THE EFFECT OF HEAD INJURY ON FRACTURE HEALING - CLINICAL AND EXPERIMENTAL STUDIES

BY

ROBERT F SPENCER

THESIS PRESENTED FOR THE DEGREE OF DOCTOR OF MEDICINE OF THE UNIVERSITY OF EDINBURGH

1989

DECLARATION

The work of which this thesis is a record, and the composition of the thesis have been completed by myself.

This thesis has not been submitted or accepted in any previous application for a degree.

CONTENTS

ACKNOWLEDGEMENTS

Professor Theodore Sarkin of Durban and Professor David Hamblen of Glasgow have been a source of great encouragement to me over the years, and this has resulted in my preparation of this thesis. Many others, notably Mr. K.S. Naidoo of Durban, have provided inspiration and support.

I am grateful to Professor John Brock-Utne for permission to use the animal facilities in Durban, and to Dr. Brian Wessels for his expert veterinary advice, and my advisor, Mr. C. Court-Brown of Edinburgh, for his timely words of encouragement and guidance.

The assistance of Mr. Ross Bullock (now of Glasgow) in some of the neurosurgical aspects of the animal study was indispensable. Professor Rob Norman (now of Adelaide, Australia) provided many useful pieces of advice on the biochemical and endocrine aspects of the study. Dr. Kum Cooper and Dr. Bernard Ackerman of the Pathology Department of the University of Natal rendered valuable assistance in the assessment of bone and brain specimens. Similarly, the advice given by Dr. Piet Becker, of the Institute of Biostatistics, Johannesburg, was most important.

I would like to thank Dr. Justin Naude of Durban for his help in reviewing the patients with poliomyelitis, and Professor Stephen Hough and Dr. Sue Honiball of Tygerberg for painstakingly performing the Vitamin D analysis.

Geoff Wyatt-Goodall provided superb care for the animals, and his tireless attention to detail with many aspects of the animal study was much appreciated. Similarly, Eddie Thackray lent valuable help with the technical aspects of using the stereotaxic apparatus.

Miss. E. Margheriti typed the manuscript without many of the modern technological aids, and I am most grateful for her punctilious and prompt efforts. The Medical Illustration Departments of Addington Hospital and the University of Natal performed a great deal of work on my behalf, and for this I am most grateful.

Similarly, I would like to thank the staff of the Departments of Radiology, Chemical Pathology and Biochemistry of the University of Natal for their willingness to perform extra work in an already full working day.

The South African Orthopaedic Research Foundation, the Medical Research Council of South Africa, and the University of Natal Research Fund provided financial assistance, without which my work would not have been possible.

I would like to express my gratitude to my parents for their continuing interest in my career.

Last, but most of all, I would like to thank my wife and children for their support and understanding over the last four years.

ABSTRACT

ABSTRACT

The possible association of cerebral injury with augmented osteogenesis around bone fractures has been one of the mysteries faced by clinicians during this century. It has remained thus partly due to the non-quantitative nature of most reports, and the lack of experimental work.

These shortcomings have been addressed, first using a simple method of quantifying fracture healing to compare 53 patients with limb fractures and severe head injuries with 30 patients with comparable fractures but no head injury. Two further clinical studies were performed, one assessing 10 patients with neural injury who produced massive amounts of new bone in association with fractures, the other observing the osteogenic capacity of 283 patients with poliomyelitis who had been subjected to surgical osteotomy in 11 cases, and who had sustained a total of 25 fractures. Finally, an experimental study was performed, using 27 domestic cats. Certain animals were subjected to bilateral fibular fractures and stereotaxic brain lesions to produce unilateral spasticity, and these animals were used as their own controls in respect of fracture healing phenomena, but compared with a separate group with identical fractures but no brain lesion in respect of certain biochemical and endocrine parameters.

The clinical studies indicated greater amounts of new bone and more rapid union of fractures in association with neural injury. This new bone was atypical in nature, and in many cases resembled heterotopic bone more than fracture callus. Detailed neurological assessment indicated that limb spasticity may be an important factor, and the fracture healing behaviour in association with lower motor neuron lesions was unremarkable.

In the animal study, more new bone was formed in spastic limbs, with slightly earlier union. No significant systemic biochemical or endocrine changes occurred. Histomorphometric analysis of fibular specimens showed few differences between spastic and non-spastic limbs. Whether the enhanced bridging callus production in spastic limbs occurred due to local mechanical, biochemical or endocrine factors, or a combination, could not be stated with certainty.

INTRODUCTION

INTRODUCTION

Two patterns of unusual osteogenic behaviour in relation to neural injury have been observed with regularity, these being the tendency of some individuals to form bone spontaneously in soft tissues, and the tendency of some individuals to heal fractures with greater amounts of callus and with greater rapidity than normal. Whether the two processes are related is not known although, as Smith (1987) observed, both must depend on the activity of osteogenic cells.

McKusick (1983) infers that an awareness of soft tissue ossification may date back to ancient times but the link with neural injury did not become apparent until the latter half of the 19th Century, when sporadic reports began to appear in the French and German literature.

Since the turn of the century, the majority of reports have concerned heterotopic ossification following cord injury, but fracture healing behaviour following head injury has become a topic of increasing interest in recent years. Most studies have been accounts of clinical experience, with few attempts at elucidating the aetiology. It is surprising, that in an age when orthopaedic surgeons expend a great deal of energy on scientific appraisal of the many methods of assisting fracture healing, that so few attempts have been made to explore the mysteries of this subject. (See Fig 1 and Table 1).

Bayley (1979), in a review of the issue of neurogenic heterotopic ossification, stated that the complication may follow tetanus, poliomyelitis, tabes dorsalis, syringomyelia, myelitis, myelodysplasia, spinal cord injury, anoxic brain damage, and stroke. There are other causes, including measles encephalomyelitis and tuberculous meningitis (See Table). Indeed, a wide variety of cerebral and cord injuries have been incriminated.

Connor (1983) stated that heterotopic ossification in paraplegic patients is never found above the level of the paralysis, an interesting observation which highlights the role of the neural injury itself, rather than any systemic factor. However, some general influence may exist, for the condition has been seen in patients with chronic infection and burns (Heffner, 1984).

In relation to abundant callus formation following neural injury, Sevitt (1981) noted certain neurological disorders which may influence fracture healing including peripheral nerve injury, anterior poliomyelitis, traumatic paraplegia, cerebrovascular disease, cerebral injury, and cerebral fat embolism. In addition, he cited numerous chemical and endocrine factors of importance, including tissue oxygen tension, enzymes (including alkaline phosphatase) Vitamin C (deprivation leads to failure to heal fractures), Vitamin D, and Vitamin A (hypervitaminosis A predisposes to fractures).

He indicated that the formation of heterotopic bone may be related to fracture callus production under certain circumstances.

A notable feature of many of the reports of augmented bone repair in relation to neural injury has been the failure to quantify fracture healing in such patients and make comparisons with a control group. Similarly, particularly in the context of head-injured patients, the cerebral injury itself has rarely been assessed in detail. In addition, the material produced around fractures in such patients is frequently referred to as "callus", but this may not be the most appropriate term as ossification may occur spontaneously in the limbs of these patients (Garland, Blum and Waters, 1980).

Therefore, an initial study (Section A) was designed, to establish the quantity and nature of the fracture healing response in patients with precisely defined levels of head injury. Following this study it was felt that failure to identify a single factor responsible for augmenting fracture healing may have resulted from review of patients with varying peripheral neurological effects, those with genuine augmentation being mixed with those without.

A second study (Section B) sought to examine the issue in reverse, by identifying patients who laid down very large amounts of new bone in association with neural injury, to attempt to find a common denominator.

At the same time, it was possible to review fracture healing and the presence or absence of heterotopic ossification in a large number of patients with poliomyelitis. It was felt that this would afford an opportunity of observing the effects of the lower motor neuron lesion in relation to ossification (Section C).

Finally, an animal study is reported. This was performed to determine the effect of a consistent neural injury affecting one limb in animals with bilateral fibular fractures, so that each subject may be used as its' own control in respect of fracture healing observations. In addition, another group were subjected to bilateral fibular fractures without neural injury, in order to allow comparison between brain-lesioned animals and those without, in respect of certain biochemical and endocrine parameters (Section D).

TABLE 1

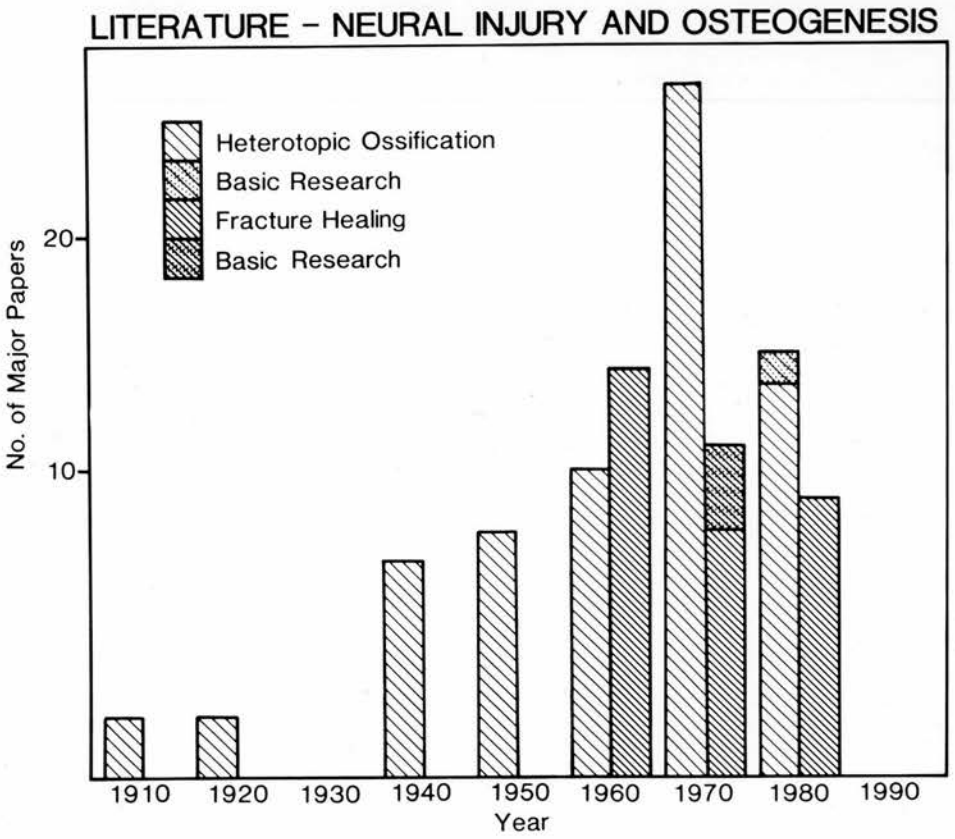
NEURAL INJURY AND ABNORMAL OSSIFICATION – CLASSIFICATION ACCORDING TO PATHOLOGY

CH n=30	Déjerine & Ceillier(1918); Déjerine, Ceillier & Déjerine(1919); Meyer (1927); Brailsford(1946); Hielbrun & Kuhn(1947); Abramson(1948); Roche & Jostes(1948); Abramson & Kamberg(1949); Miller & O'Neill(1949); Soule(1945); Armstrong-Ressy, Weiss & Ebel(1959); Damanski(1961); Benassy, Mazabraüd & Diverres(1963); Hardy & Dickson(1963); Freehaffer, Yurick & Mast(1966); Hossack & King(1967); Lee(1962); Wharton & Morgan(1970); Heuwinkel(1979); Nicholas(1973); Hassard(1975); Hsu, Sakimura & Stauffer(1975); Stover, Hataway & Zieger(1975); Takada(1977); Hernandez et al(1978); Tibone et al(1978); Vogel, Vliegen & Ketz(1972); Blane & Perkash(1981); Chantraine & Minaire(1981); Lynch, Pont & Weingarden(1981).
HIF n=24	Gibson(1960); Wray & Davis(1960); Calandriello(1964); Meacham(1964); Irving & Irving(1967); Reichert & Schweikert(1967); Campanacci & Vellani(1969); Herold, Tadmor & Hurvitz(1970); Weissman & Khermosh(1970); Hoffer et al (1971); Glenn, Miner & Peltier(1973); Knoch, Diettrich & Knoch(1973); Bellamy & Brower(1974); Fry, Hoffer & Brink(1976); Jastrzebski, Opolski & Podlewski(1977); Garland & Rhoades(1978); Garland,& Toder(1980); Garland, Rothi & Waters(1982); Garland & Miller(1984); Kernohan et al(1984); Perkins & Skirving(1987); Spencer(1987); Stone, Newman & Mukherjee(1987); Wood & Hoffer(1987).
HIH n=13	Bour et al(1966); Roberts(1968); Money(1972); Noh & Ouest(1972); Mendelson et al(1975); Mielants et al(1975); Mahmud et al(1978); Roberts & Pankratz(1979); Garland, Blum & Waters(1980 Sazbon et al(1981); Garland, Razza & Waters(1982); Hagel et al(1983); Goldberg(1977).
GR n=8	Rossier et al(1973); Bayley(1979); Sevitt(1981); Garland(1982); Connor(1983); Heffner(1984); Lane & Werntz(1987); Smith(1987).
PH n=5	Drehmann(1926); Costello & Brown(1951); Hess(1951); Hannson & Austlid(1955); Stoikovic, Bonfiglio & Paul(1955).
CF n=4	Comar, Hutchinson & Bors(1962); Eichenholtz(1963); McMaster & Stauffer(1975); Freehaffer, Hazei & Becker(1981).
HLAH n=4	Minaire, Betuel & Pilonchery(1978); Weiss et al(1979); Hunter et al(1980); Larson et al(1981).
MH n=2	Irving & Le Brun(1954); Radt(1979).
NIF n=2	Cunningham et al(1971); Frymoyer & Pope(1971).
RGH n=1	Scher(1976)
TH n=1	Gunn & Young(1959)
TBMH n=1	Lorber(1953)
MEH n=1	Jacobs(1962)
PF n=1	Robin(1966)
FEF n=1	Weiss, Fishman & Steiner(1969)
CCH n=1	Spencer(1988)

KEY (PREDOMINANT TOPIC)

CH	– CORD INJURY/HETEROTOPIC BONE
HIF	– HEAD INJURY/FRACTURE HEALING
HIH	– HEAD INJURY/HETEROTOPIC BONE
GGR	– GENERAL REVIEW (MAINLY HETEROTOPIC OSSIFICATION)
PPH	– POLIOMYELITIS/HETEROTOPIC BONE
CF	– CORD INJURY/FRACTURE HEALING
HLAH	– HLA TISSUE TYPES/NEUROGENIC HETEROTOPIC OSSIFICATION
MH	– HEMIPLEGIA (e.g. STROKE)/ HETEROTOPIC BONE
NIF	– PERIPHERAL NERVE INJURY/FRACTURE HEALING
RGH	– DIFFERENT RACIAL GROUPS/NEUROGENIC HETEROTOPIC OSSIFICATION
TH	– TETANUS/HETEROTOPIC BONE
TBMH	– TB MENINGITIS/HETEROTOPIC BONE
MEH	– MEASLES ENCEPHALITIS/HETEROTOPIC BONE
PF	– POLIOMYELITIS/FRACTURE HEALING
FFEF	– CEREBRAL FAT EMBOLISM/FRACTURE HEALING
CCH	– CEREBRAL CYSTICERCOSIS/HETEROTOPIC BONE

Figure 1



A histogram detailing the number of major articles on neurogenic heterotopic ossification and fracture healing in association with neural injury during this century. The contribution of basic research is indicated.

MATERIALS AND METHODS

MATERIALS AND METHODS

SECTION A

(THE EFFECT OF HEAD INJURY ON FRACTURE HEALING - A QUANTITATIVE ASSESSMENT).

During a two-year period between October 1983 and October 1985, 366 patients with significant head injuries were admitted to King Edward VIII Hospital, Durban. Forty-five (12%) died as a result of their injuries. Fifty-three patients with severe head injuries and fractures of the limbs, spine or pelvis survived. Their head injuries were rated, in the first 48 hours, at 10 or less on the Glasgow coma scale. There were 47 males and 6 females with an age range of 4 to 67 years (average 30 years). Motor vehicle accidents were the commonest cause of injury. A total of 82 fractures were sustained (Table 2); 32 patients had two or more fractures (the tibia and fibula, and the radius and ulna each counted as only one fracture). Patients suffering from alcohol withdrawal or fat embolism were excluded.

Most of the fractures were treated conservatively, but internal fixation was used for eight fractures, seven of which involved the femur. The head injuries also were mostly treated conservatively by observation and intracranial pressure monitoring, but in 10 patients burr holes were made or a craniotomy performed.

The factors assessed were the fracture healing response (see below), the time to clinical union (see below), the cerebral CT scan findings, the severity and duration of neurological deficit and any complications.

The fracture healing response was calculated by the simplest possible method which allowed reproducibility. The intention was to produce an index which related closely to perceived differences in callus/new bone production. The healing mass is frequently fusiform, though often irregular and eccentric, resembling no mathematically definable shape. However, the largest diameter of even the most amorphous tube-like structure is substantially the most important determinant of volume in absence of massive variations in length. A numerical value for fracture healing response was therefore calculated as follows :

Fracture healing response (FHR) = A/B

where A is the largest diameter of the healing mass measured from serial radiographs taken at 90° to each other and B is the bone diameter at or adjacent to the fracture site on the same radiograph (Figure 2).

It was conceded that this value would differ greatly in respect of various different bones, but it was thought that it would provide a satisfactory assessment of healing response when similar fractures of the same bone were compared.

Union time is difficult to establish with certainty. A fracture may retain a degree of mobility until the process of consolidation is well advanced. There exists, however, a phase when fracture mobility is lost, and the bone becomes splinted by bridging callus. At this stage union has occurred (Apley and Solomon, 1982). An estimate of union time was based on these clinical and/or radiological criteria.

The numerical values for fracture healing response and union time were then used to compare the patients who had head injuries and fractures of the tibia, femur and/or humerus, with a group of 30 controls matched for age and sex who had similar fractures but no head injury. A similar number of open fractures was present in both groups. Patients aged under 16 years, and fractures which underwent internal fixation were not used for comparative purposes.

In addition, the fracture healing area was biopsied for histological examination in patients undergoing late internal fixation in two with and two without head injury, to determine if any difference existed between the two groups in the structure of the new bone at a microscopic level.

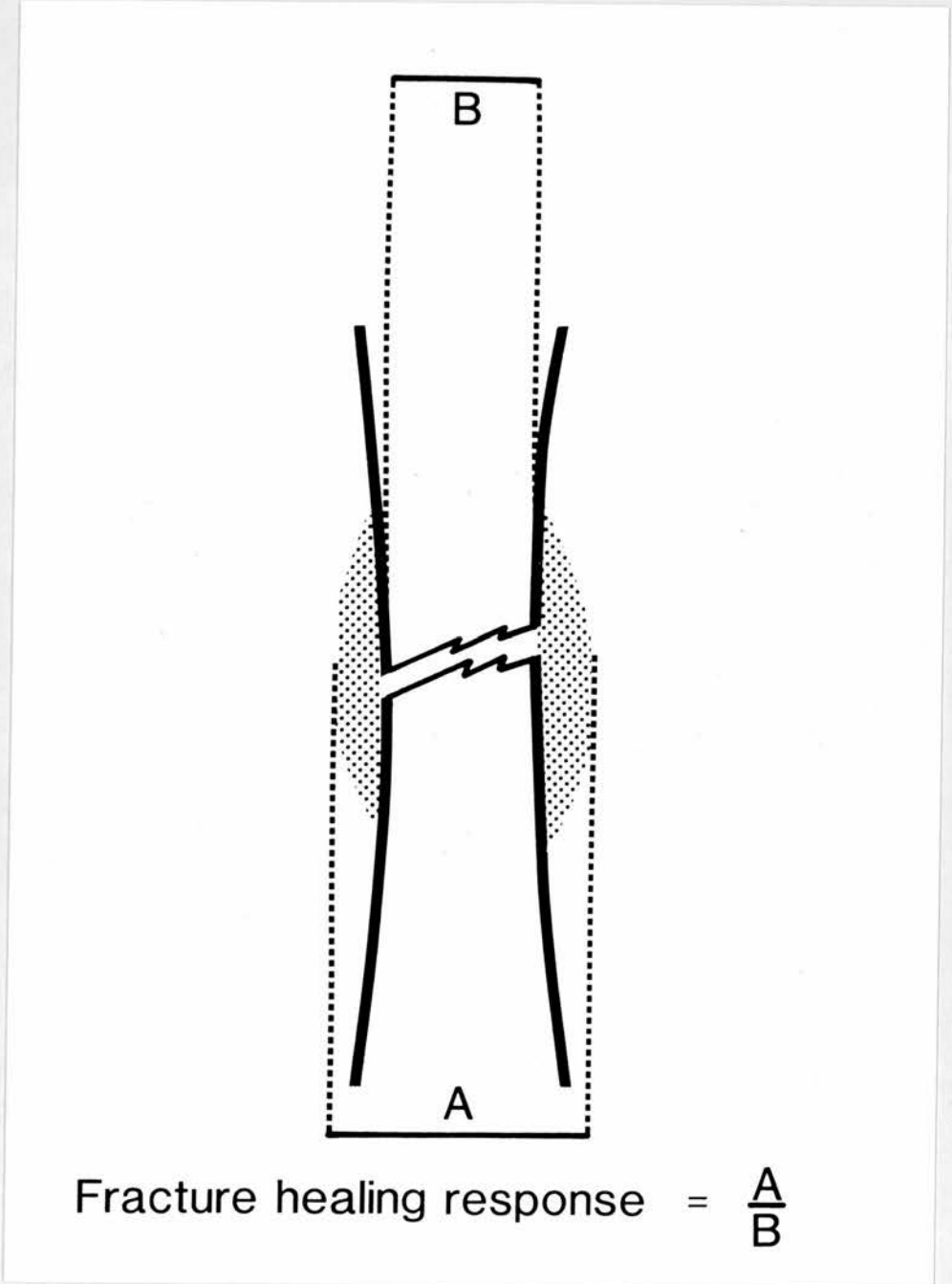
TABLE 2

The 82 fractures sustained in 53 patients with head injuries.

Tibia and fibula	20
Femur	15
Humerus	12
Pelvis	7
Clavicle	5
Radius / ulna	5
Hand	4
Cervical spine	4
Tibial plateau	2
Ankle	2
Fibula	2
Foot	1
Olecranon	1
Scapula	1
Femoral condyle	1

FIGURE 2

FRACTURE HEALING RESPONSE



MATERIALS AND METHODS

SECTION B

(ASSESSMENT OF MASSIVE NEW BONE FORMATION AROUND FRACTURES IN ASSOCIATION WITH NEURAL INJURY).

Ten patients with neural injury who demonstrated very large amounts of new bone formation around fractures were treated at King Edward VIII and Addington Hospitals, Durban, between September 1986 and September 1988.

The patients were aged 20-63 years (average 29,3 years). There were 7 males and 3 females. The commonest cause of injury was a motor vehicle accident. A total of 18 major skeletal injuries were sustained, and 8 patients sustained more than one orthopaedic injury.

All but one of the fractures were managed by early internal fixation.

The factors assessed were the amount of new bone (see below), and the neurological findings in the limbs affected.

Massive new bone formation was defined as new bone extending more than one bone diameter away from the cortex. In all cases the fracture healing response (see p 16) exceeded 2,5.

Because new bone was frequently seen distant from the fracture site, a grading system similar to that used to quantify heterotopic bone (Brooker, Bowerman, Robinson et al, 1976) following total hip replacement was used. This was as follows :

GRADE I : Callus/new bone visible on at least one Xray extending further away in one direction at least from the bone than the diameter of the bone itself.

GRADE II : **(a)** As grade I plus extension of of new bone in linear fashion along muscle/tissue planes distant from the fracture site.

(b) As above but with heterotopic bone at another site in the same limb.

Neural injury as it affected the limb or limbs in question was assessed as follows. The author attempted to review as many patients as possible with major neural and skeletal injuries from September 1986 onwards. 51 such patients were seen during a two-year period. A complete neurological examination was performed shortly after admission. From this group those with evidence of massive new bone formation were assessed on a daily basis from around 2-3 weeks post-injury until discharge from hospital, and thereafter at monthly intervals.

This continuing neurological assessment concentrated on the limb or limbs involved. Because sensory and lower motor neuron signs were not detected, attention was concentrated on the upper motor neuron lesion, and the presence or absence of spasticity.

Signs were recorded as follows :

A - Resistance to passive stretch of one or more muscle groups (normally extensors).

B - Clasp-knife effect.

C - Brisk tendon reflexes.

D - Extensor plantar response.

E - Clonus (ankle and patella).

F - Hoffman's sign positive (upper limb injuries).

MATERIALS AND METHODS

SECTION C

(ASSESSMENT OF OSTEOGENIC CAPACITY IN PATIENTS WITH POLIOMYELITIS).

Records and Xrays of 283 patients with late effects of poliomyelitis admitted to King Edward VIII and Addington Hospitals, Durban, during the years 1983-1987 were reviewed. There were 166 males and 117 females with an age range of 6 months to 63 years (average 12.46 years).

The precise date of initial illness was difficult to determine, though it generally occurred in infancy or early childhood.

The site of main involvement was as follows;

one lower limb only	168 cases
both lower limbs	94 cases
both upper and both lower limbs	6 cases
one upper limb and the contralateral lower limb	5 cases
one upper limb and the ipsilateral lower limb	3 cases
one upper limb and both lower limbs	2 cases
one upper limb only	1 case
both upper limbs and one lower limb	1 case
not certain	3 cases

In addition, 22 of the above patients displayed a significant scoliosis.

Patients were assessed according to surgical procedures performed on the limbs, the presence or absence of heterotopic bone around affected joints (particularly following surgical procedures), and fracture or osteotomy healing.

The fracture healing response was observed (See p 16) and particular efforts were made to identify patients who healed fractures or osteotomies with abundant callus or new bone formation.

In addition, time to union was estimated, when possible, in weeks.

MATERIALS AND METHODS

SECTION D

(ANIMAL STUDY - THE EFFECT OF SPASTICITY DUE TO A BRAIN LESION ON FRACTURE HEALING).

Ethics

Animal experimentation has entered a controversial era. A clear advantage to society (even to animals themselves) must be deemed possible. The author considers these requirements to be met as follows :

(a) Augmentation of fracture healing is desirable under certain circumstances. Further knowledge in this area may lead to advances in the field.

(b) Fracture management in head-injured patients (and animals) can be difficult. This study may provide information of predictive value.

Significant bone fracture and neural injury have been used on their own in many studies on experimental animals. This study sought to use the minimum orthopaedic and neurosurgical injuries compatible with a useful study.

The protocol was approved by the Ethics Committee of the University of Natal, and by the Ethics Committee of the Medical Research Council of South Africa. An experienced veterinary surgeon was available for assistance at all times.

Numbers

A pilot study involving 5 animals was performed in the first instance, to demonstrate the feasibility of the methods proposed, particularly the brain stereotaxic lesion and the fibular fracture.

During this phase it was possible to refine a method of taking Xrays, and to clarify the time of fracture union. The opportunity was also taken to establish which method of anaesthesia would be most suitable in the main study.

Twenty-two healthy adult animals were then numbered on a random basis and allocated to two groups as follows ;

Group 1 Overall controls (n=8).
These animals were subjected to bilateral fibular fractures without head injury.

Group 2 Head injury (n=14).
These animals were subjected to bilateral fibular fractures and left-sided stereotaxic brain injury to produce right-sided spasticity.

The intention was to observe fracture healing phenomena in the head injured animals' right legs, using the left side as control, and to compare groups 1 and 2 in respect of biochemical and endocrine parameters.

Anaesthesia

In the pilot study, pentobarbitone sodium was first used, but this proved difficult to administer since the intravenous route was required. As a result, three animals in the pilot group were anaesthetised with ketamine, and this proved more suitable. This drug is a neurolept anaesthetic agent which is easily administered, and has been used successfully in the context of experimental brain injury in cats (Wagner, Tomheim and Eichhold, 1985).

Ketamine was given by intramuscular injection (10mg/kg repeated as necessary). This was supplemented with diazepam (1mg intramuscularly) as required. This regime was used for performing surgical procedures, and for weekly venepuncture and radiology. In addition, during and following operative procedures, vital signs were followed at 15 minute intervals for a period of 2-3 hours. Postoperative sedation and analgesia were given using intramuscular ketamine as required. At the end of the study, animals were sacrificed using an overdose of intrapleural pentobarbitone sodium while still under anaesthetic following final Xray.

Antibiotic prophylaxis

Chloremphenicol (40mg/day for 4 days by intramuscular injection) was given as prophylaxis against infection, commencing at the time of initial anaesthesia.

Head Injury

Head injury was produced using thermocouple - controlled electrodes mounted on a rectilinear stereotaxic frame with head vice as described by Carpenter and Whittier (1952). (Figs 3 and 4). The basal horizontal plane (Whittier and Mettler, 1949) was ensured using orbital jigs and clamps to external auditory meati and mouth.

It was intended to produce a lesion involving the pyramidal and extrapyramidal systems in the region of the following stereotaxic targets; H_2, field of Forel, subthalamic nucleus and internal capsule to produce maximum contralateral spasticity. These coordinates were determined from a cat brain stereotaxic atlas (Reinoso-Suarez 1961) to be 5mm and 7mm lateral to the midline, 22-23mm deep from the outer table of the skull, and 8,9 and 10mm behind the Bregma (coronal suture) (Fig 5). The spread of coordinates was accommodated by creating a 5mm lesion to compensate for differences from these guidelines (Whittier and Mettler, 1949), and tested on egg white before proceeding to pilot animals.

It was noted that Tsementzis (1984) had been successful in producing decerebrate rigidity in cats by means of mesencephalic lesions using similar stereotaxic technique.

In this study double electrodes, insulated with heat-baked varnish (Fig 6) were introduced through a cranial burr-hole and subjected to charge from a controlled system (Fig 7) (Leksell Stereotacic System, Arex, Sweden), to produce a lesion of consistent size and timing. The skin only was then closed using an absorbable material.

Neural injury was observed on the first post-operative day and twice weekly thereafter. The presence or absence of hemiplegia and the onset of spasticity were noted. Spasticity was deemed to be present in a particular limb if the following criteria were met :

1. Increase in resistance of a particular muscle group (normally "extensors" such as quadriceps and triceps solei) (Bannister, 1980) to manually induced passive movement (Bajd and Bowman, 1982).

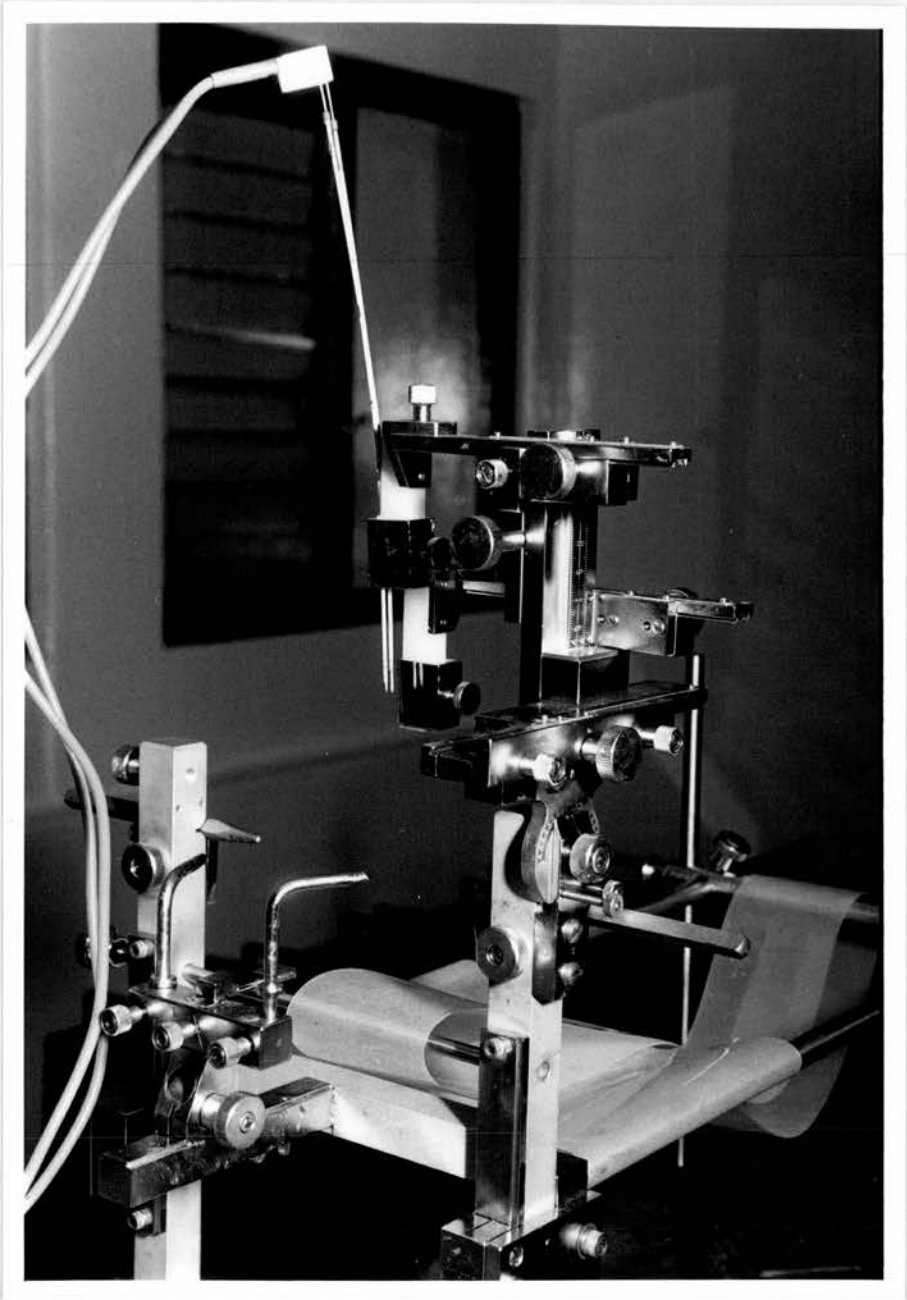
2. Increased resistance to passive stretch, exaggerated deep tendon reflexes, and enlarged reflexogenic area (Kane, 1964).

3. Clasp-knife effect (Bannister, 1980).

On sacrifice, the brains were removed by circumferential craniotomy, then inverted and suspended by the basilar artery in 10% formal saline for 3 weeks or more prior to section. Sequential coronal cuts were then made in the plane of the lesion, to establish that the brain had been damaged in the prescribed area.

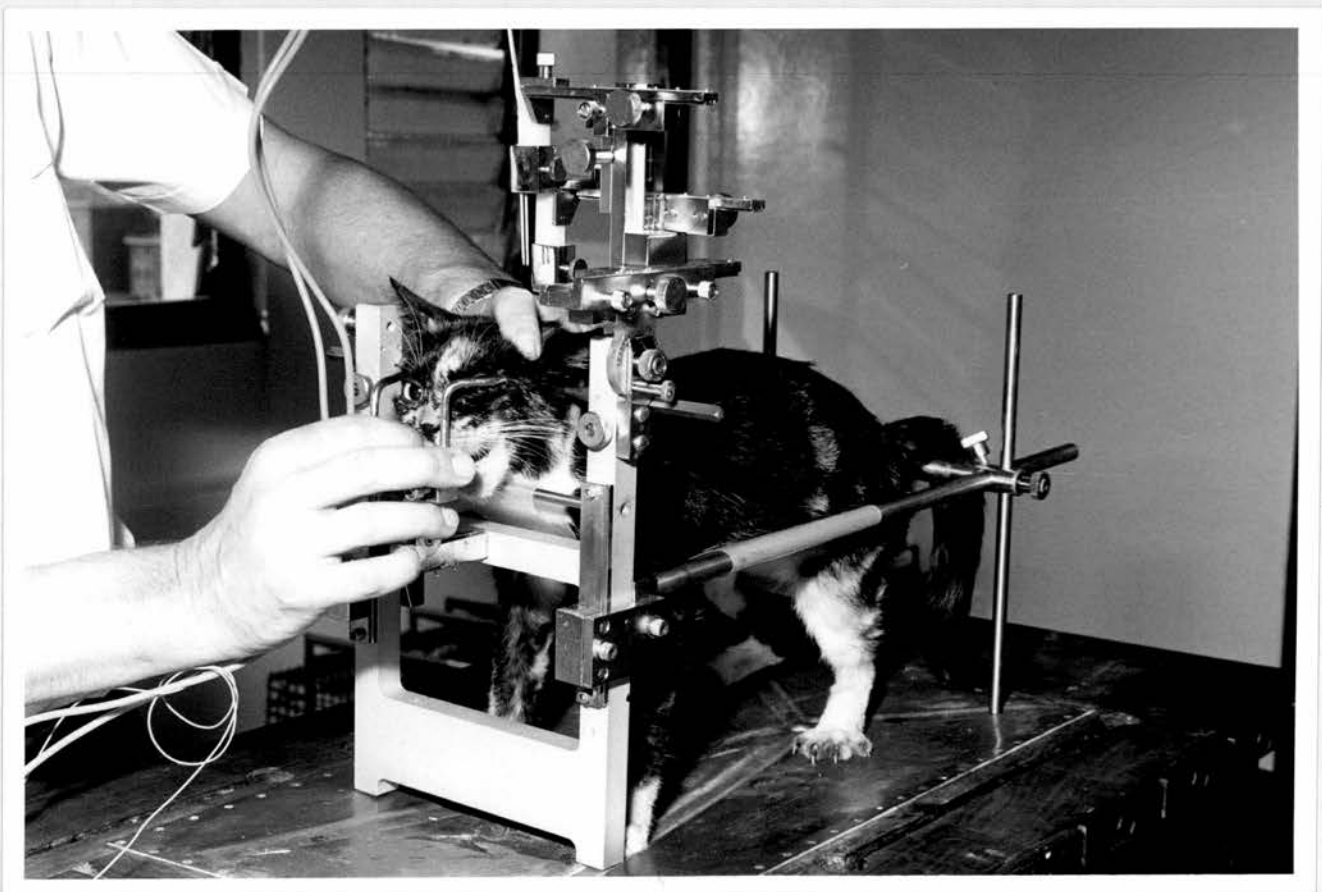
Specimens were taken from the site of the lesion and submitted to staining with haematoxylin and eosin for microscopic examination. In a few cases, Luxol fast blue staining was used to highlight myelin degeneration within the internal capsule.

