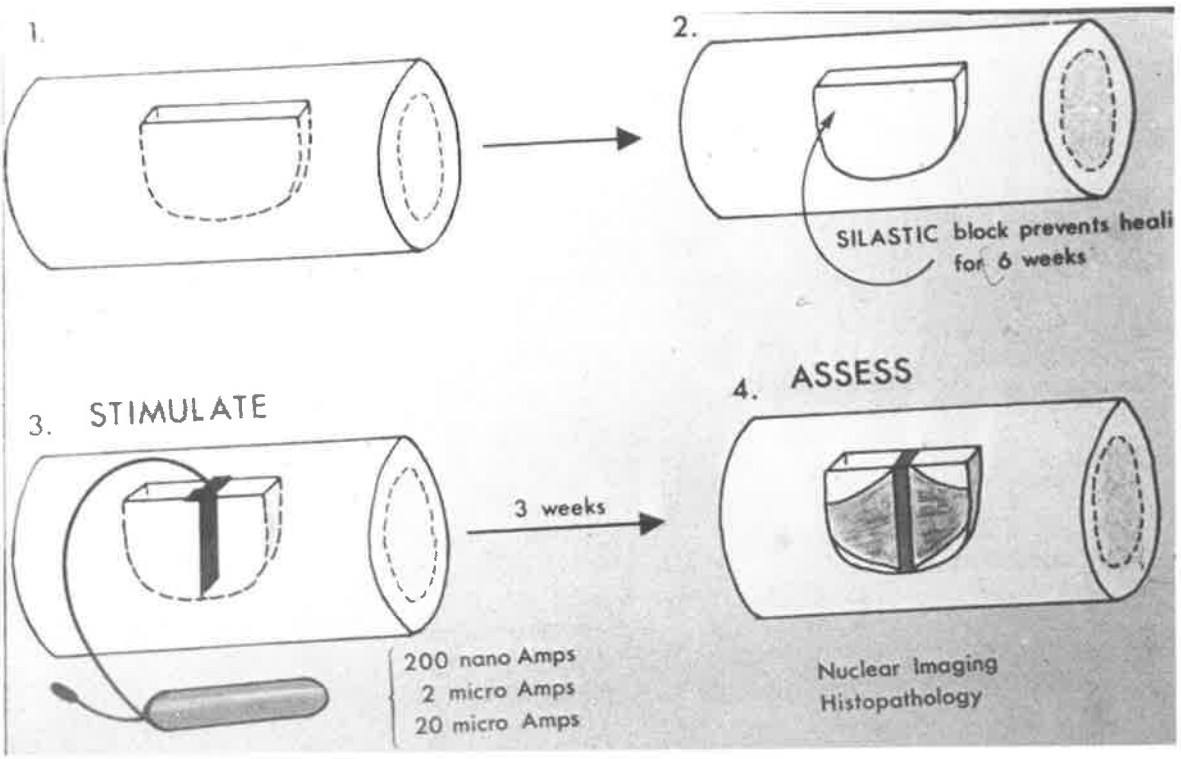

Fig. 6.1 Plan of the model

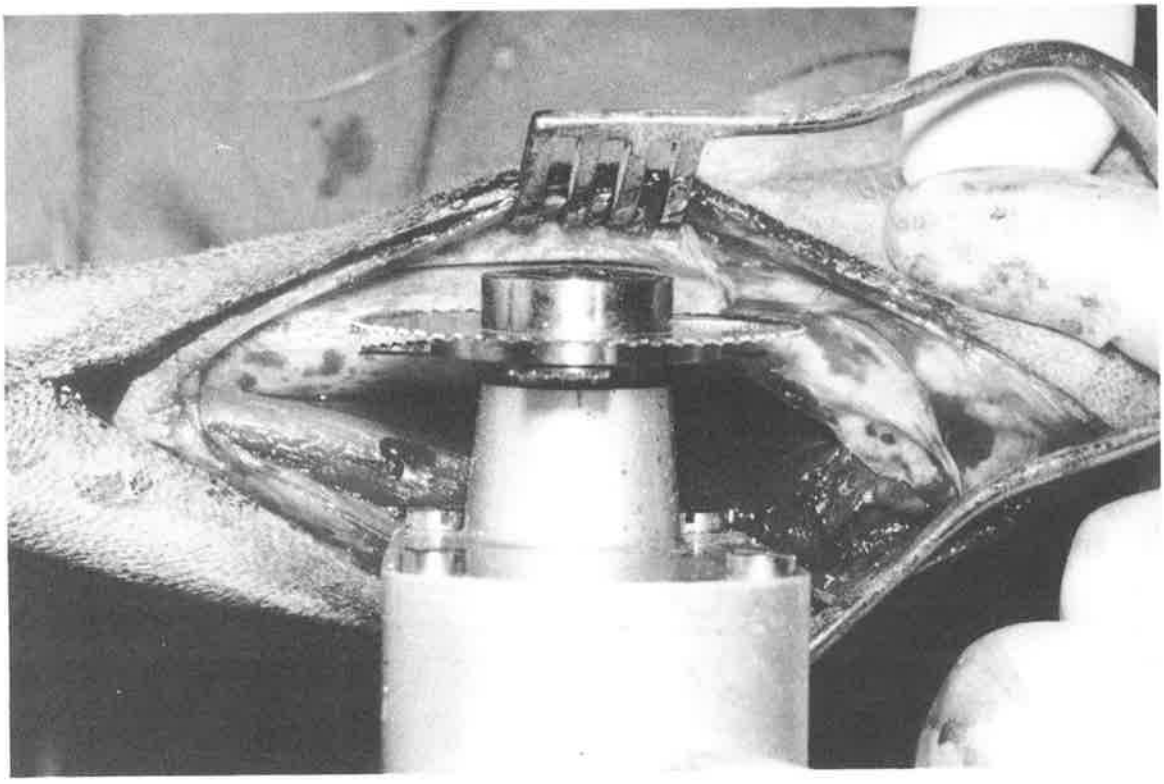

Fig. 6.2 The defect is created with a double bladed saw

The femur or tibia of adult dogs was exposed, the periosteum was excised and diathermied for approximately 10 mms around the proposed defect site after which the defect was cut longitudinally in the line of the bone using a double-bladed saw (Fig. 6.2). A curved defect measuring 3.5 cms long, 1 cm deep in the centre and 0.4 cm wide was made in one cortex of the bone and the area was prevented from healing for six weeks by inserting a D-shaped block of Silastic into the defect created (Fig. 6.3). A special jig was inserted into the defect in order to allow 0.4 cm holes to be drilled at either end and in exactly the same longitudinal and vertical planes as the defect itself (Fig. 6.4). Teflon tubes measuring 0.39 cm in diameter were inserted into these holes in order to keep them patent and allow accurate alignment subsequently of the specimens so that all the defects could be sectioned identically. The block of Silastic was held in place with nylon transfixing sutures (Fig. 6.5). The dogs walked within 24 hours post-operatively and all wounds healed.

Serum calcium, serum inorganic phosphorus [139] and serum alkaline phosphatase estimations were carried out pre-operatively, at one and two days post-operatively and then weekly for six weeks.

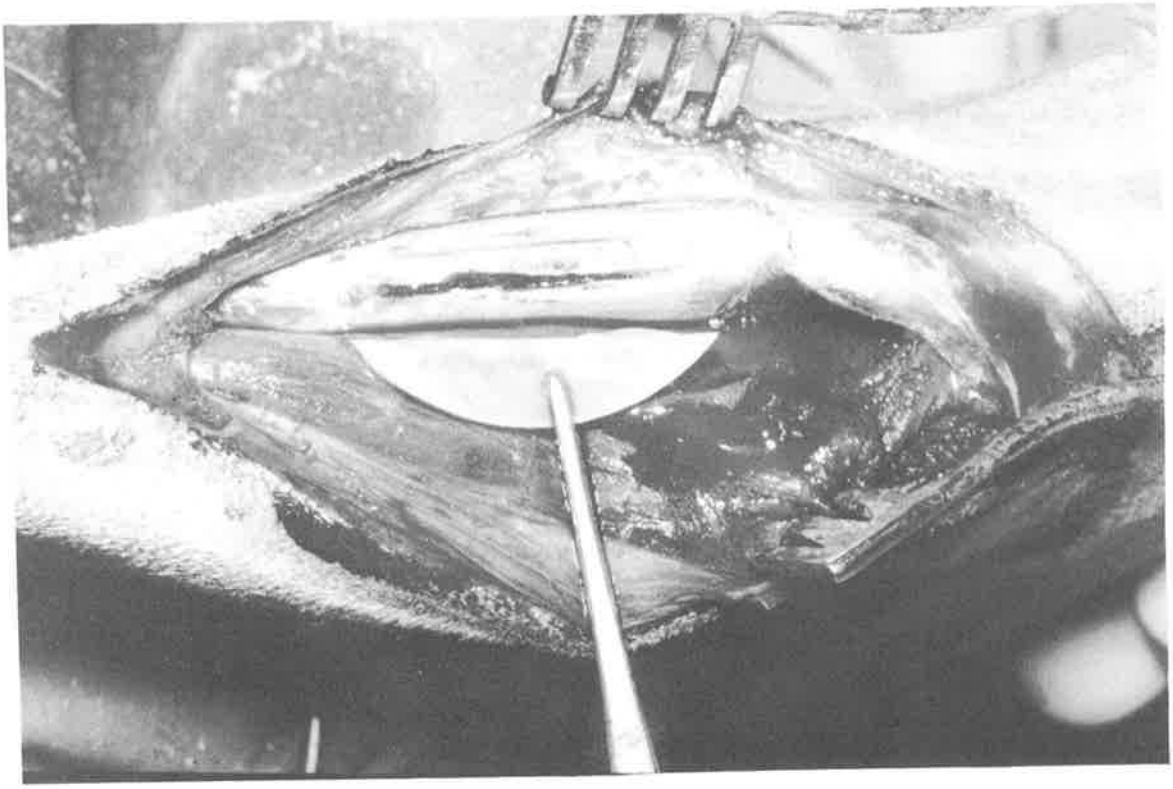

Fig. 6.3 The standard curved silastic block

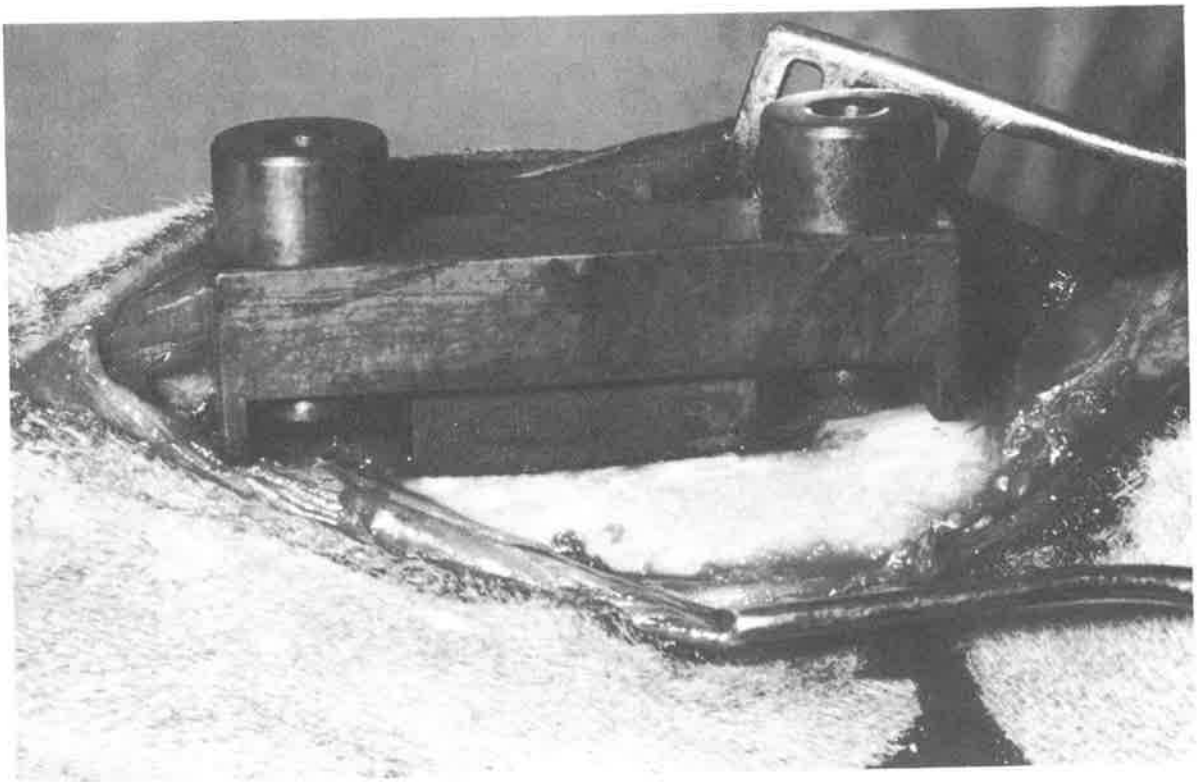

Fig. 6.4 The special jig

(b) Trial with different electrical currents

Thirty dogs were used in this study. Osteostim S12 bone growth stimulators were provided in pre-packed, sterilised and coded pairs and were inserted into each dog. Each pair of stimulators were identical to external and radiological examination and the three direct current levels were tested. The stimulators were checked by an electronics engineer at implant and explant to ensure that there was one active and one inactive stimulator in each pair. An independent assessor had the code numbers and independently assessed the results.

Six weeks after the defect was made, the bones were exposed and the Silastic blocks removed leaving a clean, membrane lined defect (Fig. 6.6). A pair of coded stimulators were provided for each dog.

The generator together with the platinum anode was placed at a distance from the defect and beneath the deep fascia. The titanium cathode wire was passed to the defect and the bare end was attached to a special T-shaped titanium cathode plate (Fig. 6.7) 0.4 cm wide and of the same surface area - 70 sq. mm - as the cathode helix used in previous animal and clinical work [202, 203, 204, 205]. The cathode was inserted into the mid point of the defect and held in place with nylon transfixion sutures (Fig. 6.8). The dogs suffered minimal morbidity and post-operatively

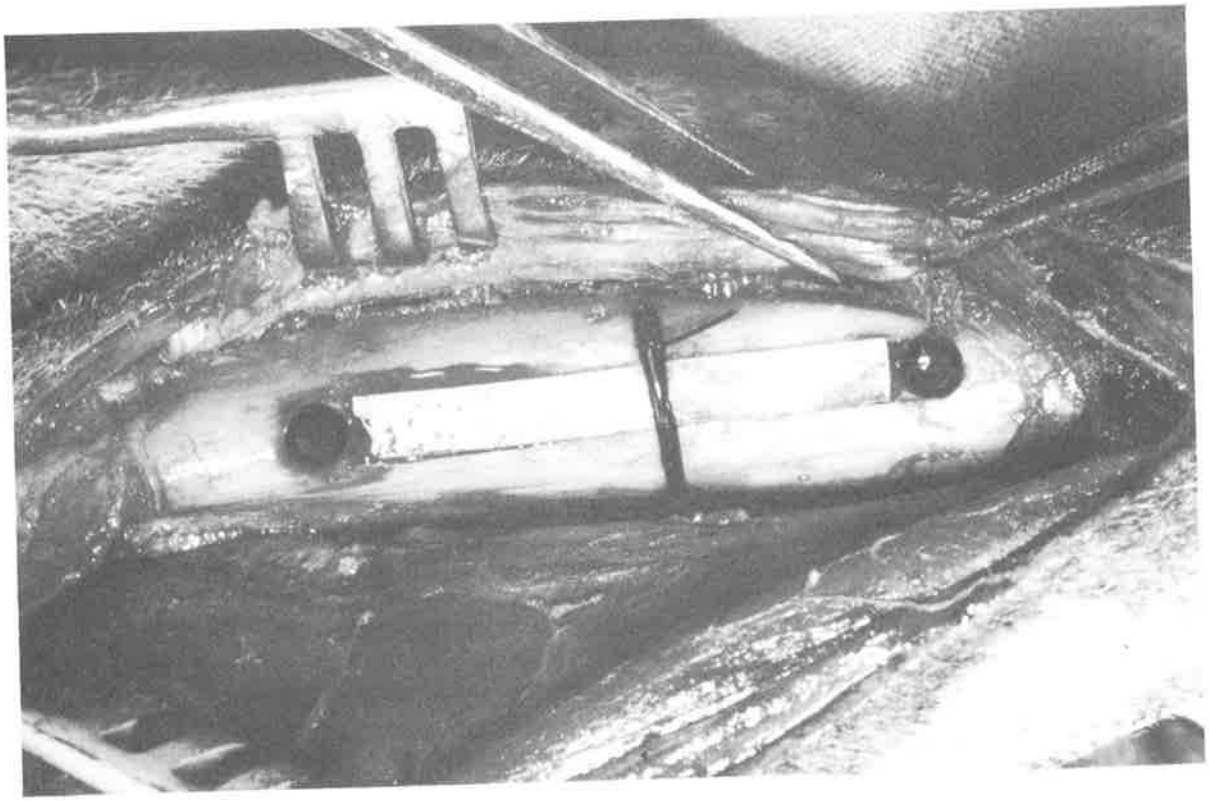

Fig. 6.5 The silastic block in situ with teflon tubes in 0.4 cm drill holes at each end

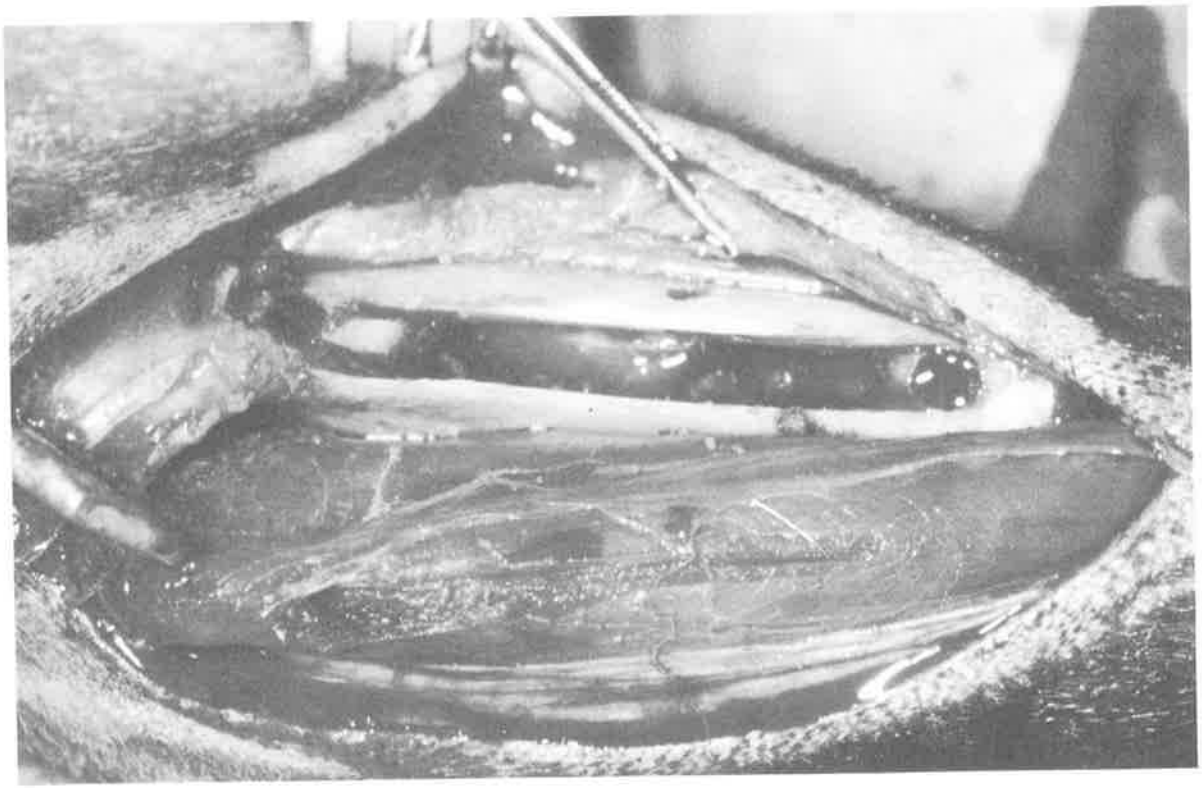

Fig. 6.6 The defect after removal of the silastic block

Fig. 6.7 The T shaped titanium cathode plate attached to the titanium cathode wire

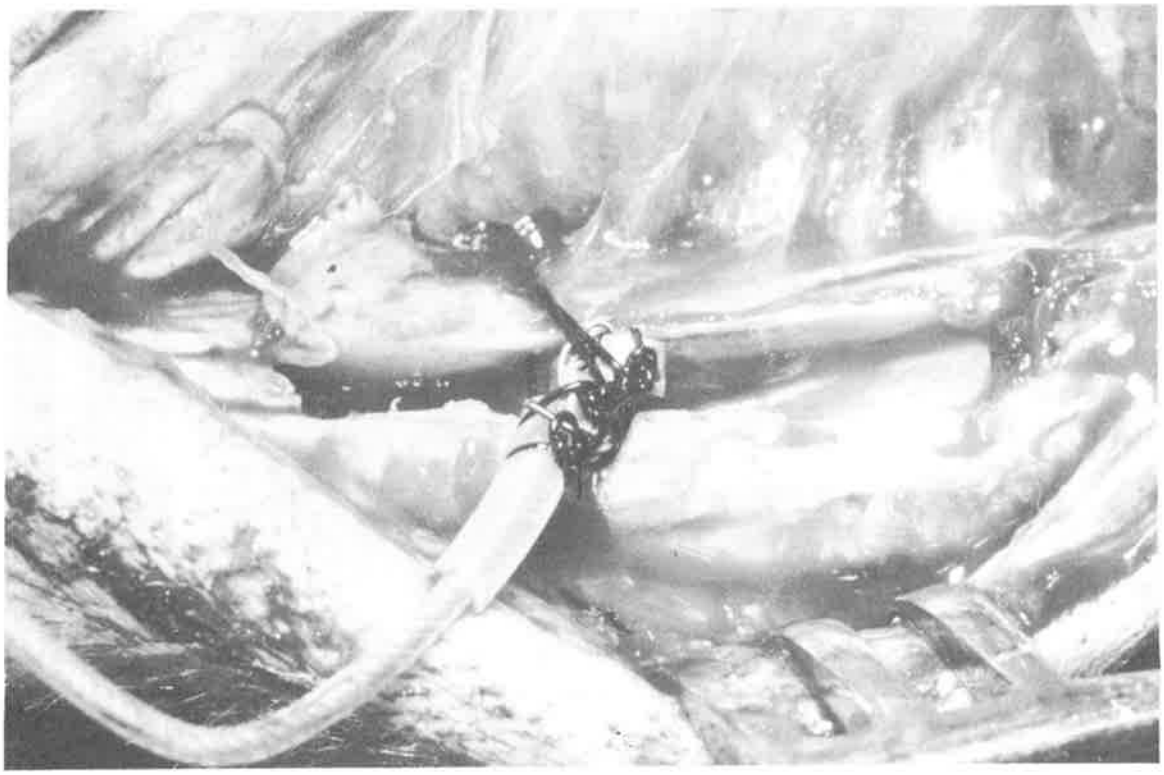

Fig. 6.8 The cathode plate fixed in the defect

similar blood specimens were taken as indicated previously. Electrical stimulation continued for three weeks.

(c) Preparation of histological sections

A longitudinal slice of bone, containing the defect area and the guide holes, was taken with a band saw. After formalin fixation and decalcification, a special jig (Fig. 6.9) positioned the specimen using the guide holes so that the plane of the defect was parallel to the final cutting surface of the block and the slices were then embedded in paraffin (Fig. 6.10). The block was then trimmed on a large sledge microtome until the guide holes, and thus the defect itself, were just coming into the plane of section. Seven step sections, 5-7 microns thick, were taken at 500 μ intervals in such a way that the fourth section was approximately through the centre of the defect, and they were stained with hematoxylin and eosin. Large photographs were then made of the defect area and on these photographs the boundaries of the defect and the areas of new bone within it were outlined with ink. Using a Hewlett-Packard electronic image analyser (Fig. 6.11), the amount of new bone, expressed as a percentage of the total area of the defect, was calculated for each section and the results for each specimen printed out in parallel with those of the specimen from the other leg of the same animal.

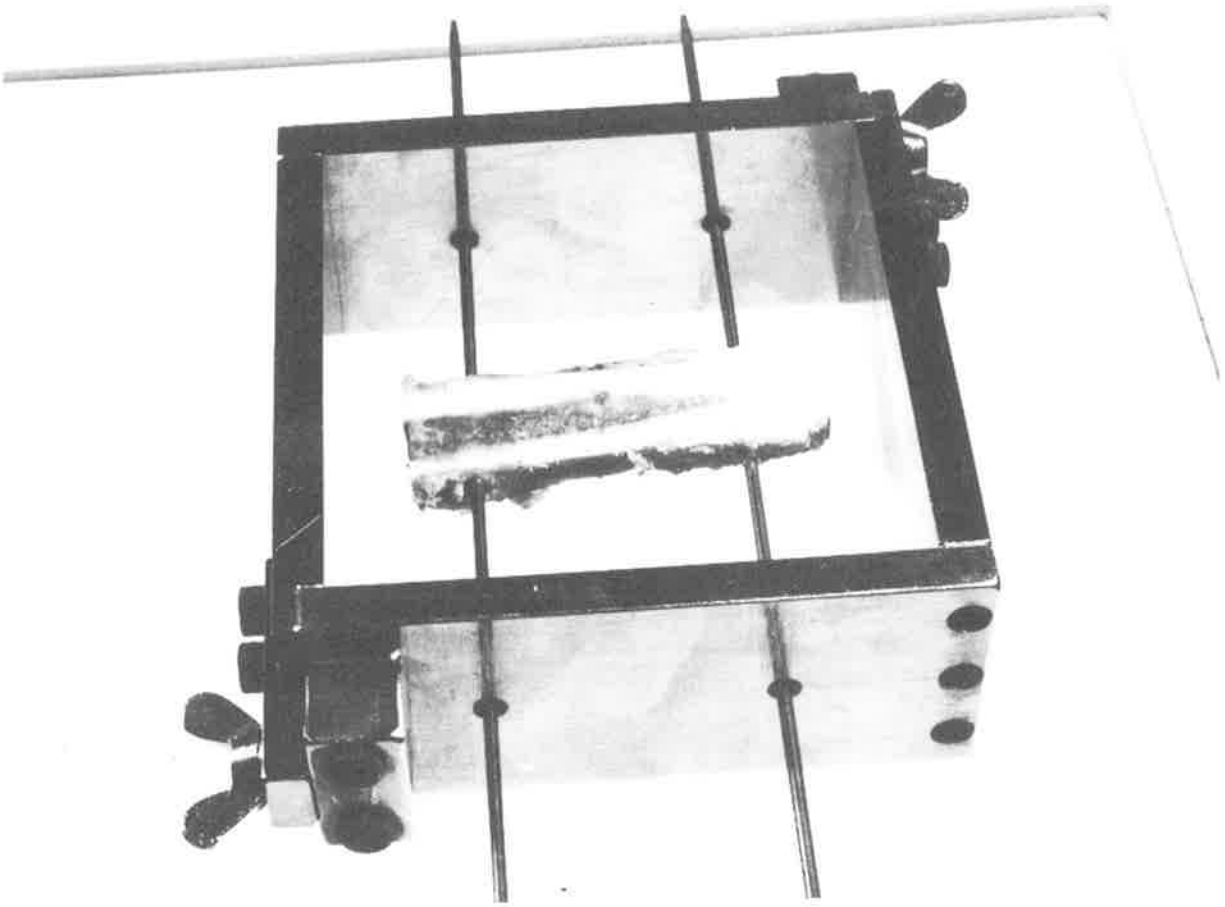

Fig. 6.9 The embedding box with metal rods in the guide holes in the bones

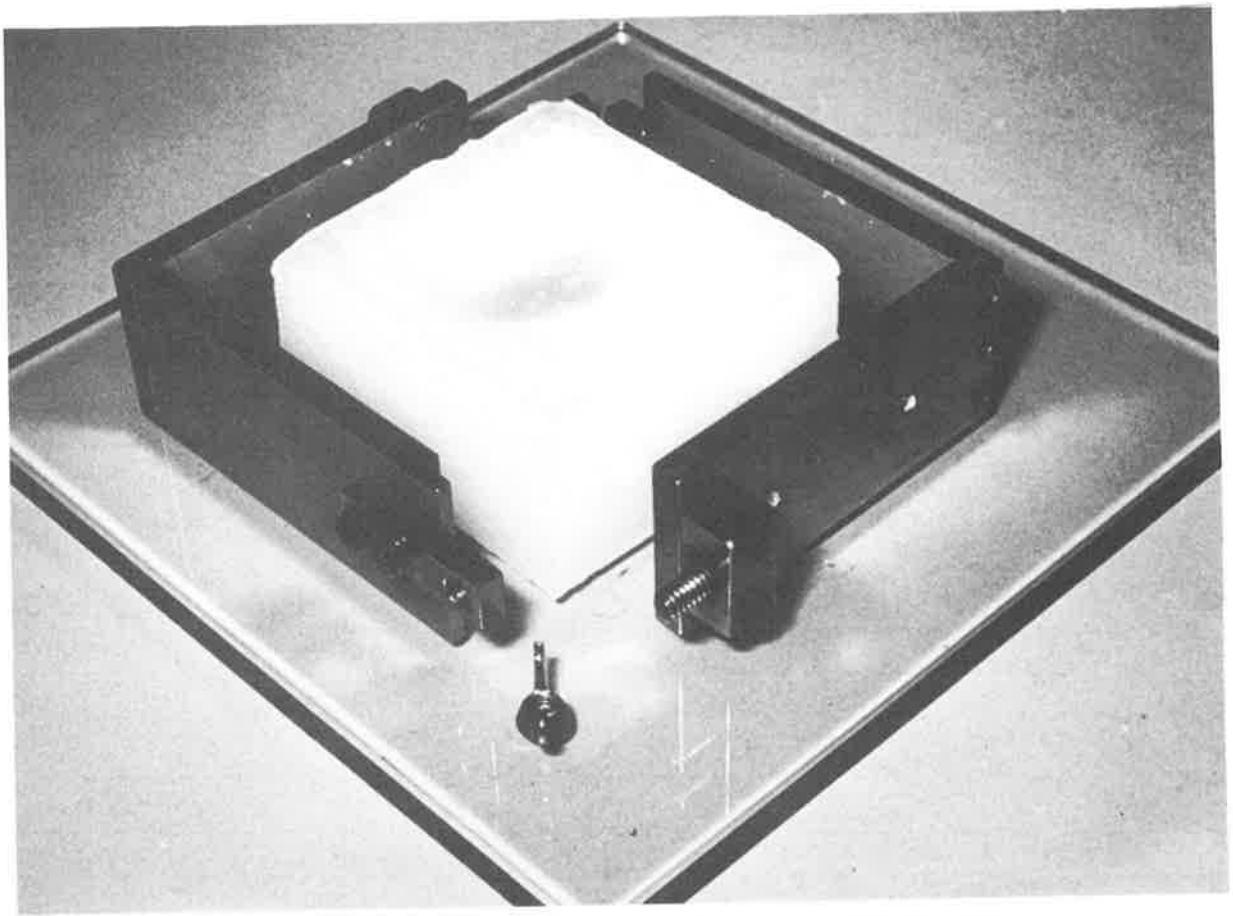

Fig. 6.10 The dismantled portion after bone has been embedded in paraffin wax

Fig. 6.11 The cursor of the Hewlett Packard digitizer in position on an enlarged photograph of the defect in which the outline of the defect and areas of new bone have been emphasized with black lines

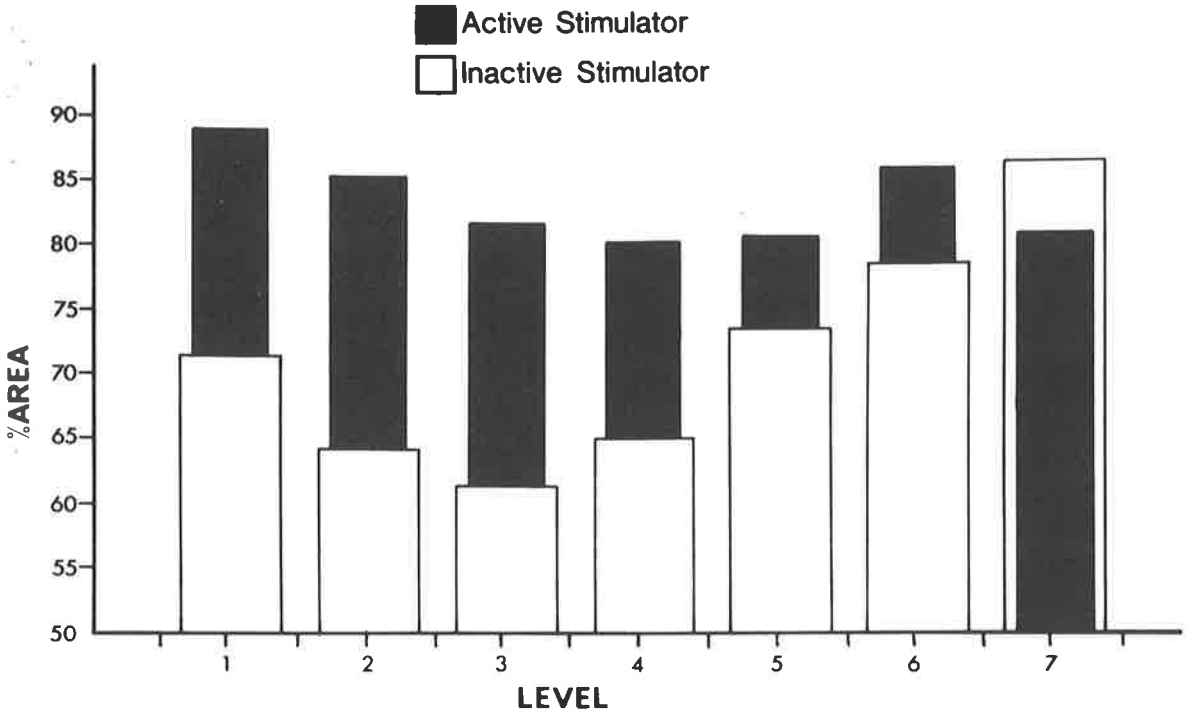

Fig. 6.12 A comparative histogram

Any difference between the two legs was calculated numerically from a comparative histogram of the results (Fig. 6.12).

3. RESULTS

(a) Evaluation of the delayed union model and the ideal period of electrical stimulation

While the concept of the defect was similar to that used in previous experimental work [203], it was significantly different in that the defect was surrounded by intact cortical bone. It was important to determine (a) when healing in the defect was sufficiently delayed for the effect of electrical stimulation to be assessed and (b) when the maximum difference of bone formation could be determined between the stimulated and the unstimulated leg.

Initially, a series of dogs were used to evaluate these aspects by -

(i) histology

One dog was killed at weekly intervals from 2-8 weeks after insertion of the silastic block. Sections were examined and it was considered that the tissues bounding the defect had finished their active phase of healing by the fourth week (Fig. 6.13) and beyond that time there appeared to be no difference in the tissue activity surrounding the defect (Fig. 6.14). It was hoped that this indicated a significant degree of delayed union although, of course, it was realized

Fig. 6.13 Section of defect four weeks old (silastic block removed). The typical crescentic shape of the defect is apparent as are the sectioning alignment guide holes traversing the shaft of the bone at each end of the photograph. In this specimen regrowth of periosteum across the defect is also illustrated. Note the trabeculae of new medullary bone surrounding the defect and the smooth lining of fibrous tissue

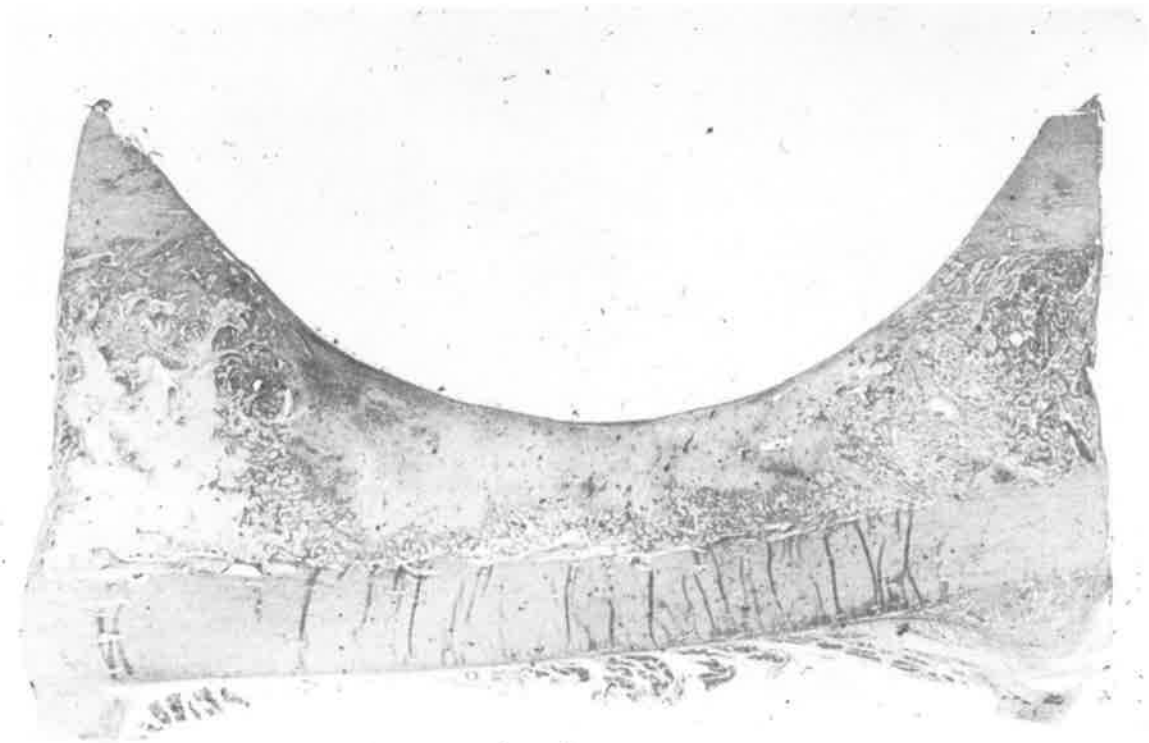

Fig. 6.14 Section of a defect six weeks old. The fibrous lining of the defect and surrounding new medullary bone are essentially the same as in Fig. 6.13

that with the silicone block still in situ, new bone growth might be inhibited.

In order to elucidate this matter, a small pilot study was done. Four dogs had silicone blocks removed at six weeks after which the bones were stimulated with a known 20 microampere direct current stimulator on one side and an inactive stimulator on the other. One dog was killed weekly. The defect areas were examined histologically and an apparent difference was found between "normal" unstimulated and "activated" bone healing in the defects with a maximum difference at about three weeks (Fig. 6.15, 6.16).

(ii) nuclear scan

Ten dogs were scanned with technetium 99m methylene diphosphonate at two weekly intervals for six weeks after the silastic block was inserted.

The scan uptake in the area from the knee to the ankle was quantified. The computerized results, displayed in graph form, showed peaks of activity at the knee and ankle. Initially, a "hot spot" of activity was seen at the defect and showed (Fig. 6.17) a biphasic peak corresponding to the upper and lower ends of the defect and a "trough" in between where healing activity had been impaired. Over six weeks, this activity declined and the biphasic appearance became somewhat flattened indicating that the normal bone reaction to injury was subsiding.

