THE NATURAL HISTORY OF POST-TRAUMATIC ALGODYSTROPHY

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Algodystrophy, particularly in it's less severe form, is a poorly recognised and ill-understood condition which, when it occurs after fracture, delays rehabilitation. This study investigated the incidence, natural history and morbidity of post-traumatic algodystrophy. In addition a therapeutic trial of nasal calcitonin was undertaken.

Quantitative and semi-quantitative techniques were devised to assess the clinical, skeletal and biochemical features of the condition. Several were shown to be sufficiently sensitive and specific to be of value in assessing the disorder and were applied prospectively to 274 patients who had sustained a Colles' fracture.

The features of algodystrophy were significantly clustered (p < 0.0001), confirming the presence of a distinct syndrome which affected 28% of patients with Colles' fracture. Six months after fracture, the proportion of algodystrophic patients complaining of swelling had fallen to 20-30%, vascular instability and tenderness to 50%, and stiffness to 80%. These abnormalities were associated with a significant (p < 0.0001) loss of function. At one year stiffness was still apparent in 50% of cases. In the absence of the other features, stiffness would not necessarily be attributed to algodystrophy and may explain the low reported incidence of this condition following fracture. It may, however account, at least in part, for the permanent loss of hand function seen following Colles' fracture. The present survey also showed a more marked and persistent loss of bone in patients with algodystrophy than in Colles' fracture controls. This was associated with a significantly increased uptake on bone scintigraphy and decrease in bone formation as measured by serum osteocalcin. The

mechanism causing these skeletal changes and their implications are discussed. Treatment with nasal calcitonin did not alter the natural history of the disorder.

This study has shown that post-traumatic algodystrophy is more common than originally thought, is associated with significant short-term morbidity and may be responsible, at least in part, for long-term loss of function after Colles' fracture. In addition, it is associated with a persistent loss of skeletal mass.

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INTRODUCTION

CHAPTER 1: HISTORICAL REVIEW

The first record of algodystrophy is probably in the sixteenth century when Ambrose Paré reported that after phlebotomizing Charles IX, the king developed severe pain in the arm. Fortunately, the pain eventually resolved spontaneously. Two centuries later, in 1766, John Hunter described a sympathetic effect on muscles which atrophied and lost their power following trauma. This was followed by Percival Potts in the late eighteenth century who described "certain painful afflictions of the nerves" in connection with injuries of the extremities (Webb and Davis 1948). Algodystrophy was first recognisably described in 1813 by Alexander Denmark. During the battle of Badajoz in 1812, one of Wellington's troopers was struck by a musket ball in the distal humerus resulting in a radial nerve palsy. Denmark described the intense burning pain, trophic changes and loss of function following this injury. The patient was treated successfully by above elbow amputation even though Denmark originally believed that section of the nerve above the level of the lesion would have been equally effective.

During the American Civil War, Mitchell, Morehouse and Keen, in 1864 were the first to give an accurate account of the various aspects of the clinical syndrome we recognise today as algodystrophy. The observations were made on soldiers who had sustained peripheral nerves injuries following gun-shot wounds. They coined the term *causalgia* from the Greek, literally meaning "burning pain", but this emphasised only one aspect of the condition they described. They also drew attention to the fact that:

"The skin affected in these cases was deep red or mottled, or red and pale in patches."

"The surface of all the affected part was glossy and shining as though it had been skilfully varnished."

"In some form, pain has been an invariable attendant upon the diseased state of the skin which we have tried to describe."

"In other instances, there was associated with this, acute or aching pain which extended beyond the diseased tissues."

"It consists essentially of a painful swelling of the joints which may attack any or all of the articulations of a member."

"Once fully established it keeps the joints stiff and sore for weeks or months."

In the same year Sir James Paget (1864) also gave a classical description of the condition in it's severest form.

Post-traumatic rarefaction of bone was first noted by Volkmann in 1882 and later by Destot in 1898 who also commented on the intensity of the pain and the traumatic aetiology in his case report. Sudeck in 1900 at the 29th Congress of the German Society of Surgery, delivered a paper on "Acute inflammatory bone atrophy". This was followed by two articles published in 1901 providing a complete and thorough radiographic description of algodystrophy following various forms of trauma including soft tissue injury. He studied the evolution of bone demineralisation with serial radiographs and noted that the condition resolved spontaneously. In prolonged atrophy the bone architecture however remained abnormal.

Sudeck (1901) also attempted to describe the pathophysiology of the condition stating: "It is likely that, in sites distant from the site of the illness, it takes the form of an inflammatory irritation, which involves nutritional problems... and in consequence resorption of bone." Evidently, it is not by nature a physiological resorption of inactive bone but... an *active atrophy*." He named the condition, *acute atrophy of bone* but it was Nonne in 1901, working in the same clinic as Sudeck, who coined the term *Sudeck's atrophy*.

During the First World War, Babinski and Froment published four papers (1915-1918) which drew attention to the "the vasomotor and thermal problems of reflex origin" that occurred in algodystrophy. An aspect of the condition largely ignored until then, despite the vasomotor and trophic changes that had been described in the late nineteenth century following nerve injury (Charcot 1868). Indeed Vulpian in 1886 described: "the cyanotic or dark pink colour that the skin may exhibit,.... the local cooling, the moisture of the hand or foot,.... the oedema." In 1923 the "persistent vasomotor derangement" was studied by Leriche using clinical observations and oscillometry, which eventually led to the development of sympathetic ablation as a successful method of treatment (Leriche 1926). This confirmed Destot's earlier suggestion in 1904 that the condition occurred as a result of a lesion of the sympathetic nervous system. He wrote that "in certain bone conditions which develop after an insignificant trauma, there is skeletal resorption, without any subjective or objective evidence of a nervous lesion being found. Is one led to ascribe these lesions as well to a lesion of the sympathetic nervous system?"

In the 1920's and 1930's research into algodystrophy continued to be dominated by Leriche and his colleagues Policard, Jung and Fontaine such that the condition became known as *painful post-traumatic osteoporosis of Sudeck and Leriche.*

In 1926 the phenomenon was first specifically mentioned in the English literature by Noble and Hauser, followed by Buchmann in 1928 describing osteoporosis of the carpal bones. In 1926 a paper by Leriche and Policard had been translated into English by Moore and Key. However, it was not until 1933 that the first significant contribution was made by Fontaine and Herrmann. This again came from Leriche's clinic in Strasbourg and not surprisingly recommended sympathectomy almost to the exclusion of other methods of treatment. Following this and upto the Second World War many descriptions are found in the English literature (Gurd 1934; Herrmann 1934;

Cravener 1936; Gurd 1936; Simpson 1937; Livingstone 1938; Miller and de Takats 1941).

A multiplicity of names and syndromes have been used to describe this entity by various authors who have focused their attention on different aspects of the same phenomenon (Table 1.1).

In 1937, De Takats coined the term *reflex dystrophy* to describe the vasomotor and trophic changes. Later in 1940, Homans used the term *minor causalgia* in order to infer a relationship between Mitchell's causalgia (termed *major causalgia*) and similar conditions arising without direct nerve injury. It was shown subsequently that algodystrophy without nerve injury was much more common, and for this reason de Takats in 1945 used the term *causalgic states*. Patman *et al.* (1973) used the Greek term *mimo*, meaning to mimic, to coin *mimo-causalgia* as a collective term for this group of disorders. In 1973, Glick introduced the term *algoneurodystrophy* to describe the changes seen after minor trauma. He thought this stressed the three essential features of the disorder: pain, neurological origin and the association with tissue dystrophy.

In 1947, Steinbrocker introduced the term *shoulder-hand syndrome* which is often considered to be a separate disorder from algodystrophy. The clinical picture had been first described by Oppenheimer in 1938 in a report on 14 patients with cervical disc degeneration and subsequently by a number of authors giving the syndrome a variety of names. Steinbrocker (1947) from a review of the literature, grouped these syndromes under the heading shoulder-hand syndrome, and suggested that they represented varying degrees of reflex sympathetic dystrophy. In 1964, de Seze described retractile capsulitis (frozen-shoulder) which has been likened to the shoulder-hand syndrome "without the hand" by a number of authors and particularly Lequesne and Auquier (1968).

Table 1.1. The various names used to describe algodystrophy in the English and French literature.

In the English literature:	In the French literature:
Acute bone atrophy	Algodystrophy
Algoneurodystrophy	Algodystrophy decalcifiante
Causalgia	Algodystrophy reflexe
Major causalgia	Algodystrophy sympathique
Minor causalgia	Algoneurodystrophy reflexe
Migratory osteolysis	Osteoporose algique post-traumatique
Post-traumatic arteriospasm	Osteoporose algique essentielle du pied
Post-traumatic oedema	Osteoporose-osteoarthrite dystrophique
Post-traumatic painful osteoporosis	Pied decalcifie douloureux idiopathique
Post-traumatic sympathetic dystrophy	Pseudo-rhumatisme
Post-traumatic vasomotor syndrome	Rhumatisme neurotrophique
Reflex dystrophy	Syndrome de Sudeck-Leriche
Reflex sympathetic dystrophy syndrome	
Regional migratory osteolysis	
Shoulder-hand syndrome	
Sympathetic reflex dystrophy	
Transient osteoporosis	
Transitory osteoporosis	

The different names for this syndrome reflect the various observations of it's localisation, and theories as to it's aetiology and pathophysiology. Since the 5th International Conference on Rheumatic Diseases (June 1972) they have been considered to belong to the same entity. A workshop held at the Royal College of Physicians under the auspices of the British Association for Rheumatology and Rehabilitation (BMA Editorial 1978) considered that there were three essential diagnostic features of algodystrophy. These comprised firstly, intense, ill-defined pain and hyperaesthesia: secondly, vasomotor and sudomotor changes; and thirdly osteoporosis. These features are present to some extent in the various syndromes described over the years. Recently an attempt has been made to group all patients with an excessive, non-anatomical or otherwise seemingly abnormal pattern of pain by whatever cause under the general heading of *pain dysfunction syndrome* (Fields 1987). Although the nomenclature needs rationalising, this would appear to be an over-simplification, including conditions without the characteristic sympathetic dysfunction.

The term *algodystrophy* was introduced by French rheumatologists in the late 1960's. This seems the most satisfactory as it does not imply involvement of any particular tissue, location or aetiology but reflects the clinical combination of pain and dystrophic changes. For these reasons this term has been used in this thesis to describe the disorder.

CHAPTER 2: AETIOLOGY

A major drawback to the investigation of the aetiology of algodystrophy is the absence of a satisfactory animal model. The available data comprised mainly retrospective or anecdotal studies using a variety of diagnostic criteria. The confusion over nomenclature of the disorder reflects the multitude of factors which have been thought to be of significance in it's development. Indeed workers in all fields of medicine and surgery have assumed that there were several distinct clinical entities.

It would appear however that algodystrophy does not have a single cause at least in terms of it's initiation. There are a variety of precipitating factors which, if they occur in an individual who has a particular predisposition, results in the characteristic features of the disease. The features themselves are now thought to be the result of an abnormal sympathetic reflex, the pathophysiology of which remains unknown.

A. Precipitating factors

i) Primary or idiopathic algodystrophy

Lee Lankford (1982) stated that a persistent painful stimulus (traumatic or acquired) was necessary to initiate the condition. However in some cases no precipitating factors could be found. These idiopathic or primary algodystrophies are frequently reported but in varying numbers (Table 2.1). Indeed Serre *et al.* (1973) and Kleinert *et al.* (1973) make no mention of idiopathic algodystrophy. It is difficult to explain the difference in the reported incidence but there may be factors which remained undetected. Alternatively, the precipitating factors identified in some series may be chance rather than causal associations.

Duncan *et al.* (1973) described a type of primary algodystrophy which they termed "migratory regional osteoporosis". Despite the clinical course of this syndrome being identical to algodystrophy, they maintain that it should be considered a separate entity on the grounds that it is recurrent and it has no precipitating factors (although of his fifteen patients, two may have had a history of some minor trauma).

Table 2.1. The prevalence of algodystrophy without obvious precipitating factors (primary algodystrophy). The prevalence in the literature cited varies from 8% to as high as 75% when the hip is involved.

	No: cases	Incidence	Site
Steinbrocker (1958)	146	23%	Upper limb
Drucker et al.(1959)	61	8.2%	All sites
Ravault et al. (1961)	**	33%	Upper limb
Lequesne et al. (1968)	**	50%	Hip
		25%	Feet
Pak et al. (1970)	140	15%	All sites
Patman et al. (1973)	88	4.4%	All sites
Renier et al. (1973)	66	18.4%	All sites
Schiano et al. (1974)	103	11.4%	All sites
Doury et al. (1981)	250	37%	All sites
		27%	Upper limb
		43%	Lower limb
		75%	Hip
Subbarao et al. (1981)	125	10.4%	Upper limb

ii) Secondary algodystrophy

In the majority of instances there is an obvious precipitating factor responsible for the initiation of the condition (Table 2.2). These factors may produce unusual clinical features but the evolution of the syndrome remains the same. It seems justifiable therefore to group them all under the one heading of secondary algodystrophy.

Table 2.2. Causes of secondary algodystrophy.

Trauma	- Soft tissue
	- Fracture and dislocation
	- Surgery
Nervous system	- Central
	- Peripheral
Cardiac disease	
Pulmonary disease	
Miscellaneous	

a) Trauma

In Mitchell's original description (1864), the syndrome was associated with penetrating injuries causing direct trauma to the nerves. Whilst this is still recognised, it is far outweighed by trauma with no overt evidence of neural damage. Although Leriche (1939) maintained that trauma was essential for the development of algodystrophy, it has come to be recognised more often in it's absence. The incidence of trauma precipitating algodystrophy varies markedly (Table 2.3). The variable incidence of trauma as a precipitating event no doubt reflects the bias in the clinical interests of

the authors. Kleinert *et al.* (1973) and Serre *et al.* (1973) reported a traumatic incident in excess of 90% in large series. The lowest incidence appears to occur in association with the shoulder-hand syndrome (Rosen *et al.* 1957; Steinbrocker 1958)

Kleinert *et al.* (1973), reported their experience in 506 cases over a five year period, and found crush injuries with lacerations and subcutaneous soft tissue destruction were the commonest types of trauma leading to algodystrophy. Associated fractures or amputations were present in approximately half of these crush injuries. Lacerations without soft tissue contusion or crush were the next most common injury. Interestingly, of the closed fractures reported, there was a higher than expected incidence following Colles' fracture. They proposed that this may be due to swelling in the carpal tunnel and consequent median nerve compression.

Although Kleinert *et al.* (1973) do not specify the severity of the trauma, Serre *et al.* (1973) in another large series of 188 cases, noted that approximately 50% of their patients had suffered minimal trauma. Also it appeared that there was no correlation between the severity of the trauma and the severity of the subsequent algodystrophy. To further complicate matters, several authors (Herrmann *et al.* 1942; Weil and Gerard-Marchant 1954; Fontaine *et al.* 1957; Beasley 1964; Ivins *et al.* 1969; Serre *et al.* 1973; Bernstein *et al.* 1978; Kim *et al.* 1979; Goldner 1980; Fam and Stein 1981) have claimed that immobilisation rather than the initial trauma may be the precipitating factor. Serre *et al.* (1973) reported that out of 188 cases, 7 were caused and 37 were aggravated by the immobilisation. Untimely or over-enthusiastic rehabilitation after injury has been noted to cause or exacerbate algodystrophy (Savin 1974). These observations however, are subjective and controlled prospective trials on the role of immobilisation and physiotherapy have not been reported and are clearly needed.

Table 2.3. The role of trauma in the incidence of algodystrophy. In the major series reported, trauma was the commonest aetiological factor in the development of algodystrophy. The exceptions to this where in those series reporting the shoulder-hand syndrome (*).

Series	Number of cases	Trauma and fracture (%)	Trauma without fracture (%)	Surgical trauma (%)	Total with trauma (%)
De Takats (1945)	36	25	50	0	75
Rosen et al. (1957) *	73	?	?	4.1	6.8
Steinbrocker et al. (1958) *	14	?	?	?	10
Drucker et al. (1959)	61	22.6	52.8	4.9	83.6
Pak et al. (1970)	140	20	28.6	16.4	65
Wirth et al. (1970)	32	31.3	31.3	15.6	78.2
Kleinert et al. (1973)	506	10	57	26	93
Patman et al. (1973)	113	37.5	42.1	6.8	86.4
Renier et al. (1973)	66	24.2	30.3	18.7	72.7
Serre et al. (1973)	111	36.9	46.9	8.2	92
Schiano et al. (1976)	103	?	?	?	59.2
Doury et al. (1981)	250	14.4	33.6	4.4	52.4
Subbaraoa et al. (1981)	125	24.8	20	8.8	53.6

b) Diseases of the Nervous system

Peripheral nervous system. As discussed, trauma of the peripheral nerves was the first recognised cause of algodystrophy. Radiculopathy is also described as a precipitating factor, usually due to disc herniation or root entrapment in the lateral recess secondary to degenerative disease (Oppenheimer 1938; Rosen and Graham 1957; Steinbrocker and Argyros 1958; Drucker *et al.* 1959; Serre *et al.* 1973; Carlson *et al.* 1977; Bernard and Perlo 1980; Bernini and Simeone 1981). Oppenheimer in 1938 noted algodystrophy of the upper limb in 14 patients associated with constriction of the intervertebral foramina in the upper cervical spine on the affected side. Of the 7 patients treated with ultra short wave therapy to the cervical spine, 6 were cured. Serre *et al.* in their 188 cases (1973), reported 12 secondary to a radiculopathy. Myelography (Morretin and Wilson 1970) and spinal anaesthesia (Drucker *et al.* 1959) have also resulted in algodystrophy, presumably again due to nerve root trauma. I have seen one case with algodystrophy of the foot following an L5-S1 decompression for root pain.

Sudeck in 1901 was the first of many authors to associate herpes zoster with the development of algodystrophy. Most reports describe the shoulder-hand syndrome as a consequence of this infection (Berthier 1949, Margarot 1952, Richardson 1954, Steinbrocker and Agyros 1958, Graudal 1959, and Baer 1966).

Central nervous system. It is difficult in reviewing these cases to distinguish whether the precipitating factor is the disease itself or the associated investigations and treatments. Of the acute conditions described, cerebral infarction due to cerebro-vascular accident appears to be the most common aetiological factor, particularly with regard to the development of the shoulder-hand syndrome (Swan 1954; Rosen and Graham 1957; Moskowitz and Bishop 1958; Steinbrocker and Argyros 1958; Davis *et al.* 1977; Eto *et al.* 1980). Davis *et al.* (1977) in a 5 year retrospective study found a 12.5% incidence of shoulder-hand syndrome in hemiplegic patients. Rosen and

Graham (1957) also reported algodystrophy following sub-arachnoid haemorrhage, severe head injury and cervical cord injury.

Of the chronic diseases, brain tumours (Vaernet 1952; Renier and Ceguillaume 1966; Walker *et al* 1983), subacute combined degeneration of the cord (De Takats 1945), syringomyelia (De Takats 1945; Evans 1947; Owens 1957) and Guillain- Barre's syndrome (Serratrice *et al* 1971) have been implicated.

c) Cardiovascular disease

Osler in 1901 described a "motor disability" following anginal attacks. Originally this disability was described as only affecting the shoulders but from 1940 there were several reports of the true shoulder-hand syndrome associated with angina which was best described by Steinbrocker's in 1947. Lenegre (1946) reported a 4% incidence of algodystrophy following "scenes douloureuses coronariennes" with Froment *et al* (1956) further subdividing the incidence following cardiac ischaemia to 10-20% following a myocardial infarct and 1% after an episode of angina. They reviewed 138 cases reported in the literature and noted that algodystrophy followed 4-8 weeks after the myocardial episode. The left limb was involved in 58% of cases, the right in 11% with 31% occurring bilaterally, of these the left was more symptomatic. It would therefore appear that the referred pain can be the trigger for the development of algodystrophy.

Other cardiovascular conditions which have been reported to result in algodystrophy are arterial or venous thrombosis (De Takats 1945; Evans 1947; Steinbrocker *et al* 1948; Owens 1957; Drucker *et al* 1959; Speilman *et al* 1981), aortic injury (Szeinfeld *et al* 1982), acute pericarditis (Moreau *et al* 1955), mitral valve disease with paroxysmal tachycardia, constrictive pericarditis (Schiano *et al* 1976) and cardiac surgery (Kohler 1968).

d) Pulmonary disease

Ravault *et al.* (1955) cited many instances of algodystrophy, particularly of the upper limb, following thoracic disease or surgery. Carcinoma of the bronchus, particularly of the apex of the lung (Cremieux 1974), is one of the more frequent aetiological factors. This may be associated with Horner's syndrome providing direct evidence of sympathetic nerve involvement and thus a neurological factor in the aetiology. The role of pulmonary tuberculosis is more contentious as the precipitating factor may well be the chemotherapy used in it's treatment. Rosen and Graham in 1957 also described algodystrophy in a patient with pulmonary fibrosis.

In all these conditions, the algodystrophy appears a few days or weeks after the initiating event with stiffness rather than pain being the dominant feature.

e) Inflammatory conditions

Numerous authors have reported soft tissue infections as a causative factor (De Takats and Miller 1943, Owens 1957, Rosen and Graham 1957, Steinbrocker and Argyros 1958 and Wirth and Rutherford 1970). The importance of inflammation may have been overemphasised since in the early stages of algodystrophy, a pseudoinflammatory phase may be mistaken for infection.

Non-infective inflammatory conditions such as fasciitis, tendonitis, bursitis and acute gout have been incriminated (De Takats 1943; Evans 1947; Steinbrocker and Argyros 1958; Drucker *et al.* 1959; Pak *et al.* 1970; Itzkowitch *et al.* 1981) so too have various connective tissue disorders including rheumatoid arthritis, ankylosing spondylitis, Reiter's syndrome, polymyalgia rheumatica, periarteritis nodosa and Weber-Christian disease (Steinbrocker *et al.* 1948; Steinbrocker and Argyros 1958; Villaumey *et al.* 1979; Wysenbeek *et al.* 1981).

f) Miscellaneous

Algodystrophy has also been reported following prolonged bed rest (Rosen and Graham 1957) and with a strong familial history (Albert and Ott 1983).

B. Predisposing factors

Although there is usually a precipitating factor, it appears that the chance of developing algodystrophy is increased in the presence of certain conditions. These predisposing factors, whilst not triggering the algodystrophic process, provide the most suitable "terrain" for it's development.

i) Psychogenic

A patient's reaction to pain is modified by the basic organisation of his or her personality, the meaning of the injured part to the patient, racial and cultural expectations, support mechanisms that are provided by the family and the community, age, the cumulative effect of previous losses (physical and psychological), and the potential for secondary psychological gain in patient-spouse, patient-employer, patient-physician, or other conflicts (Katon *et al.* 1982). Litigation and worker's compensation are other complicating issues that may prevent the amelioration of the symptoms.

The combination of the emotional sequelae of the illness and the disparity between the degree of pain and the physical examination lead many physicians to think that the pain is of psychogenic origin (Owens 1957; Bergann and Conn 1968; Wirth and Rutherford 1970). This, in addition to misguided therapeutic efforts and intractable pain, further aggravates the patient's psychological symptoms (Wirth and Rutherford 1970; Walton 1983). Anxiety also increases sympathetic discharge, which exacerbates the pain (Doupe *et al.* 1944; Holden 1948; Drucker *et al.* 1959).

It had been suggested as early as the 1940's (De Takats 1943 and De Takats and Miller 1943) that patients with algodystrophy seem emotionally unstable, anxious and socially withdrawn. Although any "normal" individual can develop algodystrophy, Hill (1980) states that it is more often seen in inadequate personality types and in outright neurotics. Pak *et al.* (1970) found that of 140 patients, 37% had a "history of

psychiatric problems or emotional disturbances prior to the onset of the present illness". Twenty-five had normal psychiatric consultations and 7 others were thought to have psychiatric problems. Omer and Thomas (1971) reported that 45% of their patients required psychiatric consultation, most of them were manic. Bernstein (1978) reported similar findings with children suffering from algodystrophy. He found that the overwhelming majority of children had a history of overt parental conflict in their families, accepted responsibility beyond their years, had difficulty expressing anger or being assertive, and were indifferent to the implications of their condition and future activities.

The use of the MMPI (Minnesota Multiphasic Personality Inventory) or other personality inventories is frequently helpful in identifying more subtle personality factors, particularly for the physician who has not had psychiatric training (Cox *et al.* 1978; Southwick and White 1983; Rucker *et al.* 1986). Subbarao and Stillwell (1981) using this technique showed a hysterical personality, hypocondriasis, and/or depression in 80% of the 45 cases studied (36% of the study total). Similarly, Pelissier *et al.* (1981) using the same method of assessment noted an increased frequency of hysterical or depressive neuroticism.

Not all investigations have found associations between abnormal personality and susceptibility to algodystrophy. Wilson *et al.* in 1977, used the MMPI on a consecutive group of algodystrophic patients as well as on patients with physical injuries that were not complicated by pain. None of the patients with pain demonstrated any pathological deviations from normal. They concluded that patients with abnormal personality traits were not predisposed to the development of algodystrophy. However, when severe pain occurs, an individual's ability to handle the situation may be compromised by any personality defects.

Vincent *et al.* (1982) found great difficulties in applying the MMPI, preferring to use Rorscharch's test which is based on the influence of the person's personality on his

perception of visual images. Using this system, he failed to confirm the findings of

Pelissier or Subbarao and was unable to pinpoint a single psychological abnormality.

To my knowledge no study has conclusively proved or disproved the relationship

between a psychiatric condition and the development of algodystrophy. As Subbarao

and Stillwell stated, no definite conclusions could be drawn because of small numbers

and indefinite criteria used to grade the outcome results. Some reports claim that in

patients observed before and after relief of algodystrophy, the emotional disturbance

resolved completely with successful treatment of their condition (Lehman 1934; Echlin

et al. 1945; Spiegel and Milowski 1945). Also, no significant differences could be found

in the personality traits of patients with algodystrophy when compared with patients

with nerve injuries without algodystrophy (Wilson 1981).

ii) Hyperthyroidism

A number of studies have noted the association between hyperthyroidism and

algodystrophy. Indeed Layani (1946) described this as "thyroid rheumatisms". It

appears that the high incidence may be secondary to treatment, particularly with ^{131}I,

rather than the disease process itself. Schiano *et al.* (1976) noted that in 14 (13.6%)

cases of algodystrophy were associated with hyperthyroidism; six occurred with

untreated hyperthyroidism and 8 after treatment with antithyroid chemotherapy or

^{131}I. Methlin *et al.* in 1971 reviewed 720 patients who had been treated with ^{131}I and

found 24 patients (3.3%) with evidence of algodystrophy. Twenty of these occurred after

treatment. Half presented with the shoulder-hand syndrome and the remainder with

capsulitis of the shoulder. These features occurred bilaterally in 75% of cases.

Recently there has been a fall in the reported frequency of algodystrophy following ^{131}I

treatment which may be due to prior control of the disease with other chemotherapeutic

agents.

iii) Diabetes Mellitus

Algodystrophy is reported to occur in both newly diagnosed diabetics and those in whom hyperglycaemia is adequately controlled. Schiano *et al* (1976) reported two cases of diabetes mellitus out of 103 (2%) and Doury *et al* (1981) reporting eight out of 108 cases (7.4%). Lequesne *et al* (1977) reported 11 cases though four had other precipitating factors. The prevalence of diabetes mellitus in France varyies from 2-20 per thousand of the general community. The upper limb was exclusively involved in Lequesne and Schiano's series but this was found in only two out of the eight described by Doury.

iv) Hyperlipidaemia

Recently there has been some evidence to associate hyperlipidaemia with algodystrophy. Pinals and Jabbs in 1972 reported three cases of transient osteoporosis of the hip associated with a type-IV hyperlipoproteinaemia. All three were heavy social drinkers. Amor *et al* (1980) investigated this finding further by studying 34 algodystrophy patients and 11 controls before and after the ingestion of alcohol. They found that the peak triglyceride levels were higher in the algodystrophy group than in the control group (p<0.02). They also noted 5 patients with diabetes mellitus and five with hyperuricaemia.

In a further study Amor *et al* (1982), reporting the French Society of Rheumatology national study of algodystrophy, investigated the association between hyperlipidaemia, hyperglycaemia and hyperuricaemia and algodystrophy in more detail. Out of 80 patients, 49 (61.25%) had hypertriglyceridaemia and 54 (67.5%) had at least one of the three metabolic abnormalities. When hyperglycaemia or hyperuricaemia are present it was almost always in association with hypertriglyceridaemia.