Figure 3



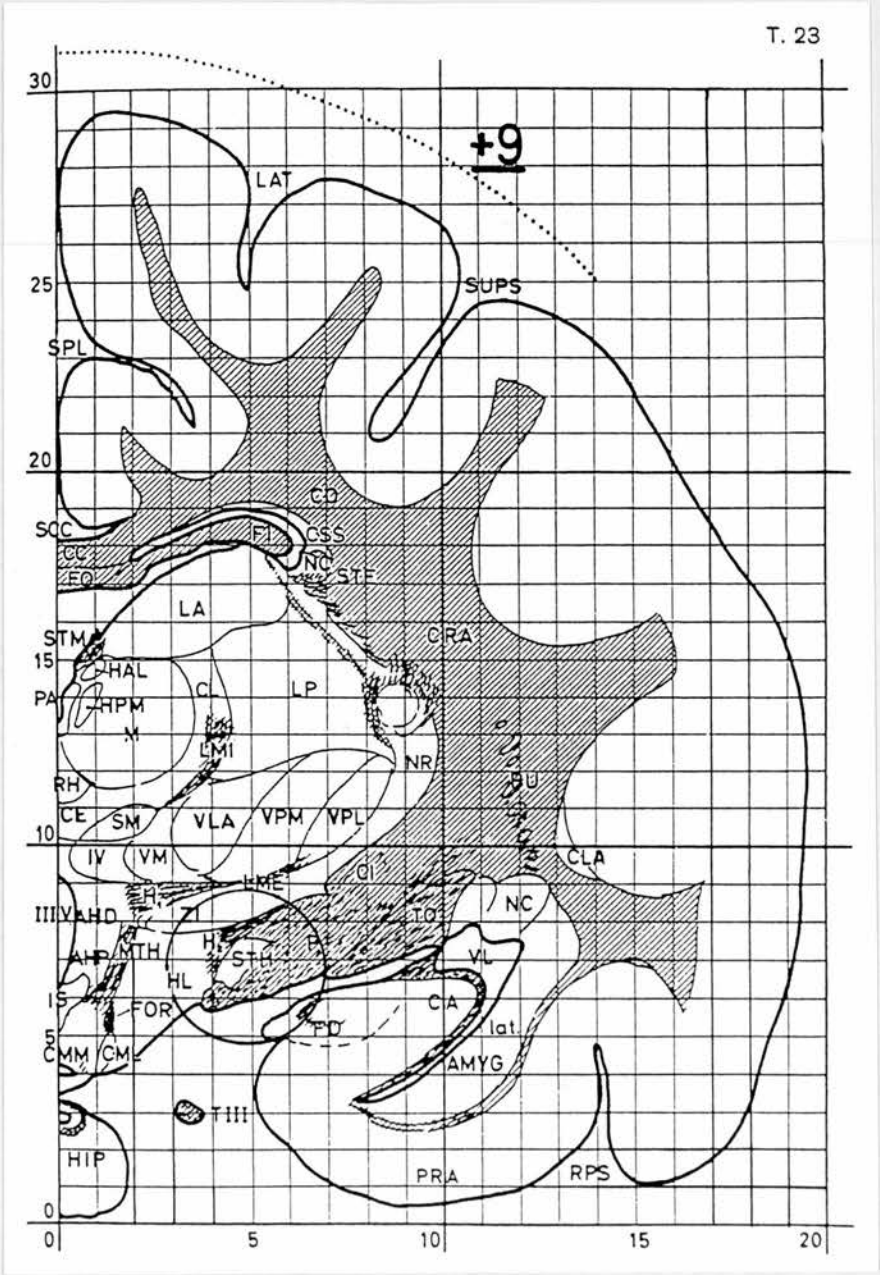
The stereotaxic frame (See text).

Figure 4



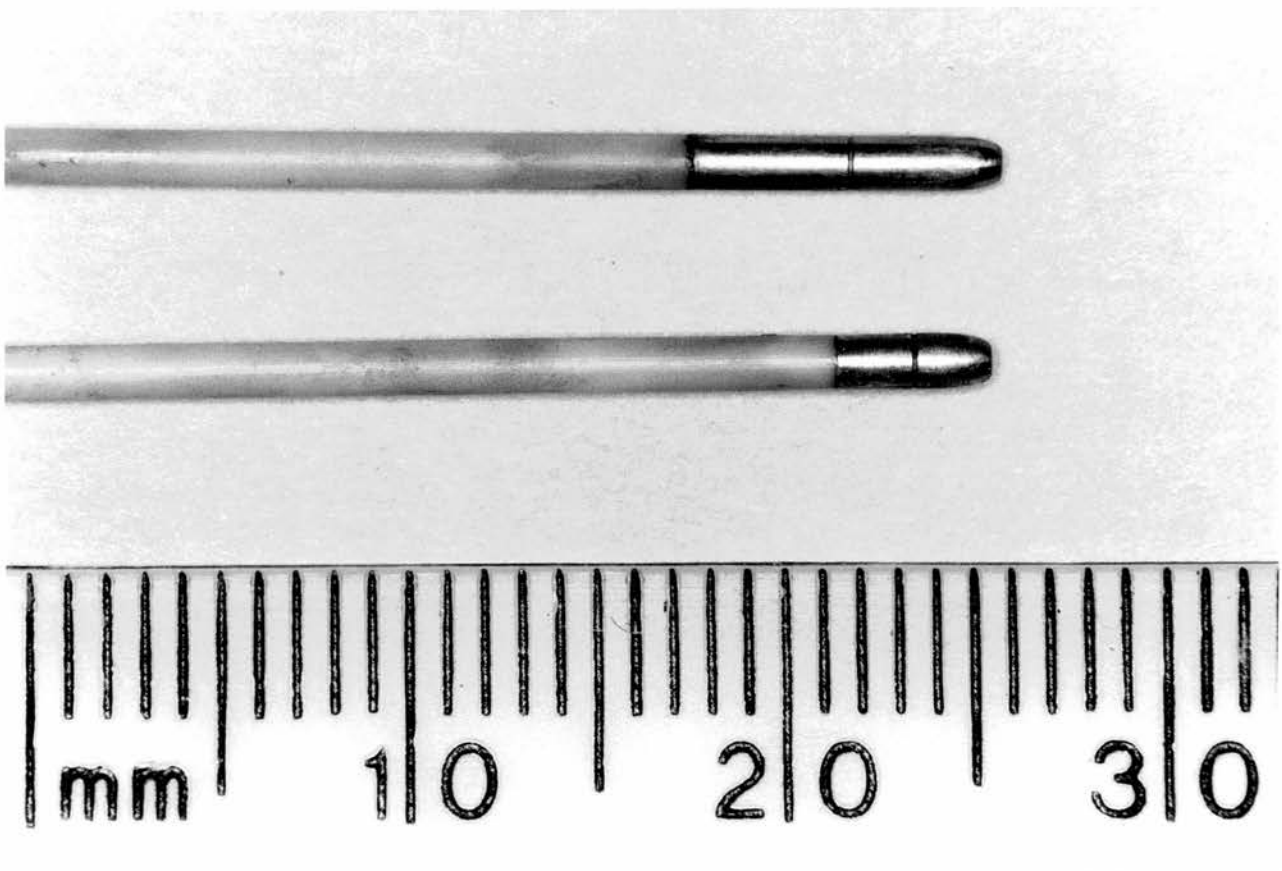
Positioning of the animal in the stereotaxic frame. (See text).

Figure 5



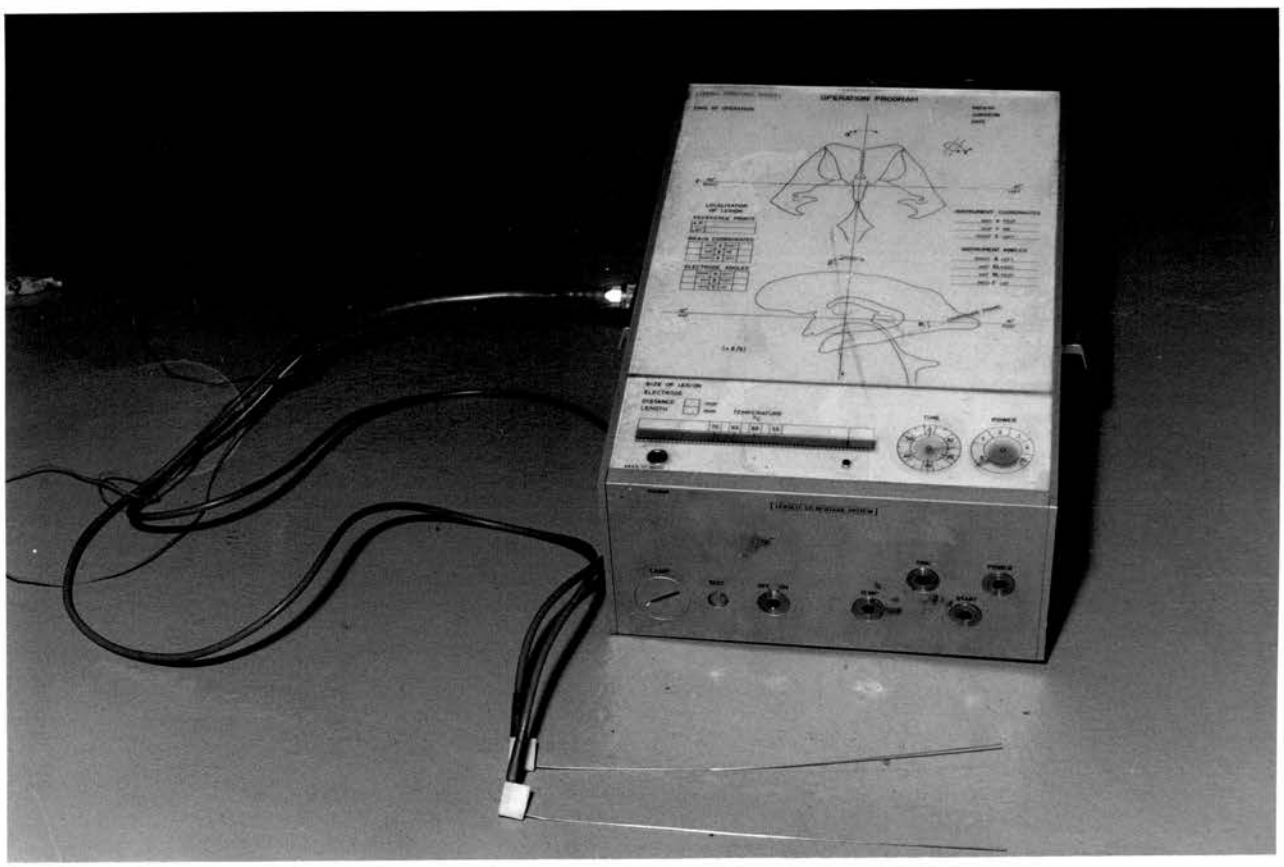
The stereotaxic lesion. A circle indicates the site.

Figure 6



Stereotaxic electrodes (x5) showing 5mm separation as used in this study.

Figure 7



The stereotaxic system. Note temperature, timing and power control.

Fibular fractures

Bilateral fibular fractures in the mid-shaft of the bone were created using a lateral intermuscular approach. The periosteum was not disturbed, and the bone was divided transversely using fine bone cutters. While it was not possible to ensure that division occurred exactly at the mid-shaft, every effort was made to ensure that comparable fractures were created on each side, by measuring a fixed distance from the proximal end. No splintage was required, due to interosseous attachment to the tibia, and the wound was closed using a subcuticular stitch of absorbable material.

The fibular fractures were assessed by Xrays to observe the following :

1. The rate of appearance of new bone.
2. The fracture healing response (p16).
3. Union time.

Following union, the healing areas were removed and the following were performed :

1. Photography.
2. Mass assessment of the healing area.

Finally, the healing areas were subjected to histomorphometic analysis to assess the following :

1. The overall composition of the healing area.
2. The composition of the area between the bone ends. (the fracture line).

Xrays were taken at weekly intervals after initial surgery. They were performed under general anaesthesia, using a radiolucent board to which were attached four pegs to retain the limb. The foot was rotated until the pads were parallel with the board, and the leg was then strapped down. Identification of animals according to number, time since fracture, and labelling (left/right) was performed by various members of the radiography staff of King Edward VIII Hospital, Durban. The exposure time for both fibulae was the same in each animal.

The Xrays were assessed in detail at the end of the study. They were randomised by taping out animal details, and the amount of new bone measured by overhead projection (x4 magnification) to calculate the fracture healing response (see p 16).

Union time was difficult to assess with absolute certainty. Since detailed examination of fracture healing was performed on a weekly basis, a precise numerical value was therefore attached to a continuous process. Fracture union was deemed to have occurred when physical examination revealed loss of mobility at the fracture site, and Xrays revealed splintage by bridging callus (see p 17).

Immediately after bilateral union was deemed to have occurred, the animals were sacrificed and a long segment of both fibulae removed. Soft tissue was trimmed off and the specimens were placed above a metric scale and photographed by members of the Medical Illustration Department (University of Natal).

The photographer placed the specimens according to side, the right fibula being situated to the right of the photograph.

All remaining soft tissue except periosteum was then removed, and the specimens dried in tissue paper prior to weighing. During the initial phases of the pilot study, the mass of healing tissue was weighed by scraping it from the fibular surface. However, the line of demarcation with the fibula itself was difficult to determine, and material tended to remain on the bone, and on the surface of the knife. The mass of the healing area was therefore calculated as follows (Fig 8 , p 40):

Exactly 1cm of fibula immediately below the healing mass was measured by micrometry and removed by bone cutters. This was then weighed. The fibula was then cut immediately above and below the healing area, the length of fibula contained therein measured by micrometry, its' mass estimated and subtracted from the total mass of the healing area, to give the mass of healing tissue (thought to be mainly new bone). The measurements were made with the labels on the specimen bottles for left and right sides temporarily concealed. Estimations of mass were made using an Ohaus scale (Model 1500D) (Ohaus Scale Corporation, Florham Park, New Jersey, USA).

The resected healing areas were then fixed in 10% formal saline for 48 hours before they were decalcified and cut longitudinally. Several cuts from each specimen were then stained with haematoxylin and eosin.

The most central fibular cuts were selected for histomorphometric analysis and photographed by light microscopy to produce black and white 5" x 7" prints (x15 the original specimen).

A transparent grid of cross intersects spaced 5mm apart was then made and placed over the photographs. The following measurements were made (See Fig 9 on p 41).

(1) The volume fraction of new bone in the healing area (to determine if the healing area did indeed consist mainly of new bone).

(2) The volume fractions of fibrous tissue (F), hyaline cartilaginous tissue (H) and fibrovascular tissue (FV) lying within the fracture line.

The volume fractions were calculated according to the method described by Elias, Hennig and Schwartz (1971), and may be summarised as follows :

n F = the number of intersects lying on fibrous tissue.

n H = the number of intersects lying on cartilaginous tissue.

n FV = number of intersects lying on fibrovascular tissue.

n F + n H + n FV = Total.

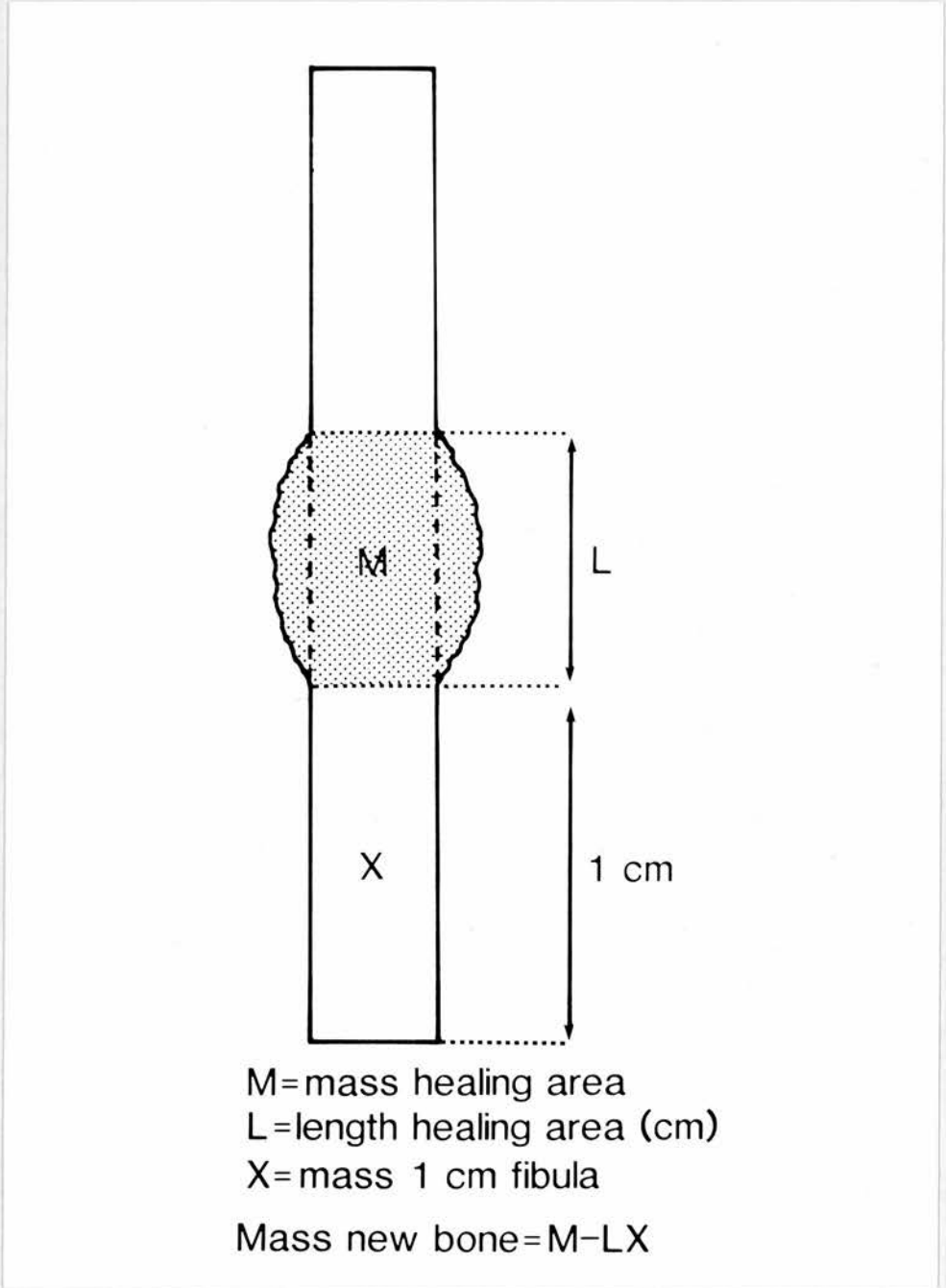
Volume Fraction F = nF / Total.

Volume Fraction H = nH / Total.

Volume Fraction FV = nFV / Total.

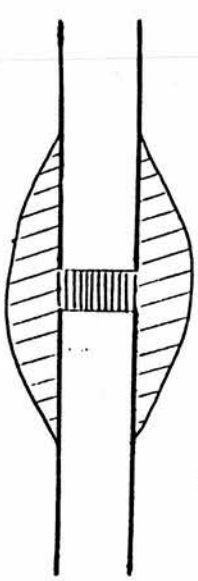
As is advised in the literature, the observations were made on at least 2 different occasions with different grid orientation to improve accuracy.

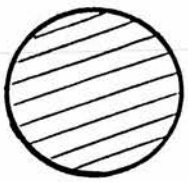
Figure 8



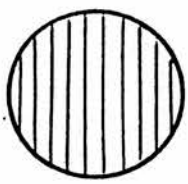
Method of calculating healing mass (thought to be mainly new bone).

Figure 9





Area A - inside periosteum ("bridging callus").



Area B - ("medullary callus").

The healing areas of the fractures seen.

Biochemistry

Prior to surgery, and at weekly intervals thereafter, blood was taken either from the external jugular or femoral veins, in a quantity of approximately 4.5cc. 1cc was immediately submitted in a plain tube (no anticoagulant) for albumin, calcium, phosphate, and alkaline phosphatase assay. Serum albumin (by a dye technique), calcium and phosphate (by colorimetry) were estimated using an Arachi 737 analyser (random access) (Boehringer Mannheim, South Africa / Germany). Serum alkaline phosphatase was assayed by the same equipment, using an enzymatic technique.

Endocrinology

Immediately on blood sampling (i.e. on day 0 and at weekly intervals thereafter) 1cc of blood was placed in a tube containing EDTA, and 2.5cc in a plain tube. Both were then centrifuged on ice at 3000 rpm for 5 minutes. Plasma (for cyclic AMP assay) and serum (for cortisol, triodothyronine and T4, and 25 OH cholecalciferol assay) were then placed in separate tubes using a micropipette to draw samples of exactly 300 microlitres or multiples thereof, labelled and stored at $-20^{o}C$.

Cyclic AMP assay was chosen because of the difficulty in performing certain peptide hormone assays on cats due to differences in structure of such hormones compared with human counterparts (notably, thyroid stimulating hormone, growth hormone, parathyroid hormone and calcitonin).

Although urinary assay is preferred for parathyroid hormone activity (Chase and Aurbach, 1970), this proved impractical in this experiment. What was sought was the cyclic AMP behaviour as a "second messenger" of many peptides (Sutherland, Robinson, and Butcher, 1968).

The assay was performed in duplicate by radioimmunoassay using the cAMP (^{125} I) assay system (single range). (Amersham International plc, Amersham, UK). Difficulties were encountered using this assay on cat serum, due to its tendency to agglutinate at the low temperatures required.

Cortisol assay was performed in duplicate using the radioimmunoassay "coat-a-count" technique. (DPC Diagnostic Products Corporation, Los Angeles, USA). Serum 25 - OH - Vitamin D was calculated by a modification of the method of Haddad and Cheyne (1971) using stock solutions obtained from Amersham UK (Amersham International plc, Amersham UK). The method involved prolonged extraction techniques, silicic acid chromatography, and a 25 - OH D_3 protein binding assay. Triiodothyronine (T_3) and thyroxine (T_4) estimated by radioimmunoassay, and results read manually on a β counter. Only T_4 activity was found.

In order to prevent unnecessary expenditure, hormonal assays were performed as follows :

1. 25OH Vitamin D
   Cats No 03, 08, 09, 13, 20, 22
   on Day 0 and at 4 weeks (during visible fracture healing phase).

2. Thyroxine
   Cats No 01, 03, 05, 06, 07, 12, 14, 16, 17, 18, 21 on Day 0 and at 4 weeks (during visible fracture healing phase).

Proforma

All relevant information was recorded on a proforma for each animal (p 45).

THE EFFECT OF HEAD INJURY ON FRACTURE HEALING / ANIMAL STUDY

PROFORMA

DOMESTIC CAT/IDENTIFYING FEATURES : 1. Colour
2. Ear clipping
Age
Sex M/F
Date of commencement
Date of sacrifice
Left-sided head injury YES/NO
No head injury YES/NO
Mass of animal at start
Mass of animal at end
Time to union right fibula
Time to union left fibula
Mass of new bone right fibula
Mass of new bone left fibula
Histomorphometry F/H right fibula
Histomorphometry F/H left fibula

WEEKLY OBSERVATIONS

0	1	2	3	4	5	6	7	8	WEEKS
Albumin									
Calcium									
Phosphate									
Alk. Phos.									
c AMP									
Cortisol									
Vitamin D									
T_3									
T_4									
FHR									
HEMIPLEGIA									
ONSET OF SPASTICITY									
TIME TO UNION (MARK X)									

COMMENTS

RESULTS

RESULTS

SECTION A

(THE EFFECT OF HEAD INJURY ON FRACTURE HEALING - A QUANTITATIVE ASSESSMENT).

The healing response in tibia, femur and humerus is shown in figures 10, 11 and 12 and the estimated time to clinical union in figures 13, 14 and 15 . A significant difference between patients with head injuries and the controls was found with respect to both healing response and time to union. Moreover, a correlation was found between the healing response and the time to union in the patients with head injuries (Table 3 on p 55).

In the patients with head injuries the radiographs often showed rapid formation of a peripheral layer of radiodensity. By contrast, the controls exhibited a standard healing response, a zone of callus spreading in uniform density outwards. Similarly, histological analysis of the healing mass sampled three weeks after injury showed peripheral maturity in the patients with head injuries but not in the others (Fig 16).

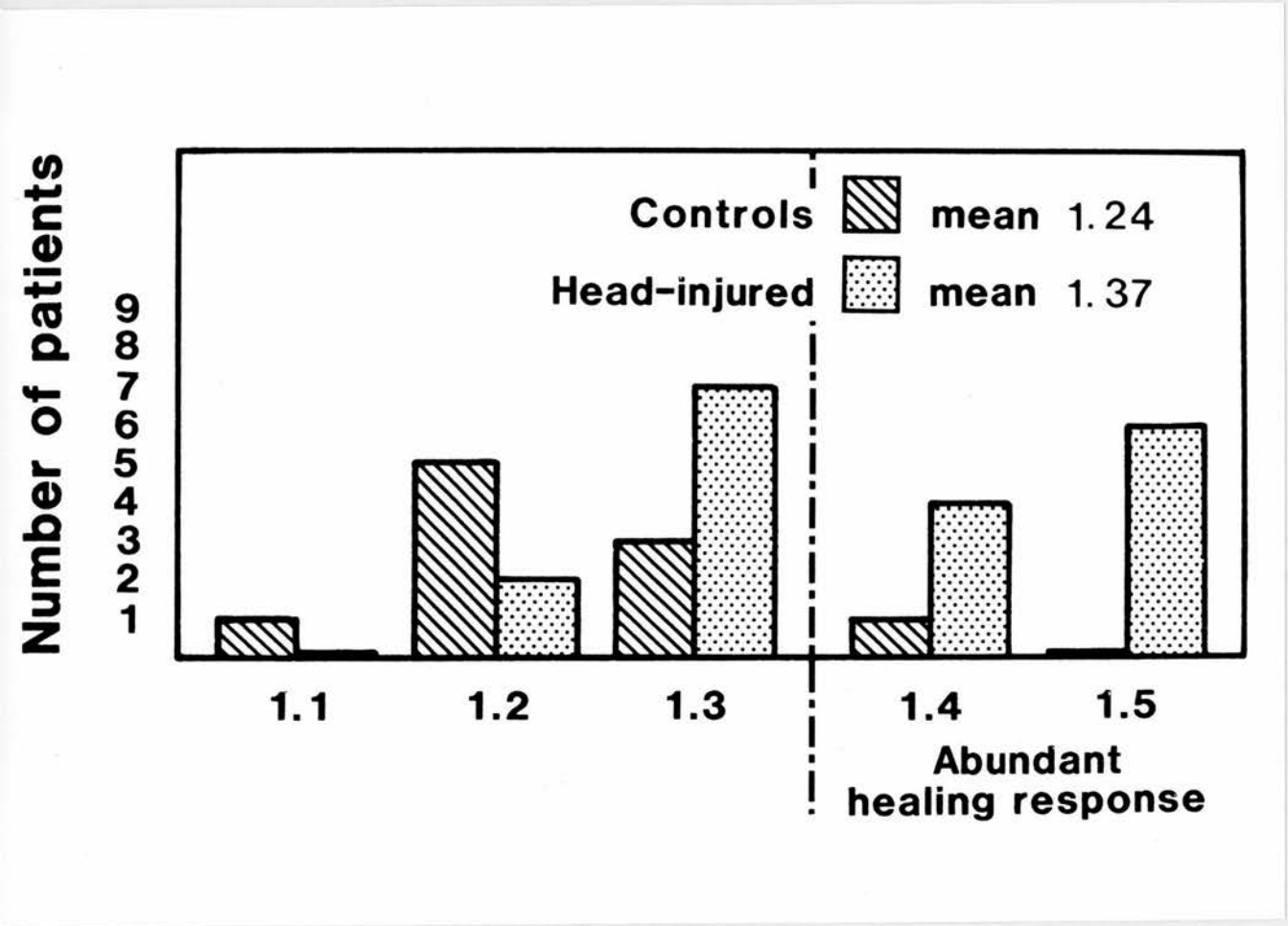
Internal fixation appeared to potentiate the healing response in the patients with head injuries (Fig 17), suggesting that surgical trauma or the release of osteogenic cells in the vicinity of the fracture encourages new bone formation.

Malunion, including shortening, occurred in 12 fractures, eight of which showed an "abundant" healing response. The bones most commonly affected were the humerus and the femur.

Delayed diagnosis (over 48 hours after admission) of a significant injury occurred in 11 patients. Fractures accounted for seven of these, knee ligament injuries for two, a brachial plexus injury and a ruptured spleen for one each.

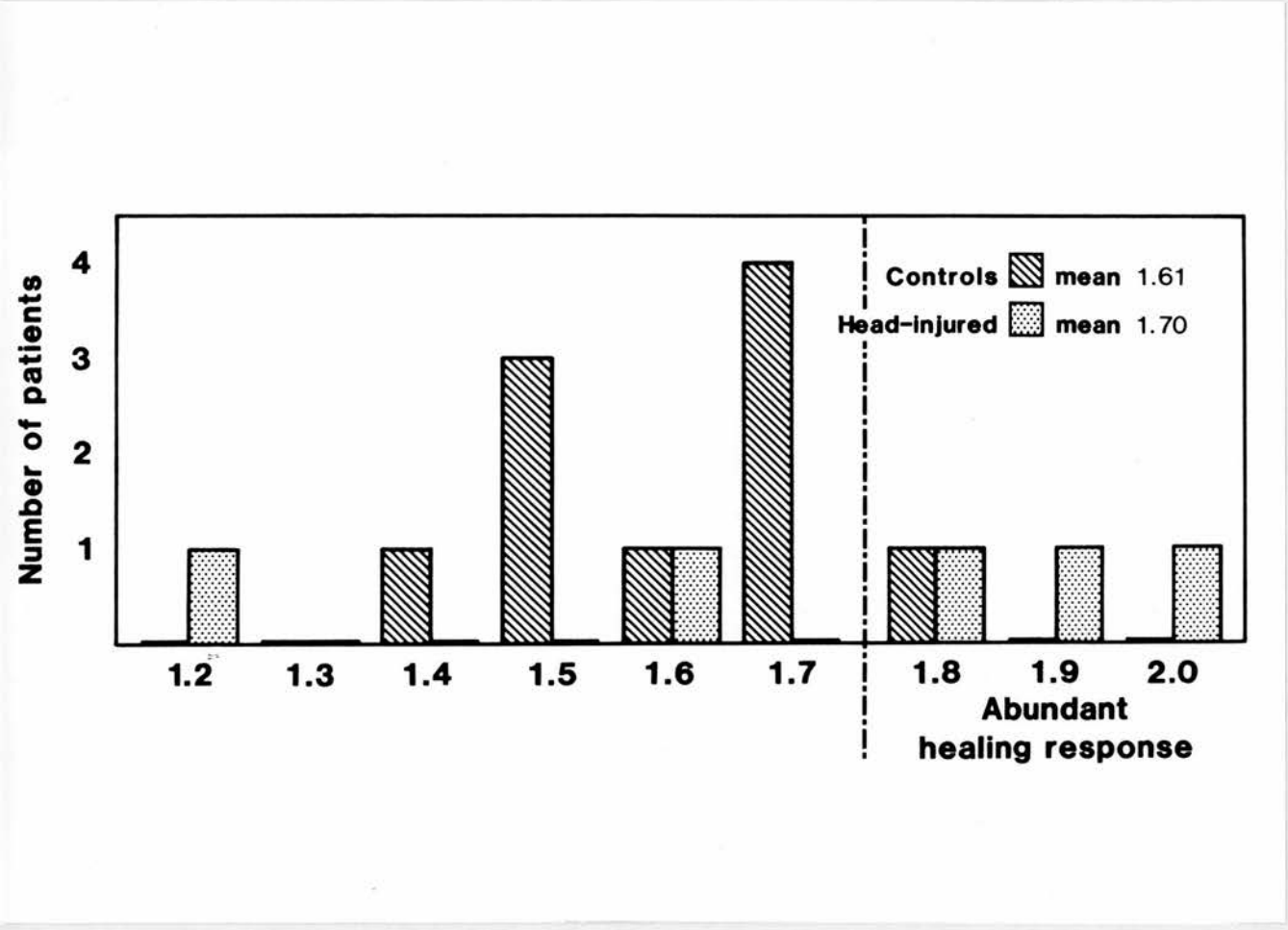
Head injuries. The CT scans of the 53 patients with head injuries revealed an intracerebral haematoma or a contusion in 18, cerebral oedema in 17, a subdural haematoma in 16, and an extradural haematoma in two patients. An abundant fracture healing response (defined as a response equal to or greater than the upper limit in the control group) was observed in 73% of patients with the more severe degrees of cerebral injury. There was no clear statistical correlation between the healing response and spasticity, although many of the patients with an abundant healing response did exhibit spasticity in affected limbs. No correlation was found between the healing response and the time taken to reach a stable neurological status (range 4 hours to 3 months), or with the depth of coma on admission, which ranged from 3 to 10 on the Glasgow coma scale. Twenty-seven patients (51%) made a complete neurological recovery.

Figure 10



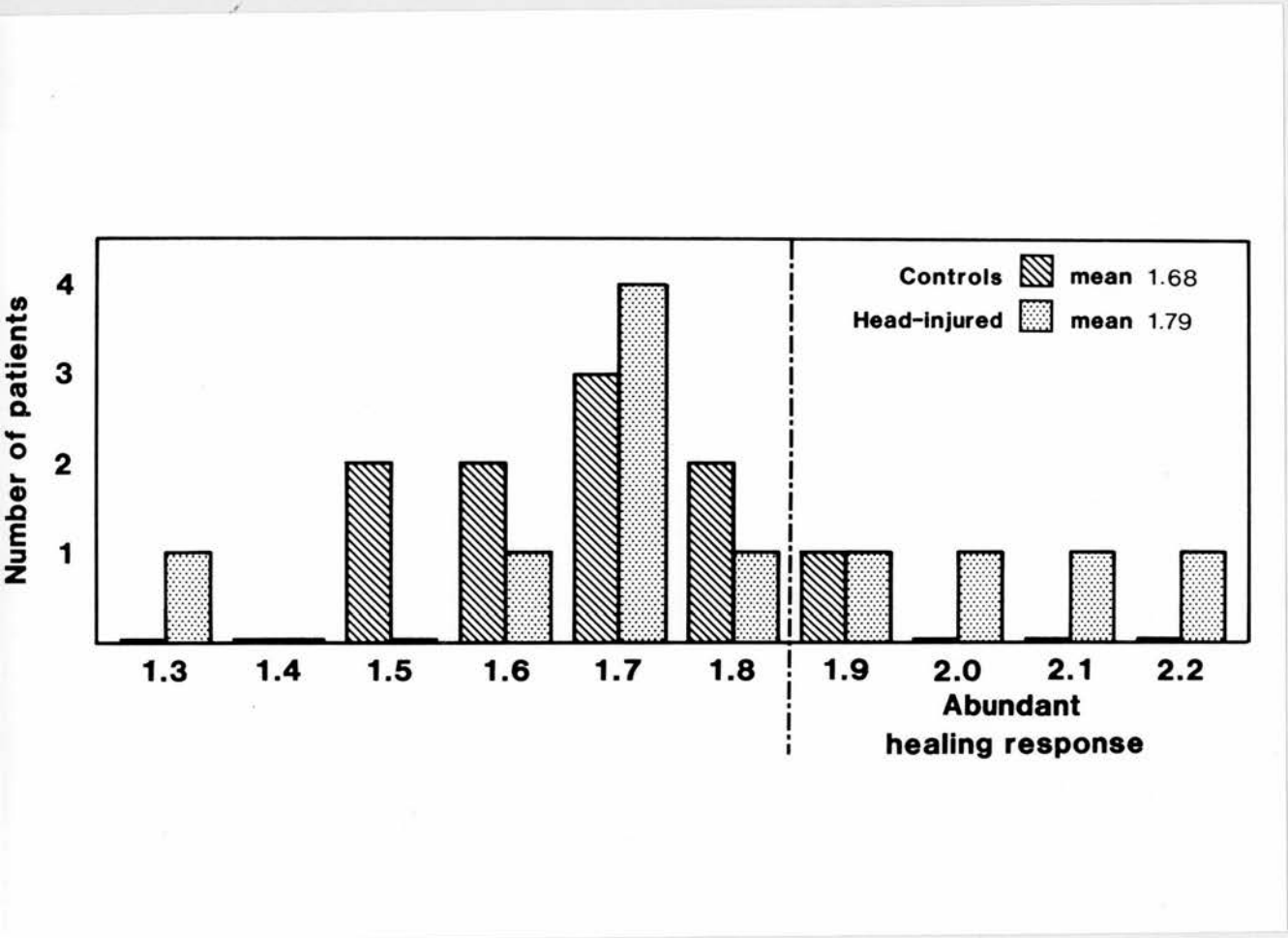
Healing response - tibia.