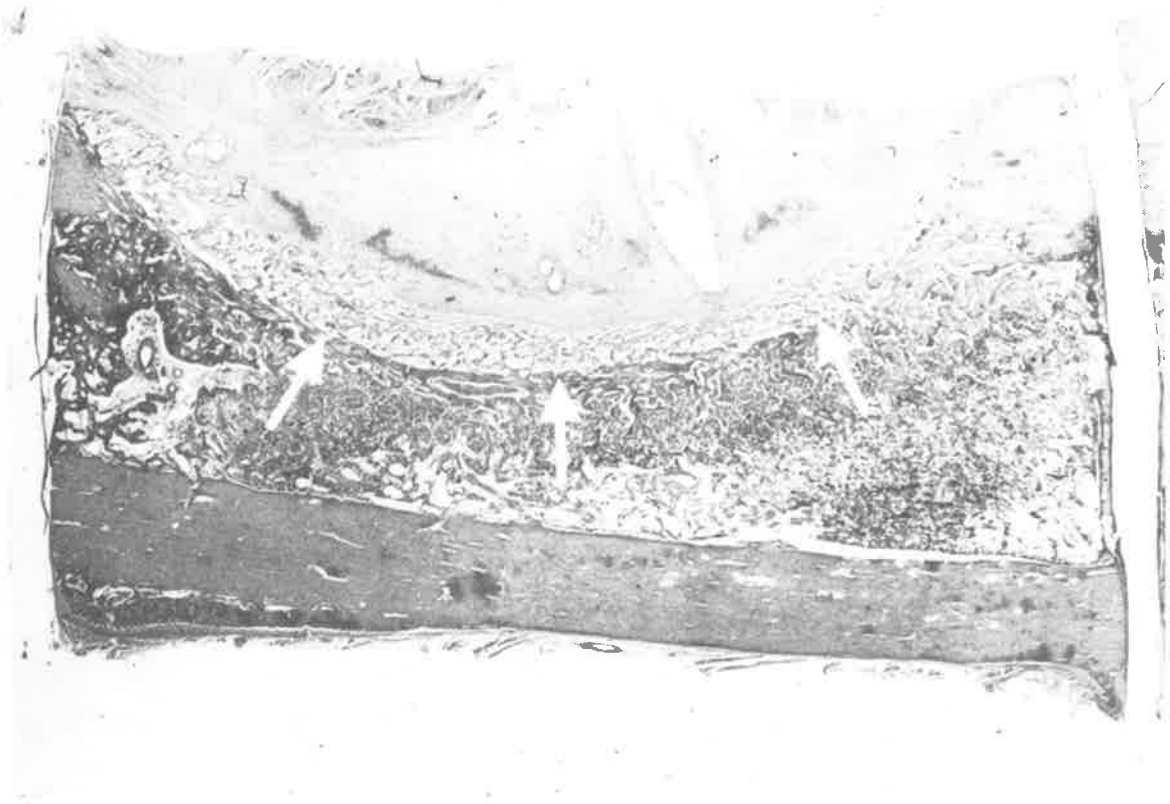

Fig. 6.15 3 weeks after an inactive stimulator, there is a small amount of new bone present in the depths of the defect. The remainder of the defect is filled with dense fibrous tissue. Note the large gap, wider at the top, left by the cathode, suggesting excessive movement of the cathode

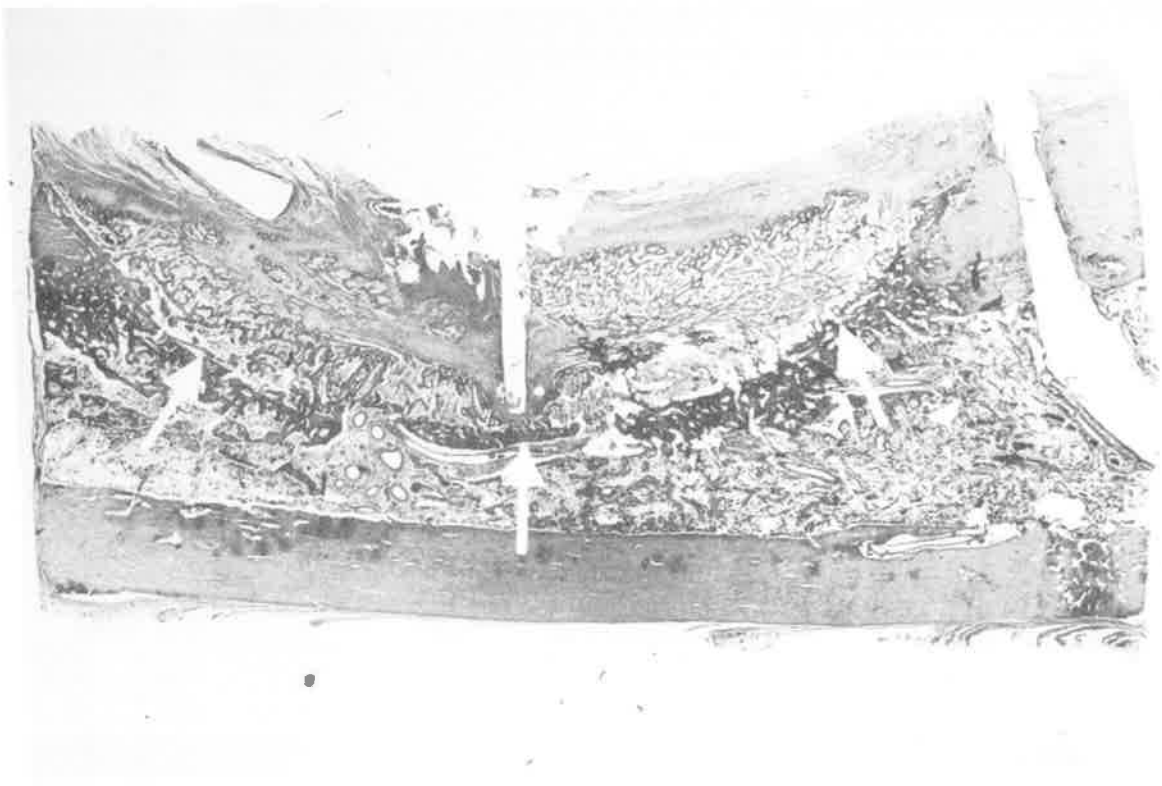

Fig. 6.16 Active stimulator, the outline of the defect is still obvious (arrows) but there is much more new bone in the defect area. Note the more appropriate size of the cathode defect compared with Fig. 6.15 and the surrounding layer of fibrous tissue

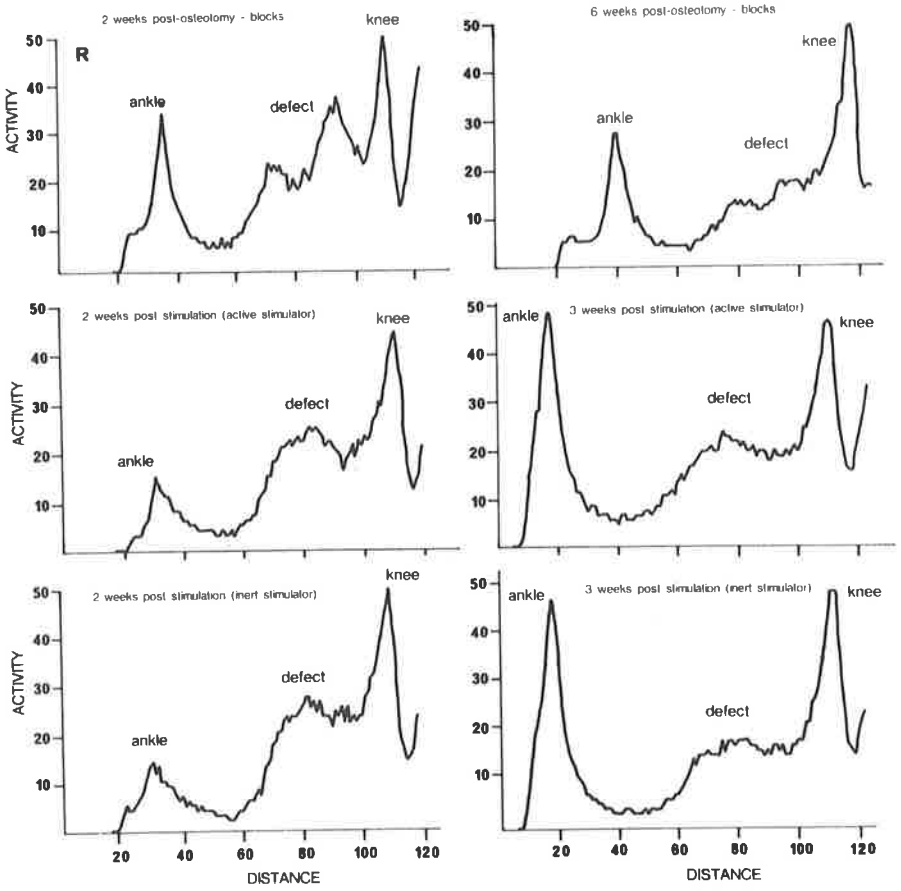

Fig. 6.17 Nuclear scan uptake displayed graphically

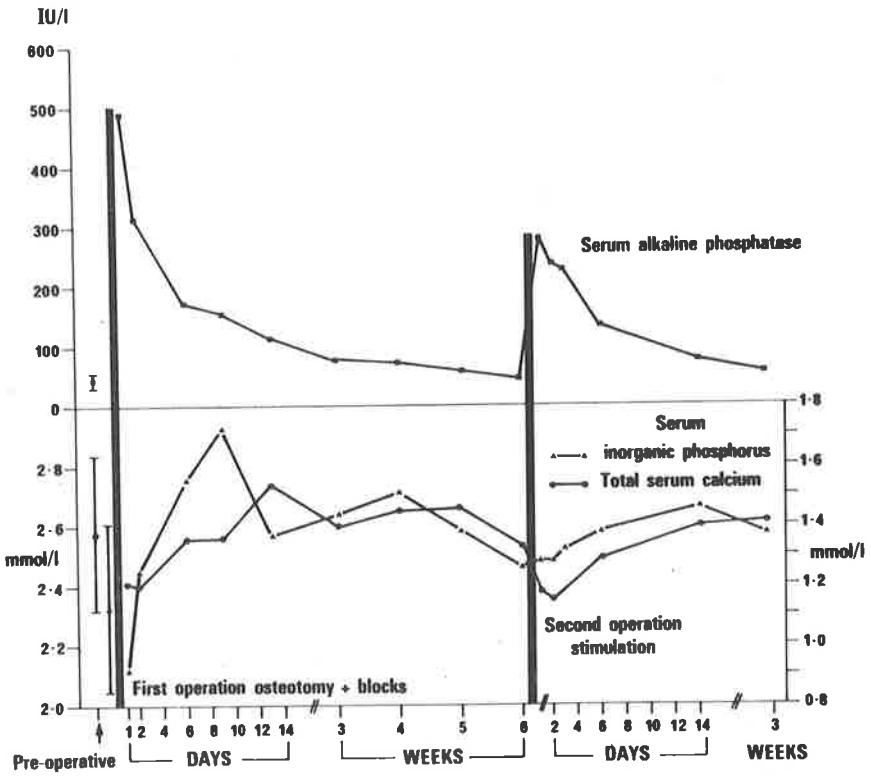

Fig. 6.18 Estimations of serum calcium, phosphorus and alkaline phosphatase

Eight of the original ten dogs received active and inactive electrical stimulation at the end of the sixth week and the defects were subsequently scanned after two and three weeks. There was a renewed peak of activity at the second week which subsided by the third week but there was no clear cut difference in the legs with either active or inactive stimulators. It was not possible to differentiate the actively stimulated site in greater than 50% of the animals. The increased activity of the intact posterior, medial and lateral cortices together with loss of the "trough" in the defect area made it impossible to evaluate whether the defect activity was from electrical stimulation or from natural bone healing. Consequently, this method of assessment was abandoned.

(iii) blood chemistry

After the defect was created, there was an elevation of the serum alkaline phosphatase and a fall in the levels of serum calcium and phosphorus, returning to normal by the fourth week. This indicated that reactive healing had largely settled by this time. After removal of the silastic blocks and insertion of the electrical stimulators, a similar sequence of events occurred again returning to normal some two weeks later (Fig. 6.18).

(iv) radiography

This was not used because the intact fibula obscured the defect created. The small size of the defect in the tibia made it impossible to evaluate any radiological changes and tomography was impracticable.

(v) conclusions

After assessment of this small pilot study by histological, nuclear scan and biochemical methods, it was considered that reactive bone healing had largely subsided after 4-6 weeks and this model represented sufficient delayed healing of bone to justify further evaluation. Further, the optimum time to detect histological differences appeared to be three weeks post-stimulation although no firm conclusions could be drawn from this finding because of the small numbers involved.

(b) Bone formation with different currents of electrical stimulation

As assessments of the model of delayed union by nuclear scan, chemical tests and radiography were unsatisfactory, the success or otherwise of the project depended on the histopathological assessments. The sections were analyzed subjectively to determine the relative amounts of new bone formed in the defect area of each section.

Certain histological features were apparent:-

1. the defect was clearly demarcated from normal bone and was filled with a mixture of bone and fibrous tissue in both stimulated and unstimulated specimens. In most cases, trabecular bone was formed from the floor of the defect (Fig. 6.16) while the new bone in the defect was of normal woven bone (Figs. 6.19, 6.20).
2. on the surface of the bone, there was fibrous reaction in relation to the cathode and its junction with the polyethylene coated titanium wire. There was always a thin layer of fibrous tissue around the cathode even when new bone had grown up to it. Fibrous tissue tended to be found maximally around the cathode plate (Figs. 6.15, 6.16).
3. the gap left by removal of the cathode plate was larger than the cathode and was often greater nearer the surface (Figs. 6.15, 6.16).

The numerical data from the quantitative assessment were independently analyzed and subjected to statistical analysis using the Wilcoxon-T-test.

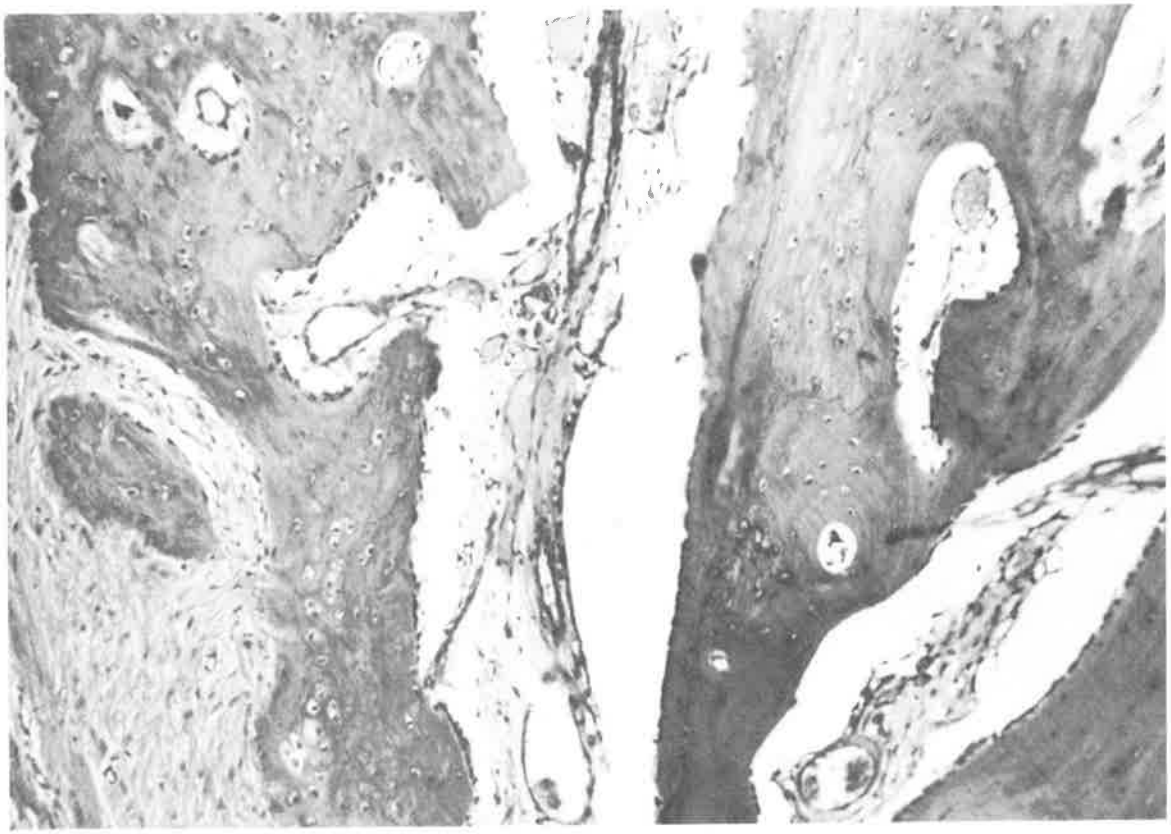

Fig. 6.19 Photomicrograph of same specimen as Fig. 6.16 taken from the junction zone at base of defect. Fairly mature medullary bone surrounding the defect is shown on the right separated by a small gap from immature new bone formed in the defect on the left (H & E)

Fig. 6.20 The same field as Fig. 6.19 photographed by polarised light. The medullary bone on the right shows birefringent lamellar bone while the new bone in the defect to the left is woven bone (H & E polarised light)

The results, once the code was revealed, indicated that with:-

1. 0.2 microamperes direct current
   there was a positive correlation of new bone formation with an active stimulator in 6 of the 7 dogs and a negative correlation in 1 dog.
   Calculations, however, did not indicate statistical significance.

   (n = 7, T_t = 23.5, p = no significant difference)

2. 2.0 microamperes direct current
   there was a positive correlation of increased bone formation in 4 of the 11 dogs with an active stimulator and a negative correlation in 7. Statistically, there was no significant difference in bone formation between the active and inactive stimulators at this current level.

   (n = 11, T_t = 22, p = no significant difference)

3. 20 microamperes direct current
   there was a positive correlation of increased bone formation with an active stimulator in 4 of 10 dogs and a negative correlation in 6 dogs. These results were not found to be statistically significant.

   (n = 10, T_t = 18, p = no significant difference)

A further computer assessment of new bone within a 0.5 cm radius on either side of the cathode was carried out as it has been our experience [203, 204, 205] that the cathode has a field of influence of about 5 mm from any point on the cathode. This failed to show any major difference of new bone formation with either of the three current levels being tested.

(c) Complications

A total of 49 dogs had the defect created initially - 27 mongrels and 22 beagles. Nineteen dogs were killed - because of fractures (16) and other causes (3). Clearly, a small defect in the femur or tibia was sufficient to interfere with the overall strength of the bone. The alternative of internal fixation with plates was not considered as this would interfere with the electrical field. After insertion of the electrical stimulators, no further complications occurred in the remaining 30 dogs - 16 mongrels and 14 beagles. At explant of the stimulators, discolouration of the anode - "anodizing" - was noted in approximately one third of the specimens. This occurred with the active stimulators only and was not associated with any abnormality or necrosis of the muscle around the anode.

4. DISCUSSION

The original delayed union model [203] allowed the area to be stimulated by direct current, and adequate nuclear scan and histological assessments of the tissue in the defect to be made. There were significant disadvantages of this model, in particular the inability to operate on both legs of the same animal at the same time with resultant difficulties in obtaining suitable controls.

An effort was made to find a simple model of delayed union of a long bone to allow evaluation of different current strengths. The histological, nuclear scan and serum biochemical tests in the preliminary trial suggested that bone activity had subsided by six weeks and that at least delayed healing of bone had occurred by this time. Further, the pilot study indicated that the maximum difference between normal unstimulated and stimulated bone healing occurred after three weeks stimulation.

In the main trial, the differences between bone healing with different currents were evaluated quantitatively to determine the proportion of new bone in the whole area of the defect and the results were integrated by computer and assessed for significance using the Wilcoxon-T-test. It is important to remember that previously [203] it had been shown that a current level of 20 microamperes produced significant new bone in a model of delayed union. This present study, however, was not able to detect any

difference in bone formation between the stimulated and non stimulated specimens let alone detect any difference between different current levels. Only at 0.2 microamperes direct current was there a consistent trend to a positive correlation between bone formation in the stimulated leg (6 of 7 animals) but in most cases, the differences in the amount of osteogenesis were small and the final statistical calculations showed no significant difference.

In all probability, the defect was too small and was surrounded by too great an area of normal bone forming tissues. As a result, bone healing probably occurred normally at a maximum rate once the silastic block had been removed and the model was therefore not as representative of delayed healing as had been hoped from the pilot study. This was probably due to insufficient numbers in the pilot study and, consequently, the model created was really more consistent with a fresh fracture. Removal of the silastic block might itself have induced sufficient stromal oedema to induce maximum osteogenic activity regardless of any superimposed electrical stimulation as it has been suggested [60] that stromal oedema may be the triggering event in electrical stimulation. This suggests that electrical stimulation is not effective when the normal osteogenic potential is still present. It follows

that if there was no detectable difference in osteogenesis between stimulated and unstimulated specimens, the model could not be expected to show finer differences between different current levels. In addition, the bulk of the electrode plate and the titanium cathode wire were subsequently shown to be associated with excessive movement of the cathode plate producing a large gap with fibrous tissue around the cathode.

The biochemical data, although of no value in assessing differences in healing of the defects, are of some interest. It has been reported previously by Masureik and Eriksson [189] that after electrical stimulation of a fresh fracture of the mandible the serum alkaline phosphatase level falls to a minimum at seven days, then rises to an elevated level at fourteen days and then returns to normal. They reported a corresponding rise in serum calcium and serum phosphorus followed by a lowered level at fourteen days and then a return to normal. These findings are directly opposite to the normal responses to trauma [124, 227, 236] where there is a rise in the serum alkaline phosphatase and a fall in the serum calcium and serum phosphorus in the first week after the fracture. In the present study, our findings are in agreement with the normally accepted responses to trauma.

5. SUMMARY

An effort has been made to find a simple model of delayed union of a long bone that could be used to evaluate the osteogenic effect of different current strengths. It is important that the optimum current strength be determined. Any such model should be able to produce a difference of new bone formation with an active and an inactive stimulator, particularly one using a 20 microamperes direct current. This did not happen here. This model was unsatisfactory probably because the defect was too small, was surrounded by normal bone, and excessive movement occurred at the cathode plate. The optimum range of electrical stimulation using a titanium cathode has not been established in this work. The accepted responses of serum alkaline phosphatase, serum calcium and serum phosphorus to trauma have been shown to be the same with electrical stimulation of bone formation.

CHAPTER 7

BONE FORMATION AND IMPEDANCE OF ELECTRICAL CURRENT FLOW

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BONE FORMATION AND IMPEDANCE OF ELECTRICAL CURRENT FLOW

1. INTRODUCTION

Although the clinical application of electrical stimulation of bone growth has become well established [136], the underlying mechanism is still not fully understood. The impedance of bone to the flow of electrical currents is a basic parameter in the design of circuits for the electrical stimulation of bone formation. Recently, several studies have investigated this parameter [50, 95, 231]. Bone has been electrically characterized as "... poorly conducting tubes filled with highly conducting vascularized marrow ..."[119]. However, a detailed electrical model must also account for streaming potentials [93, 100] piezoelectric effects [17, 48, 184, 257], cellular potentials [111], and the role of overlying nerves and muscles [36, 281]. Bone impedance is one of the important parameters determining the interaction of these factors.

Cortical bone impedance has been reported to be in the range of 2-5 x 10^5 ohm-cm [174, 255]. More recently, the four-point probe technique of semiconductor research was utilized to eliminate polarization effects and much lower values were obtained [86, 120, 121, 167, 231, 232]. Using this newer technique, investigators studying freshly excised sheep metatarsal reported cortical impedance of 7-12 x 10^3 ohm-cm, which was 4-8 times higher than bone marrow values [95].

It has been reported that during formation of bone around an electrically stimulated intramedullary stainless steel wire the impedance between anode and cathode increased by a third [112]. Although this rise could be related to bone formation, the experimental design did not allow precise localization of this change.

The prime objective of the present study was to test the hypothesis that, as a result of bone growth stimulation in the vicinity of a titanium cathode, there would be a temporal relationship between bone formation and the impedance to current flow to the cathode. If this hypothesis were correct, monitoring of the impedance from a cathode implanted in a non-united fracture could provide an estimation of the state of union, providing the clinician with a useful indicator. A second objective was to evaluate the use of titanium as a cathode using both quantitative and qualitative methods. A canine tibial delayed union model was established. Impedance monitoring, clinical, radionuclide, radiographic, light microscopic, and ultrastructural methods of analysis were employed.

2. MATERIALS AND METHODS

(a) Delayed union model

The canine delayed union model (Chapter 3) provided a standard tibial defect [203]. A system of rigid external fixation and cast protection was devised to

allow frequent impedance measurements from external leads without animal interference. The stability of the delayed union defects was maintained for the duration of the trial despite full weight-bearing on the legs.

Thirty-two skeletally mature colony-bred beagles under the routine care of a veterinary surgeon were utilized and maintained on a commercial pet food diet (Luv, Quaker Products, Australia). The hind leg to be operated on was randomly assigned and the identity of the dog maintained with ear tattooing.

After the dogs were anaesthetised, a 1.5 cm defect of the midshaft of the tibia was made and a cylinder of Silastic * was placed into the defect as a spacer. A Knowles pin was passed distally through a drill hole in the proximal tibia, down the intramedullary cavity into the distal tibia by passing it through the centre of the Silastic cylinder thereby anchoring it firmly by a lag-screw effect. Routine wound closure in layers was performed. No further fixation was required despite immediate weight-bearing by several dogs when they were allowed to run in open pens for eight weeks.

* Manufactured by Dow Corning Corp. Medical Products, U.S.A.

(b) Electrode implant and experimental design

The 30 dogs were randomly divided into three groups of 10 (Fig. 7.1). In each group, 5 dogs had electrically stimulated electrodes and 5 had unstimulated electrodes. The groups were monitored for 4, 8 and 12 weeks. Two additional dogs were stimulated and monitored for 12 weeks and were included in the assessment of this series. In all cases the surgeon did not know if the electrodes he was inserting were to be actively stimulated.

Titanium cathodes and platinum anodes were inserted 8 weeks after the creation of the delayed union defect. There was no evidence clinically of bone union in the defects. Bacteriological cultures of the defects were sterile, and every dog that entered the trial completed it.

The Knowles pin was exposed and removed through the previously made knee arthrotomy incision leaving the Silastic cylinder undisturbed.

Two pairs of threaded 316L stainless steel 2.38 mm diameter Steinmann pins were inserted percutaneously through the tibia, each pair at least 2 cm above and below the delayed union defect with a 45^{o} angle between the pins of each pair (Fig. 7.2). These transtibial pins were stabilized medially and laterally by longitudinal stainless steel rods bonded

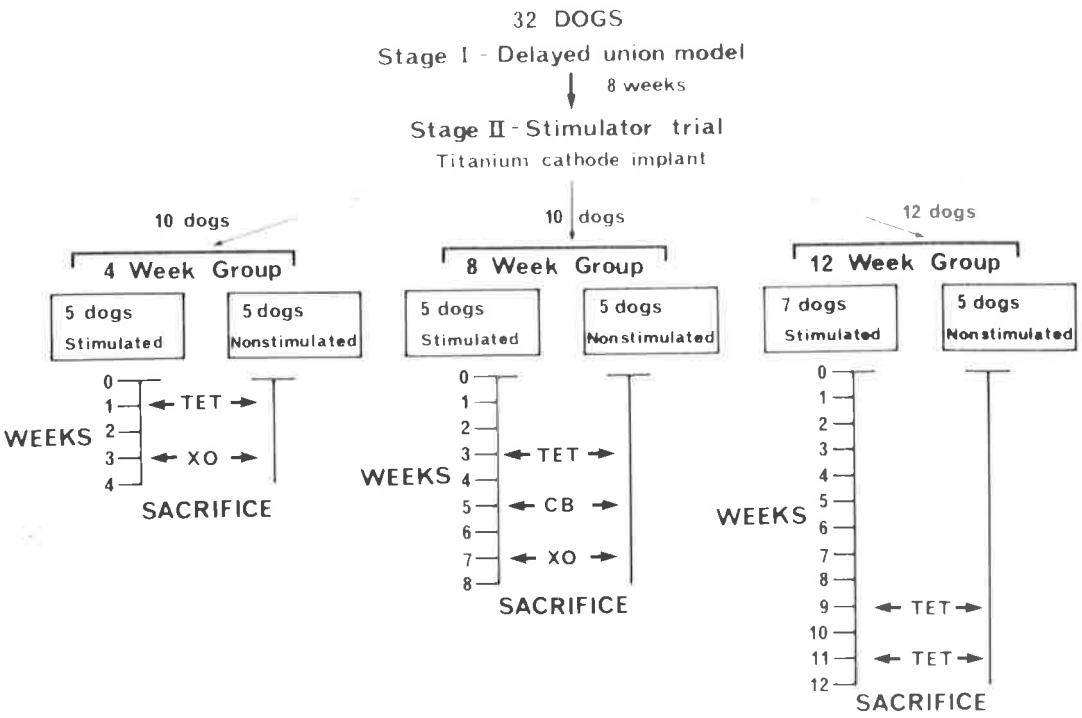


Fig. 7.1 Outline of the study
TET = Tetracycline, 50 mg/kg
XO = Xylenol orange, 50 mg/kg
CB = Calcium blue, 30 mg/kg

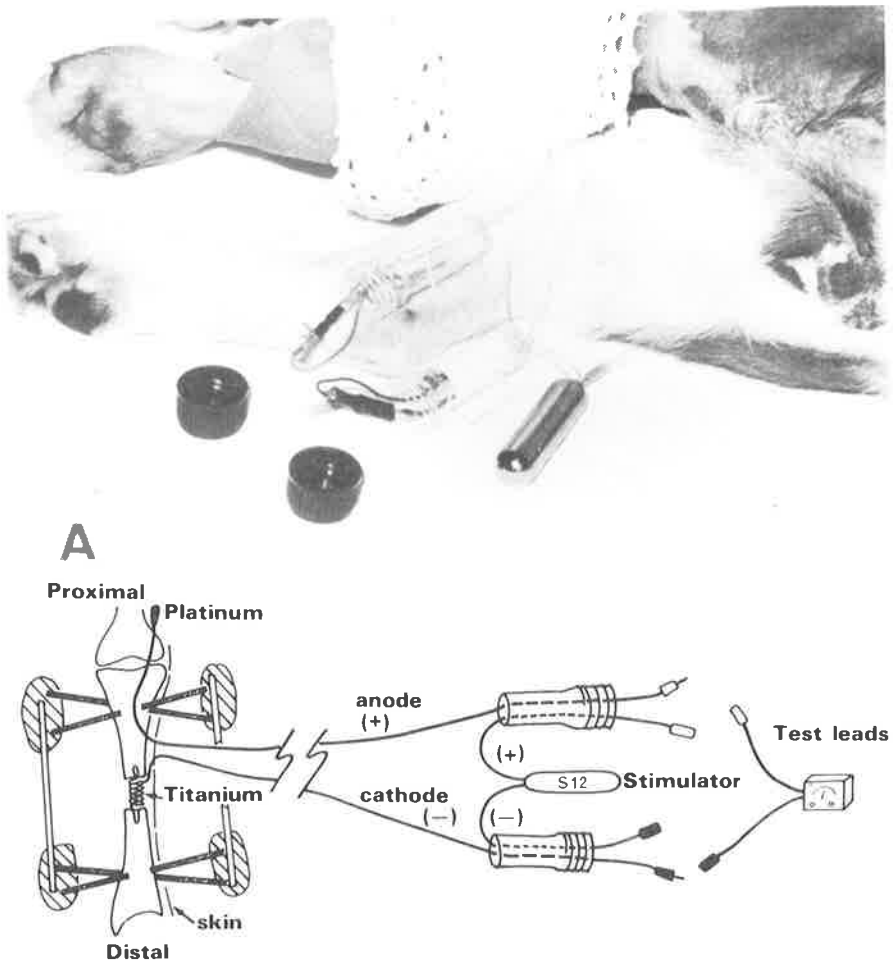


Fig. 7.2 (a) Stimulator, connectors, containers and leads about to be encased in protective cast

(b) Schematic outline of the experimental model

with bone cement * producing rigid external fixation. When the external fixation was completely stable, the delayed union site was exposed medially and the Silastic cylinder removed, leaving soft tissue covering the bone ends.

A coiled, triple-stranded titanium cathode wire was placed into the defect (Fig. 7.3). The platinum anode was placed subcutaneously in the thigh and both electrode leads were externalized laterally on the leg, carefully preserving the integrity of their insulation and ensuring that neither lead contacted the other or the fixation pins (Fig. 7.4). The woundswere closed in layers and a radiograph taken to ensure accurate position of the cathode.

Colour-coded male microconnectors were crimped on to the anode and cathode leads and placed into separate plastic watertight screw-top containers to prevent short circuits or poor connections. The appropriate lead from a 20 microampere constant current generator ** was also brought into the correct container and crimped on to a female micro-connector so that when the connectors were engaged this current flowed through the biologic circuit (Fig. 7.2).

* Polymethylmethacrylate: Paladur, Kulzer & Co. West Germany

** Telectronics Pty. Ltd., Sydney, Australia

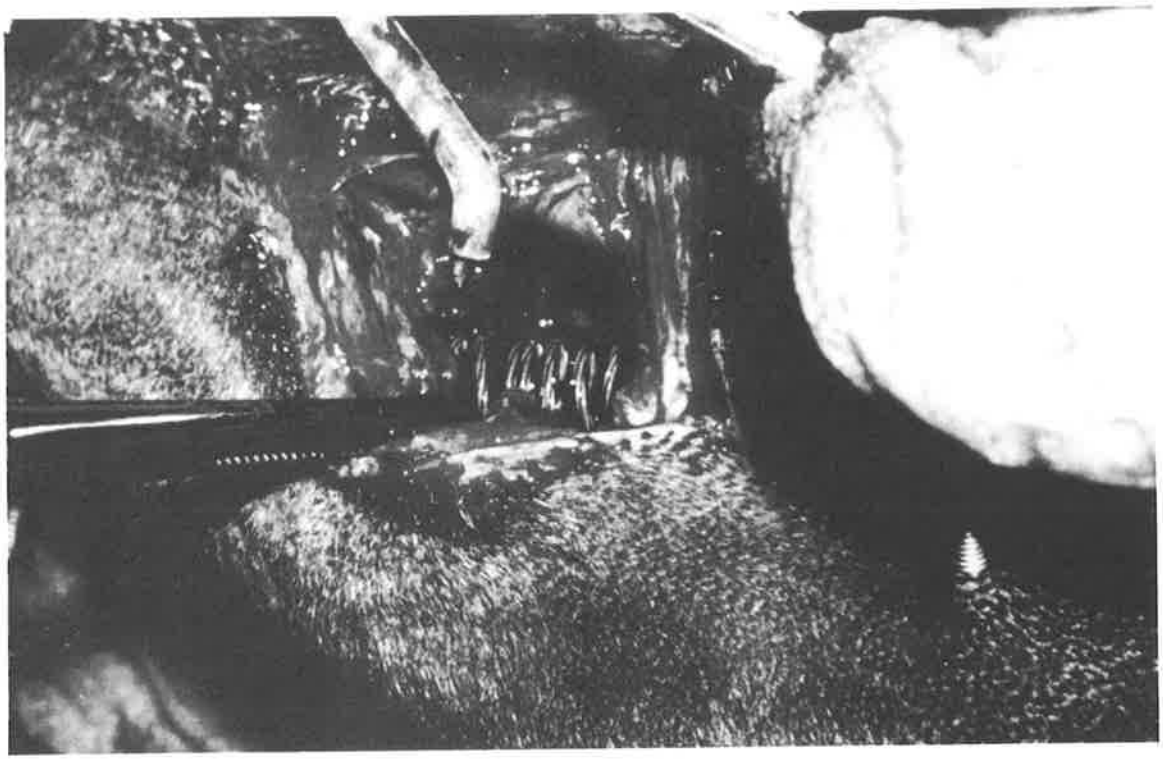


Fig. 7.3 Placing the titanium cathode across the delayed union defect in the tibia

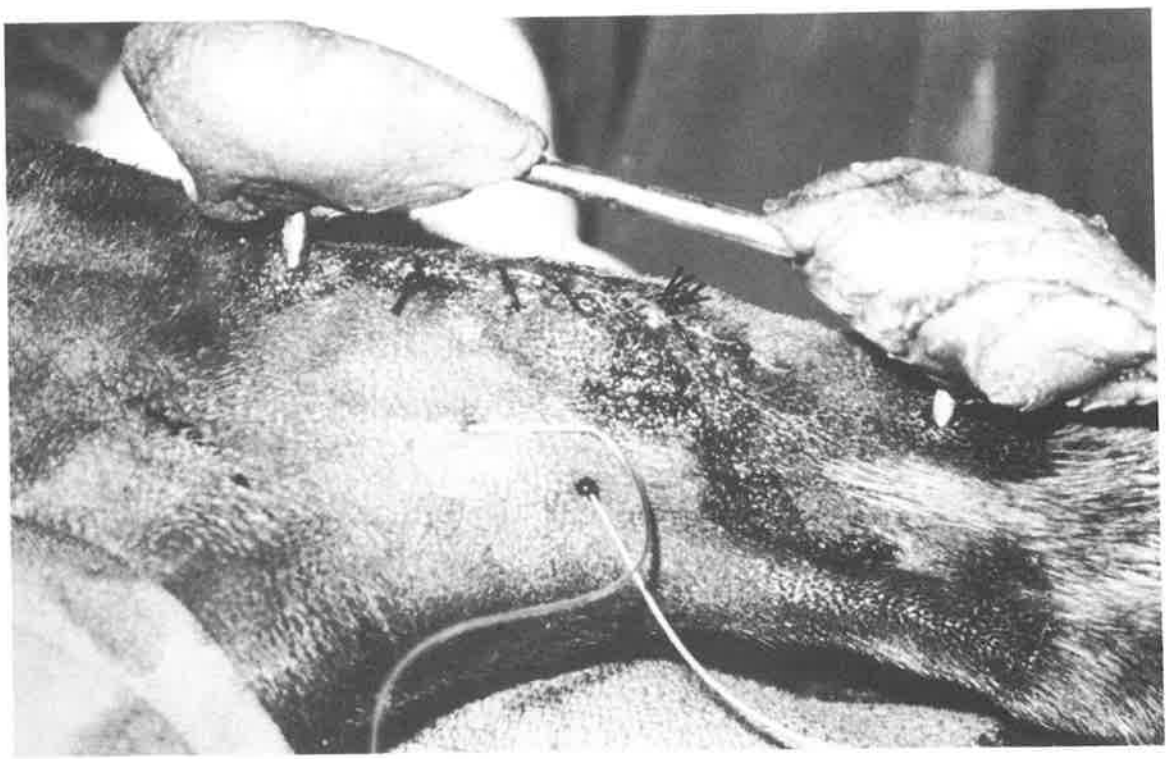


Fig. 7.4 The gap maintained with external fixation; while the platinum anode and the titanium cathode electrodes are brought through the skin

After testing the circuit, the constant current generator, connector containers, and externalized leads were encased in a Hexcelite * cast, a polymer composite cast, incorporating the external fixation and protecting them from animal interference. The hexcelite was reinforced with bone cement at strategic areas and the circuit again tested. Immediate use of the leg caused no complications or change in cathode position on interval radiographs.

At the conclusion of the four-, eight- and 12-week trials, technetium 99m methylene diphosphonate radionuclide scans were performed, the dogs were sacrificed, and the current generators were checked. The tibial specimen was dissected, with care being taken to avoid disturbance of the delayed union site. The contralateral tibia and eleventh rib were sampled as a means of standardization [4, 5, 6, 7].

(c) Method of impedance assessment

In order to characterize the impedance changes that might occur at the anode and cathode, the direct current resistance and the alternating current impedance at frequencies of 2, 10, 100, 1000,and 10,000 Hz were monitored. Anode/cathode, anode/reference, and cathode/reference measurements were obtained using a silver/silver-chloride electrode, coated with electrode gel **, as a reference electrode.

* Hexcel Medical Products, U.S.A.

** Telectronics Pty. Ltd., Sydney, Australia

The classic method of establishing the direct current resistance by passing a known current through the circuit, measuring the potential difference between electrodes, and calculating the resistance with Ohms law was used. It was accepted that the value of the potential difference would include the galvanic cell potentials generated at the platinum anode/tissue interface and the titanium cathode/tissue interface. It was assumed for this study that the galvanic cell potentials would be constant over the implant period and not affect the interpretation of changes in resistance. The electrode/tissue interface included a capacitive component which resulted in an exponential rise in potential when a constant direct current was applied. In the unstimulated electrodes this potential rise took up to 30 minutes to reach an equilibrium value during the direct current tests. The potential was, however, recorded precisely 30 seconds after application of the test direct current because changes in impedance rather than absolute values were being tested over the 12 week period. It was found that potential measurements at 30 seconds were directly proportional to the final steady state values and therefore could be used to detect any impedance changes. The stimulated electrodes were at the equilibrium potential prior to disconnection and returned to this value within seconds of the

test current application. Measurements from these electrodes were taken when the rate of potential change was less than 1 millivolt per second. The test direct current source delivered 20 microamperes and maintained 1% constancy over the range of 1000 to 100,000 ohms in load resistance. A Fluke model 8600A Digital Voltmeter * was used for the direct current measurements.

The alternating current impedance results were obtained by applying a 100 millivolt r.m.s. sine wave from a Wavetek model 180 function generator ** through a 5,000 ohm resistor in series with the electrodes. Potential drops across the 5,000 ohm resistor and the electrodes were measured using a 8600A Fluke Digital Voltmeter * for the 10, 100, 1000 and 10,000 Hz frequencies and a 8922A true r.m.s. Fluke Digital Voltmeter through a 0.1 μF direct current blocking capacitor for the 2 Hz measurements.

The alternating current flowing through the circuit was determined from the potential drop across the 5,000 ohm resistor and this value was used, together with the potential drop between the electrodes, to calculate the alternating current impedance between each electrode pair.

* Fluke Co., U.S.A.

** Wavetek, U.S.A.

The testing protocol consisted of daily impedance monitoring for the first week after electrode implant, every second or third day for the next seven weeks and weekly for the final four weeks. The dogs did not require sedation during these measurements.

(d) Radionuclide scanning

On the day of sacrifice each dog received a 5 mCi intravenous dose of technetium 99m diphosphonate and three hours later a Pho-gamma 4 scanning camera * was used to scan both the operated-on and contralateral normal leg for radionuclide activity. The results were processed by an in-line computer plotter which simultaneously provided a graph of activity along each leg (Fig. 7.5). The minimal activities at the delayed union sites were subjected to statistical analysis using the Student's-t-test [239].

(e) Clinical assessment

Immediately after dissection of the operated-on tibia, the same examiner made a clinical evaluation of resistance to bending in all specimens.

(f) Radiographic assessment

High resolution radiographs of each specimen were obtained with an X-ray cabinet ** and were subjected to two types of evaluation. First, the

* Nuclear Chicago, U.S.A.

** Hewlett-Packard Corporation, U.S.A.

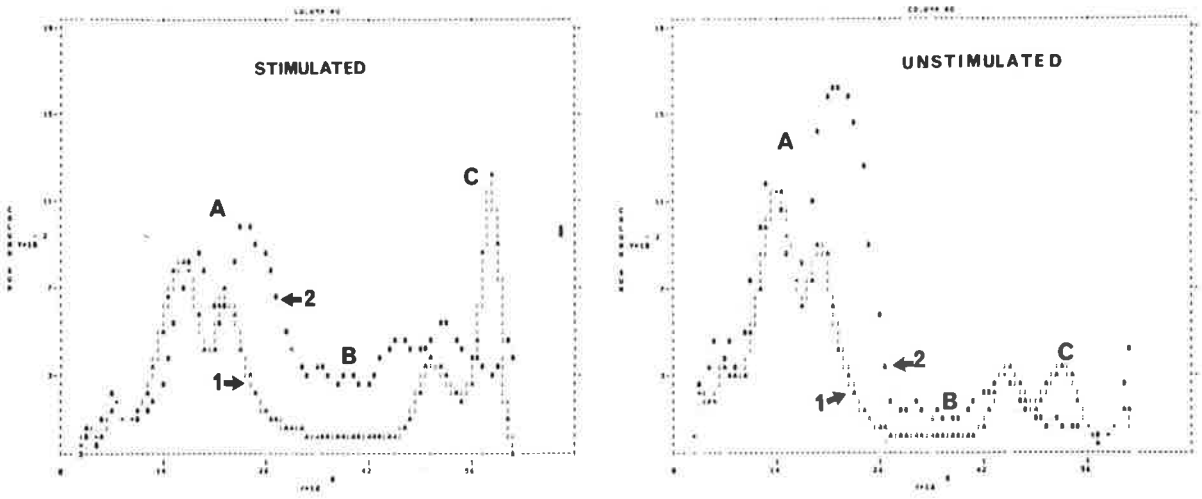


Fig. 7.5 Radionuclide scans of 12 weeks stimulated and unstimulated defects. A = knee activity; B = defect activity; C = ankle activity; 1 = normal leg curve; 2 = operated-on leg curve. Note increased activity in stimulated defect (B) relative to unstimulated defect (B)

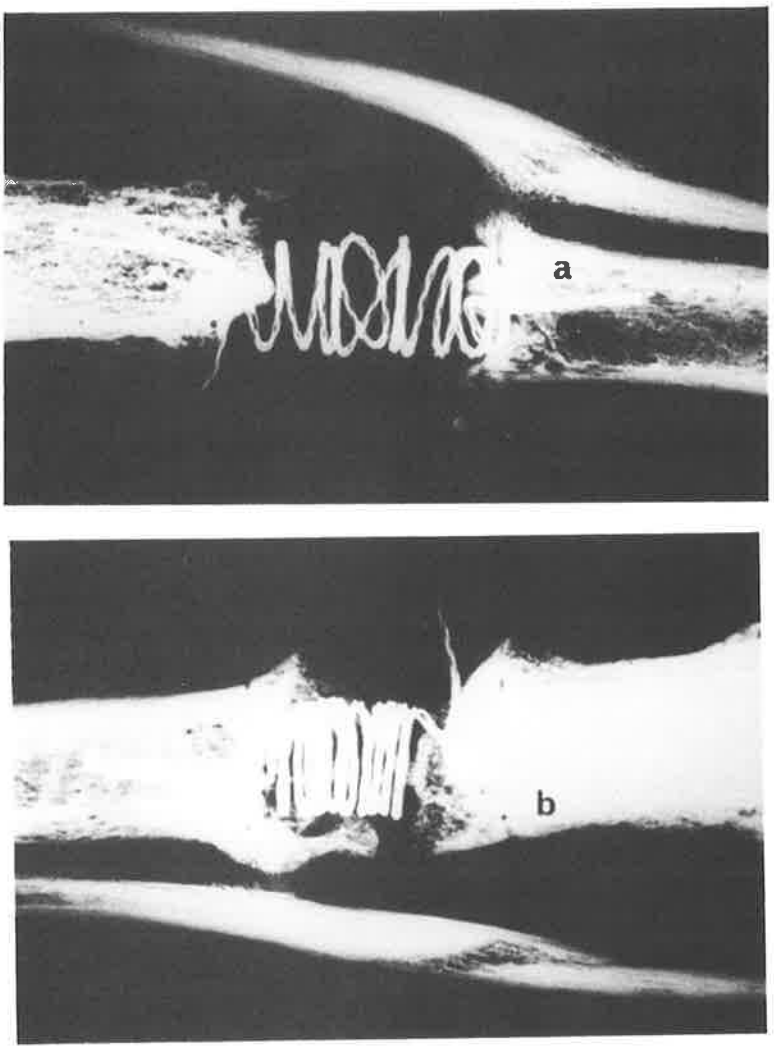


Fig. 7.6 Radiographs of 12 week specimens after (a) inactive (b) active stimulation. The ratio of the area of new bone formed to the area of the initial delayed union defect was measured

ratio of the area of new bone formed to the area of the initial delayed union defect was measured with a Digitizer * and this radiographic mineralization ratio was subjected to statistical analysis using the Student's-t-test. Second, the radiographs for the 12-week series were independently graded for new bone formation by four radiographs in a "blind" fashion using a four-point scale (Fig. 7.6). These data were subjected to statistical analysis using the chi^2 test [239]. Although interval radiographs were taken they did not show sufficient detail to allow quantitative evaluation of formed bone.

(g) Histological assessment

During the study, the dogs underwent intravital bone labelling on a predetermined schedule with xylenol orange ** 50 mg/kg [212], calcein blue 30 mg/kg ** [211], or tetracycline 50 mg/kg *** [230, 260, 268] (Fig. 7.1). Bone specimens were placed in absolute ethanol and, when fixed, were sliced longitudinally into slabs three millimetres in thickness using a rotating diamond saw. These slabs were examined under a dissecting microscope and the fragments of titanium cathode were gently extracted (Fig. 7.7). After specimens were embedded into

* Hewlett-Packard Corporation, U.S.A.