<u>v) Iatrogenic</u>

The role of surgery in the development of algodystrophy has been described in the section on trauma.

a) Phenobarbitols

Barbiturate induced algodystrophy was first described in 1925 by Maillard and Renard and then later by Beriel and Barbier in 1934. Since then there have been numerous reports. It is difficult to estimate the true incidence of this phenomenon but it must be small considering it's frequent use, particularly in the past. Bouvieret *et al.* (1973) in a series of 100 cases report 25 with a history of barbiturate ingestion. Although in 21 cases there was another precipitating factor found, it is possible that individuals taking barbiturates may be predisposed to developing algodystrophy. In the series reported by Schiano *et al.* (1976) and Doury *et al.* (1981), 11 out of 103 cases (10.7%) and 6 out of 250 (2.4%) respectively had been treated with barbiturates. This fall in incidence may reflect the decline in the use of barbiturates.

b) Isoniazid

The introduction of isoniazid as an anti-tuberculous chemotherapeutic agent seems to be directly associated with a number of cases of algodystrophy. Brouet *et al.* in March 1961 reported the first four cases followed in September of the same year with a report from McKusick and Hsu. Since then there have been a number of similar reports but some authors maintain that it is the tuberculosis itself rather than the treatment which is the cause (Franklin and Nemcick 1959; Johnson 1959; Fisher *et al.* 1963; Carriere and Kerambrun 1967). Although there are number of chemotherapeutic agents used in the treatment of tuberculosis, isoniazid is found to be a common denominator in all the studies. Clinically, the most characteristic appearance is bilateral shoulder-hand syndrome which occurs in 50% of cases. Stopping treatment with isoniazid is usually associated with resolution of the symptoms.

It is unknown how treatment with isoniazid results in algodystrophy but it has been shown to accentuate the fibrosis caused by serotonin (Good *et al.* 1965), a substance which may be final chemical mediator in the production of the contractures seen in algodystrophy (page 34).

vi) Miscellaneous

a) Pregnancy

In 1953 Curtiss reported three cases of algodystrophy of the hip during the third month of pregnancy. Almost all cases reported since then have involved the hip. Of the 250 cases reported by Doury *et al.* (1981), two occurred during pregnancy. As Guaquiere (1969) reports, algodystrophy can also occur following delivery.

b) Smoking

An *et al.* (1988) in a retrospective study on 53 patients with algodystrophy found a significantly increased frequency of cigarette smoking (p<0.001) using matched hospitalized controls. They proposed that smoking may cause algodystrophy by enhancing sympathetic activity or vasoconstriction.

c) Hyperviscosity

Ernst *et al.* (1988) showed that plasma viscosity, red cell aggregation and ESR were significantly higher in 14 patients with algodystrophy compared with matched controls. During treatment with hydroelectric therapy in a longitudinal study involving 5 patients, all subjects became progressively normal. Although these effects may well be secondary to an imbalance in the autonomic nervous control, they might contribute to a disruption of the microcirculation.

CHAPTER 3: PATHOGENESIS

A wide variety of pathological manifestations have been incriminated in the aetiology of algodystrophy but all result in similar clinical manifestations which would suggest a common pathophysiological process.

Attention was directed early to the autonomic system because interruption of the sympathetic efferent impulses either temporarily or permanently was found to be effective in treating patients with algodystrophy (Leriche 1924 and 1926). It was thought that the pain and dystrophic changes were a result of increased peripheral blood flow due to sympathetic activity. Indeed increased blood flow was recorded by many authors (Miller and De Takats 1941; Scheibe and Karitzky 1954; Hartley 1955 and Senis; Centrone 1955 and Plewes 1956) using a variety of techniques. Conversely, Mayfield and Devine (1945), Holden (1948) and more recently Doury et al. (1981) could not demonstrate any consistent abnormality in the circulation and they describe a clinical picture of intermittent vasodilation and vasoconstriction. Doupe et al. (1944) and Nathan (1947) discounted vascular changes as the cause of the pain because the production of vasodilation by means other than sympathectomy did not relieve the pain. For these reasons the vascular instability seen in algodystrophy have not been considered the cause but the result of the pathological process.

The efficacy of sympathectomy as a treatment has led to the proposal that a variety of neural mechanisms are responsible for the development of symptoms. Indeed any neuro-physiological explanation of the propagation of pain must take into account the unusual features seen in algodystrophy such as the onset and character of the pain and the ease with which pain is aggravated by activity elsewhere in the nervous system. There are two possible sites for the origin of the pain impulses: peripherally at the site of the original stimulus and the central nervous system.

A. Peripheral origin of pain

The essential feature of the peripheral hypothesis is that the cutaneous area in which the pain is felt is the source of the pain-producing impulse. These impulses could arise in several ways.

1) Ischaemia and nutritional disturbances causing artificial synapses between the sympathetic and sensory fibres at their termination.

2) The release of pain-producing substances into the tissues of the skin as a result of chronic irritation of the injured sensory fibres.

3) From the accumulation of pain-producing substances in the tissues as a result of vasoconstriction and ischaemia secondary to the irritation of vasomotor nerve fibres.

There are a number of possible objections to these theories. The sensation of pain in these instances relies upon an intact sensory input from the periphery. Algodystrophy may occur after complete division of a nerve or the symptoms may persist after blocking the nerve thus preventing the central transmission of sensation. Similarly the causalgic pain in phantom limbs occurs where the peripheral component is missing. The immediate onset of pain seen in some cases cannot be explained by a process which takes some time to develop, in particular the production of artificial synapses. The relief obtained by sympathectomy is unlikely to be due to the removal of pain-producing substances because vasodilation may already be present prior to operation.

B. Central origin of pain

Leriche (1949) believed the sympathetic system to be fundamental in the role of pain sensitivity. He thought it acted in three main ways: (1) by afferent transmission of pain impulses; (2) by a vasoconstrictor action, which provoked painful conditions; and (3) by a metabolic action, which induced an alteration of the state of sensitivity of pain. He stressed that the afferent component of the sympathetic system was due not only to impulses in sensory fibres passing through the ganglia to reach the dorsal roots, but also to true sympathetic afferent impulses which reached the sympathetic ganglia and were reflected by efferent fibres to the periphery, where they induced painful conditions. This concept of a reflex arc, although modified, remains a fundamental component of the current theories of it's pathophysiology.

Leriche's explanation depends upon there being an afferent component to the sympathetic system which the French and German schools have long held to be true (Francois-Franck 1899, Pette 1927, Doring 1946 and Leriche 1949). The English schools have been strongly influenced by the work of Langley (1898, 1903 and 1921) who introduced the term "autonomic nervous system". Although he recognised afferent fibres in the sympathetic system he thought they were somatic in nature. In fact, he wrote that "the afferent nerves of the sympathetic system are indistinguishable in form and position from those of the somatic system" (1898). This difference of opinion is still in evidence today but there is increasing evidence in the English literature that visceral sensation is transmitted by sympathetic afferents (Malliani 1984, Paintal 1986, and Widdicombe 1986).

There is some clinical evidence that afferent somatic fibres are present in sympathetic nerves. Some patients with complete spinal transection at the level L1-L2 report pain in the lower limbs which disappeared after sympathectomy (Foester et al. 1929). Other patients with complete spinal transections, who felt burning pain in the

lower limbs, had anterolateral tractotomy performed immediately above the level of the transection; this only caused a reduction in the intensity of the pain. A trachtotomy at the T1-T2 level brought about a complete disappearance of the pain (Freeman and Watts 1951). It is interesting to note that the afferent fibres found in the sympathetic system contain small diameter unmyelinated C axons. These are identical to the axons found in somatic nerves which are thought to be responsible for the transmission of a burning, persisting and spreading pain.

Although the presence of true somatic afferents in the sympathetic system is still open to debate, it has been known for years that the sympathetic system does modulate pain sensation. In Claude Bernard's original studies (1858 and 1879) he observed that sympathectomy in cats and rabbits affected their response to painful stimuli.

Livingstone in 1943 developed Leriche's reflex arc theory. He thought that the dystrophy and pain was due to a vicious circle of impulses "periphery-spinal cord-sympathetic efferents-periphery". This vicious circle could be maintained and enlarged both by dystrophic conditions in the periphery and by the activation of internuncial pools of neurones. This concept was further stressed by De Takats (1965) and Bonica (1979). There has been recent controversy as to whether the efferent arc is purely sympathetic. Moruzzi (1968) and Zimmerman (1979) among others feel that it is impossible to distinguish a purely sympathetic action from a somatic component in the reflex arc. As Moruzzi wrote "sympathetic and somatic neurones are often at the end of the final common pathways and that in the periphery it is well known that the sympathetic action can modulate the somatic action".

A further theory along the lines of a vicious circle was proposed by Doupe et al. and Granit et al. in 1944. They proposed that an artificial synapse, or ephapse, is produced between the efferent sympathetic fibres and the afferent somatic fibres after nerve injury. Sympathetic outflow being directly transmitted to the spinal cord and

higher centres and interpreted as pain. This theory does not explain how the ephapses which occur rarely and late account for causalgic pain which can occur within hours. Also it presupposes that some form of trauma has occurred which is not always the case, particularly in variants such as the shoulder-hand syndrome.

Walker and Nulsen in 1948 made some clinical observations which are thought to support the ephapse theory. Stimulation of de-centralised sympathetic nerves in patients suffering from causalgia following nerve injury reproduced their characteristic pain. This was not the case in patients who had undergone sympathectomy without causalgia. It was thought that the stimulated sympathetic fibres caused direct stimulation of the somatic fibres due to the presence of an ephapse. This same effect however could be caused by modulation of the somatic action in the periphery (Moruzzi 1968 and Zimmerman 1979), particularly in an individual in whom the causalgic pain is centralised.

Melzack and Wall in 1965 produced the gate-control theory of pain sensation. They proposed that there are facilitatory and inhibitory mechanisms in the substantia gelatinosa of the spinal cord in which fine and large sensory fibres play opposing roles in influencing onward transmission through the dorsal horn. The lesion in causalgia is postulated to be one which selectively damages the large myelinated sensory fibres. This disturbs the balance in favour of fine fibre activity which, now unopposed, opens the gate. Small fibre activity through the system is thereby increased and pain results. This does not explain the pain found in algodystrophy where there is no evidence of trauma. The afferent fibres within the sympathetic system are the same small unmyelinated fibres that are required to open the gate and they may therefore play a role in pain transmission.

Conversely, stimulating large fibres "closes the gate" and reduces or stops the pain. This is the basis of the therapeutic use of large fibre stimulation for the relief of intractable pain. In a later paper Melzack (1971) elaborated on a central control

mechanism in the brain stem reticular system which could modify the perception of pain by influencing the transmission of impulses through the gate.

Although the original painful lesion in algodystrophy is peripheral in most cases, and the perception of pain may well be due to a selective processing of impulses as proposed by the gate theory, there must therefore be a central mechanism responsible for the characteristic features seen in algodystrophic pain. These include the character of the pain, it's spread to adjacent areas, the ease with which the pain is aggravated by activity elsewhere in the nervous system, the failure of sympathectomy in late cases and its eventual resolution in the majority of cases.

Livingstone in 1943 proposed that the chronic afferent impulses stimulated an internuncial pool of neurones. As Lorent de No had shown in 1938 this pool consists of two systems. A so-called multiple system, in which the stimulations successively reach the neurons of the second and then of the third order in the higher centres, and a closed system around which an impulse circulates. These internuncial neurons carry the influx not only to the lateral column of the same medulla level and to several over and underlying levels, but also to the contralateral side. This could account for the spread of the pain to adjacent areas or even to the opposite limb. The increase in internuncial pool activity may then cause a continuous and increased stimulation of the efferent motor and sympathetic neurones.

This has been confirmed in a series of experiments by Procacci et al. (1974 and 1979) and Francini et al. (1979). In controls and patients with algodystrophy, they measured cutaneous sensory thresholds, in order to assess the afferent activity, examined the galvanic skin reflex by measuring the reflex variations of cutaneous potentials (Wang 1985), in order to assess the efferent sympathetic activity, and the EMG, in order to assess the efferent motor activity. They found that in patients with algodystrophy there was an abnormal difference in cutaneous sensory thresholds between the affected limb and the contralateral one in basal conditions, and an

abnormal pattern of skin potential and EMG variations induced by cutaneous stimulation both in the effected limb and in the contralateral one. After blocking the sympathetic chain ipsilateral to the affected limb with local anaesthetics, the sensory thresholds of both limbs changed and tended to the same value, and the pattern of skin potential and EMG responses became similar to the pattern found in normal subjects. They concluded that both the sensory thresholds and cutaneous and muscular reflexes are controlled by a loop "periphery - afferent discharge - efferent somatic and sympathetic discharge - periphery" and that this loop through a mechanism of central transfer affects a similar loop on the contralateral side.

Sunderland (1976) claims that the characteristic features of causalgic pain are caused by a hyperactive focus of abnormal activity in the cord caused by retrograde cell death due to peripheral nerve injury. Transynaptic changes, including cell degeneration, may then affect second and third order neurones. This theory does not explain the pain of non-traumatic aetiology.

Recent work by Roberts (1986) and Cook et al. (1987) has reinforced the classical view expressed by Livingston. Prolonged abnormal stimulation of the internuncial pool may cause a resetting of the sensory thresholds which persists after the initial stimulus has been removed. Both workers agree that primary afferent C-fibres can clearly modify the response properties of the dorsal horn neurones, including projecting neurones, for prolonged periods. This may include the afferent C-fibres found in the sympathetic system.

C. Local factors

Although the sympathetic system undoubtedly plays a fundamental role in the development of algodystrophy, this does not adequately explain the disturbance in the microvasculature or the articular stiffness.

The microcirculation is composed of arterioles which divide into smaller muscle-walled vessels, sometimes called metarterioles, and these in turn feed into capillaries. In some of the vascular beds that have been studied in detail, a metarteriole is connected directly with a venule by a capillary thoroughfare vessel which has thick, muscular walls. The true capillaries are an anastamosing network of side branches of this thoroughfare vessel. The openings of the true capillaries are surrounded on the upstream side by minute smooth muscle precapillary sphincters. It is unsettled whether the metarterioles are innervated, and it appears that the precapillary sphincters are not. They can however respond to local or circulating vasoconstrictor substances (Table 3.1). The walls of the venules are only slightly thicker than those of the capillaries. They contain relatively little smooth muscle, but considerable venoconstriction is produced by activity in the sympathetic nerves to the veins and by agents such as noradrenaline.

Belenger (1956) maintains that microvascular changes occur in three phases in algodystrophy:

1) vasodilation of short duration.

2) vasoconstriction during which the metarterioles close; the blood passes via the thoroughfare channels to the veins which are in spasm. This results in a reflux of blood into the caplillaries causing exudation into the interstitial space.

3) vasomotor atony

According to Ficat (1968), the vicious circle of events is dominated by the capillary stasis, which is responsible for hyperpressure and hyperpermeability of the

capillaries with plasma exudation, microthrombosis and increased blood viscosity. This has been confirmed by Renier *et al.* (1979) who conducted extensive dynamic isotope studies on 20 patients with algodystrophy examining the local blood flow, vascular volume and interstitial fluid volume. They demonstrated an increase in the vascular volume and interstitial fluid volume combined with a decrease in blood flow on the affected side resulting in a local stasis as proposed by Belanger (1956). These findings also substantiate the histlological findings of capillary dilatation and blood stasis (Rutishauser *et al.* 1956), and the high intramedullary pressure measurements found using intraosseous phlebography (Arlet *et al.* 1981).

These vascular phenomenon cause tissue anoxia and acidosis which also contributes to the increased capillary permeability thus completing the cycle of events. After the oedema has regressed, fibrosis develops, diminishing the capillary permeability and hindering metabolic exchanges resulting in the atrophic changes seen in the late stages of algodystrophy.

Chemical factors which affect the microcirculation include histamine, bradykinin, noradrenaline, adrenaline, angiotensin II and serotonin. There are also local agents produced from the tissues during episodes of ischaemia. Their actions on arterioles are summarised in Table 3.1. The exact role of these agents either as final chemical mediators of the sympathetic dysfunction or normal physiological responses to the local effects of the sympathetic dysfunction is unknown.

Table 3.1. Summary of local and systemic factors which affect vascular tone in the arterioles and pre-capillary sphincters.

CONSTRICTION	DILATION
Increased noradrenaline discharge	Decreased noradrenaline discharge
Circulating catecholamines (except adrenaline in skeletal muscle and liver)	Circulating adrenaline in skeletal muscle and liver
Circulating angiotensin II	Activation of cholinergic dilators in skeletal muscle
Locally released serotonin	Decreased local temperature
	Histamine
	Kinins
	"Axon reflex"
	Decreased O_2 tension
	Increased CO_2 tension
	Decreased pH
	Lactic acid, potassium, adenosine
	Increased local temperature

Serotonin has a number of interesting pharmacological effects which may implicate it as the final chemical mediator. It produces arteriolar and venous contraction, dilatation and stasis in the capillaries, increased capillary permeability and, perhaps, dilatation in the arteriovenous anastomosis. Moreover it is found in abundance in capillary pericytes and platelets and is released in response to tissue trauma.

Serotonin is also thought to have a sclerogenic action shown both clinically and experimentally.

1) In carcinoid syndrome, where there is tumoural hypersecretion of serotonin, there is endocardial and retroperitoneal fibrosis.

2) Intra-articular injection of serotonin in the monkey provokes an articular fibrosis, which is accentuated in animals treated by isoniazid (Good et al. 1965).

It is of interest that isoniazid and phenobarbitol, known predisposing factors for the development of algodystrophy, induce increased levels of serotonin.

Besides it's vasomotor effects, the sympathetic system may have a direct trophic effect on the tissue. According to Lequesne and Auquier (1968), serotonin could be the natural sympathetic mediator between the sympathetic influx and the retraction of the joint capsules and aponeuroses.

D. Summary

Most evidence would suggest that an initial painful stimulus is transferred to the spinal column by way of both somatic and sympathetic afferents. The C-fibres in the sympathetic system along with the somatic C-fibres "open the gate" as described by Melzack and Wall, or cause direct stimulation of dorsal horn neurones. This results in stimulation of the internuncial pool neurones which induces overactivity which is dependant upon prolonged stimulation and modification of the afferent impulse by the higher centres. This modification is likely to depend upon many factors including environmental or emotional circumstances and accounts for the spontaneous pain and vascular instability associated with seemingly unrelated instances such as a cold weather, a loud noise, or fear.

The internuncial pool neurones convey impulses not only to the higher centres but other ipsilateral and contralateral medullary levels resulting in signs and symptoms distant to the initiating lesion. If the internuncial pool remains hyperactive then the efferent stimulus to the periphery and higher centres will become self-perpetuating resulting in symptoms and signs long after the initial stimulus has disappeared. Continuing impulses to the higher centres will also account for the perpetuation of perceived pain despite sympathectomy or dorsal horn neurotomy which should eliminate the afferent stimulation.

To complete the loop to the periphery, there is somatic efferent and sympathetic efferent stimulation. In the periphery, the sympathetic efferent discharge modulates the somatic action affecting afferent impulses. Moreover the sympathetic vasomotor and sudomotor actions, in themselves, increase the original peripheral stimulus.

The exact role of local agents either as final chemical mediators is unknown. It may be that the sympathetic system releases factors such as serotonin that have both vasomotor and trophic effects on the tissue. It is more likely that sympathetic

dysfunction induces the normal physiological response to trauma, this perpetuates

capillary hypertension and exudation resulting in the clinical features of algodystrophy.

CHAPTER 4: CLINICAL FEATURES OF ALGODYSTROPHY

A. Presentation

Algodystrophy commonly follows a discernable precipitating factor (see chapter 2), most commonly trauma, although some present for no obvious reason. The most frequently affected site is in the distal limb with the lower limb more commonly involved than the upper limb (Doury et al. 1981). Although involvement of the shoulder is well recognised in the shoulder-hand syndrome described by Steinbrocker, isolated involvement of the shoulder (commonly termed "frozen shoulder" in the English literature) is recognised by a number of authors (de Seze *et al* 1964; Doury *et al* 1981). The condition is also well described in the knee (Renier 1958; de Seze *et al* 1960; Blauth 1962; Doury *et al* 1978), hip (Duncan *et al* 1967; Hunder and Kelly 1968; Lequesne 1968), elbow (Ravault 1951; Schiano *et al* 1976) and more rarely the spine (Serre *et al* 1968 and 1974).

The age of presentation varies widely but most frequently occurs in later adulthood; 40-60 years of age (Table 4.1). These large reviews report very few patients under 20 years of age. In 1978, Bernstein reported 23 cases in children between the ages 9-16 years and Aftimos (1986) reported a further six. They emphasised that the condition is often overlooked in children and consequently under-reported. Although classically the condition is thought to occur predominantly in males, this has not been confirmed by all workers (Table 4.1.).

Table 4.1. Age and sex distribution in algodystrophy. Algodystrophy occurs most commonly between 40 and 60 years of age. Although less common, the condition has been reported in children.

	Number of cases	Age range (yrs)	M:F ratio
Bouvier *et al.* (1973)	100	40-70; mean 55	1.2
Kleinert *et al.* (1973)	506	15-80; mainly 30-60	1.2
Renier *et al.* (1973)	66	20-80; mainly 35-65	1.8
Patman *et al.* (1973)	113	11-80; mainly 40-60	0.8
Louyot *et al.* (1967)	140	15-80; mainly 30-65	2.0
Acquaviva *et al.* (1976)	90	20-80; mean 53	1.2
Doury *et al.* (1981)	250	19-81; mean 52	1.4
Subbarao *et al.* (1981)	123	16-80; median 54	0.4

B. Clinical features

Despite the variation in aetiology there are number of clinical features that are consistently found in algodystrophy. These comprise:-

i) pain

ii) swelling

iii) vasomotor and/or sudomotor instability

iv) articular stiffness

and have been well described in a number of clinical reports (Schiano *et al.* 1976; Doury *et al.* 1981).

i) Pain

The character of the pain varies both between patients and within the evolution of the condition in an individual patient. It is usually described as a "nagging " or "tearing " pain and, less commonly, as the classical causalgic "burning" pain. It is usually made worse by attempts at passive or active mobilisation such that the patient may involuntarily splint the affected part to prevent initiating the pain. Painful paraesthesia to light touch may occur though less commonly. The pain may also be aggravated by emotional or environmental factors such as anger or changes in temperature. The intensity of the pain varies from a moderate and tolerable one, well relieved by rest, to a severe, persistent pain, interfering with sleep and considerably affecting the individuals lifestyle. Initially the pain may be localised to the affected area but may spread to include adjacent areas.

ii) Swelling

Swelling is the most constant physical finding which, like the pain, is greater and more persistent than expected. It is particularly noticeable when the distal

extremities are affected. The oedema is diffuse and pitting in nature resulting in the loss of skin folds, particularly over the dorsum of the hand. The oedema is most marked in the earlier stages of the disease and gradually resolves.

iii) Vascular and sudomotor instability

Vascular instability occurs frequently but varies with the evolution of the condition. Initially the extremity is red and warm. As the condition progresses, and the oedema settles this is replaced by a blue, cyanotic, mottled appearance with the hand feeling abnormally cold. Again, these features may be modified by environmental or emotional factors. The sudomotor instability is less common resulting in excessive sweating, particularly in the earlier stages.

iv) Articular stiffness

This is probably the most distressing feature for the patient, particularly when the pain is less severe. It is present from an early stage, initially appearing to be secondary to the oedematous changes in the soft tissues but becoming fixed contractures as the oedema settles. The stiffness may persist long after the pain and vascular changes have subsided.

Despite the often pseudo-inflammatory appearance of the limb, there is an absence of systemic signs. The patient does not appear toxic with a tachycardia, pyrexia or regional lymphadenopathy. They have a normal white cell count and erythrocyte sedimentation rate (Serre *et al* 1967; Doury *et al* 1981).

C. Evolution

These features, although characteristic of algodystrophy, are modified depending upon the site affected and precipitating factors. As this thesis is principally concerned with algodystrophy of the upper limb following trauma, the evolution of the condition will be described with particular reference to these features.

In 1946 Ravault described neurotrophic rheumatism of the upper limb" dividing the condition into two stages. Steinbrocker one year later described the shoulder-hand syndrome, dividing it into three stages. This method of staging was used by Lee Lankford and Thompson (1977) in their description of the condition and was later modified by Doury et al. in 1981. All the authors stress the variable nature of the evolution particularly in the time span of the various stages. The following is based on Steinbrocker's original description.

i) Stage 1

(Ravault's stage 1, Doury's stages 1 and 2)

This stage may run from the time of onset for a few weeks to three months. The time span between the initial trauma and the appearance first signs varies from a few days to a months (five months according to May et al. (1973), two months according to Schiano et al. (1976)). This large variation is most likely due to the retrospective nature of most studies. The features described largely concern the hand. The stage is characterised by the appearance of pain which is worse on movement, the intensity varying from patient to patient. There is tenderness to palpation or pressure on the joints and phalanges of the fingers. The swelling is initially marked and more · responsive to elevation than in the later stages. The skin takes a pink, red or sometimes purplish colour and feels warm to touch. This may be associated with increased sweating, particularly in the palm. There is limitation in flexion and

particularly extension of the fingers. The thumb is usually only minimally affected. Pain and limitation in movement are the overriding features when the shoulder is involved (Fig 4.1).

ii) Stage 2

(Ravault's stage 2, Doury's stage 3)

In this stage the pain gradually begins to subside though in certain, more severe cases it may become more constant in nature and radiates proximally. The pitting oedema resolves to be replaced by a more brawny oedema and the appearance of fixed joint contractures. This is associated with a change in the vascular instability with the skin becoming cooler and more cyanotic in appearance. The loss of skin folds, particularly over the dorsum of the hand, associated with the brawny oedema results in a glossy appearance to the skin.

iii) Stage 3

(Ravault's stage 2, Doury's stage 3)

This stage is dominated by the onset of trophic changes. The pain and vascular instability has usually completely subsided. The hand looks atrophic with muscle wasting and prominence of the interphalangeal joints of the hand. The overriding feature is the articular stiffness, particularly of the proximal interphalangeal joints of the fingers. There may be lack of both full extension and curl-up of the fingers (Fig 4.2).

The eventual evolution of the condition is favourable with complete recovery within several months to two years. There may be sequelae, particularly in the hand, such as mild trophic changes in the skin and limitation in the range of movement of the fingers.

Fig 4.1. Stage I algodystrophy. The hand is classically swollen with pink or red discolouration of the skin. There is stiffness of the fingers which are held in slight flexion at the interphalangeal joints.

Fig 4.2. Stage III algodystrophy. The hand has taken on a dystrophic appearance with wasting which is most prominent in the fingers. This accentuates the interphalangeal joints which were also stiff.

CHAPTER 5: TREATMENT

"Diseases desperate grown

By desperate appliance are cured

Or not at all"

Anon

Over the past one hundred and twenty years, a wide variety of therapies have been recommended for the treatment of algodystrophy. The first documented cure of a patient with causalgia was reported in 1930 by Spurling, a neurosurgeon, who performed a successful cervicothoracic sympathectomy. Prior to this event, patients with severe algodystrophy endured drug addiction, mental deterioration and chronic invalidism.

Fortunately, although the optimum method of management is still being debated, the prospects for these patients has become more encouraging particularly with the use of calcitonin. There is, however, a consensus that early treatment will achieve the best results regardless of the method employed (Eisinger *et al.* 1974; Doury *et al.* 1981; Schutzer and Gossling 1984; Wang *et al.* 1985). Despite this, long-term cures have been reported in some late-stage patients.

The approaches to treatment are summarised in Table 5.1 and discussed below.

Table 5.1. Treatments used in algodystrophy.

Conservative:

    Physiotherapy

    Transcutaneous nerve stimulation

    Miscellaneous

Sympathetic interruption:

    Regional sympathetic blockade

    Surgical sympathectomy

    Chemical sympathectomy

Drug treatment:

    Corticosteroids

    Beta-blockers

    Calcitonin

    Miscellaneous

A. Conservative Treatment

i) Physiotherapy

Physiotherapy is often the initial treatment of choice, either solely or in combination with other treatments. However, the role of physiotherapy remains an area of controversy replete with anecdotal comments (Schumacker and Abramson 1949; Queneau *et al.* 1956; Johnson and Pannozzo 1966; Samuel 1970; Kim *et al.* 1979). This is largely because of the variety of therapeutic protocols and the lack of clinical documentation in the literature. This is illustrated in the general belief that early mobilisation of an injured extremity prevents the development of algodystrophy. Although this would appear sound in theory, no one has demonstrated it's value in a controlled prospective and double blind study.