Figure 11



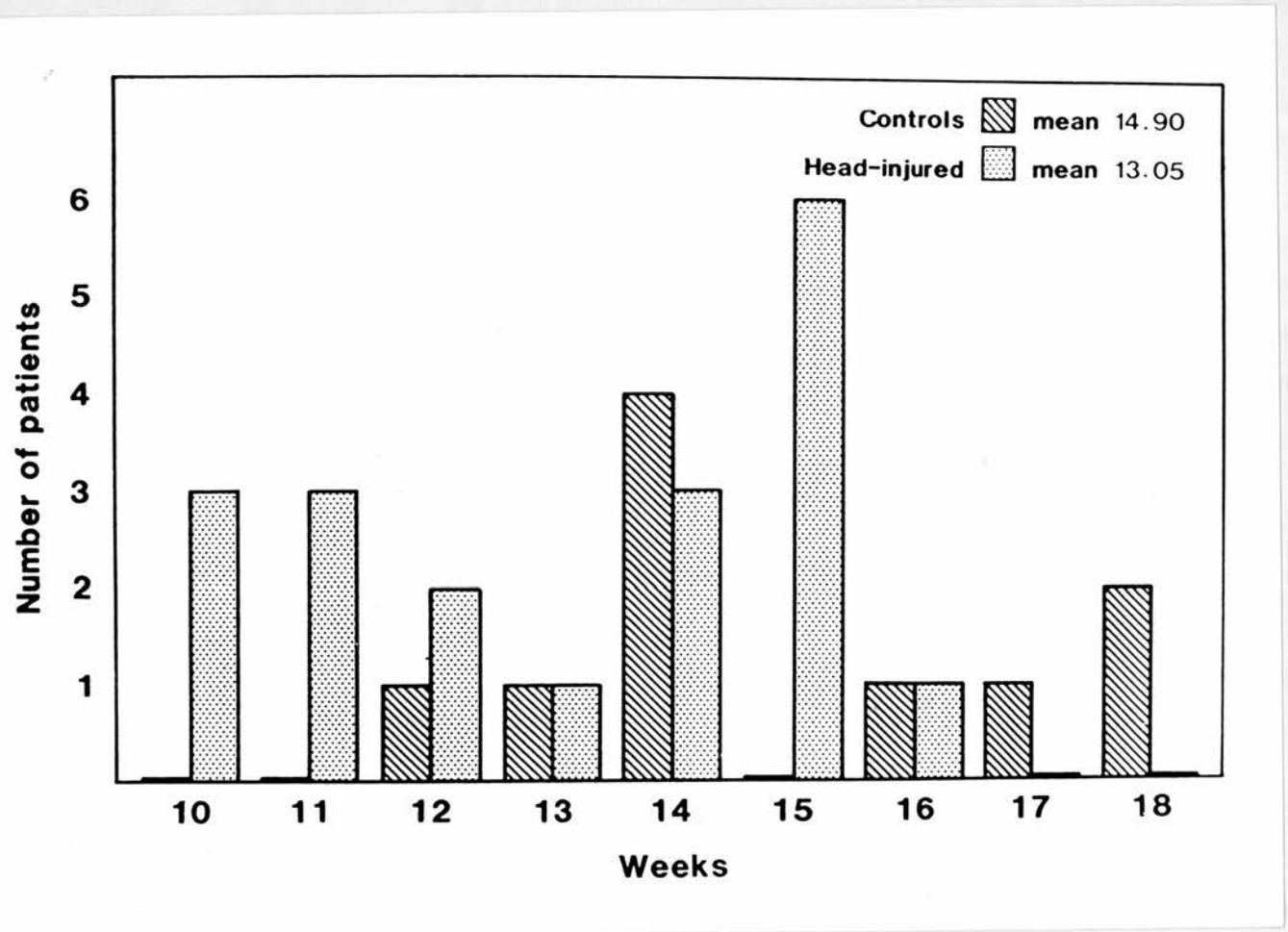
Healing response - femur.

Figure 12



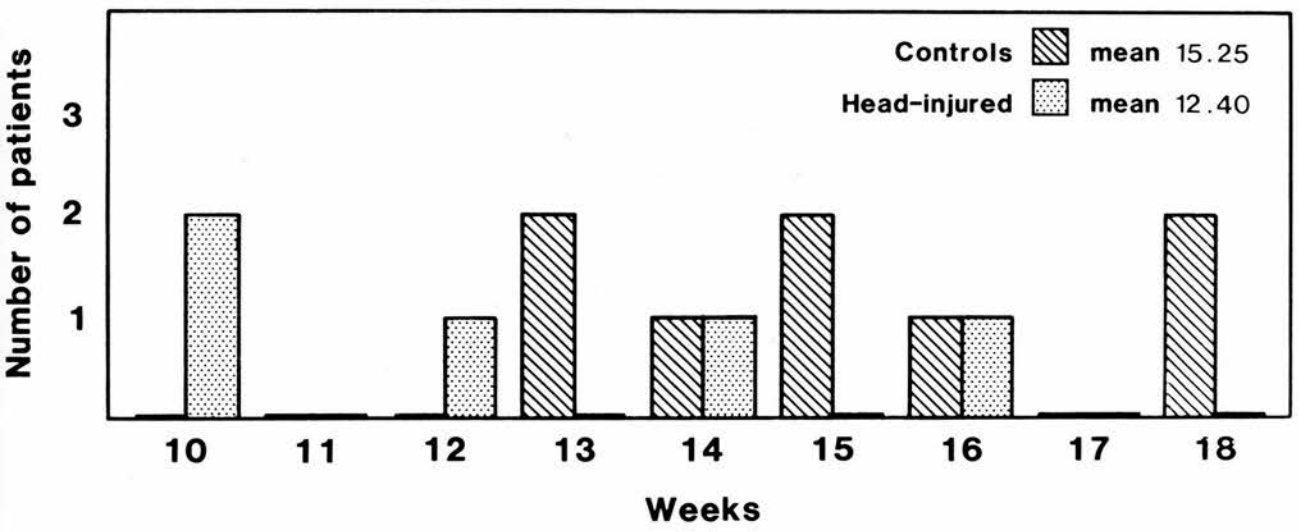
Healing response - humerus.

Figure 13



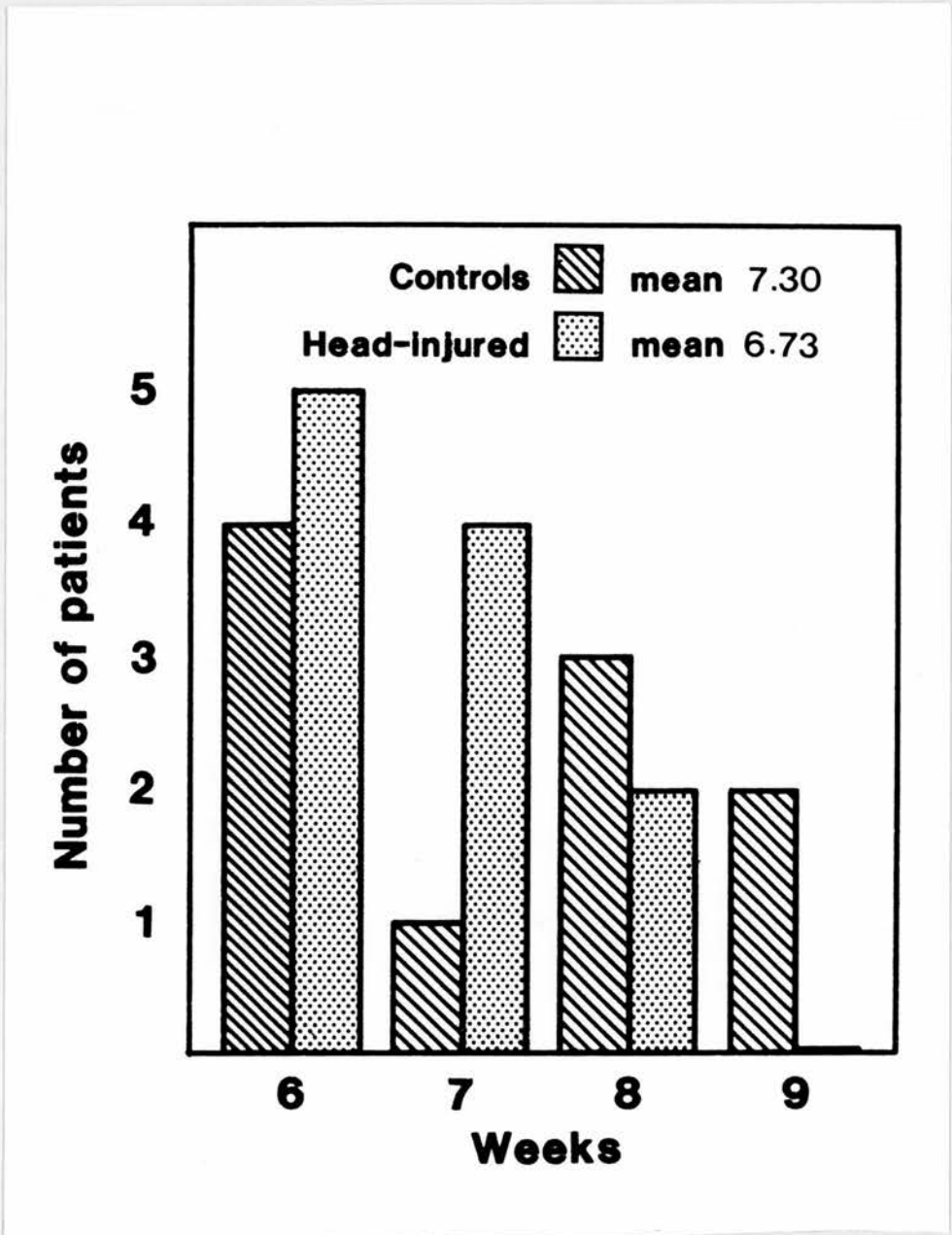
Union time - tibia.

Figure 14



Union time - femur.

Figure 15



Union time - humerus.

TABLE 3

Mean Values

	NEW BONE	TIME
Controls	1.51071	12.3214
Head injured	1.55143	10.9714
t-value	2.581	3.467
p-value	0.0124*	0.0010**

* Significant at a 5% level
** Significant at a 1% level

For TYPE which has three levels, tests were performed with the significance level adjusted by means of Bonferroni's procedure to compensate for the three comparisons made.

Correlation Coefficients

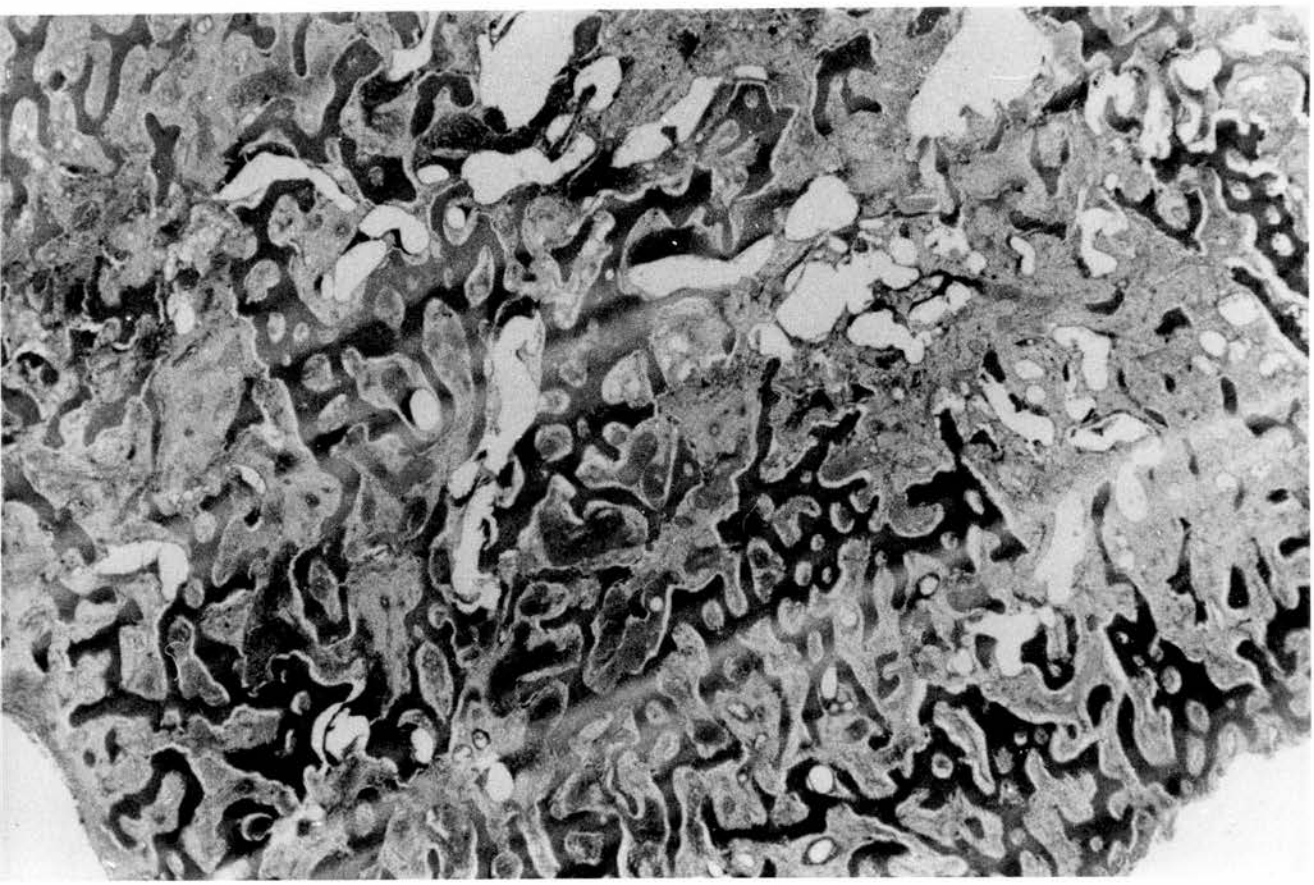
Correlation between the healing response and time to union in patients with head injuries.

	n	Correlation Coefficient	p value
Tibia	19	- 0.7754	0.0001**
Femur	5	- 0.0513	0.9347
Humerus	11	- 0.8433	0.0011*

* Significant at a 5% level

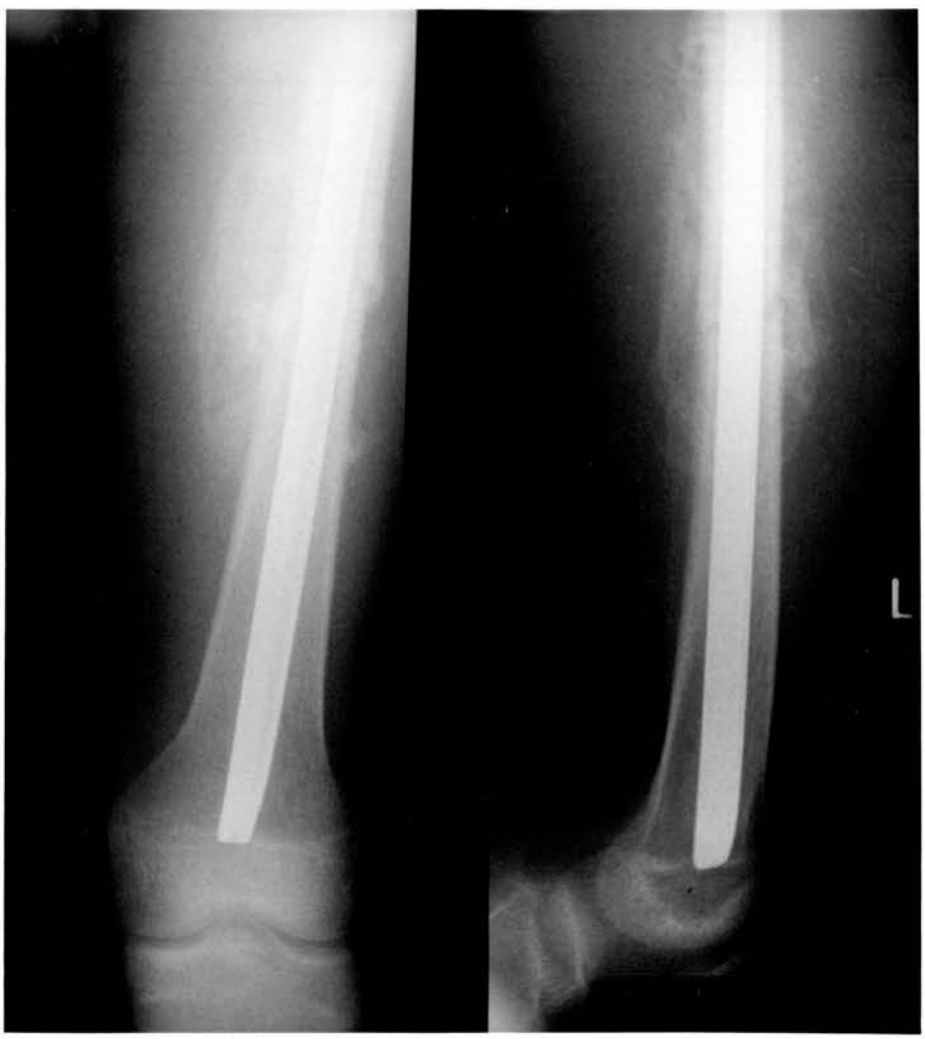
** Significant at a 1% level

Figure 16



A section of periphery of the healing mass from a femoral shaft fracture in a patient with head injuries; at three weeks there is mature woven bone (x120).

Figure 17



Man aged 25 with head injury. Healing response at 6 weeks following internal fixation.

RESULTS

SECTION B

(ASSESSMENT OF MASSIVE NEW BONE FORMATION AROUND FRACTURES IN ASSOCIATION WITH NEURAL INJURY).

A total of 11 fractures demonstrated massive new bone formation in this series, 10 of which involved the femur and one the humerus(Table 4). A review of other significant skeletal injuries (1 fractured clavicle, 1 fractured orbit and mandible, 1 fractured pelvis, 1 fractured tibial plateau, 1 dislocation C1/C2 in a patient with fractured ribs, 1 supracondylar fracture of the femur) did not reveal large amounts of new bone formation. Two (fractured tibial plateau, supracondylar fracture of the femur) occurred in limbs affected by spasticity, but they were managed by early rigid internal fixation with plates and screws, and they occurred through cancellous bone.

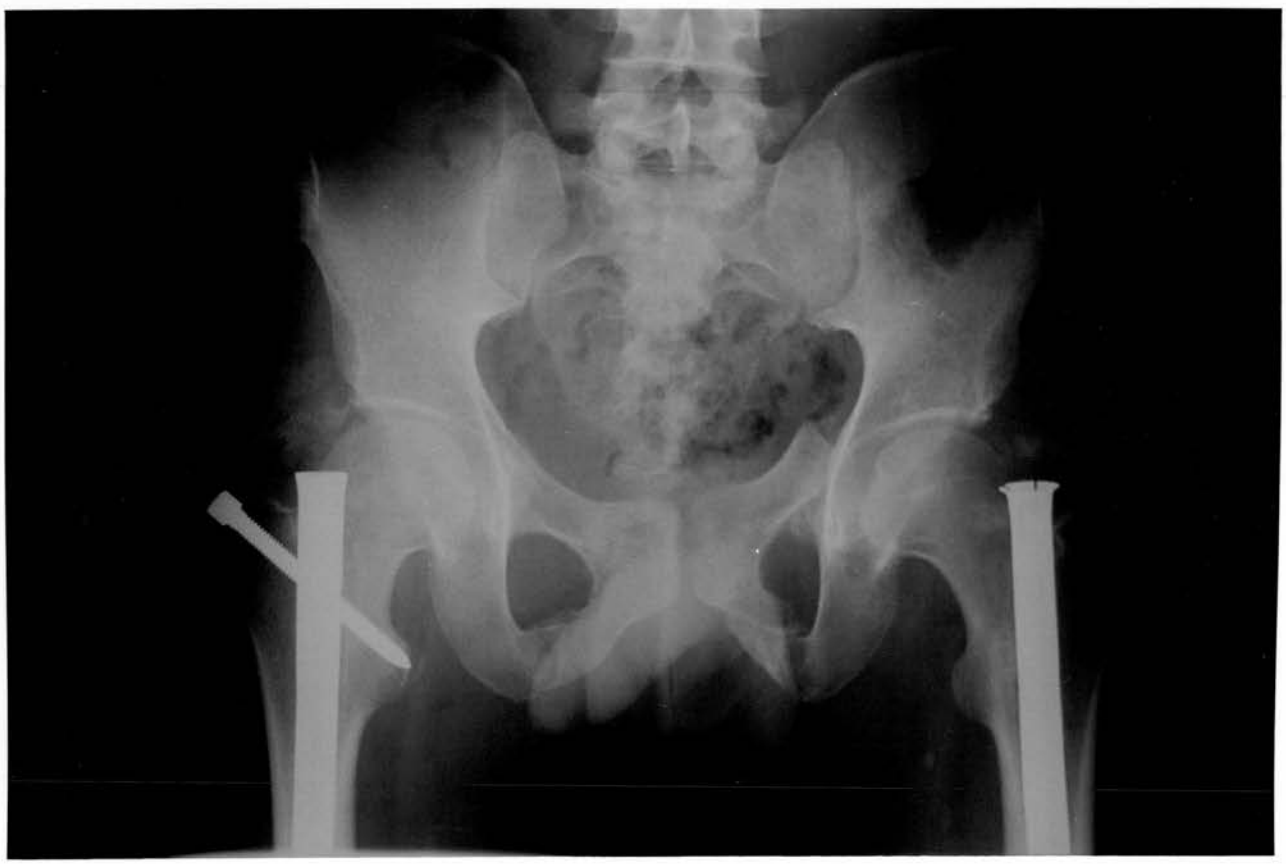
All patients sustained significant cranial trauma, but significant coma was not necessarily persistent. One patient sustained a high cord injury which recovered slowly and was the probable cause of spasticity. Eight of the patients developed clear evidence of spasticity in limbs affected by massive new bone formation, and in one such case heterotopic bone was formed at the site of insertion of bilateral intramedullary nails (Fig 18). In two patients, although there was resistance to passive stretch of muscle groups in limbs demonstrating abundant fracture healing, it was not possible to determine if this was due to upper motor neuron effects. The absence of other signs of spasticity made this unlikely.
Results are summarised in Table 4 . (See Figs 19-21).

TABLE 4

PATIENT NO.	AGE	SEX	MECHANISM OF INJURY	ORTHOPAEDIC INJURIES & MANAGEMENT	NEUROLOGICAL INJURY CT SCAN	NEUROLOGICAL FINDINGS	GRADE CALLUS/NEW BONE	BONE(S) INVOLVED
1	22	M	MVA	1. Closed fracture mid-shaft right femur (Closed Nail 48 hrs). 2. Fracture right clavicle. 3. Cerebral injury.	Intracerebral haematoma frontal lobes & left parietal lobe posteriorly.	1. Glasgow Coma Scale 7/15 on admission. 2. Early onset, (5-7 days) of spasticity in lower limbs (ABCDE).	2a	Right femur
2	20	M	MVA	1. Open fracture proximal left femur (Pin & Plate 48 hrs). 2. Fracture (L) orbit and (L) mandible. 3. Cerebral injury.	Not done	1. Glasgow Coma Scale 7/15 on admission, 12/15 after 48 hrs. 2. Onset of mild spasticity lower limbs (7 days) (ABC).	1	Left femur
3	20	M	PEDESTRIAN STRUCK BY BUS	1. Closed fractures mid-shaft both femurs (Closed nails 24 hours). 2. Fractured pelvis (Locking nail right femur). 3. Cerebral injury.	Cerebral contusions.	1. Glasgow Coma Scale 7/15 on admission 13/15 after 2 weeks. 2. Early onset(7 days) of spasticity both lower limbs. (ABCDE)	2b	Both femurs
4	27	M	MVA	1. Closed fracture mid-shaft right femur (Closed nail 24 hours).	Nil	1. Glasgow Coma Scale 10/15 on admission. Recovery 48 hours. 2. No spasticity.	1	Right femur
5	63	M	MVA	1. Closed fracture proximal right femur. Conservative treatment. (Skin problems). 2. Old tuberculous meningitis.	Nil	1. Tuberculous meningitis 20 years before with residual spasticity both lower limbs (ABCE).	1	Right femur
6	28	M	MVA	1. Closed fractures mid-shaft both femurs. (Closed nailing 24 hours).	Nil	1. Glasgow Coma Scale 9/15 on admission. Recovery 24 hours. 2. No spasticity.	2a	Both femurs
7	22	F	MVA	1. Closed fractures pubic rami mid-shaft left humerus. (Plating on admission). Left tibial plateau (Plating on admission). 2. Cerebral injury.	Cerebral contusions	1. Glasgow Coma Scale 5/15 on admission - slow recovery (6 weeks to 14/15). 2. Spasticity (10 days onset - 2 weeks). Upper and lower limbs (ABCF).	1	Left humerus
8	31	F	MVA	1. Closed fracture mid-shaft right femur (Closed nail 24 hours).	Not done	1. Glasgow Coma Scale 7/15 on admission - recovery 15/15 in 7 days. 2. Spasticity (onset 7 days) Lower limbs (ABC).	1	Right femur
9	30	M	PEDESTRIAN STRUCK BY CAR	1. Dislocation C1 on C2 (Fusion at 2 weeks). 2. Multiple rib fractures (Shock lung). 3. Closed fracture mid-shaft left femur (nailed closed at 4 days). 4. Cerebral injury. 5. Initial quadriplegia.	Not done	1. Glasgow Coma Scale 8/15 on admission. Recovery 24-48 hours. 2. Spasticity in lower limbs from 10 days (ABCDE).	2a	Left femur
10	30	F	MVA	1. Closed fracture mid-shaft left femur (open nail at 4 days). 2. Supracondylar fracture right femur (internal fixation 4 days). 3. Cerebral injury.	Cerebral contusions.	1. Glasgow Coma Scale 6/15 on admission. Recovery 4 weeks. 2. Spasticity in lower limbs from 2 weeks (ABCE).	1	Left femur

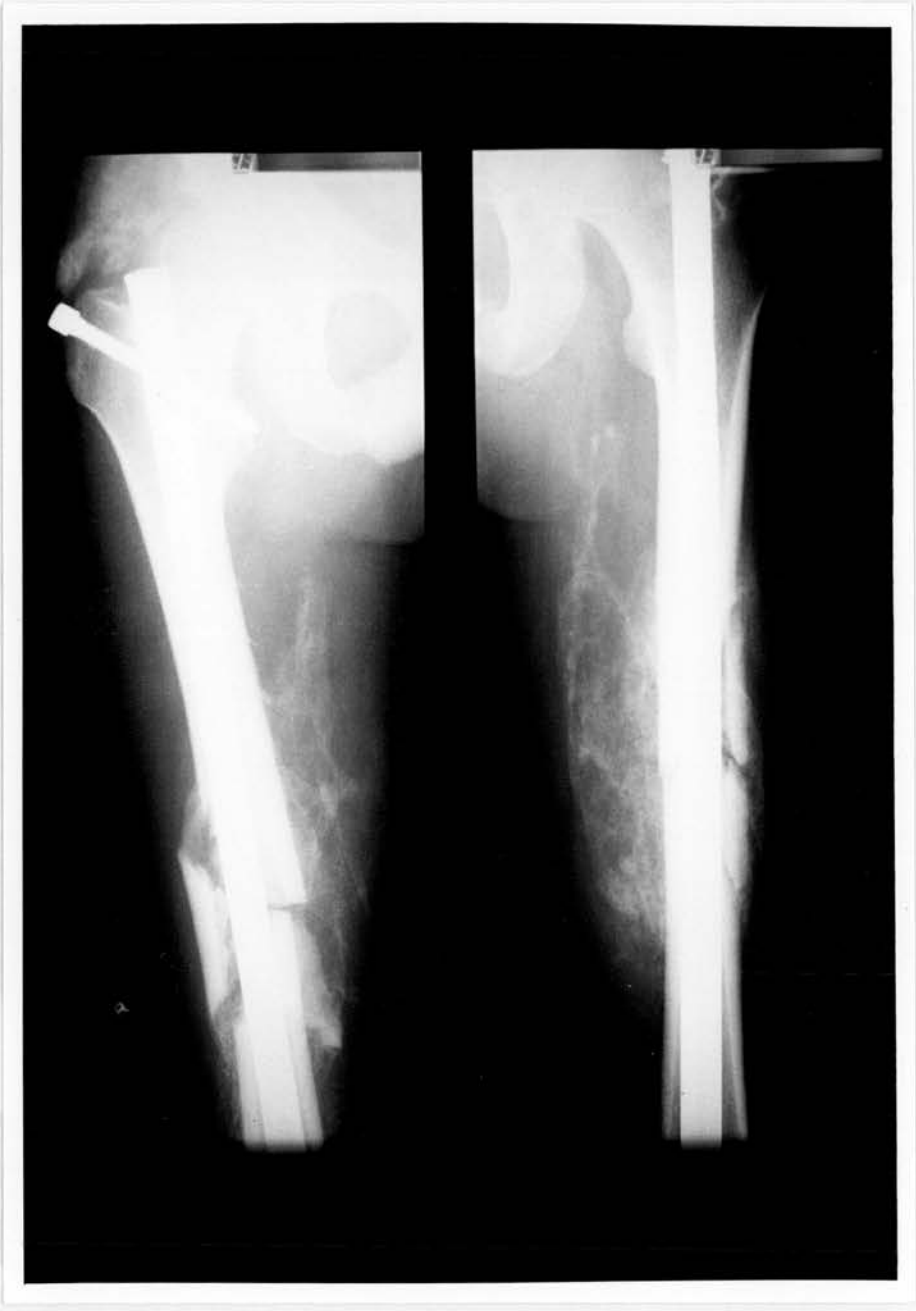
A Resistance to passive stretch. B Clasp-knife effect. C Brisk tendon reflexes. D Extensor plantar response E Clonus (ankle & patella) F Hoffman's sign positive.

Figure 18



Patient No. 3
Heterotopic bone proximal to both intramedullary nails.

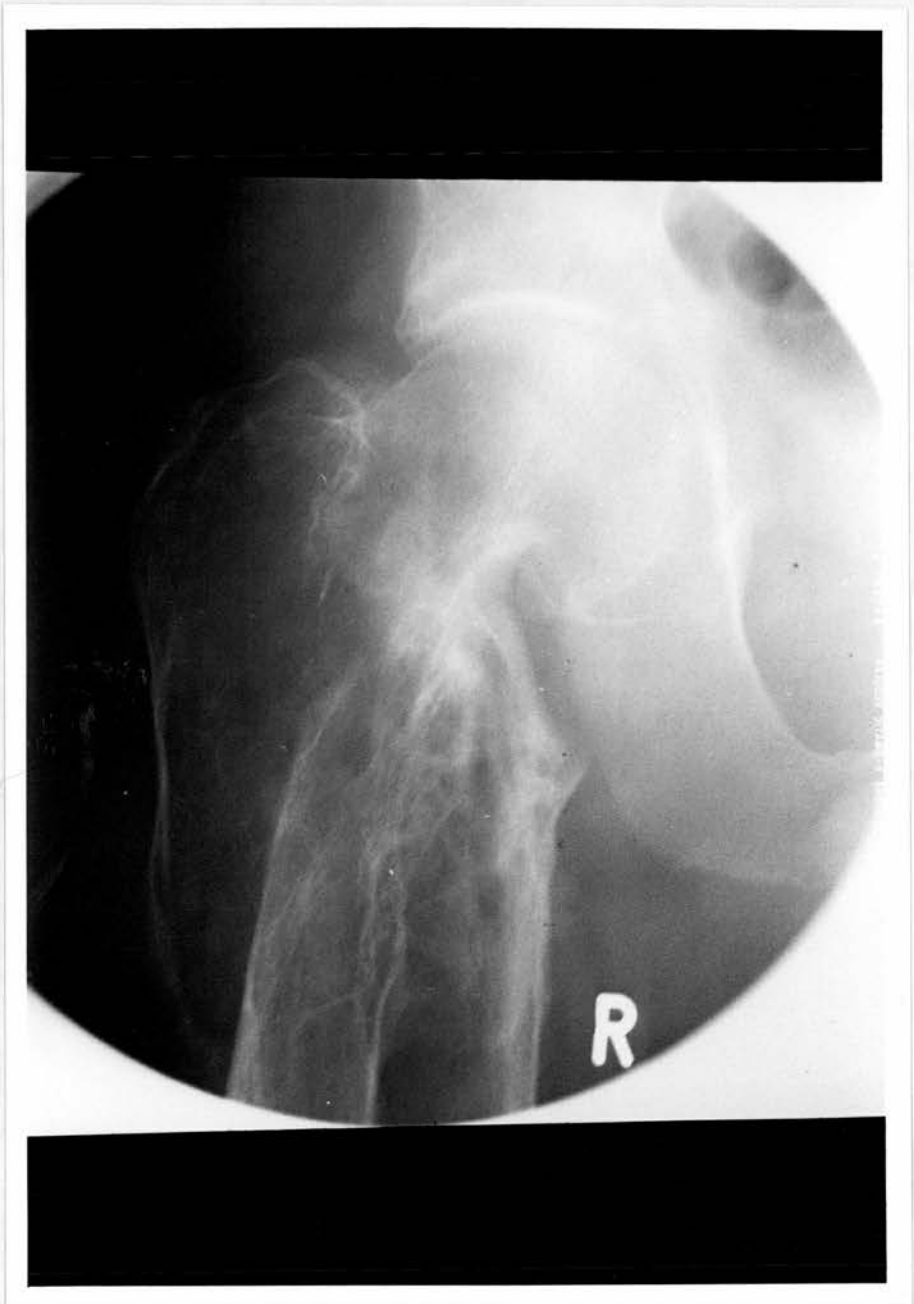
Figure 19



Patient No. 3

Extensive callus / new bone around fracture of the right femur, with new bone extending proximally in soft tissues.

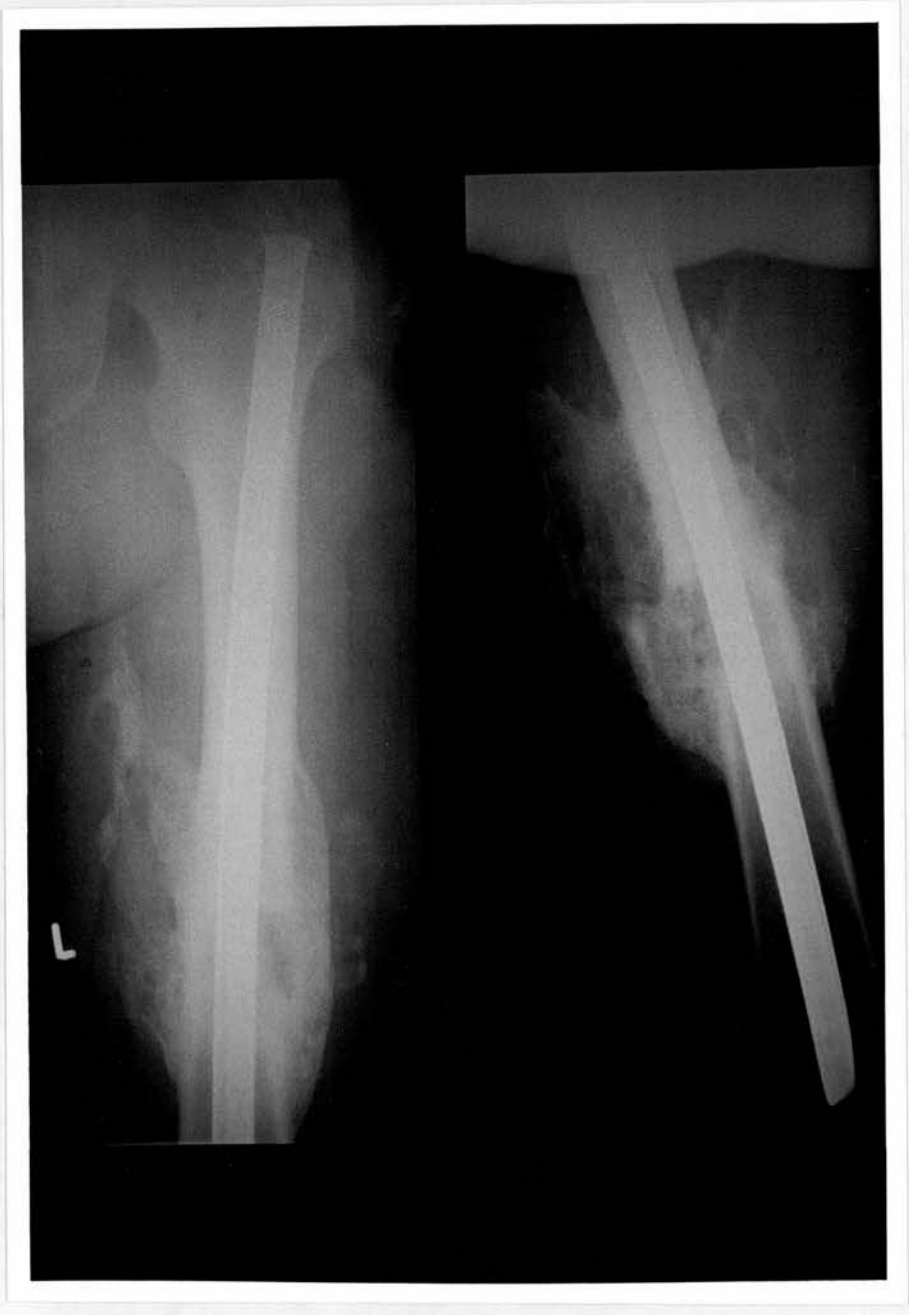
Figure 20



Patient No. 5

Healed fracture of the proximal right femur with massive callus / new bone formation.