** Sigma Chemical Co., St. Louis, U.S.A.

*** Reverin, Hoechst Australia Ltd.

Fig. 7.7 3 mm longitudinal sections were cut and the fragments of the titanium cathode were gently extracted under a dissecting microscope

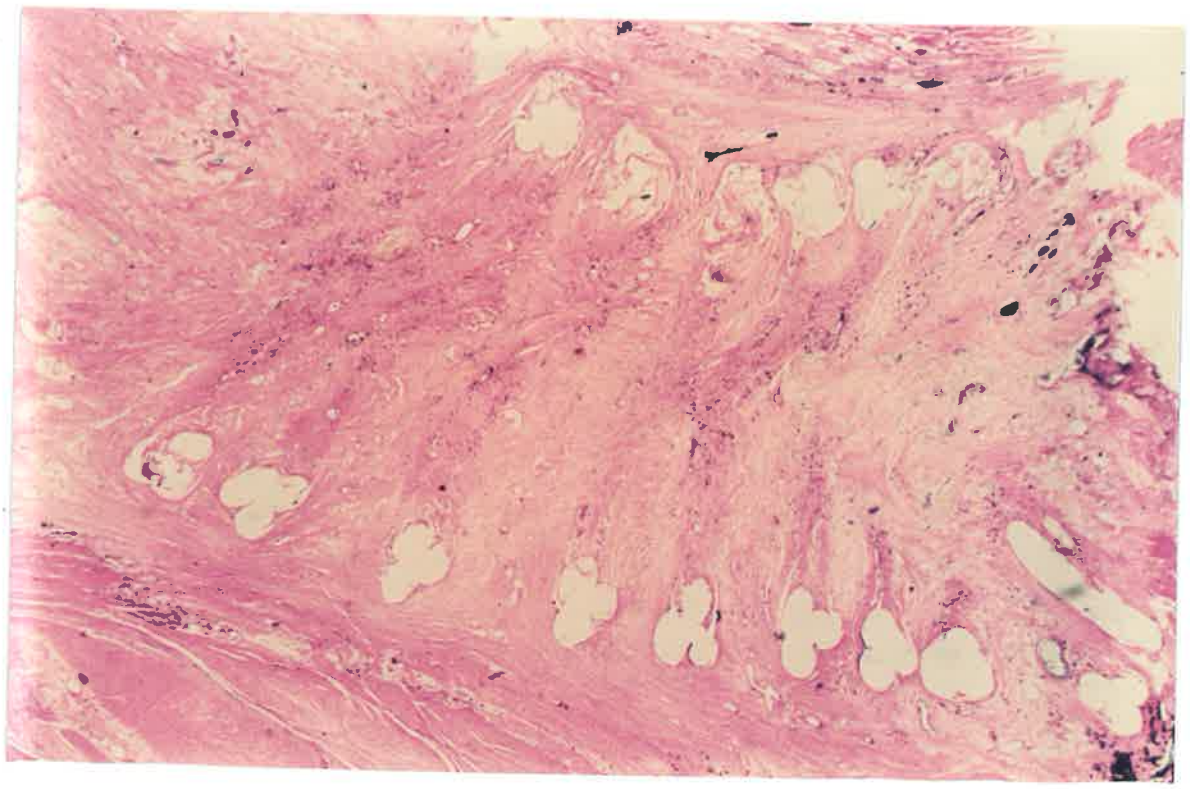


Fig. 7.8 Section stained with Hemotoxylin and Eosin showing where the cathode wires have been removed without disturbing the histological details of the fibrous tissue

epoxy resin, sections were cut with a motorized sledge microtome * and stained with hematoxylin/eosin (Fig. 7.8) or silver/van Gieson which stained mineralized bone black and unmineralized osteoid pink. Unstained sections were examined by ultraviolet light microscopy to evaluate the intravital bone labelling. The ratio of the mineralized area in the defect to the area of the initial delayed union defect was computed from the sections stained with silver/van Gieson (Fig. 7.9) using a Quantimet image analyser ** [103] and this histological mineralization ratio was subjected to statistical analysis using the Student's-t-test. Selected sections were examined for ultrastructural detail with an electron microscope *** including energy dispersive analysis to identify metallic tissue deposits [98, 288].

3. RESULTS

(a) Impedance

The graphs of the potentials between anode/cathode, cathode/reference, and anode/reference versus time are shown for direct current, 10 Hz and 10 kHz test frequencies (Fig. 7.10). For clarity, only the first seven days are plotted

* R. Jung, West Germany

** Cambridge Instruments, U.K.

*** Jem 100C, Jeol Co. Ltd., Japan

Fig. 7.9 Section stained with silver/van Gieson stain where mineralized bone stains black and unmineralized osteoid tissue stains pink

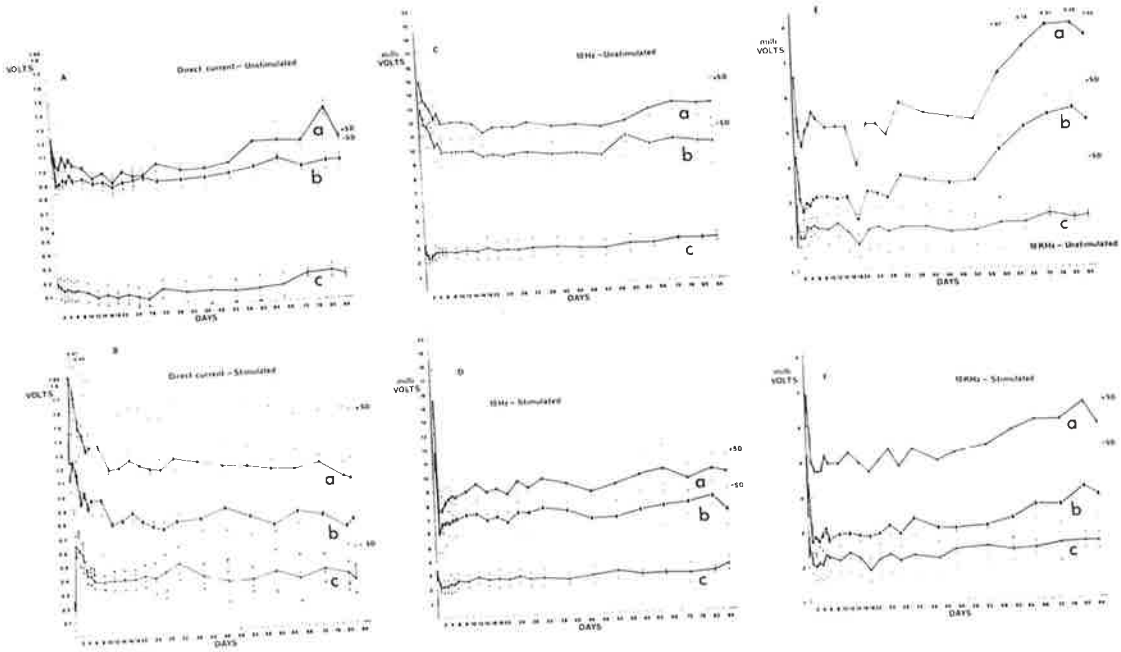


Fig. 7.10 Graphs of potential plotted against time for direct current tests (A = unstimulated, B = stimulated); 10 Hz tests (C = unstimulated, D = stimulated); 10 kHz tests (E = unstimulated, F = stimulated). Standard deviations are shown in brackets (a = anode/cathode, b = anode/reference, c = cathode/reference)

individually; three-day averages are provided for the next three weeks and weekly averages are given for the final eight weeks. The graphs for 2, 100 and 1000 Hz were similar to those for direct current, 10 Hz, and 10 kHz. Since impedance is directly related to the potential between electrodes and since the test conditions remained constant, the graphs of impedance versus time are qualitatively similar to the graphs of potential versus time.

For all electrode pairs and at all frequencies the graphs showed an initial high potential at implant which then fell to a lower, stable value. The cathode/reference potentials for all frequencies essentially remained at this steady state value even in the one defect which united. The anode/reference values remained at this stable level until about the seventh week, after which there was a steady rise in the 10 Hz and an even greater rise in the 10 kHz values. This indicated a rise in the impedance between the anode and reference electrodes. The anode/cathode curve was essentially the sum of the anode/reference and the cathode/reference curves because the same reference electrode was used. The anode/cathode curve shape thus resembled the anode/reference curve because the cathode/reference curve remained stable.

The initial peak potentials and the average of the steady state potentials over the final ten weeks of the trial for direct current, 10 Hz, and 10 kHz test frequencies and each electrode pair are shown (Table I). Except for the direct current measurements, there were no significant differences between the stimulated and unstimulated electrode pairs. The difference in the direct current measurements was due to the recording of the unstimulated electrode potentials before equilibrium was reached with the test direct current. Chart recordings of potential versus time during the direct current tests revealed that the stimulated and unstimulated curves would have been quantitatively and qualitatively similar if the unstimulated electrodes had been allowed to reach equilibrium before the values were taken. The high value of the calculated direct current resistance relative to the alternating current impedance was a result of electrode interface effects, including the galvanic cell potentials.

(b) Radionuclide

Radionuclide scans show peaks of activity at the knee and ankle joints with less uptake in the area of the defect (Fig. 7.5). At 12 weeks the defect activity was greater in the stimulated defects ($p \leq 0.05$). At four and eight weeks there was no significant difference.

(c) Clinical

Manual evaluation at sacrifice revealed that at 12 weeks 5 out of 7 stimulated defects showed obvious clinical stability and all but one of the unstimulated defects were unstable. None of the four- or eight-week defects showed obvious stability with the exception of the one unstimulated eight week defect that had united.

(d) Radiography

In all of the specimens some bone formation occurred at the margins of the defect. In some, this had the appearance of a typical fracture callus, while in others the predominant bone growth was within the defect. The radiographic mineralization ratios at four, eight and 12 weeks are shown (Fig. 7.11). At 12 weeks, the ratio of new bone area was greater for the stimulated defects ($p<0.05$). There was no significant difference between the groups at four and eight weeks.

The radiologist's assessment confirmed that, at 12 weeks, there was more bone in the stimulated defects ($p<0.05$). In the unstimulated specimens the regions proximal and distal to the defect appeared less dense than in the stimulated specimens.

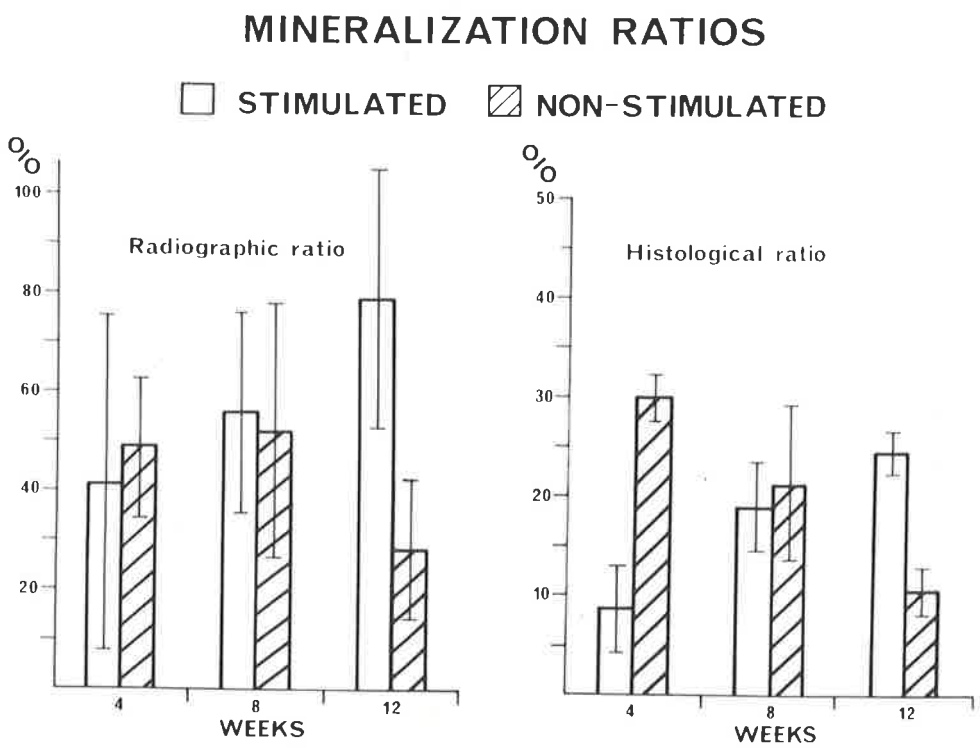


Fig. 7.11 Radiographic and histologic mineralization ratios. Graphs shows progressive increase in mineralized bone in stimulated animals and decline in nonstimulated animals

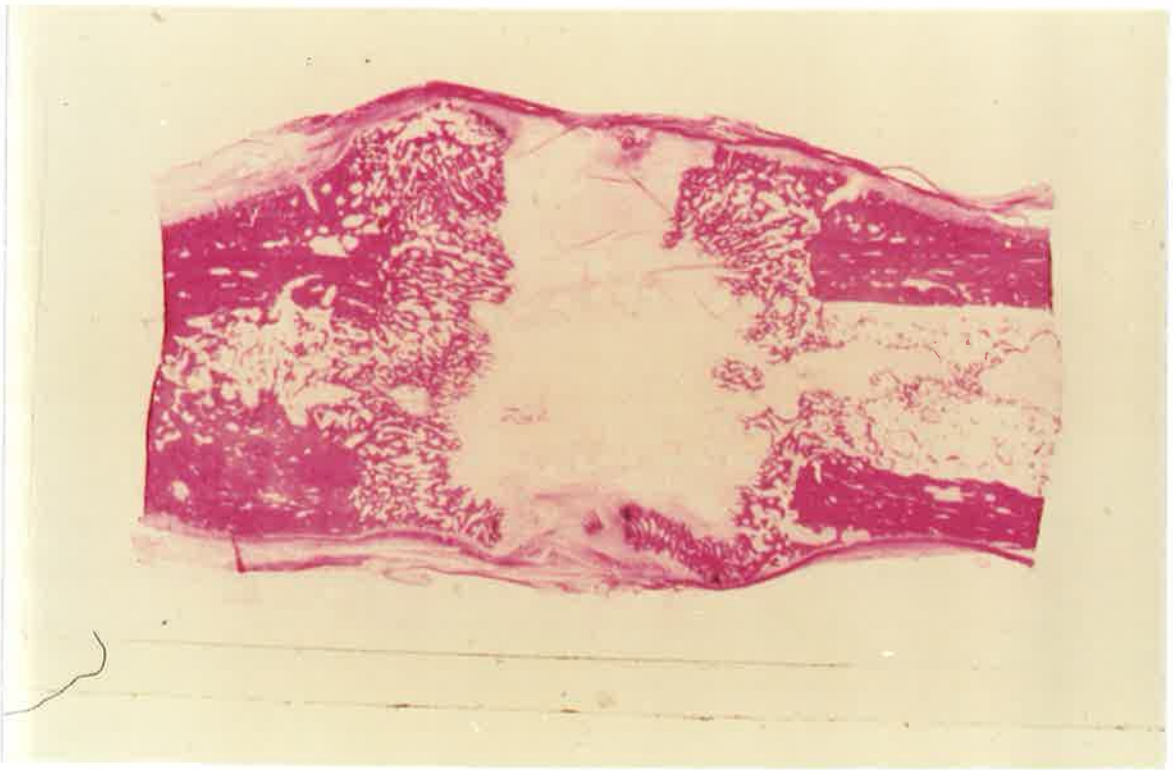


Fig. 7.12 4 weeks (unstimulated); osteogenesis is present at the bone/fibrous tissue interface

(e) Histological

(i) Light microscopy - general features

Light microscopy of undecalcified thin sections allowed detailed inspection of the defect site and adjacent bone ends. With the exception of the one defect which had united and remodelled at eight weeks, in all specimens bone union of the defect had not occurred. In these 31 specimens the defect was filled with mature, heavily collagenized fibrous tissue oriented generally along the long axis of the bone. Immediately surrounding the cathode wire there was a circumferential arrangement of collagen fibres and viable fibrous tissue. There was no evidence of necrosis, inflammation or infection. The holes left by removal of the cathode wire fragments were clearly defined and showed that the removal process had not disturbed the surrounding histologic features.

A striking feature of both stimulated and unstimulated sections was the presence of black particulate material located within macrophages immediately around the cathode wire, since clumps of discrete particles were identified by energy dispersive analysis as titanium.

There was no tendency for bone to form directly around the cathode wire either in stimulated or in unstimulated specimens. Where a portion of the

cathode wire was incorporated in bone, a viable fibrous tissue layer was interposed between the wire and bone.

(ii) Light microscopy - specific findings

Four weeks: Examination of the four week unstimulated specimens revealed active bone formation, predominantly by ossification of cartilage as in fracture callus. At the bone/fibrous tissue interface in the defect and within the intramedullary cavity, osteogenesis was noted (Fig. 7.12). Fluorescent microscopy confirmed this bone-forming activity with widespread deposition of fluorochromes.

Although bone formation was seen also in the four-week stimulated specimens, there was a striking lack of the cartilagenous callus response seen in the unstimulated group. Cortical, intramedullary, and bone/fibrous tissue interface osteogenesis was noted (Fig. 7.13). Fluorescent microscopy disclosed that the external callus in the stimulated group exhibited less active bone formation than did the callus in the unstimulated group.

Eight weeks: In the eight-week unstimulated group, the callus response noted previously was not seen. The external callus, cortical bone, and intramedullary trabeculae revealed widespread osteoclastic resorption and the bone/fibrous tissue interface in the defect appeared sharply defined with little or no evidence of bone formation.

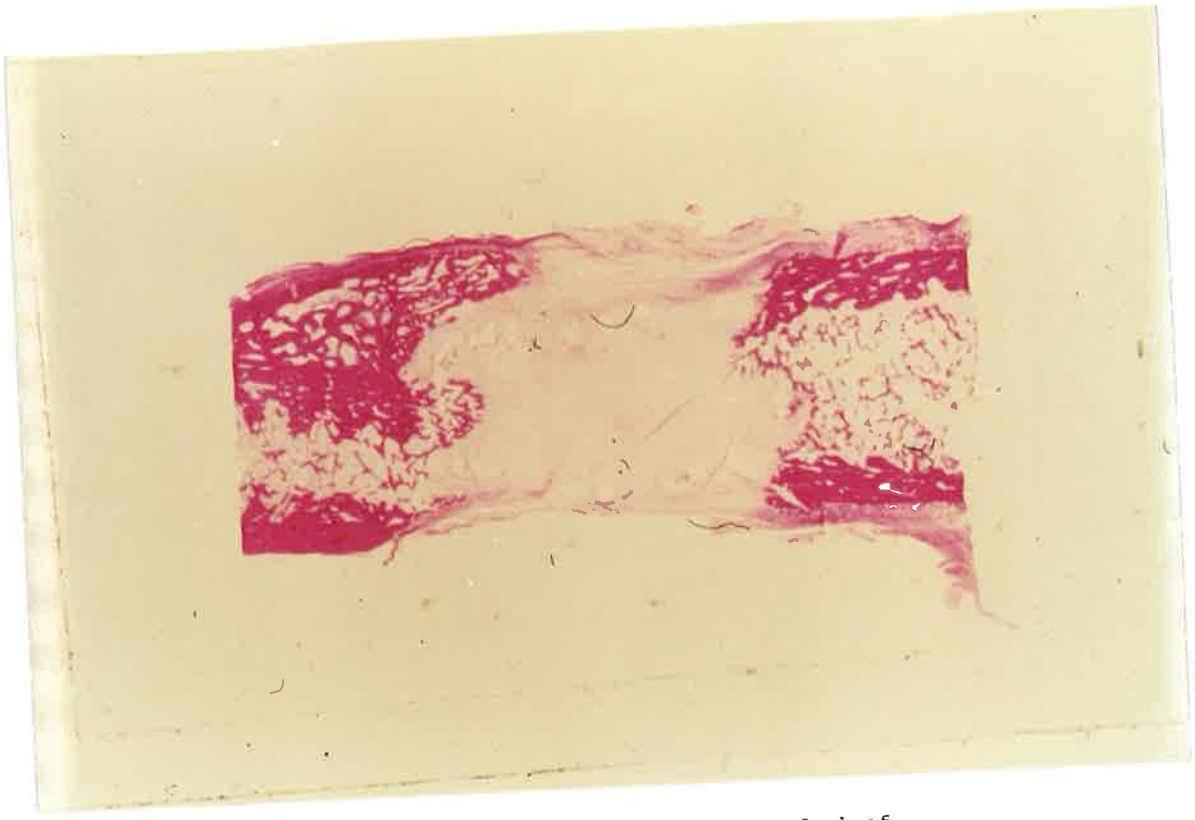


Fig. 7.13 4 weeks (stimulated); a striking lack of cartilaginous callus response. Fluorescent microscopy showed less active bone formation also

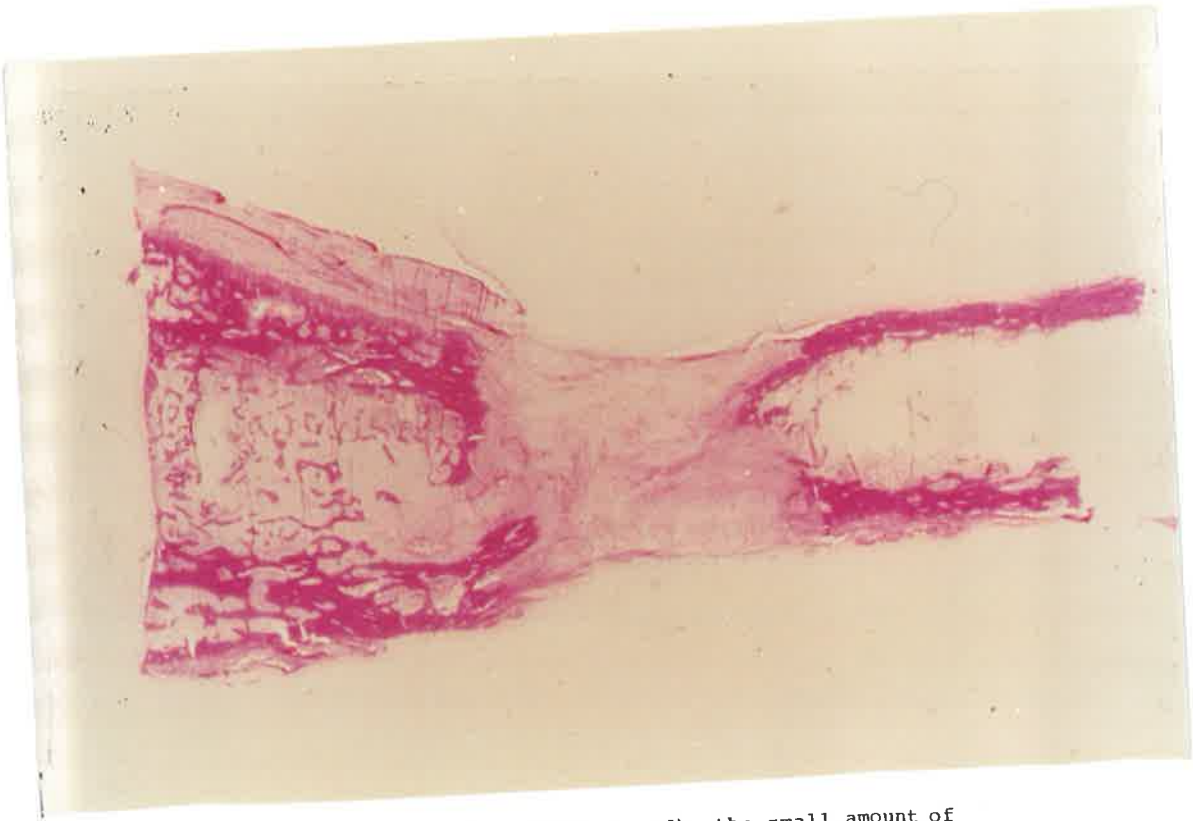


Fig. 7.14 12 weeks (unstimulated); the small amount of external callus was undergoing active resorption

Fluorescent microscopy confirmed resorption of bone previously formed and reduced bone-forming activity at the interface.

By contrast, the stimulated group revealed active bone formation on most surfaces. The bone/fibrous tissue interface in the defect continued to form bone and the cortical and intramedullary trabeculae were lined with osteoblasts. Fluorescent light microscopy confirmed this continued osteogenesis and disclosed little evidence of resorption.

Twelve weeks: In the 12-week unstimulated group a continuation of the previously noted remodelling process was evident. The small amount of external callus was undergoing active resorption, and osteoclastic lacunae lined the cortical bone and remaining trabecular surfaces (Fig. 7.14). These changes correlated well with the decreased bone density observed on the radiographic studies. The bone/fibrous tissue interface was sharp and without evidence of osteoblastic activity (Fig. 7.15). Fluorescent microscopy confirmed this general lack of osteogenesis and showed the bone/fibrous tissue interface to be dormant by an almost complete lack of fluorochrome deposition.

The stimulated 12-week sections revealed a marked contrast to the unstimulated group (Fig. 7.16) with active osteoblastic activity in all areas, including sites distant from the defect (Fig. 7.17). On

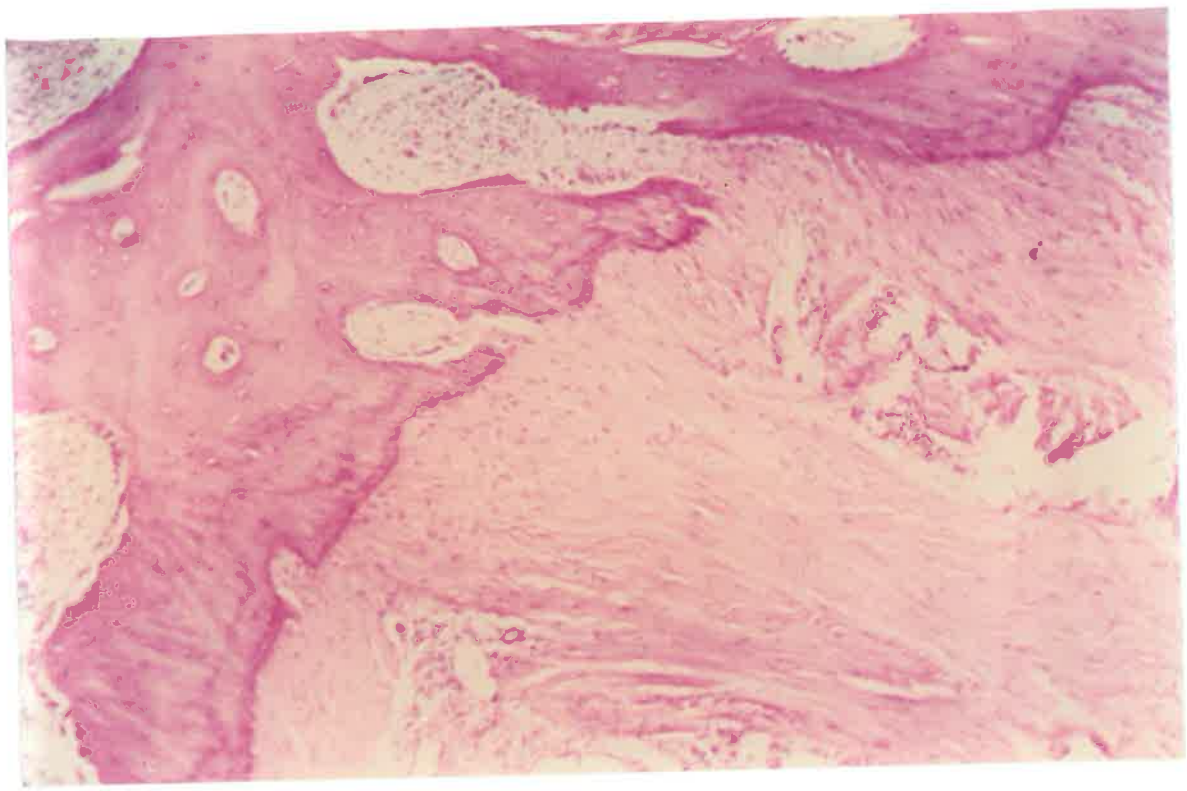


Fig. 7.15 12 weeks (unstimulated); the bone/fibrous tissue interface showed a general lack of osteogenesis and little osteoblastic activity

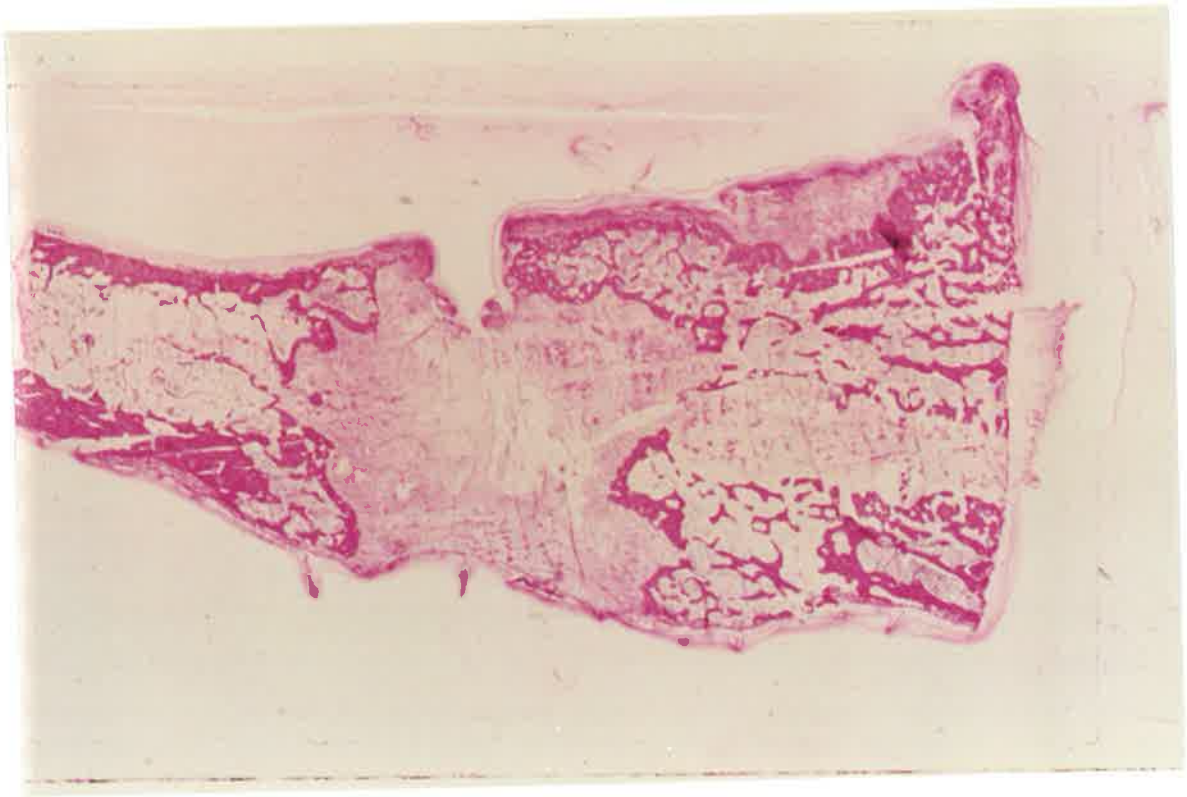


Fig. 7.16 12 weeks (stimulated); active osteoblastic activity in all areas

fluorescent microscopy the bone/fibrous tissue interface in the defect revealed continued osteoblastic activity (Fig. 7.18). Trabecular surfaces and haversian systems demonstrated similar active bone accretion (Fig. 7.19).

In summary, the light microscopic assessment revealed that unstimulated defects showed an early fracture-like callus response which had been followed by widespread osteoclastic resorption and minimal continued osteogenesis at 12 weeks. In contrast, the stimulated defects revealed a poor callus-like response initially but this was followed by progressive bone growth throughout the 12-week trial.

(iii) Quantimet analysis of histological sections

The histological mineralization ratio of silver/van Gieson stained sections obtained by Quantimet analysis for the four-, eight- and 12 weeks series are shown in Figure 7.11. At twelve weeks there was more bone in the stimulated group ($p \leq 0.05$). At eight weeks the groups were not statistically different. At four weeks there was more bone ($p \leq 0.05$) in the unstimulated group. The Quantimet results correlated well with results obtained from the hematoxylin stained sections and from fluorescent microscopy.

(iv) Ultrastructural analysis

Energy dispersive analysis revealed the particulate material seen on light microscopy to be titanium of the same composition as a sample of cathode wire analysed by the same technique.

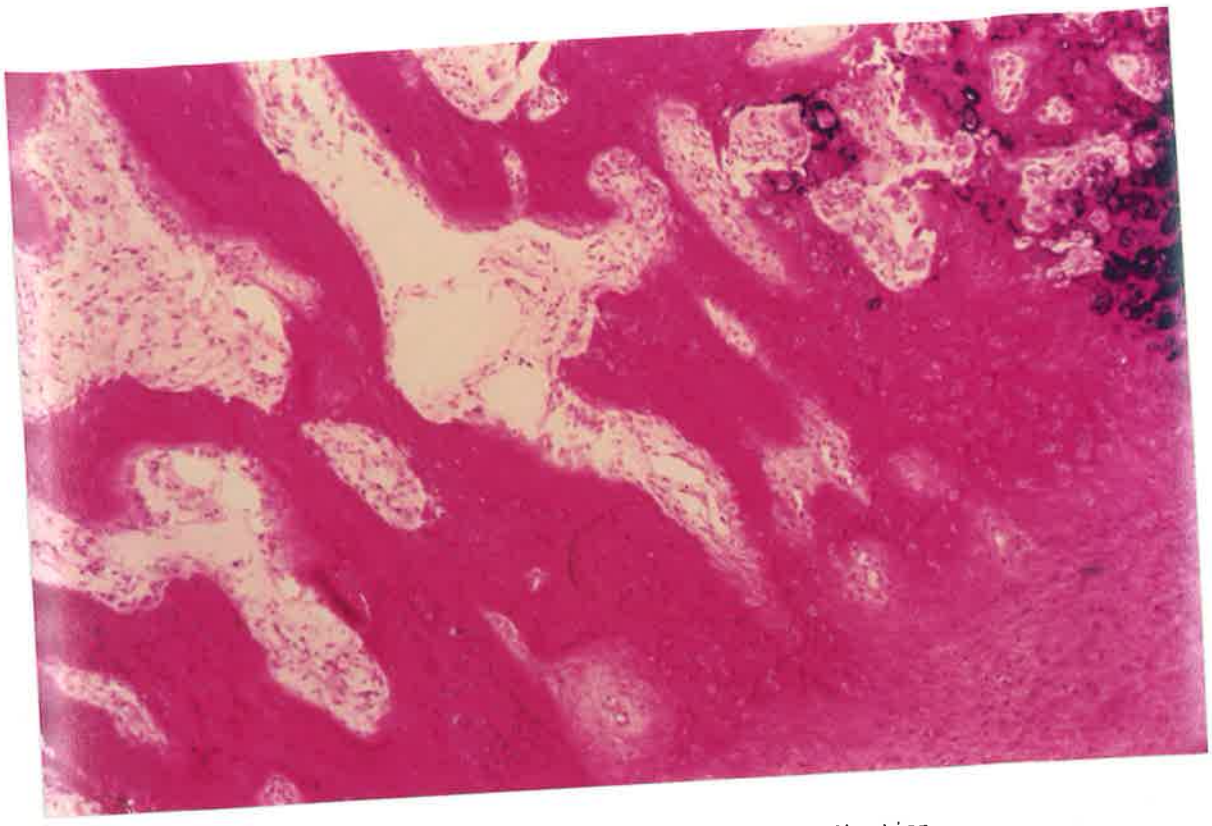


Fig. 7.17 12 weeks (stimulated); a high magnification showing fibrous tissue (right) active bone (left) and (top right), active cartilage formation - marked osteogenesis

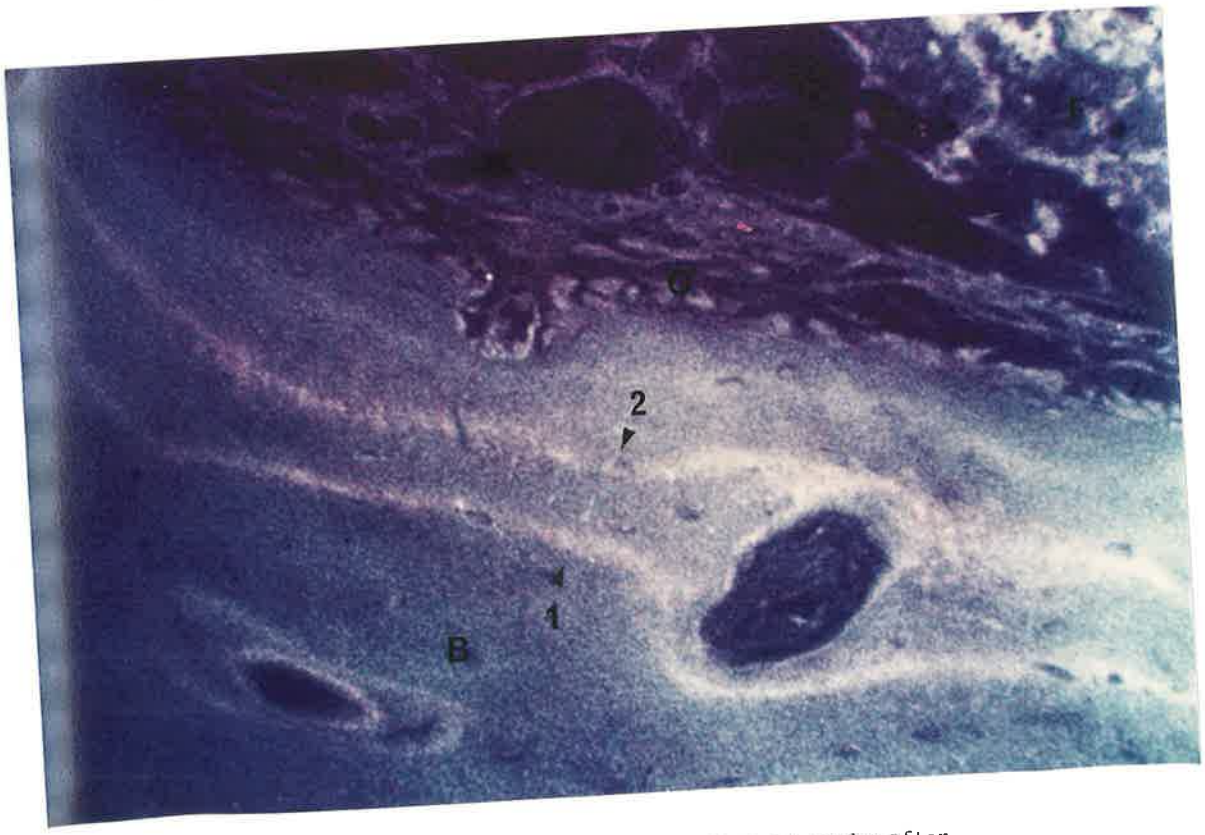


Fig. 7.18 Bone/fibrous tissue interface 12 weeks after insertion of an electrically active titanium cathode. Fluorescent microscopy with Tetracycline shows active osteoblastic formation (O) and separate fluorescent bands (1 and 2)

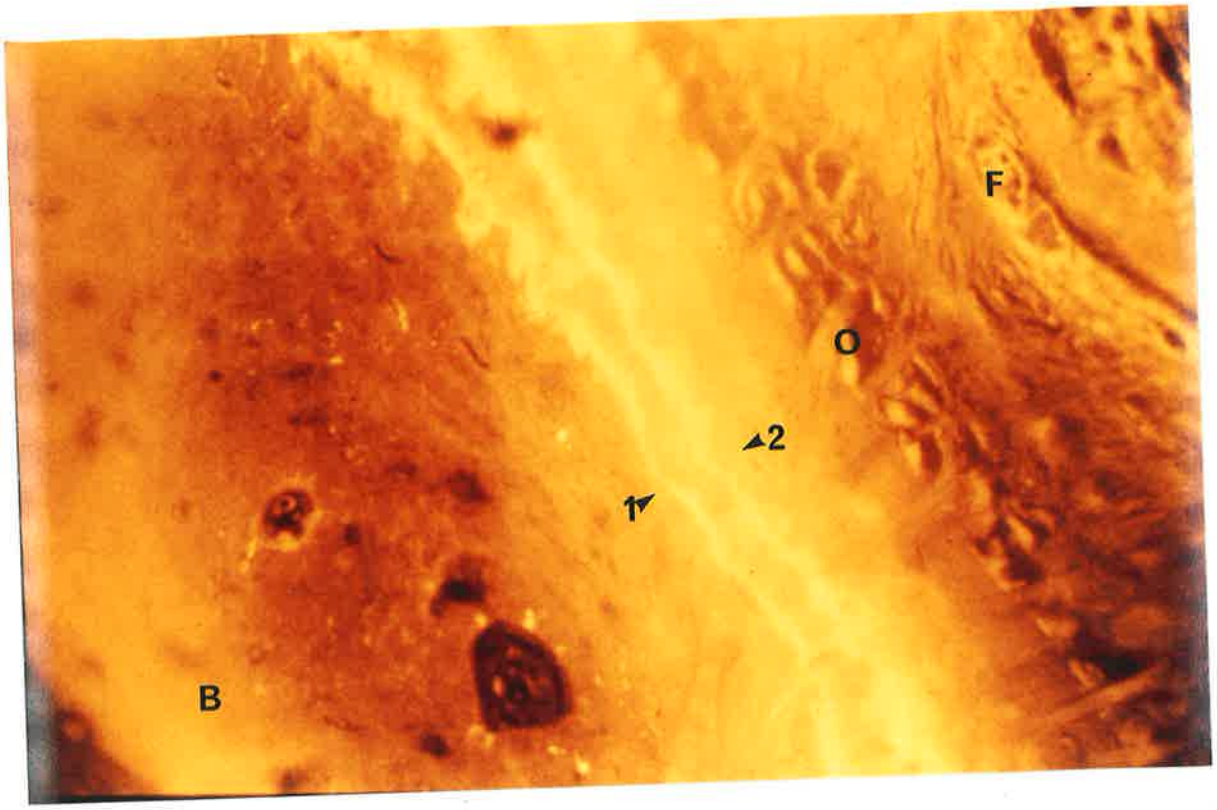


Fig. 7.19 Medium power photomicrograph of bone/fibrous tissue interface 12 weeks after insertion of an electrically active titanium cathode. Xylenol orange had been given one and three weeks before sacrifice. Fluorescent microscopy showed separate fluorescent bands (1 and 2) indicating Xylenol orange incorporation into bone (B) and osteogenesis at the interface with the fibrous tissue (F). Osteoblasts (O) line the interface surface

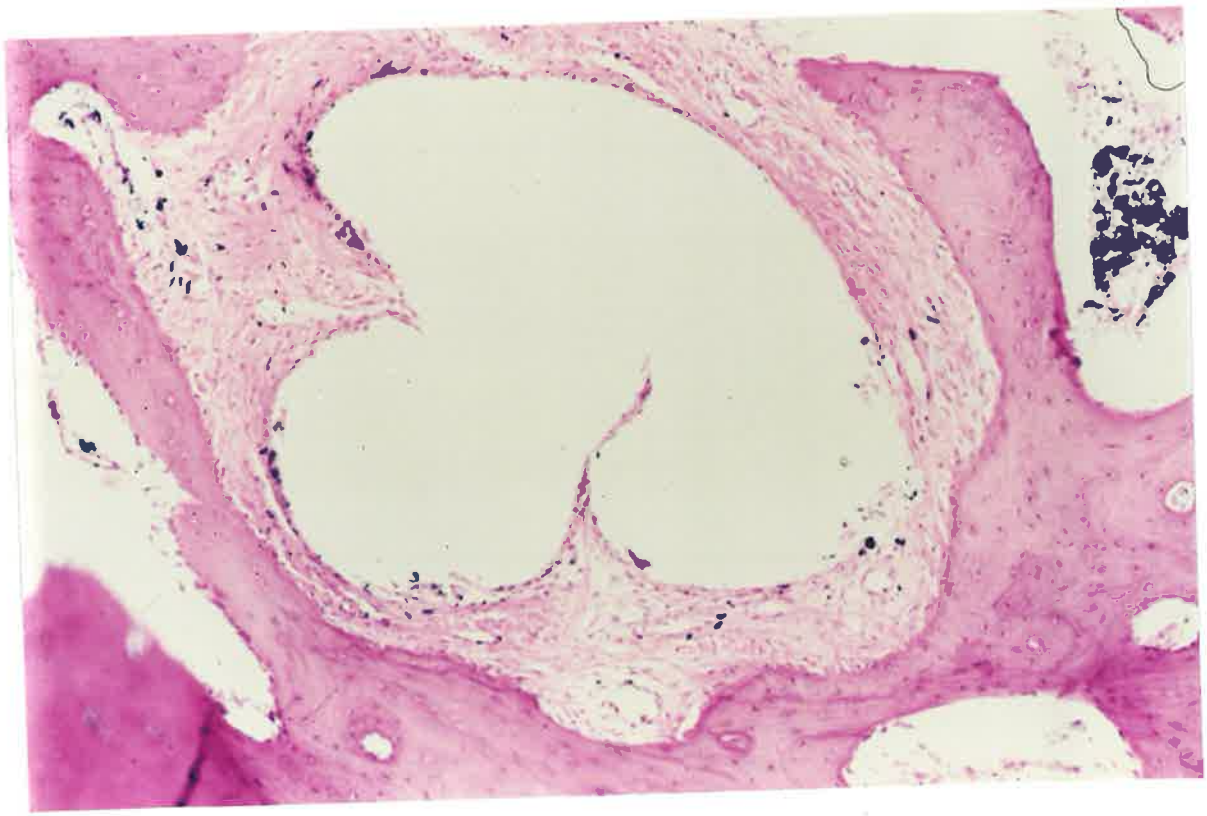


Fig. 7.20 12 weeks (stimulated); a layer of viable non-osseous tissue was present around the titanium cathode. The black dots were established by electronmicroscopy using Energy Dispersive Analysis X-rays as titanium and they were not surrounded by any inflammation

4. DISCUSSION

The findings from the monitoring of impedance between implanted electrodes in a delayed union model over 12 weeks of implant did not support the hypothesis of a temporal relationship between electrically induced bone formation and the impedance to current flow to the cathode. However, in this model, the findings clearly support the use of titanium as a cathode material for electrical stimulation of bone growth.