Physiotherapy is aimed initially at improving the active range of movement. Passive mobilisation should be avoided, at least initially, as forcing motion to the point of discomfort may aggravate the condition resulting in more intense pain, swelling and stiffness (Savin 1974). Similarly the use of heat or ice-packs should be avoided as extremes of temperature may increase afferent transmission and exacerbate the condition.

ii) Transcutaneous nerve stimulation (TNS)

During the past decade numerous reports of the favourable results obtained with different kinds of TNS in acute and chronic pain disorders have been published (Long 1974; Melzack 1975; Long 1977; Rosenberg *et al.* 1978), including algodystrophy (Goodman 1971; Stilz *et al.* 1977; Richlin *et al.* 1978). Although the mechanism of action is unknown, Melzack (1975) speculated that TNS, at levels capable of producing cutaneous tingling, could activate transmission in large fibres. According to the gate-control theory of pain (Melzack and Wall 1965), this would decrease the transmission of

pain to higher centres. One study demonstrated it's effect in altering sympathetic tone

by raising skin temperature in normal subjects (Owens *et al* 1979). Another study

found no alteration in skin temperature, blood flow, or other autonomic functions either

in normal subjects or in patients with intractable pain, although some of these patients

experienced pain relief (Ebersold *et al* 1977). While some patients have been afforded

long-term pain relief with a single treatment, most patients require multiple sessions

over several days. A series of eight patients found that TNS provided long-lasting relief

in 25%, transient relief in 50% and no relief in 25% of those observed (Meyer and Fields

1972). TNS has also been used successfully in two isolated cases in children (Stiltz *et*

al 1977; Richlin *et al* 1978).

iii) Miscellaneous

Other treatments include direct peripheral nerve stimulation (Nashold *et al*

1982), radiotherapy (Edeiken and Wolferh 1936; Munford 1938), electro-acupuncture

(Chan and Chow 1981; Leo 1983), active-stress loading (Watson *et al* 1986) and

ultrasound to the stellate ganglion (Goodman 1971). None have been adequately

investigated in prospective controlled studies.

B. Sympathetic Interruption

The rationale for sympathetic blockade in patients with sympathetic dystrophy is the interruption of the abnormal reflex mediated by the autonomic nervous system. Regardless of the inciting event, successful blockade is nearly always of value in the early stages. The blockade can be achieved by regional sympathetic block or surgical sympathectomy. Alternatively, intravenous infusion of reserpine or guanethedine have been used, which effectively produce a transient chemical sympathectomy,.

i) Regional sympathetic block

Sympathetic blocks were first used by Leriche (1939) and later by Homans (1940) and Livingstone (1943). The use of regional sympathetic blockade in a patient serves as both a diagnostic and therapeutic function. Patients who do not experience any pain relief from a technically successful block should be suspected of having a problem other than algodystrophy. In it's early stage, a prolonged remission may be obtained from a single stellate or lumbar sympathetic block. Far more commonly, however, multiple blocks are required for pain control. While some authors have described the use of as many as ten to fifteen blocks (Steinbrocker 1968), the more commonly accepted practice is to limit the number to a maximum of three or four (Kleinert *et al* 1973; Lankford and Thompson 1977). If a patient demonstrates a clinical response, but requires more than four blocks, consideration should be given to surgical sympathectomy.

In a series of 69 patients, Steinbrocker *et al.* (1946), using serial ganglionic blocks achieved excellent results in 32%, some benefit in 49% and no benefit in 19%. The same study compared these with another group of 13 patients treated with corticosteroids, finding the blocks more effective. Duration of follow-up was not reported. Another series of 32 patients found that 63% had a definite improvement

although the effects were permanent in only a third (Schumacker and Abramson 1949).

In a series of 26 patients undergoing follow-up for a period of three years, excellent

results were noted in 32% and good results in 50%; two recurrences were reported

(Steinbrocker and Argyros 1958). Kleinert et al. (1973) in a series of 183, reported an

improvement in 144 (79%) patients. The improvement was permanent in 121 (66%); a

further 23 (13%) underwent surgical sympathectomy after a temporary response and 39

(21%) showed no improvement. More recently Wang et al. (1985) reported a three year

follow-up on 71 patients, 27 treated conservatively and 43 with sympathetic blocks. Of

those treated conservatively, 11 (41%) showed signs of improvement at three years

compared with 28 (65%) in the group treated by sympathetic blocks.

Infusions of local anaesthetic by an indwelling catheter have been utilized to

achieve prolonged paravertebral sympathetic blockade. In a series of 160 patients, 57%

were noted to have an excellent response, and 27% were noted to have a good response

but, in the more severe cases, local anaesthesia yielded only temporary palliation

(Betcher et al. 1953). Another series of 25 patients reported improvement in 90% but

with a 25% relapse rate over the subsequent three years (Linson et al. 1983).

ii) Surgical sympathectomy

Periarterial sympathectomy, described in a case report by Heymann in 1924, is

the first mention of surgical sympathectomy. Leriche (1926) was so impressed by it's

effects that it became the treatment of choice for osteoporotic syndromes in Strasbourg

in the 1920's. It has now been superseded by paravertebral sympathectomy which has

been shown to be more effective (Herrmann et al. 1942; Rasmussen and Freedman

1946).

The current indication for surgical sympathectomy is a diagnosis of

algodystrophy in any patient who has obtained even partial, short-lived, relief from

regional sympathetic blockade, but who has had four such blocks without a permanent

cure. Several large series have examined the results of paravertebral sympathectomy, and 58% to 100% of the patients observed (mean 84%) had complete relief of symptoms (Echlin *et al.* 1945; Evans 1946; Rasmussen and Freedman 1946; Holden 1948; Schumacker and Abramson 1949; Barnes 1953; Hardy *et al.* 1958; Wirth and Rutherford 1970; Kleinert *et al.* 1973; Patman *et al.* 1973; Lankford and Thompson 1977). The follow-up period in these series ranged from six months to 17 years. Those patients in whom pain was not relieved by ganglionectomy usually had incomplete sympathetic denervation or severe, long-standing disease.

iii) Chemical sympathectomy

a) Guanethedine

In 1974 Hannington-Kiff introduced intravenous regional sympathetic block with guanethedine as an alternative to traditional sympathetic neural blockade. The procedure is essentially the same as for intravenous regional neural blockade to induce local anaesthesia, using a modification of the technique described by Bier in 1908, but substituting guanethedine for local anaesthetic. Pharmacologically, the false transmitter guanethedine, is actively taken up by the sympathetic nerve-endings and then displaces noradrenaline from it's storage sites (Hannington-Kiff 1982).

Excellent results for pain relief utilizing this technique have been reported by many authors (Loh *et al.* 1980; Glynn *et al.* 1981; Tabira *et al.* 1983). The pain relief usually lasts from 12 to 36 hours, but it can be as long as six months (Loh *et al.* 1980). Thomsen *et al.* (1982) have documented a threefold rise in total blood flow in the forearm following sympathetic block with intravenous guanethedine, and the changes persisted for 48 to 72 hours. Since no associated increase in muscular blood flow was reported, they concluded that the rise was secondary to augmented skin flow, as confirmed by concomitant elevation of the skin temperature. In a series of 20 patients

who were followed-up for three months, guanethedine administered by Bier's block was compared with stellate ganglion blockade (Bonnelli *et al.* 1983). Guanethedine was equally effective for pain relief and was slightly longer lasting. In another series of 47 patients however, 21% of those observed received no benefit, 51% had less than 24 hours pain relief and in only 13% did the pain relief last more than six months (Loh *et al.* 1980). The greatest effect was noted in patients with marked hyperaesthesia. Glynn *et al.* (1981) in a double-blind study involving 31 patients demonstrated significant pain reduction following a block with intravenous guanethedine compared with physiological saline. However, several patients who were treated with intravenous saline also experienced amelioration of pain, suggesting a strong placebo effect. There was no effect on palmar sweating.

b) *Reserpine*

Reserpine injected intra-arterially is effective in the pain relief of pain and vasospasm associated with Raynaud's phenomenon and frostbite (Romeo *et al.* 1970; Tindall *et al.* 1974; Porter *et al.* 1976). Successful treatment of algodystrophy with intravenous reserpine has also been reported (Benzon *et al.* 1980; Chuinnard *et al.* 1980). Reserpine, like guanethedine, can produce a sympathetic block when administered by Bier's technique. It's mechanism of action is the reduction of storage-vesicle re-uptake of catecholamines, thereby slowly depleting noradrenalin stores in sympathetic nerve-endings.

McKain *et al.* (1983), in a prospective, randomised double-blind study, evaluated the sympatholytic effects of intravenous guanethedine and reserpine in asymptomatic volunteers. Saline or 0.25% lignocaine was used as a control solution. Sympathetic adrenergic and cholinergic activity was specifically and independently investigated. Reserpine had no effect, in comparison with the pre-study baseline or control solutions, on either adrenergic or cholinergic function. Guanethedine, however, consistently

produced selective adrenergic blockade with resultant peripheral vasodilation, at the

same time having no effect on the sympathetic cholinergic functions such as sweating.

It appears that guanethedine may be useful in the treatment of pure vasospastic

conditions. The absence of any effect on sympathetic cholinergic activity, however, may

make it inferior to the more global action of conventional sympathetic blocks or

sympathectomy in the treatment of algodystrophy. Although the reported complications

with the use of guanethedine and reserpine have been few, prolonged othostatic

hypotension, dizziness, somnolence, and nausea and vomiting can occur.

C. Drug Treatment

i) Corticosteroids

The results of treatment with systemic corticosteroids have been examined in several studies since they were first used in 1958 by Steinbrocker and Argyros (Rosen and Graham 1957; Glick 1973; Flatt 1974; Kozin *et al.* 1976; Bulgen *et al.* 1978; Kozin *et al.* 1981; Christensen *et al.* 1982). Their effectiveness however still remains controversial as many of the trials were uncontrolled. Consequently, some authors claim it has no role in the management of algodystrophy (Serre *et al.* 1967; Schiano *et al.* 1976).

Corticosteroids are typically given in short courses, being initially used in high doses (60 to 80 mg of Prednisoline per day) and then quickly tapered off. In a series of 53 patients, Kozin *et al.* (1976 and 1981) obtained encouraging results using this regime in the treatment of patients suspected of having algodystrophy. In a subset of patients who met all the criteria for definite algodystrophy, 82% had a good or excellent subjective response to the steroid regime. This fell to 76% when all patients with a probable or possible diagnosis of algodystrophy are included. Although the results did not appear to be related to the duration of existing symptoms before steroid treatment, several patients who achieved good responses later required re-treatment. No placebo treated controls were included in the investigation. In a smaller series using much larger doses (100 to 200 mg daily for two weeks), Rosen and Graham (1957) reported a good or excellent result in 67% of patients. There was no long-term follow-up.

In one of the few randomised, controlled studies, Christensen *et al.* (1982) investigated the response of 23 patients to either prednisolone or placebo. Ten milligrams, three times a day, was given until there was a clinical response, upto a maximum of 12 weeks. They observed that in all 13 patients treated with prednisolone

the pre-treatment score improved by 75%, whereas only 20% of the patients who

received placebo experienced relief.

The mechanism of action of corticosteroids in this condition remains unknown.

Kozin et al (1976 and 1981) demonstrated a chronic perivascular infiltrate on synovial

biopsy specimens from involved sites. The potent anti-inflammatory properties of

prednisolone may account for it's therapeutic effect.

Poplawski et al (1983) recently reported their results with a new method of

treatment based on a further modification of the Bier block. Intravenous regional

blocks of 1% lignocaine combined with Solu-Medrol (80 mg methylprednisolone sodium

succinate) were administered to 28 patients with algodystrophy. There was significant

improvement in 21 of the patients usually after several treatments. Local steroid

injection has also been used with some effect, particularly in the treatment of the

shoulder-hand-syndrome (Berger 1954; Serre et al 1967; May et al 1973).

The side-effects of steroid therapy are rarely mentioned. Glick (1973), however,

found unacceptable weight gain and moon facies in two patients and dyspepsia in three

patients. Schiano et al (1976) also found it illogical to prescribe steroids for a condition

which includes a regional osteoporosis as one of it's features.

It would appear therefore that, although steroids may have an effect, their use is

purely empirical and should only be considered for patients who either refuse or cannot

tolerate the more recognised therapeutic regimes.

ii) Beta-Blockers

There have been conflicting results of the use of beta-blockers in isolated cases

of algodystrophy. Several recent larger series have suggested however that they may be

effective. Schiano et al (1976), in a small study of seven patients obtained promising

results. May et al (1977) reported 30 "good or very good" results out of 34 patients

with improvement as early as the seventh day. In another study 72% had an excellent and 13% a good result (Ziegler *et al.* 1979). Neither of these studies were controlled.

Propranolol is the agent most often used though it's mode of action is poorly understood. It has a central action, reducing anxiety and regulating the preganglionic sympathetic tone; and a peripheral action, slowing down nerve conduction in the reflex arc and blocking the sympathetic affects on the microcirculation.

iii) Calcitonin

This will be dealt with in detail in the next chapter.

iv) Miscellaneous

Other drug treatments include griseofulvin (Cohen *et al.* 1960; Cherot and Amor 1983), nifedepine (Prough *et al.* 1985), alpha-blockers (David-Chausse *et al.* 1957).

CHAPTER 6: CALCITONIN

A. Introduction

Since its discovery by Copp *et al.* in 1962, calcitonin has been widely studied and most of it's actions elucidated. Nevertheless, calcitonin's role is still under discussion both in physiological and in pathological conditions, so that it has been refered to as "a hormone in search of a function".

Calcitonin is a peptide hormone secreted by the parafollicular or C-cells of the thyroid gland (Foster *et al.* 1964; Pearce 1966). It is composed of 32 amino acids with a 1-7 disulphide bridge and a prolineamide at the carboxy-terminus. It is initially synthesised as a larger precursor form and may be present in the blood stream in various forms of different molecular weight.

The amino acid sequence of many species of calcitonin have been determined to date, and four have been used therapeutically; extracted porcine and synthetic salmon, eel and human. In spite of the similarity between the various calcitonins, there are considerable differences in half life, metabolic clearance and some biological activities, especially between mammalian and non-mammalian calcitonins.

B. Mode of Action of Calcitonin in Algodystrophy

Calcitonin has been widely used in the treatment of bone disease characterised by active bone turnover, such as Paget's disease of bone and hypercalcaemia due to malignancy. In these conditions, the beneficial effect of calcitonin is due to its ability to block bone resorption (Freidman and Raisz 1965).

As one of the major features of algodystrophy is the marked bone resorption, it therefore seemed logical to use an agent with an anti-osteolytic action. In January 1973, Eisinger *et al.* reported the first ten cases of algodystrophy to be treated with calcitonin, seven of whom had a rapid clinical response. The rapid resolution of pain and vascular instability in these early studies indicated however, that calcitonin had effects other than preventing bone resorption.

These effects will now be considered in more detail.

i) Pain

Several lines of evidence suggest that calcitonin is both a peripheral and a central modulator of the neural activity evoked by painful stimuli.

a) Peripheral

One reasonable hypothesis about the analgesic action of calcitonin is that it influences the production of pain-inducing or pain-exacerbating substances. Indeed, in skeletal diseases in which there is intensified bone resorption, local increases of H^+, kinins and prostaglandins appear to contribute to pain in the bone as well as in other tissues. In particular, arachidonic acid metabolites may be important in hyperalgesia, since they are known to be general pain amplifiers (Ferreira *et al.* 1973)

That calcitonin may interfere with the prostaglandin system has been suggested indirectly by its anti-inflammatory action in carragenin-induced oedema of the foot

(Abdullahi *et al.* 1975) and directly by its inhibition of prostaglandin and thromboxane

synthesis in *vitro* (Ceserani *et al.* 1979). Evidence for a direct anti-inflammatory action

of calcitonin has been obtained by Strettle *et al.* (1980), who have shown a potent

inhibition of histamine-induced vascular leakage, which would appear not to be

dependant on the effect of calcitonin on plasma calcium concentration. This action of

calcitonin could account partially or fully for the resolution of the acute inflammatory

appearance seen in algodystrophy

This peripheral action of calcitonin would account for the success in early

treatment of algodystrophy, before the pain in the spinal or higher centres becomes self-

propagating.

b) Central

Calcitonin has been found in inframammalian species lacking a bony skeleton

(Copp 1962); this finding suggests the possibility of a new role for the hormone.

Recently, the presence of immunoreactive calcitonin has been demonstrated in the

human pituitary gland and cerebrospinal fluid (Cooper *et al.* 1980; Pavlinac *et al.* 1980),

and the presence of binding sites for calcitonin in the human brain (Pecile 1983). The

most striking feature of this work was the dense clustering of calcitonin binding sites in

some of the brain stem and cord structures that participate in the regulation of pain

perception. It is of interest that a primary condition of high calcitonin levels in

cerebrospinal fluid has been found to accompany a syndrome of congenital insensitivity

to pain (Fabri *et al.* 1983).

The intracerebroventricular administration of calcitonin in animals (Pecile *et al.*

1975) and the subarachnoid injection of calcitonin in man (Fraioli *et al.* 1982) result in

analgesia. Since similarities have been observed between morphine- and calcitonin -

induced analgesia, it has been thought that the hormone's analgesic effect may involve

the endogenous opiate system, in particular Beta-endorphins. Recent data have shown

a rapid increase in circulating Beta-endorphin like immunoreactivity in man after intravenous infusion of salmon calcitonin (Gennari 1983). Nevertheless, the role of endogenous opiates in mediating the analgesic effect of the hormone is still debated. Some authors report that calcitonin-induced analgesia is not reversed by naloxone, the opiate antagonist (Braga *et al.* 1978); others claim that the analgesic effect of calcitonin can be reversed by the use of naloxone at doses 10 to 1000 times greater than those required to antagonize the effects of morphine (Bates *et al.* 1981). At such high doses of naloxone however, the effects of the drug on the opiate receptors might well be non-specific. A possible resolution of this paradox may lie in studies suggesting the existence of different mechanisms and receptors for analgesia specific to calcitonin (Pecile 1983).

It is difficult however to envisage a direct central action fron calcitonin administered in it's parenteral form, as in algodystrophy, because their is no evidence to suggest that calcitonin crosses the blood brain barrier.

ii) Vascular instability

Calcitonin has been shown experimentally to have a vaso-active effect on vascular smooth muscle. Driessens *et al.* (1981), studying isolated blood vessels in canine tibia, believed that some of the skeletal effects of calcitonin may be due to it's direct action on the vascular smooth muscle cell of bone blood vessels. They showed that calcitonin caused a dose-dependant increase in perfusion pressure indicating that it caused constriction of bone blood vessels. In a clinical context, medullary carcinoma of the thyoid secretes excess calcitonin which results in symptoms of flushing. This may be due in part to another peptide encoded by the human calcitonin gene, calcitonin gene related peptide (CGRP), which is found in the circulation and is the most powerful vaso-dilator known to man (Struthers *et al.* 1986).

Renier *et al.* (1979) demonstrated vascular stasis in patients with algodystrophy using dynamic isotope studies, one feature of which was an increase in the vascular volume. Following treatment with calcitonin the vascular volume was decreased without entailing a decrease in the bone uptake. This led them to think that the therapeutic efficiency of calcitonin was derived from it's vascular effect rather than from an action on bone. Calcitonin has also been used in other conditions where there is an abnormality of the micro-circulation such as migraine and Raynaud's disease with some effect (Schiano and Acquaviva 1976; Vayssairat *et al.* 1980).

iii) Increased bone resorption

Milhaud *et al.* (1965) was the first to suggest that calcitonin acted by inhibiting bone resorption. *In vitro* studies by Freidman and Raisz (1965) using bone cultures confirmed this finding. A direct action of calcitonin on bone was also demonstrated by perfusion studies using the isolated cat tibia (MacIntyre *et al.* 1967). They showed that infusion of porcine calcitonin caused an arteriovenous difference in calcium concentration of upto 5%, corresponding to a net retention of calcium in bone. In addition, when calcitonin was infused into rats there was a marked reduction in urinary hydroxyproline (Martin *et al.* 1966). These results indicated that calcitonin acted by inhibiting bone resorption, thereby decreasing the circulating levels of the products of resorption; calcium, phosphate and hydroxyproline-containing peptides.

It was subsequently established that this inhibition of bone resorption was brought about by an inhibitory effect of calcitonin on the osteoclast (loss of ruffled borders, reduction in cell size and numbers). The hypocalcaemic effect is not seen normally in the adult as bone turnover is relatively low. Even pharmacological doses of calcitonin cause only a transient fall in serum calcium in normal adults (Foster *et al.* 1966; Singer *et al.* 1969). When bone turnover is high however, such as in childhood or

conditions such as Paget's disease, calcitonin causes a sharp decrease in serum calcium (Woodhouse *et al.* 1970; MacCredie *et al.* 1971).

Although a stimulatory effect of calcitonin on bone formation cannot be excluded, experiments both *in vivo* and *in vitro*, have failed to establish any increase in osteoblast formation (Milhaud *et al.* 1965; Raisz 1965; Robinson *et al.* 1967; Reynolds *et al.* 1968).

Thus in algodystrophy, where there is a regional increase in bone turnover, calcitonin will prevent excessive resorption and may speed skeletal recovery as the condition subsides. It is unlikely however that this effect on bone is related to the alleviation of symptoms seen following treatment with calcitonin.

C. The Use of Calcitonin in Algodystrophy.

Since the report by Eisinger *et al.* in 1973, the beneficial effects of calcitonin

have been confirmed (Acquaviva *et al.* 1976; De Bastiani *et al.* 1978; Ginsberg *et al.*

1978; Doury *et al.* 1981; Martin 1985; Gobelet *et al.* 1986). Calcitonin appears to have

a dramatic effect, particularly in the early stages, but unfortunately only one

randomised double-blind study has been published (Doury *et al.* 1981). They used 100

units of salmon calcitonin or placebo intramuscularly per day for four weeks in 28

patients suffering from stage I algodystrophy of the lower limbs. At 14 days there was

an appreciable improvement of their pain in 64% of those receiving calcitonin compared

with 25% in the placebo group (p<0.001). At 28 days both groups had improved such

that there was no significant difference in their pain. Although this study demonstrates

the rapid effect of calcitonin, it also confirms the spontaneous resolution of symptoms

that can occur in algodystrophy. Open studies evaluating the use of calcitonin should

therefore be interpreted with caution. This criticism is true of most studies on the

treatment of algodystrophy and highlights the need for more information on the early

natural history of the condition.

Martin in 1985 published the results of a multicentre study involving 432

patients using 80 units of salmon calcitonin intramuscularly six days a week for three

weeks followed by three injections a week for a further two weeks. Pain had

disappeared at one week in 58% and in 75% by three weeks. The rapid resolution of

pain was also reported by Ginsberg *et al.* (1978) with an 80% good or very good

response in 14 patients. There is a similar resolution seen in the vasomotor symptoms,

swelling and stiffness.

At present, the dose of calcitonin used appears to be purely empirical. Most

studies use 80-100 units of salmon calcitonin by daily intramuscular or subcutaneous

injection daily for four weeks which is equivalent to 160 units of porcine calcitonin (De

Bastiani *et al.* 1978). Only one study has looked at the effect of a smaller dose. Acquaviva *et al.* (1976) in an open study involving 90 patients compared the effect of 100 units of salmon calcitonin with a control dose of 1 unit. Of the 79 (88%) patients who received the larger dose, 54 (60%) derived benefit, whereas none of the 11 (12%) in the other group improved. Although the lack of any improvement in the control group is surprising considering the presumed incidence of spontaneous improvement, it indicates that doses as small as 1 unit have no effect. More controlled studies are needed to define the optimum dose.

Side-effects following treatment with injected calcitonin are common. Doury *et al.* (1981) observed intolerance in 20-35% though the incidence may be as high as 60% (Gennari *et al.* 1983). The symptoms however, were seldom intense enough to interrupt treatment. The side-effects are usually only troublesome; consisting of vasomotor symptoms such as hot flushes, nausea and vomiting or lethargy. They appear rapidly within minutes and upto an hour after the injection and last several hours. Over the course of the treatment period, the side-effects often become less troublesome or can be controlled with symptomatic therapy. An advantage of a smaller dose of calcitonin, if it can be shown to be effective, may be a lower incidence of side-effects.

Antibody formation may be a problem with non-human calcitonins; it has recently been shown that up to 57% of patients treated with salmon calcitonin may develop antibodies to the hormone. Furthermore, clinical resistance may occur in upto 23% of patients (Singer 1980). The human hormone is thought to be non-antigenic (Dietrich and Fischer 1977) but may be associated with more side-effects than salmon or eel calcitonin at equivalent doses (Gennari *et al.* 1985). The short duration of treatments used in algodystrophy makes antibody formation a theoretical rather than practical problem.

D. Nasal Calcitonin

The administration of peptide hormones (insulin, calcitonin) is restricted to the parenteral route as proteolytic digestion prevents administration by mouth (Stevenson *et al.* 1981). This is one of the major drawbacks to the use of calcitonin in conditions such as algodystrophy where a regimen of regular daily injections is required. For this reason other non-parenteral routes have been sought. Various substances, including vasopressin, leuteinising hormone releasing hormone, insulin and glucagon are absorbed by the mucosa of the respiratory system.

In 1984, Reginster *et al.*, reported the results of nasally administered calcitonin in Paget's disease with encouraging results. There have since been a number of studies confirming the use of nasally administered calcitonin in conditions with increased bone resorption though with conflicting data concerning it's efficacy compared with subcutaneous administration (Eisinger 1985; Benjamin *et al.* 1986; Elomaa *et al.* 1986; Nagent de Deuxchaisnes *et al.* 1987). This is largely because there are few dose-response data for the parenteral route and it is therefore difficult to assess the bioequivalence of intranasal calcitonin. However in the doses used intranasally (upto 400 units), the decrease in bone turnover in both the acute and long-term appear to be less marked than with the subcutaneous administration of calcitonin. These findings suggest a lower bioequivalence.

This reduced absorption may also account for the lack of systemic side-effects seen. It has been argued however, that steady absorption from the nasal mucosa avoids the peak to peak variation in absorption from a subcutaneous site. The high calcitonin levels in circulation at each peak accounting for the side-effects. Of the 100 patients studied (Eisinger 1985; Benjamin *et al.* 1986; Elomaa *et al.* 1986; Nagent de Deuxchaisnes *et al.* 1987) none developed systemic side-effects and only 17 developed local side-effects with 3 withdrawing from treatment.

Pontiroli *et al.* (1985) compared the acute effects of human calcitonin using the same dose given intravenously and intranasally but with the addition of sodium glycholate as a surfactant to increase absorption via the nasal route. They found no difference in the hypocalcaemic response or the incidence and severity of side-effects between the two groups.

It would appear therefore that calcitonin is absorbed through the nasal mucosa in sufficient quantity to have some effect on bone turnover though the magnitude of this effect is not known. Further studies are needed to confirm that the addition of a surfactant to the nasal spray will improve the efficacy. If so this may be at the expense of systemic side-effects similar to those seen with parenterally administered calcitonin.

CHAPTER 7: AIMS OF THESIS

Although there is a great deal of disagreement about the incidence of algodystrophy, it is becoming increasingly recognized that the condition is far more common than originally thought. A high incidence has been recognized in the French literature for many years perhaps because in Britain and North America the less severe forms of the condition have been ignored.

Even though the condition was described over a century ago, little is known about the early natural history of the condition and the degree of morbidity it causes, particularly in it's less severe form. This is due to a number of reasons, not least of all the confusion over the nomenclature of the syndrome. The reported studies are almost universally retrospective and poorly constructed incorporating patients with a variety of aetiological factors, sites of involvement and stages of disease into one group. The results are consequently difficult to analyze. There is also a lack of quantitative methods of assessment to accurately follow the progression of the disease. The same criticisms can also be levelled at the various therapeutic trials described.

The first aim of this thesis was to document the incidence and natural history of algodystrophy following Colles' fracture. Colles' fracture appeared to be a reasonable model of post-traumatic algodystrophy since it is common, occurs in a fairly homogeneous population (post-menopausal women) and follows a reasonably constant type of trauma. Even so, the reported incidence in the literature ranges from 2 - 30%, probably related to non-uniform criteria for the selection, evaluation and diagnosis of the disorder.