Figure 21



Patient No. 9
Massive callus / new bone formation in association with fracture of the left femur.

RESULTS

SECTION C

(ASSESSMENT OF OSTEOGENIC CAPACITY IN PATIENTS WITH POLIOMYELITIS).

A total of 323 operative procedures were performed on the 283 patients with poliomyelitis, some simultaneously (e.g. Steindler release plus ETA) (Table 5). Operations were performed in the region of larger joints most prone to develop heterotopic bone (hips, shoulders, elbows and knees) on 120 occasions.

No evidence of heterotopic new bone formation was found, either on pre or post-operative Xrays. Moreover, no patient with periarticular inflammation and/or ankylosis was seen.

A total of 25 fractures were sustained, 21 of which involved an area affected by poliomyelitis (Table 6). In addition, 11 surgical osteotomies were performed, 8 of which were in long bones or in periarticular locations around major joints (Table 5).

No evidence of plentiful callus/new bone formation was found. In fact, the fracture healing response in fractures or osteotomies involving the femur (the majority) did not exceed 1.5 (p 16) (Fig 22). Although assessment of union time could not be made with great accuracy, no evidence could be found for marked acceleration of union, taking into account the site of fracture or osteotomy, and the age of the patient concerned.

TABLE 5

Operative procedures on limbs of patients with poliomyelitis.

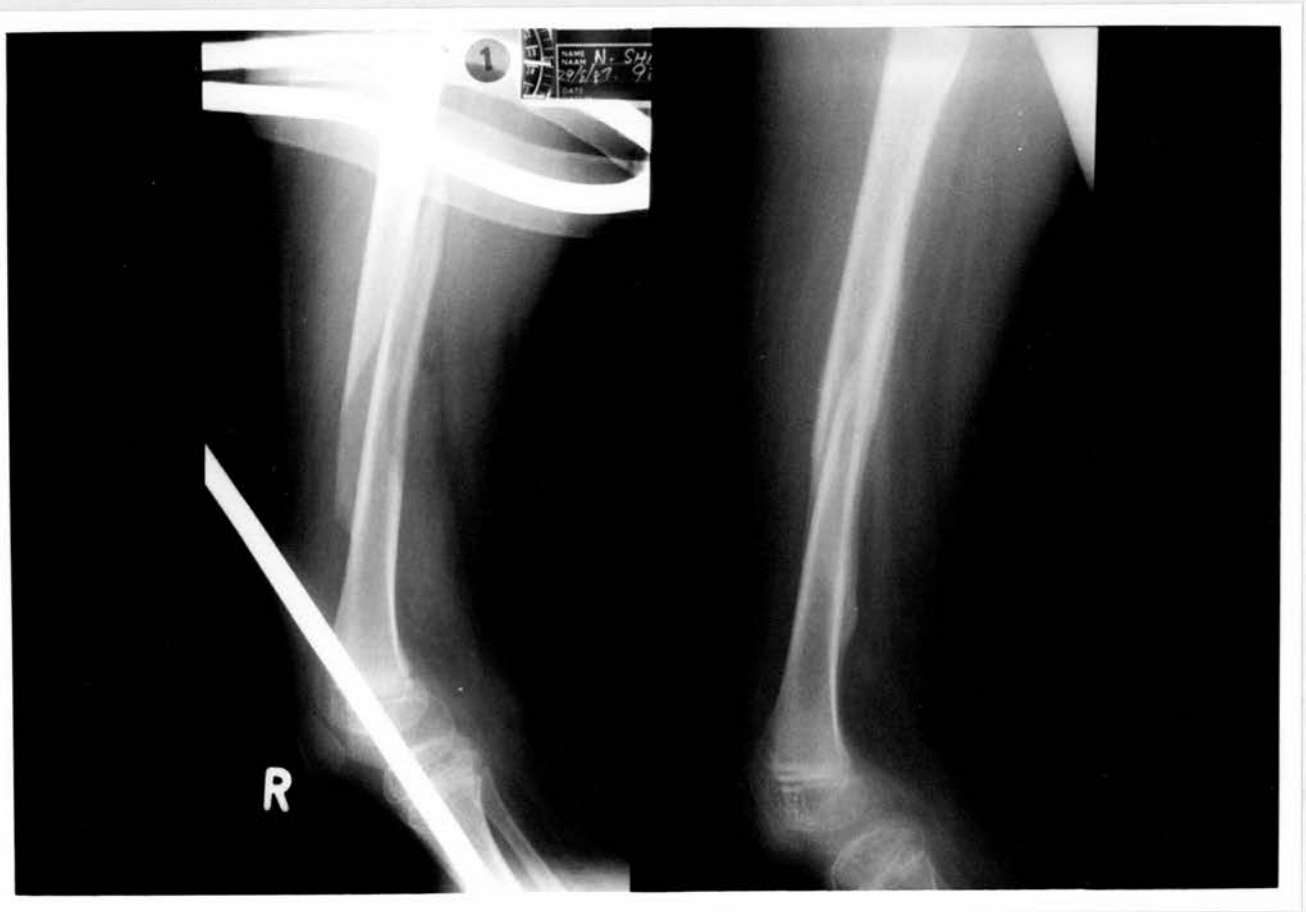
Elongation tendo Achilles	115	Sliding screw & plate	2
Soft tissue release hip	59	Soft tissue release elbow	2
Triple arthrodesis	29	Supramalleolar osteotomy	2
Tendon transfer (foot & ankle)	28	Subtalar fusion	1
Steindler release (foot)	19	Arthrodesis hallux	1
Soutter slide	19	PIP fusion toe	1
Yount's procedure	12	Opponeus plasty hand	1
Soft tissue release knee	10	Arthrodesis hip	1
Osteotomy femur (1 plated)	4	Proximal osteotomy	1
Wedge osteotomy foot	3	Debridement compound fracture	1
Posteromedial release foot	3	Thomson's hemiarthroplasty	1
Campbell release hip	2	Chiari osteotomy	1
		Mustard transfer	1

TABLE 6

FRACTURES AND THEIR MANAGEMENT IN PATIENTS WITH POLIOMYELITIS.

	FRACTURE	TREATMENT
1	Intertrochanteric	Pin and Plate
2	Shaft of femur	Conservative
3	Subtrochanteric	Pin and Plate
4	Shaft of femur	Conservative
5	Pubic rami	Conservative
6	Shaft of femur	Conservative
7	Supracondylar area femur	Conservative
8	Greater trochanter	Conservative
9	Supracondylar humerus	Conservative
10	Shaft of femur	Conserative
11	Greater trochanter	Conservative
12	Shaft of femur	Conservative
13	Pubic rami	Conservative (Unaffected area)
14	Supracondylar humerus	Conservative (Unaffected area)
15	Distal femur	Conservative
16	Shaft of femur	Conservative
17	Shaft of femur	Conservative (Unaffected area)
18	Crack fracture tibia	Conservative
19	Distal femur	Conservative
20	Distal femur	Conservative
21	Intertrochanteric	Conservative
22	Medial epicondyle	Conservative (Unaffected area)
23	Subcapital femur	Thomson's prosthesis (Unaffected area)
24	Shaft of femur	Conservative
25	Tibia and fibula	Debridement and plaster

Figure 22



Lateral Xrays of the right femur of a 10 year old boy with poliomyelitis show a spiral fracture (left) healed with minimal callus formation at 6 weeks (right).

RESULTS

SECTION D

(ANIMAL STUDY - THE EFFECT OF SPASTICITY DUE TO A BRAIN LESION ON FRACTURE HEALING).

Animals excluded

The following animals were removed from the study for the various reasons given :

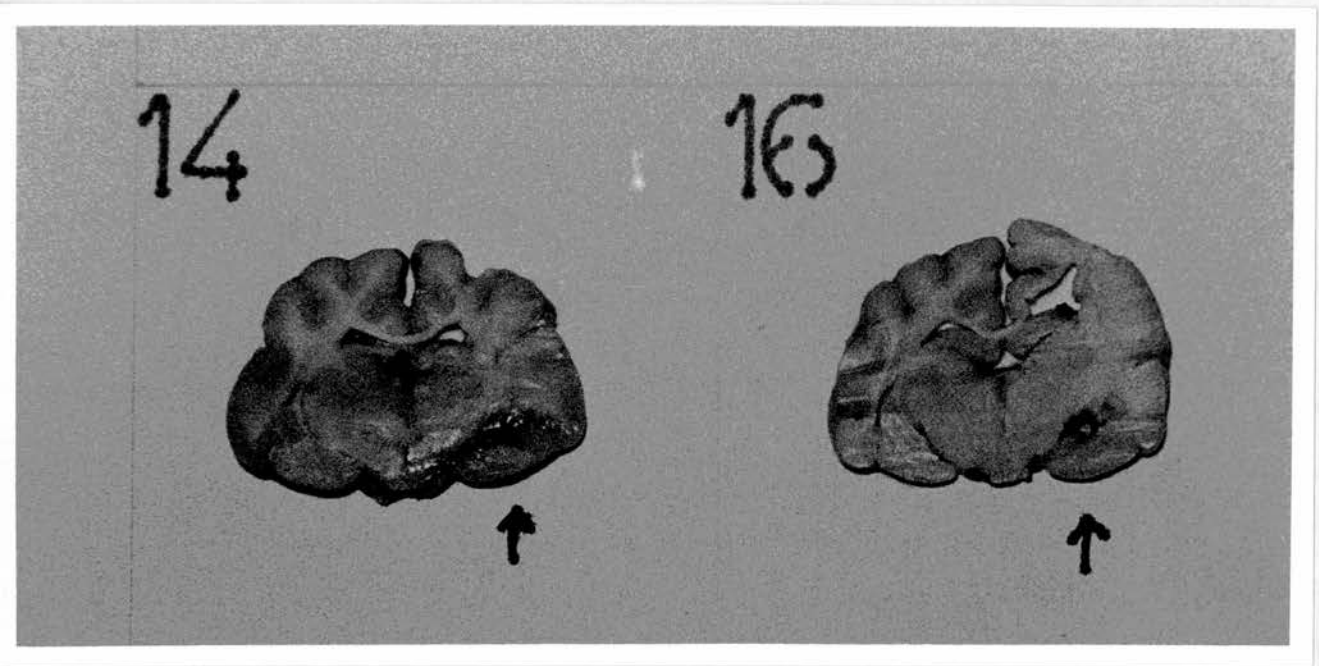
02 - sepsis around leg wounds.
04 - sepsis around leg wounds.
11 - failure to produce observable neural injury.
15 - failure to produce observable neural injury.
- sepsis of leg wound (R).
19 - failure to produce observable neural injury.

Neural injury

Eleven animals (09, 10, 12, 13, 14, 16, 17, 18, 20, 21 and 22) demonstrated evidence of a successful brain lesion. This was first manifest by right hemiplegia. Evidence of spasticity followed within 7-14 days (p 29). Although some reservations were felt before the pilot study regarding the possible implications of the neural lesion, the animals remained able to walk throughout, experiencing slight difficulty only on the first 2 or 3 postoperative days. The animals were able to feed normally soon after surgery (in many cases later the same day and in all cases within 18 hours). Bowel and bladder function was unaffected.

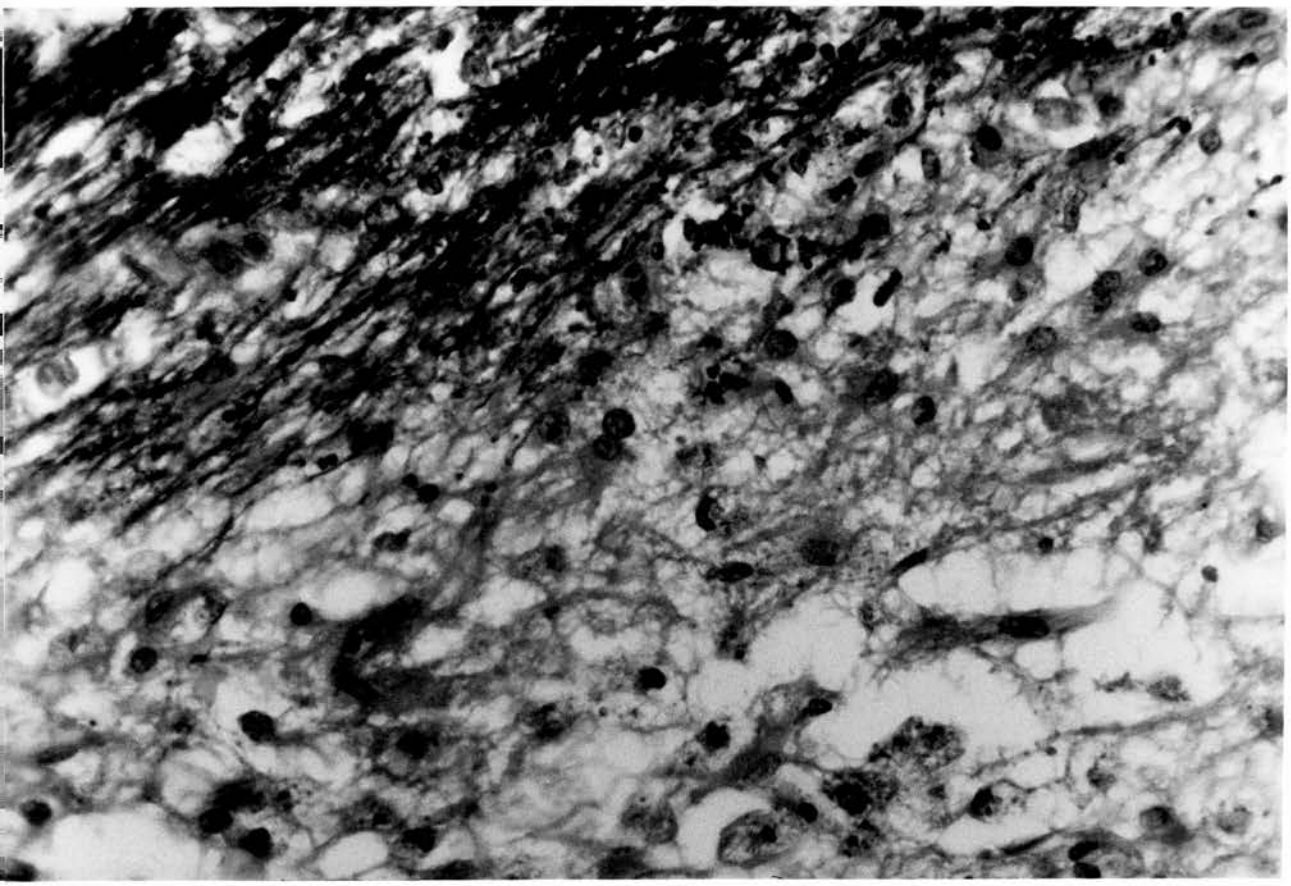
On coronal brain slicing following the study lesions were found at the prescribed stereotaxic target site in the animals who demonstrated neurological signs. Histological features consisted of areas of necrosis infiltrated by compound granular corpuscles, with resorption of necrotic material and cyst formation (Figs 23 and 24).

Figure 23



Brain slices from animals with hemiplegia and spasticity. (Cats No. 14 and 16) showing the stereotaxic lesion.

Figure 24



Myelin degeneration of the internal capsule, cyst formation and invasion by compound granular corpuscles (Luxol fast blue x200).

Xray analysis (Figs 26- 47, p 81 - 89).

1) First appearance of callus/new bone.
Left ("normal") and right (spastic) sides were compared in animals with brain lesions. Results are shown in Table 7 .

Table 7 **Week of first appearance of callus/new bone on Xray**

Animal	Left	Right
09	2	2
10	2	2
12	3	2
13	3	3
14	2	2
16	4	3
17	2	2
18	3	3
20	2	2
21	2	2
22	2	2

No significant difference was found (Sign test not significant).

2) Rate of appearance of callus/new bone (rate of increase of FHR value).

FHR values for brain-lesioned animals are shown in Table 8 . The rate of increase did not differ when left and right sides were compared (Sign test not significant).

TABLE 8 FHR MEASUREMENTS

		1	2	3	4	5	6	7	8	WEEK
09	R	1.0	1.6	2.1	1.7	1.9	2.0			
	L	1.0	1.7	2.1	2.0	2.0	2.0			
10	R	1.0	1.6	1.9	2.1	2.2	2.2			
		1.0	1.2	1.5	1.7	1.7	1.8			
12	R	1.0	1.2	1.9	2.2	2.0	2.0			
	L	1.0	1.0	1.3	1.5	1.3	1.5			
13	R	1.0	1.0	1.8	1.9	1.9				
	L	1.0	1.0	1.6	1.8	1.8				
14	R	1.0	1.1	1.3	2.0	2.0	2.1			
	L	1.0	1.1	1.3	1.7	1.8	2.1			
16	R	1.0	1.0	1.3	1.2	1.3	1.5			
	L	1.0	1.0	1.0	1.2	1.6	1.6			
17	R	1.0	1.2	1.4	1.5	1.7	2.1	1.8		
	L	1.0	1.4	1.5	1.7	1.7	2.0	2.0		
18	R	1.0	1.0	1.3	1.8	2.1	2.2	2.2		
	L	1.0	1.0	1.2	1.7	1.5	1.5	1.5		
20	R	1.0	1.3	1.4	2.0	2.1	2.1			
	L	1.0	1.4	1.5	1.7	1.8	1.7			
21	R	1.0	1.3	1.9	2.2	2.2	2.0			
	L	1.0	1.2	1.4	2.1	2.2	2.2			
22	R	1.0	1.2	1.7	1.9	2.1	2.3			
	L	1.0	1.2	1.4	1.6	1.4	1.4	1.8		

3) Greatest amount of callus/new bone on Xray (Greatest value of FHR).

The highest value of FHR was usually, though not always, observed at fracture union. Results are shown in Table 9 .

Table 9	Greatest value of FHR	
Animal	**Left**	**Right**
09	2.1	2.1
10	1.8	2.2
12	1.5	2.2
13	1.8	1.9
14	2.1	2.1
16	1.6	1.5
17	2.0	2.1
18	1.7	2.2
20	1.8	2.1
21	2.2	2.2
22	1.8	2.3

A significant difference was found, the healing response being greater on the right side (Wilcoxon signed ranks test $p = 0.0209$).

Union time (See Figs 26 - 47 , p 81 - 91).

Union time, assessed both clinically and radiologically, was difficult to determine with certainty. In effect, a discrete value was given to a continuing process (see p 37). A statistician was willing to perform the analysis on the understanding that results were biased by the observer in favour of there being no difference. For example, cat x would be believed to have united the right fibula at around 4 weeks. Ay 6 weeks the left side had reached a united similar state, while the right still showed a little residual mobility. The values would be recorded thus : Left side 6 weeks ; right side 5 weeks. Results are shown in Table 10.

Table 10	Union time (weeks)	
Animal	**Left**	**Right**
09	6	5
10	6	5
12	6	5
13	5	4
14	6	5
16	6	6
17	7	6
18	7	6
20	6	5
21	6	5
22	7	6

A significant difference was found (Sign test p = 0.0020), union being faster on the right side. However, this conclusion may be misleading, given the inexact nature

of the analysis (see above, p 75 , and Discussion, p 121).

Mass of new bone (healing area) (See Figs 26 - 47 , p81-91).

Under the assumption that the healing mass consisted principally of new bone, the mass was measured in all animals (including those without brain lesions). The principal interest lay in any difference which may exist between the right and left fibulae in brain-lesioned animals. (For method of calculation see p38).

Results are recorded according to measurements made (Table 11 and Figure 25).

The mean mass of new bone in the limbs of animals without brain lesions was 0.21g. In the brain-lesioned group, the mean mass on the right (spastic) side was 0.28g and on the left (non spastic) side was 0.20g.

Comparison was made between the right and left sides in head-injured animals using three statistical tests. The ordinary paired t-test revealed a p-value of 0.0084. A trimmed sample, in which outliers are discarded first, revealed a p-value of 0.0179. For small samples it is preferred to make use of non-parametric analysis. For this reason, Wilcoxson's matched-pairs signed-ranks test was also performed, and revealed a p-value of 0.0039.

These results, indicating a significantly greater amount of new bone around identical fractures in spastic compared with non-spastic limbs in the same animal, are summarised below (Table 10).

TABLE 10

	MEAN MASS(grams)	STATISTICAL TEST	p-VALUE
OVERALL CONTROLS (NO HEAD INJURY(01-08) BOTH FIBULAE	0.21		
RIGHT-SIDED SPASTICITY RIGHT FIBULA (09-22)	0.28	MATCHED t	0.0084
		MATCHED t	0.0179
RIGHT-SIDED SPASTICITY LEFT FIBULA (09-22)	0.20	WILCOXSON (NON - PARAMETRIC)	0.0039

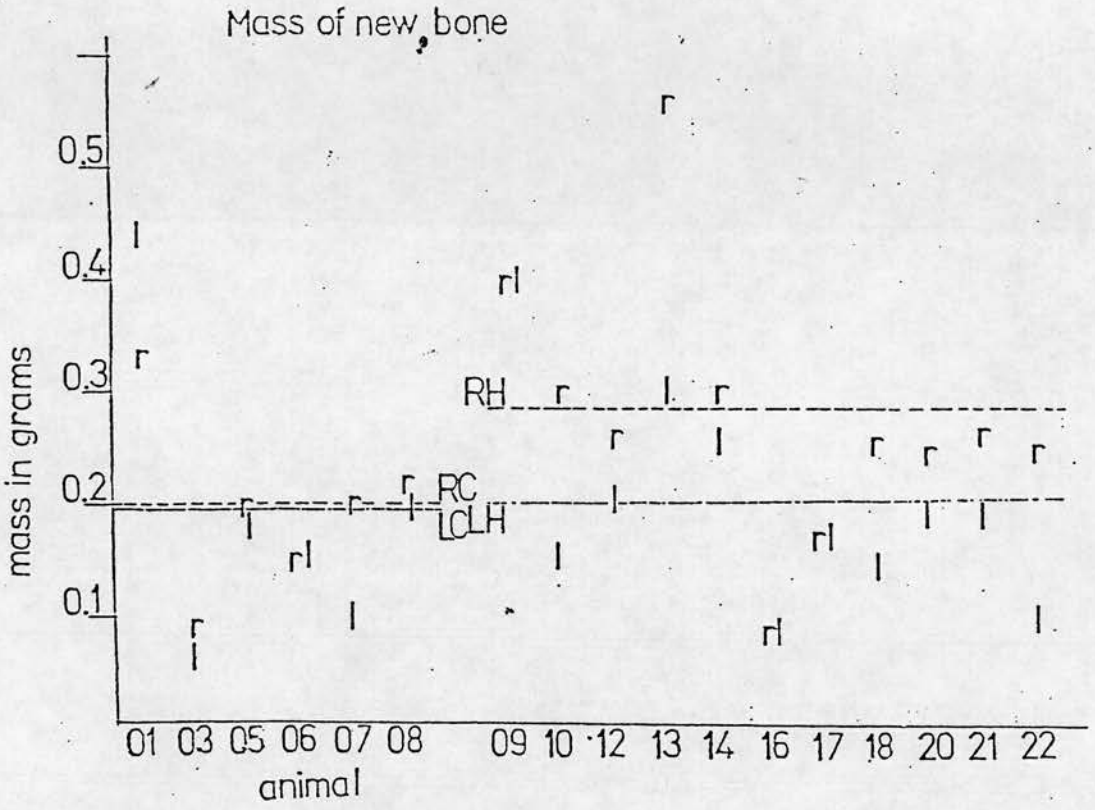
TABLE 11

RESULTS OF MASS MEASUREMENTS OF FIBULAE

NUMBER			LENGTH OF HEALING AREA (cm)	MASS/cm OF FIBULA	TOTAL MASS OF HEALING AREA	MASS NEW BONE (g)
No head injury	01	Right	1.2	0.10	0.45	0.33
		Left	1.4	0.10	0.57	0.43
No head injury	03	Right	1.3	0.10	0.21	0.08
		Left	1.5	0.10	0.21	0.06
No head injury	05	Right	1.2	0.07	0.27	0.19
		Left	1.2	0.06	0.24	0.17
No head injury	06	Right	1.6	0.08	0.28	0.15
		Left	1.6	0.08	0.29	0.16
No head injury	07	Right	1.3	0.06	0.28	0.20
		Left	1.3	0.06	0.18	0.10
No head injury	08	Right	1.0	0.09	0.33	0.24
		Left	1.4	0.10	0.34	0.20
NUMBER						
Head injury	09	Right	1.8	0.15	0.67	0.40
		Left	2.1	0.15	0.71	0.40
Head injury	10	Right	1.4	0.09	0.43	0.30
		Left	1.0	0.09	0.24	0.15
Head injury	12	Right	1.2	0.10	0.37	0.25
		Left	1.2	0.10	0.32	0.20
Head injury	13	Right	1.5	0.10	0.71	0.56
		Left	1.5	0.10	0.45	0.30
Head injury	14	Right	1.5	0.09	0.43	0.30
		Left	1.3	0.09	0.38	0.26
Head injury	16	Right	0.8	0.07	0.14	0.08
		Left	0.8	0.07	0.14	0.08
Head injury	17	Right	0.9	0.09	0.25	0.17
		Left	0.9	0.09	0.25	0.17
Head injury	18	Right	1.1	0.10	0.36	0.25
		Left	1.0	0.10	0.23	0.13
Head injury	20	Right	1.5	0.11	0.39	0.23
		Left	1.3	0.11	0.32	0.18
Head injury	21	Right	1.6	0.10	0.42	0.26
		Left	1.5	0.10	0.34	0.19
Head injury	22	Right	1.1	0.08	0.33	0.24
		Left	0.8	0.08	0.15	0.09

RIGHT = SPASTIC SIDE
LEFT = NON-SPASTIC SIDE

Figure 25



Mass of new bone in grams (all animals)

r = right
l = left

RH = mean right side brain lesion
LH = mean left side brain lesion
RC = mean right side no brain lesion
LC = mean left side no brain lesion

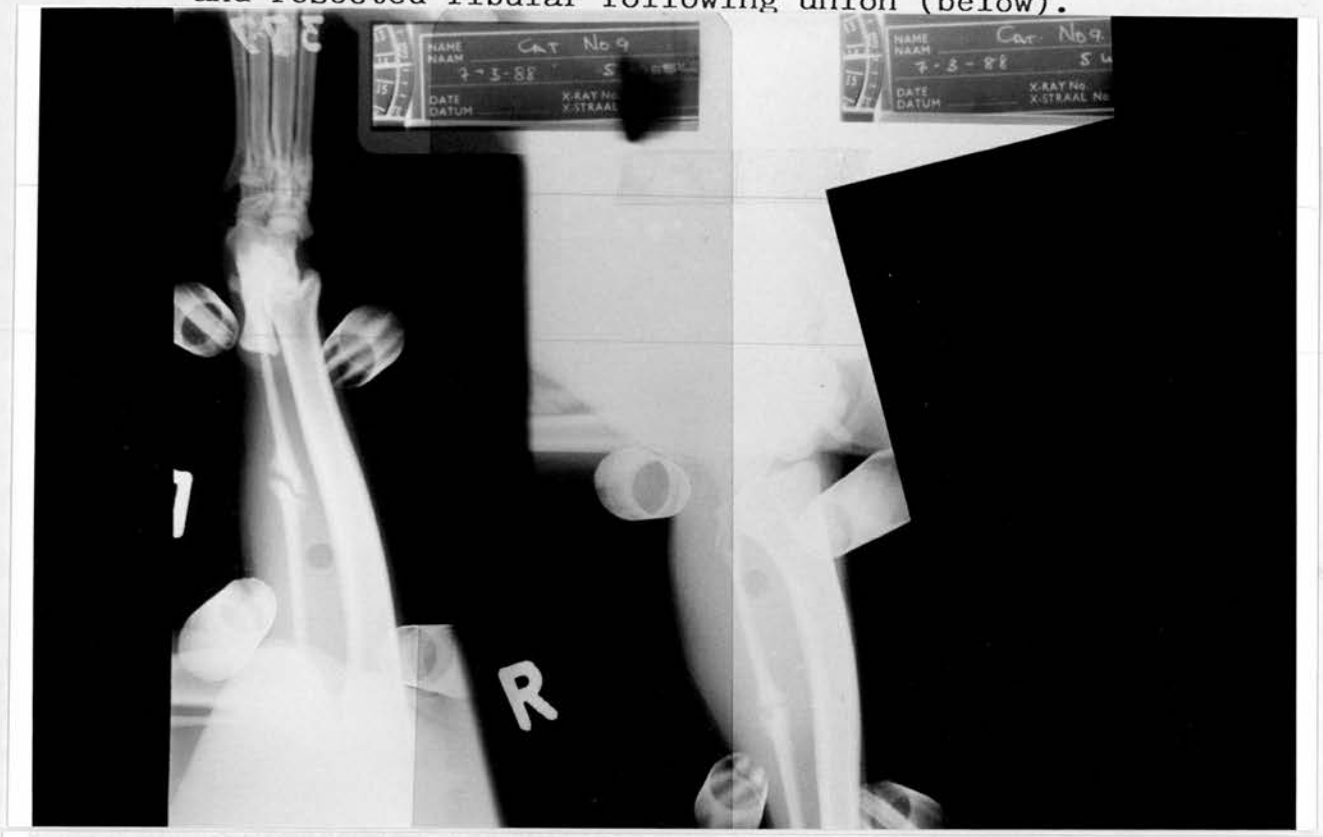
Figures 26 - 47 (p 81 - 91).

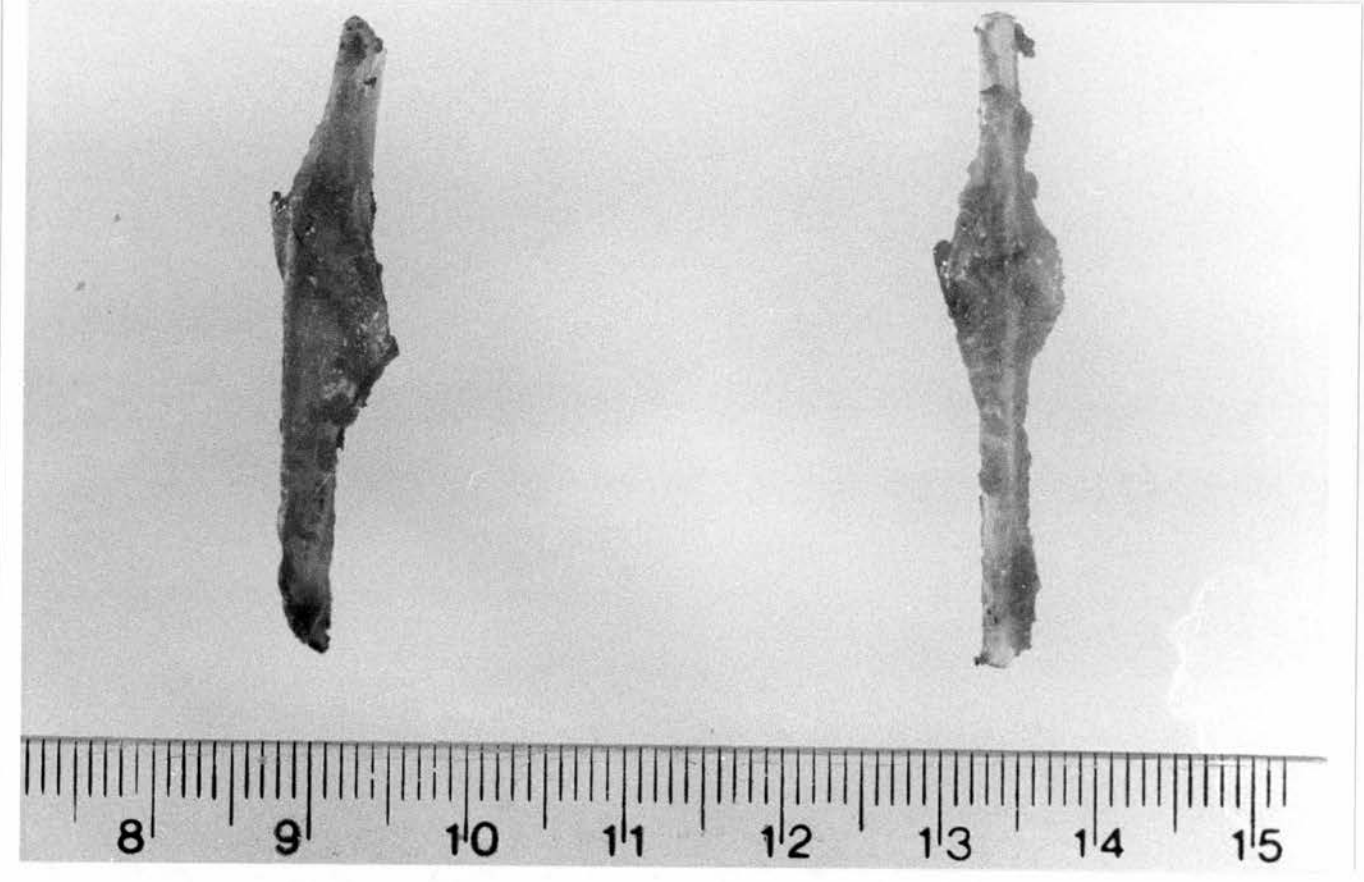
The following figures on pages 81 to 91 show Xrays and resected fibular specimens from animals 09, 10, 12, 13, 14, 16, 17, 18, 20, 21 and 22 (those with observable neurological signs in the right leg).

Xrays shown were taken on the same day in each animal. They have been selected according to ease of photographic reproduction, and are not necessarily those taken immediately prior to fibular resection.

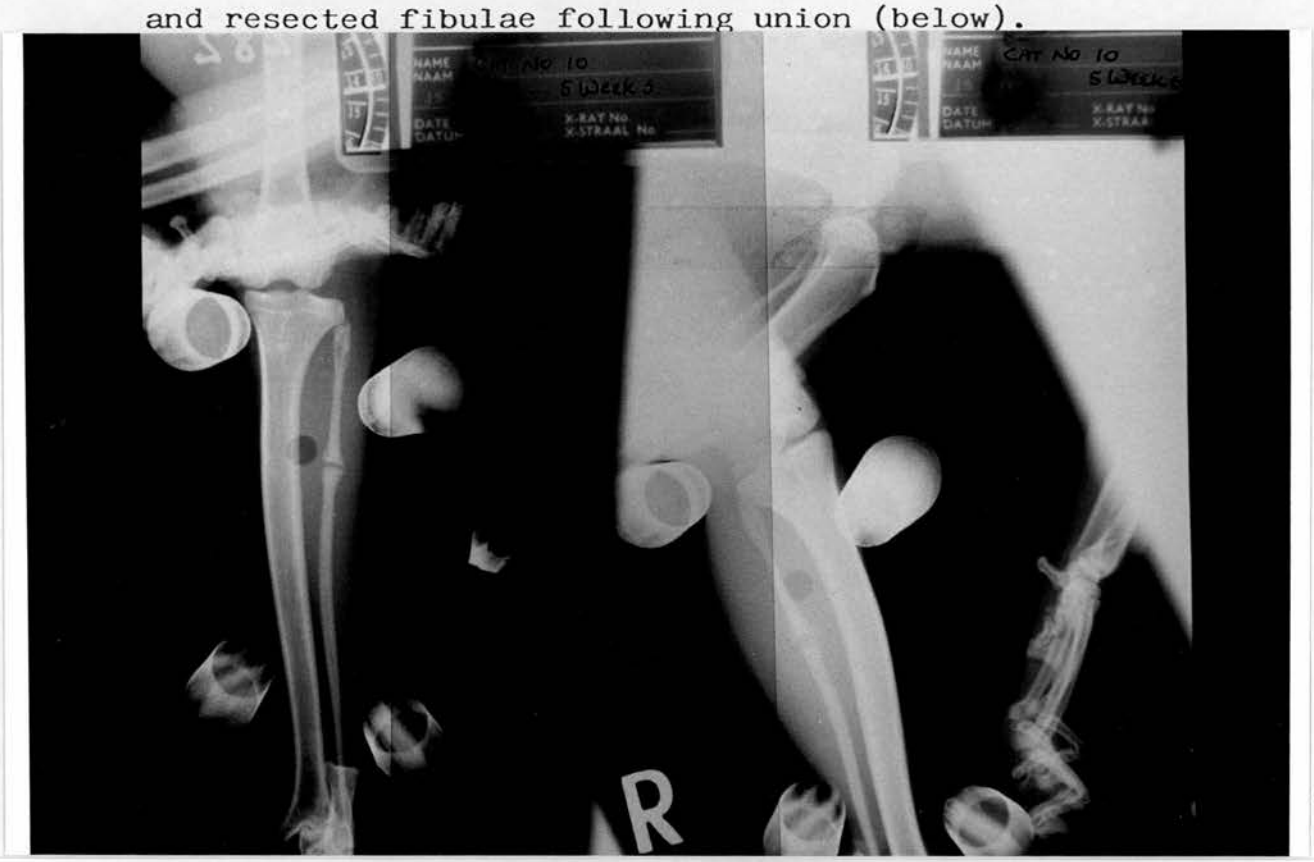
Fibulae are shown with the right side to the right of the photograph.