The histological examination at 12 weeks indicated that without intervention this model would progress to nonunion. One defect united and remodelled in eight weeks possibly because of a failure to remove all of the periosteum when the model was created. This specimen was included in the analysis of the eight-week group.

The direct current measurements electrically reflect the characteristics of the electrode/tissue interface. The post-implant behaviour of both the titanium cathodes and the platinum anodes, represented by the cathode/reference and anode/reference values respectively, were similar for the stimulated and unstimulated circuits under direct current test conditions. The initial high potential difference or resistance at implant fell to a lower, stable value reflecting the normal maturation of the electrodes in their *in vivo* environment. Similar maturation curves have been shown for titanium and several of its alloys during *in vitro* testing [138]. This *in vivo*

maturation probably represented alterations in the oxide coating which gives titanium its resistance to corrosion [242, 282].

The resistance to which the constant current circuitry responds is represented by the direct current anode/cathode curve, and the stability of this curve after maturation suggested that, in this model, a self-regulating constant current generator may not be needed. This is not necessarily true for other electrode systems and other stimulation conditions.

The 10 kHz measurements reflect the electrode geometric area and the tissue impedance in the region of the electrodes and since both stimulated and unstimulated cathode/reference values remained essentially stable, the tissue impedance around the cathodes did not change appreciably. The impedance calculated from the steady state potential values at 10 kHz for the cathode/reference electrodes was approximately 300 ohms which was close to the values found for other soft tissues [50, 119]. This indicated that a high impedance region did not surround the cathode.

The consistent finding of a viable non-osseous tissue layer around the cathode supported the impedance measurement data (Fig. 7.20). Friedenberg also noted a non-osseous tissue layer around the cathode in several specimens in which an impedance rise between anode/cathode occurred [112]. This suggested the anode to be the location for the impedance rise in this study, since the tissue layer around

the cathode probably would provide a low impedance pathway. The increase in anode/cathode impedance in the present study was due to increased impedance at the anode as shown by the late rise in the anode/reference curve at 10 kHz. Tissue response to anodic reaction products was a possible reason for this change; however, the most striking rise occurred at the unstimulated anodes. The reason for this rise was not obvious. However, for this study, insulated stainless steel leads were crimped on to platinum anodes to provide greater lead length. Tissue fluid leakage into the joint was suggested by discolouration of the wire in several unstimulated anodes and may have occurred, resulting in stainless steel corrosion. This may have caused tissue irritation which may have contributed to the impedance rise [62].

The difference between the direct current and the 10 kHz anode/reference curves was due to the relatively large direct current resistance at the electrode/tissue interface which obscured the relatively small increase in the 10 kHz impedance. The anode/reference impedance rise in the stimulated defects at 10 kHz, although small, does suggest that even platinum under anodic stimulation may cause tissue reaction. Spadaro & Becker [248] have recently shown that for various metallic electrodes a current density above 5 microamperes per mm^2 can be associated with tissue necrosis. In the present study, the anodes operated at a current density of approximately

0.4 microamperes/mm^2 and the cathodes operated at approximately 0.33 microamperes/mm^2.

The clinical stability to bending did not correlate with union in this model inasmuch as none of the defects showing stability at 12 weeks were united. However, there appears to be some degree of correlation of stability with electrical stimulation. The longitudinal arrangement of collagen fibres has been associated with increased tensile strength [271]. This pattern was seen in both stimulated and unstimulated specimens and suggests that other factors, such as the increased calcification in the stimulated specimens or total collagen content (which was not measured in this study) were important in determining defect stability.

Activity in the radionuclide scans using technetium 99m methylene diphosphonate tracer has been correlated with active bone formation [116] and localization of the tracer to newly formed matrix [153, 233]. The increased radionuclide activity in the stimulated defects correlated well with histological evidence of increased bone formation and quantitatively could be useful in the evaluation of progress of bone union during clinical electrical stimulation. The inability of the radionuclide scan to differentiate between stimulated and unstimulated groups at four weeks was due to increased tracer uptake in the fibula adjacent to the defect as a result of trauma during the operative procedures in the region.

The radiographs did not disclose differentiation between these groups at four weeks despite clear histological evidence of larger bone area in the unstimulated specimens. In this connection, it is known that the woven bone of callus, which stains as though it is fully mineralized, varies in its degree of calcification and therefore in radiopacity. By contrast, mature lamellar bone is always fully mineralized, and the predominance of lamellar bone formation induced by electrical stimulation would explain the increased radiographic density seen in the 12-week stimulated specimens.

The small amount of external callus on histological examination in the four-week stimulated specimens compared with the unstimulated group suggested that electrical stimulation could have changed the response to cathode insertion. It is possible that the localized callus-like woven bone response in unstimulated defects is diverted by stimulation to a more generalized osteoblastic response with the production of predominantly lamellar bone. This second type of response resembles normal remodelling in compressively stressed bone with thickening of trabeculae and cortical structures. These histological findings support the theory that an electrical signal underlies Wolff's law of bone remodelling to stress, which is further supported by the finding of endosteal bone formation at sites both proximal and distal to the stimulated defect. The smaller amount of callus formation in the stimulated group of this model suggests that the use of electrical stimulation in acute fractures

should be investigated. However, its use in delayed union or for reactivating a nonunion is strongly supported, especially by the increased osteogenesis at the stimulated bone/fibrous tissue interfaces disclosed by fluorescent microscopy.

Although bone formation has been noted in close apposition to intramedullary stainless steel cathodes,[112] this localization was not noted for the titanium cathodes in this study (Fig. 7.20). It has been suggested that cathodically stimulated stainless steel and titanium induce bone formation by different mechanisms which may account for this histological difference [187]. Variation in ability to reduce oxygen for different metals under cathodic stimulation has been proposed to explain this finding [248]. These differences could possibly allow more precise localization of bone growth with electrical stimulation by selection of cathode material.

The titanium found in the tissue surrounding the cathode appeared similar on light microscopy to the type B particles noted by Meachim and Williams [190]. Theories have been proposed to explain the release of titanium despite its lack of corrosion in the body [242], and the benign nature of these deposits has been commented on by several authors [210, 259, 282, 283]. It is significant that there appeared to be no difference between stimulated and unstimulated groups in the amount or location of titanium observed.

5. SUMMARY

The impedance to current flow to an electrically stimulated cathode did not change appreciably over a 12-week measurement period and did not support the hypothesis of a temporal relationship between bone formation and impedance to current flow in the region of the cathode.

The use of an electrically stimulated titanium cathode at a current density of 0.33 microamperes/mm^2 in this model of canine delayed union resulted in significant bone formation when analysed by quantitative and qualitative methods.

Sequential quantitative radionuclide scanning correlated well with the histological appearance of bone formation and was a sensitive indicator of electrically induced osteogenesis.

TABLE I

	Peak Potentials	Peak Resistance/ Impedance	Steady State Potential	Steady State Resistance/ Impedance
DIRECT CURRENT - STIMULATED CIRCUITS				
Anode to Cathode	1.85 volts	92,500 OHMS	1.16 volts	58,000 OHMS
Cathode to Reference	0.64 "	31,500 "	0.38 "	19,000 "
Anode to Reference	1.24 "	61,000 "	0.78 "	39,000 "
DIRECT CURRENT - UNSTIMULATED CIRCUITS				
Anode to Cathode	1.22 "	61,000 "	1.02 "	51,000 "
Cathode to Reference	0.19 "	8,700 "	0.10 "	5,000 "
Anode to Reference	1.14 "	52,300 "	0.92 "	46,000 "
ALTERNATING CURRENT 10 Hz - STIMULATED CIRCUITS				
Anode to Cathode	15.5 millivolts	761 "	9.35 millivolts	467 "
Cathode to Reference	3.03 "	150 "	2.71 "	135 "
Anode to Reference	11.8 "	580 "	7.24 "	362 "
ALTERNATING CURRENT 10 Hz - UNSTIMULATED CIRCUITS				
Anode to Cathode	15.3 "	760 "	11.7 "	587 "
Cathode to Reference	2.88 "	143 "	2.74 "	137 "
Anode to Reference	12.92 "	642 "	9.63 "	483 "
ALTERNATING CURRENT 10 kHz - STIMULATED CIRCUITS				
Anode to Cathode	6.91 "	346 "	5.46 "	274 "
Cathode to Reference	2.58 "	129 "	2.35 "	118 "
Anode to Reference	4.32 "	216 "	3.25 "	163 "
ALTERNATING CURRENT 10 kHz - UNSTIMULATED CIRCUITS				
Anode to Cathode	6.58 "	330 "	5.87 "	295 "
Cathode to Reference	2.32 "	116 "	2.24 "	113 "
Anode to Reference	4.27 "	214 "	3.82 "	192 "

Peak Potential = Highest potential reached in first two days
Peak Resistance/ Impedance = Calculated resistance/impedance from peak potential
Steady State Potential = Average potential from day nine to day eighty four
Steady State Resistance/Impedance = Calculated resistance/impedance from steady state potential

CHAPTER 8

THE DESIGN OF A TITANIUM CATHODE FOR IMPLANT SURGERY

CHAPTER 8

THE DESIGN OF A TITANIUM CATHODE FOR IMPLANT SURGERY

1. INTRODUCTION

One of the major advances in orthopaedic surgery in the past 20 years has been the development of total joint replacement prostheses. Permanent stability of the implant has continued to be a biochemical and clinical problem. Prostheses which are impacted into bone are held in place by compressive residual stress interaction and their success has often been dependent on favourable anatomical situations such as the impaction of the stem of a femoral prosthesis into the marrow cavity of the femur [194]. Despite the evolution of super strength metal alloys and numerous design modifications of prostheses and the major advance in fixation of the prosthesis within the cortical bone with methyl methacrylate cement [77, 78], loosening of the implant has continued to be a cause of failure of joint replacement surgery as methyl methacrylate has failed to achieve stabilisation of the prosthesis [274].

Whilst hip procedures have, on the whole, been very satisfactory, this cannot be said of joint replacements in the knee and elbow joints where fixation is dependent on the bonding of cement to the surrounding cancellous and

cortical bone. Loosening of the femoral prosthesis has varied from 0.25% to 6.6%, [81, 89, 122, 197, 208]. In total knee and elbow replacements, the incidence of prosthetic loosening is significantly higher [213, 237, 243].

Charnley [79] said that "the making of a permanent bond between an inert surgical implant and a living bone which will remain sound even though transmitting the forces produced by the weight of the body, was a major subject for research in orthopaedics. It remains the main limiting factor in modern joint replacement surgery". The success of any porsthesis is dependent on the bond that can be obtained and maintained between the prosthesis and the living bone [282]. This bond is dependent on the mechanical interaction of the surface of the implant with the adjacent tissue, and the manner in which such interaction transfers stress between the implant and the adjacent skeleton [140]. Clinical experience with cemented implants has shown that if a prosthesis is to remain symptomless over a period of years, little or no movement must occur between the implant and the skeleton and the area of contact between the two must be high [270].

Attempts are being made to implant prostheses in such a way that living bone is in direct, permanent contact with large surface areas of the implant and, if possible, to induce bone to grow into the implant

itself so as to lock it in place [270]. Klawitter [155] showed that bone grew into apertures which must be above a certain minimum size and one possible solution to the problem of skeletal attachment is to provide a porous material coating for orthopaedic implants, into which bone can grow.

So far as can be ascertained, bone growth into apertures or indentations has not previously been carried out in association with electrical stimulation and this may provide a vital link for adequate and rapid bone ingrowth which would avoid prolonged immobilisation following total joint replacement.

The aim of this study was to carry out a pilot project to determine the maximum aperture dimension for the ingrowth of bone in association with electrical stimulation and, as a consequence, to design an appropriate titanium cathode which could be attached to the surface of a porous coated implant in order to eliminate the need for bone cement without prejudice to the mechanical integrity of the prosthesis/bone interface.

2. MATERIALS AND METHODS

The pilot study aimed to determine bone ingrowth as a direct consequence of electrical stimulation. Initially, trauma was minimized by avoiding the medullary cavity but it was realized that the mechanism and type of bone growth may be different outside the cortex as

compared with inside the medullary cavity. It became necessary to insert a titanium mesh within the cortex of the long bone.

(a) Materials

This project was divided into three phases.

In Phase I a plate, measuring 50 x 10 x 0.4 mm thick made of commercially pure titanium ASTM-B-265 grade 1 was used (Fig. 8.1). In Phase II, a plate of the same dimensions but 6 mm thick was made from pure titanium ASTM-B-265 grade 3 (Fig. 8.2). The plates were shaped to the contour of the lateral aspect of the femur with a radius curvature of 8 mm. Each plate had a row of four different sized holes - 1 x 8 mm diameter, 2 x 4 mm diamter, 3 x 2 mm diameter, and 3 x 1 mm diameter and all equally spaced. The cathode electrode was connected to each plate by either attaching it to a small extension of the plate (Fig. 8.1) or by passing the cathode through a small hole at the end of the plate (Fig. 8.3). The plate was fixed to the femur by a single screw.

In Phase III a mesh was made from 30 guage titanium wire (0.254 diameter) with an opening size of 500 micrometres. The mesh formed a roll of 6.5 cm in length and was placed into the medullary cavity of the upper end of the femur (Fig. 8.4).

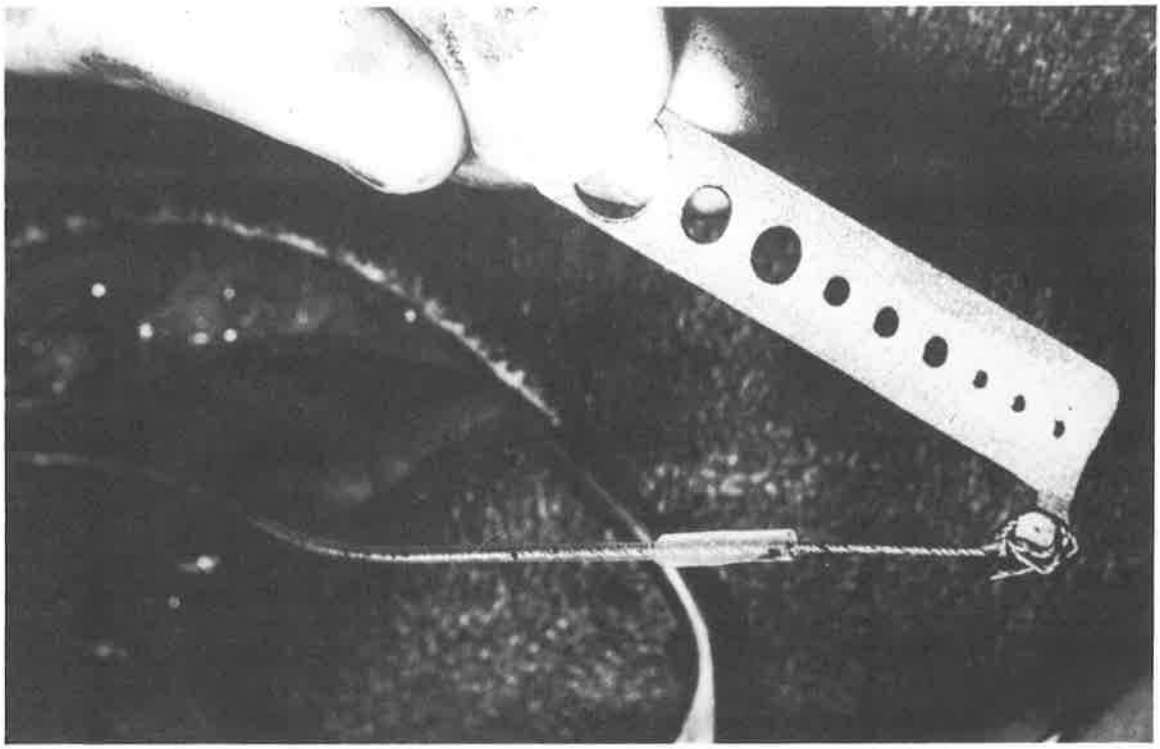


Fig. 8.1 Thin plate of pure titanium measuring 50 x 10 x 0.4 mms thick with extension for attachment of the titanium cathode

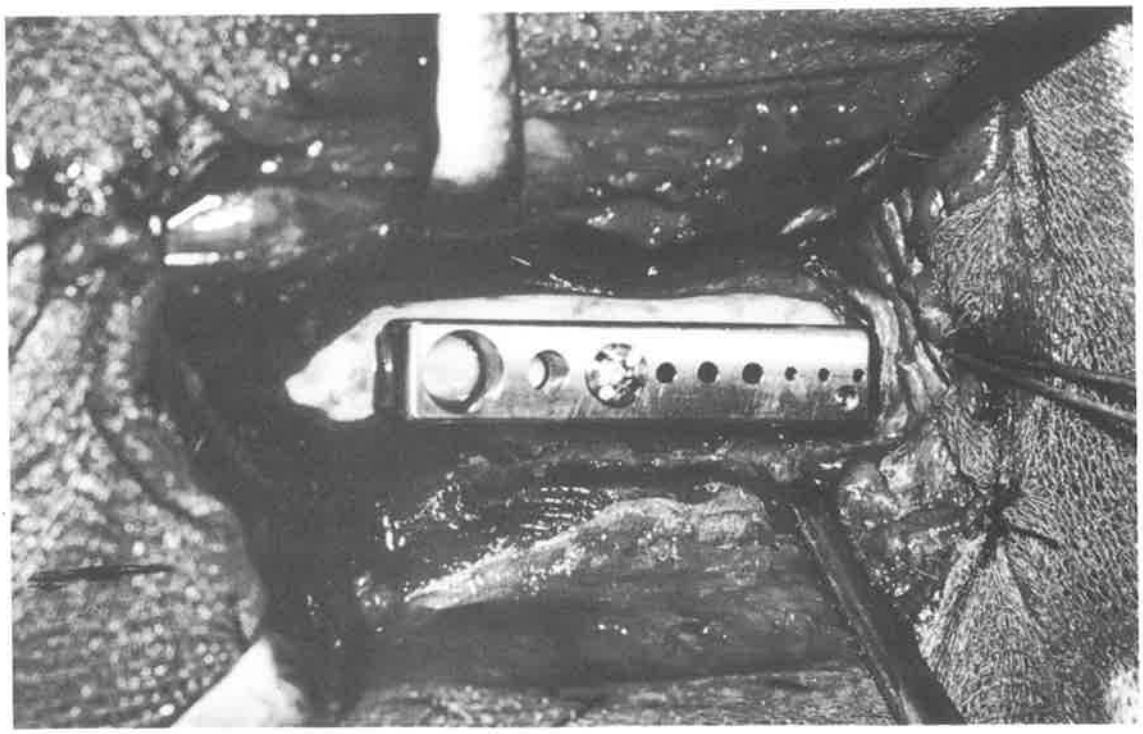


Fig. 8.2 Thick plate of pure titanium measuring 50 x 10 x 6 mms thick and fixed with one screw to the cortex of the femur

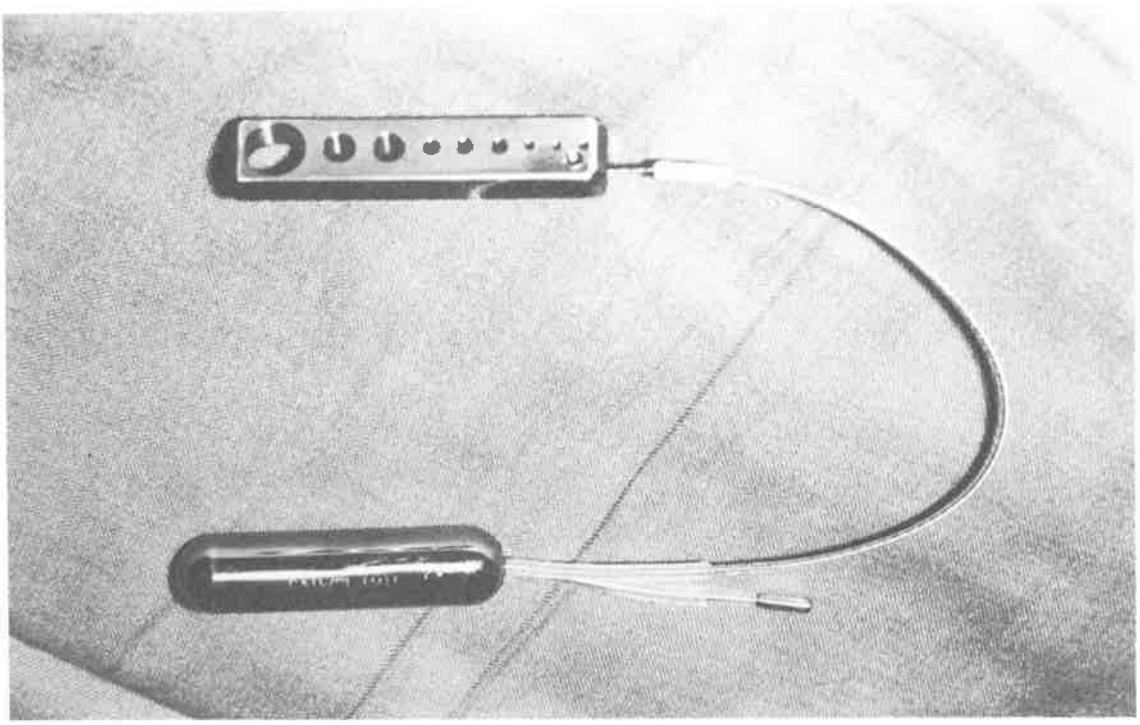


Fig. 8.3 Attachment of the titanium cathode of the Osteostim S12 to a separate hole in the plates

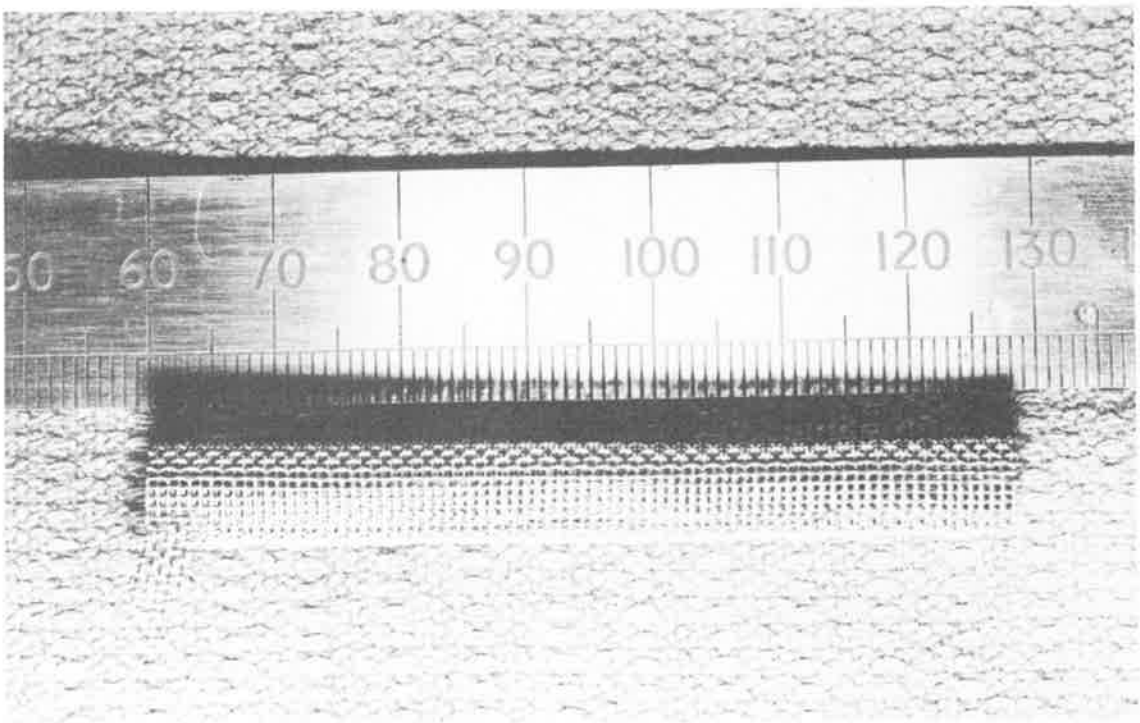


Fig. 8.4 30 guage titanium wire mesh with an opening size of 500 micrometres

Pairs of pre-packed, sterilised and coded bone growth stimulators, Osteostim S12, were prepared and tested as before and were inserted into each hind leg of the adult dogs. The cathodes were attached to the titanium implants.

(b) The project

(i) Surgical technique

Phases I and II - After the dogs were anaesthetised, the skin was incised over the lateral aspect of the thigh and the tensor fascia lata divided. A plane was developed between vastus lateralis and biceps femoris muscles to expose the shaft of the femur. The periosteum was divided in an I shape and separated from the bone. A 3.6 mm hole was drilled on the lateral aspect of the femur and the plate was attached to one cortex of the bone by a vitallium screw (Fig. 8.2). The bone growth stimulator (Osteostim S12)* with the anode were placed proximally beneath the deep fascia and the cathode electrode was anchored by passing it through fibres of the rectus femoris muscle and attached to the plate. The tissues were approximated and the skin was closed. The dogs were allowed to move freely once they had recovered from the anaesthesia.

* Telectronics Pty. Ltd., Sydney, Australia

Phase III - The upper end of the femur was cleaned and draped in order to leave the leg free for gentle manipulation of it. The skin was incised over the lateral aspect of the greater trochanter. The gluteal muscles were detached from the proximal aspect of the trochanter to expose the trochanteric fossa. The gemellus muscles were detached from their insertion into the trochanteric fossa and the superior aspect of the base of the femoral neck. A 6.4 mm hole was drilled through the superior aspect of the neck into the medullary cavity (Fig. 8.5). It was important that this drill hole was not placed too far medially as this weakened the superior and inferior cortices of the femoral neck and produced a fracture. The titanium mesh was inserted into the medullary canal (Fig. 8.6) and the cathode electrode was looped a few times around a small extension at the proximal end of the mesh to secure it firmly (Fig. 8.7). The stimulator was placed beneath the deep fascia and the skin closed (Fig. 8.8).

(ii) Control study

Two dogs had the same surgical procedure performed on both sides without the insertion of any metallic devices. A further three dogs had the surgical exposure and insertion of the metallic devices without any electrical stimulation.

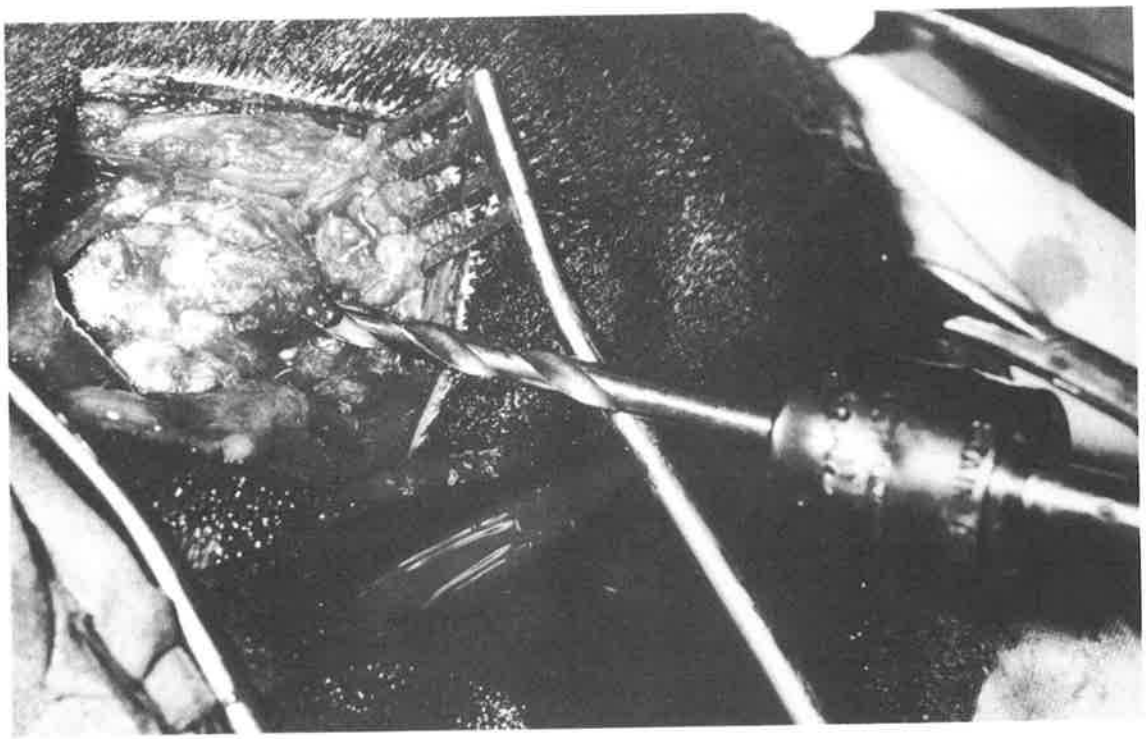


Fig. 8.5 6.4 mm hole drilled through the neck of the femur into the medullary cavity

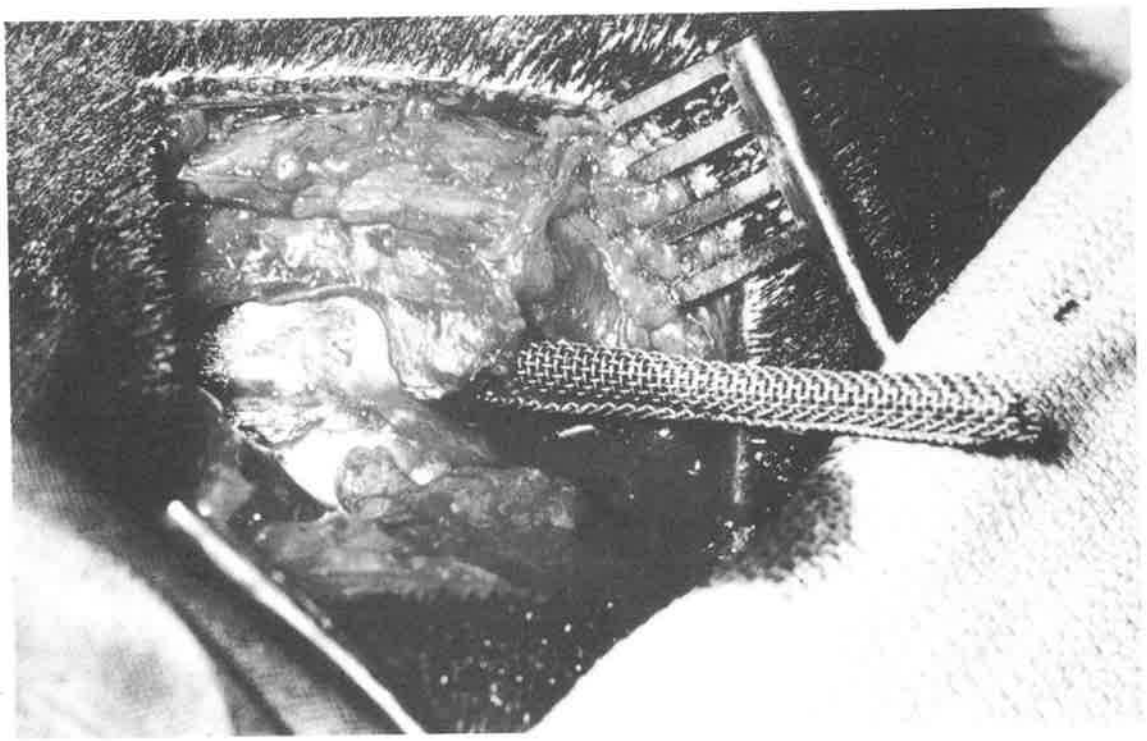


Fig. 8.6 Insertion of the titanium mesh into the medullary cavity

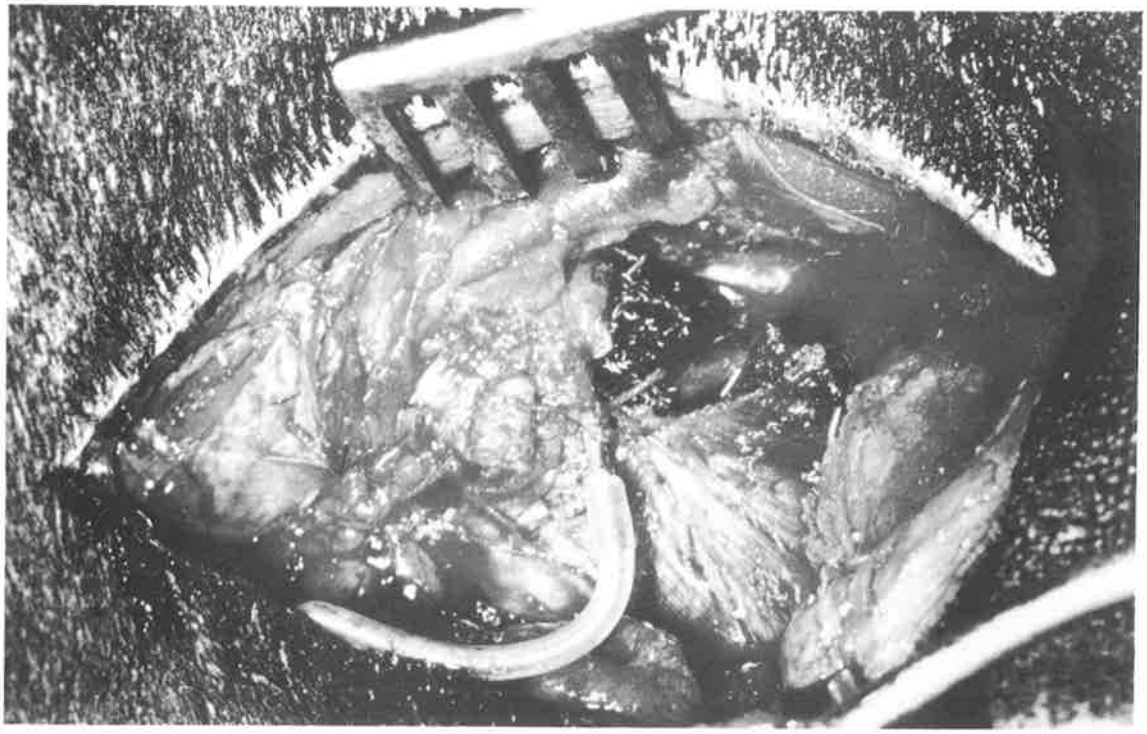


Fig. 8.7 Attachment of the titanium cathode electrode to the titanium mesh

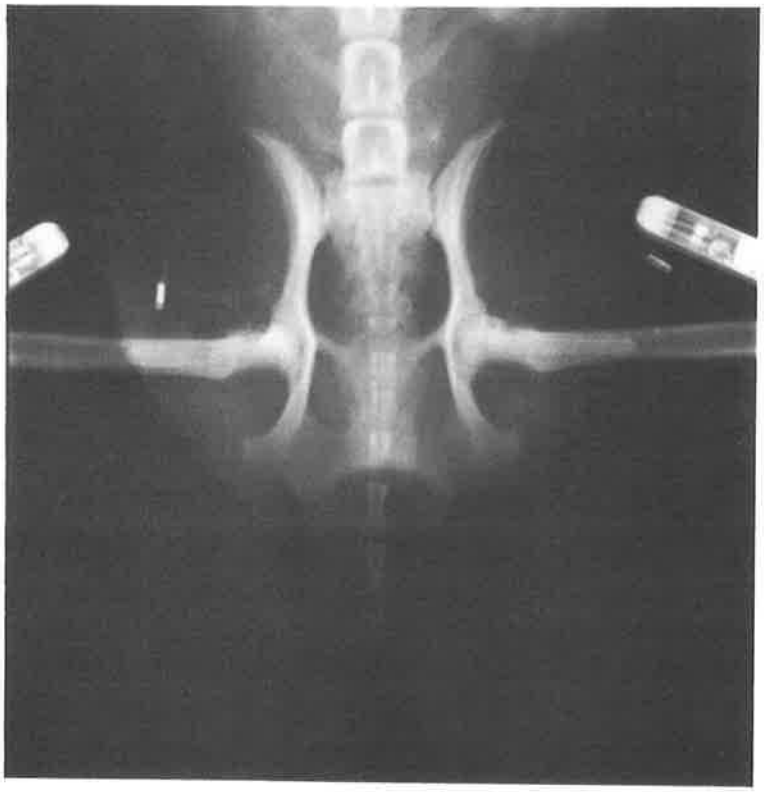


Fig. 8.8 Radiograph of the titanium mesh in situ in the medullary canal of the femur

(iii) Dogs

Fifty-two adult mongrels and beagles were used in this study.

Phase I - Fourteen dogs had the thin plate inserted. Four dogs were killed at each of 3, 6 and 12 weeks and two dogs were discarded with wound infection.

Phase II - Six dogs had the thick plate inserted. Four dogs were killed at 3 weeks and two dogs at 6 weeks.

Phase III - Twenty-seven dogs had the intramedullary mesh inserted. Three dogs developed fractures of the femoral neck and a further two dogs were discarded as the implant had extruded from the medullary cavity. Seven dogs were killed at 2 weeks, five at 4 weeks, seven at 8 weeks and three at 12 weeks.

None of the electrodes broke and none of the cortical plates became loose.

(iv) Pilot study

A further experiment was carried out inserting similar fenestrated intramedullary tubes into the upper end of two adult sheep and attaching an active and inactive bone growth stimulator.

(v) Preparation of the titanium implants

Phases I and II

The specimens of bone (Fig. 8.9) were fixed in 10% aqueous formalin buffered to neutrality for at least two weeks and were finally placed under negative pressure in a vacuum desiccator for seven days. They were then dehydrated progressively in alcohol, then infiltrated with acetone and an Araldite mixture and finally allowed to polymerise at 60°C for 24 hours.

When polymerised, these blocks were cut up (Fig. 8.10) with a hack saw along the lines indicated (Fig. 8.11), thereby allowing future sectioning to be made through the holes in the implants. These blocks of bone required further treatment with Araldite after which sections approximately 200-250 μ were cut using a low speed saw with a 10 cm diamond blade (Fig. 8.12).

It was difficult technically to grind these samples (Fig. 8.13) to sections measuring 40-50 micrometres but once this was achieved, the sections were stained by the von Kossa technique which stained mineralized bone black (Fig. 8.14). The sections were mounted on glass slides using a chrome-alum-gelatin (subbing) solution [201] (Appendix J).

The amount of new bone formed, both internal and external was assessed subjectively.

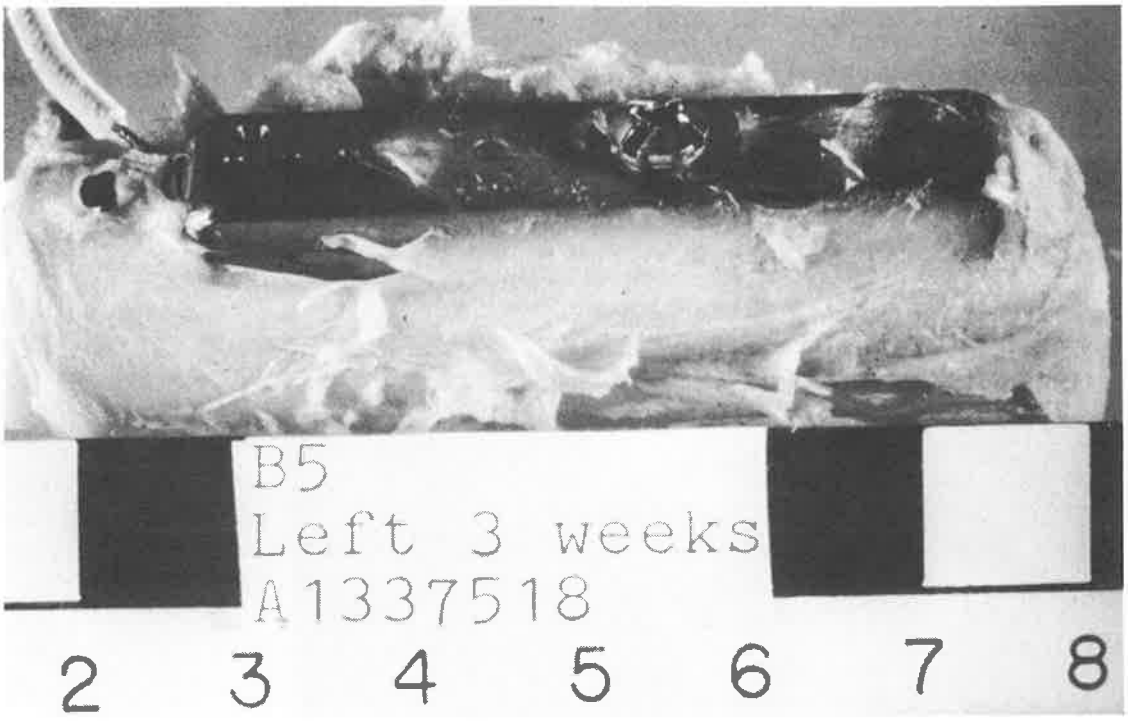


Fig. 8.9 A specimen of bone removed with its attached plate for sectioning

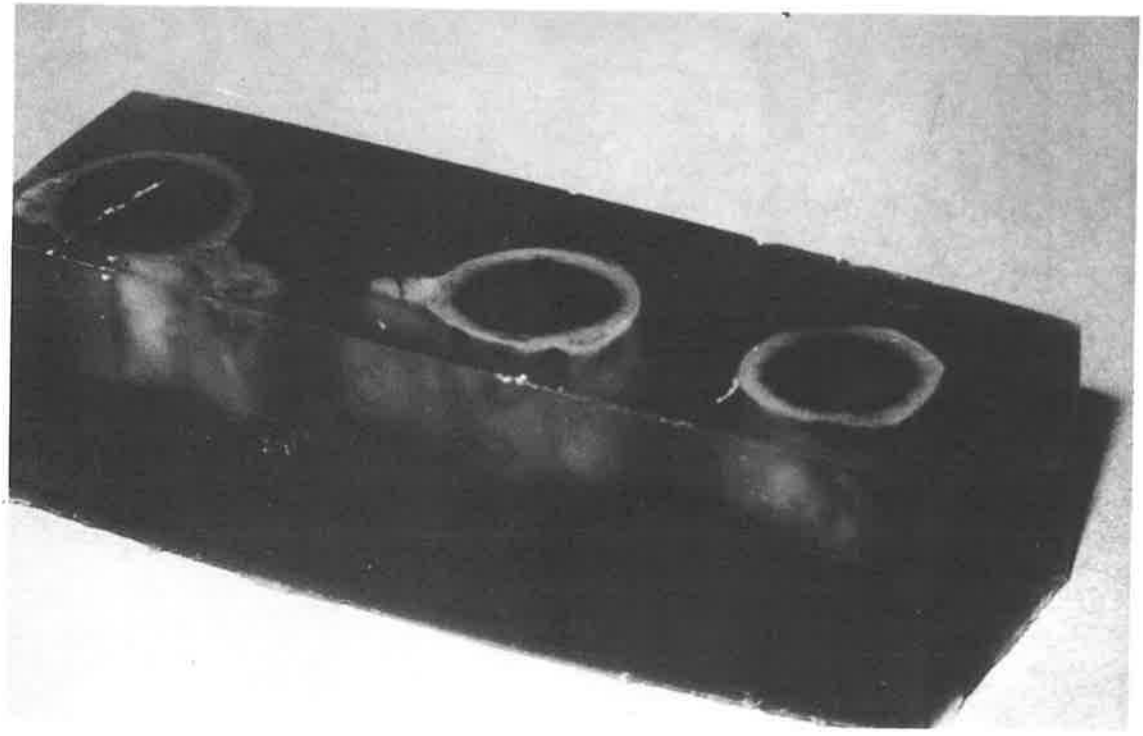


Fig. 8.10 Sections of bone fixed in an Araldite mixture

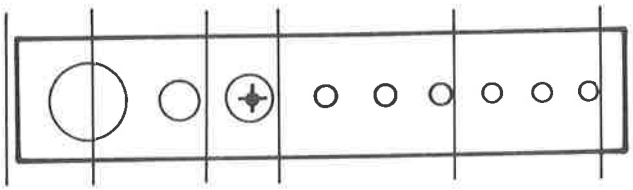


Fig. 8.11 The plates were sectioned through identical lines

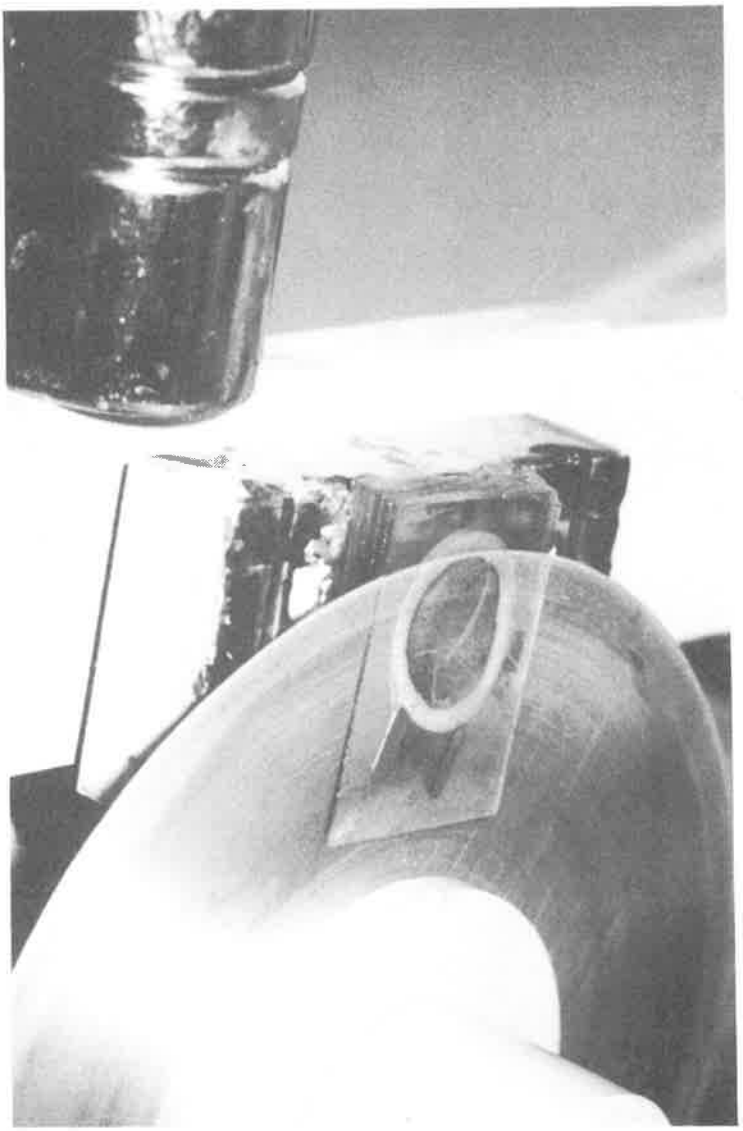


Fig. 8.12 Sections being cut with a low speed saw using a 10 cm diamond blade

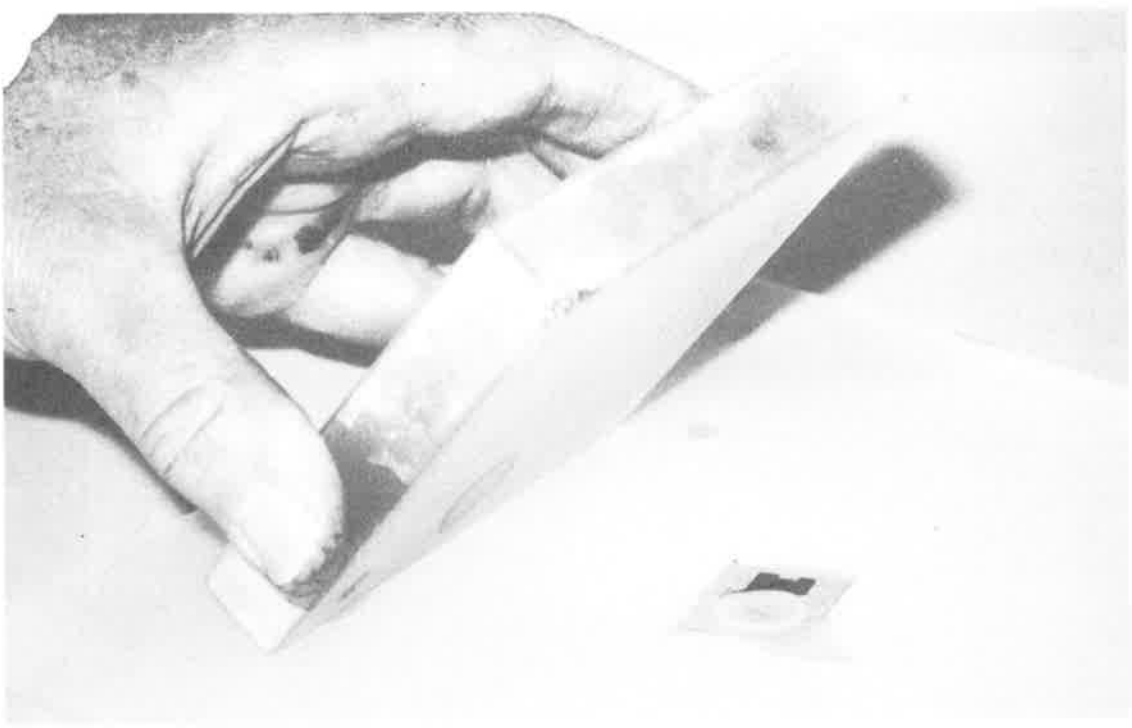


Fig. 8.13 Sections being ground

Fig. 8.14 Sections ground to 40 micrometres and stained by the von Kossa technique

Phase III

Initially, attempts were made to cut 3 mm sections using a rotating diamond saw. This was technically difficult and it was not possible to remove the titanium mesh from each section. Difficulties were also experienced with the Jung K sledge microtome. For a variety of technical and other reasons, it was not possible to analyse the presence of more or less bone using these techniques. As a result, high resolution radiographs* were made of the sections using the microtome, leaving the titanium mesh in situ, and the amount of intramedullary new bone formed was subjectively compared in a pair of legs. It was not possible to quantitatively assess this using the Hewlett Packard Digitizer.