A second aim was to define the early natural history of the condition following Colles' fracture in a controlled fashion using quantitative methods of assessment which include clinical observations, radiographs, Technetium isotope scans, single photon absorption scans, laser Doppler angiography and serum and urine biochemistry. These

methods were used to identify the various features of the disease and follow their development with time. From this it was hoped to identify certain features at presentation which would accurately predict the course and severity of the condition. This would enable the most appropriate form of treatment to commence at an earlier and probably more effective stage. I also aimed to document the morbidity caused by the various degrees of severity found in the condition to determine whether it's increasing recognition was of clinical significance.

A sound knowledge of the natural history of the condition is necessary for the evaluation of therapeutic regimes, particularly since there may be a high incidence of spontaneous resolution. It was intended to use the quantitative methods of assessment as a method to determine the effects of therapeutic intervention. The use of calcitonin has gained favour in the treatment of algodystrophy with particular interest in the nasal form of administration which improves patient compliance. The rationale for the use of calcitonin was that it had analgesic properties, affected the microcirculation and prevented bone resorption, all of which might have been beneficial in algodystrophy. The results of therapeutic intervention are however difficult to evaluate because of the lack of controlled trials and the subjective method of assessment. For this reason the final aim was to thesis examine the role of nasal calcitonin in a double blind controlled clinical trial.

METHODOLOGY

CHAPTER 8: STUDY DESIGN

A. Introduction

A criticism of many previous studies of algodystrophy has been the variable nature of the study group with regard to aetiology, site of involvement and stage of disease. In an effort to avoid these pitfalls, we attempted to select a uniform population for study.

Colles' fracture was considered an appropriate clinical model for a number of reasons. The fracture is one of the most frequent fractures in man: only fractures of the fingers and ribs are more frequent (Conwell 1970) and accounts for 8-15% of all bony injuries (Golden 1963; Sturm 1969). Before the age of forty, the incidence of Colles' fractures is about equal in males and females. In men, the incidence rises slightly from forty to eighty years of age, whereas in women the incidence rises 8-10 times from forty to sixty after which it remains constant (Alffram and Bauer 1962; Newton-John and Morgan 1970; Falch 1983). This difference is associated with the higher incidence of osteoporosis after the menopause in women (Reifenstein 1957; Bate 1969; Newton-John and Morgan 1970). The fracture is usually caused by a simple fall on the outstretched hand with the wrist in dorsiflexion (Bacorn and Kurtzke 1953; Frykman 1967). Thus the degree and type of trauma required to produce a Colles' fracture is fairly uniform. This may not be true in younger patients as the amount of energy required to produce the fracture is greater (Alffram and Bauer 1962), indeed describing these fractures as Colles' fractures may be misleading. Also, the method of treatment, which has been implicated as a factor in the development of algodystrophy, is identical within the orthopaedic department from which the patients in this study were collected.

In summary we chose to study algodystrophy in a fracture which is common, which occurs in a relatively uniform population (post-menopausal females), arises in a

comparable manner with regard to type and degree of trauma and is treated in a standardised manner.

Despite numerous papers on Colles' fractures in the English literature, the incidence of algodystrophy has only been reported in upto 2% cases (Bacon and Kurtzke 1953; Plewes 1956; Lidström 1959; Frykman 1967; Poole 1973; Stewart et al. 1984). The studies are generally retrospective and the presence of algodystrophy is usually considered an incidental finding to the main topic of the paper. Thus the 2% may reflect the incidence of algodystrophy in it's fully established and most severe form. In contrast, in a study designed specifically to investigate algodystrophy, Aubert (1980) recorded an incidence of 29%. The increase in incidence is probably accounted for by the detection of a greater number of milder cases. This was confirmed recently by Atkins et al. (1990).

Patients who have sustained a Colles' fracture appear to be suitable for both an investigation into the natural history of algodystrophy and as a therapeutic model.

B. Study Design for Natural History

Between December 1987 and April 1989, 274 patients were reviewed personally after attending the Accident and Emergency Department at the Royal Hallamshire Hospital with a Colles' fracture. No attempt was made to influence their initial management. An undisplaced fracture was immobilised in a moulded plaster of Paris radial slab over a single layer of plaster wool with the hand held in radial deviation and slight flexion to prevent displacement. A displaced fracture was reduced under regional (Bier's block) or general anaesthesia and the position held in a radial slab in the position described above. Rarely the fracture was immobilised in a below elbow cast. All patients were given a broad arm sling to elevate the fracture for two to three days and encouraged to mobilise fingers, elbow and shoulder. They were also instructed to return if concerned about pain or swelling and discolouration of the fingers. They were then reviewed the following day to ensure that there was no impairment of circulation or neurology and to check the adequacy of the plaster. A radiograph was taken at one week to ensure there had been no loss in position in which event a further manipulation of the fracture was performed.

The plaster was removed at four to five weeks when details concerning the type of fracture, their management or problems while in plaster were recorded (Table 8.1). The fracture was described using Frykman's classification (Frykman 1967) based on the postero-anterior and lateral radiographs taken at initial presentation. This description is dependant upon involvement of the distal radio-carpal or radio-ulna joint with or without avulsion of the ulna styloid and consists of a scale of 8 different types with an increasingly unfavourable prognosis (Table 8.2). No attempt was made at this stage to evaluate the presence of the various features of algodystrophy because the patients were understandably anxious and any data gained might not accurately reflect the true

clinical state. The patients were given general advice regarding mobilising fingers, wrist and forearm and asked to return in two weeks.

The main features of algodystrophy, namely pain, vascular instability, swelling and stiffness, were evaluated with a variety of clinical and laboratory techniques. These included serum and urine biochemistry, bone scintigraphy, radiology, photon absorptiometry and laser Doppler angiography and will be referred to in detail later. For logistic reasons, not all patients were fully investigated (excluding clinical evaluation), particularly those patients who had no evidence of algodystrophy (Appendix I). Sufficient patients without algodystrophy were enrolled however, to act as representative controls for each of the techniques described (excluding laser Doppler angiography), details of which are given in the subsequent sections of this chapter.

At two weeks out plaster, the patients were first fully clinically assessed. They were then reviewed monthly, initially upto 6 months in those with no evidence of algodystrophy, or until they were asymptomatic in those with algodystrophy. The investigations were performed at two weeks and subsequently at varying intervals during the progression and resolution of the disease process (Table 8.3). Patients were rarely offered formal physiotherapy but were instructed in the mobilisation of their upper limb, particularly fingers and wrist. Ten patients, none with algodystrophy, who were young and required a higher degree of function from their hand were referred for more intensive treatment.

The patients who developed algodystrophy were a ready source of clinical material for the investigation of the effect of nasal calcitonin. Details of this study design and it's links with the larger study into the natural history of algodystrophy are given later.

Table 8.1. Data recorded on entry to the study.

NAME:

ADDRESS:

DATE OF BIRTH.:

SEX:

DATE OF ENTRY TO STUDY:

HOSPITAL NO:

INITIAL ASSESSMENT

DATE OF FRACTURE:

SIDE FRACTURED:

FRYKMAN TYPE:

? MANIPULATION: YES   NO

        IF YES - HOW OFTEN   DAYS

                TIME FROM # TO M.U.A.   HRS.

                TYPE OF ANAESTHETIC (SPECIFY)

TYPE OF PLASTER APPLIED: RADIAL SLAB

                HALF ARM P.O.P.

                OTHER (SPECIFY)

TIME IN PLASTER: DAYS

PHYSIOTHERAPY: YES   NO

        IF YES - FOR HOW LONG:

HANDEDNESS:

PROBLEMS IN PLASTER (SPECIFY):

Table 8.2. Frykmans classification of Colles' fracture. The classification depends upon the fracture of the distal radius involving the radio-carpal or distal radio-ulna joint with or without avulsion of the ulna styloid.

Frykman type	Radio-carpal joint involvement	Radio-ulna joint involvement	Avulsion ulna styloid
1	-	-	-
2	-	-	+
3	+	-	-
4	+	-	+
5	-	+	-
6	-	+	+
7	+	+	-
8	+	+	+

Table 8.3. Schedule of investigation in patients with algodystrophy. The first assessment was made two weeks after the plaster was removed which was approximately seven weeks after fracture. Further assessments were made at monthly or three monthly intervals.

	Weeks after fracture											
	7	11	15	19	23	27	31	35	39	43	47	51	55
Clinical assessment	+	+	+	+	+	+	+	+	+	+	+	+	+
Biochemistry	+	+	+	+	+	+	+	+	+	+	+	+	+
Radiography	+			+			+			+			+
Scintigraphy	+			+									
Photon Absorptiometry	+			+			+			+			+
Laser Doppler Angiography	+	+	+	+									

CHAPTER 9: CLINICAL METHODS OF ASSESSMENT

A. Pain and tenderness

Two different approaches are generally used in the assessment of pain in clinical studies. These are semi-quantitative assessments based on visual analogue scales (VAS) or questionnaires, or the application of a quantifiable noxious stimulus to a tender region. The VAS has been demonstrated to be a reliable and reproducible evaluation of pain intensity for patients with chronic pain (Huskinsson 1974). However, it is generally considered limited by it's unidimentional character of pain assessment. The McGill Pain Questionnaire (MPQ) (Melzack 1975) was developed to overcome this problem by generating information concerning affective, sensory and evaluative aspects of pain.

Although the VAS was originally used as a component of the pain assessment in this study, it quickly became apparent that patients had difficulty in differentiating the pain due to algodystrophy from that of their fracture. Whilst the MPQ may have overcome these problems, it was considered too time consuming to be used on an essentially elderly population and, as Davidoff et al. (1988) found, appeared to be inferior to the VAS as a brief clinical assessment of patient progress. In these studies the patients were asked if they had any pain in the hand, specifically excluding the wrist, or in the shoulder. Their reply was recorded as a simple yes or no. No attempt was made to quantify the degree or type of pain.

The importance attached to tests for pain sensitivity may be gauged by the numerous methods designed for ascertaining it. In 1943, Goetzl et al. noted 82 different methods involving the application of mechanical, chemical, electrical and thermal stimulation. The simplest mechanical test was described by Libman (1934) which involved a semi-quantiative assessment of thumb pressure applied to the styloid

process. The simplest modification of this method, to allow an accurate measurement of the stimulus, is the pressure algometer or dolorimeter. This instrument was used as far back as the Victorian days for assessment of analgesia in tabetics. It has been used recently in rheumatoid arthritis (McCarty *et al* 1965 and 1968), algodystrophy (Kozin *et al* 1976) and exhaustively investigated by Atkins *et al* (1989). This instrument therefore appeared the most appropriate to assess pain and tenderness in algodystrophy.

i) Dolorimetry technique

The dolorimeter used was a modification of a compresion-extension gauge provided by a small engineering company (Salter Bros., Sheffield) (Fig 9.1). It consisted of a hollow metal cylinder, open at one end, containing a spring. One end of the spring was attached to the closed end of the cylinder and the other end attached to a metal rod which protruded from the cylinder. There was a slit in the side of the metal casing alongside which was a graduated scale measuring kilograms of pressure upto 11 kg. A pointer was attached to the junction of the spring and rod which, when the spring was at its normal length, registered zero on the scale. A small plastic button tipped with felt was attached to the free end of the rod to prevent damage to the patients skin.

To maximise reproducibility, the technique used in each examination was identical. The normal hand was always examined first to gain the patient's confidence and allow them to become accustomed to the technique before the affected hand was measured. All the joints and the proximal and middle phalanx of the fingers were examined sequentially starting with the distal interphalangeal joint (DIPJ) of the index finger and working towards the little finger. Then the middle phalanx was measured, again starting with the index finger.
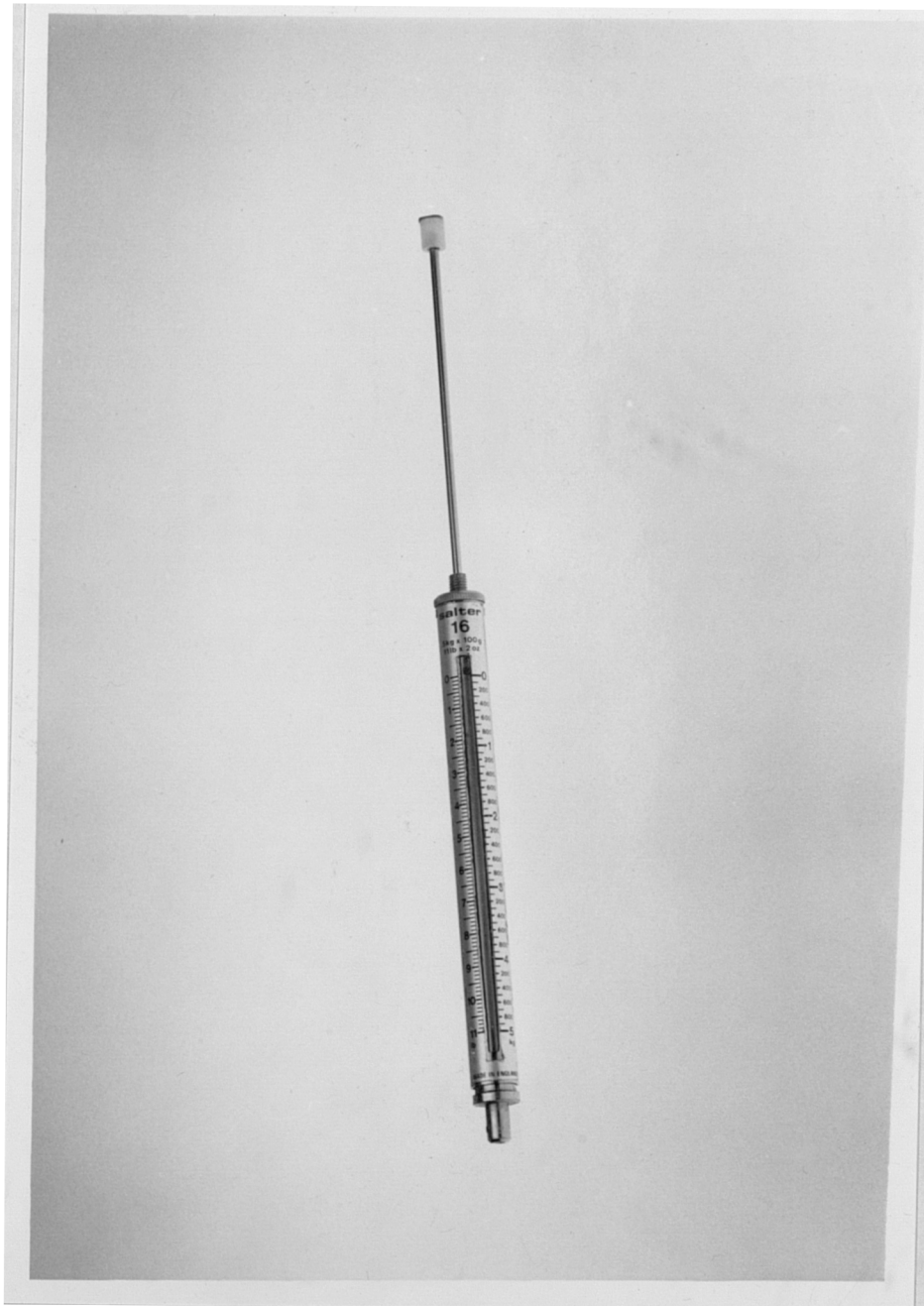
Fig 9.1. The dolorimeter used to quantify the degree of tenderness in the bones and joints of the hand. It was a modification of a compression-extension guage with a scale in Kg upto a maximum of 11 on the side of the cylinder.
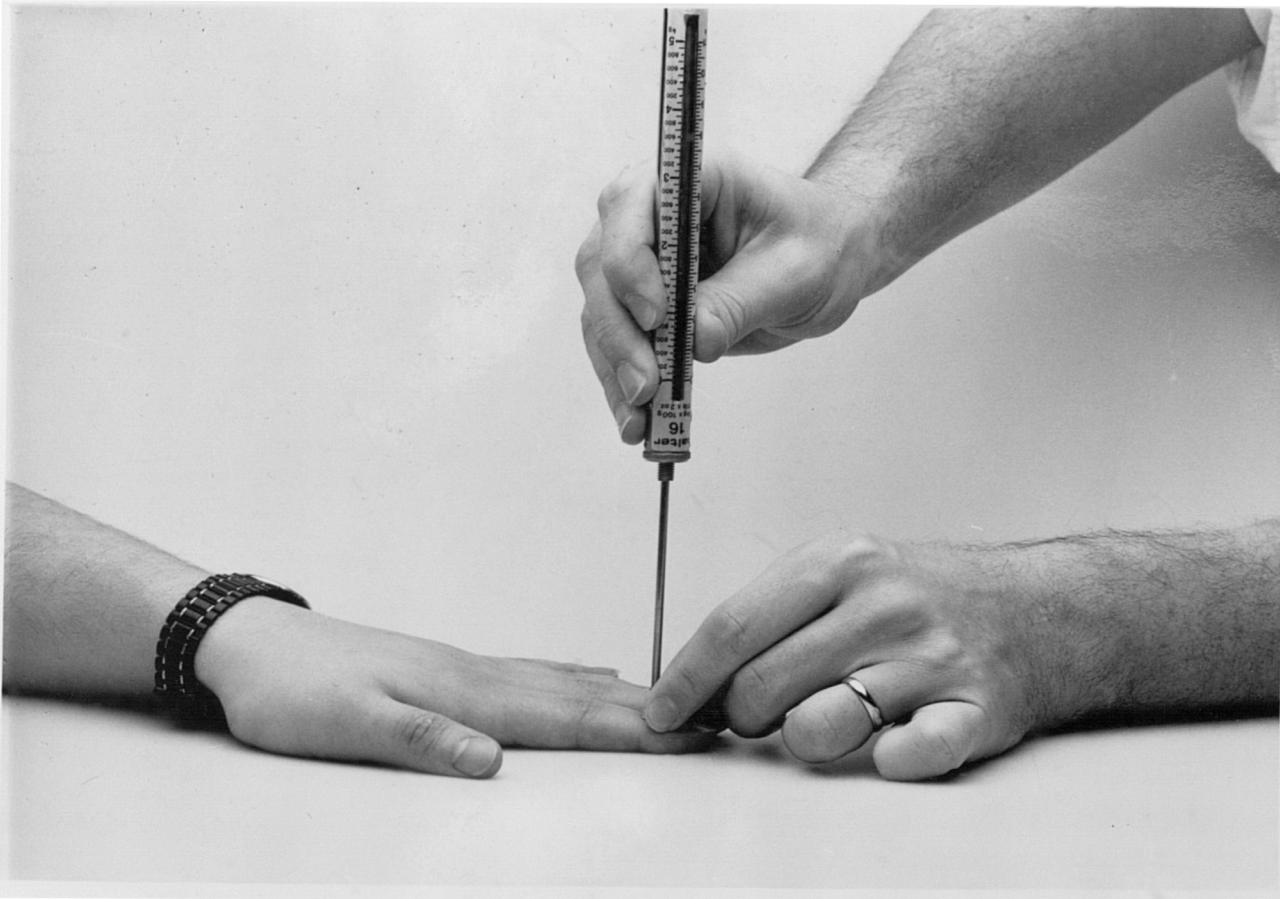
Fig 9.2. The tip of the dolorimeter applied to the area of measurement and steadied

with the examiners left hand. The cylinder was then depressed until the patient

indicated the first perception of pain at which point no further pressure was applied.

The maximum deflection was recorded from the Kg scale on the barrel.

As the examination by necessity produces a noxious stimulus, the technique was fully explained to the patient beforehand. The intention was to identify the point at which the pressure applied was first perceived as pain. When the threshold was reached, the patient was instructed to give a pre-arranged signal so that no further pressure was applied and a reading could be taken from the scale on the dolorimeter. It was stressed that the signal should be made at the point the sensation first changed to pain and not when the pain became intolerable.

The hand was placed flat on the table and the felt-covered plastic button was placed on the skin and steadied between the index finger and thumb of the examiners left hand (Fig 9.2). The barrel of the dolorimeter was then gripped in the fingers of the right hand and held perpendicular to the table, allowing full view of the scale, and a steady downward pressure applied. This pressure was transferred through the spring to the patients finger. At the pre-arranged signal the pressure ceased and the reading was made. A low reading indicated a more tender area. This was then repeated in the sequence described above. The pressure was applied at approximately 3 kg per second, as recommended by Atkins et al. (1989). If the rate was increased, the pain threshold was perceived earlier and an abnormally low reading was recorded. Examination of both hands rarely exceeded five minutes.

Patients with algodystrophy commonly had fixed flexion deformities and were unable to lay their hands flat on the table. Pressure then applied to the arched finger was abnormally painful and a falsely low reading was recorded. This was overcome by placing the hand over a purpose built arch providing contact with all the fingers. The dolorimeter was then held perpendicular to the surface of the arch beneath the joint or phalanx being examined, pressure applied as before, and a reading taken.

The technique is mildly uncomfortable provided that the dolorimeter is only applied upto the threshold from pressure to pain. No patients refused either an initial or subsequent examination. Problems did arise occasionally with stoical patients,

usually male, who maintained that they could have withstood far more pressure.

Careful explanation that the test was meant to find when pain first appeared and not

when it became intolerable usually sufficed. At the end of the examination, there were

skin dimples at the sites measured which disappeared within ten minutes and on no

occasion was the skin damaged.

Another potential pitfall was the anxious patient who at the beginning of the

examination recorded abnormally low pressures. This was immediately obvious as the

remaining readings were at a higher and steady level. This was overcome by careful

explanation of the technique and beginning on the distal inter-phalangeal joint of the

index finger on the unaffected hand which Atkins *et al.* (1989) had demonstrated to be

the least painful site. On the rare occasions this problem arose, the examination was

repeated and in no instance did it recur in subsequent examinations.

a) Reproducibility and Normal range

In order to assess the reproducibility and calculate the normal range, 24 female

and 2 male patients with a mean age of 64 $\pm$ 3.5 years were studied. The age range and

sex ratio were selected so as to resemble the population of Colles' fracture to be studied.

They were all hospital in-patients with no recent history of a distal radial fracture and

no evidence of algodystrophy in the upper limb. The dolorimetry was performed as

described above and repeated the following day with no reference to the previous day's

score.

The distribution of the dolorimetry readings was investigated using Probit

analysis and the significance of the difference between dolorimetry readings assessed

using Student's t test or analysis of variance. The coefficient of variation for paired

measurements was computed as:

$$CV\ (\%) = \underline{\text{standard deviation of the difference}} \quad \times\ 100$$

mean value

The normal range (mean + 2 standard deviations (SD)) was then calculated for the most reproducible technique.

ii) Results

There was no significant difference in the dolorimetry score between the two hands at any anatomical site or with the hand taken as a whole (Table 9.1). Also, when comparing sites within a hand, the joints were no more tender than the phalanges. Similarly there was no difference between the dominant and non dominant hand.

Coefficients of variation (Table 9.1) were calculated for both the absolute values and the ratio of scores between the two hands (calculated as second hand/first hand). They were greater for the absolute measurements rather than the ratios and decreased the greater the number of recordings made (ie. whole hand < all joints < all phalanx). Therefore the most reproducible measurement was for the ratio between the two hands which involved 20 measurements per hand.

The values for the ratio of the dolorimetry scores were normally distributed (Fig 9.3; Probit analysis; r = 0.97). The range of dolorimetry scores expected in normal subjects at the 95% confidence interval was 0.92 - 1.08.

Table 9.1. The mean dolorimetry score, standard deviation (SD) and coefficient of reproducibility (CV) are given at each anatomical site in 26 patients with no evidence of algodystrophy or recent Colles' fracture. There was no difference in the scores between hands or between the various anatomical sites within the hand. The most reproducible method was the ratio of total hand scores.

Site	Second hand			First hand			Ratio 2nd/1st		
	mean	SD	CV (%)	mean	SD	CV (%)	mean	SD	CV (%)
Phalanx									
Proximal	35.0	6.0	20	34.7	5.7	19	1.00	0.05	10
Middle	35.8	5.5	15	35.2	5.3	17	0.99	0.06	9
Total	70.8	11.1	10	69.9	10.9	10	0.99	0.05	8
Joints									
Metacarpo-phalangeal	34.8	5.7	17	35.1	5.5	18	1.01	0.10	12
Proximal inter-phalangeal	35.1	5.2	15	35.1	5.2	14	1.00	0.05	11
Distal inter-phalangeal	35.2	5.7	14	35.7	4.9	19	1.02	0.10	11
Total	105.1	15.2	11	105.8	15.2	10	1.01	0.05	8
Hand	176.0	26.9	16	175.7	25.9	17	1.00	0.04	6
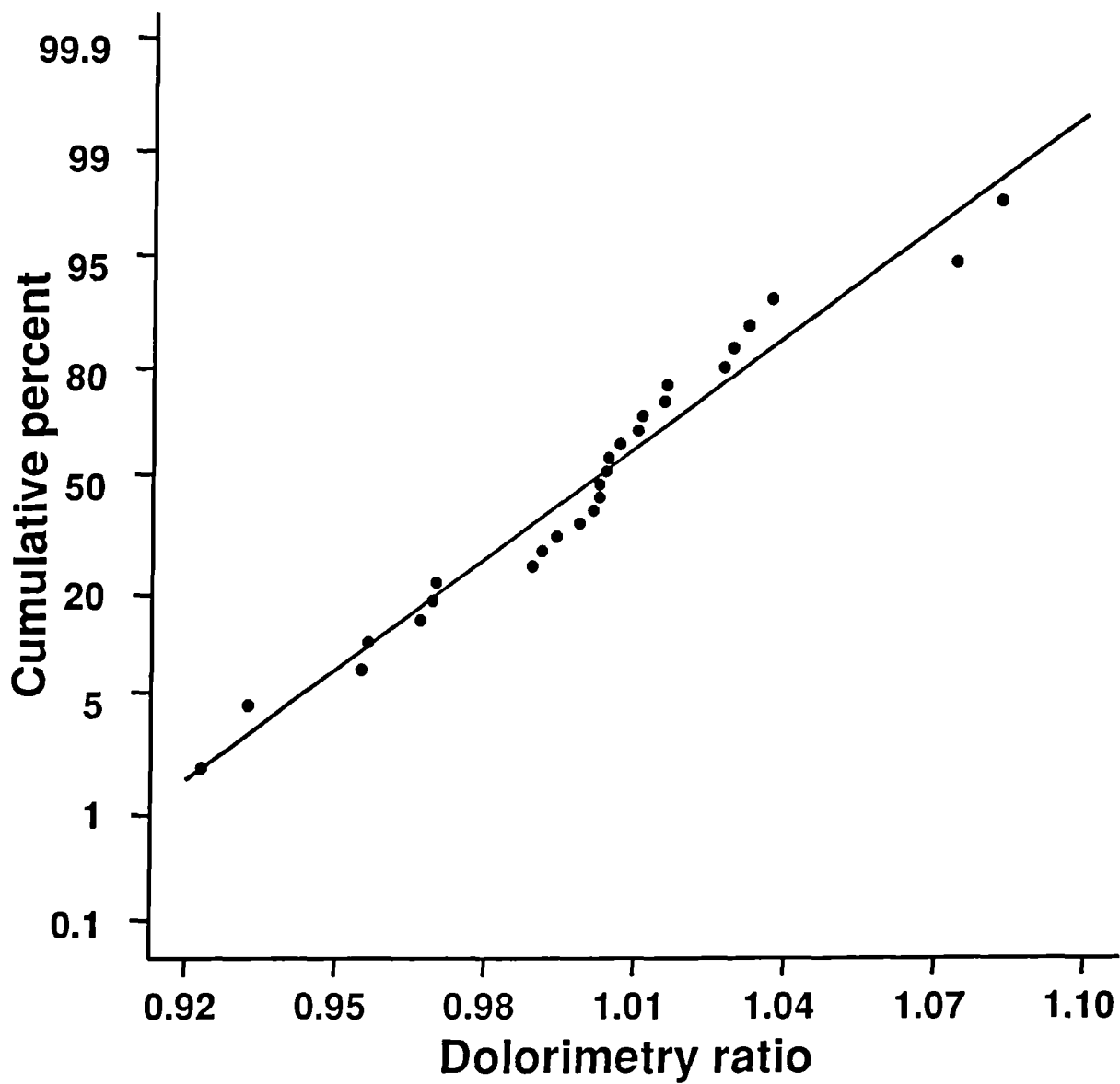
Fig 9.3. Probit analysis was performed on the dolorimetry ratios in 26 patients
who had no evidence of algodystrophy or recent distal radial fracture. Since
the ratios, which were expressed as the score for the second hand examined
divided by the first, were normally distributed, the 95% confidence interval was
used to calculate the normal range for finger tenderness.

iii) Discussion

In the normal population examined in this study, there was no increased tenderness over the joints, unlike that described by Atkins *et al.* (1989). Kozin *et al.* (1976) suggested however that the algodystrophic process was associated with a specific increase in tenderness of the joints rather as compared with the bones. Therefore measurement of the joints alone would be sufficient to provide adequate data on the amount of tenderness. In making these conclusions however, they may have misinterpreted their data since the joints on the unaffected side were also more tender. This was confirmed by Atkins *et al.* (1989) who showed that in patients with algodystrophy, although the joints were more tender than the phalanx, there was increased tenderness throughout the affected side when compared with the normal side.