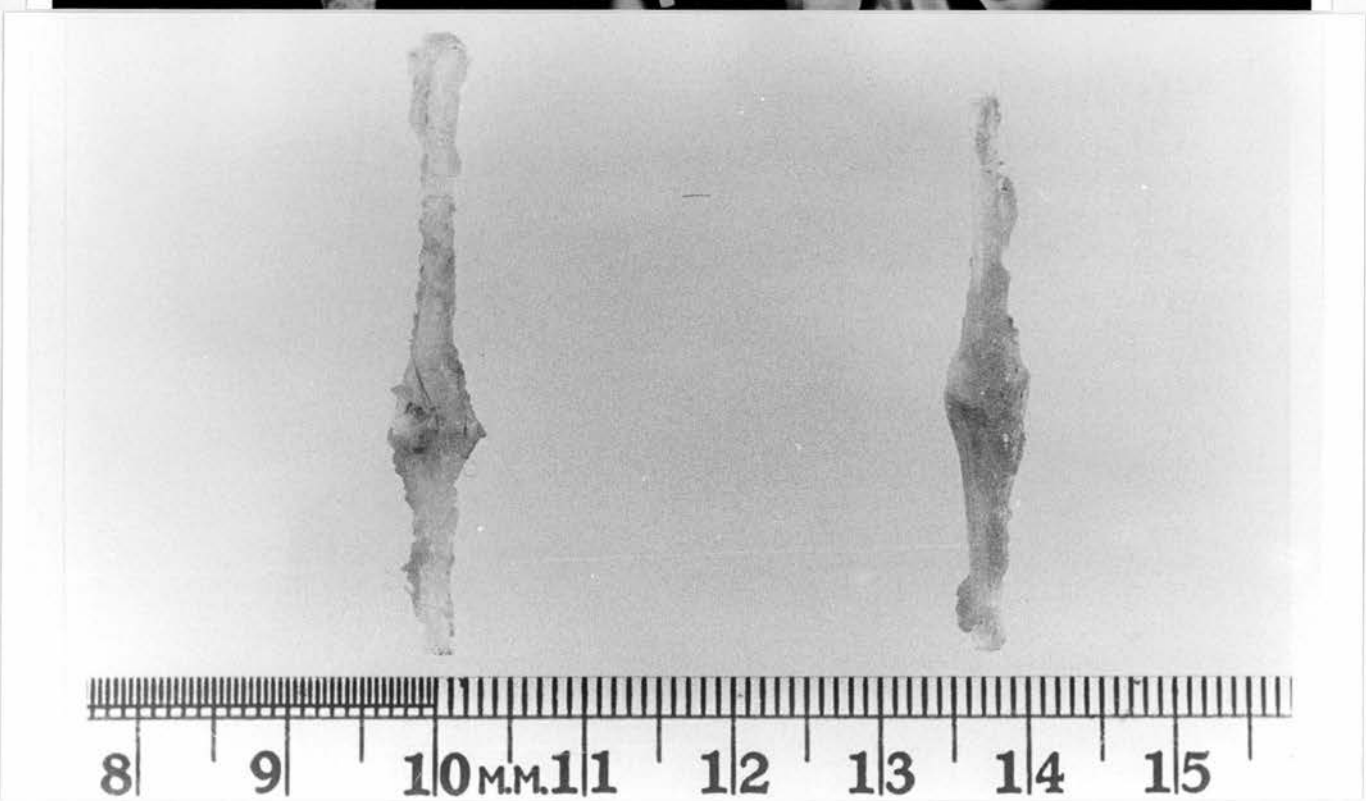
Figures 26 and 27 Cat No 9 ; Xrays at 5 weeks (above), and resected fibular following union (below).



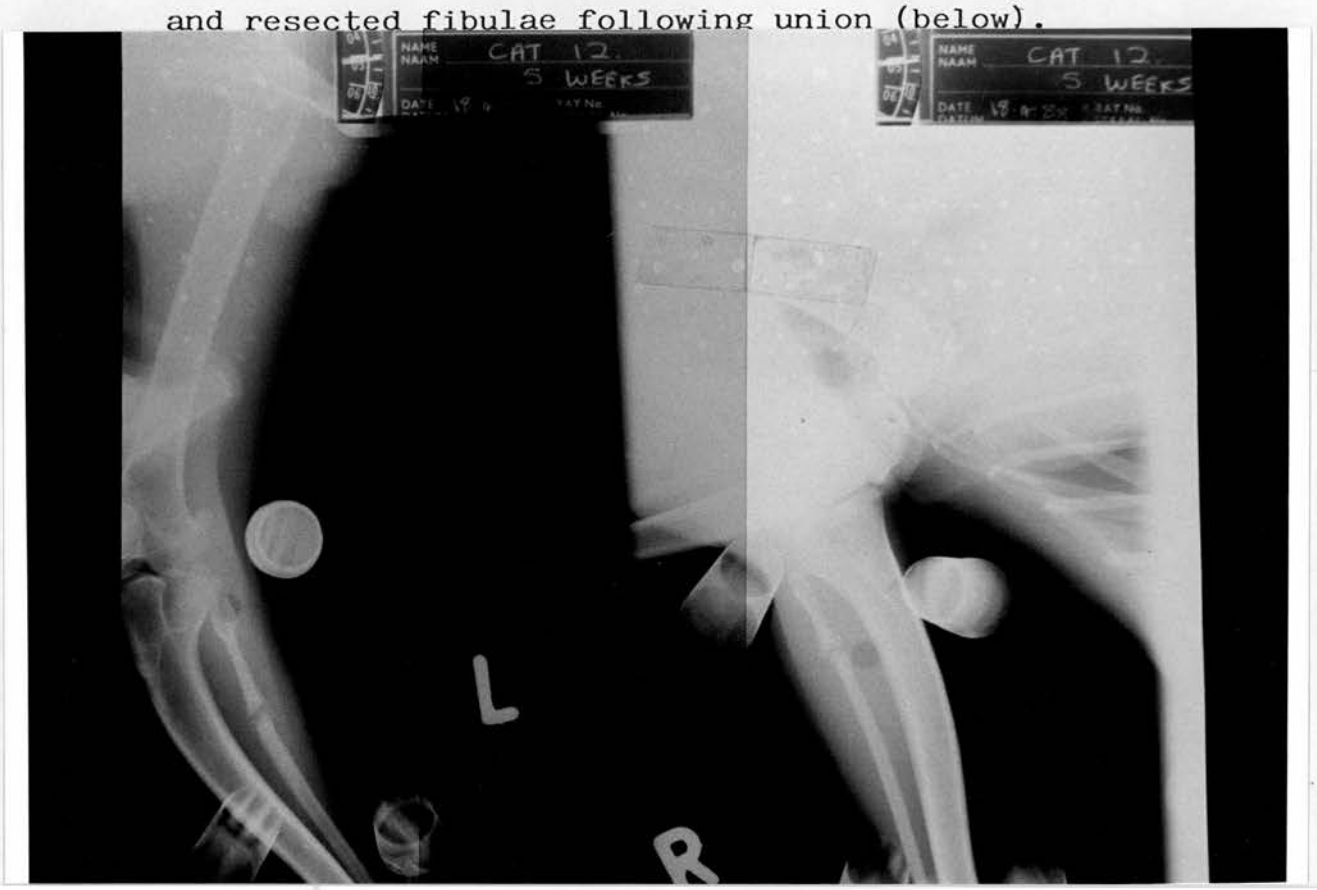


Figures 28 and 29 Cat No 10 ; Xrays at 5 weeks (above), and resected fibulae following union (below).

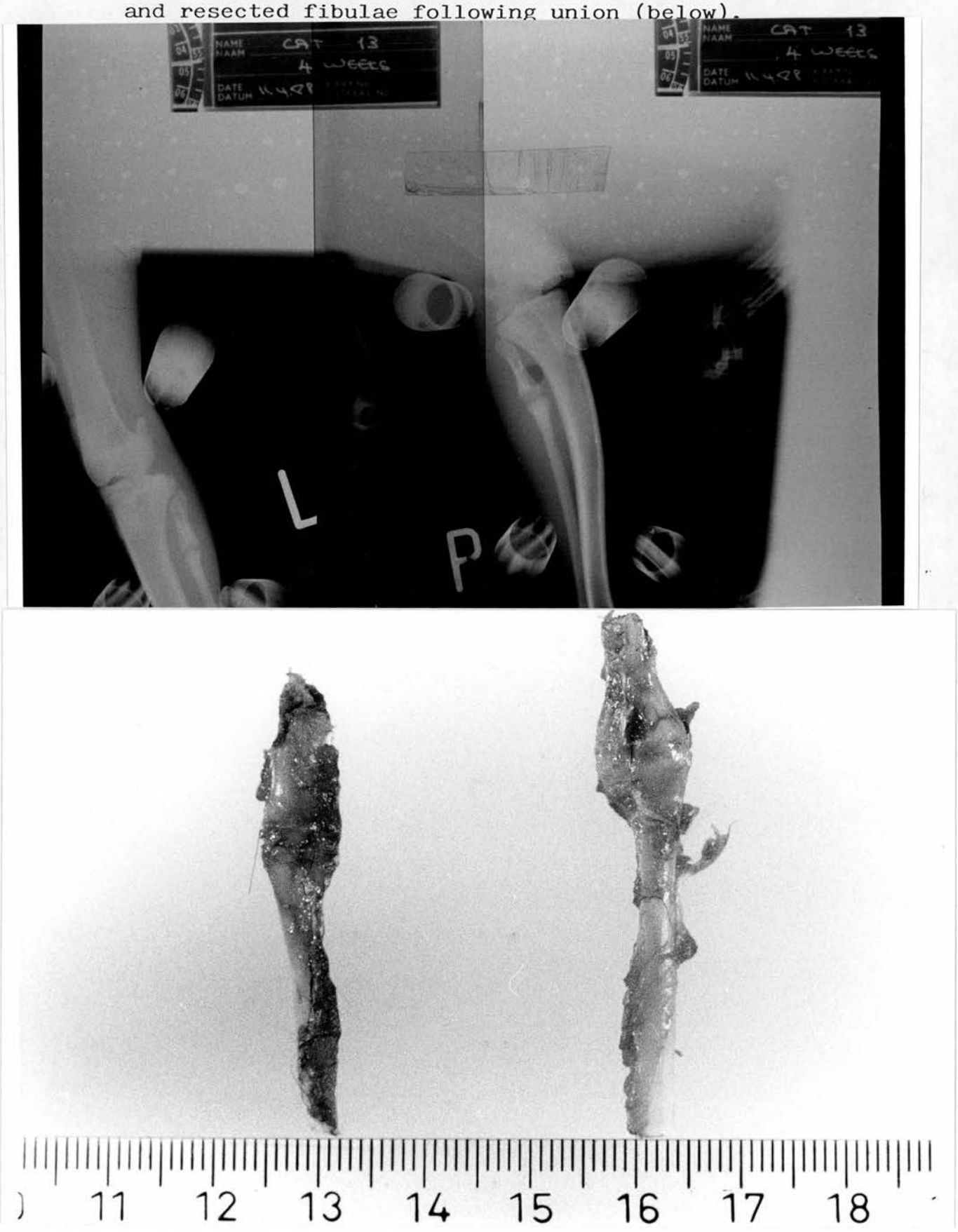




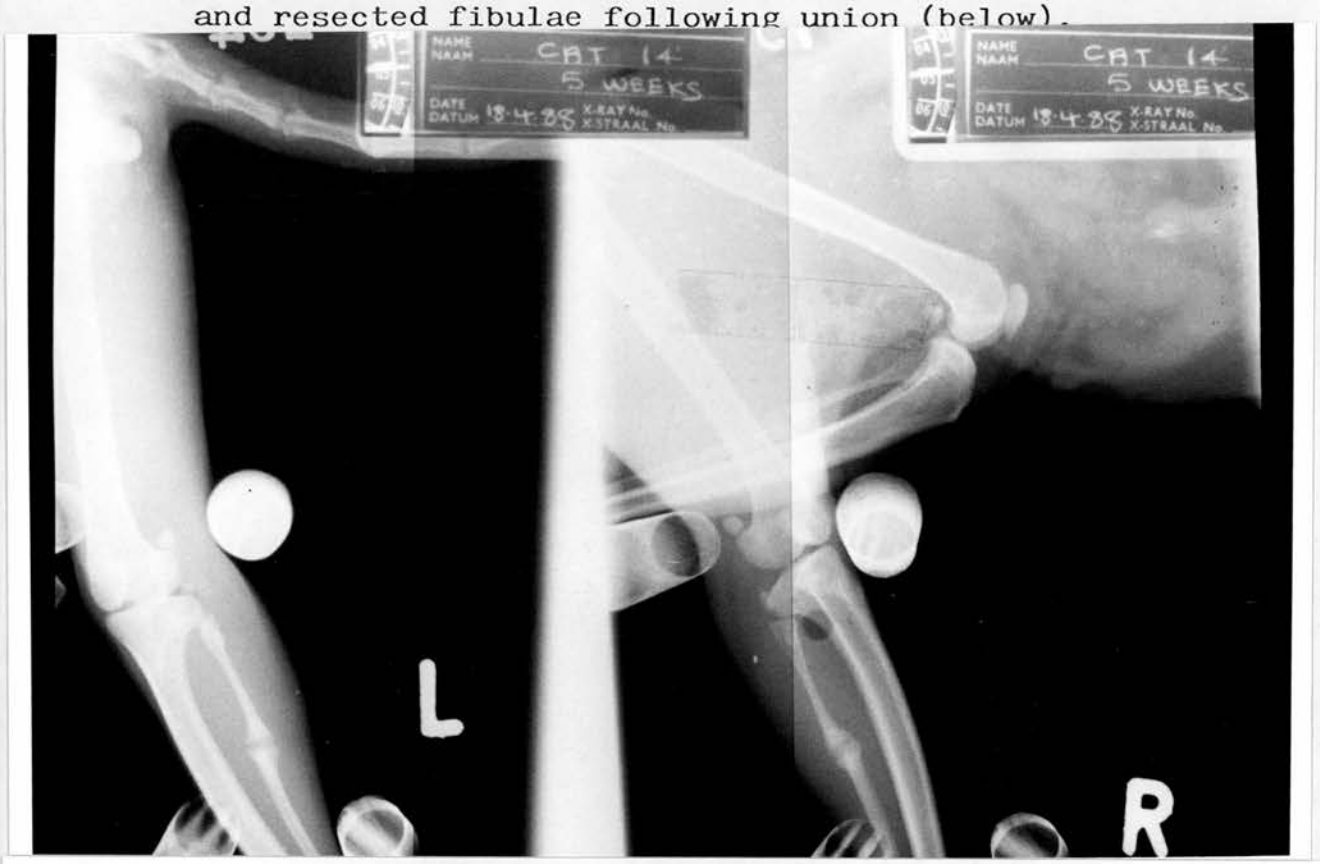
Figures 30 and 31 Cat No 12 ; Xrays at 5 weeks (above), and resected fibulae following union (below).

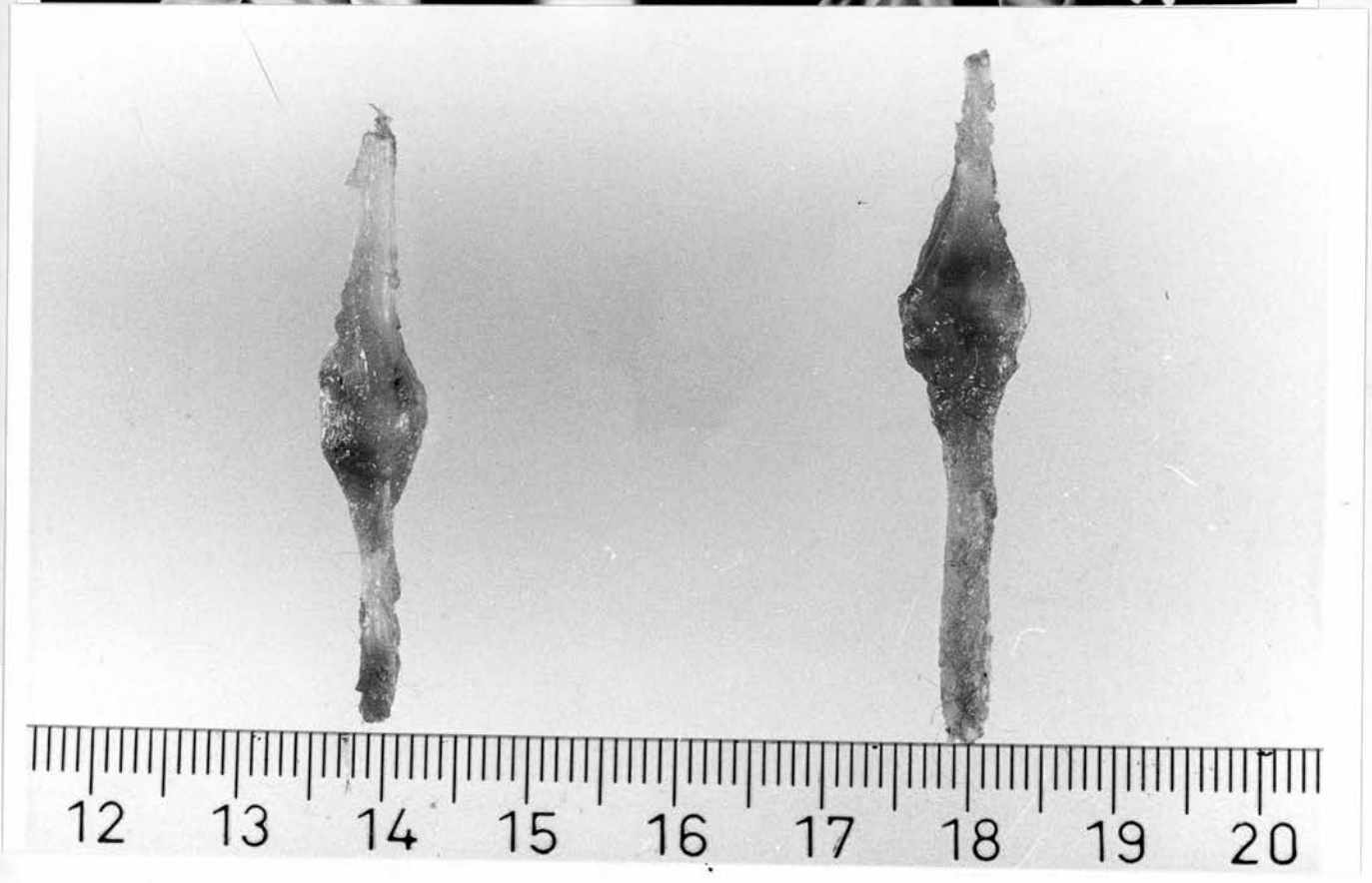


Figures 32 and 33 Cat No 13 ; Xrays at 4 weeks (above), and resected fibulae following union (below).

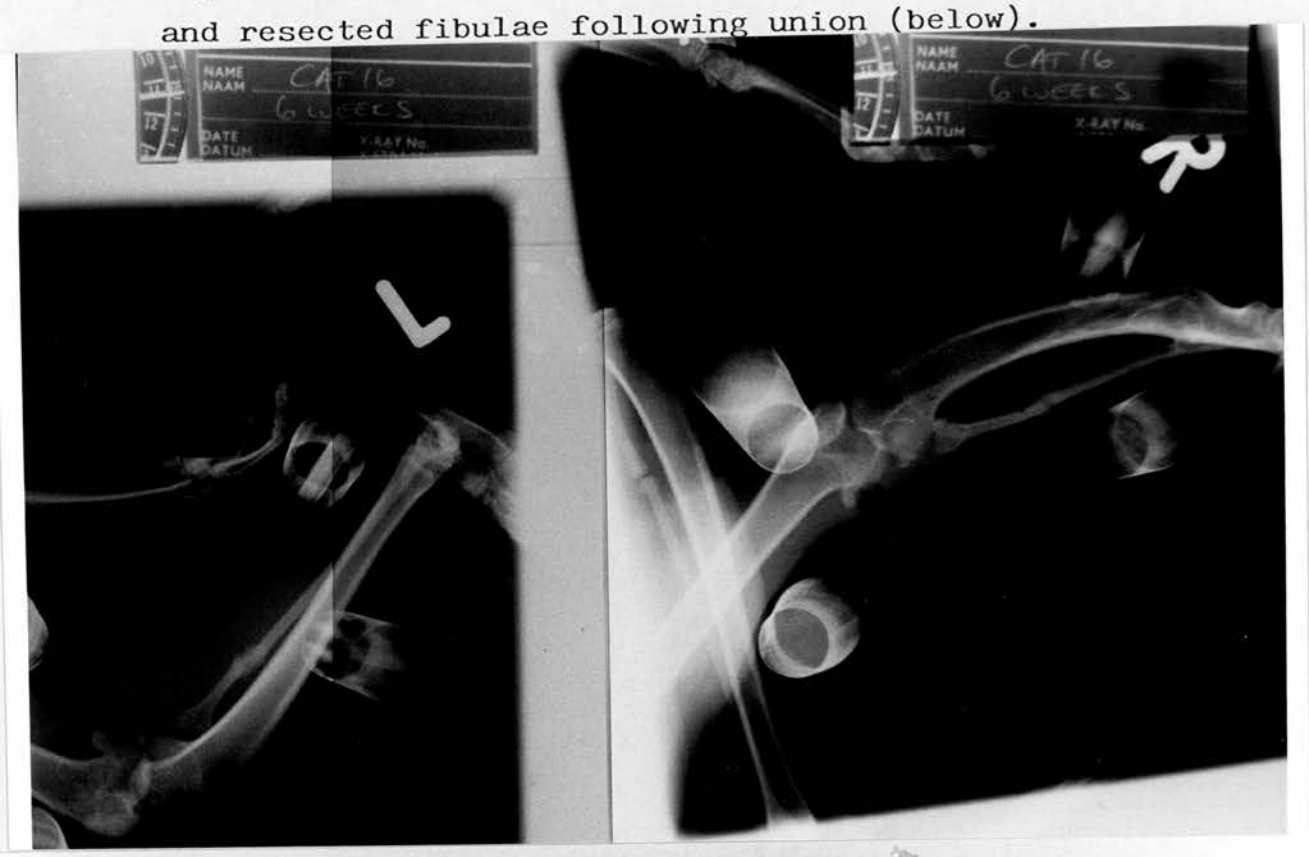


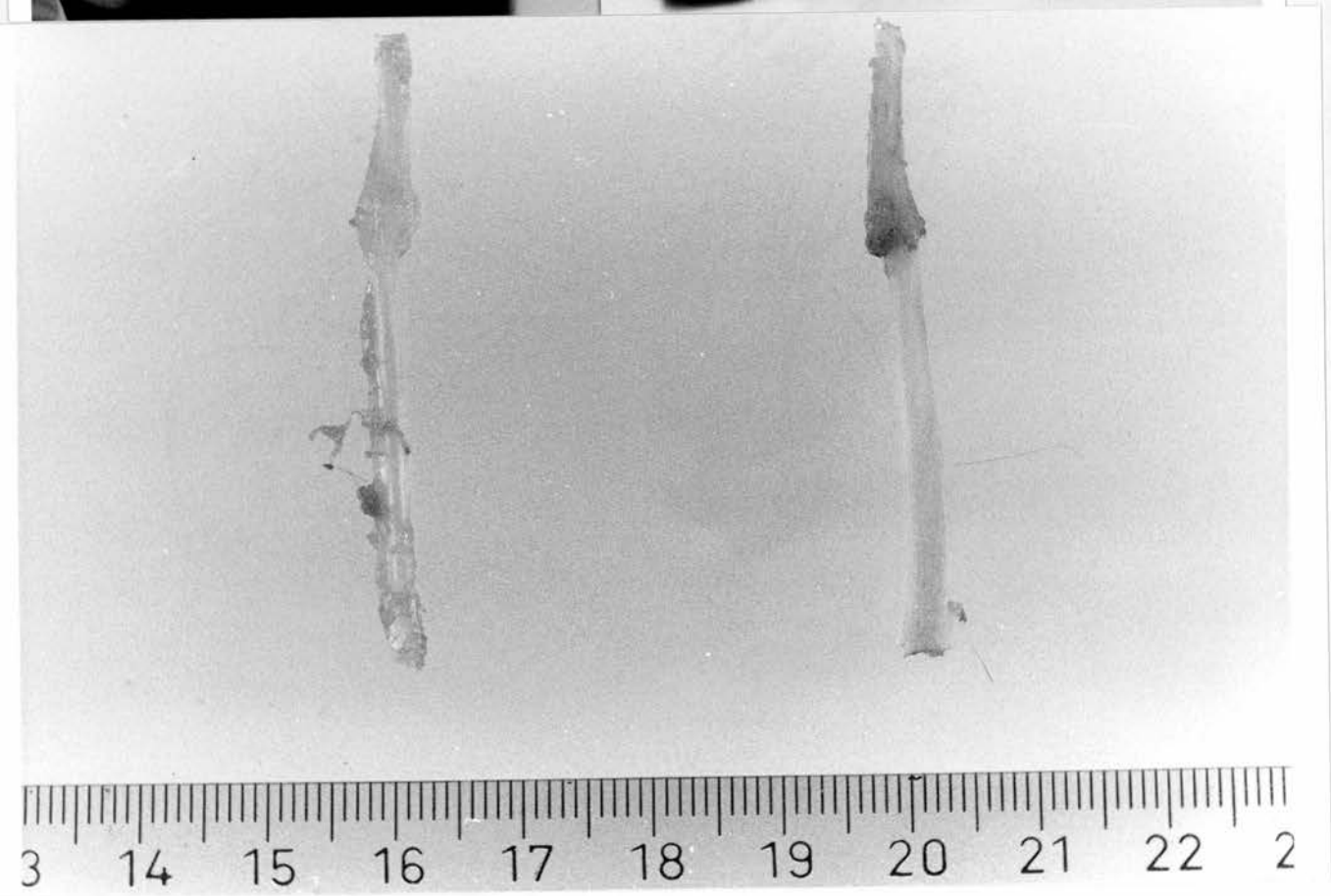
Figures 34 and 35 Cat No 14 ; Xrays at 5 weeks (above), and resected fibulae following union (below).



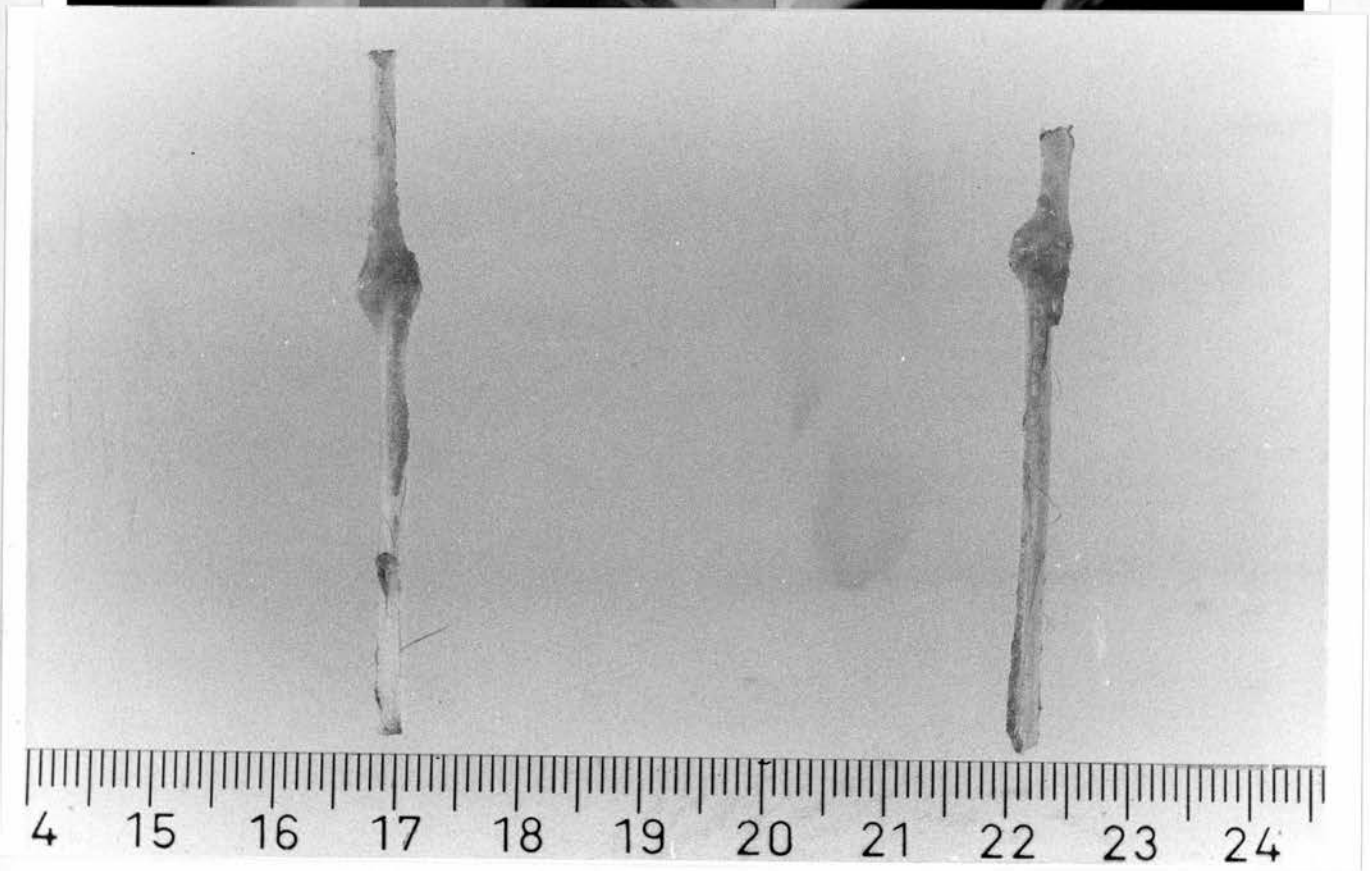


Figures 36 and 37 Cat No 16 ; Xrays at 6 weeks (above), and resected fibulae following union (below).

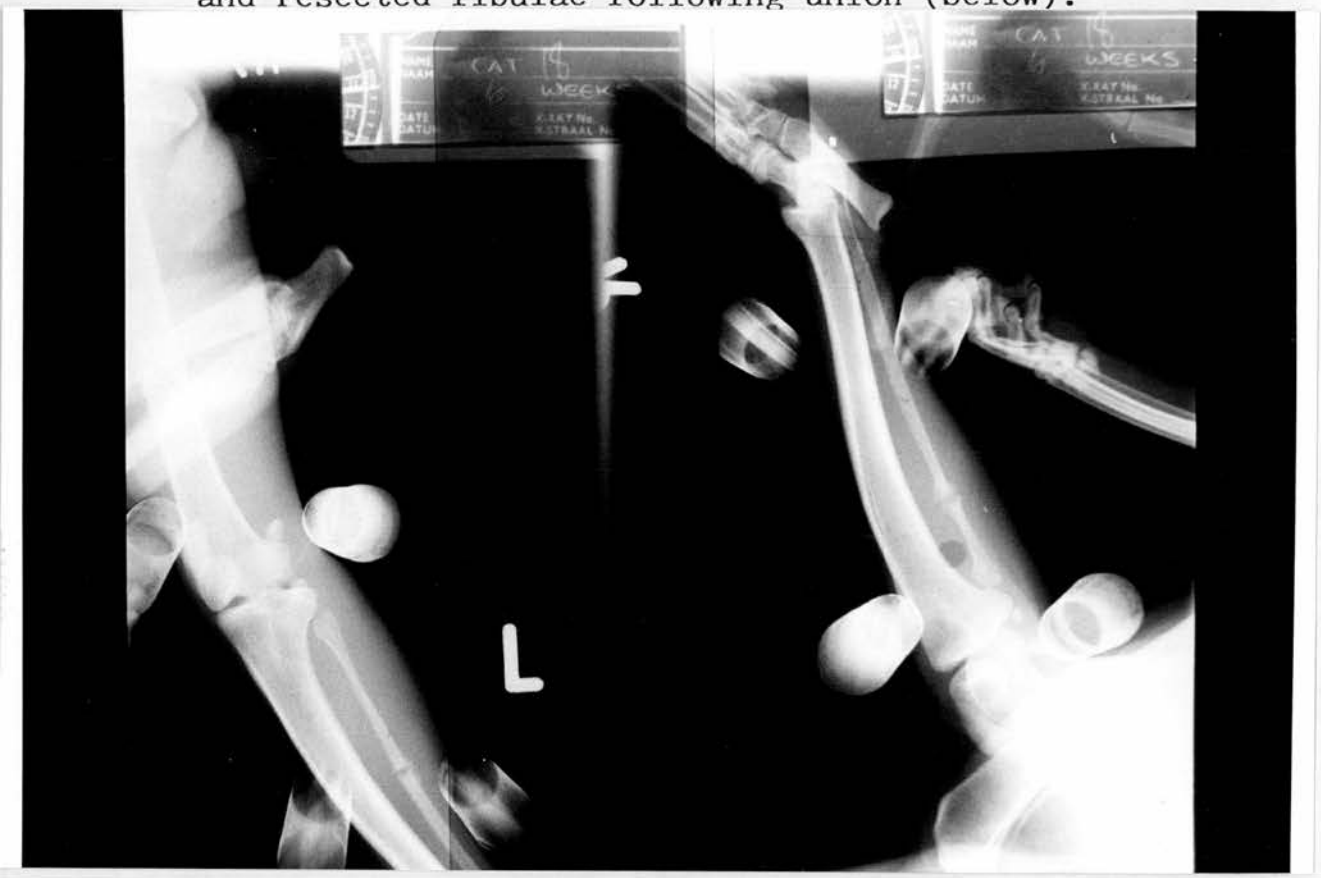


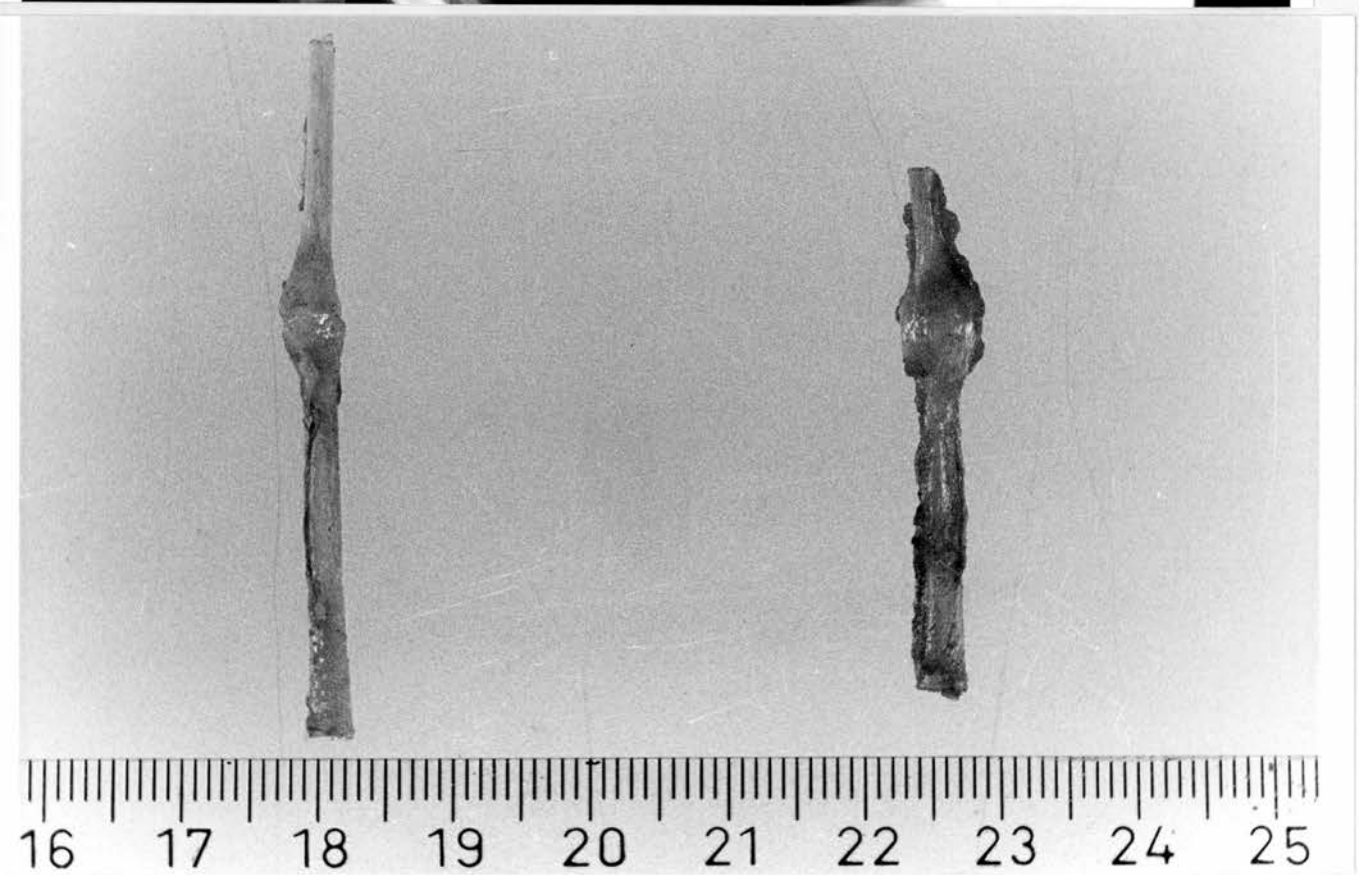


Figures 38 and 39 Cat No 17 ; Xrays at 6 weeks (above), and resected fibulae following union (below).