3. RESULTS

(a) In Phase I, dogs were killed at each of

(i) 3 weeks when one dog had more bone with an active stimulator, one dog had more bone both internally and externally with an inactive stimulator (Fig. 8.15) whilst two dogs had no significant difference.

* Using an X-ray Cabinet (Hewlett Packard Corp. U.S.A.)

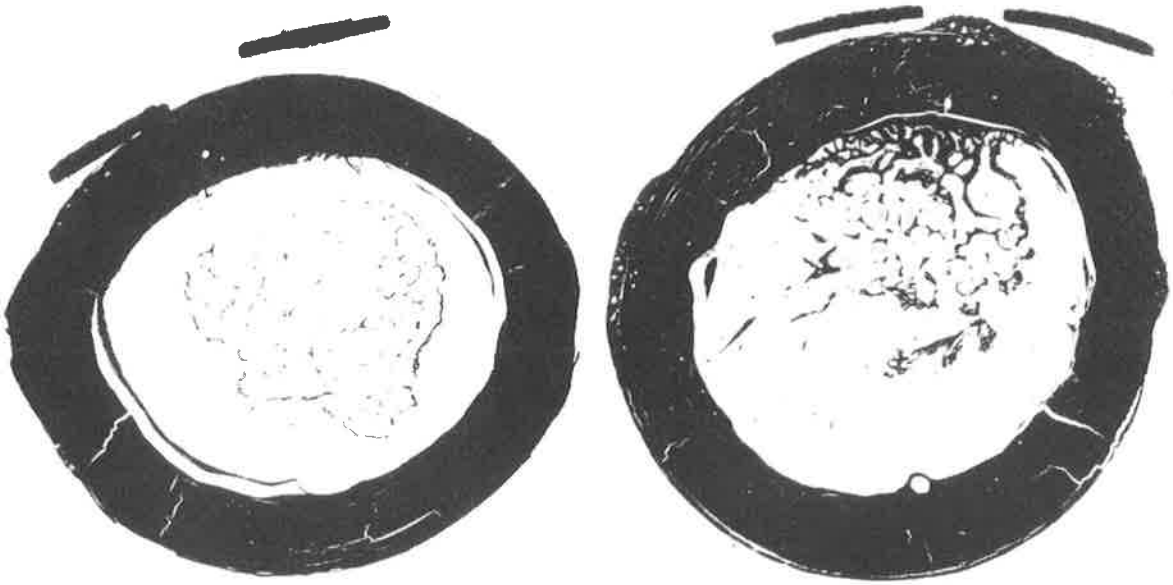


Fig. 8.15 A thin plate specimen at 3 weeks with marked internal bone formation associated with an inactive (right) stimulator, no bone formed with an active (left) stimulator

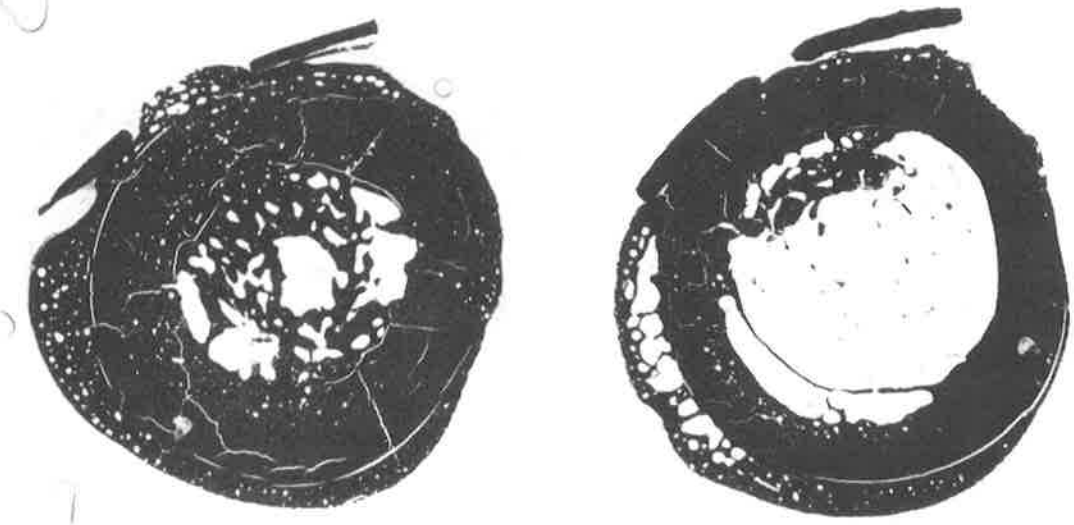


Fig. 8.16 A thin plate specimen at 12 weeks showing more active bone formation in the medium holes with an active (left) stimulator than an inactive (right) stimulator

(ii) 6 weeks when no dogs had increased bone formation with either stimulator.

(iii) 12 weeks when two dogs had more bone formation internally and externally with an active stimulator particularly in the medium holes (Fig. 8.16), one had minimal response and another had similar bone growth in both the active and inactive legs (Fig. 8.17).

In summary, there was minimal bone response in the medium holes and, in half of the specimens, there was some internal bone formation but there was no significant difference in bone formation with an active or inactive stimulator.

(b) In Phase II there was no active bone formation in two dogs killed at 3 weeks and one dog killed at 6 weeks. In three, there was more external bone formation with the active stimulator - two being killed at 3 weeks (Fig. 8.18) and one killed at 6 weeks.

In summary, there was no significant difference between the 3 and 6 weeks specimens. More bone was however present in the medium and large holes (Fig. 8.19). There was also less internal bone formation than with the thin plate.

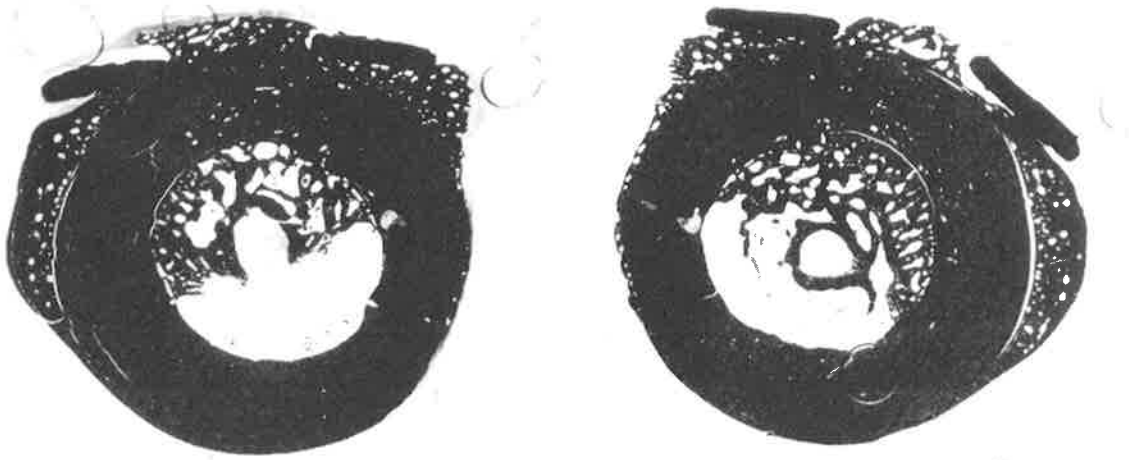


Fig. 8.17 A thin plate specimen at 12 weeks showing similar bone formation in the medium holes with both active (left) and inactive (right) stimulators

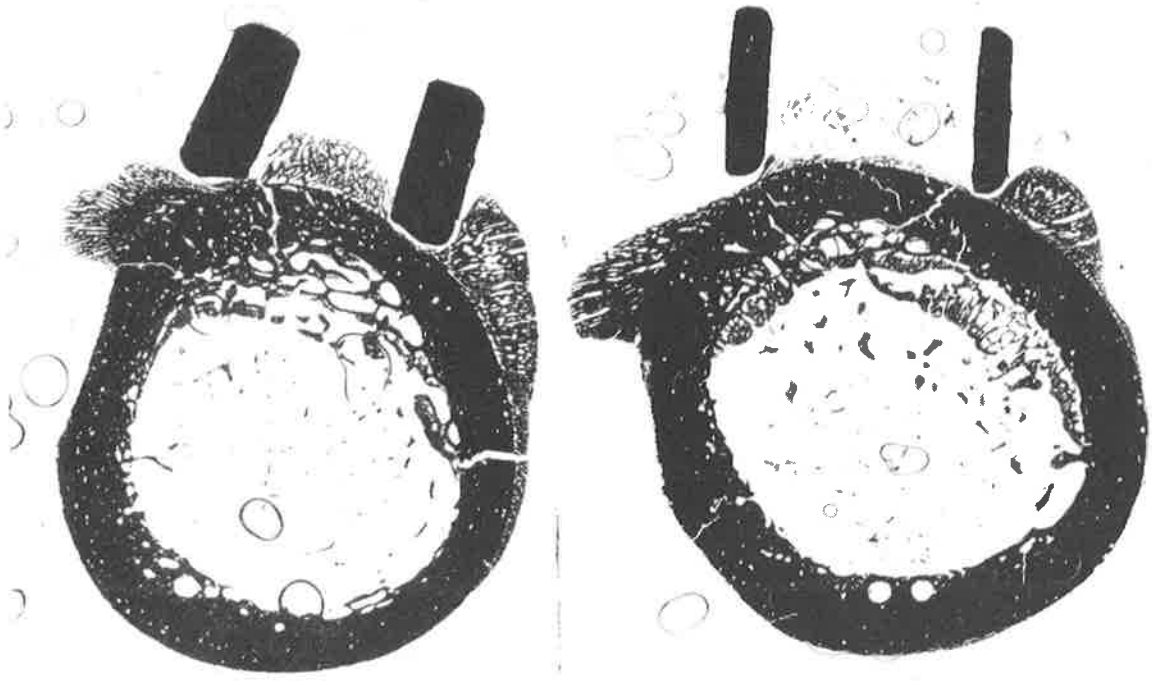
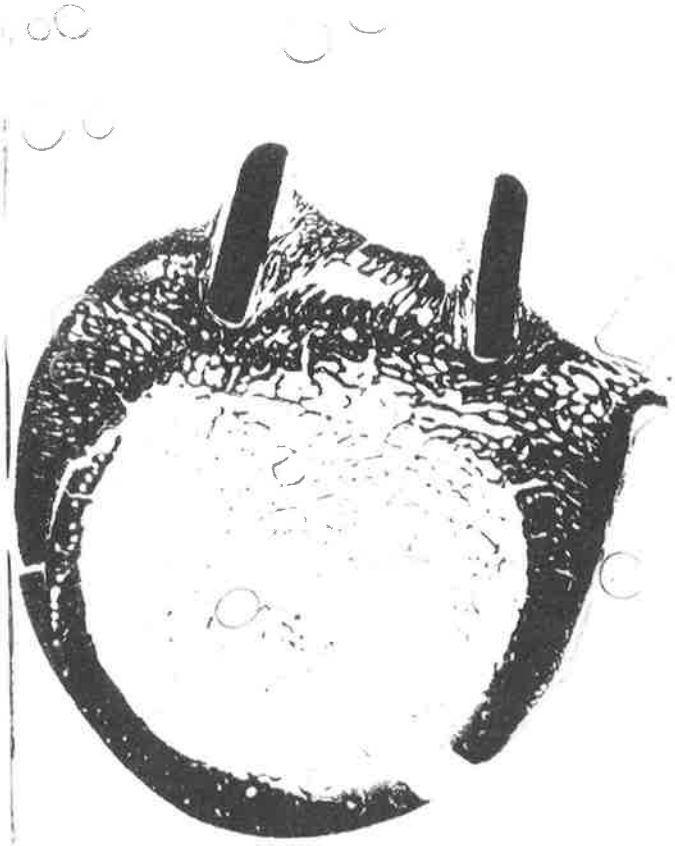
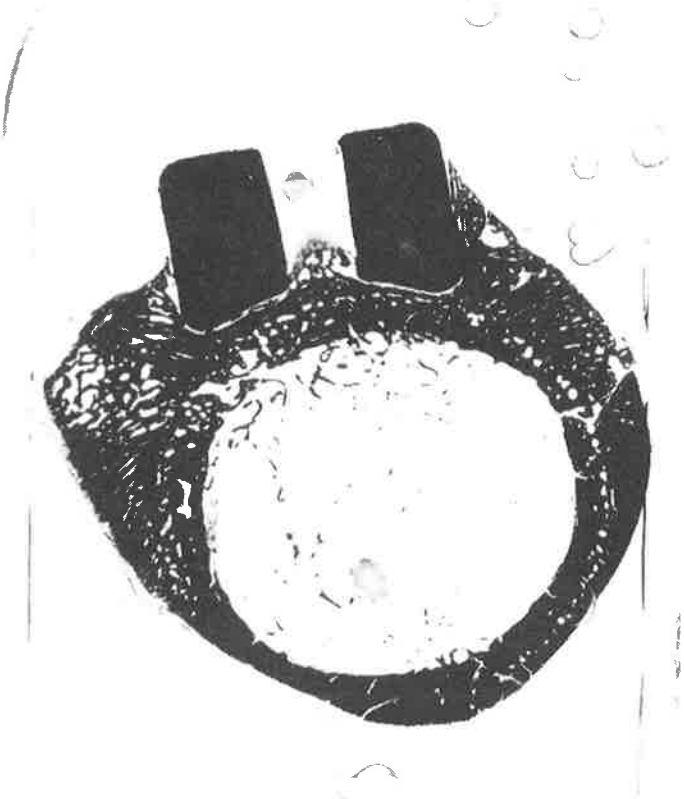


Fig. 8.18 A thick plate specimen at 3 weeks showing more external bone formation in the medium and large holes with an active (left) rather than inactive (right) stimulator



a



b

Fig. 8.19 A thick plate specimen at 6 weeks with an active stimulator with more bone formation in a large hole (a) than smaller hole (b)

(c) In Phase III, seven dogs were killed at 2 weeks, five at 4 weeks, seven at 8 weeks and three at 12 weeks. There was

(i) at 2 weeks, more bone formed in five dogs with actively stimulated titanium meshes (Fig. 8.20) and no difference in two dogs.

(ii) at 4 weeks, more bone in one dog (Fig. 8.21), slightly more in three and no difference in another dog.

(iii) at 8 weeks, more bone present in four dogs with actively stimulated meshes (Fig. 8.22) and no difference in three dogs.

(iv) at 12 weeks no difference in any dog (Fig. 8.23).

In summary, there was more bone with active stimulation in 13 of the 22 dogs and no difference in 9 dogs.

(d) Control study

There was no bone formation in the five dogs used as a control experiment. This at least indicated that the surgical procedures were atraumatic.

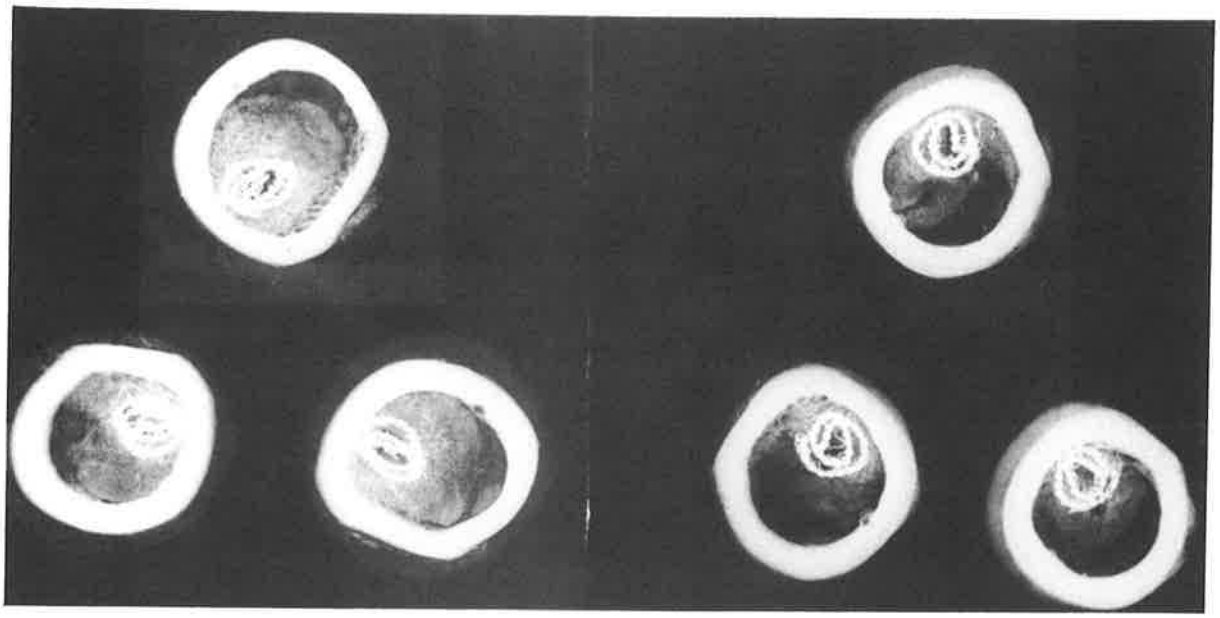


Fig. 8.20 A titanium mesh at 2 weeks with more intramedullary bone formation associated with an active (left) stimulator than (right) inactive one

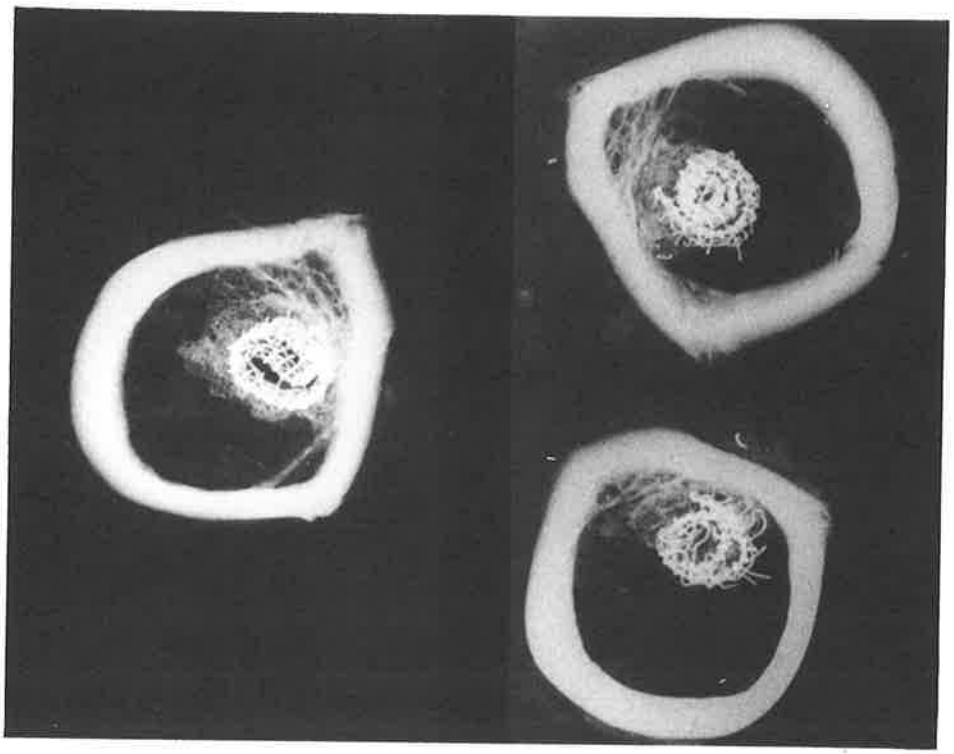


Fig. 8.21 Titanium mesh at 4 weeks with more bone associated with an active (left) stimulator than inactive (right) one

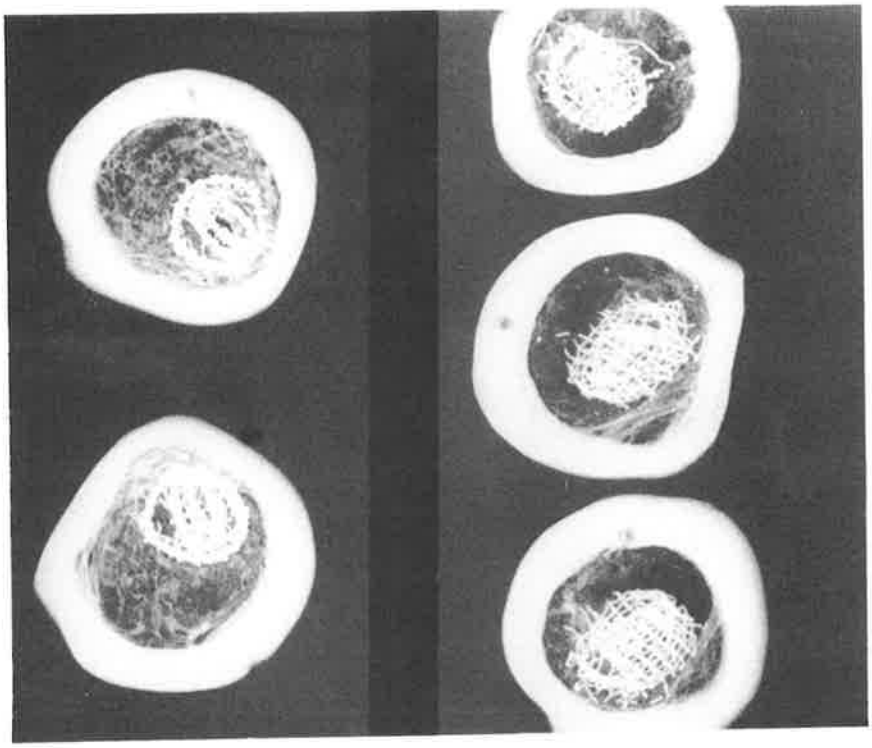


Fig. 8.22 Titanium mesh at 8 weeks with more bone associated with an active (left) stimulator than inactive (right) one

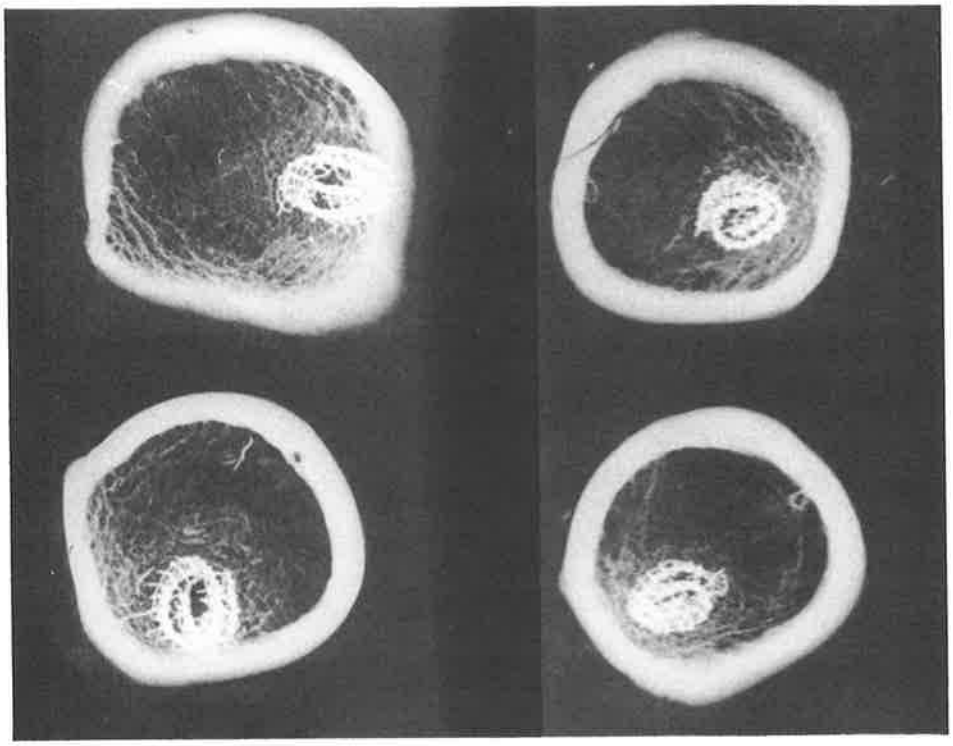


Fig. 8.23 Titanium mesh at 12 weeks with insignificant difference between the active (left) and inactive (right) stimulators

(e) Pilot experiment

After four weeks, a significant amount of bone formation was associated with the actively stimulated tube and this was confirmed by a pull-out test where there was no resistance to withdrawal of the inactively stimulated tube (Fig. 8.24).

(f) Summary of results

There was little evidence of bone formation with the thin plate irrespective of the size of the aperture, though there was perhaps a little more bone in the medium sized holes. In a few dogs, there was, in addition to periosteal bone formation, some intramedullary reactive bone but its significance was unclear.

There was an impression of some increased external bone growth with electrical stimulation into the medium and large apertures of the thick plates. Again, there was some endosteal bone formation.

There was clear evidence of more bone formation associated with an actively stimulated titanium mesh and with the actively stimulated fenestrated intramedullary tube.

The differences in these studies were not significant.

There were too many variables in this study. They included the different sized animals, the use of thin and thick plates with different sized

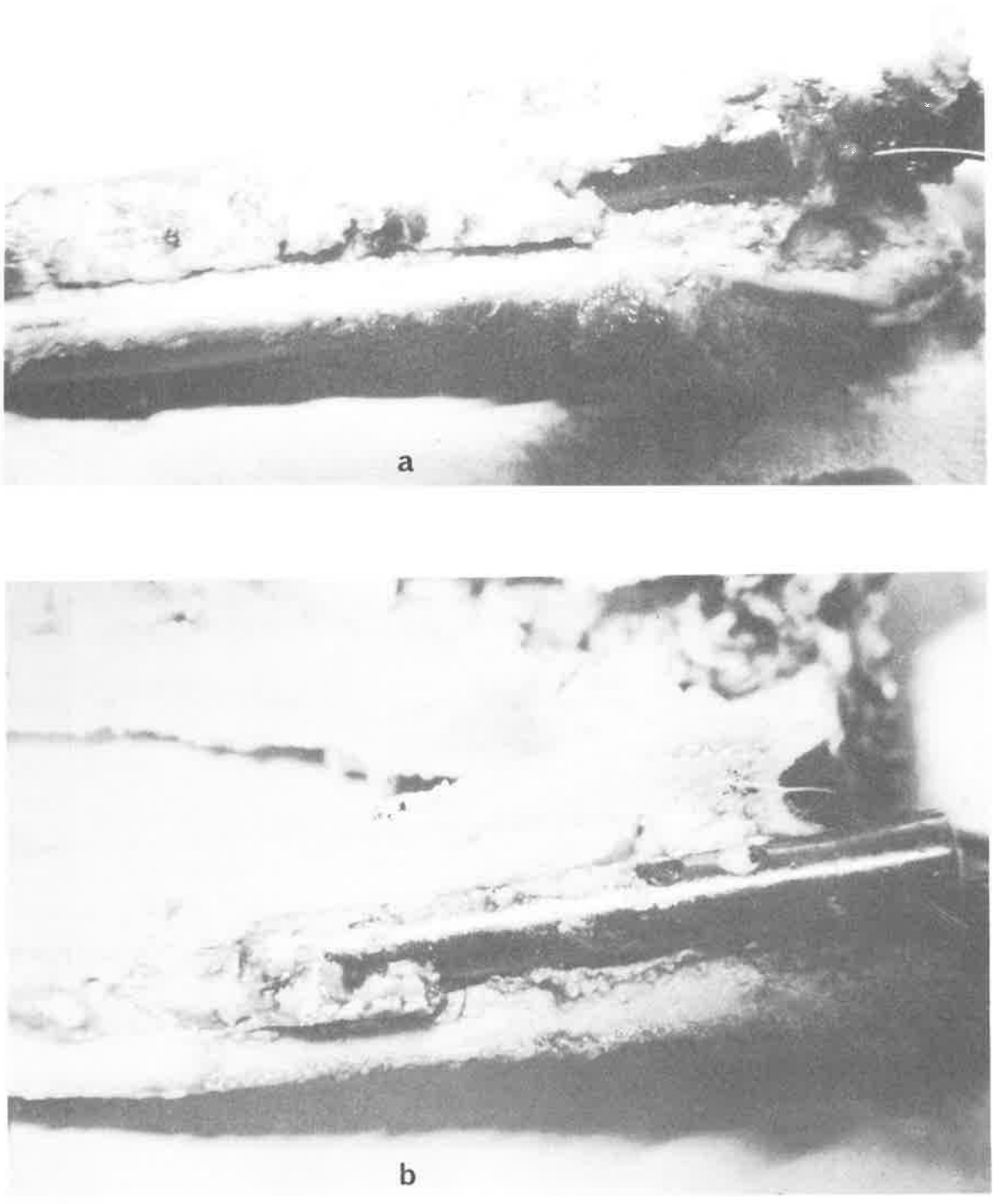


Fig. 8.24 Significantly more bone around a fenestrated intramedullary tube associated with an active(a) stimulator than inactive(b) one

holes and different metals for the plates and screws. The significance of these variables was uncertain.

This study using the intramedullary titanium mesh was of more value for future use in implant surgery.

4. DISCUSSION

After nearly two decades of experience with total hip arthroplasty, surgeons have become aware of the complications inherent in the procedure [3, 11, 80] and these are more evident with similar operations in other joints.

The use of methyl methacrylate cement has, at the time of operation, produced firm fixation between the implant and bone and a high area of contact as the cement fills the dead space and moulds itself to the surfaces of both the prosthesis and the cortical trabeculae as it polymerises [77].

Histologically, the bone/cement interface passes through three phases after surgery [270]. There is an initial phase lasting about three weeks after the operation where a zone of dead bone and bone marrow is found extending up to 5 mms from the cement surface. This may be due to the trauma and heat involved in the surgery or from the heat produced during polymerisation of the monomeric methyl methacrylate. Secondly, there is

a reparative phase lasting up to two years. This is characterized by removal of the dead bone and bone marrow and formation of an acellular fibrin-like layer in contact with the cement and an outer layer of collagenized fibrous tissue up to 1 mm thick at the junction between the main cement mass and the revascularised implant bed. Finally, there is a stabilization phase where the "permanent" implant bed consists of this aceullar tissue and the fibrous tissue layer may persist. Loosening of the implant may be related to the presence of this fibrous tissue layer between living bone and the cement.

While the proper technique of insertion of the cement is very demanding [81], many other undesirable aspects of the use of methyl methacrylate cement have been reported [2, 71, 89, 166, 197, 259, 275, 285]. There is a worldwide move to find ways to improve the method of fixation of such prosthetic devices [259]. Increasing interest has developed towards biological fixation of prostheses by which a highly inert porous material will provide a biocompatible scaffolding into which living bone will grow into the implant itself and thereby anchor the porous material to the skeletal system. The concept of biological growth is by no means new; it was first introduced into orthopaedic surgery by Smith in 1963. [238] Since that time numerous porous materials have been developed [114, 155, 250, 279]. More recently,

there have been encouraging experimental and clinical reports following insertion of porous coated, non-cemented, femoral prostheses using polysulfone [99, 252], porous proplast [258], porous chrome cobalt and porous high density polyethylene [176] on the intramedullary stem of the prosthesis. The bone growth into porous polysulfone coated prostheses on functioning canine hip prostheses produces interfacial shear strengths greater than that achieved by bone cement [252, 253]. Spector et al [251] also consider that the porous material should have a modulus of elasticity close to that of bone. The concept of biological attachment using porous materials attached to the stem of the prosthesis has great promise.

Klawitter and Hulbert [155] emphasized that the induction and maintenance of new bone into a porous material would depend largely on the stress relationship existing between the implant and the surrounding live bone. Clearly, the success of porous materials for skeletal attachment would depend on simulating acceptable stress patterns as well as designing a material with a pore structure capable of accepting bone ingrowth. Further, precise surgical techniques would be required since the capacity of bone to grow beyond its confines to fill a "dead space" is limited and perhaps gaps of 2 mm represent the practical limit. Consequently, such prostheses would need to be implanted in such a way that they would make perfect contact with the skeleton over much of the surface.

Pore sizes greater than 100 micrometres have produced histological evidence of significant ingrowth [155, 168, 176, 252, 252, 279]. Reports indicate porous implants require a pore size in the range of 100-700 micrometres and the best pore size to allow inflow of osteocytes and blood vessels is in the range of 200-500 micrometres. Pore sizes of 75 or less micrometres produce fibrous tissue. If human bone grows 1-2 mms into a dead space from a cut surface of bone, then the ideal porous material should have a pore size range of 200-500 micrometres and recesses to a depth of 0.5 mms.

Three factors have been shown to be important if living bone is to be in contact with an implant. Firstly, the preparation of the bone surface must be as atraumatic as possible and must shape the bone to be an exact fit for the prosthesis. Secondly, while bone can certainly be induced to grow into an implant, the movement between the prosthesis and the skeleton must be prevented for the first 3-6 months after implantation, a requirement which makes weight bearing on the limb undesirable. If movement is permitted, a fibrous envelope develops around the prosthesis [266]. Finally, the implant must be biologically inert, a requirement equally well met by several metals today and coated with a porous material with a pore size between 200-500 micrometres.

In addition, rapid bone fixation is essential to avoid prolonged immobilisation after join replacement surgery when using porous implants instead of fixation

with methyl methacrylate. It is conceivable that bone formation could be augmented by electrically stimulating an implanted porous coated prosthesis [133].

This pilot study has clearly shown little evidence of bone forming into large apertures of the cortical plates and also that electrical stimulation has no effect in this situation. However, it has been shown that, not only did bone grow into and around titanium mesh with a pore size of 500 micrometres, but more bone was present in association with active electrical stimulation especially in the dogs stimulated for 2-8 weeks - after this, no difference was apparent.

Titanium is the lightest of the implant alloys and offers superior tensile and fatigue strength. It possesses an impressive combination of biocompatibility and mechanical strength [284]. Titanium has been used in implant surgery for over 20 years and, while small particles of titanium may be liberated into tissues adjacent to titanium implants [190, 294], there have been no reports of allergy, sensitivity or local effects unlike the well known sensitivity associated with stainless steel and cobalt/chromium alloy.

It is conceivable that a titanium mesh, with its known resistance to corrosion [282], could be incorporated around a porous coated implant, have a pore size of 200-500 micrometres and be associated with more rapid bone fixation when associated with active electrical

stimulation. If this was established, it would significantly reduce the period of immobilisation following total joint surgery with porous coated implants inserted without methyl methacrylate cement. This would be a major advance in orthopaedic surgery.

As a result of this pilot study, a controlled trial will determine if there is any significant benefit in adding electrical stimulation to the stem of a porous coated femoral prosthesis in adult dogs. A titanium mesh cathode has been designed and already there is evidence (Fig. 8.25) that bone growth occurs more quickly and more strongly into porous polysulfone coatings on functioning canine hip prostheses when electrical stimulation is added.

5. SUMMARY

This study aimed to add to our knowledge about bone ingrowth into different sized apertures, particularly titanium mesh. The preliminary results suggest that an electrically stimulated titanium mesh surrounding a porous surface coating on the intramedullary stem of a metal implant may augment the formation of new bone thereby bridging the gap between the surrounding cortical bone and the prosthesis. A controlled animal trial to evaluate this is being planned.

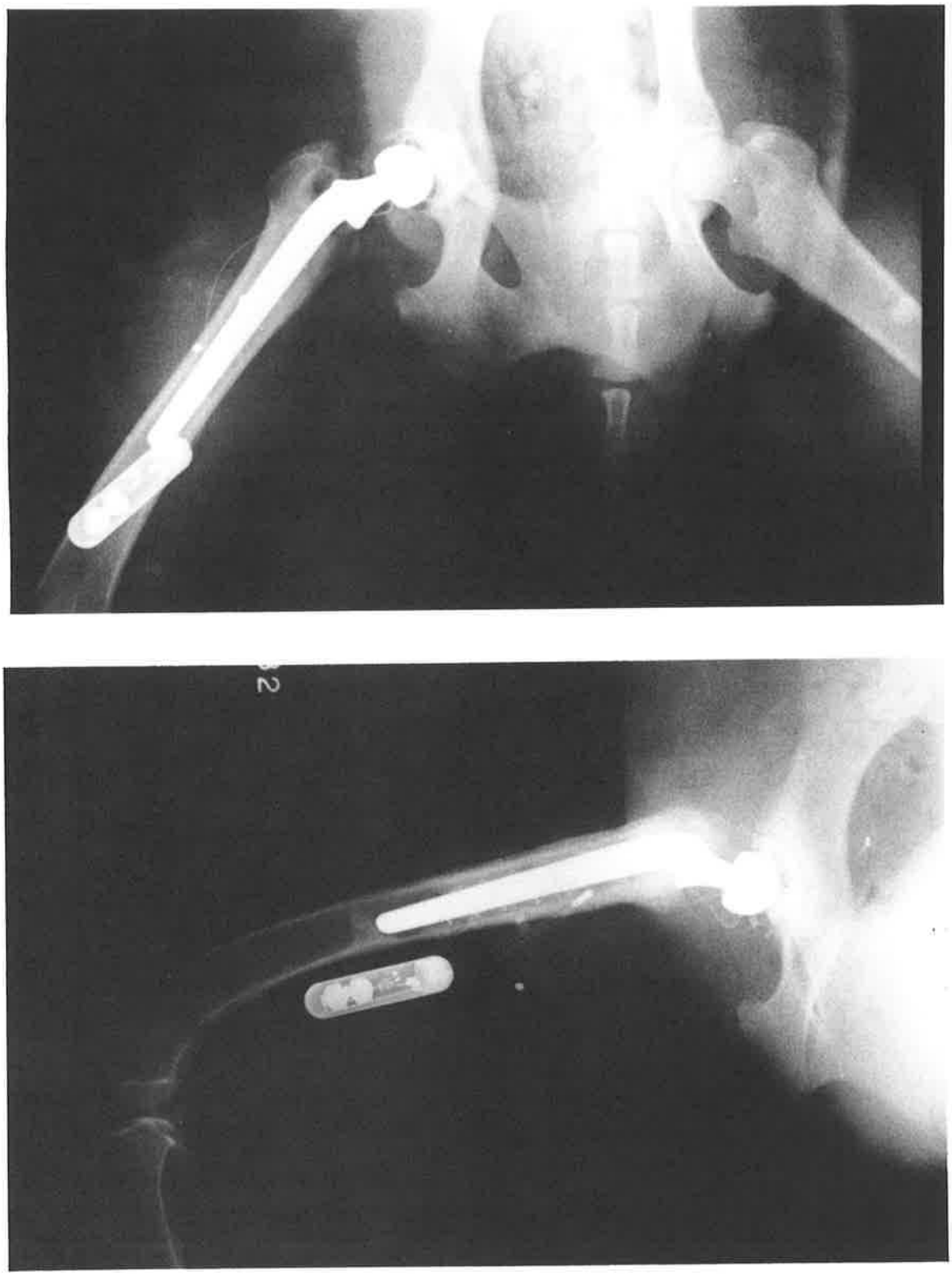


Fig. 8.25 A titanium cathode attached to the porous polysulphone coating of the intramedullary stem of a canine hip prosthesis

CHAPTER 9

THE FUTURE USE OF ELECTRICAL STIMULATION

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1. GENERAL

There can be no doubt that electrical stimulation produces osteogenesis and that this occurs around the negative electrode. Much experimental work and clinical experience has now substantiated these two important findings.

Three methods of electrical stimulation are currently in use to induce osteogenesis - totally invasive, semi-invasive and non-invasive techniques - and reports of extensive clinical use of all three have indicated comparable clinical success rates when used for delayed-union and non-union of fractures of long bones. Further, these success rates are very similar to accepted surgical procedures, in particular cancellous bone grafting. Electrically induced osteogenesis should, therefore, be accepted as a form of treatment in these conditions.