The reproducibility of the technique could also be further improved if all sites on the hand were used and increased further still if the ratio of the scores rather than the absolute measurements were used. This contrasts McCarty *et al.* (1965) who suggested that the absolute dolorimetry reading alone was highly reproducible. This latter study however was undertaken on rheumatoid patients with bilateral involvement of the hands. Clearly a relapse in the condition would not alter the ratio of the scores but the absolute score for each hand would decrease uniformly.

The precision of the technique using the ratio of scores for both hands is clearly sufficient to enable the sequential evaluation of patients in a study of the natural history of algodystrophy and their response to treatment with nasal calcitonin. It is likely to be more precise than the semi-quantitative method described by Davidoff *et al.* (1988).

As the distribution of the dolorimetry scores in the present study was normal, the range of values for unaffected subjects was calculated as 0.92-1.08 using the 95% confidence interval. This is not dissimilar to Atkins *et al.* (1989). Therefore one of the

clinical criteria used to assess the presence of algodystrophy was a dolorimetry score of

less than 0.92.

B. Vascular and Sudomotor Instability

Techniques such as thermography (Perelman *et al.* 1987), oscillometry (Scheibe 1969; Renier *et al.* 1973), ultrasonic (Doury *et al.* 1981) and laser Doppler angiography (Cochrane *et al.* 1986), and galvanic skin reflex (Wang 1985) have been used to investigate alterations in the microcirculation or sweating and may be of use therefore to investigate the natural history of algodystrophy and it's response to treatment. They are of little value however, for screening a population for evidence of algodystrophy as they are too time consuming.

In the absence of a rapid, objective method of assessing vascular or sudomotor instability, a modification of the questionnaire described by Atkins *et al.* (1990) was used to define the presence of an abnormality.

i) Method

Vascular instability in algodystrophy manifests itself as a change in skin colour, a temperature change, or an abnormal response to changes in environmental temperature. Sudomotor instability presents as increased or decreased sweating in the affected limb. The questionnaire was designed to record features in the affected hand which did not occur on the opposite side or before the Colles' fracture. To decrease observer bias as much as possible, the same standard questions were read out to the patients before any other clinical information was sought. The questions asked were as follows:

1)   Have you noticed any change in the colour of your hand since the accident?

        If yes - red or blue?

2)   Has the temperature of your hand felt in any way different from the other since the accident?

        If yes - hot or cold?

3)   Has your hand responded differently to changes in the temperature since your

accident?

4)   Has your hand sweated more than it used to since the accident?

5)   Has your hand felt clammy since the accident?

Originally the patients were asked if the features they described were getting

better or worse on subsequent visits. It quickly became apparent however that they

found it difficult to recall this information and it would have been of negligible

statistical value.

The hands were also examined for clinical evidence of vascular instability in

addition to swelling, dysthesia and shiny skin. The examination took place immediately

after the questionnaire, ensuring that the techniques used to measure tenderness or

hand volume did not affect the clinical signs. The features were recorded as follows:

1)   Dysthaesthesia   Yes   No

2)   Oedema   Yes   No

3)   Shiny skin   Yes   No

4)   Altered colour   Yes   No

        If yes: Red   Blue.

5)   Altered temperature   Yes   No

        If yes: Warmer   Cooler

ii) Discussion

Other than using the more invasive techniques described earlier, there have

been no attempts in the literature to quantify vascular instability on purely clinical

grounds. Indeed some studies of treatment efficacy disregard it completely. Although

subjective, the standardised questions and the simple yes or no answers used in this

study were designed to limit the observer's influence on the results. The questions also

gave information concerning the different features of vascular instability and not simply it's presence or absence.

Although it is difficult to prove the validity of such an examination there were certain indications that it was of value. All patients who had other features of algodystrophy such as pain, abnormal tenderness, swelling and stiffness replied positively to at least part of the questionnaire, indicating the presence of vascular instability. This contrasts with the majority of patients following a Colles' fracture with no evidence of algodystrophy who denied any problem. These findings will be described in more detail in chapter 15. Occasionally patients with algodystrophy were relieved they had been questioned on signs and symptoms that they did not understand and were grateful to discuss them.

C. Swelling

As with the assessment of vascular instability, a rapid and reproducible method of recording changes in hand volume was sought. Two previously described methods; hand volume measurement (Stenberg *et al.* 1980; Davidoff *et al.* 1988) and digital circumference (Wilkins *et al.* 1974; Kozin *et al.* 1974) were further investigated.

i) Method

The presence or absence of swelling on questioning the patient and on examination were recorded in addition to a quantitative method of assessment.

a) Hand volume

A two litre perspex cylinder with a centimeter scale on the side was used for the measurement of hand volume (Fig 9.4). The cylinder was sufficiently spacious to comfortably immerse the hand in the position of rest. The cylinder was half-filled with warm water and the level of water recorded before each examination. Extremes of temperature were avoided as this might have exacerbated the symptoms due to algodystrophy in those affected. The patient was asked to stand and place their unaffected hand in the water keeping the hand completely relaxed. The observer steadied the hand by gripping the distal forearm and lowered the hand until the water-level reached the distal wrist crease (Fig 9.5). A reading was then made from the centimeter scale on the cylinder. The same procedure was then performed with the affected hand. The volume of each hand was then calculated as the volume of water displaced, the whole procedure took 1-2 minutes.
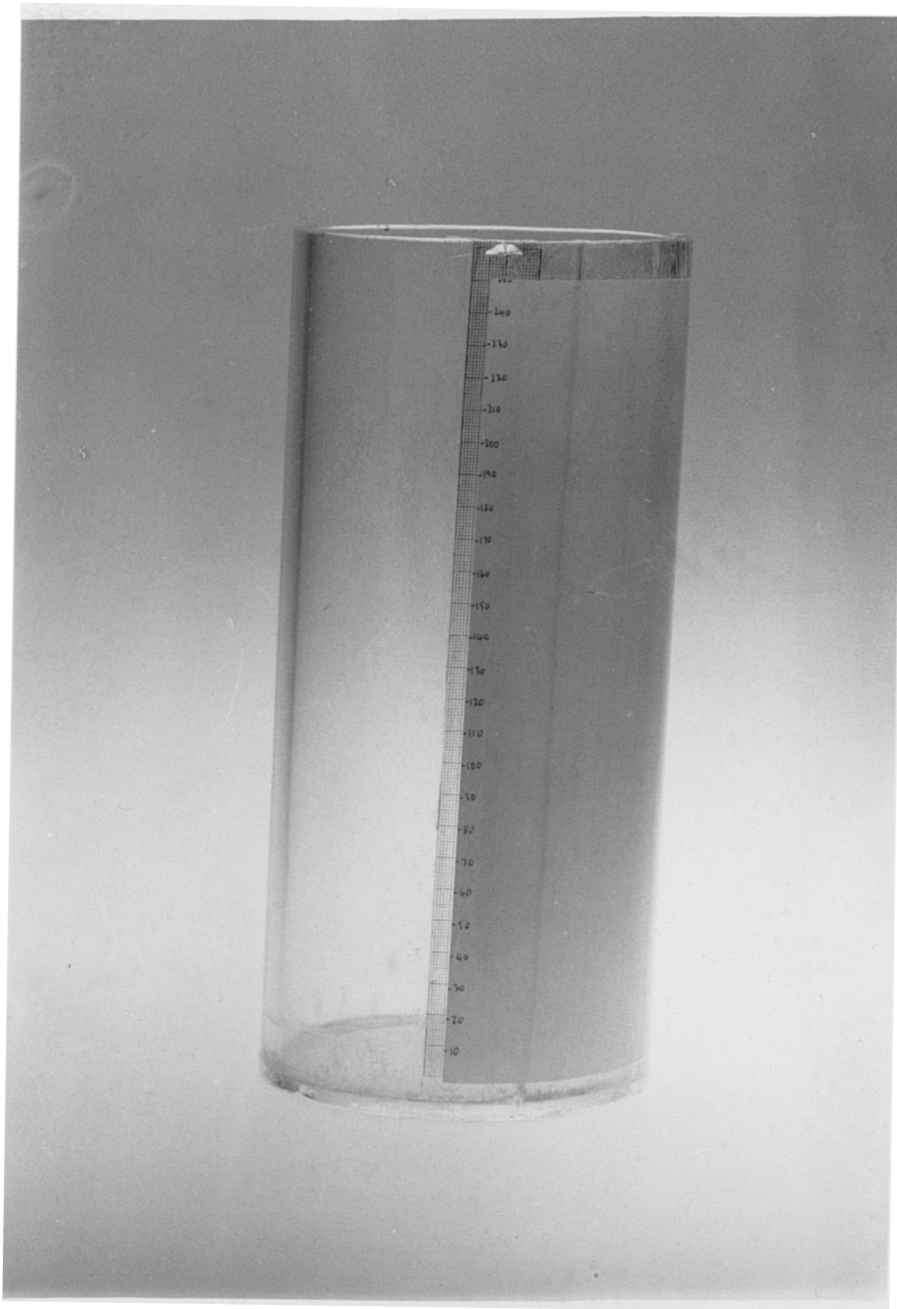
Fig 9.4. A two litre perspex cylinder, half filled with water, was used to measure hand volume. The hand was immersed in the water and the amount of displacement measured off a centimeter scale.
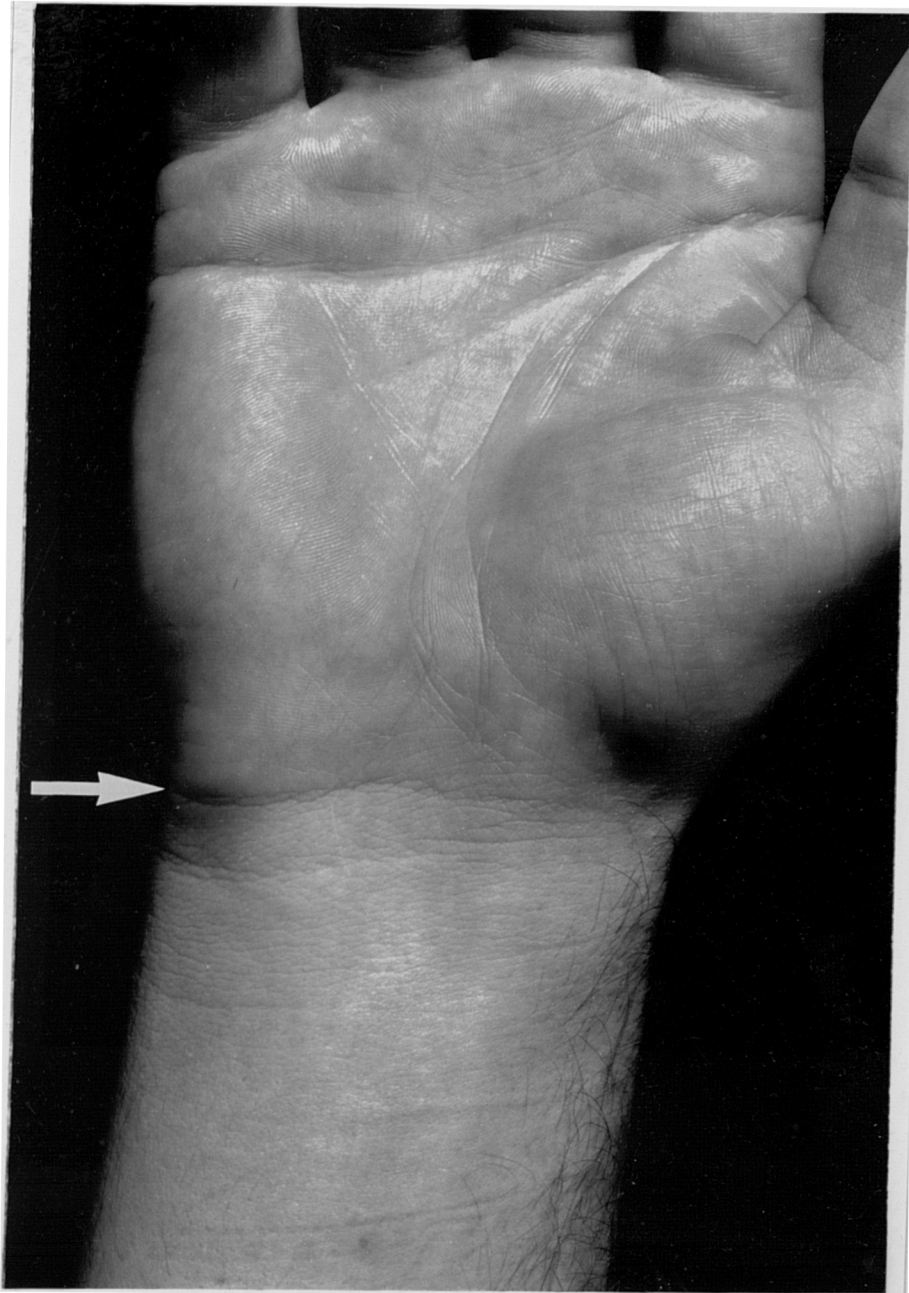
Fig 9.5. The hand was immersed until the water level reached the distal wrist crease. This anatomical landmark was constant and distal to the fracture site therefore avoiding swelling of the fracture site itself.

b) Digital circumference

The instrument used to measure digital circumference was similar in principal to that described by (Wilkins *et al.* 1974) but measured three sites rather than one Fig 9.6). At the upper end of the instrument there is a groove where the finger is placed over which are three aluminium strips. The strips are incorporated into a scale measuring arbitrary units which runs down the length of the instrument. At the end of each strip is a marker indicating the point on the scale at which to take the reading. Attached to each of the markers is a lightly coiled spring which, at rest, maintains the markers at zero. At the base of the three markers traversing the scale is a bar which when pushed moves the markers along the scale, tenses the spring and loops the aluminium strips over the groove for the finger. The finger is then inserted into the groove with the instrument held on it's dorso-medial aspect (Fig. 9.7) preventing flexion of the finger. The springs are then relaxed which applies tension in the three aluminium strips over the finger. A reading can then be made off the scale for each aluminium strip. Difficulty was encountered when centering the strips over the distal interphalangeal joint as the distal phalanx was often too narrow to register on the instrument. Similar difficulties were also encountered when measuring the little finger even with the strips centered over the proximal interphalangeal joint (PIPJ). It was therefore decided to measure the diameters of the proximal and middle phalanx and PIPJ of the index, middle and ring fingers of each hand with the middle strip centered accurately over the PIPJ. The normal hand was measured first.
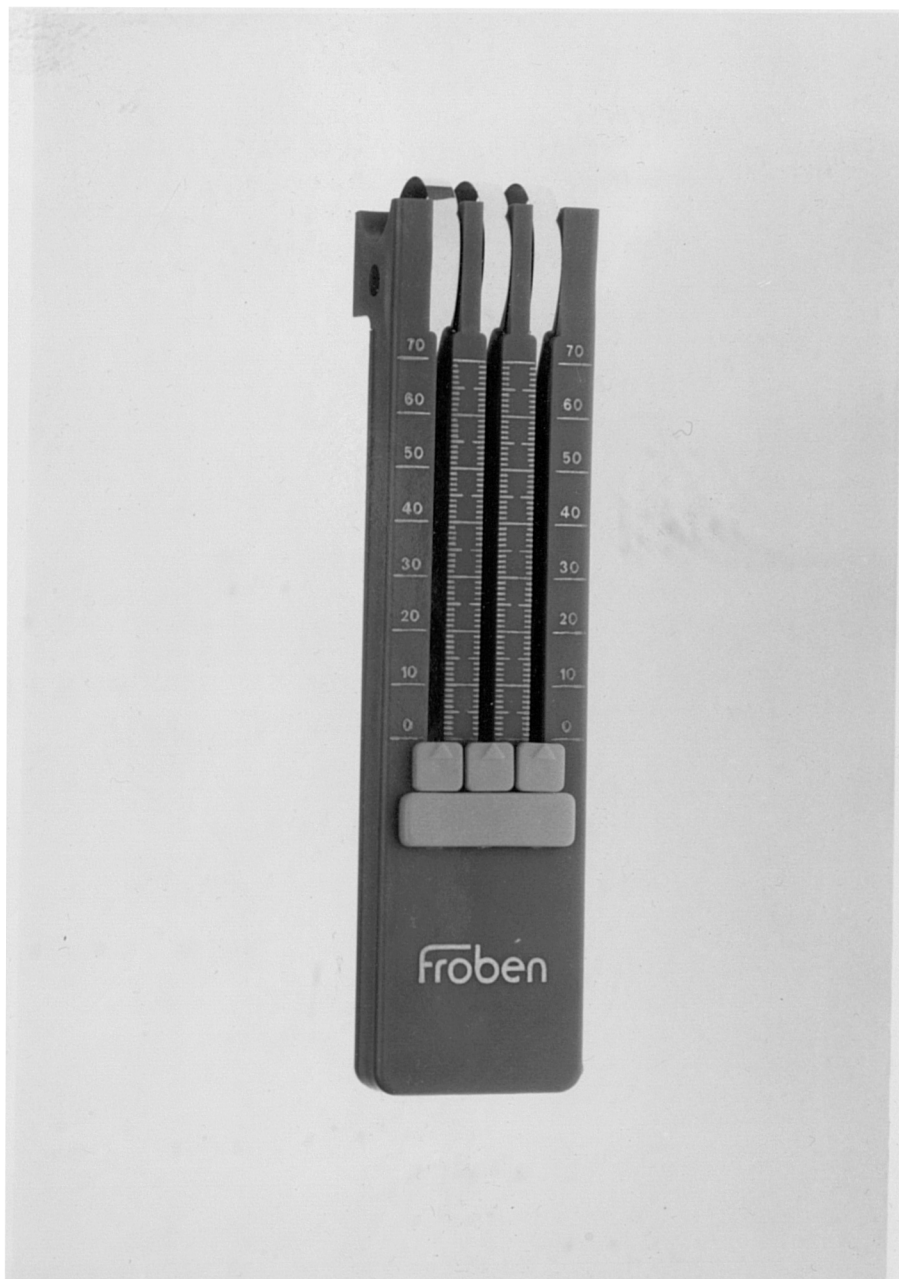
Fig 9.6. The arthrocircometer was used to measure digit circumference at the proximal phalanx, proximal inter-phalangeal joint and middle phalanx of the index, middle and ring fingers.
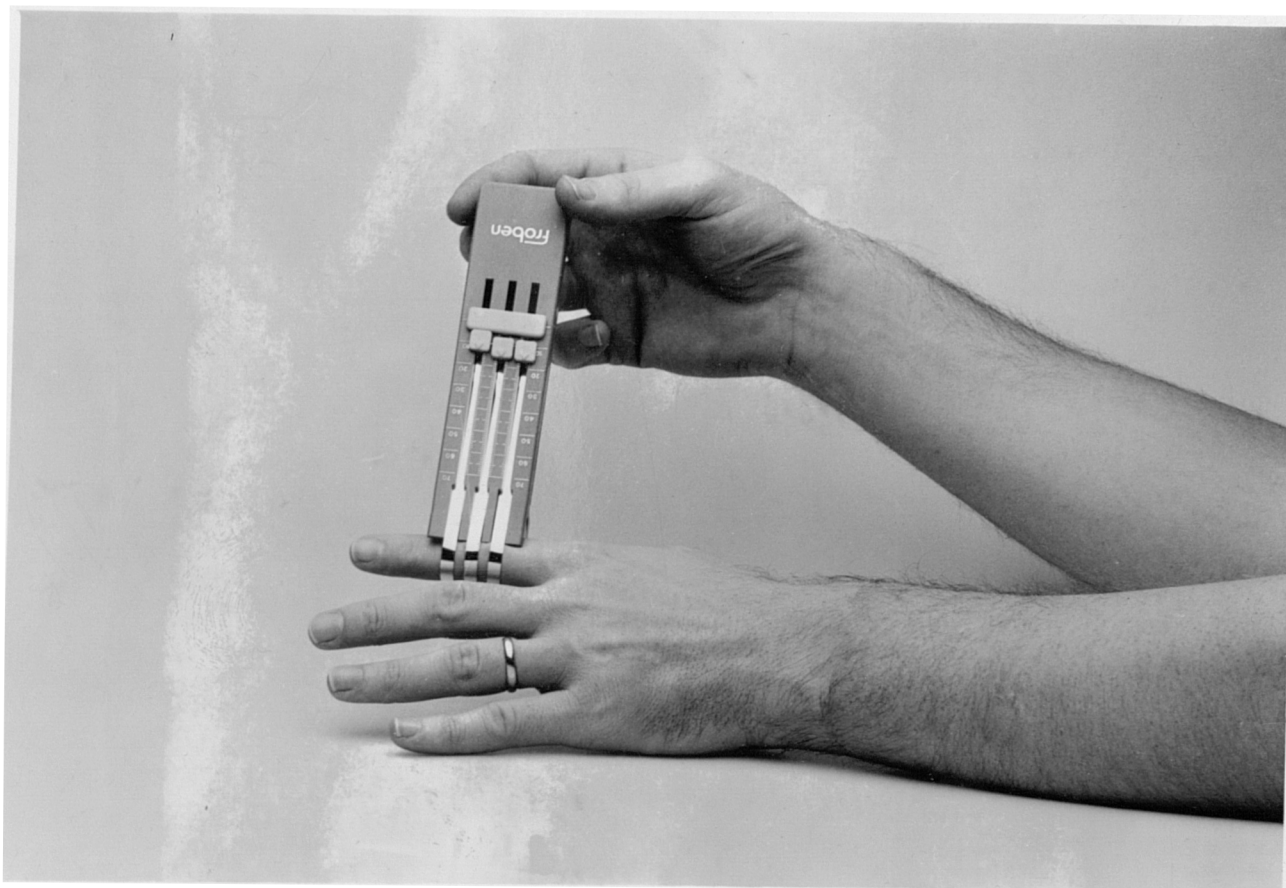
Fig 9.7. The finger was inserted into the groove on the instrument and the aluminium strips tightened over the three measurement sites. The degree of swelling at the three sites was measured in arbitrary units off a scale on the body of the instrument.

c) Patients

The reproducibility of hand volume measurement was studied in 24 female and 2 male patients with a mean age of 64 ± 3.5 years. They were the same patients used to assess dolorimetry. The age range and sex ratio were similar to those expected in patients with Colles' fracture. They were all hospital in-patients with no recent history of a distal radial fracture and no evidence of algodystrophy in the upper limb.

Hand volume and digital circumference measurements were repeated after an interval of 24 hours without reference to the previous days score. As the dominant side may have conceivably been larger, this was recorded for later evaluation. The statistical methods were the same as those used in the reproducibility studies on dolorimetry.

ii) Results

a) Hand volume

The measurement of hand volumes for both the absolute measurements and ratios were highly reproducible (Table 9.2). Not surprisingly there was a large population variation in the absolute measurement of hand volume for both the dominant and non-dominant hand (standard deviation (SD) 62.3 and 60.7 respectively). This population variation was reduced considerably if the ratio of dominant to non-dominant hand was used (SD 0.03). The dominant hand was neither consistently nor significantly larger than the non-dominant hand, and in order to avoid any spurious but statistically significant swelling, two ratios were calculated for each pair of measurements, dominant to non-dominant and non-dominant to dominant. All the ratios were then summed which gave a mean of 1.00, as expected, and SD of 0.05 which was slightly greater than the SD based solely on the dominant to non-dominant ratio (Table 9.2). Probit analysis of the ratios showed them to be normally distributed (Fig 9.8). The normal range for dominant to non-dominant, using the 95% confidence

interval, was calculated as 0.90 to 1.10 (mean ± 2 SD). From the reproducability of the measurement (5%), a 10% change in hand volume in an individual would therefore be likely to be a significant ($p < 0.05$) change.

Table 9.2. The hand volume and digit circumference were measured in 26 patients with no evidence of algodystrophy or recent Colles' fracture. The mean and standard deviation for each measurement demonstrate the large variation in absolute measurements which became less apparent when the ratio of dominant to non-dominant hand was used. This, however resulted in slightly less reproducibility in the assessment of hand volume.

| Measurement	Dominant hand			Non dominant hand			Ratio dominant/non dominant		
	mean	SD	CV	mean	SD	CV	mean	SD	CV
Hand volume	291.2	62.3	3.3	279.4	60.7	3.2	1.05	0.03	3.8
Digital circumference									
index finger	36.2	14.2	7.2	33.6	14.5	10.1	1.11	0.15	14.5
middle finger	38.0	16.0	5.0	33.3	15.6	6.4	1.17	0.17	14.5
ring finger	27.7	13.2	14.3	24.5	13.7	12.8	1.21	0.28	19.7
Total	101.9	42.8	6.1	91.4	43.3	6.8	1.13	0.10	10.2
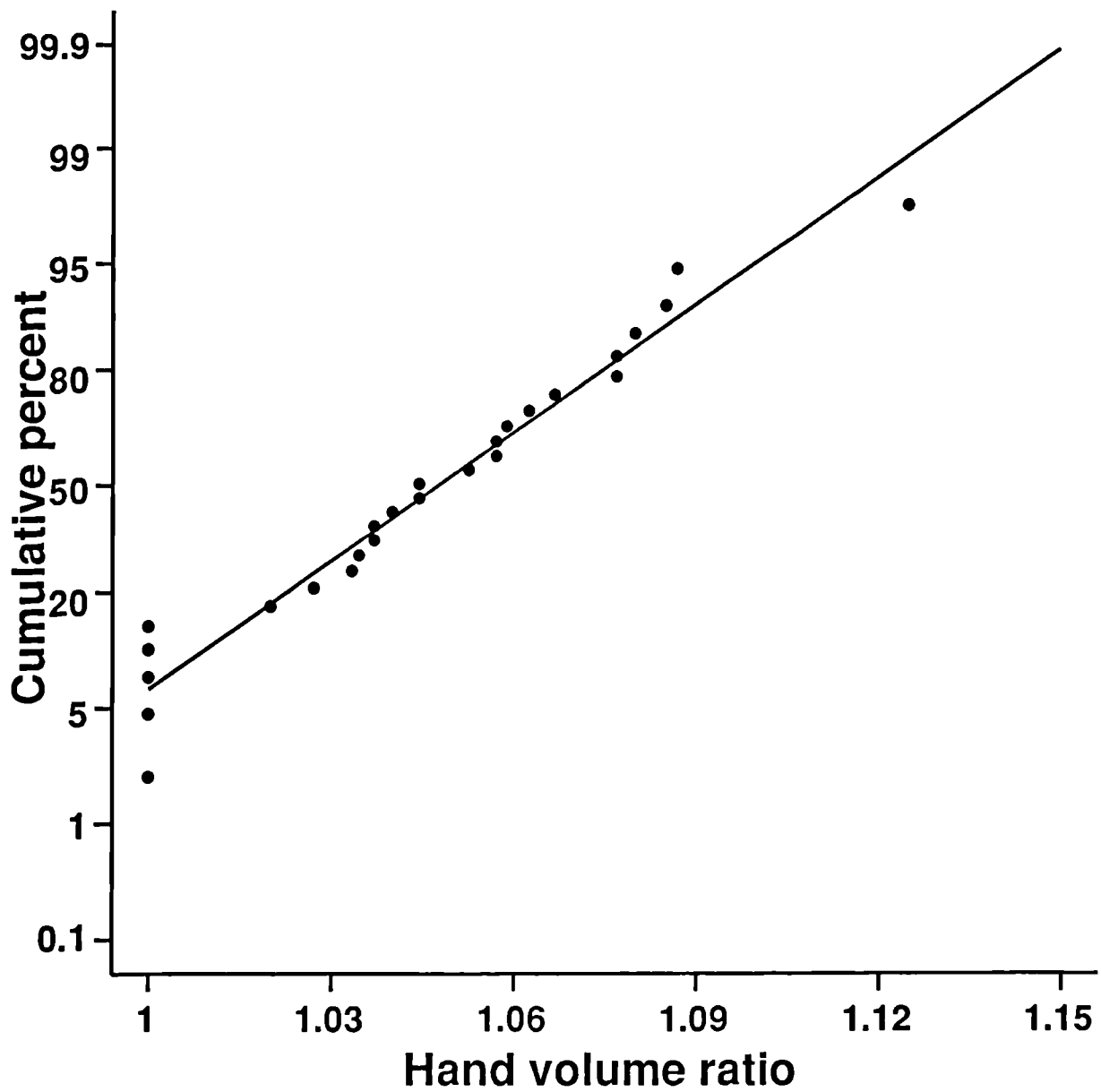
Fig 9.8. Probit analysis was performed on the hand volume ratios in 26 patients
who had no evidence of algodystrophy or recent distal radial fracture. Since
the ratios, which were expressed as the score for the second hand examined
divided by the first, were normally distributed, the 95% confidence interval was
used to calculate the normal range for hand volume.

b) Digital circumference

The measurement of digit circumference was a less reproducible than measurement of hand volume, particularly the ring finger. The most reproducible measurements were on the absolute values for the middle finger but with a wide standard deviation of the population (Table 9.2). The most reproducible measurement for the ratios (where there was less variation between measurements) was for the total score (coefficient of variation for paired measurements - 10%; Table 9.2). Therefore to be of value in detecting changes in finger swelling in an individual, there would have to be a 20% change in size. As with the hand volume measurements the dominant was not significantly or consistently larger. As the ratios were normally distributed (Fig 9.9), the normal range for the ratio of dominant to non-dominant hand total scores using the 95% confidence interval (mean $1.00 \pm 2SD$) was calculated as 0.78 - 1.22.