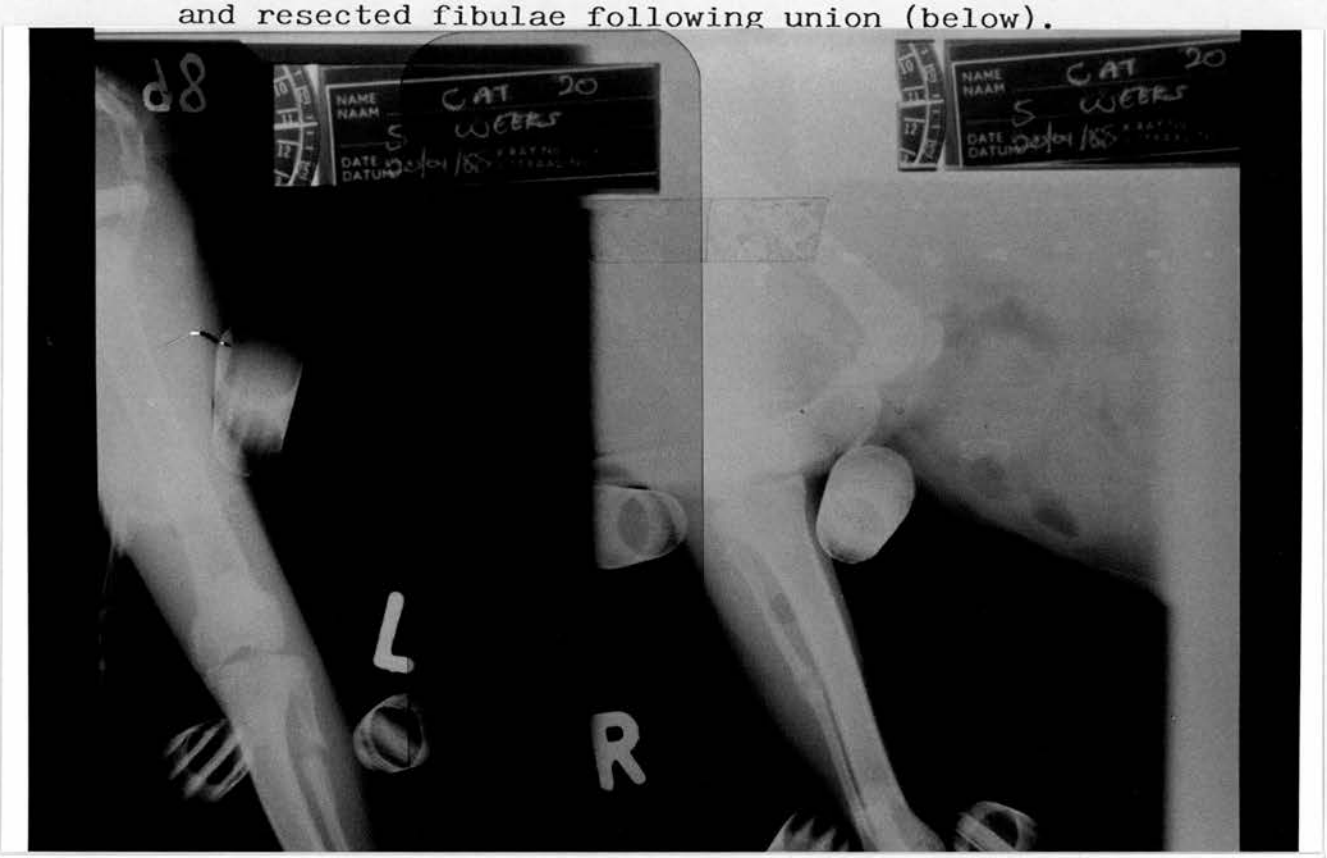


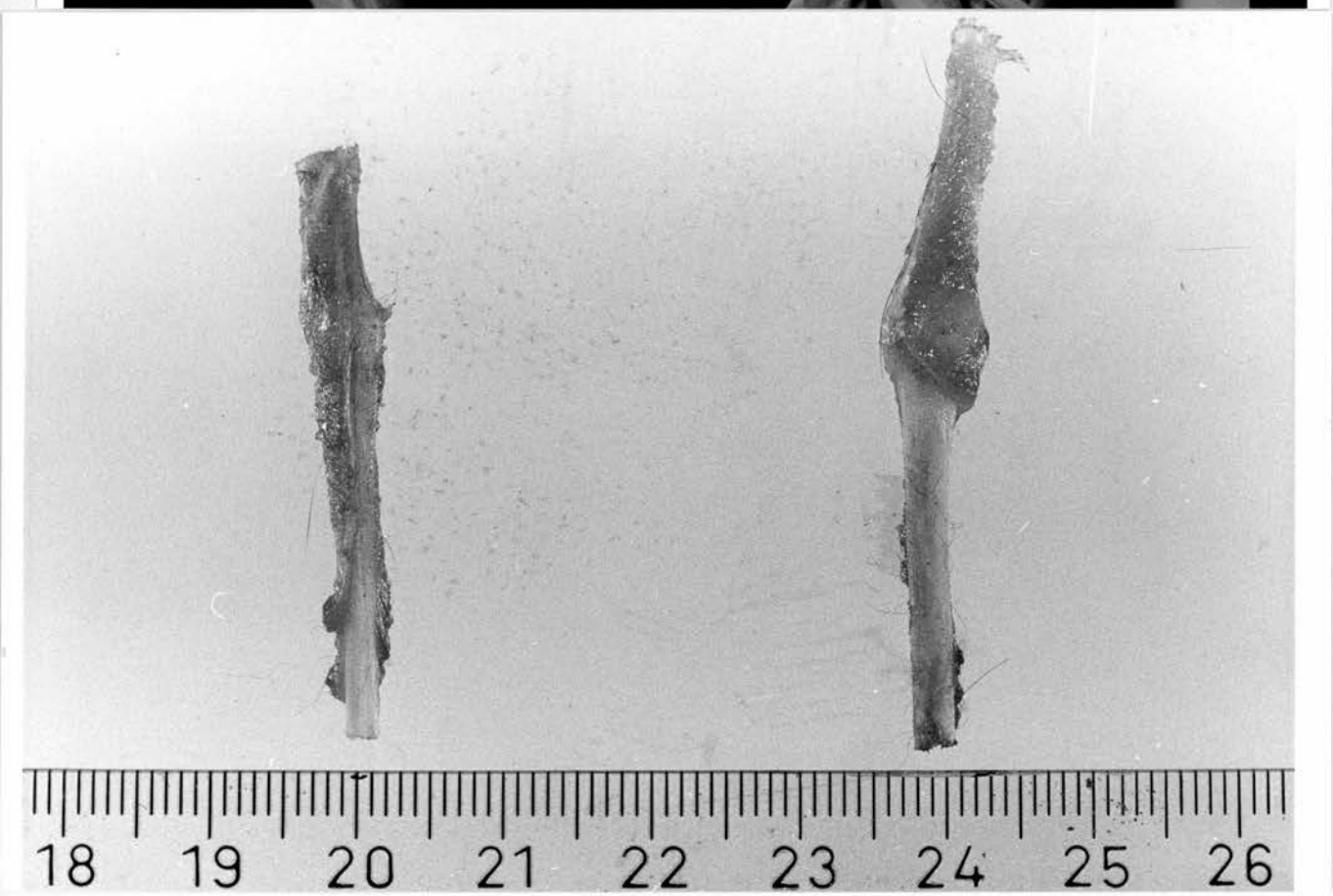
Figures 40 and 41 Cat No 18 ; Xrays at 6 weeks (above), and resected fibulae following union (below).



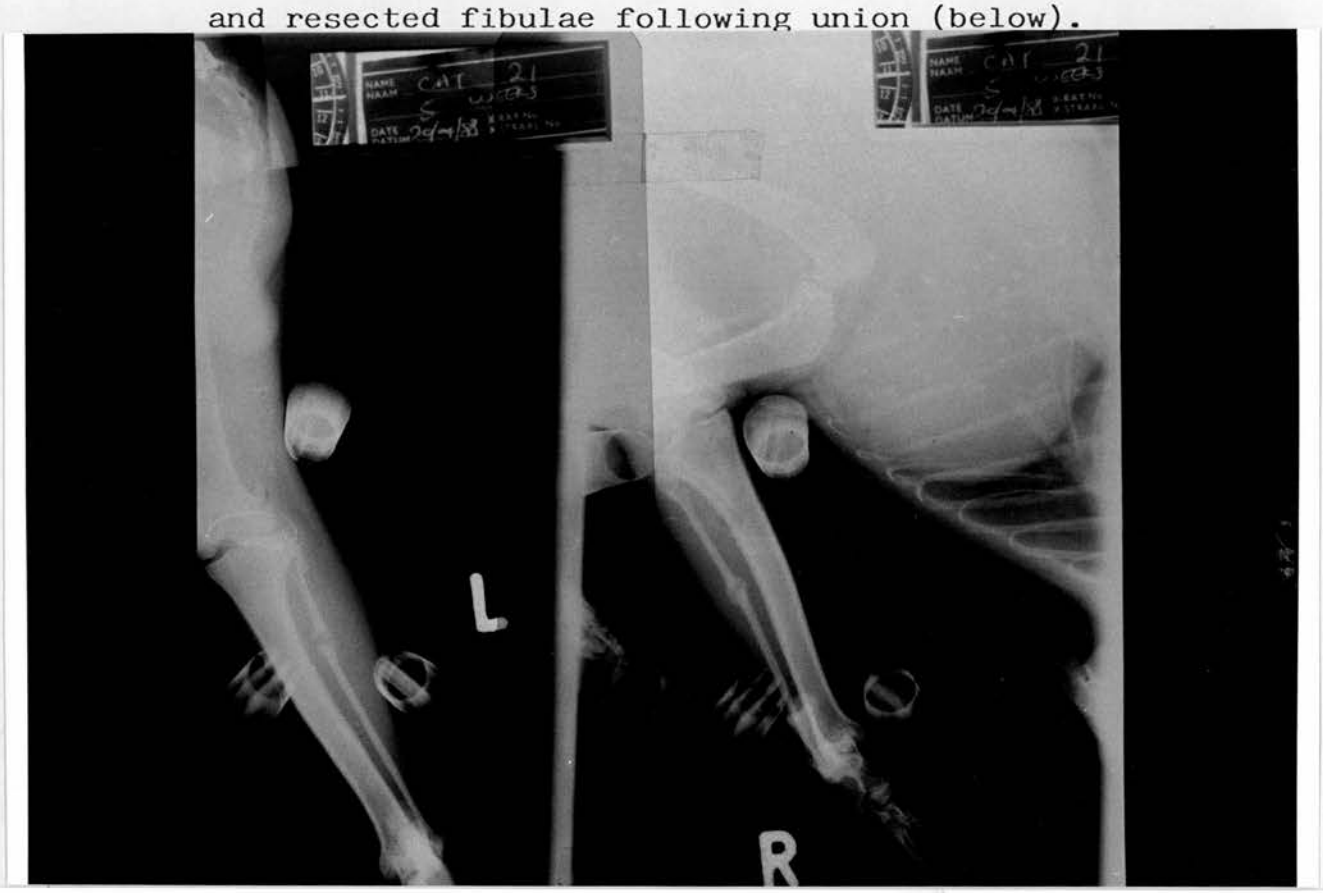


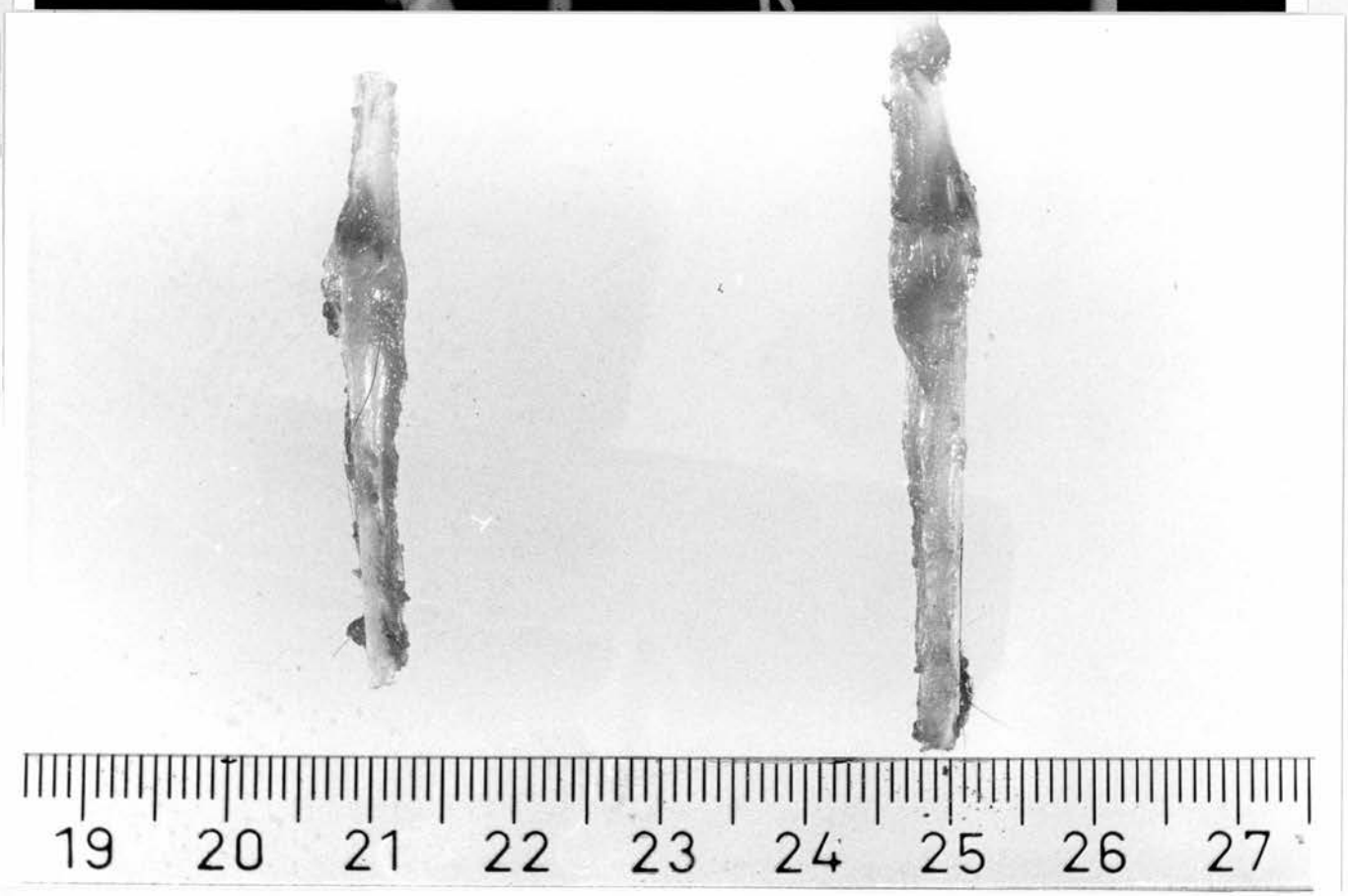
Figures 42 and 43 Cat No 20 ; Xrays at 5 weeks (above), and resected fibulae following union (below).



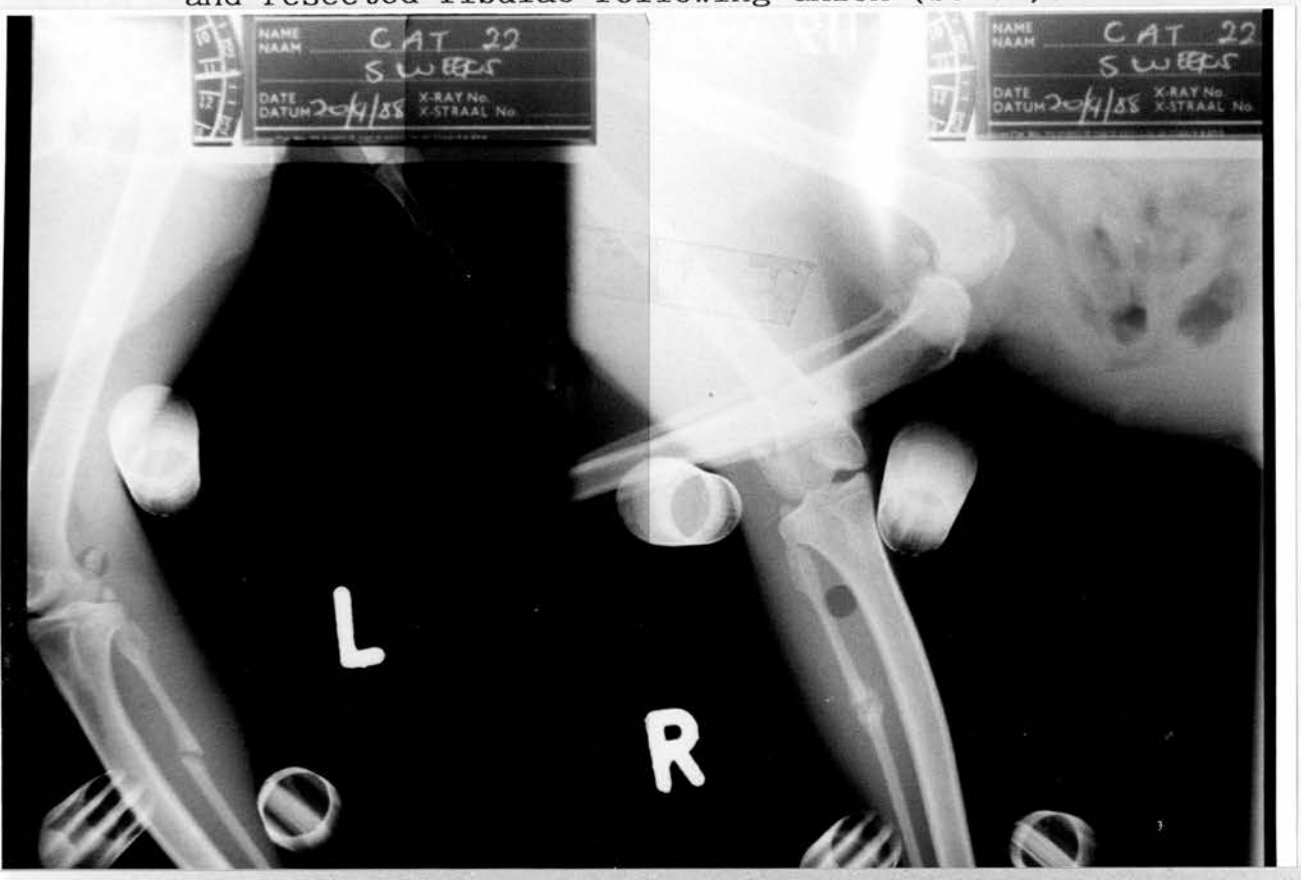


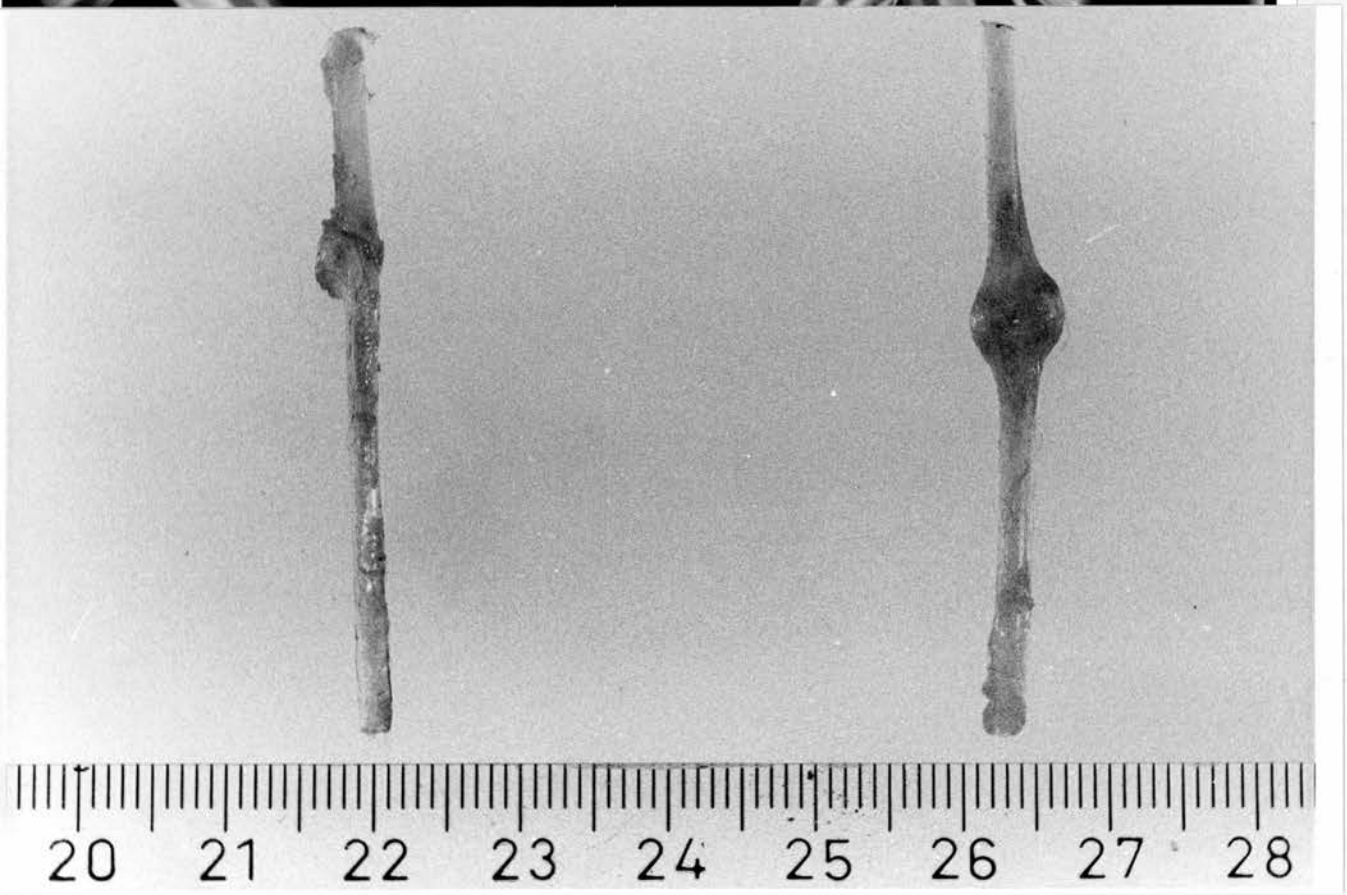
Figures 44 and 45 Cat No 21 ; Xrays at 5 weeks (above), and resected fibulae following union (below).





Figures 46 and 47 Cat No 22 ; Xrays at 5 weeks (above), and resected fibulae following union (below).





Histomorphometry

Volume fractions were calculated in 10 animals (Animal No 10 was excluded as sections were performed incorrectly).

The results for Area A and Area B (see p 39 and Fig 9 on p 41) are shown in Tables 12 and 13 .

The composition of Area A ("bridging callus") on left and right sides in brain-lesioned animals was broadly comparable, with over 80% of the material being osseous in nature. A front of endochondral ossification was consistently seen adjacent to the fracture line (Figs 48 - 51).

In Area B ("medullary callus") slightly less hyaline cartilage, slightly more fibrovascular tissue, and similar quantities of purely fibrous tissue (on average) were seen between the bone ends on the right side.

Statistical analysis was not performed, since each of the tissues were considered to represent points on a continuum. Moreover, numbers were small, and numerous variables were present (See Discussion p 122).

TABLE 12

Volume fractions in healing area (Area A) ("bridging callus").

ANIMAL	LEFT			RIGHT		
	B	H	F	B	H	F
09	0.84	0.16	0.00	0.80	0.16	0.04
10	0.70	0.25	0.04	0.77	0.23	0.09
12	0.88	0.12	0.00	0.84	0.12	0.04
13	0.88	0.08	0.04	0.86	0.12	0.03
14	0.80	0.20	0.00	0.85	0.15	0.00
17	0.75	0.25	0.00	0.80	0.20	0.00
18	0.84	0.12	0.04	0.88	0.08	0.04
20	0.85	0.15	0.00	0.76	0.21	0.04
21	0.83	0.12	0.03	0.88	0.12	0.00
22	0.80	0.20	0.00	0.86	0.14	0.00
Average	0.82	0.17	0.02	Average 0.83	0.15	0.03
	(To nearest decimal point)			(To nearest decimal point)		

B = Bone

H = Cartilage

F = Fibrous tissue

(no other tissue seen in significant amounts).

TABLE 13

Volume fractions between bone ends (Area B)("medullary callus").

ANIMAL	LEFT			RIGHT		
	H	FV	F	H	FV	F
09	0.39	0.57	0.04	0.13	0.75	0.13
10	0.23	0.70	0.08	0.24	0.71	0.06
12	0.53	0.47	0.00	0.00	0.64	0.36
13	0.35	0.37	0.27	0.31	0.63	0.06
14	0.12	0.77	0.12	0.27	0.73	0.00
17	0.29	0.61	0.10	0.17	0.72	0.10
18	0.12	0.64	0.24	0.17	0.47	0.37
20	0.08	0.84	0.08	0.26	0.55	0.19
21	0.59	0.41	0.00	0.58	0.42	0.00
22	0.53	0.41	0.06	0.20	0.80	0.00
Average	0.32	0.58	0.10	Average 0.25	0.64	0.12
	(To nearest decimal point)			(To nearest decimal point)		

H = Cartilage

FV = Fibrovascular tissue

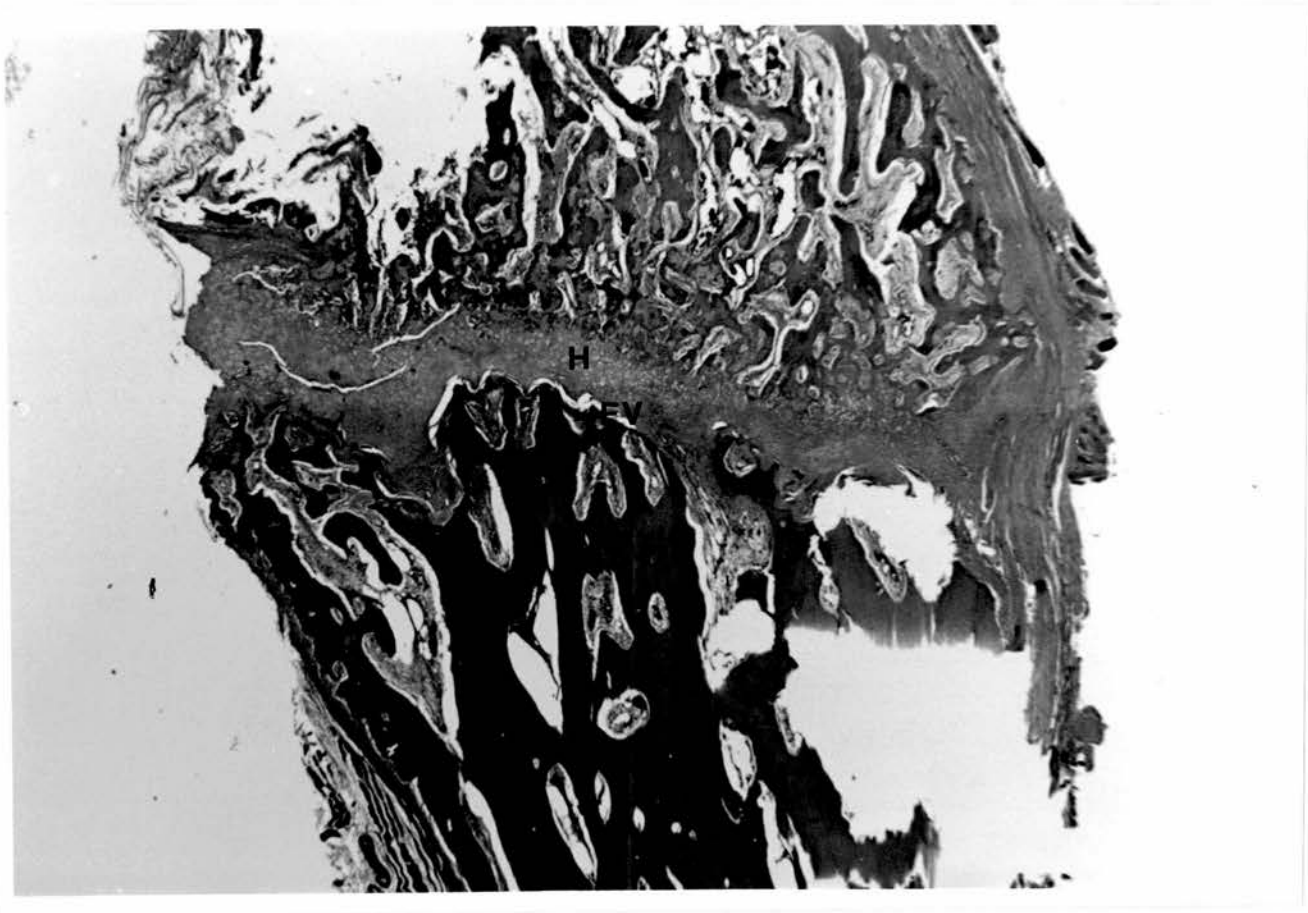
F = Fibrous tissue

(ossified fibrovascular tissue excluded).

Figure 48

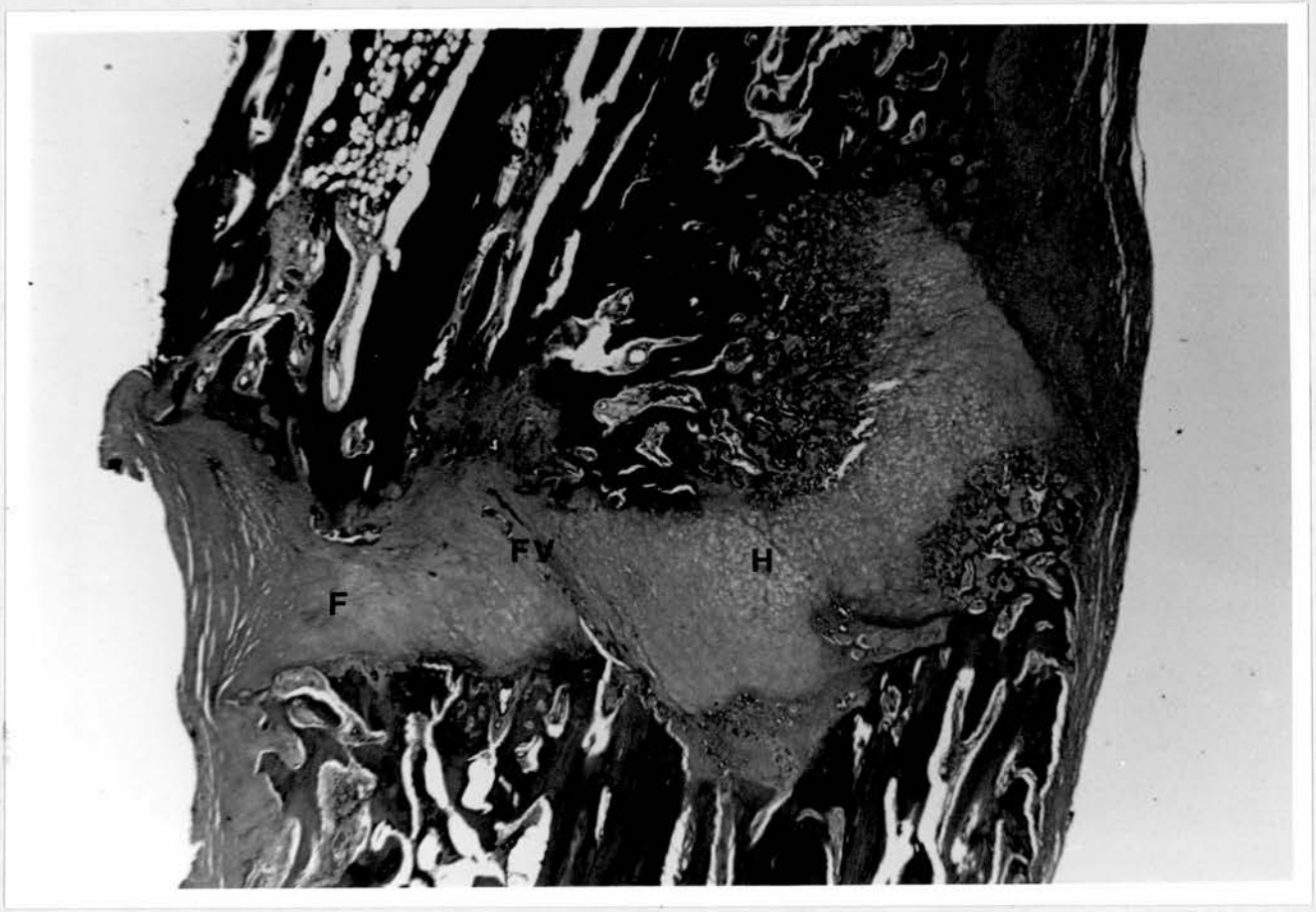
Animal No.18 Right fibula.
Low power view shows that the healing areas outside the fracture line consist principally of osseous material (B). A front of endochondral ossification is seen (H) (x7.5).

Figure 49



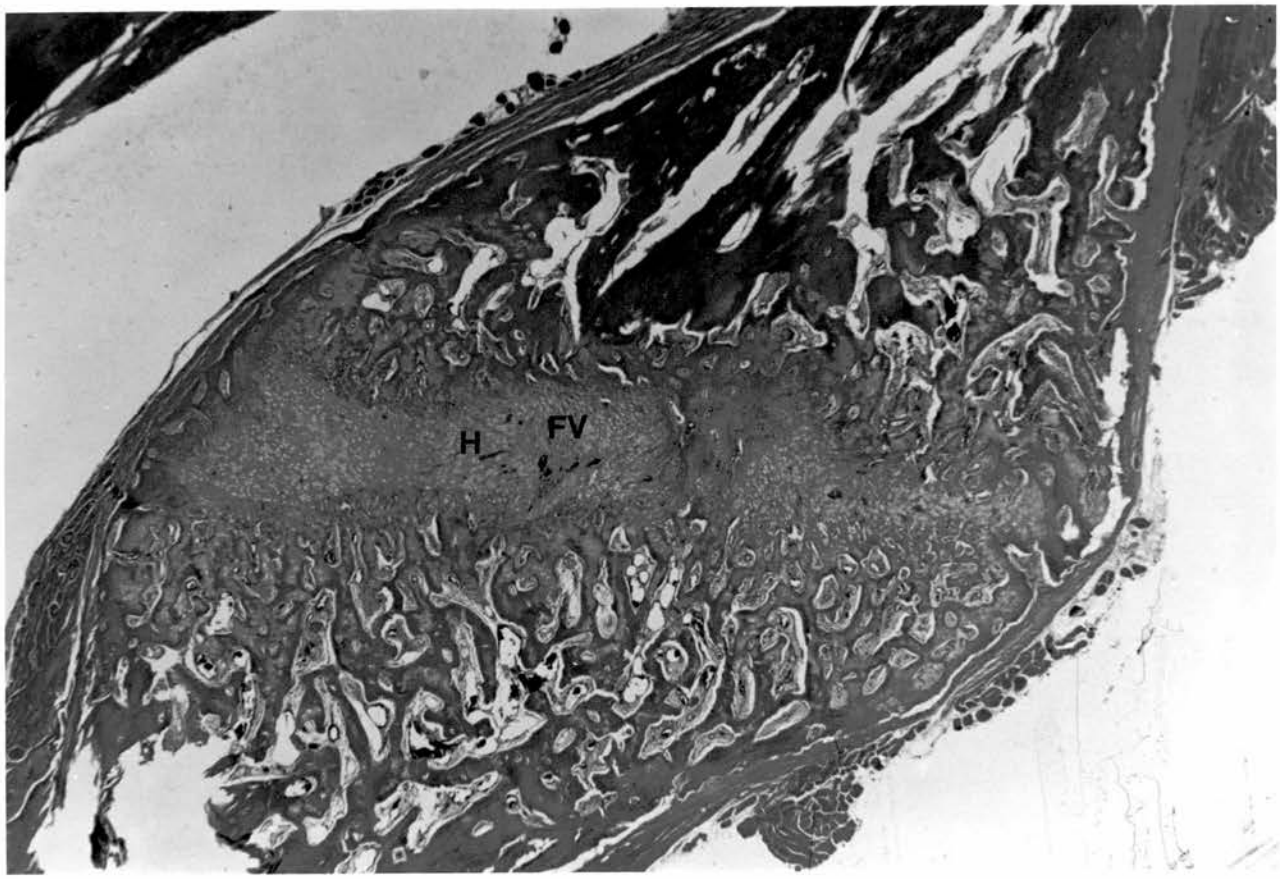
Animal No.12 Left fibula.
Hyaline cartilage (H) and fibrovascular tissue (FV) are seen within the fracture line (x15).