(a) The Osteostim XM12 and S11

There are advantages in all three methods and time alone will determine which is the preferred method and technique. Although the Osteostim requires an operation, it is a simple operation which is associated with insignificant morbidity. There are no contra-indications to its use.

It has been shown to have wide applications. It can be used in the presence of chronic and long standing infection. Importantly, it does not require patient cooperation and, therefore, interferes little with the patient's lifestyle.

The Osteostim was not used clinically until such time as detailed experimental studies had established that significant osteogenesis was induced by it. Subsequently, the Osteostim has been widely used in Australia, North America and Europe with similar success rates in these countries. Electrical stimulation using the Osteostim is, therefore, an effective method of treatment for ununited fractures of long bones, failed posterior spinal fusion and congenital pseudarthrosis of the tibia.

(b) Optimum current

The optimum direct current varies from 5-20 microamperes. So far, however, the optimum current, the optimum electrode and the most satisfactory method of administration have not been established. As a consequence, Becker [44, 46] considers that electrically induced osteogenesis should be restricted to those cases in which the risk-benefit ratio would be

favourable and that the trend by some to use the technique to hasten the healing rate of normal uncomplicated fractures is unjustified and possibly dangerous at the present time.

(c) Possibility of neoplastic change

Some [18, 38, 44, 45, 46, 84, 178, 185] have expressed concern that electrical stimulation might produce neoplastic changes.

Marino [185] thought that several aspects of electrical stimulation required considerable cogitation. First, the artificial acceleration of a complex cellular activity involving dedifferentiation and mitosis may well carry a risk of neoplasia. Second, the biological effects of electromagnetic fields are subtle and a number of them are harmful. He advocated caution before there was widespread clinical use of electrical stimulation.

Becker [46] using human fibrosarcoma cells in culture has noted a threefold increase in cell multiplication at both the anode and the cathode on 24 hour exposure to 360 nanoamperes direct current using stainless steel electrodes. No attempt was made to study the mitotic rate in these cultures and although mitoses were common, there were many binucleate cells and the possibility of amitotic divisions could not be excluded. Becker

concluded that it would be prudent to avoid electrical stimulation in cases in which malignant or pre-malignant lesions were known to exist within the current pathway. A very real concern seemed to be the stimulation of an unsuspected pre-existing malignant lesion of any tissue in the treatment area or even within the path of the current.

2. OTHER USES OF ELECTRICAL STIMULATION

Other potential and rather exciting uses for electrical stimulation have become apparent in recent years.

(a) Infection

Many [16, 40, 43, 45, 46, 185, 225, 245] have noted the bacteriostatic effect of electrical stimulation. Rowley [225] noted a marked decrease in the growth of micro-organisms following electrical stimulation. Becker [43, 45, 185] chose 99.99% pure silver as their electrode material based on its lower interfacial resistance *in vivo*. They found that the silver electrode became a locally bacteriostatic agent when operated anodically with small currents and that silver ions had an extremely broad spectrum of antibacterial activity. They considered that this property was unique to silver and could be used when a previously quiescent infection became active in the region of the silver

electrode. Recently, Becker [43] reported successful clinical experience using electrically generated silver ions as adjunctive treatment in the management of chronic osteomyelitis.

(b) Wound healing

Increasing interest has been shown in healing chronic skin ulcers with electrical stimulation [129] as it has been known for a long time that wounds, even infected wounds, will heal with electrical stimulation [12, 70]. This has been evident in all of this experimental and clinical work with the Osteostim.

(c) Longitudinal bone growth

This does not appear to be a very profitable area for electrical stimulation. Tonna [261] unsuccessfully attempted to stimulate periosteal growth with electrical stimulation. Many [31, 106, 178 286] have failed to show any stimulation of longitudinal bone growth of the tibia of immature animals with direct current stimulation.

At this time, it must be accepted that electrical stimulation does not produce longitudinal growth of bones.

(d) Regeneration of articular cartilage and electrically stimulated growth of bone into porous coated orthopaedic implants

Perhaps the two most important potential uses for electrical stimulation relate to the regeneration of articular cartilage [14, 37, 39] and electrically induced osteogenesis to bond a porous coated orthopaedic implant to the surrounding cortical bone [134, 253].

Major advances have taken place in orthopaedic surgery in the last two decades with the replacement of missing or damaged skeletal parts by metallic or plastic implants. Becker [37] stated that "the best replacement for a damaged femoral head would be a new structure regenerated by the individual himself and perhaps this is a possibility in the future". Already Baker [14] has obtained partial regrowth of resected humeral heads in the laboratory rat following electrical stimulation of hyaline joint cartilage.

The distinct possibility of eliminating the need to use methyl methacrylate cement in joint reconstructive surgery by incorporating a titanium cathode around the porous coated intramedullary stem of an orthopaedic implant would be a major technical advance in orthopaedic surgery.

3. THE FUTURE

Becker [44] stated "the 20-30 year lead time for malignant transformation in man must wait the elapse of that time in regard to clinical objects ... The 'turning on' of any growth process in which major cellular activity is stimulated carries the inherent risk of malignant transformation either early or late. Theoretically, this would appear to be reduced the closer the stimulating conditions approximate those occurring naturally ... Until answers are obtained bearing on the question of long-term side-effects, particularly malignant transformation, it would appear that the use of these techniques should be strictly limited to those cases of established nonunions proven recalcitrant to other accepted modes of therapy. The proposal has surfaced from time to time that the techniques of electrical osteogenesis should be clinically utilized as a means of accelerating the healing time of normal fractures. This procedure would appear to be particularly hazardous ... In view of the fact that the vast majority of such fractures heal without complications, such an application would appear to be unconscionable under the risk-benefit concept ... Electrical osteogenesis may be the opening wedge into the future, its responsible development can bring the future closer sooner; its irresponsible development may well result in again putting off the future for another 100 years".

Despite more than two decades of scientific investigation and one decade of clinical experimentation, much still remains to be learnt. The great importance of the concept of electrically induced osteogenesis and its implications for future treatment requires that present clinical applications be made with great care and deliberation.

Orthopaedic surgeons should no longer be sceptics about the value of electrical stimulation for impaired bone healing. Used responsibly, electrical stimulation has an important place in surgical treatment in the future and may well be the exciting development in orthopaedic surgery in this decade.

REFERENCES

1. Aegerter E.E.
The possible relationships of neurofibromatosis, congenital pseudarthrosis and fibrous dysplasia
J. Bone Joint Surg. 32A: 618, 1950

2. Amstutz H.C.
Skeletal fixation and loosening of total hip replacement
In: Instructional Course Lectures
The American Academy of Orthopaedic Surgeons
23: 201, 1974
The C.V. Mosby Co., St. Louis

3. Amstutz H.C., Markolf K.L., McNeice G.N., and Gruen T.A.
Loosening of total hip components; cause and prevention
"The Hip" 102, 1976
The C.V. Mosby Co., St. Louis

4. Anderson C., and Danylchuk K.D.
Bone-remodelling rates of the beagle: a comparison between different sites on the same rib
Am. J. Vet. Res. 39, 11: 1763, 1978

5. Anderson C., and Danylchuk K.D.
Studies on bone-remodelling rates on the beagle: a comparison between similar biopsy sites on different ribs
Am. J. Vet. Res. 40, 2: 294, 1979

6. Anderson C., and Danylchuk K.D.
Age-related variations in cortical bone-remodelling measurements in male beagles 10 to 26 months of age
Am. J. Vet. Res. 40, 6: 869, 1979

7. Anderson C.,and Danylchuk K.D.
Appositional bone formation rates in the beagle
Am. J. Vet. Res. 40, 7: 907, 1979

8. Anderson G.
Bone grafting of fractures of the tibia shaft with special reference to the use of the Phemister principle
Aust. N.Z. J. Surg. 37: 159, 1967

9. Anderson K.S.
Congenital pseudarthrosis of the leg
J. Bone Joint Surg. 58A: 657, 1976

10. Anderson W.V.
Lengthening of the lower limb: its place in the problem of limb length discrepancy
In: Modern Trends in Orthopaedics
Edited by W.D. Graham, Butterworths, London, 5: 1, 1967

11. Andersson G.B.J., Freeman M.A.R. and Swanson S.A.V.
Loosening of the cemented acetabular cup in total hip replacement
J. Bone Joint Surg. 54B: 590, 1972

12. Assimacopoulos D.
Wound healing promotion by the use of negative electric current
American Surgeon 34 (6): 423, 1968

13. Badgley C.E., O'Connor S.J. and Kudner D.F.
Congenital kyphoscoliotic tibia
J. Bone Joint Surg. 34A: 349, 1952

14. Baker B.E., Spadaro J.A., Marino A., and Becker R.O.
Electrical stimulation of articular cartilage regeneration
Ann. N.Y. Acad. Sci. 238: 491, 1974

15. Barber C.G.
Congenital bowing and pseudarthrosis of the lower leg; manifestations of von Recklinghausen's neurofibromatosis
Surg. Gynaecol. Obstet. 69: 618, 1939

16. Barranco S.D., Spadaro J.A., Berger T.J. and Becker R.O.
In vitro effect of weak direct current on staphylococcus aureus
Clin. Orthop. 100: 250, 1974

17. Bassett C.A.L., Becker R.O.
Generation of electric potentials by bone in response to mechanical stress
Science 137: 1063, 1962

18. Bassett C.A.L., Pawluk R.J. and Becker R.O.
Effects of electric current on bone *in vivo*
Nature 204: 652, 1974

19. Bassett C.A.L.
Electric effects in bone
Scientific Am. 213: 18, 1965

20. Bassett C.A.L.
Electromechanical factors regulating bone architecture
Third European Symposium on calcified tissues
Fleisch H., Blackwood H.J.J., Owen M. (Eds).
Springer-Verlag, Berlin, Heidelberg, New York, 78, 1966

21. Bassett C.A.L.
Biophysical principles affecting bone structure
In: The Biochemistry and Physiology of Bone
Bourne G.H. (Ed) New York: Academic Press 1971 Vol III

22. Bassett C.A.L., Pawluk R.J. and Pilla A.A.
Acceleration of fracture repair by electromagnetic fields - a surgically non-invasive method
Ann. N.Y. Acad. Sci. 238: 242, 1974

23. Bassett C.A.L., Pawluk R.J. and Pilla A.A.
Augmentation of bone repair by inductively coupled electromagnetic fields
Science 184: 575, 1974

24. Bassett C.A.L., Pawluk R.J.
Non-invasive methods for stimulating osteogenesis
J. Biomed. Mater. Res. 9: 371, 1975

25. Bassett C.A.L., Pilla A.A. and Pawluk R.J.
The use of inductively-coupled electromagnetic fields in the treatment of congenital and acquired pseudarthroses: a preliminary report
Presented at the Sixth Combined Meeting of the Orthopaedic Associations of the English Speaking World, London, 1976

26. Bassett C.A.L., Pawluk R.J. and Pilla A.A.
A non-operative salvage of surgically resistant pseudarthroses and non-unions by pulsing electromagnetic fields. A preliminary report
Clin. Orthop. 124: 128, 1977

27. Bassett C.A.L.
Electrobiology of bone
Audiosynopsis July 1977

28. Bassett C.A.L., Chokshi H.R., Hernandez E., Pawluk R.J. and Strop M.
The effect of pulsing electromagnetic fields on cellular calcium and calcification of nonunions
In: Electrical Properties of Bone and Cartilage: Experimental Effects and Clinical Applications
Edited by C.T. Brighton, J. Black and S.R. Pollack
Grune & Stratton Inc. New York, 427, 1979

29. Bassett C.A.L., Mitchell S.N., Norton L., Caulo N. and Gaston S.R.
Electromagnetic repairs of non-unions
In: Electrical Properties of Bone and Cartilage: Experimental Effects and Clinical Applications
Edited by C.T. Brighton, J. Black and S.R. Pollack
Grune & Stratton Inc. New York, 605, 1979

30. Bassett C.A.L., Mitchell S.N., Gaston S.R.
Treatment of ununited tibial diaphyseal fractures with pulsing electromagnetic fields
J. Bone Joint Surg. 63A: 511, 1981

31. Becker R.O.
The bioelectric factors in amphibian limb regeneration
J. Bone Joint Surg. 43A: 643, 1961

32. Becker R.O.
Electron paramagnetic resonance in non-irradiated bone
Nature 199: 1304, 1963

33. Becker R.O., Bassett C.A.L., and Bachman C.H.
Bioelectric factors controlling bone growth
In: Bone Biodynamics (Ed) H. Frost
Little, Brown & Co., New York, 209, 1964

34. Becker R.O. and Brown F.M.
Photoelectric effects in human bone
Nature 206: 1325, 1965

35. Becker R.O. and Marino A.A.
The electron paramagnetic resonance spectra of bone and its major components
Nature 210: 583, 1966

36. Becker R.O. and Murray D.G.
The electrical control system regulating fracture healing in amphibians
Clin. Orthop. 73: 169, 1970

37. Becker R.O.
Augmentation of regenerative healing in man - a possible alternative to prosthetic implantation
Clin. Orthop. 83: 255, 1972

38. Becker R.O. and Spadaro J.A.
Electrical stimulation of partial limb regeneration in mammals
Bull. N.Y. Acad. Sci. 48: 627, 1972

39. Becker R.O. and Baker B.E.
Electrical stimulation of hard tissue growth as possible alternative to prosthetic devices
Report to the National Institute of Health, 1973

40. Becker R.O.
In vitro effect of weak current on Staphylococcus aureus
Clin. Orthop. 100: 254, 1974

41. Becker R.O., Spadaro J.A. and Marino A.A.
Clinical experiences with low intensity direct current stimulation of bone growth
Clin. Orthop. 124: 75, 1977

42. Becker R.O.
Electrical osteogenesis - Pro and Con
Calcif. Tiss. Res. 26: 93, 1978

43. Becker R.O. and Spadaro J.A.
Treatment of orthopaedic infection with electrically generated silver ions
J. Bone Joint Surg. 60A: 871, 1978

44. Becker R.O.
The significance of electrically stimulated osteogenesis: more questions than answers
Clin. Orthop. 141: 266, 1979

45. Becker R.O., Spadaro J.A.
Experience with low-current/silver electrode treatment of non-union
In: Electrical Properties of Bone and Cartilage: Experimental Effects and Clinical Applications
Edited by C.T. Brighton, J. Black and S.R. Pollack
Grune & Stratton Inc. New York, 631, 1979

46. Becker R.O.
Personal communication (1981)

47. Bernstein J.
Uber den zeitlichen Verlauf der negativen Schwankung des Nervenstroms
Arch. Ges. Physiol. 1: 173, 1868

48. Black J. and Korostoff E.
Strain-related potentials in living bone
Ann. N.Y. Acad. Sci. 238: 95, 1974

49. Black J. and Brighton C.T.
Mechanisms of stimulation of osteogenesis by direct current
In: Electrical Properties of Bone and Cartilage: Experimental Effects and Clinical Applications
Edited by C.T. Brighton, J. Black and S.R. Pollack
Grune & Stratton Inc. New York, 215, 1979

50. Black J., Marcum S., Brighton C.T.
The low frequency electrical resistivity of rabbit tissue *in vivo*
Trans. of the 26th Orthop. Res. Soc. 5: 230, 1980

51. Blumenfeld I.
Pseudarthrosis of the long bones
J. Bone Joint Surg. 29: 97, 1947

52. Boyd H.B.
Congenital pseudarthrosis: treatment by dual bone grafts
J. Bone Joint Surg. 23: 497, 1941

53. Boyd H.B. and Sage F.P.
Congenital pseudarthrosis of the tibia
J. Bone Joint Surg. 40A: 1245, 1958

54. Boyd H.B., Lipinski S.W.
Causes and treatment of non-union of the shafts of long bones with a review of 741 patients
In: Instructional Course Lectures
The American Academy of Orthopaedic Surgeons
17: 165, 1960
The C.V. Mosby Co., St. Louis

55. Boyd H.B., Lipinski S.W. and Wiley J.H.
Observations on non-union of the shafts of long bones with a statistical analysis of 842 patients
J. Bone Joint Surg. 43A: 159, 1961

56. Boyd H.B., Anderson L.D. and Johnston D.S.
Changing concepts in the treatment of non union
Clin. Orthop. 43: 37, 1965

57. Brighton C.T., Adler S., Howell D.S., Pita J.C., Marquez A.F., Madruga J.E.
Petition of calcium, phosphate and protein in the fluid phase aspirated at calcifying sites in epiphyseal cartilage
J. Clin. Invest. 47: 1121, 1968

58. Brighton C.T. and Heppenstall R.B.
Oxygen tension in zones of the epiphyseal plate, the metaphysis and diaphysis. An *in vitro* and *in vivo* study in rats and rabbits
J. Bone Joint Surg. 53A: 719, 1971

59. Brighton C.T. and Friedenberg Z.B.
Treatment of non-union with electric current
J. Bone Joint Surg. 56A: 1542, 1974

60. Brighton C.T. and Friedenberg Z.B.
Electrical stimulation and oxygen tension
Ann. N.Y. Acad. Sci. 238: 314, 1974

61. Brighton C.T., Adler S., Black J., Itada N. and Friedenberg Z.B.
Cathodic oxygen consumption and electrically induced osteogenesis
Clin. Orthop. 107: 277, 1975

62. Brighton C.T., Friedenberg Z.B., Zemsky L.M. and Pollis P.R.
Direct current stimulation of non-union and congenital pseudarthrosis
J. Bone Joint Surg. 57A: 368, 1975

63. Brighton C.T., Friedenberg Z.B., Mitchell E.I. and Booth R.E.
Treatment of non-union with constant direct current
Clin. Orthop. 124: 106, 1977

64. Brighton C.T.
Transcripts of the Orthopaedic Research Society
3: 30, 1978

65. Brighton C.T., Friedenberg Z.B., Day L.J., Clarke R.N., Connolly J.F.
Treatment of non-union with direct current: a multi-center study
Presented to the American Academy of Orthopaedic Surgeons Meeting, San Francisco, 1979

66. Brighton C.T.
Preface *In:* Electrical Properties of Bone and Cartilage: Experimental Effects and Clinical Applications
Edited by C.T. Brighton, J. Black and S.R. Pollack
Grune & Stratton Inc. New York, IX, 1979

67. Brighton C.T., Friedenberg Z.B. and Black J.
Evaluation of the use of constant direct current in the treatment of non-union
In: Electrical Properties of Bone and Cartilage: Experimental Effects and Clinical Applications
Edited by C.T. Brighton, J. Black and S.R. Pollack
Grune & Stratton Inc. New York, 519, 1979

68. Brighton C.T., Black J., Friedenberg Z.B., Esterhai J.L., Day L.J., and Connolly J.F.
A multicentre study of the treatment of non-union with constant direct current
J. Bone Joint Surg. 63A: 2, 1981

69. Brighton C.T.
The treatment of non-unions with electricity
J. Bone Joint Surg. 63A: 847, 1981

70. Carey L.C. and Lepley D.
Effect of continuous DC electric current on wound healing
Surgical Forum: Clinical Congress 1962
American College of Surgeons 13: 32, 1962

71. Casagrande P.A. and Danahy P.R.
Delayed sciatic-nerve entrapment following the use of self-curing acrylic
J. Bone Joint Surg. 53A: 167, 1971

72. Cass C.A.
Some experiences of a battery stimulator in fractures with well established non-union
J. Bone Joint Surg. 57B: 251, 1975

73. Cave E.F.
Delayed union and non-union of fractures
In: Fractures and Other Injuries
Chicago Year Book Publishers Inc. 1960

74. Chacha P.B.
Salvage of severe open fractures of the tibia that might have required amputation
Injury 6: 154, 1974

75. Charnley J.
Congenital pseudarthrosis of the tibia treated by the intramedullary nail
J. Bone Joint Surg. 38A: 283, 1956

76. Charnley J.
The closed treatment of common fractures
E. & S. Livingstone Ltd., Edinburgh & London,
1957 (first edition), 1963 (second edition)

77. Charnley J.
Anchorage of the femoral head prosthesis to the shaft of the femur
J. Bone Joint Surg. 42B: 28, 1960

78. Charnley J.
Arthroplasty of the hip; a new operation
Lancet 1: 1129, 1961

79. Charnley J.
A biomechanical analysis of the use of cement to anchor the femoral head prosthesis to the shaft of the femur
J. Bone Joint Surg. 47B: 354, 1965

80. Charnley J.
Fracture of femoral prosthesis in total hip replacement
Clin. Orthop. 111: 105, 1975

81. Charnley J.
Low friction arthroplasty of the hip
Springer-Verlag, Berlin, Heidelberg, New York 1979

82. Cieszynski T.
Studies on the regeneration of ossal tissue III - influence of positive and negative electricity upon callus formation in humans
Arch. Immunol. Ther. Exp. 12: 269, 1964

83. Cochran G.V.B., Pawluk R.J., Bassett C.A.L.
Electromechanical characteristics of bone under physiologic moisture conditions
Clin. Orthop. 58: 249, 1968

84. Cochran G.V.B.
Experimental methods for stimulation of bone healing by means of electrical energy
Bull. N.Y. Acad. Med. 48: 899, 1972

85. Connolly J.F., Hahn H. and Jardon O.M.
The electrical enhancement of periosteal proliferation in normal and delayed fracture healing
Clin. Orthop. 124: 97, 1977

86. Cordey J., Steinemann S. and Perren S.M.
Electrochemical phenomena related to electrodes used for stimulation of bone formation
In: Electric Stimulation of Bone Growth and Repair
Edited by F. Burny, E. Herbst, M. Hinsenkamp
Springer-Verlag, Berlin, Heidelberg, New York, 69, 1978

87. Crawford R.R.
Treatment of non-union of fractures in the 19th century
J. Bone Joint Surg. 55A: 1685, 1973

88. Crelin E.S., Dueker D.K.
The response of the femur to trauma, a foreign body and a direct electrical current in mice
Yale J. Biol. Med. 43: 71, 1970

89. Dandy D.J. and Theodorou B.C.
The management of local complications of total hip replacement by the McKee-Farrar technique
J. Bone Joint Surg. 57B: 30, 1975

90. Darder A. and Gomar F.
A series of tibial fractures treated conservatively
Injury 6: 225, 1975

91. Davis L., MacKenzie D.A., Lavorgna J., Morrissy R., Graham J. and Akins C.
The establishment of a canine fracture healing model
Personal communication, 1976

92. Dawson W.J., Mead N.C., Sweeney H.J. and Schafer M.F.
Onlay fibular bone grafting in treatment of tibial fracture non-union
Clin. Orthop. 130: 247, 1978

93. Digby P.S.B.
Potentials and calcification in mammalian teeth and artery: an electrochemical basis
Ann. N.Y. Acad. Sci. 238: 202, 1974

94. Ducroquet R.
A propos des pseudarthrosis et inflexions congenitales due tibia
Mem. Acad. Chir. 63: 863, 1937

95. Durand B., Christel P., and Assailly J.
In vitro study of electric impedance of bone
In: Electric Stimulation of Bone Growth and Repair
Edited by F. Burny, E. Herbst, M. Hinsenkamp
Springer-Verlag, Berlin, Heidelberg, New York, 1978

96. Dwyer A.F. and Wickham G.G.
Direct current stimulation in spinal fusion
Med. J. Aust. 1: 73, 1974

97. Dwyer A.F.
The use of electrical current stimulation in spinal fusion
Orthop. Clin. North Amer. 6: 265, 1975

98. Emneus H., Stenram U., and Baecklund J.
An x-ray spectrographic investigation of the soft tissue around titanium and cobalt alloy implants
Acta. Orthop. Scand. 30: 226, 1960

99. Engh C.A., Bruno P.D., Kenmore P.I., Chandler H.P.
Porous-coated hip replacement; a three year follow up study
The American Academy of Orthopaedic Surgeons, 1981

100. Eriksson C.
Streaming potentials and other water-dependent effects in mineralised tissues
Ann. N.Y. Acad. Sci. 238: 321, 1974

101. Evans E.M., Freeman M.A.R., Miller A.J. and Vernon-Roberts B.
Metal sensitivity as a cause of bone necrosis and loosening of the prosthesis in total joint replacement
J. Bone Joint Surg. 57B: 289, 1974

102. Eyre-Brook A.L., Baily R.A.J. and Price C.H.G.
Infantile pseudarthrosis of the tibia: three cases treated successfully by delayed autogenous by-pass graft with some comments on the causative lesion
J. Bone Joint Surg. 51B: 604, 1969

103. Fisher C.
The new Quantimet 720
Microscope 19: 1, 1971

104. Forbes D.B.
Subcortical iliac bone grafts in fracture of the tibia
J. Bone Joint Surg. 43B: 672, 1961

105. Friedenberg Z.B. and Brighton C.T.
Bioelectric potentials in bone
J. Bone Joint Surg. 48A: 915, 1966

106. Friedenberg Z.B. and Kohanim M.
The effect of direct current on bone
J. Surg. Gynaecol. and Obstet. 127: 97, 1968

107. Friedenberg Z.B. and Smith H.G.
Electrical potentials in intact and fractured tibias
Clin. Orthop. 63: 223, 1969

108. Friedenberg Z.B., Andrews E.T., Smolenski B.I., Pearl B.W. and Brighton C.T.
Bone reaction to varying amounts of direct current
J. Surg. Gynaecol. and Obstet. 131: 894, 1970

109. Friedenberg Z.B., Roberts P.G., Didizian N.H. and Brighton C.T.
Stimulation of fracture healing by direct current in the rabbit fibula
J. Bone Joint Surg. 53A: 1400, 1971

110. Friedenberg Z.B., Harlow M.C. and Brighton C.T.
Healing of non-union of the medial malleolus by means of direct current; a case report
J. of Trauma 11: 883, 1971

111. Friedenberg Z.B., Harlow M.C., Heppenstall R.B. and Brighton C.T.
The cellular origin of bioelectric potentials in bone
Calcif. Tiss. Res. 13: 53, 1973

112. Friedenberg Z.B., Zemsky L.M., Pollis R.P. and Brighton C.T.
The response of non-traumatized bone to direct current
J. Bone Joint Surg. 56A: 1023, 1974

113. Fukada E. and Yasuda I.
On the piezoelectric effect of bone
J. Physiol. Soc. Jap. 12: 1158, 1957

114. Galante J., Rostoker W., Lueck R., Ray R.D.
Scintered fiber metal composites as a basis for attachment of implants to bone
J. Bone Joint Surg. 53A: 101, 1971

115. Galvani A.
Commentarius 1791

116. Garcia D.A., Tow D.E., Kapur K.K. and Wells H.
Relative accretion of 99m Tc-polyphosphate by forming and resorbing bone systems in rats: its significance in the pathologic basis of bone scanning
J. Nuclear Med. 17: 93, 1976

117. Garrett A.C.
Electrophysiology and electrotherapeutics
Boston, 1860

118. Gayda T.
Recherches d'Electrophysiologie sur les Tissues de Soutien
Arch. Ital. Biol. 58: 417, 1912

119. Geddes L.A. and Baker L.E.
The specific resistance of biological material - a compendium of data for the biomedical engineer and physiologist
Med. & Biol. Eng. 5: 271, 1967

120. Greatbatch W. and Chardack W.M.
Myocardial and endocardiac electrodes for chronic implantation
Ann. N.Y. Acad. Sci. 167: 234, 1969

121. Greatbatch W., Piersma B., Shannon F.D. and Calhoon S.W.Jr.
Polarization phenomena relating to physiological electrodes
Ann. N.Y. Acad. Sci. 167: 722, 1969

122. Griffith M.J., Seidenstein M.K., Williams D. and Charnley J.
Eight year results of Charnley arthroplasties of the hip with special reference to the behaviours of cement
Clin. Orthop. 137: 24, 1978

123. Gupta R.C., Kumar S. and Gupta K.K.
A clinical evaluation of osteomedullography in diaphyseal fractures
J. Trauma 20: 507, 1980

124. Guyton A.C.
Textbook of Medical Physiology
W.B. Saunders Co., Philadelphia, 915, 1956

125. Hamblen D.L.
Scientific basis of present day fracture treatment
J. R. Coll. Surg. Edin. 24 (6): 340, 1979

126. Hanson L.W. and Eppright R.H.
Posterior bone grafting of the tibia for non-union; a review of twenty-four cases
J. Bone Joint Surg. 48A: 27, 1966

127. Hardinge K.
Congenital anterior bowing of the tibia
Ann. R.Coll. Surg. Eng. 51: 17, 1972

128. Harmon P.H.
A simplified approach to the posterior tibia for bone grafting and fibula transference
J. Bone Joint Surg. 27: 496, 1945

129. Harrington D.B., Meyer R., Klein R.A.
Effects of small amounts of electric current at the cellular level
Ann. N.Y. Acad. Sci. 238: 300, 1974

130. Harris W.H., Thrasher E.L., Moyen B.J., Cobden R.H., Davis L.A., MacKenzie D.A. and Cywinski J.
Stimulation of fracture healing by direct current: an experimental study in dogs
22nd Annual Orthopaedic Research Society Meeting, New Orleans, Louisiana, 1976

131. Hartshorne E.
On the Causes and Treatment of Pseudarthrosis and Especially of That Form of It Sometimes Called Supernumerary Joint
Am. J. Med. Sci. New Series 1: 143, 1841

132. Hassler C.R., Rybicki E.F., Diegle R.B., Clark L.C.
Studies of enhanced bone healing via electric stimuli: comparative effectiveness of various parameters
Clin. Orthop. 124: 9, 1977

133. Hassler C.R., CummingsK.D., Clark L.C., Rybicki E.F. and Diegle R.B.
Augmentation of bone healing via electrical stimuli
In: Electrical Properties of Bone and Cartilage: Experimental Effects and Clinical Applications
Edited by C.T. Brighton, J. Black and S.R. Pollack
Grune & Stratton Inc. New York, 155, 1979

134. Heimel R., Zichner L., Schmidt A. and Happel M.W.
Electrical stimulation of cement-free implantation of hip and knee endoprostheses
In: Electrical Properties of Bone and Cartilage: Experimental Effects and Clinical Applications
Edited by C.T. Brighton, J. Black and S.R. Pollack
Grune & Stratton Inc. New York, 665, 1979

135. Heppenstall R.B., Grislis G. and Hunt T.K.
Tissue gas tensions and oxygen consumption in healing bone effects
Clin. Orthop. 106: 357, 1975

136. Herbst E.
Electric stimulation of bone growth and repair: a review of different stimulation methods
In: Electric stimulation of Bone Growth and Repair
Edited by F. Burny, E. Herbst, M. Hinsenkamp
Springer-Verlag, Berlin, Heidelberg, New York, 1, 1978

137. Herbst E. and von Satzger G.
Electrical pulsed current stimulation in five cases of congenital pseudarthrosis of the tibia
In: Electrical Properties of Bone and Cartilage: Experimental Effects and Clinical Applications
Edited by C.T. Brighton, J. Black and S.R. Pollack
Grune & Stratton Inc. New York, 639, 1979

138. Hoar T.P. and Mears D.C.
Corrosion-resistant alloys in chloride solutions: materials for surgical implants
Proc. R. Soc. (London) 294A: 486, 1966

139. Hohenwallner W. and Wimmer E.
The malachite green micromethod for determination of inorganic phosphate
Clinia. Chimica Acta. 45: 169, 1973

140. Homsy C.A.
Implant stabilization, chemical and biochemical consideration
Orth. Clin. of North America 4: 295, 1973

141. Iida H., Ko S., Miyashita Y., Savada S., Maeda M., Nagayama H., Kawai A., Kitamura S.
On electric callus produced by alternating current
J. Kyoto Pref. Coll. Med. 60: 561, 1956

142. Inoue S., Ohashi R., Imae R., Ichida M. and Yasuda I.
The electrical induction of callus formation and external skeletal fixation using methyl methacrylate for delayed union of open tibia fracture with segmental loss
Clin. Orthop. 124: 92, 1977

143. Jackson R.W. and MacNab I.
Fractures of the shaft of the tibia
Am. J. Surg. 97: 543, 1959

144. Jaffe J.
Tumours and tumorous conditions of bones and joints
Kimpton, London, 252, 1958

145. Jahn T.L.
A possible mechanism for the effect of electrical potential on apatite formation in bone
Clin. Orthop. 56: 261, 1968

146. Janssen L.W.M., Roelofs J.M.M., Visser W.J. and Wittebol P.
Hypothesis of bone remodelling and fracture healing by electro-stimulation
In: Electric Stimulation of Bone Growth and Repair
Edited by F. Burny, E. Herbst, M. Hinsenkamp
Springer-Verlag, Berlin, Heidelberg, New York, 61, 1978

147. Jones K.G. and Barnett H.C.
Cancellous bone grafts for non-union of the tibia through the postero-lateral approach
J. Bone Joint Surg. 37A: 125, 1955

148. Jones A.G., Francis M.D. and Davis M.A.
Bone scanning; radionuclide reaction mechanisms
J. Nuclear Med. 6: 3, 1976

149. Jorgensen T.E.
The effect of electric current on the healing of crural fractures
Acta. Orthop. Scand. 43: 421, 1972

150. Jorgensen T.E.
Electrical stimulation of human fracture healing by means of a slow pulsating asymmetrical direct current
Clin. Orthop. 124: 124, 1977

151. Kane W.J.
The use of supplementary electronic bone growth in primary and secondary lumbosacral fusions
In: Electrical Properties of Bone and Cartilage: Experimental Effects and Clinical Applications
Edited by C.T. Brighton, J. Black and S.R. Pollack
Grune & Stratton Inc. New York, 563, 1979

152. Kane W.J.
Posterior spinal fusion using the osteostim implantable bone growth stimulator model S11
Submission to the U.S.A. Food & Drug Authority 1981

153. Kaye M., Silverton S. and Rosenthall L.
Technetium-99m-pyrophosphate: studies *in vivo* and *in vitro*
J. Nuclear Med. 16: 40, 1975

154. King K.F.
Periosteal pedicle grafting in dogs
J. Bone Joint Surg. 58B: 117, 1976

155. Klawitter J.J. and Hulbert S.F.
Application of porous ceramics for the attachment of load bearing internal orthopaedic applications
J. Biomed. Mater. Res. Symp. 2: 161, 1971

156. Kraus W., Lechner F.
Die Heilung von Pseudarthrosen und Spontanfrakturen durch strukturbildenede elecktrodynamische Potentiale
Münch. Med. Wochenschr 114: 118, 1972

157. Kraus W.
Apparatus and method for aiding formation of bone forming material
Patent specification 1, 311, 519 London:
The Patent Office 1973

158. Lamb R.H.
Posterolateral bone graft for non-union of the tibia
Clin. Orthop. 64: 114, 1969

159. Lavine L.S., Lustrin I. and Shamos M.H.
The influence of direct electric current *in vivo*
Calcif. Tiss. Res. 2 (Supplementary); 9, 1968

160. Lavine L.S., Lustrin I. and Shamos M.H.
Experimental model for studying the effect of electrical current on bone *in vivo*
Nature 224: 1112, 1969

161. Lavine L.S., Lustrin I., Shamos M.H. and Moss M.L.
The influence of electric current on bone regeneration *in vivo*
Acta. Orthop. Scand. 42: 305, 1971

162. Lavine L.S., Lustrin I., Shamos M.H., Rinaldi R.A. and Liboff A.R.
Electric enhancement of bone healing
Science 175: 1118, 1972

163. Lavine L.S.
Healing fractures electrically
Med. World News 14: 20, 1973

164. Lavine L.S., Lustrin I., Rinaldi R. and Shamos M.H.
Clinical and ultrastructural investigations of electrical enhancement of bone healing
Ann. N.Y. Acad. Sci. 238: 552, 1974

165. Lavine L.S., Lustrin I. and Shamos M.H.
Treatment of congenital pseudarthrosis of the tibia with direct current
Clin. Orthop. 124: 69, 1977

166. Lazunsky M.G.
Materials for total hip replacement
In: Instructional Course Lectures
The American Academy of Orthopaedic Surgeons
23: 164, 1974
The C.V. Mosby Co., St. Louis

167. Lechner F. and Ascherl R.
Experiences and results of the electrodynamic fields treatment in cases of pseudarthroses and delayed bone repair
Acta. Orthop. Belg. 44: 699, 1978

168. Lembert E., Galante J. and Rostoker W.
Fixation of skeletal replacements by fiber metal composites
Clin. Orthop. 87: 303, 1972

169. Lente R.W.
N.J. Med. Collateral Sci. 5:
New Series, New York 1850

170. Levy D.D.
Induced osteogenesis by electrical stimulation
Ph.D. Thesis (Bioengineering)
The Polytechnic Institute of Brooklyn 35, 1971

171. Levy D.D.
Induced osteogenesis by electrical stimulation
J. Electro-Chem. Soc. 118: 1438, 1971

172. Levy D.D. and Rubin D.
Inducing bone growth *in vivo* by pulse stimulation
Clin. Orthop. 88: 218, 1972

173. Levy D.D.
Pulsed electrical stimulation technique for inducing bone growth
Ann. N.Y. Acad. Sci. 238: 478, 1974

174. Liboff A.R., Rinaldi R.A., Lavine L.S. and Shamos M.H.
On electrical conduction in living bone
Clin. Orthop. 106: 330, 1975

175. Lloyd-Roberts G.C. and Shaw N.E.
The prevention of pseudarthrosis in congenital kyphosis of the tibia
J. Bone Joint Surg. 51B: 100, 1969

176. Lunceford E.
Personal communication, 1981

177. McBryde A.M.Jr. and Stelling F.H.
Infantile pseudarthrosis of the tibia
J. Bone Joint Surg. 54A: 1354, 1972

178. McElhaney J.H., Stalnaker R. and Bullard R.
Electrical fields and bone loss or disuse
J. Biochem. 4: 47, 1968

179. McElhannon F.M. Jr.
Congenital pseudarthrosis of the tibia
South. Med. J. 68 (7): 324, 1975

180. McFarland B.
Birth fracture of the tibia
Br. J. Surg. 27: 706, 1940

181. McFarland B.
Pseudarthrosis of the tibia in childhood
J. Bone Joint Surg. 33B: 36, 1951

182. McNeil D.R.
Analysis of bone growth stimulator: patient data 1979
Personal communication

183. Marino A.A. and Becker R.O.
Piezoelectric effect and growth control in bone
Nature 228: 473, 1970

184. Marino A.A. and Becker R.O.
Origin of the piezoelectric effect in bone
Calcif. Tiss. Res. 8: 177, 1971

185. Marino A.A. and Becker R.O.
Electrical osteogenesis: an analysis
Clin. Orthop. 123: 280, 1977

186. Martin C.St., Parsons J.R., Weiss A.B. and Alexander H.
The distribution of direct current stimulated bone growth about long titanium cathodes
Presented to the Ann. Meet. Amer. Acad. of Orth. Surg. 1980

187. Martin C. St., Parsons J.R., Weiss A.B. and Alexander H.
The distribution of direct current stimulated bone growth about long titanium cathodes
Trans.26th Orthop. Res. Soc. 5: 113, 1980

188. Masserman R.L., Peterson H.A. and Bianco A.J.
Congenital pseudarthrosis of the tibia
Clin. Orthop. 99: 140, 1974

189. Mazureik C. and Eriksson C.
Preliminary clinical evaluation of the effect of small electrical currents on the healing of jaw fractures
Clin. Orthop. 124: 84, 1977

190. Meachim G. and Williams D.F.
Changes in Nonosseous tissue adjacent to titanium implants
J. Biomed. Mater. Res. Symp.7: 555, 1973

191. Meyer S., Weiland A.J., and Willenegger H.
The treatment of infected non-union of fractures of long bones
J. Bone Joint Surg. 57A: 836, 1975

192. Miller W., Grady L.J. and Gael R.F.
Posterior bone grafts in non-union of fractures of the shafts of the tibia
South.Med. J. 62: 1254, 1969

193. Minkin C., Poulton B.R. and Hoover W.H.
The effect of direct current on bone
Clin. Orthop. 57: 303, 1968

194. Moore A.T.
The self-locking metal hip prosthesis
J. Bone Joint Surg. 39A: 811, 1957

195. Nicoll E.A.
Fractures of the tibia shaft
A survey of 705 cases
J. Bone Joint Surg. 46B: 373, 1964

196. Nicoll E.A.
Infantile pseudarthrosis of the tibia (Editorial)
J. Bone Joint Surg. 51B: 589, 1969

197. Nolan D.R., Fitzgerald R.H.Jr., Bechenbaugh R.D. and Coventry M.B.
Complications of total hip arthroplasty treated by re-operation
J. Bone Joint Surg. 57A: 977, 1975

198. O'Connor B.T., Charlton H.M., Currey J.D., Kirby D.R.S. and Woods C.
The effects of electric current on bone *in vivo*
Nature 222: 162, 1969

199. O'Reilly R.J., Gaffney R.D., Paterson D.and Cook D.J.
An algorithm for the automatic computer analysis of 99mTc-pyrophosphate scans of fractures of the tibia
Aust. Phys. Sci. Med. 2: 29, 1979

200. O'Reilly R.J., Cook D.J., Gaffney R.D., Angel K.R. and Paterson D.C.
Can serial scintigraphic studies detect delayed fracture union in man?
Clin. Orthop. 160: 228, 1981

201. Pappas P.W.
The use of chrome-alum-gelatin (subbing) solution for a general adhesive for paraffin sections
Stain Technol. 46: 12, 1971

202. Paterson D.C., Hillier T.M., Carter R.F., Ludbrook J., Maxwell G.M., Savage J.P.
Electrical bone-growth stimulation in an experimental model of delayed union
The Lancet, 1278, 1977

203. Paterson D.C., Hillier T.M., Carter R.F., Ludbrook J., Maxwell G.M., Savage J.P.
Experimental delayed union of the dog tibia and its use in assessing the effect of an electrical bone growth stimulator
Clin. Orthop. 128: 340, 1977

204. Paterson D.C., Lewis G.N. and Cass C.A.
Treatment of delayed union and non-union with an implanted direct current stimulator
Clin. Orthop. 148: 117, 1980

205. Paterson D.C., Lewis G.N. and Cass C.A.
Treatment of congenital pseudarthrosis of the tibia with direct current stimulation
Clin. Orthop. 148: 129, 1980

206. Paterson D.
Clinical use of the osteostim - an implanted bone growth stimulator - for impaired bone healing
In: Instructional Course Lectures
American Academy of Orthopaedic Surgeons 1982 (in press)
The C.V. Mosby Co., St. Louis

207. Pawluk R.J. and Bassett C.A.L.
Electromechanical factors in healing cortical bone defect
Calcif. Tiss. Res. 4 (Supplement): 120, 1970

208. Pellicci P.M., Salvati E.A. and Robinson H.J.
Mechanical failures in total hip replacement requiring re-operation
J. Bone Joint Surg. 61A: 28, 1979

209. Phemister D.B.
Treatment of ununited fractures by onlay bone grafts without screw or tie fixations and without breaking down of the fibrous union
J. Bone Joint Surg. 29: 946, 1947

210. Rae T.
A study of the effects of particulate metals of orthopaedic interest on murine macrophages *in vitro*
J. Bone Joint Surg. 57B: 444, 1975

211. Rahn B.A. and Perren S.M.
Calcein blue as a fluorescent label in bone
Experientia 26: 519, 1970

212. Rahn B.A. and Perren S.M.
Xylenol orange, a fluorochrome useful in polychrome sequential labelling of calcifying tissues
Stain Technol. 46: 125, 1971

213. Ranawat C.S., Insall J. and Shine J.
Duo-condylar knee arthroplasty
Clin. Orthop. 120: 76, 1976

214. Rathgeb J.M., Ramsey P.L. and Cowell H.R.
Congenital kyphoscoliosis of the tibia
Clin. Orthop. 103: 178, 1974

215. Richez J., Chamay A. and Bieler L.
Bone changes due to pulses of direct electric microcurrent
Virchow's Arch. Abt. A. Path.Anat. 357: 11, 1972

216. Riseborough E.J., Morrissy R.T., Hall J.E., Bernal J. and Trott A.W.
Congenital pseudarthrosis of the tibia - results in forty patients
J. Bone Joint Surg. 56A: 1312, 1974

217. Robinson R.A.
Healing of bone discontinuity in puppies and dogs
J. Bone Joint Surg. 53A: 1017, 1971

218. Rogers W.J.
Iliac inlay-on-edge bone graft
J. Bone Joint Surg. 50A: 1410, 1968

219. Rokkanen P., Slatis P. and Kallio E.
Subcortical bone grafting (Phemister-Charnley) in the treatment of delayed union of tibial shaft fractures
Acta. Chir. Scand. 133: 523, 1967

220. Rokkanen P. and Slatis P.
Subcortical cancellous bone grafting in the treatment of delayed union of tibial shaft fractures
J. Trauma 12: 1075, 1972

221. Rose R.M., Radin E.L., Paul I.L.
Repairing the human skeleton: materials for orthopaedics
Technol. Rev. 33: 41, 1974