Using simple regression analysis, there was no siginificant correlation between the hand volume ratio and digital circumference for the index, middle, ring or all three fingers.
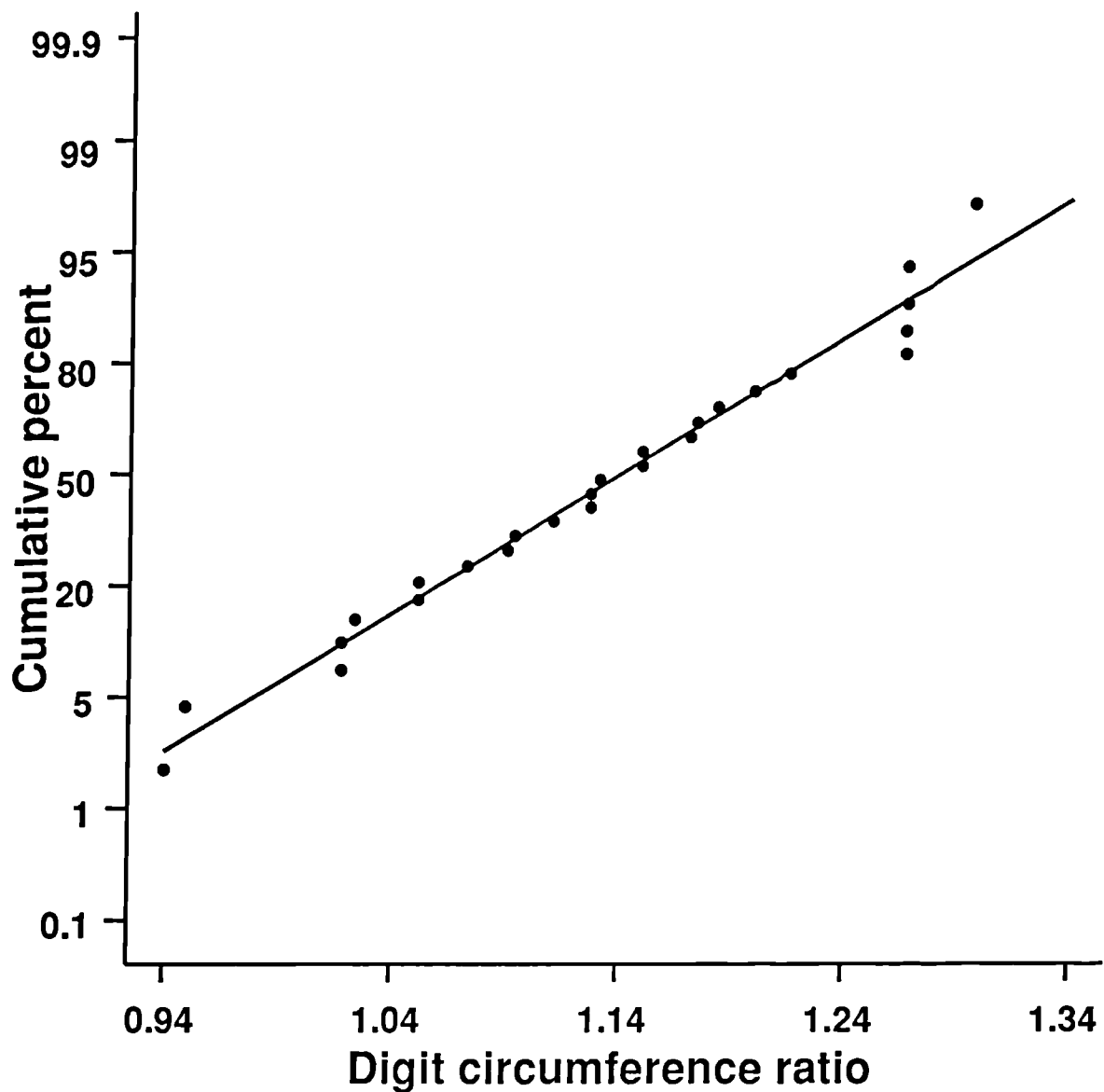
Fig 9.9. Probit analysis was performed on the grip strength ratios in 26
patients who had no evidence of algodystrophy or recent distal radial fracture.
Since the ratios, which were expressed as the score for the second hand examined
divided by the first, were normally distributed, the 95% confidence interval was
used to calculate the normal range for grip strength.

iii) Discussion

The requirements of the measurement of hand volume to be faced in the fracture study were that it should be accurate, simple, painless, convenient, noninvasive, inexpensive and reproducible. In fulfilling these criteria it would be of value not only as a research tool but in normal clinical practice.

Water displacement has been used by a number of authors as a method of assessing changes in hand volume over time (Stenburg *et al.* 1980; Wilson-MacDonld *et al.* 1984; Davidoff *et al.* 1988) and all claim good reproducibility. Davidoff *et al.* (1988) claimed a difference of greater than 5% between the affected and unaffected to be abnormal. Stenberg *et al.* (1980) used a modification of a test used to measure changes in limb oedema in the rat (Kishore *et al.* 1976). This involved filling a container to the brim, immersing the hand and measuring the amount of water displaced in a separate container. Although accurate, this method was more time consuming and inconvenient.

Davidoff *et al.* (1988) used a technique identical to that described in this study except in the identification of the end-point for the depth of immersion of the hand. They used the tip of the ulna styloid which can be difficult to accurately identify and may lead to spurious changes in volume when taking serial measurements. I used the distal wrist crease as this is easily identified, does not change position with time and is distal enough to exclude any changes in volume attributable to resolution of fracture swelling.

Not surprisingly there was a large coefficient of variation in the volume of hands measured (dominant 21.7%; non-dominant 21.4%) and therefore using the ratio of one hand to the other (coefficient of variation - 2.9%) would be a more representative assessment of changes in hand volume with time and for comparison with other patients. The technique was highly reproducible with a coefficient of variation for paired measurements of 3.8% using the ratio of dominant to non-dominant hand.

Although the mean value for the dominant hand was slightly larger, this difference was not significant. In the fracture study the volume ratio will be expressed as the affected to unaffected side because the affected hand is not always the dominant hand, the calculation of the normal range based on the dominant to nondominant may introduce a spurious difference. It was therefore decided to use two ratios for each pair of measurements, dominant to non-dominant and non-dominant to dominant, which were then summed. This provided a mean of 1 but a slightly larger SD due to the wider distribution of the ratios around this mean and therefore a slightly wider normal range. The normal range for hand volume ratio lay between 0.90 - 1.10 (mean 1.0 ± 2 SD).

The method of measuring digital circumference was a modification of the arthrocircometer used by Willkens $et\ al.$ (1973) which was described for use in rheumatoid arthritis. These instruments are a development of the jeweler's rings (Heyman 1974) or jeweler's tape (Kozin $et\ al.$ 1976). The advantage of the instrument used in this study is that three measurements can be made at once, theoretically cutting the time taken for the examination by one third. Technical problems with the instrument used in this study prevented it's use in measuring the distal interphalangeal joints and the joints of the little finger.

There was however a larger variation in the digital circumference than hand volume ratios giving a wider normal range of 0.78 - 1.22. The technique was also less reproducible than the measurement of hand volume (coefficient of variation of 10%). As a 20% change in digital circumference was required to be significant in individuals, it was decided not to use this method of assessment. The measurement of hand volume, which was more reproducible with a narrower normal range, was selected for use in subsequent studies.

D. Function

Although Atkins *et al.* (1989) described a syndrome of pain, stiffness, vascular instability, and swelling, which would be consistent with a diagnosis of algodystrophy, there was no formal assessment of hand function. It is also unclear whether the presence of these features indicate future functional impairment. For this reason the functional outcome was investigated by measuring grip strength, the presence of finger stiffness and a functional score.

i) Method

a) Grip strength

The grip strength was measured using a purpose built instrument measuring in pounds/inch^2 (Fig 9.10). The patient held the bulb of the instrument in the unaffected hand with the dial facing the observer and, when instructed, made a power grip. The maximal deflection was then recorded. This was repeated three times and an average score calculated. The procedure was then repeated on the affected hand.

To test the reproducibility and calculate the normal range, grip strength measurements were performed on the same population used in the evaluation of dolorimetry, hand volume and digital circumference. Their grip strength was then remeasured 24 hours later without reference to the previous results. The normal range and coefficients of variation were calculated as previously described.

Fig 9.10. The grip strength was measured on a guage measuring pounds/inch^2.

Using a power grip, the patient squeezed the rubber bulb, with the guage facing the

examiner. The maximum deflection on the meter was recorded for three attempts and

the mean value used in further calculations.

b) Stiffness

At each visit the patients were asked if they experienced any stiffness specifically in the fingers at any time during the day. Care was taken to avoid confusion with wrist stiffness. If stiffness was a daily occurrence, even if only transient (ie. early morning) and occurred only in the affected hand, it was recorded as a positive feature. Originally a visual analogue scale was used to grade the degree of stiffness but, as with the pain visual analogue scale, this was abandoned as the patients did not fully understand the meaning of the request and each examination became too time consuming.

c) Functional score

The scoring system was based on that described by de Brujn (1987) (Table 9.3). It takes into account complaints, motor function of the hand (including % grip strength compared with the normal hand) signs and symptoms and the cosmetic result. The penalty score assigned to the findings was based on the guidelines of the Committee on Medical Rating of Physical Impairment (1958). The maximum score possible is 132 with the majority provided by the assessment of the motor function of the hand (72) and complaints (44); signs and symptoms (11) and cosmetic appearance (5) provide the remainder. The "subjective judgement of the end result" was scored 5 if the patient complained of impaired function only during heavy work or excessive movement; and 10 when there was impaired function of daily life activities or if the general way of life was affected. "Open question for complaints" was the only parameter available for registering more minor dissatisfaction with the end result which did not include pain or impaired function (a, b, c and h). The assessment of the cosmetic appearance took into account not only features attributable directly to the fracture, such as prominence of the ulna head or dinner-fork deformity, but also the soft tissue changes seen in algodystrophy.

Table 9.3. Scoring system for the clinical evaluation of the functional result.

	score
COMPLAINTS	
a. pain while resting	10
b. pain while moving	8
c. pain during heavy work/excessive motion (if b=0)	4
d. numbness or paraesthesia in the fingers	3
e. restricted daily basic life activities	10
f. pain while wringing out cloths (if b+c=0)	3
g. loss of power	3
h. subjective judgement of the end result	5 or 10
i. open question for complaints (if a+b+c=0)	1, 2 or 3

MOTOR FUNCTIONS OF THE HAND	0-40%	40-60%	60-80%	80-90%
grip power	8	5	3	2
making a fist			8	
finger extension			8	
opposition			8	

	abnormal	impossible
opening a door	5	8
weight lifting	5	8
picking up a pen	5	8
crumpling a piece of paper	5	8
lifting a cup and saucer	5	8

SIGNS AND SYMPTOMS

swelling of hand/fingers	5
abnormal colour	2
skin atrophy/hyperaesthesia/hyperhidrosis	4
ulnar compression pain	2

Cosmetic appearance	2, 3 or 5

This system was used to assess the majority of patients suffering from algodystrophy and a representative sample of patients without algodystrophy at six months following their fracture.

ii) Results

Both the absolute measurements of grip strength for the dominant and non-dominant hand, and the ratio of dominant to non-dominant hand were highly reproducible and slightly better for the ratio of measurements (Table 9.4; 8.3%). Not surprisingly the grip strength of the dominant hand was greater than the non dominant hand, though not significantly, which accounted for the mean value of the ratio of measurements being greater than 1 (1.08). As in the calculation of hand volume and digit circumference, this may lead to spurious differences as the affected hand may not always be the dominant one. Therefore the ratios of dominant to nondominant and nondominant to dominant were doubled up to give a mean of 1.0 and slightly larger SD of 0.12. As this population was normally distributed (Fig 9.11), the normal range using the 95% confidence limit was calculated as 0.76-1.24 (mean ± 2SD).
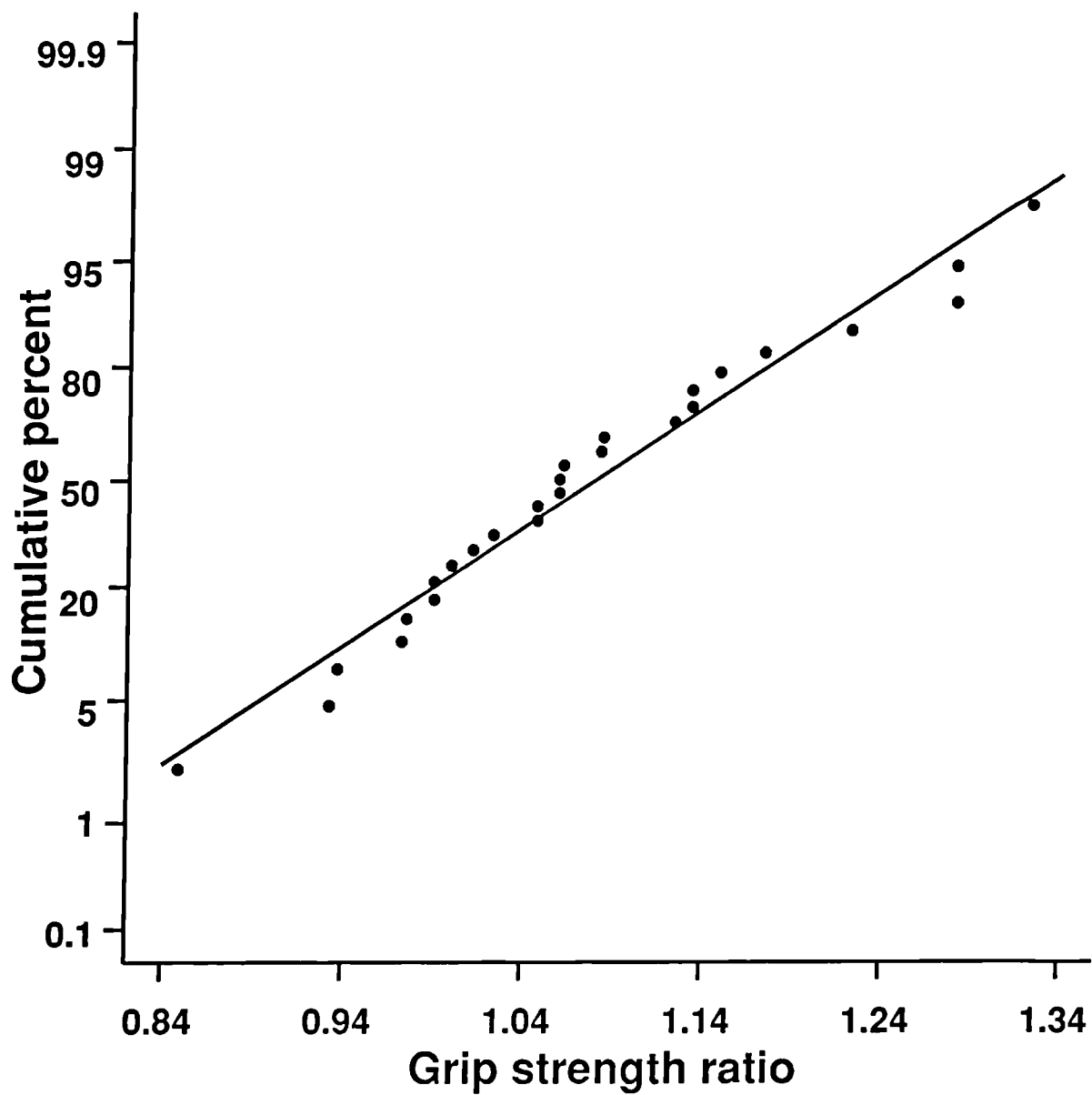
Fig 9.11. Probit analysis was performed on the grip strength ratios in 26
patients who had no evidence of algodystrophy or recent distal radial fracture.
Since the ratios, which were expressed as the score for the second hand examined
divided by the first, were normally distributed, the 95% confidence interval was
used to calculate the normal range for grip strength.

Table 9.4. The grip strength (lb/in^2) was measured in 26 control patients and expressed as the mean, standard deviation (SD) and coefficients of variation (CV) of the dominant, non-dominant and ratio of dominant to non dominant. Of the three, the coefficient of variation for the ratio was marginally better.

	Mean	SD	CV (%)
Dominant hand (lb/in^2)	16	4.8	8.9
Nondominant hand (lb/in^2)	15	4.9	8.4
Ratio	1.08	0.11	8.3

iii) Discussion

The hand and wrist are capable of performing a number of different types of grips such as pinch grip, key grip, hook grip and power grip, necessary for manipulating the environment. It is the loss of power grip, however that is most frequently complained of and most frequently tested in the clinical setting as an assessment of functional recovery. Previous studies have used a modified sphygmomanometer (Lansbury 1960; Kozin et al. 1976; Atkins et al. 1990) to assess grip strength and were able to show significant differences between the affected and normal side at presentation (Kozin et al. 1976; Atkins et al. 1990). It is unclear however whether the technique is reproducible enough to detect serial changes in grip strength in a longitudinal study. Indeed Atkins (1988), using the sphygmomanometer, found a coefficient of variation for paired measurements of 17.8%, almost twice the figure in this study. He also abandoned measurement of pinch grip as it was more time consuming and even less reproducible than the measurement of power grip. The method used in this study is therefore rapid and more reproducible than the modified sphygmomanometer described in the other studies.

Stiffness was difficult to assess as not all patients with symptoms of stiffness had measurable clinical evidence of limitation of movement. In addition care was needed to ensure that wrist stiffness, which may not be solely due to the development of algodystrophy, was not confused with stiffness of the fingers. Patients found the concept of a visual analogue scale to assess the degree of stiffness difficult to understand as the stiffness often varied from day to day or even at different times throughout the day. They also tended to mark the scale based on a global stiffness of wrist and fingers rather than fingers in isolation. It was elected therefore not to pursue this technique as a method of assessing stiffness. In view of these difficulties, no attempt was made to assess the stiffness quantitatively or develop a scoring system using a questionnaire. It was felt that similar problems in understanding the questions would be encountered and the information yielded would not warrant the time spent. The overall aim, as in the other methods of clinical assessment, was to develop rapid techniques for use in the clinical setting. Therefore the presence of stiffness of the fingers was recorded as a positive finding provided the stiffness was a daily occurrence (even if for only part of the day) and was unilateral in nature.

Many different scoring systems have been developed to assess the functional end result following a Colles' fracture, often as modifications of Lidström's (1959) or Gartland and Werley's (1951) original descriptions. These systems frequently concentrate on the range of wrist movement rather than hand function as a marker of the end result. Hand function after Colles' fracture is seldom mentioned (Lucas and Sachtjen 1981). For this reason part of de Brujn's (1987) scoring system, specifically the assessment of motion in the wrist, was excluded to concentrate solely on those features dealing with the function of the hand.

It is recognised that the functional end result following a Colles' fracture can only be judged from one year after injury (Flynn 1966; Solund *et al.* 1983). Assessment at one year however, may miss any functional impairment due to the milder forms of

algodystrophy described by Atkins *et al.* (1989). Since a major aim of this thesis was to study the early natural history, it was decided to assess the patients with algodystrophy functionally at six months and compare this to a matched group of patients with Colles' fracture but with no evidence of algodystrophy. It would have been too time consuming to use the scoring system at every clinical assessment. The measurement of grip strength and stiffness were used as a crude assessment of function on a longitudinal basis.

CHAPTER 10: RADIOGRAPHY

The radiographic changes following algodystrophy were first recognised by

Sudeck in 1900, soon after the development of radiography as a diagnostic technique.

Since then there have been numerous reports on the various radiographic features but

with little attempt to quantify changes. Most reports concentrate on the qualitative

changes that occur and there is therefore only subjective data on the progression of

radiographic changes. Although these changes deal mainly with trabecular bone,

alteration in cortical bone has also been reported (Genant *et al.* 1975; Kozin *et al.* 1976).

These radiographic changes are further complicated because the appearance of post-

traumatic algodystrophy may be similar to that of disuse bone atrophy (Steinbach 1964;

Jones 1969; Feist 1970).

A semi-quantitative scoring system was devised and tested from the radiographs

of the hand. The changes scored were based on the appearance of trabecular bone.

The use of metacarpal morphometry was also investigated as a means of assessing

progressive changes in cortical bone.

A Scoring System

i) Method

Four prominent features were apparent at sites of trabecular bone on radiographs of patients with post-traumatic algodystrophy. These comprised a generalised loss of density, patchy radio-translucencies, subchondral radio-translucencies and a loss of trabecular definition (Fig 10.1a-e). A semi-quantitative four-point scoring system was then devised based on the presence of each of the four features:

0   absent

1   borderline

2   definite changes

3   marked changes

The score for each feature was summed, and the final score expressed as the total of the individual scores giving a maximum possible score of 12.

The system was then applied to the carpus and proximal metacarpal metaphysis in patients with a Colles' fracture two weeks after removal of plaster. This area of the wrist was chosen because it avoided the fracture site and would have been immobilised equally in patients with or without features of algodystrophy, and therefore the degree of bone atrophy due to disuse was likely to have been similar.

Forty-four patients with a Colles' fracture who demonstrated abnormal pain, tenderness, vascular instability, swelling, and stiffness and were thus considered on clinical grounds to have algodystrophy, were included in this study. A postero-anterior radiograph was then taken of both hands on the same film to allow accurate comparison of the affected and unaffected hands. An identical procedure was carried out on 33 patients with Colles' fracture who had no evidence of algodystrophy. The

radiographs from both groups were then reviewed in a random fashion and scored without knowledge of the clinical findings.

a) Reproducibility

To assess the intra-observer reproducibility, 36 of the radiographs were picked at random and re-examined by the same person without reference to clinical details or the previous score. The inter-observer reproducibility was assessed in a similar fashion by a different observer. The coefficient of variation (%) for the paired measurements was calculated as:

$$\frac{\text{standard deviation of the difference}}{\text{mean}} \times 100$$
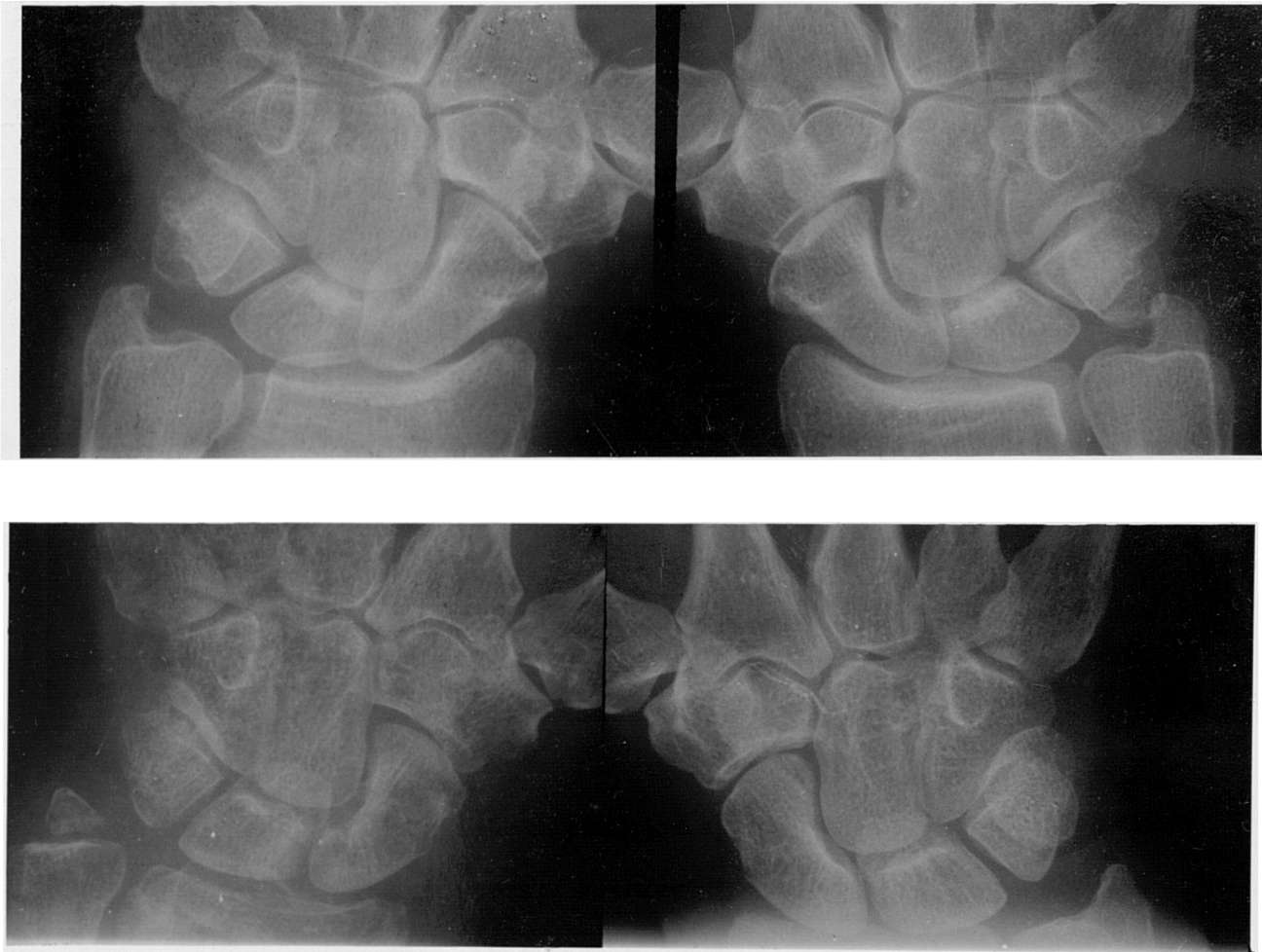
Fig 10.1a-e. Radiogaphs of the carpus taken approximately seven weeks after Colles' fracture showing varying degrees of severity of the four features examined in algodystrophy. Each panel also shows the radiograph of the unaffected carpus taken on the same plate at the same time. The patients shown in b-e all had clinical evidence of algodystrophy.

a) This patient had no evidence of algodystrophy and apart from a definite loss of density (right hand panel; grade - 2), there was no other radiographic features; total score = 2.

b) In addition to a definite loss of density (left hand panel; grade - 2) there was some evidence for increased patchy radiotranslucency (grade - 1) and loss of trabecular pattern (grade - 1); total score = 4.
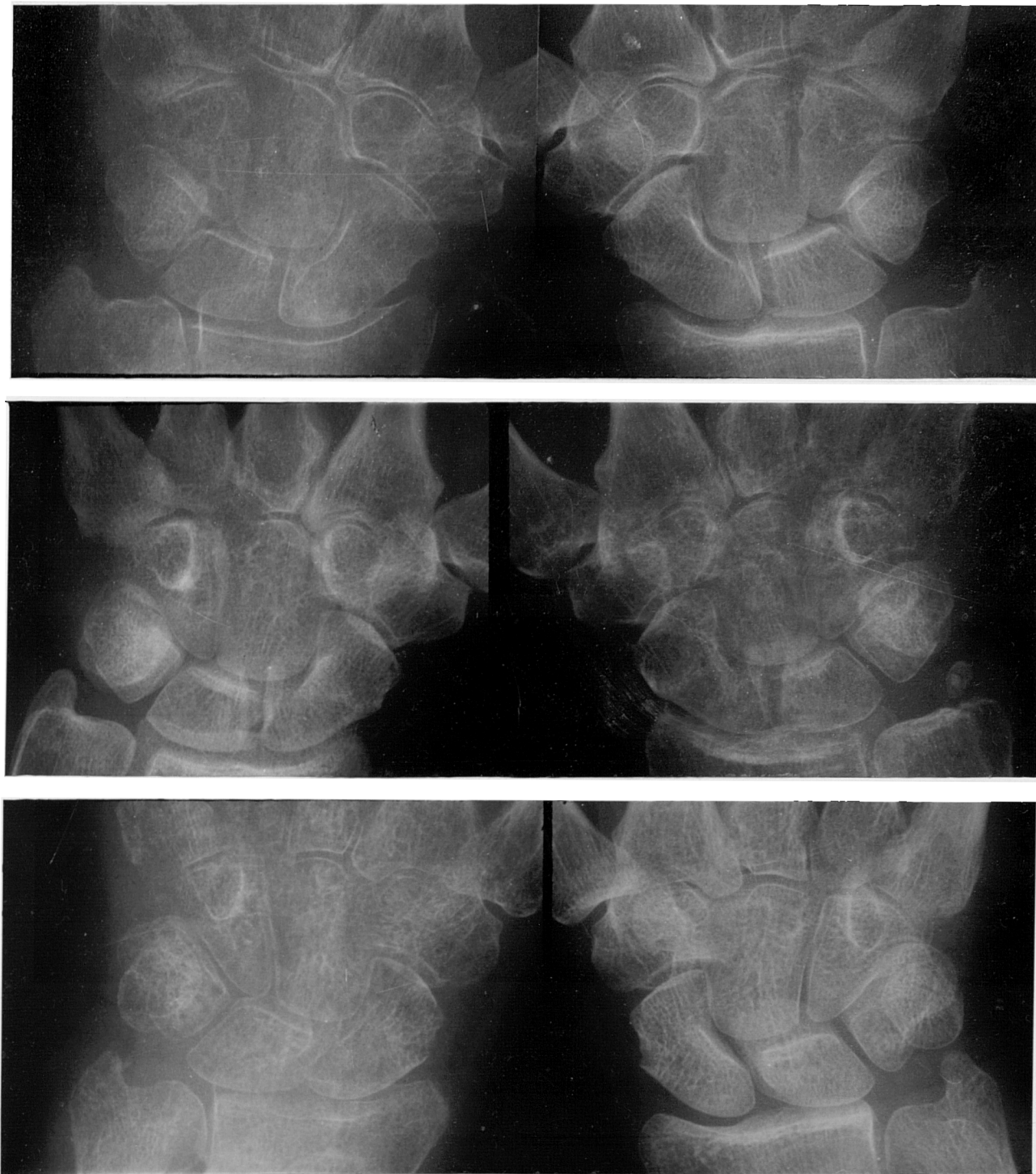
Fig 10.1a-e (cont.).

c) The right carpus showed loss of density (left hand panel; grade - 2), increased patchy radiolucency (grade - 2) and loss of trabecular pattern (grade - 1), there was also a "pencil line" appearance to the articular margin (grade - 1); total score = 6.

d) This radiograph showed a more marked patchy appearance of bone (right hand panel; grade - 3), with loss of density (grade - 2), subarticular radiolucency (grade - 2) and loss of trabecular pattern (grade - 3); total score = 10.

e) Radiograph showing the most marked changes with maximum scores for each feature; total score = 12.

ii) Results

Both groups were matched for age (mean 63 ± 7 years), sex (all female) and period of time immobilised (mean 35 ± 5 days). The coefficient of variation for the intra-observer error was 14% which was slightly lower than the inter-observer error 17%. The distribution has been represented in the form of a matrix to depict the variation between the two observers (Table 10.1). On 15 (43%) occasions the radiographic score was identical; on 18 (51%) there was a difference of one; and in the remaining three (6%), there a difference of two.