Figure 50



Animal No.20 Right fibula.
Hyaline cartilage (H), fibrovascular tissue (FV), and avascular fibrous tissue (F) are seen along the fracture line (x15).

Figure 51



Animal No. 21 Right fibula.
Hyaline cartilage (H) and ossifying fibrovascular tissue (FV) are seen along the fracture line. No fibrous tissue is seen (x15).

Biochemistry

Serum calcium (Table 14)

Animals 01-08 (no brain lesion) were compared with 09-22 (left-sided brain lesion). Weeks 0, 1 and 4 were chosen for comparative purposes, in order to obtain at least 5 observations per group.

The F-test was performed to determine differences in profile analysis. No significant difference was found (F_2; 14; 0.05 = 3.74). The overall responses did not differ (F_1; 15; 0.05 = 4.54), and any changes in value did not reach significance (F_2; 14; 0.05 = 3.74).

It was concluded that serum calcium levels remained essentially unaltered throughout the study, and serum levels were not influenced by the presence of a brain lesion.

Serum phosphate (Table 15)

(comparison between animals 01-08 and 09-22).
Weeks 0, 1 and 4 were chosen for comparative purposes. The F-test was performed to determine differences in profile analysis. No significant difference was found (F_2; 14; 0.05 = 3.74). The overall responses did not differ (F_1; 15; 0.05 = 4.54), and any changes in value did not reach significance (F_2; 14; 0.05 = 3.74).

It was concluded that serum phosphate levels remained essentially unaltered throughout the study, and were not influenced by the presence of a brain lesion.

Serum alkaline phosphatase (Table 16)

(comparison between animals 01-08 and 09-22).
Because of difficulty with occasional haemolysis of specimens, animals 8, 10, 12 and 16 were excluded due to missing values. Weeks 0, 1 and 4 were chosen for comparative purposes.

The F-test was performed to determine differences in profile analysis. No significant difference was found (F_2; 10; 0.05 = 4.10). The overall responses did not differ (F_1; 11; 0.05 = 4.84) and any changes in value did not reach significance (F_2; 10; 0.05 = 4.10).

It was concluded that serum alkaline phosphatase levels remained essentially unaltered throughout the study, and were not influenced by the presence of a brain leson.

Serum albumin (Table 17)

(comparison between animals 01-08 and 09-22)
Weeks 0, 1 and 4 were chosen for comparative purposes. The F-test was performed to determine differences in profile analysis. No significant difference was found (F_2; 14; 0.05 = 3.74). The overall responses did not differ (F_1; 15; 0.05 = 4.54). However, a significant decrease in serum albumin between weeks 0 and 1 was seen when the values were studied as a whole group (01-22) (F_2; 14; 0.05 = 3.74) (Vector of test = -4.72321 is significant).

It was concluded that a significant fall in serum albumin occurred in the first week after surgery in all animals, but profile analysis and overall levels were not influenced by the presence of a brain lesion.

Endocrinology

Plasma cyclic AMP (cAMP) (Table 18)

(comparison between animals 01-08 and 09-22)
Weeks 0, 2 and 4 were used for comparative purposes. The F-test was performed to determine differences in profile analysis. No significant difference was found (F_2; 14; 0.05 = 3.74). The overall responses did not differ (F_1; 15; 0.05 = 4.54). However, a significant decrease occurred from week 2 to week 4 when the values were studied as a whole group (01-22) (F_2; 14; 0.05 = 3.74) (vector of test = -3.20616 is significant).

It was concluded that a significant fall in plasma cAMP levels occurred between weeks 2 and 4 in all animals, but profile analysis and overall levels were not influenced by the presence of a brain lesion.

Serum cortisol (Table 19)

(comparison between animals 01-08 and 09-22).
The method of assay did not allow for values less than 27.6. Therefore, on occasions when such low values were reached, random values between 15 and 27 were inserted in order to perform statistical analysis. Weeks 0, 2 and 4 were chosen for comparative purposes.

The F-test was performed to determine differences in profile analysis. No significant difference was found (F_2; 14; 0.05 = 3.74). The overall responses did not differ (F_1; 15; 0.05 = 4.54), and any changes in value did not reach significance (F_2; 14; 0.05 = 3.74).

It was concluded that serum cotisol levels remained essentially unaltered throughout the study, and were not influenced by the presence of a brain lesion.

Serum Vitamin D (25 hydroxycholecalciferol) (Table 20)

A pilot study of 25 OH Vit D (an active metabolite involved in fracture healing) was performed. Animals were selected at random from the two groups (01-08 and 09-22) (See p 26).

Because no clear pattern emerged from this initial study, no further analyses were performed, and no statistical assessment was carried out.

Serum Thyroxine (Table 21)

(comparison between animals 01-08 and 09-22). Weeks 0 and 4 were chosen for compartive purposes (See p 44). The F test was performed to determine differences in profile analysis. No significant difference was found (F_1; 9; 0.05 = 5.12). The overall responses did not differ (F_1; 9; 0.05 = 5.12), and any changes in value did not reach significance (F_1; 9; 0.05 = 5.12).

It was concluded that serum thyroxine levels remained essentially unaltered throughout the study (at least between weeks 0 and 4), and were not influenced by the presence of a brain lesion.

SERUM CALCIUM

TABLE 14 SERUM CALCIUM (mmol/l)

CAT NO.	WEEK 0	1	2	3	4	5	6	7	8	WEEKS
01	2.24	2.43		2.43	2.43					
03	2.15	2.21		2.18	2.56	2.19	2.06	2.07	2.27	
05	2.40	2.42	2.95		2.35	2.33				
06	2.42	2.28	2.68		2.30	2.11				
07	2.63	2.54	2.73		2.39	2.21	2.18	2.35		
08	2.69	3.12		2.32	2.24		2.40			
09	2.21	2.31	2.10	2.45	2.11	2.26	2.32			
10	2.40	2.45	2.45	2.25	2.27	2.43	2.38			
12	2.53	2.48	2.37	2.55	2.30	2.56	3.01			
13	2.51	2.52	2.68	2.66	2.53	2.52				
14	2.32	2.27	2.14	2.18	2.28	2.24	3.07			
16	2.15	2.16	2.29	2.41	2.32	2.26	2.42			
17	2.26	2.19	2.25	2.39	2.16	2.30	2.25	2.31		
18	2.13	2.31	2.36	2.30	2.08	2.28	2.44	2.23		
20	2.73	2.60	2.75	2.63	2.64	2.61	3.41			
21	2.39	2.40	2.30	2.39	2.19	2.42	2.87			
22	2.26	2.26	2.36	2.26	2.25	2.27	2.30	2.16		

SERUM PHOSPHATE

TABLE 15 SERUM PHOSPHATE (mmol/l)

CAT NO.	0	1	2	3	4	5	6	7	8	WEEKS
01	1.40	1.60		1.81	1.49					
03	2.00	1.66		1.74	3.54	2.59	1.73	1.83	2.23	
05	2.14	1.62	1.80		1.89	1.51				
06	2.20	1.66	1.50		1.99	2.27				
07	2.52	1.71	1.97		1.79	1.33	2.33	3.37		
08	1.77	2.24		1.56	1.64		1.62			
09	1.99	1.67	1.15	1.47	1.49	1.86	2.14			
10	2.61	2.27	2.19	2.04	1.69	2.80	1.81			
12	2.24	1.98	2.20	1.97	1.88	2.11	2.70			
13	2.80	2.42	3.06	2.39	2.17	2.24				
14	3.11	1.82	1.92	1.72	1.69	1.54	1.98			
16	2.04	1.64	1.59	2.02	2.00	1.73	1.73			
17	1.72	1.93	1.99	1.68	1.75	1.41	2.10	1.42		
18	2.46	1.87	2.46	2.08	1.68	1.94	1.98	1.61		
20	3.63	2.16	3.48	2.70	2.41	2.32	3.00			
21	1.81	1.70	2.24	1.67	1.63	1.79	1.92			
22	1.35	1.71	2.11	1.75	2.13	1.92	1.81	2.00		

SERUM ALKALINE PHOSPHATASE

TABLE 16 SERUM ALKALINE PHOSPHATASE (U/litre)

CAT NO.	0	1	2	3	4	5	6	7	8	WEEKS
01	36	89		45	59					
03	61	54		61	98	76	67	87	55	
05	1	56	40		51	39				
06	47	48	29		36	39				
07	26	27	14		23	17	29	25		
08	0			13	3	4	13			
09	11	23	35	36	23	46	31			
10	9		11	13	17	13	21			
12		8	5	38	41	26	49			
13	77	43	64	91	90	132				
14	19	16	15	38	34	49	80			
16		7	5	42	20	3	28			
17	51	20	20	40	24	37	51	55		
18	63	53	37	28	35	46	36	48		
20	217	77	82	105	242	262	401			X
21	46	7	15	28	21	31	38			
22	94	17	18	22	17	10	19	18		

X younger animal
(epiphyses almost closed)

SERUM ALBUMIN

TABLE 17 SERUM ALBUMIN (g/l)

CAT NO.	0	1	2	3	4	5	6	7	8	WEEKS
01	28	29		27	27					
03	24	24		23	30	25	25	23	25	
05	30	28	34		28	29				
06	28	25	28		25	26				
07	33	33	33		28	27	30	29		
08	32	31		25	24	25	24			
09	27	24	25	26	27	25	26			
10	30	26	26	26	26	27	28			
12	32	28	26	27	28	27	29			
13	28	27	28	29	33	28				
14	22	19	17	20	25	24	28			
16	25	23	25	28	29	29	26			
17	26	25	23	23	22	24	25	23		
18	23	23	22	23	22	23	28	25		
20	27	26	25	24	26	27	32			
21	27	26	23	24	24	25	26			
22	26	24	24	23	23	21	23	21		

SERUM CORTISOL

TABLE 18

SERUM CORTISOL (mmol/l)

CAT NO.	0	1	2	3	4	5	6	7	8	WEEKS
01	55		149		97					
03	120		53		96		111			
05	195		173		171					
06	157		48		88		79			
07	256		107		82		85			
08	94		72		<27.6* (15)		69			
09	216		51		32		47			
10	100		191		193		111			
12	145		36		133		230			
13	249		178		91					
14	66		<27.6* (20)		<27.6* (17)		76			
16	111		42		33		34			
17	58		<27.6* (23)		<27.6* (18)		<27.6* (26)			
18	101		162		71		102			
20	105		62		38		126			
21	42		39		95		51			
22	75		29		<27.6* (27)		<27.6* (15)			

X 27.6 = lowest assay
Take rhandom numbers
between 15 and 27 - shown in
brackets

PLASMA CYCLIC AMP (cAMP)

TABLE 19

PLASMA CYCLIC AMP (cAMP) (fentomoles per tube *)

CAT NO.	0	1	2	3	4	5	6	7	8	WEEKS
01	1876		2879		3306					
03	1477		1075		629		2528			
05	5485		2115		1480					
06	5084		901		4265		2772			
07	4811		2087		2333		6332			
08	3443		4185		2265		7912			
09	1601		972		942		3132			
10	10964		7536		4727		3437			
12	2281		2229		4172		3279			
13	2186		2864		2395					
14	2911		2897		3866		2992			
16	6945		3606		4371		3660			
17	3454		2218		343		1641			
18	3517		6267		324		3996			
20	5749		4454		297		5267			
21	1705		2592		508		1934			
22	4741		6371		273		3531			

* due to difficulties with assay, values were expressed only as fentomoles per tube, each tube containing 300 microlitres of plasma.

(see p 43)

TABLE 20

SERUM 25 OH VIT D (pg/ml)

CAT. NO	DAY O	4 WEEKS
03	19.1	21.6
08	41.1	41.6
09	37.8	34.4
13	25.5	28.6
20	40.7	44.1
22	39.6	38.1

TABLE 21

RESULTS T_4 LEVELS

Animal	Results T4 Day 0	picomoles / litre 4 weeks
01	16.8	23.7
03	19.8	23.7
05	23.7	27.0
06	25.2	24.2
07	24.1	21.2
12	29.9	29.3
14	19.1	24.3
16	14.7	14.1
17	15.9	15.9
18	11.4	19.8
21	14.5	24.5

DISCUSSION

DISCUSSION

In the course of the last 80 years a great deal of evidence has emerged of a link between neural injury and osteogenesis. Numerous reports exist of rapid and abundant fracture healing in patients with head injuries. There, to a large extent, the matter has rested. There have been no real attempts at quantifying the fracture healing response, or the severity of head injury.

Therefore, an initial study was designed (Section A) to address these issues. Only fractures managed non-operatively were studied, partly because these constituted an overwhelming majority reviewed by the author at that time, and partly because it was felt that operative fixation may contribute to new bone formation via locally released morphogens (Urist et al 1978).

In the same study, an attempt was made to determine the nature of the healing mass around fractures in association with neural injury. "Heterotopic ossification" is the term used by Garland et al (1980) to describe the periarticular ossification which occurs spontaneously in some of these patients, and the same term is used by Garland and Miller (1984) to describe the nature of the fracture healing in such patients. Many other terms have been applied to this pattern of fracture healing, including "hyperplastic callus" (Glenn, Miner and Peltier, 1973), "heterotopic bone" (Garland and Rhoades, 1978), "myositis ossificans" (Bellamy and Brower, 1974), "ossifying haematoma" and "calcifying haematoma" (Kernohan et al 1984).

What emerged from this initial study was that long bone fractures in patients with severe head injuries do indeed heal with greater amounts of callus/new bone, and more rapidly than controls. Radiological and histological review revealed that the material produced was bone, and that it resembled "myositis ossificans" or "heterotopic bone" in that it tended to be mature at its' periphery (Heffner 1984). This is unlike the normal fracture healing response as described by Peacock (1984). Therefore, the term "callus" may not always be appropriate in these circumstances.

Of course many aspects of this first study were inexact, but it was felt that a framework had been established for further work.

In Section B, the issue was studied in reverse. Not all patients with neural injury demonstrate very large amounts of callus/new bone around fractures. Indeed, some heal their fractures in a predictable and unspectacular fashion. Some, however, lay down massive amounts of new bone. These patients, it was thought, might provide further clues on this subject. Detailed neurological assessment of 10 such patients revealed the common denominator of spasticity in the limb or limbs involved in 8.

Needless to say, this finding may be entirely circumstantial. Yet, there have been few such attempts at detailed neurological assessment in such cases reported in the literature, perhaps due to the tendency of orthopaedic surgeons to concentrate on the problems relating to bone and joint. What was interesting, particularly in the light of the findings in Section A, was the tendency of some of these patients to form new bone along tissue planes distant from the fracture site, and in some cases quite remote from the fracture itself. Once again, this made the term "fracture callus" seem inappropriate.

In Section C, advantage was taken of the large numbers of patients with late effects of poliomyelitis available to the author for review. Bayley (1979) and Sevitt (1981), following extensive reviews of the literature, both included poliomyelitis among factors which encourage osteogenesis. In fact, few reports have appeared. Drehmann (1927) was first to record a possible correlation, followed by Costello and Brown (1951), Hess (1951), Hansson and Austlid (1955), and Stoikovic, Bonfiglio and Paul (1955). All these reports relate to heterotopic ossification. In fact, only one report (Robin 1966) justifies the inclusion of this condition in the list of neural conditions which may encourage fracture union, and even then only on tenuous grounds. Robin states that such fractures heal with "surprising rapidity", implying that one might expect poor fracture healing potential.

The review of cases of poliomyelitis in Durban demonstrated no increased osteogenic capacity, either in relation to heterotopic new bone formation or fracture/osteotomy healing. Large joints subjected to surgery might have been expected to reveal any tendency to form new bone, but no such cases occurred. In fact, joints tended to remain mobile within a rstricted range. The inflammatory features of heterotopic new bone formation, which may mimic acute arthritis (Goldberg, 1977) were not seen, nor the subsequent ankylosis.

Of course, comparison with a control group might have provided a more conclusive assessment of fracture healing. This proved impossible, however, there being no real comparison between the low-velocity spiral fractures generally associated with poliomyelitis, and limb fractures in the general population.

An impression was gained that stimulation of osteogenesis in limbs affected by poliomyelitis must be extremely rare. Stoikovic, Bonfiglio and Paul (1955), reported an incidence of 0.3% of heterotopic ossification in affected limbs. This contrasts with the situation of traumatic paraplegia or quadriplegia, where the incidence is generally over 20% (Connor, 1983). Indeed, as suggested by Bannister (1980), some diagnostic confusion may have existed in earlier years between poliomyelitis and tuberculous meningitis. The latter was a potent cause of spasticity, and the incidence of heterotopic ossification in one series (Lorber 1953) was 50%.

The findings in these first three studies influenced the design of an animal experiment (Section D). Little basic experimental work has been performed on this subject (See p 13). Herold, Tadmor and Hurvitz (1970) studied 64 adult female guinea pigs, subjecting them to random brain injuries and foreleg fractures, and found a significantly decreased time to first appearance of callus and closing of bony defects compared with controls. In fact, several processes were being observed; the primary callus response and the subsequent healing due to medullary and bridging callus (McKibbin, 1978). All appeared to be stimulated by cranial injury, but the reasons for this were not elucidated. Cunningham et al (1971) found the rate of healing of fibular fractures in rats to be decreased after sciatic nerve section, but this finding was not confirmed by Frymoyer and Pope (1977), who found that callus formation was augmented and fracture healing faster in denervated limbs in experimental rats. Izumi (1983) found no significant difference in ectopic bone formation between paraplegic and non-paraplegic rabbits, and ascribed the endochondral ossification observed in paraplegic rabbits to poor oxygenation in affected limbs.

Experimental work to date has been largely non-quantitative, and little attention has been paid to biochemical and endocrine influences on fracture healing in association with neural injury. In Section D, an attempt was made to address these issues.

A review of the literature reveals little support for biochemical factors of importance. Connective tissue behaviour is influenced by low tissue oxygen tension (Bassett and Hermann 1961, Lee 1962 , Bour et al 1966),endochondral ossification tending to predominate and to be slow. Increased peripheral resistance in association with contractures may exacerbate the depression of tissue oxygen levels (Yonetani 1977).

Stone, Newman and Mukherjee (1987) performed magnetic resonance imaging of healing fractures in head-injured patients, and ascribed the augmented calcium salt deposition to the respiratory alkalosis of coma. This is an interesting observation, but it implies disturbance of respiration in all cases of augmented osteogenesis following nerve injury, and does not explain why cord injuries may be implicated.

Changes in serum calcium levels themselves following acute craniocerebral injury have been observed (Myshkin and Chuenkov 1963). However, Heuwinkel (1979) was unable to demonstrate significant biochemical shifts adjacent to the fracture site in head-injured patients.

Rosner, Newsome and Becker (1984) observed hyperglycaemia and raised catecholamine levels after head injury in cats, but the significance of this in relation to fracture healing is unclear. The observation (Chantraine and Minaire, 1981) of raised hydroxyproline levels in urine in association with heterotopic ossification

reflects increased bone turnover, and may yet prove a useful diagnostic tool.

However, no clear evidence emerges from the literature of an important systemic biochemical effect to explain augmented osteogenesis in association with neural injury.

The only biochemical effect I report (Section D) was a fall in serum albumin levels during the first week after surgery, but this occurred equally in all animals, and was not related to neural injury. It is likely to have been a secondary phenomenon.

Theories abound regarding possible endocrine influence on ossification. Certain hormones and vitamins influence fracture healing enormously (Sevitt 1981) and some vitamins (such as vitamin C) are essential for healing. By contrast, hypervitaminosis A may lead to a predisposition to fractures.

It has been suggested that thyrocalcitonin may boost fracture healing (Ewald and Tachdjian 1967) but evidence is uncertain, and the effect is not necessarily confirmed by Schatzker et al (1979) whose study dealt specifically with fractures in Paget's disease of bone.

Normal Vitamin D and calcium levels are necessary for bone regeneration, but further augmentation with high levels of Vitamin D does not improve the fracture healing outcome (Lane and Werntz, 1987).

Increased levels of parathyroid hormone may lead to delayed union, as may raised levels of ACTH and cortisol (Friedenberg and Brighton, 1987).

Several studies indicate a possible role for growth hormone (GH). Zadek and Robinson (1961) found that large defects in dogs' bones healed when the animals were given GH supplements. Similarly, Ray (1973) found delayed healing of bone defects in rats subjected to hypophysectomy, which was reversed with growth hormone. Tylkowski, Wegeman and Ray (1976), observed that growth hormone deficiency retards bone repair. It is known that somatomedin and growth hormone increase collagen synthesis in vitro (Canalis et al, 1977), but no observation has been made of an effect of growth hormone in relation to neural injury. An interesting observation by Ashton and Dekel (1983) that fracture healing in the somatomedin deficient Snell dwarf mouse is normal, throws further doubt on the possibility that any of the known systemic growth factors may be implicated in augmented fracture healing following neural injury.

Similarly, it is known that tri-iodothyronine and thyroxine are important for normal bone growth (Sevitt, 1981), but no evidence has emerged linking these substances to fracture healing phenomena in association with neural injury. In the same way, the observation that active metabolites of Vitamin D are involved in fracture repair (Lidor et al, 1987) is interesting, but sheds no further light on the mysteries of this subject.

Search for a mediator of bone induction has been more successful in relation to events at a local level. The description of a bone morphogenic protein (Urist, 1965; Urist et al, 1967; Urist, 1972; Urist et al, 1978; Urist et al 1982) has been a fascinating development, but it is not known whether neural injury may encourage the production and activity of this substance.

Similarly, prostaglandin activity, particularly sub-types of E and F, may be important in promoting bone healing (Ro, Sudman and Mortin, 1976; Chapman, 1987) but relation to neural injury has not been established.

The prostaglandins may be involved in the "booster" phase observed in fractures subjected to late internal fixation, a phenomenon observed clinically (Smith, 1959; Smith, 1964; Smith 1974), and experimentally (Elsasser et al, 1975), and not unlike that observed in head-injured patients with fractures.

I report only one endocrine effect of note (Section D); a fall in cyclic AMP levels between weeks 2 and 4 in experimental animals. Once again, however, this occurred equally in all animals and was not influenced by neural injury. Moreover, the significance is highly uncertain, given the difficulties encountered with cAMP analysis (See p 43).

Fracture healing behaviour was the most interesting aspect of the animal study. It was not possible to confirm the finding of an accelerated primary callus response seen by Herold, Tadmor and Hurvitz (1967). Certain observations were subjective in nature, most notably union time (See p 37). However, a certain trend did appear to emerge (see Figs 26- 47, p 81-91), union generally appearing to be slightly faster on the right (spastic) side in brain-lesioned animals. Radiological assessment of new bone formation (the fracture healing response) was supplemented by weighing of fibular specimens on completion of the study. The healing area was generally found to be greater in size and mass on the right (spastic) side in brain-lesioned animals.

There are several possible explanations for this. Simple observer error would have a profound effect in so small a series, although mass measurements were carried out with maximum objectivity.

It is possible that the author unwittingly stimulated fracture healing in right-sided fractures by showing greater interest in their behaviour, and subjecting them to more regular palpation and movement. In addition, it is possible that were the series to be repeated, the trend might be for left-sided fractures to heal more readily, although statistical analysis of mass measurements would tend not to support this suggestion.

Histomorphometric analysis indicated that the bulk of the healing area beneath the periosteum was bone. A classical appearance of bridging callus with a front of endochondral ossification adjacent to the fracture line was seen. Assessment of the fracture gap initially (incorrectly) included an area extending out as far as the periosteum. Interestingly, this appeared to show more fibrous tissue on the right side, inviting the suggestion that more movement occurred at the fracture site in these spastic limbs. However, when the analysis was restricted to the area between the bone ends ("medullary callus") and this fibrous tissue was examined more closely, it was found to consist mainly of ossifying fibrovascular tissue (a normal constituent of medullary callus) (See Table 13 p 94). In the end, few real differences in fracture morphometry could be found when spastic and non-spastic limbs were compared.

Purely fibrous tissue is formed when gross interfragmentary movement occurs (Peacock, 1984), but very little of this was seen on either side. Endochondral ossification, of which slightly more was seen on the left, occurs more frequently with low tissue pO_2 (Lee 1962, McKibbin 1978).

Thus, enhanced bridging callus and satisfactory medullary callus formation was seen in spastic limbs. The principal stimulus to the former is movement (Schenk 1987), and clinical work (Sarmiento 1974, Sarmiento et al 1974, Sarmiento 1981) and experimental studies (Hutzchenreuter, Perren and Steinemann 1969) have emphasised this.

The precise degrees of tolerance of interfragmentary motion of bridging and medullary callus are not known. It may be postulated that micromovement due to spasticity caused the enhanced bridging callus observed in spastic limbs in this study. Since such interfragmentary motion was not gross in nature, medullary callus production was allowed to proceed normally.

Of course, mechanical factors may not be the only ones of importance. If one assumes, for the moment, that neurogenic heterotopic ossification and abundant new bone around fractures in association with neural injury are similar or related processes, two observations are of interest. Connor (1983) stated that neurogenic heterotopic ossification has not been seen above the level of the paralysis. Garland, Blum and Waters (1980) suggested spasticity may be important in the aetiology. By inference, both works point to the peripheral effects of neural injury, at least in respect of spontaneous ossification.

As well as increasing muscle blood supply and regional pO_2, this neural stimulus may cause the local release of osteogenic substances including morphogens, growth factors and prostaglandins. It is in this area that the answers may lie.

CONCLUSIONS / INFERENCES

CONCLUSIONS/INFERENCES

In conclusion, it seems likely that head injury does indeed augment and accelerate fracture healing (Section A). This healing is not typical, since mature bone frequently forms distant from the fracture site (Section A and B). Spasticity may be important in producing these effects (Section B), which were not seen in relation to fractures occurring some time after lower motor neuron lesions due to poliomyelitis (Section C).

In the animal study (Section D) bone healing appeared to be enhanced in spastic limbs. No general biochemical or endocrine factors were found. Since animals were used as their own controls, the local effects of the neural injury appeared to be most important. Whether these effects were mechanical (causing controlled micromovement), biochemical (causing raised tissue pO_2), or endocrine (causing local release of osteogenic substances), or a combination of these, must form the basis of further study.

REFERENCES

REFERENCES

1. **Abramson AS.**
Bone disturbances in injuries to the spinal cord and cauda equina (paraplegia).
J. Bone and Joint Surg (Am) 1948; 30-A: 982-987.

2. **Abramson DJ, and Kamberg S.**
Spondylitis, pathological ossification and calcification associated with spinal cord injury.
J. Bone Joint Surg (Am) 1949; 31-A: 275-282.

3. **Apley AG, and Solomon L.**
Apley's System of Orthopaedics and Fractures.
6th Ed London : Butterworth Scientific, 1982.

4. **Armstrong-Ressy CT, Weiss AA, and Ebel A.**
Results of surgical treatment of extra-osseous ossification in paraplegia.
New York State J Med 1959; 59: 2548-2553.

5. **Ashton IK, and Dekel S.**
Fracture repair in the Snell dwarf mouse.
Br J Exp. Pathol 1983; 64: 479-86.

6. **Bajd T, and Bowman B.**
Testing and modelling of spasticity.
J Biomed Eng. 1982; 4: 90-96.

7. **Bannister SIR R. Ed.**
Brain's Clinical Neurology.
5th Ed. Oxford: Oxford University Press, 1980.

8. **Bassett CAL, and Hermann I.**
Influence of oxygen concentration and mechanical factors on differentiation of connective tissue in vitro.
Nature 1961; 190: 460-461.

9. **Bayley, SJ.**
Funnybones: A review of the problem of heterotopic bone formation.
Orthop. Rev. 1979; 8: 113-120.

10. **Bellamy R, and Brower TD.**
Management of skeletal trauma in the patient with head injury.
J. Trauma 1974; 14: 1021-1028.

11. **Benassy J, Mazabraud A, and Diverres J.**
L'osteogenes neurogene.
Rev chir. orthop 1963; 49: 95-116.

12. **Blane CE, and Perkash I.**
True heterotopic bone in the paralysed patient.
Skeletal Radio 1981; 7: 21-25.

13. **Boskey Al, and Posner AS.**
Bone structure, composition and mineralisation.
Orthop. Clin North Am 1984; 15: 597-612.

14. **Bour H, Tutin M, Pasquier P, and Quevanvilliers J.**
Les paraosteoarthropathies au decours des comas oxycarbónes graves.
Sem Hop Paris 1966; 42: 1912-1916.

15. **Brailsford JF.**
Changes in bones, joints and soft tissues associated with disease or injury of the central nervous system.
Br J Radiol 1946; 14: 320-328.

16. **Brooker AF, Bowerman JW, Robinson RA et al.**
Ectopic ossification following total hip replacement: incidence and a method of classification.
J Bone Joint Surg 1973; 55A: 1629-1632.

17. **Calandriello B.**
Callus formation in severe brain injuries.
Bull Hosp Jt Dis 1964; 25: 170-175.

18. **Campanacci M, and Vellani G.**
Iperplasia del callo osseo in frattura degli arti associate a gravi traumi cranici.

Chirurgia degli organi di movimento 1969; 57: 369-382.

19. **Canalis EM, Hintz RL, Dietrich JW et al.**
Effect of somatomedin and growth hormone on bone collagen synthesis in vitro.

Metabolism 1977; 26: 1079-1087.

20. **Carpenter MB, and Whittier JR.**
Study of methods for producing experimental lesions of the central nervous system with special references to stereotaxic technique.

J. Comp Neurol 1952; 96: 73-132.

21. **Chantraine A, and Minaire P.**
Paro-osteo-arthropathies. A new theory and mode of treatment.

Scand J. Rehabil Med. 1981; 13: 31-37.

22. **Chapman MW.**
Prostaglandins and Secondary Injury Phenomenon.

In: Fracture Healing: JM Lane Ed;
York Etc; Churchill-Livingstone, 1987.

23. **Chase LR, and Aurbach GD.**
The effect of parathyroid hormone on the concentration of adenosine 3,5 - monophosphate in skeletal tissue in vitro.
J Biol Chem 1970; 245: 1520-1526.

24. **Comar AE, Hutchinson RH, and Bors E.**
Extremity fractures of patients with spinal cord injuries.
Amer J Surg 1962: 103: 732-739.

25. **Connor JM.**
Soft Tissue Ossification.
Berlin Etc; Springer-Verlag, 1983.

26. **Costello FV, and Brown A.**
Myositis ossificans complicating anterior poliomyelitis.
J Bone Joint Surg 1951; 33B: 594-597.

27. **Cunningham AR, Marquez-Monter H, De Guerrero LM et al.**
Study of bone callus in denervated extremities.
Archivos de Investigacion Medica 1971: 2: 15-24.

28. **Damanski M.**
Heterotopic ossification in paraplegia.
A clinical study.
J Bone Joint Surg 1961: 43-B: 286-299.

29. **Dėjerine MME, and Ceillier A.**
Para-osteoarthropathies des paraplėgiques par lesions mėdullaries (ėtudes clinique et radiographique).

Ann Med 1918; 5: 497-535.

30. **Dėjerine MME, Ceillier A, and Dėjerine YV.**
Para-osteoarthropathies des paraplėgiques par lesions medullaries. Etudes anatomique et histologique.

Rev. Neurol 1919; 26: 399-407.

31. **Drehmann G.**
Myositis ossificans circumscripta neurotica in Verlaufe der Poliomyelitis anterior acuta.

Zentralbl Gesamte Neurol Psychiat 1927; 48: 686.

32. **Eichenholtz SN.**
Management of long-bone fractures in paraplegic patients.

J Bone Joint Surg 1963: 45-A: 299-310.

33. **Elias H, Hennig A, and Schwartz DE.**
Stereology: Applications to biomedical research.

Phys. Rev. 1971; 51(1): 158-200.

34. **Elsasser JC, Moyer CF, Lesker PA, and Simmons DJ.**
Improved healing of experimental long bone fractures in rabbits by delayed internal fixation.

J. Trauma 1975: 15: 869-876.

35. **Ewald F, and Tachdjian MO.**
The effect of thyrocalcitonin on fractured humeri.

Sirg Gynaecol Obstet 1967; 125: 1075-1080.

36. **Freehaffer AA, Hazei CM, and Becker CL.**
Lower extremity fractures in patients with spinal cord injury.

Paraplegia 1981; 19: 367-372.

37. **Freehaffer AA, Yurick R, and Mast WA.**
Para-articular ossification in spinal cord injury.

Med. Services J 1966; 22: 471-478.

38. **Friedenberg ZB, and Brighton CT.**
Biophysical induction of fracture repair.

In: Fracture Healing: JM Lane Ed;
New York Etc; Churchill Livingstone, 1987.

39. **Fry K, Hoffer MM, and Brink J.**
Femoral shaft fractures in brain-injured children.

J. Trauma 1976; 16: 371-373.

40. **Frymoyer JW, and Pope MH.**
Fracture healing in the sciatically denervated rat.

J. Trauma 1977; 17: 355-361.

41. **Garland DE.**
Head injuries in adults.

In: Orthopaedic Rehabilitation: VL Nickel Ed; New York Etc; Churchill Livingstone, 1982.

42. **Garland DE, Blum CE, and Waters RL.**
Periarticular heterotopic ossification in head-injured adults - incidence and location.

J Bone Joint Surg 1980; 62-A: 1143-1146.

43. **Garland DE, and Miller G.**
Fractures and dislocations about the hip in head-injured adults.
Clin Orthop 1984; 186: 154-158.

44. **Garland DE, Razza B, and Waters RL.**
Forceful joint manipulation in head-injured adults with heterotopic ossification.

Clin Orthop 1982; 169: 133-138.

45. **Garland DE, and Rhoades ME.**
Orthopaedic management of brain-injured adults Part II.

Clin Orthop 1978; 131: 111-122.

46. **Garland DE, Rothi B, and Waters RL.**
Femoral fractures in head-injured adults.
Clin Orthop 1982; 166: 219-225.

47. **Garland DE, and Toder L.**
Fractures of the tibial diaphysis in adults with head injuries.
Clin Orthop 1980; 150: 198-202.

48. **Gibson JM.**
Multiple injuries: the management of the patient with a fractured femur and a head injury.
J Bone Joint Surg 1960; 42-B: 425-431.

49. **Glenn JN, Miner ME, and Peltier LF.**
The treatment of fractures of the femur in patients with head injuries.
J Trauma 1973; 13: 958-961.

50. **Goldberg MA.**
Heterotopic ossification mimicking acute arthritis after neurological catastrophes.
Arch Intern Med 1977; 137: 619-621.

51. **Gunn DR, and Young WB.**
Myositis ossificans as a complication of tetanus.
J Bone Joint Surg 1959; 41-B: 535-540.

52. **Haddad JG, and Cheyne KJ.**
Competitive protein-binding assay for 25 - hydroxycholecalciferol.

J Clin Endocrinol Metab 1971; 33: 992-5.

53. **Hagel K, Ulmar G, Bockenheimer S, and Zimmerman H.**

Myositis ossificans craniocerebral trauma. Nervenarzt 1983; 54(2); 92-96.

54. **Hannson KG, and Austlid O.**
Myositis ossificans in poliomyelitis. Two case reports.

Arch Phys Med 1955; 36: 506-509.

55. **Hardy AG, and Dickson JW.**
Pathological ossification in traumatic paraplegia.

J Bone Joint Surg 1963; 45-B: 76-87.

56. **Hassard GH.**
Heterotopic bone formation about the hip and unilateral decubitus ulcers in spinal cord injury.

Arch Phys Med Rehabil 1975; 56: 355-358.

57. **Heffner RR Jr (ed).**
Muscle Pathology.

New York: Churchill Livingstone, 1984.

58. **Heilbrun N, and Kuhn WG Jr.**
Erosive bone lesions and soft tissue ossifications associated with spinal cord injuries (paraplegia).
Radiology 1947; 48: 579-593.

59. **Hernandez AM, Forner JV, de la Fuente T et al.**
The para-articular ossifications in our paraplegics and tetraplegics. A survey of 704 patients.
Paraplegia 1978; 16: 272-275.

60. **Herold HZ, Tadmor A, and Hurvitz A.**
Callus formation after acute brain damage.
Israel J Med Sci 1970; 6(1): 163-166.

61. **Hess WE.**
Myositis ossificans occurring in poliomyelitis; report of a case.
Arch Neurol Psychiatr 1951; 66: 606-609.

62. **Heuwinkel R.**
Zur Atiologie und Pathogenise der Knochenneubildungen bei Hirnverlentzten und Paraplegikem
1. Das lokale milreu - untersuchungen un Frakturhämatom.
Unafallheilkunde 1979; 82: 262-268 (English abstract).

63. **Hoffer MM, Garrett A, Brink J et al.**
The orthopaedic management of brain-injured children.
J Bone Joint Surg 1971; 53-A: 567-577.

64. **Hossack DW, and King A.**
Neurogenic heterotopic ossification.
Med J Aust 1967; 1: 326-328.

65. **Hsu JD, Sakimura I, and Stauffer ES.**
Heterotopic ossification around the hip joint in spinal cord injured patients.
Clin Orthop 1975; 112: 165-169.