222. Rosen H.
Operative treatment of non-union of long bone fractures
J. Cont. Educ. Orthop. 7 (6): 13, 1979

223. Rosenthall L. and Kaye M.
Technetium-99m-Pyrophosphate kinetics and imaging in metabolic bone disease
J. Nuclear Med. 16: 33, 1975

224. Rosenthall L., Hill R.O. and Chuang S.
Observation of the use of 99mTc phosphate imaging in peripheral bone trauma
Radiology 119: 637, 1976

225. Rowley B.L.
Electrical current effects on E. coli growth plates
Proc. of the Soc. for Exp. Biol. in Med.
137: 929, 1972

226. Russell H.K.
A modification of Movat's pentachrome stain
Arch. Pathol. 94: 187, 1972

227. Sabiston David C.
Textbook of Surgery - the biological basis of modern surgical practice
W.B. Saunders Co. Philadelphia, 10th edition, 31, 1968

228. Sage F.P.
Congenital anomalies
In: Campbell's Operative Orthopaedics
St. Louis, C.V. Mosby Co. 1971 (fifth edition)

229. Sakellarides H.T., Freeman P.A. and Grant B.D.
Delayed union and non-union of tibial shaft fractures
J. Bone Joint Surg. 46A: 557, 1964

230. Sanchis M., Zahir A. and Freeman M.A.R.
The experimental simulation of Perthes' disease by consecutive interruptions of the blood supply to the capital femoral epiphysis in the puppy
J. Bone Joint Surg. 55A: 335, 1973

231. Sansen W., De Dijcker F., Stan S., and Mulier J.C.
Four-point measurement of the impedance of bone *in vivo*
In: Electric Stimulation of Bone Growth and Repair
Edited by F. Burny, E. Herbst, M. Hinsenkamp
Springer-Verlag, Berlin, Heidelberg, New York, 15, 1978

232. Schwan H.P.
Electrode polarization impedance and measurements in biological materials
Ann. N.Y. Acad. Sci. 148: 191, 1968

233. Shamos M.H., Lavine L.S., and Shamos M.I.
Piezoelectric effect in bone
Nature 197: 81, 1963

234. Shamos M.H. and Lavine L.S.
Physical bases for bioelectric effects in mineralized tissues
Clin. Orthop. 35: 177, 1964

235. Shamos M.H. and Lavine L.S.
Piezoelectricity as a fundamental property of biological tissue
Nature (London) 213: 267, 1968

236. Siegel S.
Non-parametric statistics for the behavioural sciences
McGraw-Hill, New York, 1956

237. Skolnick M.D., Coventry M.B., Ilstrup D.M.
Geometric total knee arthroplasty
J. Bone Joint Surg. 58A: 749, 1976

238. Smith L.
Ceramic plastic material as a bone substitute
Arch. of Surg. 87: 653, 1963

239. Snedecor G.W., Cochran W.G.
Statistical Methods, Sixth edition
Ames, Iowa State Univ. Press, 1967

240. Sofield H.A. and Millar E.A.
Fragmentation, realignment, and intramedullary rod fixation of deformities of the long bones in children
J. Bone Joint Surg. 41A: 1371, 1959

241. Sofield H.A.
Congenital pseudarthrosis of the tibia
Clin. Orthop. 76: 33, 1971

242. Solar R.J., Pollack S.R. and Korostoff E.
In vitro corrosion testing of titanium surgical implant alloys: an approach to understanding titanium release from implants
J. Biomed. Mat. Res. 13: 217, 1979

243. Souter A.
Arthroplasty of the elbow with particular reference to metallic hinge arthroplasty in rheumatoid patients
Ortho. Clinics of North America 2: 395, 1973

244. Souter W.A.
Autogenous cancellous strip grafts in the treatment of delayed union of long bone fractures
J. Bone Joint Surg. 51B: 63, 1969

245. Spadaro J.A.
Antibacterial effects of silver electrodes with weak direct current
Antimicrob. Agents and Chemother. 6: 637, 1974

246. Spadaro J.A.
Electrically stimulated bone growth in animals and man
Clin. Orthop. 122: 325, 1977

247. Spadaro J.A. and Berger T.J.
Orthopaedic electrodes; metal and polarity evaluation in short term marrow cell culture
Trans. Third Ann. Meet. Soc. Biomat. 140, 1977

248. Spadaro J.A., Becker R.O.
Function of implanted cathodes in electrode-induced bone growth
Med. Biol. Eng. Comput. 17: 769, 1979

249. Spadaro J.A.
Electrical osteogenesis - role of the electrode material
In: Electrical Properties of Bone and Cartilage: Experimental Effects and Clinical Applications
Edited by C.T. Brighton,J. Black and S.R. Pollack
Grune & Stratton Inc. New York, 189, 1979

250. Spector M., Flemming W.R., Kreutner A. and Sauer B.W.
Bone growth into porous high-density polyethylene
J. of Biomed. Mater. Res. Symp. 7: 595, 1976

251. Spector M., Michno M.J., Smarook W.H. and Kwiatkowski G.T.
A high-modulus polymer for porous orthopaedic implants: biomechanical compatibility of porous implants
J. of Biomed. Mater. Res. Symp. 12: 665, 1978

252. Spector M., Davis R.J., Seigling J.A., Harmon S.L. Irvin M.P. and Ballintyn N.J.
Porous plastic coating for fixation of joint prostheses
American Academy of Orthopaedic Surgeons Scientific Exhibit, San Francisco, California 1979

253. Spector M., Harmon S.L., Elridge J.T. and Davis R.J.
Porous polymeric coatings for orthopaedic implants
In: Mechanical Properties of Biomaterials
Edited by G.W. Hastings and D.F. Williams
John Wiley and Sons Ltd. New York; 299, 1980

254. Stan S., Mulier J.C., Sansen W. and DeWaele P.
Effect of direct current on the healing of fractures
In: Electric Stimulation of Bone Growth and Repair
Edited by F. Burny, E. Herbst, M. Hinsenkamp
Springer-Verlag, Berlin, Heidelberg, New York, 47, 1978

255. Stefan S., Sansen W. and Mulier J.C.
Experimental study on the electrical impedance of bone and the effect of direct current on the healing of fractures
Clin. Orthop. 120: 264, 1976

256. Steinberg M.E., Bosch A., Schwan A. and Glazer R.
Electric potentials in stressed bone
Clin. Orthop. 61: 294, 1968

257. Steinberg M.E., Lyet J.P. III, and Pollack S.R.
Stress-generated potentials (SGPs) in fracture callus
Trans. 26th Orthopaedic Res. Soc. 5: 115, 1980

258. Sullivan B., Homsy C.A., Woods G.W. and Tullos N.S.
Stabilization of Thompson femoral head prosthesis with a porous stem coating
Clin. Orthop. 132: 136, 1978

259. Swanson S.A.V., and Freeman M.A.R.
The scientific basis of joint replacement
Pitman Medical Publishing Co., Melbourne 1977

260. Tapp E., Kovacs R., and Carroll R.
Tetracycline staining of tissues *in vitro*
Stain Technol. 40: 199, 1965

261. Tonna E.A. and Conkrite E.Q.
Cellular response to fracture studied with tritiated thymidine
J. Bone Joint Surg. 43A: 352, 1961

262. Traina G.C. and Gulino G.
Medullary rods as electric conductors for osteogenic stimuli in human bone
In: Electrical Properties of Bone and Cartilage: Experimental Effects and Clinical Applications
Edited by C.T. Brighton, J. Black and S.R. Pollack
Grune & Stratton Inc. New York, 567, 1979

263. Treharne R.W., Brighton C.T., Korostoff E. and Pollack S.R.
Application of direct current to *in vitro* foetal rat tibiae
Trans. Orthop. Res. Soc. 1: 113, 1976

264. Treharne R.W., Brighton C.T., Pollack S.R. and Korostoff E.
An *in vitro* study of electrical osteogenesis using direct and pulsating currents
Clin. Orthop. 145: 300, 1979

265. Treharne R.W., Brighton C.T., Korostoff E. and Pollack S.R.
Application of direct, pulsed and SGP-shaped currents to *in vitro* foetal rat tibiae
In: Electrical Properties of Bone and Cartilage: Experimental Effects and Clinical Applications
Edited by C.T. Brighton, J. Black and S.R. Pollack
Grune & Stratton Inc. New York, 169, 1979

266. Uhtoff H.K.
Mechanical factors influencing the holding power of screws in compact bone
J. Bone Joint Surg. 55B: 633, 1973

267. Urist M.R., Mazet R., McLean F.C.
The pathogenesis and treatment of delayed union and non-union
J. Bone Joint Surg. 36A: 931, 1954

268. Vanderhoeft P.J., Kelly P.J. and Peterson L.F.A.
Determination of growth rates in canine bone by means of tetracycline-labelled patterns
Lab. Invest. 11: 714, 1962

269. Van Nes C.P.
Congenital pseudarthrosis of the leg
J. Bone Joint Surg. 48A: 1467, 1966

270. Vernon-Roberts B. and Freeman M.A.R.
The tissue response to total joint replacement prostheses
In: The Scientific Basis of Joint Replacement
Edited by S.A.V. Swanson and M.A.R. Freeman
Pitman Medical Publishing Co. Ltd. Kent, England, 86, 1977

271. Vincentelli R., and Evans F.
Relations among mechanical properties, collagen fibres and calcification in adult human cortical bone
J. Biomech. 4: 193, 1971

272. Wagner H.
Surgical lengthening or shortening of femur and tibia. Technique and indications
In: Leg Length Discrepancy. The Injured Knee
Edited by D.S. Hungerford
Springer-Verlag, Berlin, Heidelberg, New York, 71, 1977

273. Walter C.W., Van Slyke K.K., Hufnagel C.
The mobilization and deposition of bone calcium by electrolysis: a preliminary report
In: Surgery
Edited by A. Ochsner, O.H. Wangensteen
The C.V. Mosby Co. St. Louis 145, 1941

274. Weber F.A. and Charnley J.
A radiological study of fractures of acrylic cement in relation to the stem of a femoral head prosthesis
J. Bone Joint Surg. 57B: 297, 1975

275. Weber E.R., Daube J.R. and Coventry M.B.
Peripheral neuropathies associated with total hip arthroplasty
J. Bone Joint Surg. 58A: 66, 1976

276. Weigert M., Werhahn C., Mellerowicz H., Bandow R.
Stimulation of longitudinal growth and fracture healing by electrical implants
Proceedings of 12th Congress Societe Internationale de Chirurgie et de Traumatologie 47: 1972

277. Weigert M., Werhahn C., Bandow R., Mellerowicz H.
Bone potential by electrical stimulation
Z. Orthop. 111: 778, 1973

278. Weigert M. and Werhahn C.
The influence of electric potentials on plated bones
Clin. Orthop. 124: 20, 1977

279. Welsh R.P., Pilliar R.M. and MacNab I.
Surgical implants: the role of surface porosity in fixation to bone and acrylic
J. Bone Joint Surg. 53A: 963, 1971

280. White E.H. and Earley N.W.
Screw stabilisation in fractures of the tibial shaft
J. Bone Joint Surg. 35A: 749, 1953

281. Wilber M.C.
Surface direct current bioelectric potentials in the normal and injured human thigh
Texas Rept. Biol. Med. 36: 197, 1978

282. Williams D.F.
The response of the body environment to implants
In: Implants in Surgery
Edited by D.F. Williams and R. Roaf
W.B. Saunders Co. Ltd., London, 203, 1973

283. Williams D.F.
Titanium as a metal for implantation
J. Med. Eng. and Tech. 1: 195, 1977

284. Williams D.F.
Titanium as a metal for implantation
Part 2: biological properties and clinical applications
J. Med. Eng. Tech. 1: 266, 1977

285. Willert H.G., Ludwig J. and Semlitsch M.
Reaction of bone to methacrylate after hip arthroplasty
J. Bone Joint Surg. 56A: 1368, 1974

286. Wilson C.L.
Experimental attempts to stimulate bone growth
J. Bone Joint Surg. 52A: 1033, 1970

287. Wittebol P.
Stimulation of non epiphyseal bone growth
Calcif. Tiss. Res. 4: 122, 1970

288. Woldseth R.
All you ever wanted to know about X-ray energy spectrometry
Kevex Corporation, California 1973

289. Wolff J.
Des Gesetz der Transformation der Knochen
A. Hirschwald, Berlin, 1892

290. Wollast R., Hinsenkamp M. and Burny F.
Physiochemical effect of an electric potential on bone growth
In: Electric Stimulation of Bone Growth and Repair
Edited by F. Burny, E. Herbst, M. Hinsenkamp
Springer-Verlag, Berlin, Heidelberg, New York, 29, 1978

291. Yasuda I.
Fundamental aspects of fracture treatment
J. Kyoto Perf. Coll. of Med. 4: 395, 1953

292. Yasuda I., Noguchi K. and Sata T.
Dynamic callus and electrical callus
J. Bone Joint Surg. 37A: 1292, 1955

293. Yasuda I.
Electrical callus and callus formation by electret
Clin. Orthop. 124: 53, 1977

294. Young F.A.
Porous vitallium dental implants
J. Biomed. Mater. Res. Symp. 5: 404, 1974

295. Zadek R.E. and Robinson R.A.
The healing of an osteoperiosteal discontinuity of standard length, in skeletally mature and immature canine radii in the healing of osseus tissue
Natl. Acad. Sci.
National Research Council, Washington D.C. 9, 1967

296. Zichner L.
Electrical stimulation of bone healing - a histologic study
SICOT, Kyoto, Japan, 1978

297. Zichner L. and Happel M.W.
Treatment of congenital and acquired non-unions by means of an invasive device
In: Electrical Properties of Bone and Cartilage: Experimental Effects and Clinical Applications
Edited by C.T. Brighton, J. Black and S.R. Pollack
Grune & Stratton Inc. New York 581, 1979

APPENDICES

APPENDIX A

The project reported in Chapters 2 and 3 was wholly planned, organised and actively carried out by the author. The author prepared the submission for and obtained research grants.

Dr. T.M. Hillier, as the orthopaedic/research registrar at the Adelaide Children's Hospital gave valuable assistance with the animal operating. Drs. R.F. Carter and J.P. Savage assessed the histopathology and nuclear scan findings respectively with the author prior to their independent assessment by Professor J. Ludbrook.

Professors J. Ludbrook and G.M. Maxwell gave valuable critical advice during the project and made their facilities freely available to the author for this work. Their contributions are gratefully acknowledged.

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of the thesis held in the University of Adelaide Library.

APPENDIX B

The project reported in Chapters 2 and 3 was wholly planned, organised and actively carried out by the author. The author prepared the submission for and obtained research grants.

ELECTRICAL BONE-GROWTH STIMULATION IN AN EXPERIMENTAL MODEL OF DELAYED UNION

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Summary An experimental model has been devised for the consistent production of delayed bone healing of the tibia in adult dogs. A double-blind trial, with bias eliminated, was used to evaluate the use of a commercially available direct-current bone-growth stimulator with this model. The stimulator produced a statistically significant acceleration of bone healing at four weeks in the experimental model. Osteogenesis was normal, and no dysplastic, inflammatory, or neoplastic changes were found. This research has shown that electrical stimulation of bone is safe and augments bone formation. The bone-growth stimulator unit remains on trial, but in future it may alter the management of many difficult orthopædic problems.

Introduction

STRESS-GENERATED piezoelectric potentials in bone were first described by Japanese workers[1,2] and then by workers in the U.S.A.[3-5] Others have confirmed that (1) when stressed, bone develops an electric potential proportional to the applied stress, (2) compression of bone in vivo stimulates new bone formation, (3) when excised bone is stressed, those areas under tension become positively charged,[6,7] and (4) when an electric current is passed through live bone, osteogenesis can be stimulated at the negative electrode. Several investigators[7-15] have confirmed this last observation in animals by inserting electrodes into the medullary cavity of intact long bones or by stimulating osteogenesis in fresh fractures and freshly osteotomised long bones. Hartshorne[16] in 1841 reported the first clinical use of this technique in man by a Mr Birch, surgeon, of St. Thomas' Hospital, London. The technique subsequently fell into disrepute until Cieszynski[17] reported the results of applying direct current by means of surface electrodes to bone defects in man. Since then there have been increasing numbers of reports of its use in patients with non-union of fractures, congenital pseudoarthrosis, bone defects, and in posterior spinal fusion.[18] It is still not clear, however, what type and size of electrical stimulation, field density of the current supplied, and positioning of anodes and cathodes should be used and, indeed, whether the technique has any significant effect at all. Several workers[13-17,19-21] have stressed the need for adequate clinical trials before electrical stimulation of bone becomes an accepted part of orthopædic surgical practice. We believed that before even this could be justified, proof of augmented bone formation with a bone stimulator in an extreme condition such as delayed union of the tibia in a laboratory animal was essential. We report the production of a consistently successful model of delayed union of the tibia in adult dogs, and the evaluation of the osteogenic properties of a bone stimulator in such a situation in a controlled double-blind trial.

Methods

Model of Delayed Union of Tibia

This model incorporated two factors that lead to delayed union in human fractures—interposition of soft tissues and distraction of the bone ends.

1·5 cm of the midshaft of the tibia together with its periosteum were removed extraperiosteally. The gap was maintained by inserting a slightly larger block of hard 'Silastic'—a medical grade of silicone elastomer—which was maintained in place by an intramedullary rod threaded at both ends. The dogs were allowed to be fully active for at least eight weeks after which the intramedullary rod was removed. At the same time the silicone block was approached through the previous incision by carefully incising the surrounding fibrous tissue to evaluate the state of delayed union, and then removed (fig.1). The criterion for at least delayed union was evidence of mobility at the fracture site present at this time. After removal of the silicone block, four threaded pins were inserted transversely above and below the defect area and secured by two 5-ply wooden slats to maintain the gap.

Confirmation of the persistence of delayed union was

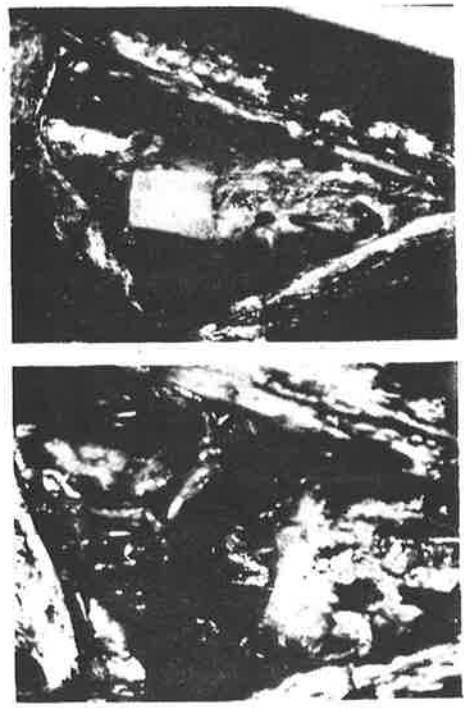

Fig. 1—Exposure of defect site and removal of silastic block.

Fig. 2—Insignificant uptake of radionuclide across gap (arrowed) at 4 wk. after removal of silastic block.

obtained from (a) radiographs of a sagittal section four weeks after the silastic block had been removed and the animal fully weight bearing, (b) the presence of fibrous tissue in microscopical sections, and (c) absence of uptake of the radionuclide, technetium-99-polyphosphate (fig. 2).

A mixed population of 69 dogs—mongrels, greyhounds, and beagles—was used. 19 dogs were destroyed during the initial postoperative week (table I). 48 survived a minimum of eight weeks with obvious mobility between the bone ends and these dogs were used to determine the value of a bone-growth stimulator.

Bone-growth Stimulator

We used the surgically implanted direct-current bone-growth stimulator (Telectronics Pty. Ltd., Sydney, Australia) which supplied a constant sum current of 20 μA through one stainless-steel cathodic electrode and had two platinum anodes carrying approximately half of the sum current (fig. 3).

Fig. 3—Direct current bone-growth stimulator.

Insertion of Bone-growth Stimulator

After removal of the silastic block, the electrodes were

TABLE I—DETAILS OF DOGS USED IN PRODUCTION OF EXPERIMENTAL DELAYED UNION AND IN ASSESSMENT OF EFFECT OF BONE-GROWTH STIMULATOR

	Mongrels	Greyhounds	Beagles	Total
Total dogs operated on	14	37	18	69
Dogs subsequently destroyed:				
Wound breakdown	1	9	0	10
Pulmonary infection	0	4	0	4
Uncontrolled hæmorrhage	1	2	0	3
Failure of intramedullary fixation	0	2	0	2
Remaining dogs healthy at 8 wk	12	20	18	50
Dogs subsequently destroyed:				
Pulmonary infection	0	1	0	1
Solid fusion	0	1	0	1
Remaining dogs with successful delayed union	12	18	18	48
Dogs subsequently died or destroyed:				
Fulminating infection	1	0	0	1
Fatal anorexia	1	0	0	1
Displaced anode	0	1	0	1
Destroyed battery	0	1	0	1
Total dogs surviving for assessment of stimulator effect	10	16	18	44 (22 pairs)

passed retrogradely into the defect area where the anodes were inserted into the medullary cavity 1·5 cm above and below the defect and the cathode was made into a helix and inserted into the defect area (fig. 4).

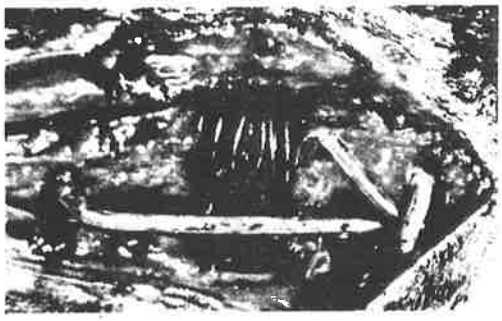

Fig. 4—Insertion of cathode and two anodes into area of delayed union.

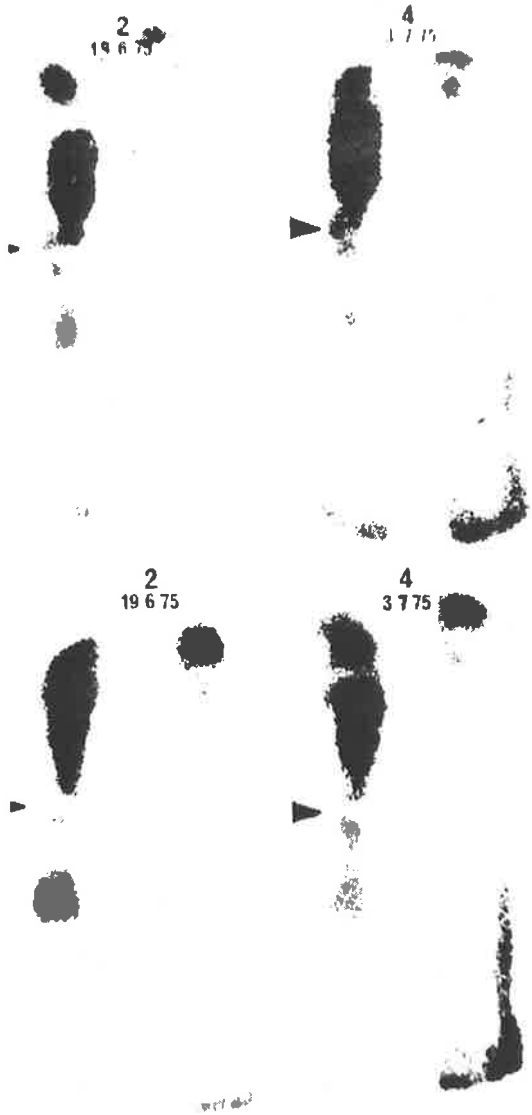

Fig. 5—Radionuclide images of a dog pair.

Upper two images were interpreted as showing a marked increase of activity within the gap between 2 and 4 wk of stimulation. Lower two images show no such increase.

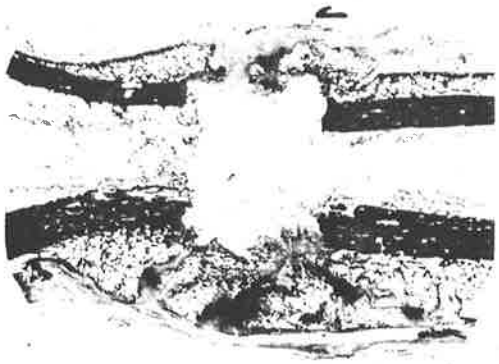

Fig. 6—Histological section of sagittal slice through area of delayed union obtained by modified Movat pentachrome technique.

Central pale area is fibrous tissue, bordered above and below by new woven bone and on either side by dark-staining original bone shafts. Amorphous grey area in new bone at the top of the photograph is cartilage.

Controlled Double-blind Trial

Pairs of prepacked, sterilised, and coded bone-growth stimulators—each pair had an active and inactive stimulator—were inserted into the 48 dogs with the established delayed union for four weeks. All stimulators at the time of removal were tested to verify that, in the active stimulators, a constant current had been maintained. Independent observers were chosen to assess and compare the amount of bone formation in each pair by the following methods:

Gamma imaging (J.P.S.) with technetium-99m-polyphosphate at two and four weeks to determine whether there was an appreciable difference in the magnitude of radionuclide uptake consistent with the degree of osteogenesis (fig. 5).

TABLE II—SCORES FOR EACH OF 3 CRITERIA OF BONE HEALING FOR ANIMAL WITH ACTIVE ELECTRODE IN EACH PAIR

Pair	Clinical union	Gamma activity	Histological appearance
1	–	–	–
2	–	–	–
3	+	–	+
4	–	–	+
5	+	–	–
6	+	–	+
7	+	–	+
8	+	+	–
9	+	–	–
10	+	–	–
11	+	–	–
12	+	–	+
13	+	–	+
14	+	+	+
15	–	–	±
16	–	+	–
17	–	+	–
18	+	+	+
19	+	+	+
20	+	+	±
21	+	+	+
22	+	+	+

Scores were assigned depending on whether healing was judged superior (+) or inferior (–) to that in the paired animal with the inactive electrode by the independent "blind" observer. Significance of the difference between animals with active versus inactive electrodes was calculated by the sign test for individual criteria and by the Wilcoxon matched-pairs sign rank sum test for all three criteria.

TABLE II—DETAILED DATA OF INDIVIDUAL ASSESSMENTS

Pair	Active stimulator			Inactive stimulator		
	Clinical union	Gamma activity	Histological appearance	Clinical union	Gamma activity	Histological appearance
1	50	—	50	100	+	87·5
2	25	—	25	100	+	50
3	75	+	30	25	—	15
4	100	+	70	50	—	35
5	25	—	5	25	+	22·5
6	75	+	60	25	—	40
7	100	+	50	50	—	40
8	25	+	7·5	25	—	22·5
9	100	+	7·5	25	—	50
10	75	+	10	25	—	27
11	75	+	17·5	25	—	7·5
12	75	—	30	25	+	7·5
13	100	+	15	25	—	7·5
14	100	+	10	25	—	0
15	50	—	25	100	+	30
16	25	+	5	100	—	50
17	25	+	20	100	—	60
18	100	+	35	25	—	5
19	100	+	40	25	—	30
20	100	+	25	25	—	25
21	100	+	50	50	—	35
22	75	+	45	25	—	35

Clinical union was graded 1–4: 1=no union; 2=mobile; 3=some movement; 4=united; results are expressed as %.
Gamma activity—amount of uptake in a given pair was estimated at 2 and 4 wk, differences being recorded as + or − (a quantitative assessment was not available at the time).
Histopathology—percentage of union by radiograph and the % of bone by histology were summated and divided. Results are expressed as %.

Clinical assessment (D.C.P. and T.M.H.) of the degree of movement in a given pair of hind legs.

Histopathological assessment (R.F.C.) of a central sagittal slice across the defect area by (a) estimating the degree of calcification in the defect and (b) a modified Movat pentachrome technique[22] to determine the percentage of new bone, cartilage, and fibrous connective tissue in the defect area (fig. 6).

Details of the bone-stimulator code and the results of all assessments were forwarded independently to one of us (J.L.)

Results

We used non-parametric methods[23] for each individual criterion separately and for all three together (tables II and III) and found that, by the sign test, osteogenesis in dogs with the active electrodes was superior to that in their pairs with the inactive electrode by the criteria of gamma imaging ($P=0.05$) and clinical union ($P=0.05$), and for all three criteria combined using the Wilcoxon matched-pairs sign rank test we found that at the 1% level of significance ($P<0.01$) healing in the dogs with the active electrodes was superior to their pairs with the inactive electrodes.

The histological assessment (R.F.C.) revealed normal bone healing by endomembranous and endochondral ossification. Inflammatory changes were insignificant and did not inhibit osteogenesis. There was no evidence of dysplastic or neoplastic changes.

Discussion

During the past twenty years, various workers have proved the existence of electromechanical behaviour in bone and have shown that osteogenesis can be induced around the cathode by electrical stimulation of bone in experimental animals. Attempts have been made to induce or accelerate bone healing by electrical stimulation in clinical disorders of bone in man and animals, but the results have been inconclusive as no properly controlled clinical trials have been undertaken. We have shown that electrical stimulation can significantly accelerate healing in an experimental situation analogous with the clinical condition of delayed bone union in man. Such stimulation does not appear, at least in the short term, to lead to neoplasia, a risk that has been suggested by some workers.[8,13,19,24,25] Obviously experiments of longer duration would be required to exclude completely this possibility.

Many other fundamental questions, such as the mechanism of electrically induced osteogenesis, the optimum field density, the size and placement of cathode and anodes, and the size and type of current to be used remain unanswered. These should be amenable to elucidation by further experimental work. The most important question of all is whether or not the technique will work in the different types of delayed bony union in man. This can only be answered by a clinical trial, and as we believe there is now sufficient justification for such a trial, we are currently carrying out a trial in collaboration with other centres throughout Australia.

We thank the staff of the departments of pædiatrics, histopathology, and nuclear medicine at the Adelaide Children's Hospital for their help and advice. We acknowledge the help of Mr B. J. Grieger, department of clinical photography of the Adelaide Children's Hospital for the illustrations and Mr D. G. Pfeiffer, medical electronics officer of the hospital. We acknowledge the very valuable cooperation and technical advice received from Mr Keith Jeffcoat of Telectronics Pty. Ltd. of Sydney, and thank Dr C. A. L. Bassett for drawing our attention to the earliest reference to electrical stimulation of bone; the Australian Orthopædic Association Research Foundation; and the Adelaide Children's Hospital Research Trust.

Requests for reprints should be addressed to D. P., Department of Orthopædic Surgery, Adelaide Children's Hospital Inc., 72 King William Road, North Adelaide 5006, Australia.

REFERENCES

1. Yasuda, I., Noguchi, N., Sata, I. *J. Bone Jt Surg* 1955, **37A**, 1292.
2. Fukada, E., Yasuda, I. *J. physiol. Soc. Japan*, 1957, **12**, 1158.
3. Bassett, C. A., Becker, R. O. *Science*, 1962, **137**, 1063.
4. Shamos, M. H., Lavine, L. S., Shamos, M. I. *Nature*, 1963, **197**, 81.
5. Shamos, M. H., Lavine, L. S. *Clin. Orthop. rel. Res.* 1964, **35**, 177.
6. Steinberg, M. E., Bosch, A., Schwan, A., Glazer, A. *Clin. Orthop. rel Res.* 1968, **61**, 219.
7. Bassett, C. A. L., Pawluk, R. J., Becker, R. O. *Nature*, 1964, **204**, 652.
8. McElhaney, J. H., Bullard, R., Stalnaker, R. *J. Biochem.* 1968, **4**, 47.
9. Friedenberg, Z. B., Kohanim, M. *J. Surg. Gynæc. Obst.* 1968, **127**, 97.
10. Friedenberg, Z. B., Andrews, E. T., Brighton, C. T., Pearl, B. W., Smolenski, B. I. *ibid.* 1970, **131**, 894.
11. Friedenberg, Z. B., Roberts, P. G., Didizion, N. H., Brighton, C. T. *J. Bone Jt Surg.* 1971, **53A**, 1400.
12. Friedenberg, Z. B., Zemski, M. D., Pollis, L. P., Brighton, C. T. *ibid.* 1974, **56A**, 1023.
13. O'Connor, B. T., Charlton, H. M., Currey, J. D., Kirby, D. R. S., Woods, C. *Nature*, 1969, **222**, 162.
14. Lavine, L. S., Lustrin, I., Shamos, M. H. *ibid.* 1969, **224**, 1112.
15. Levy, D. D., Rubin, B. *Clin. Orthop. rel. Res.* 1972, **88**, 218.
16. Hartshorne, E. *Am. J. med. Sci.* 1841, No. 1: 143–144.
17. Cieszynski, T. *Archs Immun. Ther. exp.* 1964, **12**, 269.
18. Dwyer, A. F., Wickham, G. G. *Med. J. Aust.* 1974, i, 73.
19. Cochrane, G. Van B. *Bull. N. Y. Acad. Med.* 1972, **48**, 899.
20. Becker, R. O., Spadaro, J. A. *ibid.* p. 627.
21. Rose, R. N., Radin, E. L., Paul, I. L. *Tech. Rev.* 1974, **33**, 41.
22. Russell, H. K. *Archs Path.* 1972, **94**, 187.
23. Siegel, S. Non-parametric Statistics for the Behavioural Sciences. p. 68. New York, 1956.
24. Bassett, C. A. L., Pawluk, R. J., Pilla, A. A. *Science*, 1974, **184**, 575.
25. Becker, R. O. *Clin. Orthop. rel. Res.* 1972, **83**, 255.

APPENDIX C

The clinical trial in Australia 1976-1978 (Chapter 4) was planned entirely by the author, who personally obtained the cooperation of the orthopaedic surgeons who participated in this trial.

Dr. Lewis gave valued assistance when he was the orthopaedic registrar at the Royal Adelaide Hospital and together with the author and Dr. Cass, St. Vincent's Hospital, Sydney personally demonstrated the technique and explained the protocol to the orthopaedic surgeons involved.

Orthopaedic surgeons at the Mater and Princess Alexandria Hospitals, Brisbane; the Prince of Wales and St. George's Hospitals, Sydney; the Alfred Hospital, Melbourne; and the Queen Elizabeth Hospital, Adelaide contributed 24 cases to this trial. The author acknowledges their cooperation. The remaining 60 cases were personally performed or supervised at the Royal Adelaide Hospital, Adelaide.

The author collated the protocol forms (Appendix D), evaluated the results and prepared the manuscript.

Paterson, D. C., Lewis, G. N., & Cass, C. A. (1980). Treatment of delayed union and nonunion with an implanted direct current stimulator. *Clinical Orthopaedics and Related Research, 148,* 117-128.

NOTE:

This publication is included in the print copy
of the thesis held in the University of Adelaide Library.

APPENDIX D

The protocol form used by all orthopaedic surgeons in Australia for the clinical trial with the Osteostim 1976-1978.

C O N T R O L L E D C L I N I C A L T R I A L

THIS COPY TO BE FORWARDED TO: SIR DENNIS PAT ERSON, DEPARTMENT OF ORTHOPAEDIC SURGERY, 72 KERMODE STREET, NORTH ADELAIDE. S.A. 5006 AUSTRALIA

Hospital : - Date: - - - - - - - - - -

Address : -

Surgeon/S : -

Patient

Surname Block Letters	Given Names

Age: - - - - - -Male/Female Occupation: - - - - - - - - - - - - - - - - - U.R. - - - - - - -

History: Date of Injury: - - - - - - - Type of Accident: - - - - - - - - - - - - - - - - - -

Assoc. Injuries: -

Site and Nature of Fracture: -

- -

Pre-op. X-Ray Attached Yes/No: - - - - Pre-Op. Nuclear Scan Attached Yes/No: - - - - - - -

Insertion of BGS Standard Technique/Variation (give details in separate report)

BGS Ser. No. - - - - - -Date Manufacture: - - - - - - - - Date Implant: - - - - - - - - - - -

Post Operative Pain (A) Analgesics used: -

- -

(B) Surgeons Assessment:- -

Post.Op. Wound Healing: -

- -

Infection Yes/No - Treatment: -

- -

Blood

ESR - - - - - - - - - - - WBC - - - - - - - - - - -Culture -

X-Rays & Plaster Change:

6 Weeks: -

12 Weeks: -

18 Weeks: -

Nuclear Scanning:

Pre-Op.: -

1 Week : -

2 Weeks: -

6 Weeks: -

12 Weeks: (BGS removal) -

13 Weeks: -

Copies of Post-Op. X-Rays Forwarded Yes/No. Post-Op. Nuclear Scan Copies Yes/No

Removal of BGS - Date: - - - - - Test-Yes/No Current uA: - - - - Assessment of Union:- - -

- -

- -

Final Assessment: - Date - - - - - - - - - - Comments: -

- -

- -

APPENDIX E

These cases formed part of the clinical trial of the Osteostim in Australia 1976-1978 and constitute Chapter 5 of this thesis.

The author developed the technique and was involved in the management of these cases. The author collated the results and prepared the manuscript. The cooperation of the orthopaedic surgeons from the Mater Hospital, Brisbane; The Prince of Wales and St. Vincent's Hospitals, Sydney; St. Vincent's Hospital, Melbourne is gratefully acknowledged.

Paterson, D. C., Lewis, G. N., & Cass, C. A. (1980). Treatment of congenital pseudarthrosis of the tibia with direct current stimulation. *Clinical Orthopaedics and Related Research, 148,* 129-135.

NOTE:

This publication is included in the print copy
of the thesis held in the University of Adelaide Library.

APPENDIX F

This article is a report of clinical experience with the Osteostim in Australia and the United States of America and reported in Chapters 4 and 5.

The author's submission to the Food and Drug Authority, U.S.A. was the only clinical evidence to support its use in the U.S.A. Orthopaedic surgeons using the Osteostim in the U.S.A. have been required to follow the same protocol and techniques as developed by the author in Australia. The results of the U.S.A. trial 1980-1981 have been supplied to the author.

While the author has not had direct control of the use of the Osteostim in Australia since the clinical trial ended in 1978, surgeons have continued to report their results. Hence the combined experience in Australia and the United State of America has been presented and reported here.

CLINICAL USE OF THE OSTEOSTIM - AN IMPLANTED BONE GROWTH STIMULATOR - FOR IMPAIRED BONE HEALING

by

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Australia.

The late Alan Dwyer first used the totally implantable bone growth stimulator in 1969 for failed posterior spinal fusions and subsequently reported his success with this technique [9]. The first implantable stimulator for ununited fractures of long bones was successfully inserted in Australia two years later. During the preceding 15 years, much basic research had shown, in the experimental animal, that new bone formation could be stimulated at the negative cathode.

However, by the early 1970s, no scientific work had established that electrical stimulation would augment bone healing in a situation of delayed or nonunion of a long bone. As a result, clinical use of the Osteostim was withheld until there was sufficient justification of this from animal experimentation [19, 20]. This work was based on qualitative assessments; and as a consequence more recently the same work has been done using a titanium cathode and the effect of the electrical stimulation has been assessed both quantitatively and qualitatively [8]. In the author's view, there can now be no doubt that, in an animal model of nonunion, electrical stimulation augments bone healing to a high degree.

As a result of the former work [19, 20] a clinical trial commenced in Australia in 1976 using the Osteostim S12. Rigid criteria and two standard techniques were developed [21]. Over 30 orthopaedic surgeons in Australia formed part of this trial; and by the end of 1980 the self-powered, self-contained and totally implantable Osteostim had been inserted in over 250 cases.

The Osteostim [21] has been modified - Model XM 12 - to provide additional capability for external monitoring of the current flowing, measured to the nearest microampere. It also incorporates (Fig. 1) a hermetically sealed casing with ceramic feed-through of the cathode lead, thereby enhancing protection of the power source and electronics; it incorporates the anode in the platinised hemispherical end of the case; and it contains a silicone-insulated flexible stainless steel lead that is joined to the titanium cathode by a connector. The last imparts greatly increased fatigue resistance to the lead and simplifies its removal.

The change to titanium for the case material not only affords better protection of the contents against the hostile body environment but has also resulted in only minimal soft tissue reaction. The cathode material was changed from stainless steel to titanium when it was shown that titanium produced an even growth of bone along the entire length of the cathode [17]. Stainless steel, on the other hand, is effective as a cathode material only in the area immediately adjacent to the insulation. Additionally, since some of the cathode usually remains behind when the generator is removed, the

choice of the most inert material is desirable.

TECHNIQUE

An operation is required, but it is a small operation and the simple techniques allow for great variations of the surgeon's technical skills. However, the simple technical details need to be adhered to.

In the preferred technique, the nonunion of the long bone is exposed by a direct approach and a defect is created by removing approximately 2-3 cm x 1 cm of cortical bone, making sure that the nonunion is in the centre of the defect so created. It is important to curette the sclerotic bone or fibrous tissue from the medullary cavity so that continuity across the fracture site can be ensured [21].

The generator with its incorporated platinum anode must be 8 to 10 cm from the cathode and beneath the deep fascia. In most instances an appropriate soft tissue space can be found through the single incision but, in the case of the tibia it may be more appropriate to make a separate incision in the calf and place the generator in the intermuscular plane between the gastrocnemius and soleus.

The cathode is formed into a helix, commencing at the junction of the bare titanium cathode with the insulated coating, and is then placed across the defect. It is secured by putting one loop of the helix into each medullary cavity. It must be placed centrally across the nonunion site so that the field of electrical influence will be centrally placed within the fracture site [21]. If metal is present, the cathode can be

placed in the same way provided a sliver of bone, usually from the iliac crest, is placed between it and the metal. The bone prevents contact between the two metals, which would dissipate the current over a large area and result in little or no effect. After wound closure, the fracture is immobilised in the usual way for the particular fracture.

A constant observation has been the minimal amount of postoperative pain and, where the Osteostim alone has been inserted and there are no other problems, the patient has remained in hospital for a few days only. If the fracture is stable, as would be evident with most long standing nonunions of the tibia and once wound healing had been established, a walking heel may be applied to the plaster and weight bearing encouraged. The generator and the detachable cathode are simply removed at the end of approximately six months, a minor procedure.

Patient co-operation is not required after insertion of the Osteostim since the case is treated in the usual way for the particular fracture.

USES

Some examples will illustrate how effective this method of electrical stimulation has proved to be and its wide range of applications.

Long bones

Case 1

A 46-year-old male sustained a compound fracture of the tibia and fibula in a vehicle accident.

After two failed phemister cancellous grafts over 2 years, an Osteostim was inserted. The tibia was clinically united 14 weeks later and radiologically consolidated at 6 months (Fig. 2).

Case 2

A 21-year-old male sustained a severe compound fracture of the lower end of the tibia and fibula that was treated by an intramedullary nail. Two years later, the fractured tibia was ununited; however, it was clinically united 12 weeks after insertion of an Osteostim alone (Fig. 3).

Case 3

An 18-year-old female sustained a severe compound fracture of the upper end of her tibia and fibula in a vehicle accident. Numerous attempts to obtain solid internal fixation to allow major plastic surgery to cover the extensive skin defect were performed; but at the end of 2 years, there was a profuse chronic discharge, the fracture was very mobile, and amputation was advised. An Osteostim was inserted and gradually controlled the discharge. Over a nine months period it produced union of the tibia (Fig. 4).

Case 4

A 27-year-old male sustained a severe crushing injury to his forearm in an underground coalmine accident. He had a double fracture of his radius. A Volkmann's ischaemia developed that required extensive resection of necrotic forearm skin, muscle and nerve tissues.

The forearm was covered with a split-thickness skin graft. The proximal fracture of radius failed to unite, and a chronic discharging osteomyelitis developed. Twelve months later, when amputation was being considered, a sequestrum was simply removed, a cathode in the form of a helix was placed across the nonunion site and the generator was placed beneath the deep fascia in the forearm. The discharge ceased and the fracture united (Fig. 5).

Case 5

A rhabdomyosarcoma of the thigh developed in a 5-year-old boy. He received maximal-dosage radiotherapy for it, and 18 months later his protective caliper was removed. There was a pathologic fracture that went on to nonunion. As can be expected, his skin was tissue paper thick and there was an absence of soft tissues at the site of the nonunion of his femur. An Osteostim was inserted, and the bone at the time was found to be densely sclerotic and avascular. The nonunion became firm at about 6 months, and another Osteostim was inserted. Twelve months later the bone was clinically and radiologically united. Sclerotic avascular bone developed osteogenic properties without the addition of any cancellous bone graft. (Fig. 6)

In all of these cases there was no way in which the nonunion sites could have had cancellous bone graft placed around them, because of either a discharging wound or the necrotic soft tissues.

Applications

This technique has been successfully used in all long bones of both upper and lower limbs. It has achieved union where cancellous grafting had failed in a pathologic fracture of the tibia with Paget's disease, in long-standing ununited corrective osteotomies of both femurs in renal rickets [21], in ununited fracture of the clavicle, and for failed arthrodesis of the knee, ankle and hindfoot.

Failures have occurred in approximately 10% of cases. These have been due to (a) inadequate plaster immobilisation before union had consolidated, (b) faulty technique, especially incorrect placement of the cathode centrally (Fig.7) across the nonunion site, (c) premature removal of the implant, which now has an active life of 6 months, or (d) nonunion and a chronic discharge that had been present for too long and no method, including electrical stimulation, had been able to recommence osteogenesis.