Table 10.1. Two observers were used to calculate the inter-observer reproducibility of the radiographic scoring system which is explained in Fig 10.1. In this matrix, the number of patients for each score is given for each of the individual observers.

Observer 1	Observer 2													Total
	0	1	2	3	4	5	6	7	8	9	10	11	12	
0	1	0	0	0	0	0	0	0	0	0	0	0	0	1
1	0	3	0	0	0	0	0	0	0	0	0	0	0	3
2	0	2	3	1	0	0	0	0	0	0	0	0	0	6
3	0	0	0	3	0	0	0	0	0	0	0	0	0	3
4	0	0	0	3	1	1	1	0	0	0	0	0	0	6
5	0	0	0	0	0	0	1	0	0	0	0	0	0	1
6	0	0	0	0	0	0	1	0	0	0	0	0	0	1
7	0	0	0	0	0	0	2	0	3	1	0	0	0	6
8	0	0	0	0	0	0	0	1	1	0	1	0	0	2
9	0	0	0	0	0	0	0	0	0	0	2	0	0	2
10	0	0	0	0	0	0	0	0	0	0	1	0	0	1
11	0	0	0	0	0	0	0	0	0	0	1	1	0	2
12	0	0	0	0	0	0	0	0	0	0	0	1	0	1
Total	1	5	3	7	1	1	5	1	4	1	5	2	0	36

iii) Discussion

With one observer performing all the measurements, there would have to be a 28% change in the score to be confident (p < 0.05) of an apparent difference between any two radiographs. This difference may appear large but is not unexpected considering the semi-quantitative nature of the scoring system. A difference of one point between any two radiographs immediately accounts for an 8% difference. Therefore a difference of only three points between two scores would yield a statistically significant disparity.

Genant et al. (1975) and Kozin et al. (1976) describe a patchy osteopaenic appearance in algodystrophy which they define as generalised or juxta-articular and quantify in a similar manner to this study. No attempt is made to examine the features which contribute towards this patchy appearance. After personally reviewing radiographs of disuse atrophy alone or combined with algodystrophy, it appeared that the patchy appearance in algodystrophy was due to well defined radio-translucencies and a subchondral radio-translucency which along with the generalised osteopenia accounted for the alteration in trabecular architecture. An attempt was therefore made to further quantify these features.

Originally this took the form of counting the number, or measuring the size of the radio-translucent areas but this proved to be too imprecise a technique. It was therefore elected to simply grade the appearance. Similarly the subchondral radio-translucencies were difficult to quantify other than semi-quantitatively using a standard radiographic technique. Even with the use of fine detail radiography, both Genant et al. (1975) and Kozin et al. (1976) found similar difficulties and used a subjective method of assessment. The osteopaenic appearance, radio-translucent areas and subchondral radiotranslucency combine to alter the trabecular architecture which again was assessed in a semi-quantitative manner.

A critical analysis of the part played by each of the four individual features is detailed, along with the scoring systems ability to discriminate between algodystrophy and disuse atrophy, in Chapter 19.

B. Metacarpal Morphometry

i) Method

Metacarpal morphometry was performed on the same radiographs used in evaluating the scoring system. As both hands were included on the same film, there was no difference in magnification and therefore the affected hand could be directly compared with the unaffected.

The technique used was based on Horsman and Simpson's (1975) six metacarpal hand index used in quantifying osteoporosis. This is based on manually measuring the combined cortical width of the index, middle and ring finger metacarpal bones of both hands. The total width of the metacarpal and the width of the medulla was measured at the mid-point of the metacarpal (Fig 10.2). The cortical width of the metacarpal was then calculated by subtracting the total width from the medullary width. This is then repeated on all six metacarpals and the cortical widths totalled to give a six metacarpal hand index. The modifications used in this study relate to both the method of measurement and the calculation of the final score.

The calculations of the mid-point of the metacarpal, the diameter, and radial and ulna cortical widths were performed by computer soft-ware specifically designed for this purpose with an Omega 2000 computer. The software also collected all the patient data which could be exported to a data-base for further analysis. A further advantage of the system was that it corrected for changes in magnification of the radiograph when comparing sequential changes. The system stored the length of the metacarpal and then compared this with subsequent measurements, correcting the measurement of cortical width for changes in metacarpal length.
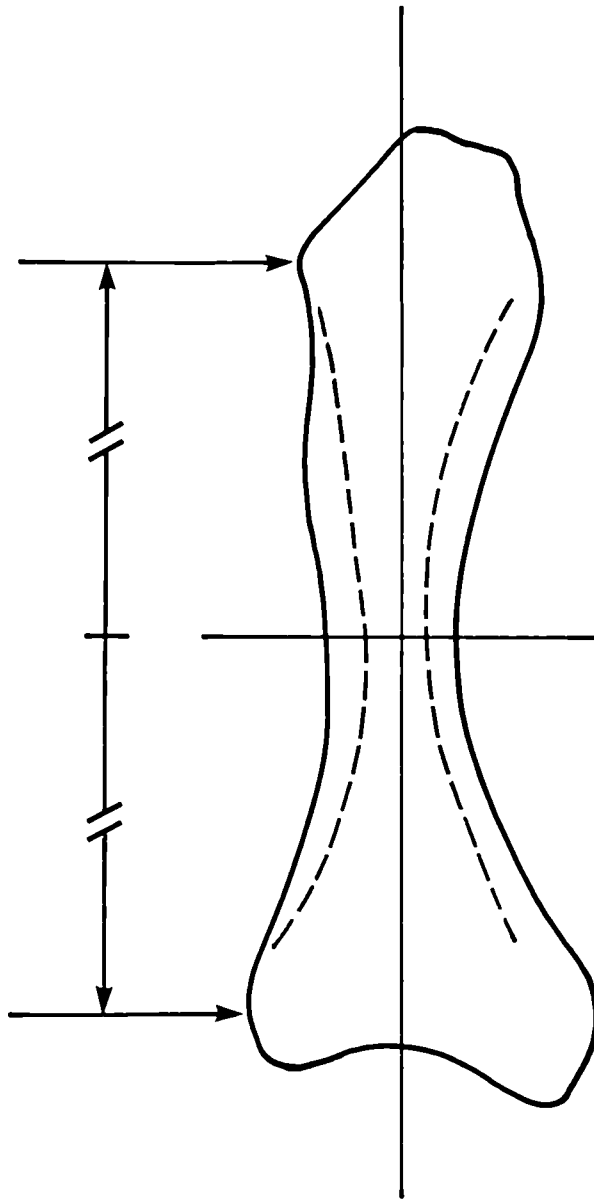
Fig 10.2. Metacarpal morphometry was based on the measurement of cortical width at

the mid-point of the metacarpal. This was performed on the index, middle and ring

finger metacarpals.

The radiograph was attached to an illuminated digitising tablet. Information on the measurement points was transmitted to the computer by a handset which consisted of an optical system with mounted cross-hairs and five buttons to relay the differing information (Fig 10.3). The cross-hairs were used to accurately position the hand-set and the position marked by pressing the appropriate button. After entering patient information, the computer then prompted the user for the data required in a set order. Initially the length of the metacarpal was measured by marking the distal and proximal ends by appropriately positioning the cross-hairs. It then automatically calculated the position of the midpoint of the metacarpal. It then prompted the user to trace the outline of the outer edge of the radial cortex followed by the inner edge of the same cortex. The distinction between the compact cortical bone and cancellous bone on the endosteal surface was less obvious, particularly on the affected hand, due to the irregularity of the surface (Fig 10.4). A consistent attempt was made however to measure the edge of the cortex at the base of the irregularities, thus excluding the apices of the saw-tooth appearance. Both cortical edges were then measured on the ulnar aspect of the metacarpal. From this input the program then calculated the diameter of the mid-point of the metacarpal and the width of the radial and ulna cortex. The whole procedure was then repeated to include the index, middle and ring finger metacarpals of both hands.

The original use of this technique was to provide a measurement of generalised osteoporosis. It's use in this study was somewhat different in that it was attempting to show a change in cortical width affecting one hand only. Therefore the calculations were expressed to demonstrate the difference between the two sides. Rather than a total six metacarpal hand score, the ratios of combined cortical width and the percentage cortical width ([combined cortical width/combined diameter] x 100) of the affected to unaffected hand were calculated. In addition the absolute values of cortical and metacarpal width were also presented.

Fig 10.3. The metacarpal morphometry was performed by a semi-quantitative technique. The radiographs were mounted on an illuminated digitising tablet and a hand set with mounted cross-hairs was used to record the position of either end of the metacarpal and to trace the periosteal and endosteal border of each cortex. This information was transmitted to a computer where the mid-metacarpal diameter and cortical widths were calculated. This data was then stored for later analysis.

Fig 10.4. In patients with algodystrophy, the endosteal border appeared particularly irregular. An attempt was therefore made to measure width at the base of the irregularities to represent the edge of the endosteal surface.

a) Reproducibility

The reproducibility of the technique was based on sequential measurements at the unaffected hand in patients with algodystrophy. These were taken at presentation and at 12 weeks. The coefficient of variation for the paired measurements of combined cortical width was calculated as previously described. The measurements were expressed as $\pm$ one SEM and any difference between groups assessed using an unpaired Student's t-test.

ii) Results

There were 44 radiographs of patients with algodystrophy and 33 with no evidence of algodystrophy (Appendix I). The combined cortical width, percentage cortical width and metacarpal diameter of the unaffected hand in patients with algodystrophy were almost identical to those of the unaffected hand in those with no evidence of algodystrophy (Table 10.2). Because there was no difference in measurement between these populations, it was assumed that measurements on the unaffected hand were not influenced by the presence or absence of algodystrophy in the contralateral hand. Indeed, though not significant, the combined cortical width and percentage cortical width were slightly less in the group with no evidence of algodystrophy. Therefore the measurements on the unaffected hands in both groups were combined and the coefficient of variation calculated on the difference between the measurements initially and 12 weeks later (Table 10.3). The techniques were highly reproducible with coefficients of variation of 1.6% for the measurement of combined cortical width and 1.7% for percentage cortical width.

Table 10.2. Cortical measurements in the unfractured side in algodystrophic and control patients. There was no significant difference between the mean (± SEM) combined cortical width and mean (± SEM) % cortical width in the unaffected hand on the initial radiographs between patients with algodystrophy and the control population.

	Algodystrophy		Control	
UNAFFECTED HAND	Mean	SEM	Mean	SEM
Combined Cortical Width (mm)	9.48	0.30	9.41	0.37
% Cortical Width	40.91	8.74	39.69	9.06
Metacarpal diameter (mm)	23.2	0.33	23.8	0.31
Number	44		33	

Table 10.3. Mean and standard deviation of combined cortical width and percentage cortical width for the initial radiograph and that at 12 weeks. Since there was no difference between the algodystrophy and control group, they were combined and used to calculate the reproducibility of the technique.

	INITIAL		12 WEEKS		C V
UNAFFECTED HAND	Mean	SD	Mean	SD	%
Combined Cortical Width (mm)	9.90	2.27	9.80	2.04	1.6
% Cortical Width	41.44	9.73	40.66	8.44	1.7

iii) Discussion

There are two main sources of error inherent in this technique. They are measurement error, and errors associated with the radiographic technique. Measurement variation arises in the assessment of the width of a cortex to two decimal places which gives a variation of $\pm$ 0.005 mm. In practice this is unlikely to be significant as with the naked eye it is impossible to define such small dimensions. The use of magnification to identify dimensions as small as 0.01 mm would only increase the difficulty in identifying the endosteal border. This is a further source of error due to the irregularity of the surface, particularly in the affected hand. Increased endosteal resorption has been demonstrated on fine detail radiography by Kozin *et al.* (1976) in patients with algodystrophy. Attempts were made to minimise this by taking the base of the irregularity as the true endosteal border.

Errors in locating the same mid-metacarpal site in sequential radiographs was minimised by the design of the software which relied on the observer simply identifying the distal and proximal extent of the metacarpal. The distal end was easily defined as it was the smooth articular surface of the metacarpo-phalangeal joint. The proximal end was less easily identified due to the superimposition of the carpo-metacarpal joint lines. In practice the most distal of the different articular margins was taken as the true proximal extent. Even when measured by hand, the degree of error only amounted to 3% of total metacarpal length (Naor *et al.* 1972) and is thus negligible. This error is likely to be further reduced as the calculation of the mid-point is not directly operator dependant.

Possible errors in radiography fall into three groups. Underexposed films may make the cortical margins difficult to identify, an incorrect film-focus distance may lead to errors in magnification and rotation of the hand may spuriously alter the cortical dimensions. The first two errors are excluded by the standard radiographic technique

employed in all the subjects. The error in rotation should be minimised by the standardised manner in which the hand was positioned. With the hand flat on the radiographic plate and the forearm in neutral rotation, it is difficult to rotate the hand unless a conscious effort is made. There is a potential source of error however in patients with algodystrophy who have a fixed flexion deformity of the fingers. This could cause an increase in the magnification of the image as the palm is lifted off the plate and a relative shortening of the metacarpal as the distal end is lifted up. This error is largely negated as the computer soft-ware makes appropriate changes to the calculation of the cortical widths when there is an apparent alteration in magnification due to alteration in the length of the metacarpal.

Both Adams *et al.* (1969) and Naor *et al.* (1972) pointed out that morphometry was less reproducible if the measurements were made over a long period of time. This was probably due to the observer unconsciously altering his criteria of measurement. In accordance with their recommendations, the measurements of all radiographs in this study took place over a two week period to minimise this potential hazard.

The standard positioning and radiographic technique, with a computer based calculation of the cortical widths including correction for magnification (the potentially greatest cause of error in sequential measurements) considerably minimised sources of error. The only real source of observer error, the identification of the endosteal border, was minimised as much as possible by the short time period between measurements. It is therefore not surprising that the technique was a highly reproducible.

Metacarpal morphometry, as an indirect measurement of bone mass, was first developed by Barnett and Nordin in 1960. The combined cortical thickness of the second metacarpal was expressed as a percentage of metacarpal diameter at the same site. It has since been used in a number of cross-sectional studies (Fujita *et al.* 1966; Garn 1970) but due to poor reproducibility, little valuable information is available in longitudinal studies. Adams *et al.* (1969) studied two replicate measurements of the

2nd metacarpal on 86 films and found the coefficient of variation for the intra-observer error to be 8-10% for the cortical width. A similar degree of measurement error for a single estimation of cortical width was demonstrated by Naor et al. (1972) but a reduction in variation was obtained (6%) using the average of two independent determinations rather than a single assessment. The technique was further refined by Horsman and Simpson in 1975, measuring the middle three metacarpals on each had in a rigidly standardised manner using needle-tipped Vernier calipers measuring to within 0.05 mm. They calculated the cortical width of the six metacarpals and expressed the metacarpal index as the mean of these six measurements. This technique proved to be highly reproducible in their hands with a measurement error of 0.072 mm (2 SD). This allowed changes in cortical width of 1.5% to be detected with 95% confidence in a population of pre-menopausal women. As they pointed out, this compared favourably with the precision of other methods such as photon absorptiometry.

The reproducibility of the technique in this study (coefficient of variation - 1.6%) is comparable to that of Horsman, using only the three metacarpals of the unaffected hand. As one might expect, the reproducibility of the percentage cortical width was slightly worse (1.7%), since another potential variable (metacarpal diameter) is involved in the calculation. Using Horsman's method of measurement, Aitken (1984) also found the percentage cortical width less reproducible (3%) so there would therefore appear to be little potential benefit in this method of calculation.

There was no difference in the cortical width of the unaffected hand between patients with algodystrophy and the control population. This suggests that the algodystrophic process does not result in changes in cortical bone measurable by this technique on the unaffected side. This finding is contrary to that of Genant et al. (1975) who used the 2nd metacarpal index in a study of 7 patients. They maintained that there was a decrease in the cortical width of the unaffected side of the contralateral

limb by comparing their values to those quoted by Garn *et al.* (1971) for the normal population. Their numbers were small and they should have used their own control population to make a more valid comparison.

Metacarpal morphometry appears therefore to be a reproducible method of assessing cortical bone. A 3% change in combined cortical width would be sufficient to show a significant ($p < 0.05$) change in an individual. When used with the scoring system previously described, it was hoped to describe the natural history of the radiographic changes in both cortical and trabecular bone due to algodystrophy (Chapter 24).

CHAPTER 11: SCINTIGRAPHY

Bone scintigraphy is a valuable diagnostic tool for the early diagnosis and follow-up of several articular disorders. It's use in the early diagnosis of algodystrophy has been demonstrated by a number of authors (Doury *et al.* 1979; Renier *et al.* 1979; Kozin *et al.* 1981; Mackinnon and Holder 1984; Constantinesco *et al.* 1986) but without standardising the population studied nor time from the initiating event. We have shown, in a study examining the uptake following a Colles' fracture in patients with and without evidence of algodystrophy, that there is still increased isotope uptake in the control group three months after the fracture (Atkins *et al.* 1990). It is questionable therefore to what extent increased isotope uptake in algodystrophy is due to fracture, simple disuse atrophy or to a factor inherent to the algodystrophic process. Accordingly there may be a source of confusion in the diagnosis of post-traumatic algodystrophy based on scintigraphy.

Scintigraphy not only analyses the bone fixation but includes the study of early bone scans which can be termed the "vascular phase". Conventionally, the interest of bone images is essentially diagnostic while the interest of the vascular images are more specifically pathophysiologic. In our own studies we intended to examine both images, to test their ability to differentiate between disuse and post-traumatic algodystrophy at an earlier stage in the disease than has been previously attempted, and to study the resolution of the scintigraphic uptake with time. Patients with hemiplegia were also studied to further delineate the part played by disuse atrophy in the scintigraphic findings of post-traumatic algodystrophy.

i) Method

An intravenous cannula was inserted into the unaffected ante-cubital fossa without the use of a tourniquet. The isotope scan was performed using a large field of

view gamma camera equipped with a high resolution parallel hole collimator. Each scan was carried out as a two stage procedure as mentioned previously. The early image or "vascular phase" consisted of four sequential 100 second images of the hands and forearms in anterior view, obtained immediately after a rapid bolus injection of 400 MBq of technetium 99 labelled methylene diphosphonate into the intra-venous cannula. The delayed image was taken of the hands, wrist, elbow and shoulder of both the affected and unaffected limb four hours after injection. In addition to analogue display on radiographic film, each image was stored in digitised form in a 128 x 128 array using a Nova series minicomputer equipped with colour display and facilities for region of interest analysis.

Quantitative analysis of the digitised anterior view of the hands on the delayed image was undertaken to assess the relative uptake of the isotope into the metacarpo-phalangeal joints (MCPJ) on the affected and unaffected sides (Fig 11.1). The isotope uptake, or metacarpal score, was then expressed as the ratio of the counts in the affected ROI over the unaffected:

ratio = counts affected

counts unaffected

To standardise the areas measured a grid was made over the ROI using the computer soft-ware. It was not possible to use a fixed grid size on all scans due to the variation in the size of the image from patient to patient. Also, in cases with markedly increased uptake, there appeared to be a "spill-over" of tracer uptake outside what would be considered the region of interest. Ignoring this "spill-over" would underestimate the magnitude of the isotope uptake. Therefore the size of the ROI to be measured was defined manually for each individual patient, and an attempt was made to use the same sized grid on the unaffected hand. To exclude any small variation in the size of the ROI between the affected and unaffected side, a scaled ratio was then calculated taking into account the size of the (ROI):

$$\text{scaled ratio} = \frac{\text{counts affected}}{\text{ROI size affected}} \quad \times \quad \frac{\text{ROI size unaffected}}{\text{counts unaffected}}$$

If the areas of interest are identical, they automatically cancel themselves out, leaving the calculation for the ratio.

Scintigraphic examinations were performed on 43 algodystrophy patients and 10 patients with a Colles' fracture but no evidence of algodystrophy who were also age and sex matched (Appendix I) two weeks after removal of plaster, at the same time as the other initial assessments. The examination was then repeated after a 12 weeks interval in those patients with algodystrophy.

Patients with a dense hemiplegia after a cerebro-vascular accident (CVA), such that there was no active movement in the affected limb, were asked to participate in a study examining the scintigraphic findings following complete disuse. As there is a recognised high incidence of algodystrophy following CVA (Chapter 2), every effort was made to exclude patients with the appropriate symptoms or signs bearing in mind their altered perception of pain. Those patients who appeared not to have algodystrophy were scanned at approximately 7 weeks after the CVA, an identical time to the fracture study group. Only the delayed scans were performed in these patients.
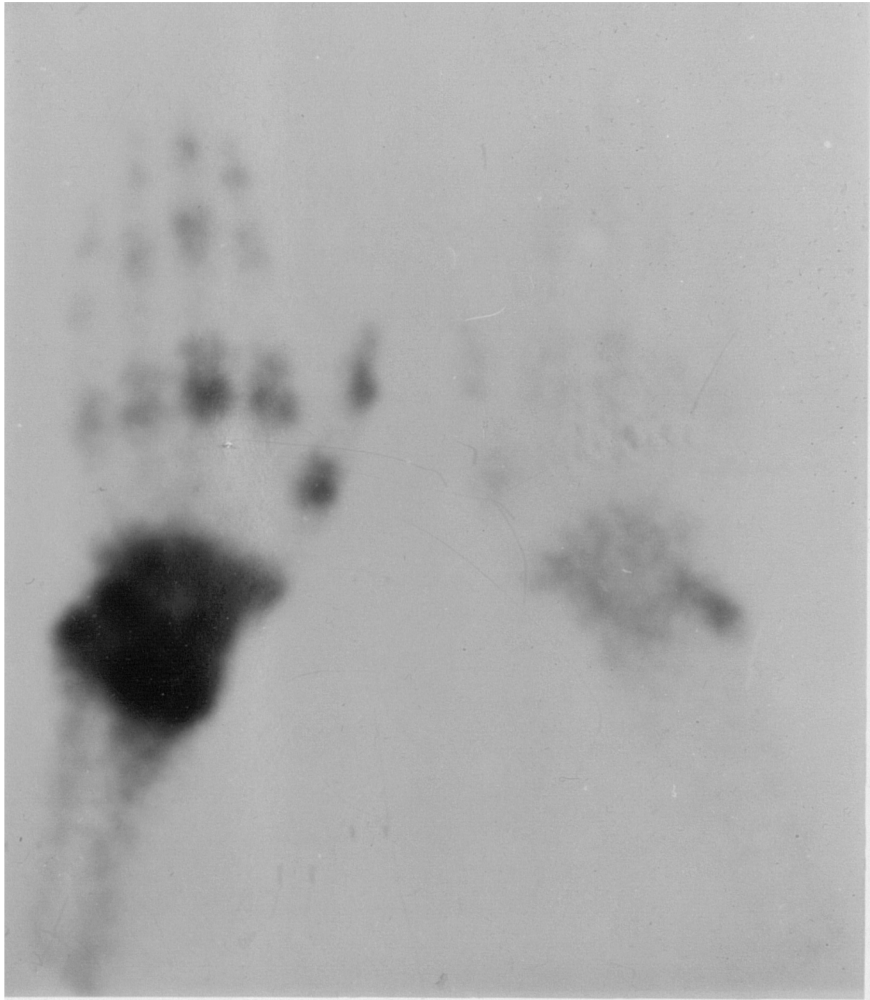
Fig 11.1. The activity on the delayed phase of the isotope scan was calculated as the ratio of counts in the affected metacarpo-phalangeal joints over the unaffected and expressed as the metacarpal score.

<u>ii) Results</u>

To identify to what extent the size of the region of interest was affecting the results, the scaled ratio was divided by the ratio:

<u>counts affected</u>   x   <u>ROI size unaffected</u>

<u>ROI size affected</u>   counts unaffected

       <u>counts affected</u>

       counts unaffected

which resolves to:

      <u>ROI size unaffected</u>

      ROI size affected

If the size of the ROI was the same for the affected and unaffected side, the result should be 1.0 and therefore the calculation for the ratio would be as valid as the scaled ratio. As a difference in the range of interest was only likely to be introduced in conditions where there was markedly high uptake, this was only calculated for the patients with algodystrophy. Including the Colles' control patients would have masked any true discrepancy in the size of the ROI.

The mean of the scaled ratio/ratio was 0.97 (SD - 0.11). Therefore the size of the ROI was on average estimated as 3% larger on the affected side. This was by no means consistent however in view of the relatively large standard deviation (0.11). The difference in the ROI therefore accounted for only a 3% disparity between the scaled ratio and the ratio. Therefore as the underestimation of the degree of "spill-over" described earlier was negligible, the metacarpal score was based on only the absolute ratio of the uptake in the affected to unaffected hand.