66. **Hunter T, Dubo HIC, Hildahl CR et al.**
Histocompatibility antigens in patients with spinal cord injury or cerebral damage complicated by heterotopic ossification.
Rheumatol Rehabil 1980; 19: 97-99.

67. **Hutzchenreuter P, Perren SM, and Steinemann S.**
Some effects of rigidity of internal fixation on the healing pattern of osteotomies.
Injury 1969; 1: 77-81.

68. **Irving J, and Le Brun H.**
Myositis ossificans in hemiplegia.
J Bone Joint Surg 1954; 36-B: 440-441.

69. **Irving MK, and Irving PM.**
Associated injuries in head trauma patients.
J Trauma 1967; 7: 500-511.

70. **Izumi K.**
Study of ectopic bone formation in experimental spinal cord injured rabbits.
Paraplegic 1983; 21: 351-363.

71. **Jacobs P.**
Reversible soft tissue ossification following measles encephalomyelitis.
Arch Dis Child 1962; 37: 90-92.

72. **Jastrzebski T, Opolski M, and Podlewski J.**
Healing of bone fractures in patients with cerebral injuries.
Chir Narzadow Ruchu Ortop Pol 1977; 42 (3): 255-258.

73. **Kane CA.**
Introductory remarks.
Clin Pharm Ther 1964; 5: 803-804.

74. **Kernohan J, Dakin PK, Beacon JB, and Bayley JIL.**
Treatment of major skeletal problems in patients with severe head injury.
Br Med J 1984; 288: 1822-1823.

75. **Knoch HG, Diettrich H, and Knoch H.**
Craniocerebral injury and bone-fracture healing.
Zentral bl Chir 1973; 98 (14): 505-509.

76. **Lane JM, and Werntz JR.**
Biology of fracture healing.
In: Fracture Healing; J.M. Lane Ed, New York Etc, Churchill Livingstone, 1987.

77. **Larson JM, Michalski JP, Collacott EA et al.**
Increased prevalence of HLA B27 in patients with ectopic ossification following traumatic cord injury.
Rheumatol Rehabil 1981; 20: 193-197.

78. **Lee WK.**
Studies on heterotopic ossification in paraplegics.
J Jap Orthop Ass 1962; 37: 1-25.

79. **Lidor C, Dekel S, Hallel T, and Edelstein S.**
Levels of active metabolites of Vitamin D3 in the callus of fracture repair in chicks.
J Bone Joint Surg 1987; 69-B: 132-136.

80. **Lorber J.**
Ectopic ossification in tuberculous meningitis.
Arch Dis Child 1953; 28: 98-103.

81. **Lynch C, Pont A, and Weingarden SI.**
Heterotopic ossification in the hand of a patient with spinal cord injury.
Arch Phys Med Rehabil 1981; 62: 291-293.

82. **Mahmud HR, Rumpf P, Saier R and Ulrich B.**
Myositis ossificans following head injury (author's translation).
Langenbecks Arch Chir 1978; 346 (4); 265-271.

83. **McKibbin B.**
The biology of fracture healing in long bones.
J Bone Joint Surg 1978; 60-B: 150-162.

84. **McKusick VA.**
Foreword.
In: Soft Tissue Ossification. Connor JM. Berlin Etc. Springer-Verlag, 1983.

85. **McMaster WC, and Stauffer ES.**
The management of long bone fracture in the spinal cord injured patient.
Clin Orthop 1975; 112: 44-52.

86. **Meacham WF.**
The management of head injuries complicated by extracranial trauma.

In : Clinical Neurosurgery: Proceedings of the Congress of Neurological Surgeons, Miami, Florida, 1964: 161-170.

87. **Mendelson L, Grosswasser Z, Najenson T et al.**
Periarticular new bone formation in patients suffering from head injuries.

Scan J Rehabil Med 1975; 7: 141-145.

88. **Meyer P.**
Dystrophische Muskelverkalkung und Verknöchening (Myositis ossificans neurotica) und 'Kalkmetastosen' der Nieren nach Querschnittslasion des Rüchenmarks.

Bruns Beitr Klin Chir 1927; 138: 233-254.

89. **Mielants H, Vanhove E, De Neels J, and Veys E.**
Clinical survey and pathogenic approach to to para-articular ossifications in long-term coma.

Acta Orthop Scandinavica 1975; 46: 190-198-

90. **Miller ES, Neoptolemos JP, Aitkenhead AR, and Fossard DP.**
Management of severe head injuries in a non-neurosurgical trauma centre.
J Roy Coll Surg Ed 1985; 30 (2): 82-87.

91. **Miller LF, and O'Neill CJ.**
Myositis ossificans in paraplegics.
J Bone Joint Surg 1949; 31-A: 283-294.

92. **Minaire P, Betuel H, and Pilonchery G.**
Systemic HLS ches les blessés médullaires atteints de para-osteo arthropathies neurogènes.
Nouv Presse Med 1978; 7 (34): 3044.

93. **Money RA.**
Ectopic para-articular ossification after head injury.
Med J Aust 1972; 1: 125-127.

94. **Myshkin KI, and Chuenkov VF.**
Shifts in the blood serum calcium level following an acute cerebrocranial injury.
Vop Neirokhir 1963; 27: 26-28.

95. **Nicholas JJ.**
Ectopic bone formation in patients with spinal cord injury.
Arch Phys Med Rehabil 1973; 54: 354-359.

96. **Noh E, and Ouest O.**
Myositis ossificans following craniocerebral injuries.
Hefte Unfallkeilkd 1972; 111: 277-280.

97. **Peacock EE Jr.**
Wound Repair.
3rd Ed, Philadelphia etc, Saunders, 1984.

98. **Perkins R, and Skirving AP.**
Callus formation and the rate of healing of femoral fractures in patients with head injuries.
J Bone Joint Surg 1987; 69-B: 521-524.

99. **Radt P.**
Peri-articular ectopic ossification in hemiplegics.
Geriatrics 1970; 25: 142-157.

100. **Ray RD.**
The role of pituitary and thyroid in the healing of standard bone defects (Abstr).
J Bone Joint Surg 1973; 55-B: 442.

101. **Reichert A, and Schweikert CH.**
Fracture healing in craniocerebral injuries.

Hefte Unfallkeilkd 1967; 91: 250-252.

102. **Reinoso-Suarez F.**
Topographic Atlas of the Cat Brain - Topograpischer Him Atlas der Katze, fur experimental.

Physiologische untersuchungen
Damstadt: E Merck, 1961.

103. **Ro J, Sudman E, and Mortin PF.**
Effects of indomethacin on fracture healing in rats.

Acta Orthop Scand 1976; 47: 588-592.

104. **Roberts JB, and Pankratz DG.**
The surgical treatment of heterotopic ossification at the elbow following long-term coma.

J Bone Joint Surg 1979; 61-A: 760-763.

105. **Roberts PH.**
Heterotopic ossification complicating paralysis of intracranial origin.

J Bone Joint Surg 1968; 50-B: 70-77.

106. **Robin GC.**
Fractures in poliomyelitis in children.
J Bone Joint Surg 1966; 48-A: 1048-1054.

107. **Roche MB, and Jostes FA.**
Ectopic bone deposits: A paraplegic complication.
Am J Surg 1948; 75: 633-636.

108. **Rosner MJ, Newsome HH, and Becker DP.**
Mechanical brain injury: The sympathoadrenal response.
J Neurosurg 1984; 61 (1): 76-86.

109. **Rossier AB, Bussat PN, Infante F et al.**
Current fact on para-osteoarthropath (POA).
Paraplegia 1973; 11: 36-78.

110. **Sarmiento A.**
Functional bracing of tibial fractures.
Clin Orthop 1974; 105 (0): 202-219.

111. **Sarmiento A.**
Closed Functional Treatment of Fractures.
New York, Springer-Verlag, 1981.

112. **Sarmiento A, Latta L, Zilioli A, and Sinclair WF.**
The role of soft tissues in the stabilisation of tibial fractures.
Clin Orthop 1974; 105 (0): 116-129.

113. **Sazbon L, Najenson T, Tartakowski M et al.**
Widespread peri-articular new-bone formation in long-term comatose patients.
J Bone Joint Surg 1981; 63-B: 120-125.

114. **Schatzker J, Chapman M, Ha'Eri GB et al.**
The effect of calcitonin on fracture healing.
Clin Orthop 1979; 141: 303-306.

115. **Schenk RK.**
Cytodynamics and histodynamics of primary bone repair.
In: Fracture Healing, JM Lane Ed,
New York Etc, Churchill Livingstone, 1987.

116. **Scher AT.**
The incidence of ectopic bone formation in post-traumatic paraplegic patients of different racial groups.
Paraplegia 1976; 14: 202-206.

117. **Sevitt S.**
Bone Repair and Fracture Healing in Man.
Edinburgh Etc, Churchill Livingstone, 1981.

118. **Smith JEM.**
Internal fixation in the treatment of fractures of the radius and ulna in adults.
J Bone Joint Surg 1959; 41-B: 122-131.

119. **Smith JEM.**
The results of early and delayed internal fixation of fractures of the shaft of the femur.
J Bone Joint Surg 1964; 46-B: 28-31.

120. **Smith JEM.**
Results of early and delayed internal fixation for tibial shaft fractures. A review of 470 fractures.
J Bone Joint Surg 1974; 56-B: 469-477.

121. **Smith R.**
Head-injury, fracture healing and callus. (Editorial).
J Bone Joint Surg 1987; 69-B: 518-520.

122. **Soule AB Jr.**
Neurogenic ossifying fibromyopathies. A preliminary report.
J Neurosurg 1945; 2: 485-497.

123. **Spencer RF.**
The effect of head injury on fracture healing : a quantitative assessment.
J Bone Joint Surg 1987; 69-B: 525-528.

124. **Spencer RF, and Ganpath V.**
Heterotopic bone formation following cerebral cysticercosis.
SAMJ 1988; 74: 35-36.

125. **Stoikovic JP, Bonfiglio M, and Paul WD.**
Myositis ossificans complicating poliomyelitis.
Arch Phys Med 1955; 36: 236-243.

126. **Stone MH, Newman RJ, and Mukherjee SK.**
Accelerated fracture union in association with severe head injury.
J Bone Joint Surg 1987; 69-B: 493 (Abstr).

127. **Stover SL, Hataway CJ, and Zieger HE.**
Heterotopic ossification in spinal cord-injured patients.
Arch Phys Med Rehabil 1975; 56: 199-204.

128. **Sutherland EW, Robison GA, and Butcher RW.**
Some aspects of the biological role of adenosine 3', 5' - monophosphate (cyclic AMP).
Circulation 1968; 37: 279-306.

129. **Takada K.**
Clinical and experimental studies on ectopic ossification in the area of paralysis due to spinal injuries.
Kotsutaisya 1977; 10: 217-222.

130. **Tibone J, Sakimura L, Nickel VL, and Hsu JD.**
Heterotopic ossification around the hip in spinal cord-injured patients. A long-term follow up study.
J Bone Joint Surg 1978; 60-A: 769-775.

131. **Tsementzis SA.**
The effect of decerebrate rigidity on intracranial pressure in man and animals.
Ann Clin Res 1984; 16 Suppl 41: 1-91.

132. **Tylkowski CM, Wezeman FH, and Ray RR.**
Humoral effects on the morphology of bone defect healing.
Clin Orthop 1976; 115: 272-285.

133. **Urist MR.**
Bone formation by autoinduction.
Science 1965; 150: 893-899.

134. **Urist MR.**
Osteoinduction in undermineralised bone implants by chemical inhibitors of endogenous matrix enzymes.
Clin Orthop 1972; 87: 132-137.

135. **Urist MR, Lietze A, Mizutan H et al.**
A bovine low molecular weight bone morphogenic protein (BMP) fraction.
Clin Orthop 1982; 162: 219-232.

136. **Urist MR, Nakagawa M, Nakata N, and Nogami H.**
Experimental myositis ossificans : cartilage and bone formation in muscle in response to a diffusable bone matrix-derived morphogen.
Arch Pathol Lab Med 1978; 102: 312-316.

137. **Urist MR, Silverman BG, Buring K et al.**
The bone induction principle.
Clin Orthop 1967; 53: 243-283.

138. **Vogel T, Vliegen J, and Kelz T.**
Ossifying myositis in neurologic syndrome.
Nervenartz 1972; 43(7): 360-367.

139. **Wagner KR, Tornheim PA, and Eichhold MK.**
Acute changes in regional cerebral metabolite values following experimental blunt head trauma.
J Neurosurg 1985; 63(11): 88-96.

140. **Weiss GM, Fishman J, and Steiner E.**
Callus formation in cases of cerebral fat embolism. A contribution to the theory of neurogenic influence on osteogenesis.
Confin Neurol 1969; 31: 362-369.

141. **Weiss S, Grosswasser Z, Ohri A et al.**
Histocompatibility (HLA) antigens in heterotopic ossification associated with neurological injury.
H Rheumatol 1979; 6: 88-91.

142. **Weissman SL, and Khermosh O.**
Orthopaedic aspects in multiple injuries.
J Trauma 1970; 10 (5): 377-385.

143. **Wharton GW, and Morgan TH.**
Ankylosis in the paralysed patient.
J Bone Joint Surg 1970; 52-A: 105-112.

144. **Whittier JR, and Mettler FA.**
Studies on the subthalamus of the rhesus monkey.
II Hyperkinesia and other physiologic effects of subthalamic lesions with special reference to the subthalaamic nucleus of Luys.
J Comp Neur 1949; 90: 319-372.

145. **Wood D, and Hoffer MM.**
Tibial fractures in head-injured children.
J Trauma 1987; 27 (1): 65-68.

146. **Wray JB, and Davis CH.**
The management of skeletal fractures in the patient with a head injury.
South Med J 1960; 53: 748-753.

147. **Yonetani T.**
Studies of the circulatory behaviour in patients with chronic spinal injury by ultrasonic doppler method.
J Jap Orthop Ass 1977; 51: 277-289.

148. **Zadek RE, and Robinson RA.**
The effect of growth hormone on healing of an experimental long-bone defect.
J Bone Joint Surg 1961; 43-A: 1261 (Abstr).

APPENDIX

Only publications referred to in this thesis have been included in this section. This has been done with the permission of the Editor of the journals concerned.

APPENDIX 1

THE EFFECT OF HEAD INJURY ON FRACTURE HEALING

A QUANTITATIVE ASSESSMENT

R. F. SPENCER

From the King Edward VIII Hospital, Durban

Using a simple method of quantifying fracture healing, 53 patients who had limb fractures and also severe head injuries were studied; they were compared with 30 patients who had limb fractures but no head injury. Those with head injuries had a greater healing response and united more rapidly.

Radiological and histological analysis revealed that the terms "myositis ossificans" and "heterotopic bone" may be more appropriate than "fracture callus" to describe the healing response in these patients.

Patients with head injuries have frequently been observed to have an abundant healing response to fractures, leading to rapid union. The author, however, is not aware of any previous report quantifying either this response, or the severity of the head injury.

The material produced around fractures in patients with head injuries is frequently referred to as "callus", but this may not be the most appropriate term as ossification may occur spontaneously in these patients (Garland, Blum and Waters 1980).

The aim of this present study was to establish the quantity and nature of the fracture healing response in patients with precisely defined levels of head injury.

Table I. The 82 fractures sustained in 53 patients with head injuries

Tibia and fibula	20	Tibial plateau	2
Femur	15	Ankle	2
Humerus	12	Fibula	2
Pelvis	7	Foot	1
Clavicle	5	Olecranon	1
Radius/ulna	5	Scapula	1
Hand	4	Femoral condyle	1
Cervical spine	4		

PATIENTS AND METHODS

During a two-year period between October 1983 and October 1985, 366 patients with significant head injuries were admitted to King Edward VIII Hospital, Durban. Forty-five (12%) died as a result of their injuries. Fifty-three patients with severe head injuries and fractures of the limbs, spine or pelvis survived. Their head injuries were rated, in the first 48 hours, at 10 or less on the Glasgow coma scale. There were 47 males and six females with an age range of 4 to 67 years (mean 30 years). Motor vehicle accidents were the commonest cause of injury. A total of 82 fractures were sustained (Table I); 32 patients had two or more fractures (the tibia and fibula, and the radius and ulna each counted as only one fracture). Patients with fat embolism or suffering from alcohol withdrawal were excluded.

Most of the fractures were treated conservatively, but internal fixation was used for eight fractures, seven of which involved the femur. The head injuries also were mostly treated conservatively by observation and intracranial pressure monitoring, but in 10 patients burr holes were made or a craniotomy performed.

The factors assessed were the fracture healing response (see below), the time to clinical union (as defined by Apley and Solomon 1982), the cerebral CT scan findings, the severity and duration of neurological deficit and any complications.

The fracture healing response was calculated by the simplest possible method which allowed reproducibility. The healing mass is frequently fusiform, though often irregular and eccentric, resembling no mathematically definable shape. However, the largest diameter of even the most amorphous tube-like structure is substantially the most important determinant of volume in the absence of massive variations in length. A numerical value for fracture healing response was therefore calculated as follows:

$$\text{Fracture healing response} = A/B$$

where A is the largest diameter of the healing mass measured from serial radiographs taken at 90° to each other, and B is the bone diameter at or adjacent to the

R. F. Spencer, FRCS, FCS(SA)Orth, Registrar in Orthopaedic Surgery Medical School, PO Box 17039, Congella 4013, Natal, South Africa.

0301-620X/87/4154 $2.00

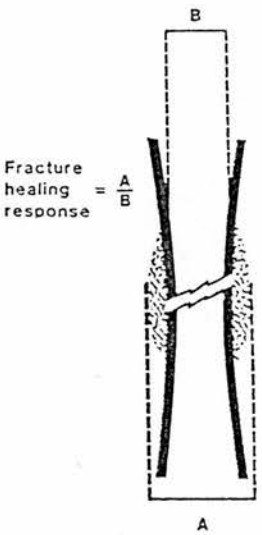
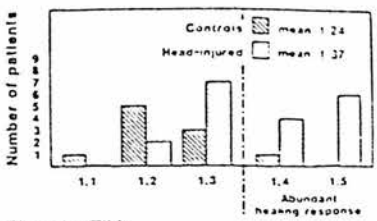


Fig. 1

Fracture healing response (A/B).



Healing response.

Figure 2 – Tibia.

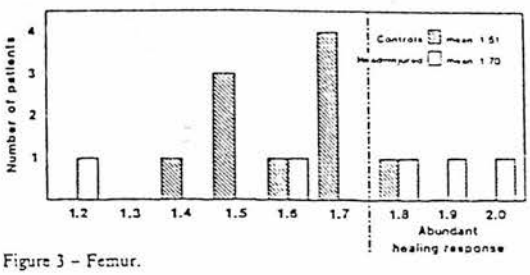


Figure 3 – Femur.

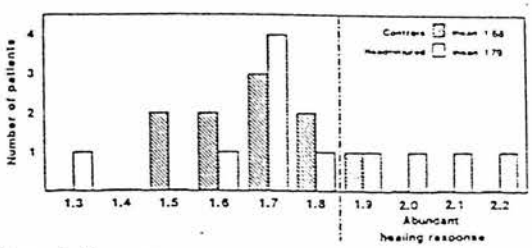


Figure 4 – Humerus.

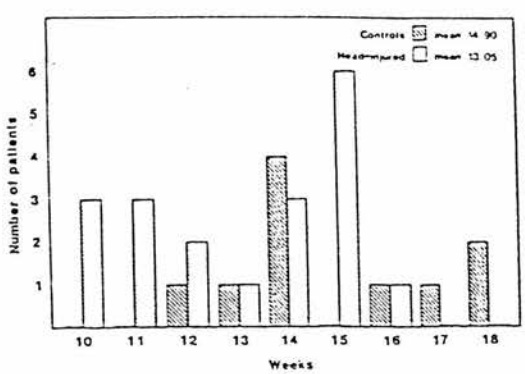


Figure 5 – Tibia.

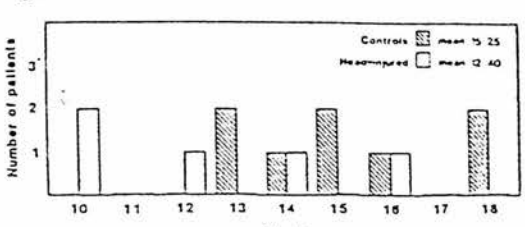


Figure 6 – Femur.

Time to union.

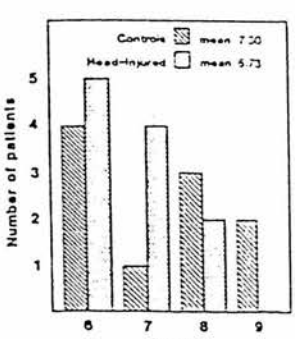


Figure 7 – Humerus.

fracture site on the same radiograph (Fig. 1). The numerical value obtained was used to compare the patients who had head injuries and fractures of the tibia, femur and/or humerus, with a group of 30 controls matched for age and sex who had similar fractures but no head injury. A similar number of open fractures was present in both groups. Patients aged under 16 years, and fractures which underwent internal fixation were not used for comparative purposes.

In addition to the radiological assessment, the fracture healing response was also assessed histologically in four patients, two in the group with head injuries and two without but who had late internal fixation.

RESULTS

The healing response in the tibia, femur and humerus are shown in Figures 2, 3 and 4, and the estimated time to clinical union in Figures 5, 6 and 7. A significant difference between patients with head injuries and the controls was found with respect to both healing response and time to union. Moreover, a linear correlation was found between the healing response and the time to union in the patients with head injuries (Table II).

In the patients with head injuries the radiographs often showed rapid formation of a peripheral layer of radiodensity. By contrast, the controls exhibited a standard healing response, a zone of callus spreading in uniform density outwards. Similarly, histological analysis of the healing mass sampled three weeks after injury showed peripheral maturity in the patients with head injuries but not in the others (Fig. 8).

Internal fixation appeared to potentiate the healing response in the patients with head injuries (Fig. 9), suggesting that surgical trauma or the release of osteogenic cells in the vicinity of the fracture encourages new bone formation.

Table II. Correlation between the healing response and the time to union in patients with head injuries

		Correlation	
	n	Coefficient	p value
Tibia	19	−0.7754	0.0001**
Femur	5	−0.0513	0.9347
Humerus	11	−0.8433	0.0011*

* Significant at a 5% level
** Significant at a 1% level

Malunion, including shortening, occurred in 12 fractures, eight of which showed an "abundant" healing response. The bones most commonly affected were the humerus and the femur.

Delayed diagnosis (over 48 hours after admission) of a significant injury occurred in 11 patients. Fractures accounted for seven of these, knee ligament injuries for two, a brachial plexus injury and a ruptured spleen for one each.

Head injuries. The CT scans of the 53 patients with head injuries revealed an intracerebral haematoma or a contusion in 18, cerebral oedema in 17, a subdural haematoma in 16, and an extradural haematoma in two patients. An abundant fracture healing response (defined as a response equal to or greater than the upper limit in the control group) was observed in 75% of patients with the more severe degrees of cerebral injury. There was no correlation between the healing response and ipsilateral spasticity, nor with bilateral spasticity.

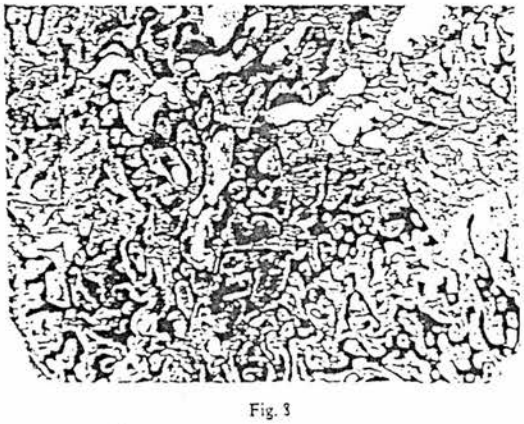


Fig. 3

A section of the periphery of the healing mass from a femoral shaft fracture in a patient with head injuries: at three weeks there is mature woven bone (× 60).

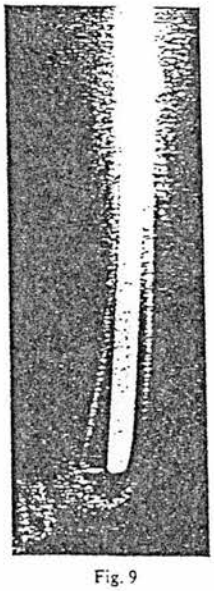


Fig. 9

Man aged 25 with head injury. Healing response at 6 weeks.

Nor was any correlation found between the healing response and the time taken to reach a stable neurological status (range 4 hours to 3 months), or with the depth of coma on admission, which ranged from 3 to 10 on the Glasgow coma scale. Twenty-seven patients (51%) made a complete neurological recovery.

DISCUSSION

Sevitt (1981) stated that some kind of influence on ossification is exerted by the nervous system; this much is well known to clinicians. However, despite numerous reports of rapid and abundant fracture healing in patients with head injuries, the matter has not been resolved, partly because of the difficulty in quantifying the fracture healing response. The severity of the head injury also is important and a precise neurosurgical diagnosis can probably be obtained only by CT scanning.

The study of internally fixed fractures to demonstrate fracture healing patterns in patients with head injuries has been used, but can be called into question, since the operation is liable to cause muscle damage, and this may contribute to new bone formation via locally released morphogens (Urist et al. 1978).

The exact nature of the healing mass in patients with head injuries has not been established. "Heterotopic ossification" is the term used by Garland et al. (1980) to describe the periarticular ossification which occurs spontaneously in some of these patients, and the same term is used by Garland and Miller (1984) to describe the nature of the fracture healing in such patients. Many other terms also have been used to describe this pattern of fracture healing, including "hyperplastic callus" (Glenn, Miner and Peltier 1973), "heterotopic bone" (Garland and Rhoades 1978), "myositis ossificans" (Bellamy and Brower 1974), "ossifying haematoma" and "calcifying haematoma" (Kernohan et al. 1984).

It is clear from the present study that the material is bone, and it resembles most closely "myositis ossificans" or "heterotopic bone" in that it tends to be mature at its periphery (Heffner 1984); this is the converse of the normal fracture healing response as described by Peacock (1984). The precise mechanism for this abnormal response is unclear, but it probably results from a combination of general and local effects. What is apparent is that movement at the fracture site, though frequently implicated, is unlikely to be the major factor. Although many questions remain unanswered, this study has demonstrated, using a simple and reproducible method, that an abundant fracture healing response occurs after severe head injury, as a result of which there is rapid union. The healing response is atypical in nature, and the term "callus" is probably not appropriate.

The author acknowledges the invaluable assistance of the Institute for Biostatistics, Johannesburg, the Medical Illustration Department at the University of Natal, and Mrs B. Katia who typed the manuscript.

REFERENCES

Apley AG, Solomon L. *Apley's system of orthopaedics and fractures*. 6th ed. London: Butterworth Scientific, 1982.

Bellamy R, Brower TD. Management of skeletal trauma in the patient with head injury. *J Trauma* 1974;14:1021–8.

Garland DE, Blum CE, Waters RL. Periarticular heterotopic ossification in head-injured adults: incidence and location. *J Bone Joint Surg [Am]* 1980;62-A:1143–6.

Garland DE, Miller G. Fractures and dislocations about the hip in head-injured adults. *Clin Orthop* 1984;186:154–8.

Garland DE, Rhoades ME. Orthopaedic management of brain-injured adults Part II. *Clin Orthop* 1978;131:111–22.

Glenn JN, Miner ME, Peltier LF. The treatment of fractures of the femur in patients with head injuries. *J Trauma* 1973;13:958–61.

Heffner RR Jr, ed. *Muscle pathology*. New York etc: Churchill Livingstone, 1984.

Kernohan J, Dakin PK, Beacon JP, Bayley JIL. Treatment of major skeletal problems in patients with a severe head injury. *Br Med J* 1984;288:1822–3.

Peacock EE Jr. *Wound repair*. 3rd ed. Philadelphia, etc: Saunders, 1984.

Sevitt S. *Bone repair and fracture healing in man*. Edinburgh etc: Churchill Livingstone, 1981.

Urist MR, Nakagawa M, Nakata N, Nogami H. Experimental myositis ossificans: cartilage and bone formation in muscle in response to a diffusable bone matrix-derived morphogen. *Arch Pathol Lab Med* 1978;102:312–6.

APPENDIX 2

SAMJ VOL. 74 2 JUL 1988 35

Heterotopic bone formation following cerebral cysticercosis

A case report

R. F. SPENCER, V. GANPATH

Summary

A patient with severe spasticity after cerebral cysticercosis formed heterotopic new bone at several sites. It is suggested that this case provides some clues to the cause of this phenomenon in patients with neural injury.

S Afr Med J 1988; 74: 35-36

Heterotopic bone formation may occur after a variety of disorders including spinal cord injury, poliomyelitis, chronic infection, and burns.[1] Numerous reports exist of atypical bone formation around fractures in patients with head injuries. However, cerebral parasitic infestation has not been recorded in this context.

The cause of new bone formation in patients with neural injury is uncertain. Local as well as general factors may play a part. Recent evidence suggests that new bone formed around healing fractures in such patients may resemble 'heterotopic bone' more closely than 'fracture callus'.[2]

Locally released morphogens in damaged muscle may play a part in allowing bone to form at unusual sites.[3] In the case presented here, a nidus may have formed around muscle cysticerci initiating the process of new bone formation.

Case report

A 33-year-old man was admitted to hospital in a comatose condition after a short febrile illness. Upper motor neuron signs were demonstrated in all four limbs. Cerebral computed tomography (CT) showed an area of decreased density in the pontine region, and a calcific focus in the proximity of the pineal gland (Fig. 1). Routine serological tests for cysticercosis were positive. A course of treatment appropriate to the cerebral condition was started.

After recovery of mental capacity the patient was discharged from hospital. He was ambulant, but found difficulty performing basic functions necessary for independence owing to severe spasticity and joint contractures.

A programme of physiotherapy produced little improvement, and further cerebral CT was performed 2 years after initial presentation. This demonstrated further lesions, including a focus of calcification behind the posterior clinoid process (Fig. 2).

However, during the next year the patient's condition improved to the extent that he was again able to drive a car to work, but was forced to accept less skilled employment than his previous clerical position. He remained disabled, with fixed deformities of the shoulders, elbows, hips and knees.

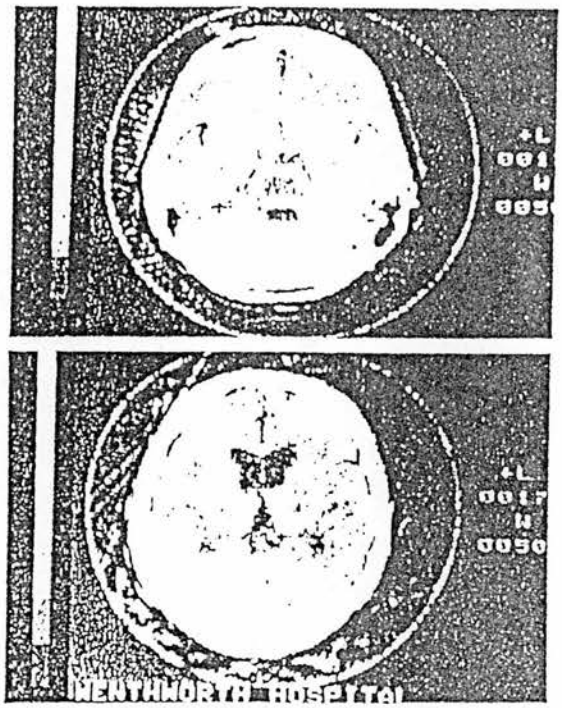


Fig. 1. Cerebral CT showing (above) an area of decreased density in the pontine region; and (below) a calcific focus in the proximity of the pineal gland.

Upper motor neuron signs persisted in all four limbs. His deformities at the time of review were most incapacitating in the left hip (fixed flexion deformity of 40° and fixed abduction deformity of 30°), left knee (fixed flexion deformity of 20°) and left shoulder (fixed abduction, flexion and internal rotation). The left hip and shoulder were ankylosed.

Radiography 6 years after the onset of the cerebral illness showed extensive peri-articular heterotopic bone formation around the left shoulder and left hip, and new bone formation posterior to the left knee (Fig. 3). It is not certain at what stage the new bone was first formed.

Discussion

Infection with *Taenia solium* is endemic in parts of South Africa, and cysticercosis has been implicated as a cause in a

Department of Orthopaedic Surgery, University of Natal and King Edward VIII Hospital, Durban
R. F. SPENCER, F.R.C.S., F.C.S. (S.A.)
V. GANPATH, F.R.C.S.

Accepted 6 Oct 1987.

Reprint requests to: Mr R. F. Spencer, Dept of Orthopaedic Surgery, University of Natal, PO Box 17039, Congella, 4013 RSA.

significant number of cases of epilepsy in Durban.[1] However, patients with the disease are rarely seen in an orthopaedic department unless muscle cysticerci are an incidental finding in radiography for other purposes.

Intracranial parasitic infestation may present as an acute encephalopathy,[5] as in the patient described here. The residual neurological deficit is seldom thought to be an indication for orthopaedic assessment. However, full recovery of mental function must be anticipated, even if this seems unlikely.

In a review of head-injured patients who developed heterotopic ossification Garland *et al.*[6] noted a correlation with spasticity. Ankylosis was found to be rare, and occurred in only 16% of joints. The abduction deformities found in our patient were not seen. Mendelson *et al.*[7] reported an incidence of 20% of heterotopic ossification in head-injured patients. It is postulated that some sort of soft-tissue injury is an important initiator of new bone formation, possibly via locally released morphogens,[3] which allow mesenchymal cells to form bone at extra-osseous sites. This process may be adjacent to a fracture,[2] a haematoma[4] or (as in our case) an intramuscular parasite.

Unfortunately, in the case reported, no attempt at appropriate early treatment was made. A combined approach involving splintage, physiotherapy, nerve blocks, intramuscular alcohol injections and the use of pharmacological agents combined with well-timed surgical release procedures may have been of benefit.[8]

Once peri-articular bone has formed, surgical removal is hazardous and the results unpredictable. It should be postponed until 2 years after the onset of the process.[9] Our patient refused such surgery and remains severely disabled.

We suggest that in patients with neural injury, particularly those with spasticity, a thorough examination for areas of soft-tissue damage elsewhere in the body should be performed so that pre-emptive measures may be initiated should heterotopic bone formation supervene.

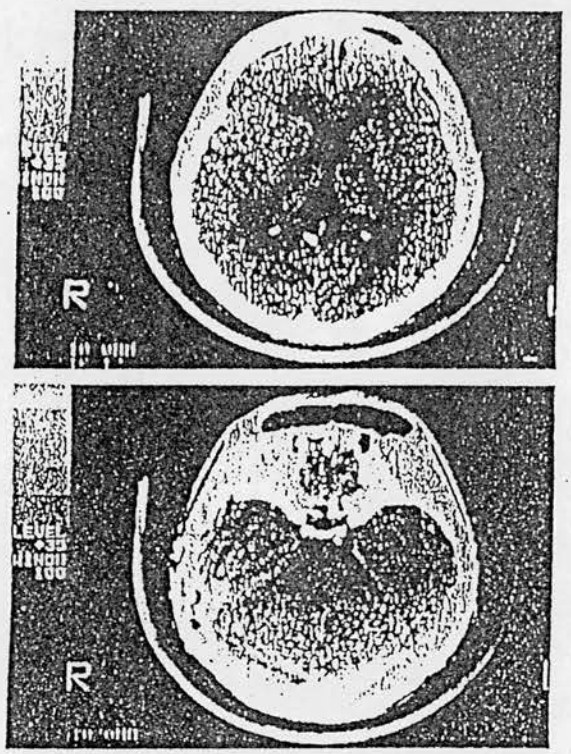


Fig. 2. Cerebral CT showing further lesions including a focus of calcification behind the posterior clinoid process.

REFERENCES

1. Helfner RR jun, ed. *Muscle Pathology*. New York: Churchill Livingstone, 1984: 177-186.
2. Spencer RF. The effect of head injury on fracture healing — a quantitative assessment. *J Bone Joint Surg [Br]* 1987; 69: 525-528.
3. Urist MR, Nakagan M, Nakata N, Nogami H. Experimental myositis ossificans: cartilage and bone formation in muscle in response to a diffusable bone matrix-derived morphogen. *Arch Pathol Lab Med* 1978; 102: 312-316.
4. Manson-Bahr PEC, Apted FIC, eds. *Manson's Tropical Diseases*. London: Baillière Tindall, 1982: 242-244.
5. Haddock RW. Neurologic illness and the tropics. In: Strickland GT, ed. *Hunter's Tropical Medicine*. 6th ed. Philadelphia: WB Saunders, 1984: 784-785.
6. Garland DE, Blum CE, Walters RL. Periarticular heterotopic ossification in head-injured adults. *J Bone Joint Surg [Am]* 1980; 62: 1143-1146.
7. Mendelson L, Grosswasser Z, Najenson T, Sandbank U, Solzi P. Peri-articular new bone formation in patients suffering from head injuries. *Scand J Rehabil Med* 1975; 7: 141-145.
8. Duthie RB, Bentley G, eds. *Mercer's Orthopaedic Surgery*. 8th ed. London: Edward Arnold, 1983: 777-779.
9. Garland DE, Rhoades ME. Orthopedic management of brain-injured adults. *Clin Orthop* 1978; 131: 111-122.

Fig. 3. Peri-articular heterotopic bone around (left) the left shoulder; (middle) the left hip (note the adductor origin); and (right) the left knee.