Complications. These have been generally minor. Soft tissue reaction was observed around the generator in earlier models. All wounds have healed, and there has been no instance of infection occurring around the cathode wound as a direct result of the operative procedure. The cathode wire has broken in four instances and, in all the generator was not placed beneath the deep fascia. Despite this,

these fractures all united.

Success rate

In over 250 cases in Australia in which the Osteostim has been used to achieve union of long bones, the overall success rate has been 89%. This compares more than favourably with the success rate in a review of the literature of tibial fractures treated by cancellous bone grafting by the Phemister [23] and/or Charnley [7] technique, whose overall success rate was 92% [21]. It should be remembered that the Osteostim was, at that stage, rarely used as the primary treatment and in most cases was used after multiple bone grafting treatments had failed.

Eighty-three percent of the cases in this series, which had failed previous Phemister grafting attempts, went on to union at an average of 16 weeks after insertion of the Osteostim. This compares favourably with the results described by Boyd et al [5, 6] in which only a 67.5% success rate was achieved with bone grafting techniques. It should be realized that patients often had poor skin cover at the time the Osteostim was inserted and this would have precluded cancellous grafting.

A chronic discharging wound is not a contra-indication to the use of the Osteostim. Boyd and Lipinski [5] believed that infection, if present, should be controlled or quiescent for at least six months before grafting. Urist et al [27] reported 20% recurrence of infection with anterior bone grafting after healing of infection. Hanson and Eppright [10] have advocated a postero-lateral approach

for bone grafting infected ununited tibial fractures, first described by Harmon, [12] and reported a success rate of 86%. Although not strictly comparable to the Hanson and Eppright series because an anterior approach has been used at all times for tibial nonunions, the success rate of infected ununited tibial fractures treated by the Osteostim alone has been 86%.

It is important to stress that the average time for union following use of the Osteostim has been 16 weeks, compared to 24 weeks following cancellous grafting for tibial fractures or 35 weeks with infected nonunions.

Initially, the Osteostim was used where there was established nonunion or where surgical treatment had failed. As experience was gained, it became the preferred operative procedure in many instances, as illustrated by a 19-year-old boy who had a gross compound fracture of the lower third of his tibia with extensive skin and soft tissue damage. He required plastic surgery to achieve full-thickness cover. The fracture was treated with external fixator apparatus, and by 14 weeks it was the surgeon's judgement that nonunion would develop. Cancellous bone grafting was deemed impossible, and accordingly an Osteostim was inserted. The fracture united. (Fig. 8).

Congenital Pseudarthrosis of the Tibia

Congenital pseudarthrosis of the tibia constitutes one of the most difficult problems in paediatric orthopaedic surgery. In spite of improved surgical techniques [4, 7, 15, 16, 25, 26] authors have remained pessimistic about the eventual outcome of treatment of this condition. The incidence of amputation remains high [2, 11, 14, 18, 24, 26] and this is generally after many operative attempts to achieve union have failed.

The Australian series is 12 cases. Of these, 8 are soundly united and two are consolidating very promisingly. The operative technique has consisted of intramedullary fixation of the hindfoot and tibia in all cases except one, insertion of the Osteostim by the technique first described, and application of cancellous bone graft obtained from the iliac crest followed by immobilisation in a hip spica for 6 months [22]. It should be stressed that the tibia must be protected after clinical and radiological union has been achieved, until normal bone texture has been restored and skeletal maturity obtained. The mean time for union is 6 months. Two illustrative cases are given:-

Case 1

A boy, now aged 5½ years, had had a deformed tibia at birth and sustained a fracture of the tibia when 11 months old. [22] He underwent an unsuccessful cancellous bone graft at 13 months; and at 18 had internal fixation, insertion of the Osteostim, and another cancellous bone graft were carried out. The tibia remains well united but has slowly deformed since the intramedullary rod was removed.

This emphasizes the need for internal fixation to be maintained and for a protective caliper to be continued indefinitely.

Case 2

A 10-year-old girl had had a deformed tibia all her life and used a staff for walking. The defect was treated by the regime as outlined, and 3 months later the tibia was united. It has continued to consolidate radiologically 9 months later (Fig. 9).

In the two failed cases [22] many operations had been performed over several years and osteogenesis was not reactivated.

There is a close association of congenital pseudarthrosis of the tibia with neurofibromatosis [1, 3, 13, 14, 26] which was noted in seven of the twelve cases in this series. It is doubtful, however, whether the presence of neurofibromatosis affects the prognosis.

The suggestion has been made [11] that an important factor in the success of treatment of this condition is the age of the child at the time of surgery. The age range has varied from 18 months to 10 years in this series, so it would appear that age is not as important a factor as was once believed.

Scaphoid

Insertion of the Osteostim is just as applicable to the scaphoid as it is to the long bones. There have been five successes in seven cases so far.

The technique involves a volar exposure of the scaphoid. A defect is created gently, and both proximal and distal fragments of the scaphoid are curetted. Stability is achieved by taking a small cortical graft from the lower end of the radius and placing it across the nonunion site to fix the proximal and distal fragments. The Osteostim is then inserted across the defect in the same way as previously described and the helix is made very much smaller, using only part of the titanium cathode. The generator is placed along the anterior surface of the interosseous membrane. The ununited scaphoid is treated in plaster of Paris in the usual way (Fig. 10). An example is:-

> A 21-year-old footballer injured his wrist and sustained a fractured scaphoid, which was treated in plaster for three months. Six months later the scaphoid fracture remained ununited. It was then treated by a bone graft and further plaster but remained ununited for 18 months. Three months after the Osteostim was inserted as described above, the fracture was united (Fig.11).

The two failures have been (1) a severe transcaphoid perilunar fracture dislocation in which many unsuccessful operations were performed over a $2\frac{1}{2}$-year period before the Osteostim was inserted and (2) a fracture through the proximal end of the scaphoid which remained ununited after 4 years of treatment and then also failed with an Osteostim.

In addition to its use for ununited fractures of the scaphoid, this simple technique may also be used as the primary treatment once radiographs illustrate that the scaphoid fracture is not uniting.

The Lumbar Spine

Another model of the Osteostim - S11 - has been produced for posterior spinal fusions. The technique has been developed by Dr. W.J. Kane of Chicago, U.S.A. and involves excision of the articular surfaces of the superior and inferior facets of the particular lumbar joint, placement of a small graft between the joint surfaces and passage of titanium cathode at right angles across the joint (Fig. 12). Dr. Kane has reported a success rate of 91.5% with this technique in posterior spinal fusions in 82 patients.

CONCLUSION

There can be no doubt now that electrical stimulation produces osteogenesis and significantly helps to achieve union where impaired bone healing exists.

One method of electrical stimulation is the self-powered, self-contained and totally implantable Osteostim. Examples have been given to show its success in ununited fractures of long bones with or without chronic infection, of very encouraging success with congenital pseudarthrosis of the tibia, of its use in small bones such as the scaphoid and in posterior spinal fusions.

The Osteostim is safe, can be used in a wide variety of situations, requires a short simple operation with strict adherence to the operative details and is associated with insignificant morbidity and a short hospital stay. There are no contraindications, and it can be used in the presence of chronic discharge. It does not require patient co-operation and it interferes little with the patient's lifestyle. A monitoring device ensures that a direct current constantly flows. The current model (Osteostim XM12) allows for easy removal of the generator and cathode.

Orthopaedic surgeons should no longer be sceptics about the value of electrical stimulation for impaired bone healing. The success so far surely justifies that the Osteostim should be accepted as a form of treatment in delayed and nonunion of bones.

And what of the future? Used responsibly, electrical stimulation has an important place in orthopaedic surgical treatment. One distinct possibility is to augment bone growth into porous materials applied around joint replacements. We are probably just beginning to see a wider application of electrical stimulation in clinical practice, and it may well be the exciting development in orthopaedic surgery in the 1980s.

REFERENCES

1. Aegerter E.E.
The possible relationships of neurofibromatosis, congenital pseudarthrosis and fibrous dysplasia
J. Bone Joint Surg. 32A: 618, 1950

2. Anderson K.S.
Congenital pseudarthrosis of the leg
J. Bone Joint Surg. 58A: 657, 1976

3. Barber C.G.
Congenital bowing and pseudarthrosis of the lower leg: manifestations of von Recklinghausen's neurofibromatosis
Surg. Gynaecol. Obstet. 69: 618, 1939

4. Boyd H.B.
Congenital pseudarthrosis: treatment by dual bone grafts
J. Bone Joint Surg. 23: 497, 1941

5. Boyd H.B. and Lipinski S.W.
Causes and treatment of non union of the shafts of long bones with a review of 741 patients
Instructional Course Lectures: American Academy of Orthopaedic Surgeons 17: 165, 1960
The C.V. Mosby Co., St. Louis

6. Boyd H.B., Lipinski S.W. and Wiley J.H.
Observations on non union of the shafts of long bones with a statistical analysis of 842 patients
J. Bone Joint Surg. 43A: 159, 1961

7. Charnley J.
Congenital pseudarthrosis of the tibia treated by the intramedullary nail
J. Bone Joint Surg. 38A: 283, 1956

8. Collins P.C., Paterson D.C., Vernon-Roberts B., Pfeiffer D
Bone Formation and Impedance of Electrical Current Flow
Clin. Orthop. 155: 196, 1981

9. Dwyer A.F. and Wickham G.G.
Direct current stimulation in spinal fusion
Med. J. Aust. 1: 73, 1974

10. Hanson L.W. and Eppright R.H.
Posterior bone grafting of the tibia for non union; a review of twenty-four cases
J. Bone Joint Surg. 48A: 27, 1966

11. Hardinge K.
Congenital bowing of the tibia
Ann. R. Coll. Surg. Engl. 51: 17, 1972

12. Harmon P.H.
A simplified approach to the posterior tibia for bone grafting and fibular transference
J. Bone Joint Surg. 27: 496, 1945

13. Jaffe H.
Tumours and tumorous conditions of bones and joints
London, Kimpton, 252, 1958

14. McBryde A.M. Jnr. and Stelling F.H.
Infantile pseudarthrosis of the tibia
J. Bone Joint Surg. 54A: 1354, 1972

15. McFarland B.
Birth fracture of the tibia
Br. J. Surg. 27: 706, 1940

16. McFarland B.
Pseudarthrosis of the tibia in childhood
J. Bone Joint Surg. 33B: 36, 1951

17. Martin C.St., Parsons J.R., Weiss A.B. and Alexander H.
The distribution of direct current stimulated bone growth about long titanium cathodes
Presented to the Annual Meeting of the American Academy of Orthopaedic Surgeons, February 1980

18. Masserman R.L., Peterson H.A. and Bianco A.J.
Congenital pseudarthrosis of the tibia
Clin. Orthop. 99: 140, 1974

19. Paterson D.C., Hillier T.M., Carter R.F., Ludbrook J., Maxwell G.M., Savage J.P.
Electrical bone-growth stimulation in an experimental model of delayed union
Lancet, 1278, 1977

20. Paterson D.C., Hillier T.M., Carter R.F., Ludbrook J., Maxwell G.M., and Savage J.P.
Experimental delayed union of the dog tibia and its use in assessing the effect of an electrical bone growth stimulator
Clin. Orthop. 128: 340, 1977

21. Paterson D.C., Lewis G.N. and Cass C.A.
Treatment of delayed union and nonunion with an implanted direct current stimulator
Clin. Orthop.148: 117, 1980

22. Paterson D.C., Lewis G.N. and Cass C.A.
Treatment of congenital pseudarthrosis of the tibia with direct current stimulation
Clin. Orthop. 148: 129, 1980

23. Phemister D.B.
Treatment of ununited fractures by onlay bone grafts without screw or tie fixations and without breaking down of the fibrous union
J. Bone Joint Surg. 29: 946, 1947

24. Riseborough R.J., Morrissy R.T., Hall J.E., Bernal J. and Trott A.W.
Congenital pseudarthrosis of the tibia - results in forty patients
J. Bone Joint Surg. 56A: 1312, 1974

25. Sofield H.A. and Millar E.A.
Fragmentation, realignment and intramedullary rod fixation of deformities of the long bones in children
J. Bone Joint Surg. 41A: 1371, 1959

26. Sofield H.A.
Congenital pseudarthrosis of the tibia
Clin. Orthop.76: 33, 1971

27. Urist M.R., Mazet R. and McLean F.C.
The pathogenesis and treatment of delayed union and non-union
J. Bone Joint Surg. 36A: 931, 1954

CAPTIONS TO ILLUSTRATIONS

Fig. 1 Osteostim XM 12 - (1) anode incorporated in the platinised hemispherical end (2) hermetically sealed casing with ceramic feed-through of the cathode lead (3) stainless steel lead joined to the titanium cathode via a connector (4) external monitor of the current flowing

Fig. 2 46-year-old male with (a) a compound fractured tibia and fibula (b) two years later after two failed phemister cancellous grafts (c) insertion of the Osteostim and (d) consolidated six months later

Fig. 3 21-year-old man sustained (a) a severe compound fracture of the tibia and fibula (b) had an intramedullary nail inserted (c) two years later the tibia was ununited (d) clinically united 12 weeks and radiologically united 26 weeks after insertion of the Osteostim

Fig. 4 An 18-year-old female with (a) a severe compound fracture of the tibia and fibula (b) internal fixation and major plastic surgery (c) two years later the Osteostim was inserted into an ununited fractured tibia with a chronic discharge (d) united 9 months later

Fig. 5 27-year-old male with (a) a severe crushed injury to the forearm (b) insertion of the Osteostim (c) the discharge ceased and the fractures were radiologically consolidated six months later

Fig. 6 A 5-year-old boy with a rhabdomyosarcoma developed (a) a pathological fracture of the femur 18 months after radiotherapy (b) ununited femur 18 months later (c) the fracture was firm six months after the Osteostim inserted (d) radiologically consolidated a further 12 months later

Fig. 7 The cathode placed too proximally

Fig. 8 A 19-year-old boy with (a) a severe compound fractured tibia and fibula (b) reduction with the external fixator (c) Osteostim inserted at 14 weeks (d) consolidated radiologically six months later

Fig. 9 A 10-year-old girl with (a) congenital pseudarthrosis of the tibia (b) three months after internal fixation, cancellous grafting and insertion of the Ostéostim

(by kind permission of Dr. K.R. Daymond)

Fig. 10 (a) preparation of the scaphoid non union
(b) formation of the cathode helix
(c) the Osteostim in place

Fig. 11 A 21-year-old footballer with (a) a fractured scaphoid (b) 18 months later after failed bone graft (c) 3 months after insertion of the Osteostim

(by kind permission of Dr. G.N. Lewis)

Fig. 12 (a) bone graft inserted between the apophyseal joints (b) insertion of the cathodes of the Osteostim S11

(by kind permission of Dr. W.J. Kane)

APPENDIX G

The author instigated this project at the Royal Adelaide Hospital during the clinical trial of the Osteostim in Australia 1976-1978 and established the protocol.

The coordination of the cases used was carried out by Dr. Angel. The scientific and technical aspects of this project were carried out by the physicians and physicists of the Department of Nuclear Medicine of the Institute of Medical and Veterinary Science, Adelaide. Their contribution to this project is acknowledged.

The author collated the clinical and scintigraphic findings with the senior author of this article and jointly prepared the manuscript which is referred to in Chapter 4.

O'Reilly, R. J., Cook, D. J., Gaffney, R. D., Angel, K. R., & Paterson, D. C. (1981). Can serial scintigraphic studies detect delayed fracture union in man? *Clinical Orthopaedics and Related Research, 160*, 227-232.

NOTE:

This publication is included in the print copy
of the thesis held in the University of Adelaide Library.

APPENDIX H

The author planned, organised and actively carried out this work which is reported in Chapter 6. The author prepared the submissions for and obtained the research grants.

Dr. Tilbury gave valuable surgical assistance as the orthopaedic/research registrar at the Adelaide Children's Hospital and his work is acknowledged.

Drs. Carter and Savage cooperated with the histopathology and nuclear scan aspects of this work and the help of these persons and their technical staff is acknowledged.

The author assessed the material with Drs. Carter and Savage prior to the independent assessment by Professor J. Ludbrook and subsequently prepared the manuscript.

THE EFFECTS OF VARYING CURRENT LEVELS OF ELECTRICAL STIMULATION

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THE EFFECT OF VARYING CURRENT LEVELS OF ELECTRICAL STIMULATION

INTRODUCTION

In the last decade there has been increasing interest in the use of electrical stimulation to achieve bone healing. Various methods of clinical application of electrical stimulation are available - a totally invasive method [10, 25, 26], a semi-invasive method [7, 8, 9, 14, 20], a totally non-invasive technique [3, 4] and other methods [6, 17, 21, 22, 30, 34] and all have used different current levels as well as different anode and cathode materials.

Friedenberg et al [14] were the first to report healing of an ununited fracture by electrical stimulation in modern times and they used a direct current of 10 microamperes based on their previous analysis of electrical potentials accompanying fracture healing [11]. Subsequently, [7, 8, 9] they used a direct current of 20 microamperes because "10 microamperes produced inadequate electricity".

Yasuda [32] in his original work used 1 microampere to produce osteogenesis in the femur of a rabbit. Subsequent workers [2, 12, 13, 19, 27, 33] have used freshly fractured or intact long bones to evaluate current levels of 5-20 microamperes. Friedenberg et al [15] stated that the greatest bone response was related to 20 microamperes and beyond 30 microamperes, osteonecrosis occurred. Becker [5] believed that the question of the optimum magnitude of the electrical current must be kept open and, in 1981 [6], he stated that "there is evident disagreement as to the optimum type and level of current and method of

administration". Treharne [31] suggested that direct current was more than twice as effective as either pulsed current or currents pulsed with the same shape as though they were stress generated.

So far as could be ascertained, no previous research has attempted to compare varying current levels in a situation of delayed healing of a long bone. In previous work [24], we have produced a reliable model of delayed union of the dog tibia which showed statistical difference in bone healing using a 20 microampere direct current. However, this model had inherent technical and sampling problems, the most notable being the necessity to control the experiment by using two animals as it was not possible to insert an active and an inactive stimulator in the one animal. It was considered that these variables might prevent the detection of potentially smaller differences of osteogenesis between different current levels. The aim of the present work, therefore, was to produce a more sensitive and better controlled experimental model that simulated delayed union of a tibia or femur in an adult dog in which varying current strengths could be applied and an assessment made of the most effective order of magnitude of direct current for bone growth stimulation.

MATERIALS AND METHODS

A simple and reproducible surgical model in adult dogs was constructed (Fig. 1). It was possible to operate on both hind legs and this allowed one leg to act as a control for the other. Direct current levels of 200 nanoamperes, 2 microamperes

and 20 microamperes were used and assessments were made to evaluate the amount of osteogenesis produced with the varying current levels. A current of 200 microamperes was not used as previous work had shown that this level was unphysiological and would lead to tissue necrosis [13, 15] or fibrous [33] rather than osseous healing.

1. *THE DELAYED UNION MODEL*

In all dogs, a general anaesthesia was induced with intravenous pentobarbitone sodium followed by intubation using nitrous oxide, oxygen and halothane. Intramuscular injections of pentazocine were given post-operatively.

The femur or tibia of adult dogs was exposed, the periosteum was excised and diathermied for approximately 1 cm around the proposed defect site after which a segment of the cortex was cut longitudinally in the line of the bone using a double bladed saw. A curved defect measuring 3.5 cm long, 1 cm deep in the centre and 0.4 cm wide was made and the area was prevented from healing for six weeks by inserting a D-shaped block of Silastic (silicone elastomer) into the defect created. The block of Silastic was held in place with nylon transfixing sutures. A special jig was inserted into the defect in order to allow 0.4 cm holes to be drilled at either end and in exactly the same longitudinally and vertical planes as the defect itself. Teflon tubes measuring 0.39 cm diameter were inserted into these holes in order to keep them patent and allow accurate alignment subsequently of the specimens so that all the defects could be sectioned identically. The dogs walked within 24 hours post-operatively and all wounds healed.

Serum calcium, serum inorganic phosphorus and serum alkaline phosphatase estimations were carried out pre-operatively, at one and two days post-operatively and then weekly for six weeks.

2. *TRIAL WITH DIFFERENT ELECTRICAL CURRENTS*

Thirty dogs were used in this study. Osteostim S12 bone growth stimulators were provided in pre-packed, sterilised and coded pairs and were inserted into each dog (D.C.P. and R.F.T.). Each pair of stimulators were identical to external and radiological examination and the three direct current levels were tested. The stimulators were checked by an electronics engineer at implant and explant to ensure that there was one active and one inactive stimulator in each pair. One of us (J.L.) alone had the code numbers and independently assessed the results.

Six weeks after the defect was made, the bones were exposed and the Silastic blocks removed leaving a clean, membrane lined defect. A pair of coded stimulators were provided for each dog.

The generator together with the platinum anode was placed at a distance from the defect and beneath the deep fascia. The titanium cathode wire was passed to the defect and the bare end was attached to a special T-shaped titanium cathode plate 0.4 cm wide and of the same surface area - 70 sq. mm - as the cathode helix used in previous animal and clinical work [24, 25, 26]. The cathode was inserted into the mid point of the defect and held in place with nylon transfixion sutures. The dogs suffered minimal morbidity and post-operatively similar blood specimens were taken as indicated previously. Electrical stimulation continued for three weeks.

3. *PREPARATION OF HISTOLOGICAL SECTIONS*

A longitudinal slice of bone, containing the defect area and the guide holes, was taken with a band saw. After formalin fixation and decalcification, these slices were embedded in paraffin and a special jig positioned the specimen using the guide holes so that the plane of the defect was parallel to the final cutting surface of the block. The block was then trimmed on a large sledge microtome until the guide holes, and thus the defect itself, were just coming into the plane of section. Seven step sections, 5-7 microns thick, were taken at 500 μ intervals in such a way that the fourth section was approximately through the centre of the defect, and they were stained with hematoxylin and eosin. Large photographs were then made of the defect area and on these photographs the boundaries of the defect and the areas of new bone within it were outlined with ink. Using a Hewlett-Packard electronic image analyser, the amount of new bone, expressed as a percentage of the total area of the defect, was calculated for each section and the results for each specimen were printed out in parallel with those of the specimen from the other leg of the same animal.

RESULTS

1. Evaluation of delayed union and the ideal period of electrical stimulation

While the concept of the defect was similar to that used in previous experimental work [24], it was significantly different in that the defect was surrounded by intact cortical bone. It was important to determine (a) when healing in the defect was sufficiently delayed for the

effect of electrical stimulation to be assessed and (b) when the maximum difference of bone formation could be determined between the stimulated and the unstimulated leg.

Initially, a series of dogs were used to evaluate these aspects by -

(a) histology

One dog was killed at weekly intervals from 2-8 weeks after insertion of the Silastic block. Sections were examined by one of us (R.F.C.) and it was considered that the tissues bounding the defect had finished their active phase of healing by the fourth week (Fig. 2) and beyond that time there appeared to be no difference in the tissue activity surrounding the defect. It was hoped that this indicated a significant degree of delayed union although, of course, it was realized that with the silicone block still in situ, new bone growth might be inhibited.

In order to elucidate this matter, a small pilot study was done. Four dogs had silicone blocks removed at six weeks after which the bones were stimulated with a known 20 microampere direct current stimulator on one side and an inactive stimulator on the other. One dog was killed weekly. The defect areas were examined histologically and an apparent difference was found between "normal" unstimulated and "activated" bone healing in the defects with a maximum difference at about three weeks (Fig. 3).

(b) nuclear scan -

Ten dogs were scanned with Technetium 99m methylene diphosphonate at two weekly intervals for six weeks after the Silastic block was inserted. One of us (J.P.S.) quantified the scan uptake in the area from the knee to the ankle. The computerized results, displayed in graph form, showed peaks of activity at the knee and ankle. Initially, a "hot spot" of activity was seen at the defect and showed (Fig. 4) a biphasic peak corresponding to the upper and lower ends of the defect and a "trough" in between where healing activity had been impaired. Over six weeks, this activity declined and the biphasic appearance became somewhat flattened indicating that the normal bone reaction to injury was subsiding.

Eight of the original ten dogs received active and inactive electrical stimulation at the end of the sixth week and the defects were subsequently scanned after two and three weeks. There was a renewed peak of activity at the second week which subsided by the third week but there was no clear cut difference in the legs with either active or inactive stimulators. It was not possible to differentiate the actively stimulated site in greater than 50% of the animals. The increased activity of the intact posterior, medial and lateral cortices together with loss of the "trough" in the defect area made it impossible to evaluate whether the defect activity was from electrical stimulation or from natural bone healing. Consequently, this method of assessment was abandoned.

(c) blood chemistry -

After the defect was created, there was an elevation in the serum alkaline phosphatase and a fall in the levels of serum calcium and phosphorus, returning to normal by the fourth week. This indicated that reactive healing had largely settled by this time. After removal of the silastic blocks and insertion of the electrical stimulators, a similar sequence of events occurred, again returning to normal some two weeks later (Fig. 5).

(d) radiological assessment -

This was not used because the intact fibula obscured the defect created. The small size of the defect in the tibia made it impossible to evaluate any radiological changes and tomography was impracticable.

(e) Conclusions

After assessment of this small pilot study by histological, nuclear scan and biochemical methods, it was considered that reactive bone healing had largely subsided after 4-6 weeks and this model represented sufficient delayed healing of bone to justify further evaluation. Further, the optimum time to detect histological differences appeared to be three weeks post-stimulation although no firm conclusions could be drawn from this finding because of the small numbers involved.

2. Bone formation with different currents of electrical stimulation

As assessments of the model of delayed union by nuclear scan, chemical tests and radiography were unsatisfactory, the success or otherwise of the project depended on the histopathological assessments. The sections were analyzed subjectively by one of us (R.F.C.) and certain histological features were apparent (Fig. 3):

(a) the defect was clearly demarcated from normal bone and was filled with a mixture of bone and fibrous tissue in both stimulated and unstimulated specimens. In most cases, trabecular bone was formed from the floor of the defect while the new bone in the defect was of normal woven bone.

(b) on the surface of the bone, there was fibrous reaction in relation to the cathode and its junction with the polyethylene coated titanium wire. There was always a thin layer of fibrous tissue around the cathode even when new bone had grown up to it. Fibrous tissue tended to be found maximally around the cathode plate.

(c) the gap left by removal of the cathode plate was larger than the cathode and was often greater nearer the surface.

The numerical data from the quantitative assessment were independently analyzed (J.L.) and subjected to statistical analysis using Students-t test.

The results, once the code was revealed, indicated that with:-

(a) 0.2 microamperes direct current
there was a positive correlation of new bone formation with an active stimulator in six of the seven dogs and a negative correlation in one dog.
Calculations, however, did not indicate statistical significance.
($n = 7$, $T_t = 23.5$, p = no significant difference)

(b) 2.0 microamperes direct current
there was a positive correlation of increased bone formation in four of the eleven dogs with an active stimulator and a negative correlation in seven. Statistically, there was no significant difference in bone formation between the active and inactive stimulators at this current level.
($n = 11$, $T_t = 22$, p = no significant difference)

(c) 20 microamperes direct current
there was a positive correlation of increased bone formation with an active stimulator in four of ten dogs and a negative correlation in six dogs. These results were not found to be statistically significant.
($n = 10$, $T_t = 18$, p = no significant difference)

A further computer assessment of new bone within a 0.5 cm radius on either side of the cathode was carried out as it has been our experience [24, 25, 26] that the cathode has a field of influence of about 5 mm from any point on the cathode. This

failed to show any major difference of new bone formation with either of the three current levels being tested.

3. Complications

A total of 49 dogs had the defect created initially - 27 mongrels and 22 beagles. Nineteen dogs were killed - because of fractures (16) and other causes (3). Clearly, a small defect in the femur or tibia was sufficient to interfere with the overall strength of the bone. The alternative of internal fixation with plates was not considered as this would interfere with the electrical field. After insertion of the electrical stimulators, no further complications occurred in the remaining 30 dogs -16 mongrels and 14 beagles. At explant of the stimulators, discolouration of the anode - "anodizing" - was noted in approximately one third of the specimens. This occurred with the active stimulators only and was not associated with any abnormality or necrosis of the muscle around the anode.

DISCUSSION

While our original delayed union model [24] allowed the area to be stimulated by direct current, and adequate nuclear scan and histological assessments of the tissue in the defect, there were significant disadvantages of this model, especially the inability to operate on both legs of the same animal at the same time with resultant difficulties in obtaining suitable controls.

An effort was made to find a simple model of delayed union of a long bone to allow evaluation of different current strengths. The histological, nuclear scan and serum biochemical

tests in the preliminary trial suggested that bone activity had subsided by six weeks and that at least delayed healing of bone had occurred by this time. Further, the pilot study indicated that the maximum difference between normal unstimulated and stimulated bone healing occurred after three weeks stimulation.

In the main trial, the differences between bone healing with different currents were evaluated quantitatively to determine the proportion of new bone in the whole area of the defect and the results were integrated by computer and assessed for significance using the Students-t test. It is important to remember that previously [24] it had been shown that a current level of 20 microamperes which is approximately four times the normal physiological current present in human tissue, produced significant new bone in a model of delayed union. This present study, however, was not able to detect any difference in bone formation between the stimulated and non stimulated specimens let alone detect any difference between different current levels. Only at 0.2 microamperes direct current was there a consistent trend to a positive correlation between bone formation in the stimulated leg (6 of 7 animals) but in most cases, the differences in the amount of osteogenesis were small and the final statistical calculations showed no significant difference.

In all probability, the defect was too small and was surrounded by too great an area of normal bone forming tissues. As a result, bone healing probably occurred normally at a maximum rate once the Silastic block had been removed and the model was therefore not as representative of delayed healing

as had been hoped from the pilot study. This was probably due to insufficient numbers in the pilot study and, consequently, the model created was really more consistent with a fresh fracture. Removal of the Silastic block might itself have induced sufficient stromal oedema to induce maximum osteogenic activity regardless of any superimposed electrical stimulation as it has been suggested [1] that stromal oedema may be the triggering event in electrical stimulation. This suggests that electrical stimulation is not effective when the normal osteogenic potential is still present. It follows that if there was no detectable difference in osteogenesis between stimulated and unstimulated specimens, the model could not be expected to show finer differences between different current levels. In addition, the bulk of the electrode plate and the titanium cathode wire were subsequently shown to be associated with excessive movement of the cathode plate producing a large gap with fibrous tissue around the cathode.

The biochemical data, although of no value in assessing differences in healing of the defects, are of some interest. It has been reported previously by Masureik and Ericksson [23] that after electrical stimulation of a fresh fracture of the mandible the serum alkaline phosphatase level falls to a minimum at seven days, then rises to an elevated level at fourteen days and then returns to normal. They reported a corresponding rise in serum calcium and serum phosphorus followed by a lowered level at fourteen days and then a return to normal. These findings are

directly opposite to the normal reponses to trauma [16, 28, 29] where there is a rise in the serum alkaline phosphatase and a fall in the serum calcium and serum phosphorus in the first week after the fracture. In the present study, our findings are in agreement with the normally accepted responses to trauma.

SUMMARY

An effort has been made to find a simple model of delayed union of a long bone that could be used to evaluate the osteogenic effect of different current strengths. It is important that the optimum current strength be determined. Any such model should be able to produce a difference of new bone formation with an active and an inactive stimulator, particularly one using a 20 microamperes direct current. This did not happen here. This model was unsatisfactory probably because the defect was too small, was surrounded by normal bone, and excessive movement occurred at the cathode plate. The optimum range of electrical stimulation using a titanium cathode has not been established in this work. The accepted responses of serum alkaline phosphatase, serum calcium and serum phosphorus to trauma have been shown to be the same with electrical stimulation of bone formation.

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REFERENCES

1. Ashihara T., Kagawa K., Kamachi M., Inoue S., Ohashi T., and Takeoka O.
$^{3}_{H}$ - Thymidine autoradiographic studies of the cell proliferation and differentiation in the electrically stimulated osteogenesis
In: Electrical Properties of Bone and Cartilage: Experimental effects and clinical applications
Edited by C.T. Brighton, J. Black, S.R. Pollack
Grune & Stratton, New York, 1979, 401

2. Bassett C.A.L., Pawluk R.J. and Becker R.O.
Effects of electric currents on bone in vivo
Nature 204: 652, 1964

3. Bassett C.A.L., Pawluk R.J. and Pilla A.A.
Augmentation of bone repair by inductively coupled electromagnetic fields
Science 184: 575, 1974

4. Bassett C.A.L., Pilla A.A. and Pawluk R.J.
Non-operative salvage of surgically resistant pseudarthrosis and non unions by pulsing electromagnetic fields.
A preliminary report
Clin. Orthop. 124: 128, 1977

5. Becker R.O., Spadaro J.A, and Marino A.A.
Clinical experiences with low intensity direct current stimulation of bone growth
Clin. Orthop. 124: 75, 1977

6. Becker R.O.
Personal communication 1981

7. Brighton C.T., Friedenberg Z.B., Zemsky L.M. and Pollis P.R.
Direct current stimulation of non-union and congenital pseduarthrosis
J. Bone Joint Surg. 57A: 368, 1975

8. Brighton C.T., Friedenberg Z.B., Mitchell E.I. and Booth R.E.
Treatment of non-union with constant direct current
Clin. Orthop. 124: 106, 1977

9. Brighton C.T., Black J., Friedenberg Z.B., Esterhai J.L., Day L.J. and Connolly J.F.
A multicentre study of the treatment of non union with constant direct current
J. Bone Joint Surg. 63A: 1, 1981

10. Dwyer A. and Wickham G.G.
Direct current stimulation in spinal fusion
Med. Journal of Australia 1: 73, 1974

11. Friedenberg Z.B. and Brighton C.T.
Bioelectric potentials in bone
J. Bone Joint Surg. 48A: 915, 1966

12. Friedenberg Z.B. and Kohanim M.
The effect of direct current on bone
J. Surg. Gynaecol. and Obstet. 127: 97, 1968

13. Friedenberg Z.B., Andrews E.T., Smolenski B.I., Pearl B.W. and Brighton C.T.
Bone reaction to varying amounts of direct current
J. Surg. Gynaecol. and Obstet. 131: 894, 1970

14. Friedenberg Z.B., Harlow M.C. and Brighton C.T.
Healing of non-union of the medial malleolus by means of direct current - a case report
Journal of Trauma 11: 883, 1971

15. Friedenberg Z.B., Zemski M.D., Pollis L.P. and Brighton C.T.
The response of non traumatized bone to direct current
J. Bone Joint Surg. 56A: 1023, 1974

16. Guyton A.C.
Textbook of Medical Physiology, Philadelphia
W.B. Saunders Co., 1956; 915

17. Herbst E. and Von Satzger G.
Electrical pulsed current stimulation in five cases of congenital pseudarthrosis of the tibia
In: Electrical Properties of Bone and Cartilage: Experimental effects and clinical applications
Edited by C.T. Brighton, J. Black, S.R. Pollack
Grune & Stratton, New York, 1979; 639

18. Hohenwallner W. and Wimmer E.
The malachite green micromethod for determination of inorganic phosphate
Clinia Chimica Acta 45: 169, 1973

19. Lavine L.S., Lustrin I., Shamos M.H. and Moss M.L.
The influence of electric current on bone regeneration in vivo
Acta. Orthop. Scand. 42: 305, 1971

20. Lavine L.S., Lustrin I., Shamos M.H., Rinaldi R.A. and Liboff A.R.
Electric enhancement of bone healing
Science 175: 1118, 1972

21. Lavine L.S., Lustrin I., Rinaldi R.A. and Shamos M.
Clinical and ultra structural investigations of electrical enhancement of bone healing
The New York Academy of Sciences 552, 1974

22. Levy D.D.
A pulsed electrical stimulation technique for inducing bone growth
Annals N.Y. Acad. Sci. 238: 478, 1974

23. Masureik C. and Ericksson C.
Preliminary clinical evaluation of the effect of small electrical currents on the healing of jaw fractures
Clin. Orthop. 124: 84, 1977

24. Paterson D.C., Hillier T.M., Carter R.F., Ludbrook J., Maxwell G.M. and Savage J.P.
Experimental delayed union of the dog tibia and its use in assessing the effect of an electrical bone growth stimulator
Clin. Orthop. 128: 340, 1977

25. Paterson D.C., Lewis G.N. and Cass C.A.
Treatment of delayed union and non-union with an implanted direct current stimulator
Clin. Orthop. 148: 117, 1980

26. Paterson D.C., Lewis G.N. and Cass C.A.
Treatment of congenital pseudarthrosis of the tibia with direct current stimulation
Clin. Orthop. 148: 129, 1980

27. Pawluk R.J. and Bassett C.A.L.
Electro-mechanical factors in healing cortical bone defect
Calc. Tiss. Res. 4 (Supplement) 120, 1970

28. Sabiston David C.
Textbook of Surgery - the biological basis of modern surgical practice
W.B. Saunders Co., Philadelphia, 10th edition, 1968; 31

29. Siegel S.
Non-parametric statistics for the behavioural sciences
McGraw-Hill, New York, 1956

30. Traina G.C. and Gulino G.
Medullary rods as electric conductors for osteogenic stimuli in human bone
In: Electrical Properties of Bone and Cartilage: Experimental effects and clinical applications
Edited by C.T. Brighton, J. Black, S.R. Pollack
Grune & Stratton, New York, 1979; 567

31. Treharne R.W., Brighton C.T., Korostoff I. and Pollack S.R.
Application of direct, pulsed and SGP-shaped currents to in vitro fetal rat tibiae
In: Electrical Properties of Bone and Cartilage: Experimental effects and clinical applications
Edited by C.T. Brighton, J. Black, S.R. Pollack
Grune & Stratton, New York, 1979; 169

32. Yasuda I., Noguchi K. and Sata T.
Dynamic callus and electrical callus
J. Bone Joint Surg. 37A: 1292, 1955

33. Yasuda I.
Electrical callus and callus formation by electret
Clin. Orthop. 124: 53, 1977

34. Zichner L. and Happel M.W.
Treatment of congenital and acquired non-unions by means of an invasive device.
In: Electrical Properties of Bone and Cartilage: Experimental effects and clinical applications
Edited by C.T. Brighton, J. Black, S.R. Pollack
Grune & Stratton, New York, 1979; 581

CAPTIONS TO ILLUSTRATIONS

Fig. 1. plan of the model

Fig. 2. section of defect four weeks old (silastic block removed). The typical crescentric shape of the defect is apparent as are the sectioning alignment guide holes traversing the shaft of the bone at each end of the photograph. In this specimen regrowth of periosteum across the defect is also illustrated. Note the trabeculae of new medullary bone surrounding the defect and the smooth lining of fibrous tissue

Fig. 3 (a) three weeks after an inactive stimulator, there is a small amount of new bone present in the depths of the defect. The remainder of the defect is filled with dense fibrous tissue. Note the large gap, wider at the top, left by the cathode, suggesting excessive movement of the cathode.

(b) active stimulator, the outline of the defect is still obvious (arrows) but there is much new bone in the defect area. Note the more appropriate size of the cathode defect compared with (a) and the surrounding layer of fibrous tissue.

Fig. 4. nuclear scan uptake displayed graphically

Fig. 5. estimations of serum calcium, phosphorus and alkaline phosphatase

APPENDIX I

The author was the main investigator in this work (Chapter 7). He organised and planned the project. The animal surgery was largely carried out by Dr. Collins as the orthopaedic/research registrar at the Adelaide Children's Hospital.

The protocol for the impedance measurements was developed by the author with Mr. Pfeiffer and the measurements were carried out by Dr. Collins.

The author acknowledges the advice and help freely given by Professor B. Vernon-Roberts whose staff carried out the technical preparations of the material in this project. The results of all the assessments were determined by the author with the help of Professor Vernon-Roberts and Dr. Collins. The author acknowledges the help of Dr. Collins in the preparation of the manuscript.

Collins, P. C., Paterson, D. C., Vernon-Roberts, B., & Pfeiffer, D. (1981). Bone formation and impedance of electrical current flow. *Clinical Orthopaedics and Related Research, 155,* 196-210.

NOTE:

This publication is included in the print copy
of the thesis held in the University of Adelaide Library.

APPENDIX J

This technique was developed by Mr. B. Hill, Senior Technician in the Department of Tissue Pathology, Institute of Medical and Veterinary Science, Adelaide for the histological assessment of the specimens in Chapter 8.

The work in Chapter 8 was planned and organised by the author. Much of the animal surgery was performed by Dr. J. Gheraibeh, the orthopaedic/research registrar at the Adelaide Children's Hospital.

The histological specimens were assessed by the author with Professor B. Vernon-Roberts.

PROCESSING OF BONES WITH TITANIUM IMPLANTS

Materials

Specimens consisted of bone from the femora of dogs from both left and right forelegs, measuring some 60-70 mm in length and 10-20 mm in diameter. Each had a titanium plate connected to the outer surface of the bone by a single screw.

The plates were of two types. The first being some 50 mm long by 10 mm wide by 0.4 mm thick and the second of the same length and breadth but 6 mm thick. Both plates had a slightly concave surface to accommodate the curvature of the bone. Both plates had a series of holes (Fig. 1) at intervals along the plate.

Methods

The specimens of bone were fixed in 10% aqueous formalin buffered to neutrality for at least two weeks. They were then placed under negative pressure in a vacuum desiccator for seven days and were then dehydrated progressively in 70%, 95% and absolute alcohol allowing seven days between each process. The dehydration was completed in acetone for a further seven days.

The specimens were then infiltrated with a mixture of equal parts of acetone and an Araldite mixture consisting of:

Ciba-Geigy Araldite Resin D	25 parts
Hardener HY-964	25 parts
Accelerator DY-064	0.8 parts

for seven days and then infiltrated with Araldite mixture alone for 48 hours at ambient temperature. The tissues were finally embedded in a fresh Araldite mixture and were allowed to polymerise at 60° C for 24 hours.

After the specimens had polymerised, blocks were cut with a hack saw along the lines indicated (Fig. 2). This allowed for future sectioning to be done through the holes in the implants.

Despite such prolonged processing times, these were found to be inadequate for complete infiltration by the Araldite into the marrow cavity of the bone. These small blocks of bone were subjected to a further 48 hours in Araldite under negative pressure and were then re-embedded in fresh Araldite once more. The new blocks were then trimmed to a suitable size for cutting.

Using a Buechler Isomet 11-1180 low speed saw with a 10 cm diamond wafering blade revolving at some 100-150 revolutions per minute and using kerosine as a blade lubricant, sections of approximately 200-250 μ were taken and stored in distilled water.

Attempts were made to grind these sawn samples, using wet and dry silicone carbide paper, but resulted in particles of the silicone becoming firmly embedded in the Araldite. Grinding with commercial sand-blasted glass plates produced too rough a surface and damaged the sections. It was finally decided to use 200 x 200 x 10 mm thick glass slabs that had been roughened by rubbing them together after they had been

sprinkled with 80 grit Aluminium Oxide powder. When this was washed away, the plates were sufficiently "sharp" to cut easily. Smaller glass slabs - 100 x 100 x 18 mm thick - were roughened in a similar manner and used as the rotating half of the grinding apparatus. With the addition of a few cubic mms of distilled water, the sections were ground down to 40-50 microns and stored in distilled water.

The grinding of a single section blunted the "sharpness" of the plates but only a few seconds exposure with Aluminium Oxide enabled a fresh surface to be cut. As there was no bond between Araldite and the implant, extreme care was needed to ensure that the implant stayed in place.

If the titanium implants became dislodged, they were replaced in the holes in the Araldite by using a dissecting microscope, and were maintained in place with a small portion of quick setting Araldite ("5 minute Araldite" Ciba-Geigy).

Sections were then stained using the von Kossa technique in which sections were placed in 5% aqueous silver nitrate solution and exposed to sunlight or ultra-violet light for 30 minutes until blackened, then washed in three changes of distilled water, fixed in 5% aqueous sodium thiosulphate and washed again in two changes of distilled water.

Tissues were mounted on glass slides that had been chrome-alum-gelatin subbed (Pappas 1971) using 2.5% aqueous gelatin heated to 65^{o} for adhesion. When dry, the sections were immersed in xylol until they were clear.

References:

Pappas R.W.
The use of chrome-alum-gelatin (subbing) solution for a general adhesive for paraffin sections
Stain Technology 46: 121, 1971

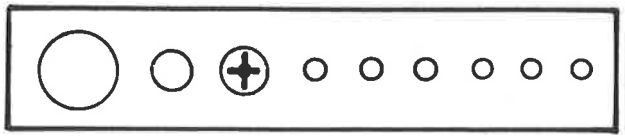

Figure 1

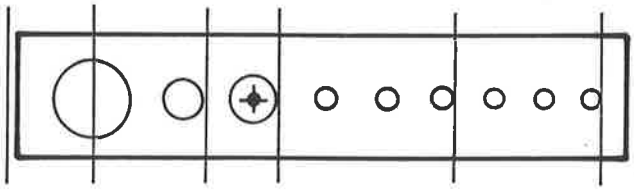

Figure 2