Ten patients with a Colles' fracture but no evidence of algodystrophy underwent isotope examination. The mean metacarpal score was 1.14 $\pm$ 0.04 with a range from 1.02 - 1.35.

iii) Discussion

Attempting to standardise the ROI does not confer any benefit as there is little difference (3%) between the counts ratio with and without correction for the area involved. The metacarpal score was therefore calculated on the basis of the number of counts alone. Theoretically this may have been influenced by a "spill-over" from the fracture site on the affected side making the metacarpal score spuriously high.

In an earlier study using a similar patient group and method of quantitation (Atkins *et al* 1990), the mean score for the control population was 1.08 ± 0.11, 14 weeks after fracture and included scores ranging from 0.7 - 1.6. In some patients, the uptake in the affected side was therefore less than the unaffected side. In this study the mean ratio was higher (1.14 ± 0.04) and in all patients the uptake in the affected side was always greater than 1. This is likely to be due to the earlier time after fracture in the present study and therefore the increased scintigraphic uptake due to disuse atrophy would be more marked. This highlights the difficulty in relying solely on the delayed scan in the early diagnosis of post-traumatic algodystrophy. Between 7 and 14 weeks the ratio improved by an increment of approximately 0.01 per week. At that rate of improvement, there would be no detectable difference between the affected and unaffected sides at approximately 23 weeks after fracture provided the recovery was linear (Fig 11.2).
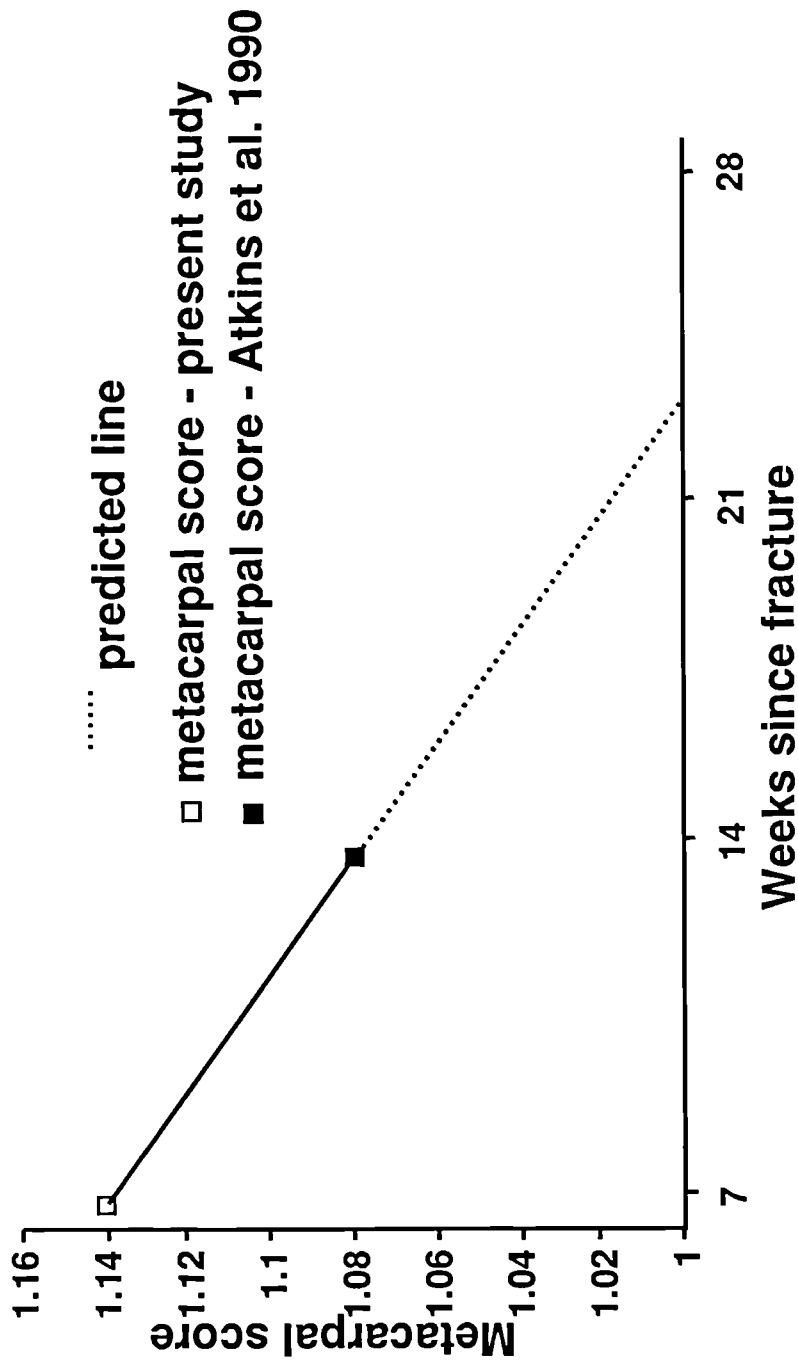
Fig 11.2. The mean metacarpal score in the 10 control patients examined 7 weeks after fracture were compared with the six control patients in the series reported by Atkins et al. (1990) using the same technique but in patients who were, on average, 14 weeks after fracture. Assuming a linear resolution in the isotope uptake, there should be no difference between the fractured and unfractured hand, in the absence of algodystrophy, by 23 weeks after injury.

CHAPTER 12: DENSITOMETRY

Apparent loss of bone density is a notable feature of algodystrophy on radiographs, but this does not provide a quantitative assessment of bone mass which is needed in evaluating the natural history of the condition or it's response to treatment. A variety of noninvasive techniques are currently available for the assessment and measurement of bone mass or bone mineral content. Some of these, such as radiogrammetry and radiographic photodensitometry, while well established and technically straightforward, have significant methodological problems that are reflected in poor measurement precision. Others, such as neutron activation analysis, have been developed and performed in research centres for many years, but are unlikely to be widely implemented because of their high cost and technical complexity. Recent advances in technology however, have presented accurate bone mass measurements in a clinical setting. These techniques include single and dual photon absorptiometry. As single photon absorptiometry is routinely used in appendicular sites it seemed appropriate to investigate the use of this technique to measure changes in bone mineral density due to algodystrophy.

i) Method

The single photon absorptiometry (SPA) scanner used was the Nuclear Data ND 1100. This instrument uses a low photon energy of 27.5 keV from it's ^{131}I photon source. The low energy provides maximum contrast between bone and soft tissue, although the high attenuation produced by all materials at these energies effectively limits usefulness of this technique to appendicular body sites such as the distal radius.

The bone mineral content was measured directly by determining the attenuation of the photon energy as it passed through bone. The changes in transmittance, which are proportional to the mineral mass in the scan path, were measured by a scintillation

detector. Difference in soft-tissue thickness alone produce transmitted-beam intensity variations, hence the total thickness of tissue traversed by the beam must be standardised. This was done by positioning the arm in an acrylic reservoir filled with water so that the only remaining variable at each measurement point was the bone mass present in the beam path. The data from each scan was automatically transferred to a Hewlett-Packard computer with standardised software. This permitted communication between the instrument and the operator via the keyboard, automatic calculation of bone mineral content and density, graphical display of the data on the monitor and a hard copy of the data on a print-out.

The scanner we employed was usually used for measurements at the distal forearm and therefore this standard technique will be described first to highlight the modifications made for this study. To prevent errors in repositioning, the patient grasped a handle in the reservoir using a power grip which automatically positioned the arm (Fig 12.1). An 8 mm gap between the radius and ulna was then identified automatically by the computer software and subsequent scans, proximal and distal, were started from this point. After the scanner had located the start position it moved 8 mm distally from the start position. It then performed four scans, 2 mm apart, moving in a proximal direction (distal; scans 1-4), followed by a further six scans 4 mm apart (proximal; scans 5-10) giving a total of 10 scans. Based on the degree of attenuation of the beam, the software calculated the bone mineral content (BMC; corrected for fat in the forearm) and the bone mineral density (BMD; BMC/bone width) for both the proximal and distal scan sites.
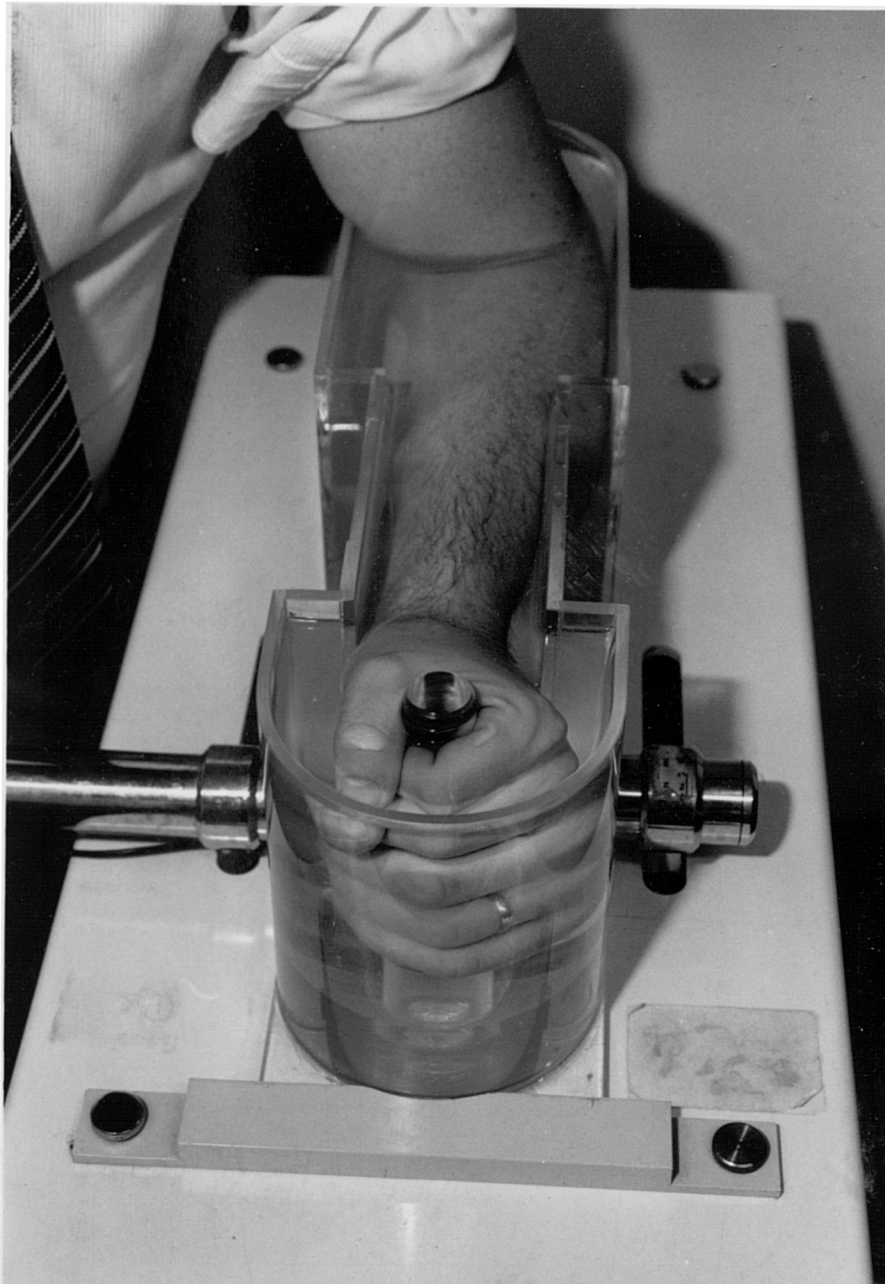
Fig 12.1. The single-photon scanner as usually used to measure bone mineral content at the distal radius and ulna. As a means of standardising the position of the wrist, the patient grasps a handle within the water bath.
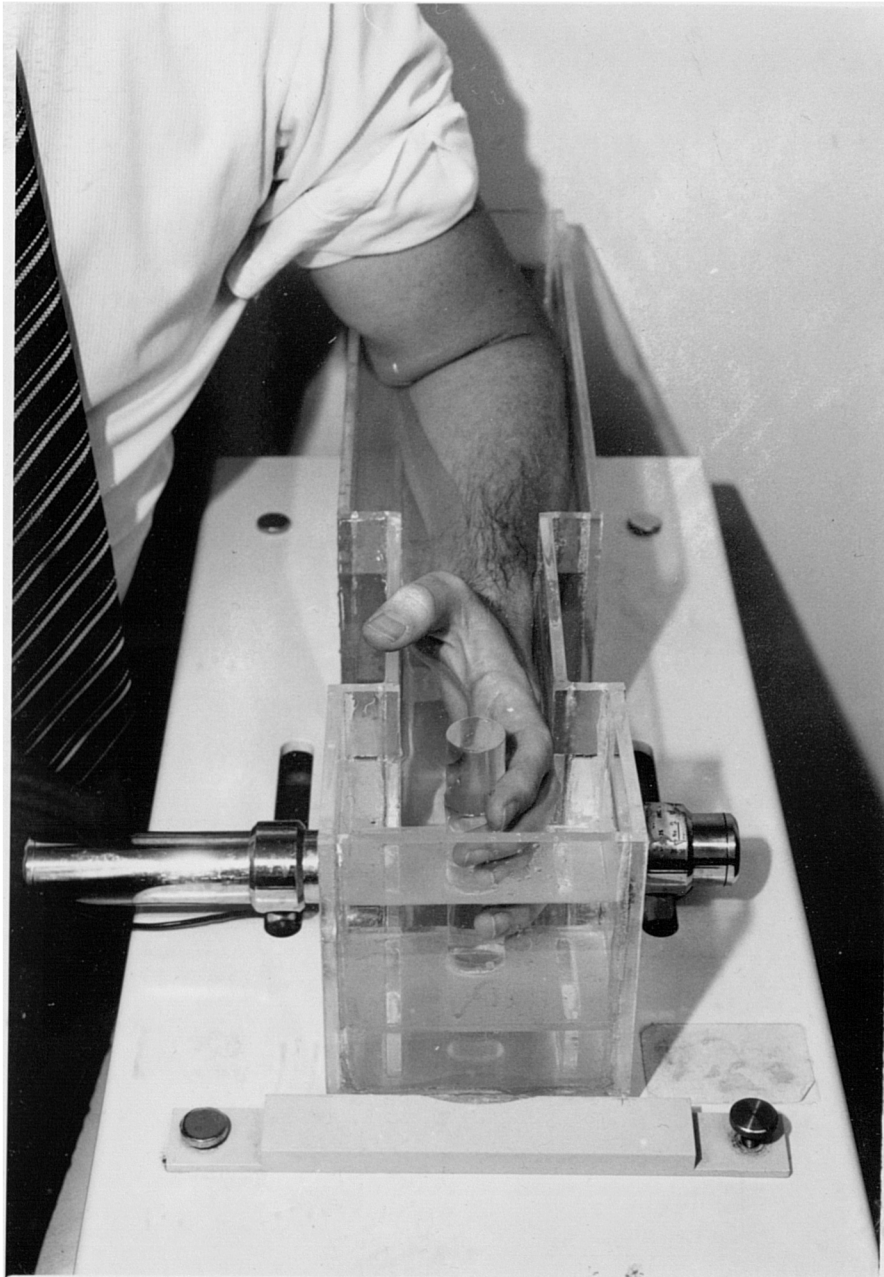
Fig 12.2. The water bath on the single-photon scanner was altered for the purpose of this study. Grasping the handle, as is standard in distal forearm measurement, would have obscured the metacarpals and therefore the bath was lengthened and the handle moved distally. The patient could then hook their fingers around the handle which allowed free access to the metacarpals.

The forearm was unsuitable in this study due to the site of the fracture. Any data reflecting demineralisation due to algodystrophy may have been masked by fracture callus giving spuriously high results. The standard measurement technique described above was therefore altered to measure the 4th and 5th metacarpals.

Grasping the handle in the reservoir as described above would obscure the metacarpals and prevent their accurate measurement. The reservoir therefore, was adapted to allow the fingers to hook over the handle (Fig 12.2) maintaining the hand, and therefore the metacarpals, in the photon beam. When the hand was scanned in this position, the computer automatically interpreted the 4th and 5th metacarpals as the ulna and radius respectively. It also searched for an 8 mm inter-osseous gap which, if found at all, was mid way along the diaphysis of the bone and not at the junction of the metaphysis/diaphysis as was intended. Therefore a method of accurately repositioning the hand was sought. Scans of the proximal metacarpal would have been ideal as, similar to the reasoning with the radiographic assessment of trabecular bone, this area is immobilised equally in patients with or without algodystrophy. Unfortunately no reproducible starting point to scan this area seemed apparent. The distal palmar crease did however provide an anatomical landmark which could be used as a starting point to scan the distal metacarpal. This was a constant anatomical feature (Fig 12.3) over the distal metaphyseal/diaphyseal junction (Fig 12.4). The scanner was therefore aligned optically over this flexor crease for it's first scan. Although the inter-osseous gap at this point is less than 8 mm, the computer soft-ware was overridden to accept this position. Subsequent scans were performed both distally (through mainly trabecular bone in the metaphysis) and proximally (through mainly cortical bone in the diaphysis) from the skin crease to provide data on the BMC and BMD of the 4th and 5th distal metacarpal.
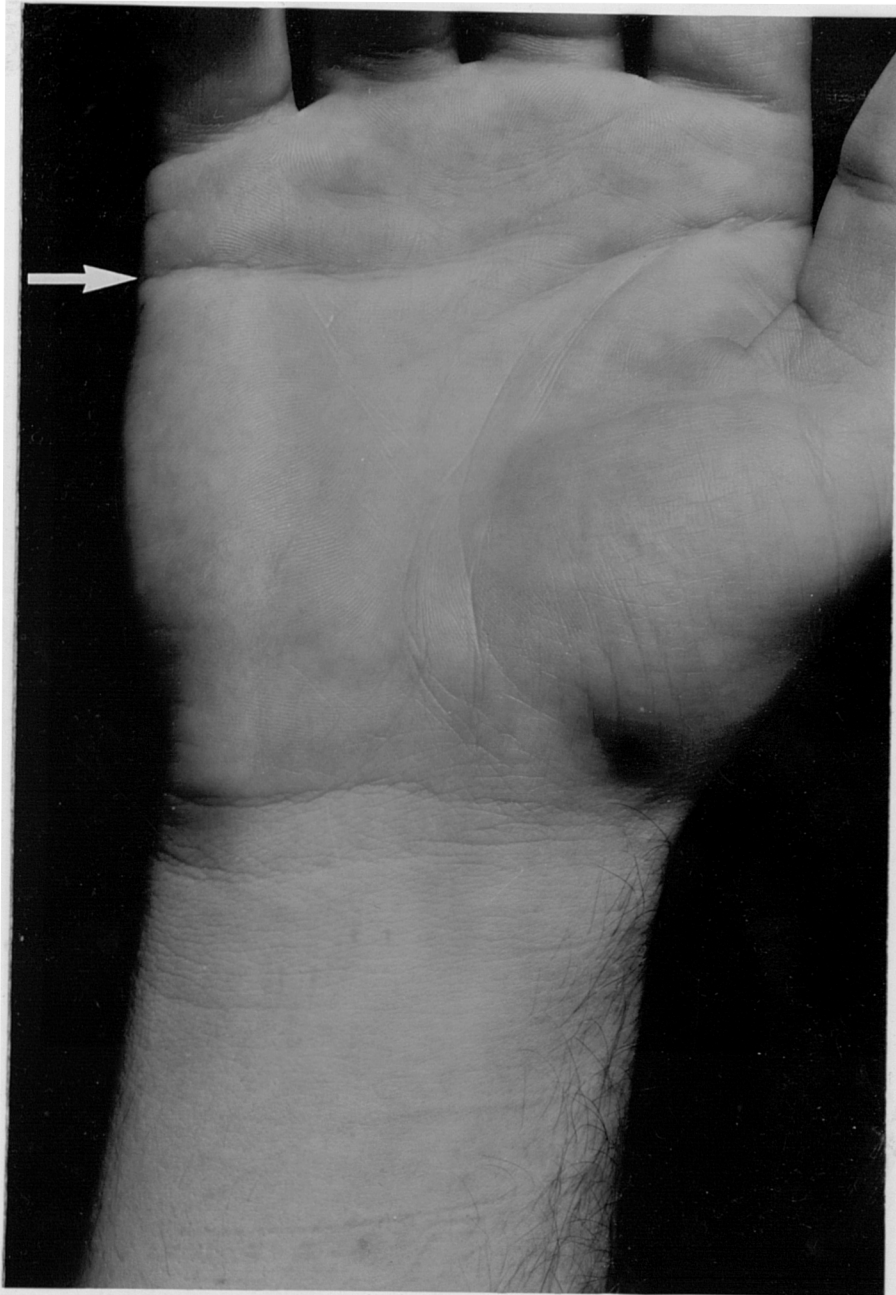
Fig 12.3. The distal palmar crease on the ulna aspect of the hand was the anatomical landmark used as the starting point for the distal and proximal single-photon scans.

Fig 12.4. A marker was placed on the distal palmar crease prior to the radiograph being taken. The marker lies over the junction of the distal metaphysis/diaphysis. Therefore single-photon scans distal to this point were through trabecular bone and proximal scans through cortical.

The scans were performed, as in the other initial assessments, 2 weeks after the plaster had been removed. The scans were then performed at monthly intervals (Table 8.3). Twenty-nine patients with algodystrophy and 23 control patients were assessed, all of whom also had radiographs taken at the same time and were used in the radiographic assessment (Chapter 10).

a) Reproducibility and Normal ranges

In order to assess the reproducibility and calculate the normal range of BMC and BMD, 18 female and 3 male patients with a mean age of 61 $\pm$ 5 years were studied. They had no evidence of algodystrophy in the hand and no recent fracture of the distal radius. A single photon scan was performed on both hands as described above. This gave a value for the BMD and the BMC for both the distal (trabecular bone) and proximal (cortical bone) scans, a total of four measurements on each hand. The scan of the dominant hand was then repeated a day later without reference to the previous day's scores. To prevent errors due to deterioration in the source or operator error, the ratio of the dominant hand to nondominant was also calculated and used to calculate normal ranges rather than the absolute values. This has a further advantage in the fracture study as the unaffected hand is used as an automatic control.

The coefficient of variation of the paired measurements was used to assess the reproducibility of the technique. The distribution of the ratios at each site were investigated using Probit analysis and the significance of the difference between ratios assessed using Students' t test. The normal range (mean $\pm$ 2 SD) was then calculated for the most reproducible technique at each site.

<u>ii) Results</u>

Coefficients of variation were calculated for the BMD and BMC at each of the two sites (Table 12.1). Although there was little difference, maximal reproducibility was

achieved measuring BMD at both the proximal (4.2%) and distal (4.4%) sites and therefore the BMD measurement was used in the further analyses.

The mean measurement were slightly greater at the dominant hand for all measurements except the BMD distally, but given the relatively large standard deviations (Table 12.1), the dominant hand was not consistently the most dense. Not surprisingly there was no significant difference between the dominant and nondominant hand (p > 0.05). In order to avoid any spurious but statistically significant difference in BMD in the fracture study, it was decided to double up the ratio of both dominant to nondominant and nondominant to dominant sides to remove any misleading, slightly skewed distribution. As the values for the BMD ratios at the distal (Fig 12.5; Probit analysis r = 0.96) and proximal (Fig 12.6; Probit analysis r = 0.97) sites were normally distributed the normal ranges at each of these sites were calculated as 0.70 - 1.30 distally and 0.76 - 1.24 proximally.

Table 12.1. The bone mineral content (BMC) and bone mineral density (BMD) were measured in the fourth and fifth metacarpals. The mean and standard deviation of the dominant and non-dominant hands were calculated in 21 patients with no evidence of algodystrophy or recent Colles' fracture. The measurements of BMD were more reproducible on both the distal and proximal scans.

Measurement	Dominant hand		Non dominant hand		Ratio		Coefficient of Variation
	mean	SD	mean	SD	mean	SD	of the ratios
Distal							
BMD (g/cm^2)	0.64	0.16	0.64	0.14	1.00	0.15	4.4%
BMC (g)	16.0	4.39	15.7	4.72	1.00	0.18	6.2%
Proximal							
BMD (g/cm^2)	0.84	0.25	0.82	0.21	1.00	0.13	4.2%
BMC(g)	16.3	5.51	15.1	5.71	1.00	0.21	5.9%
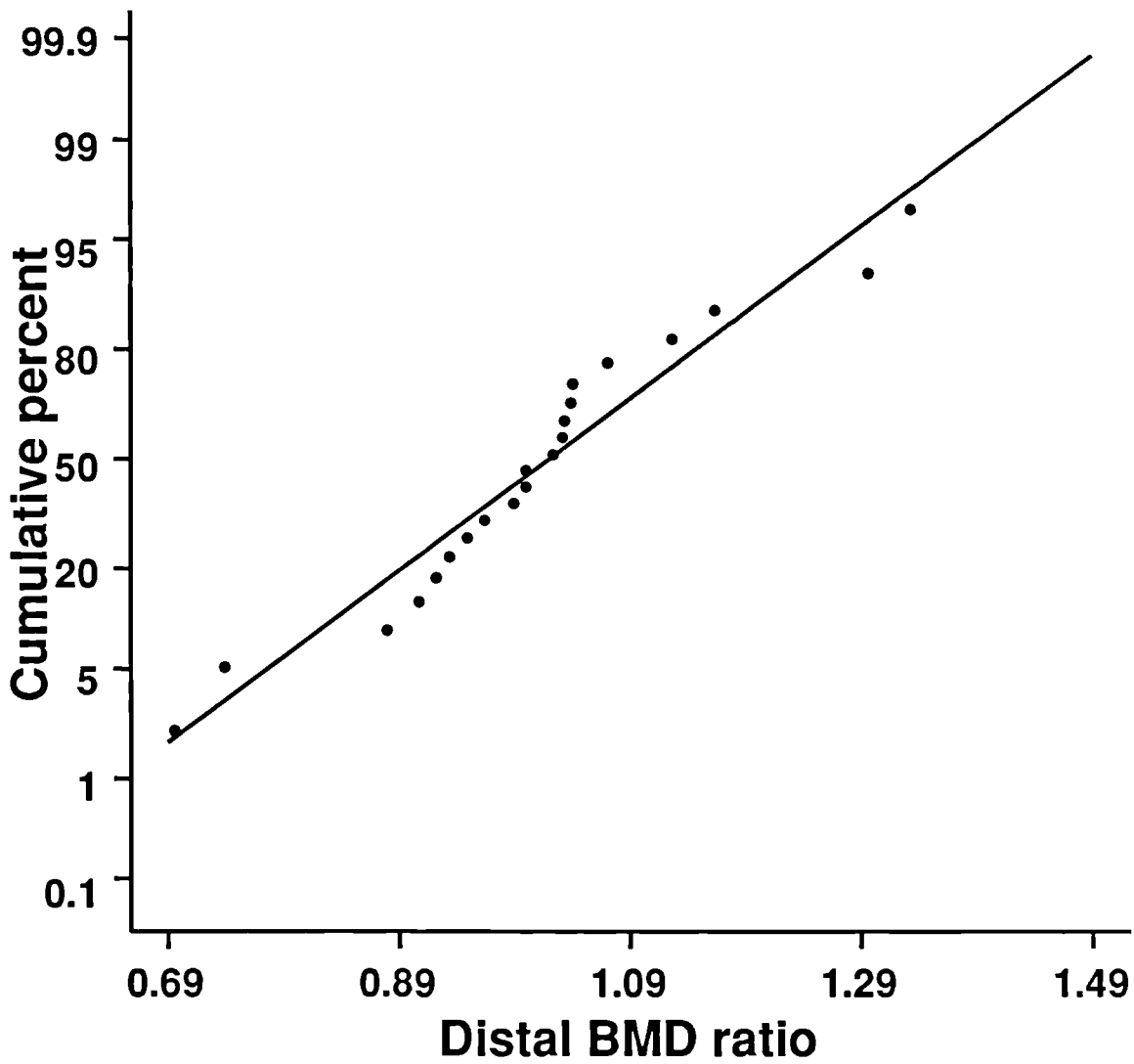
Fig 12.5. Probit analysis was performed on the distal BMD ratios in 21 patients
who had no evidence of algodystrophy or recent distal radial fracture. Since
the ratio, which was expressed as the score for the dominant divided by the non-
dominant hand, were normally distributed, the 95% confidence interval was used
to calculate the normal range.
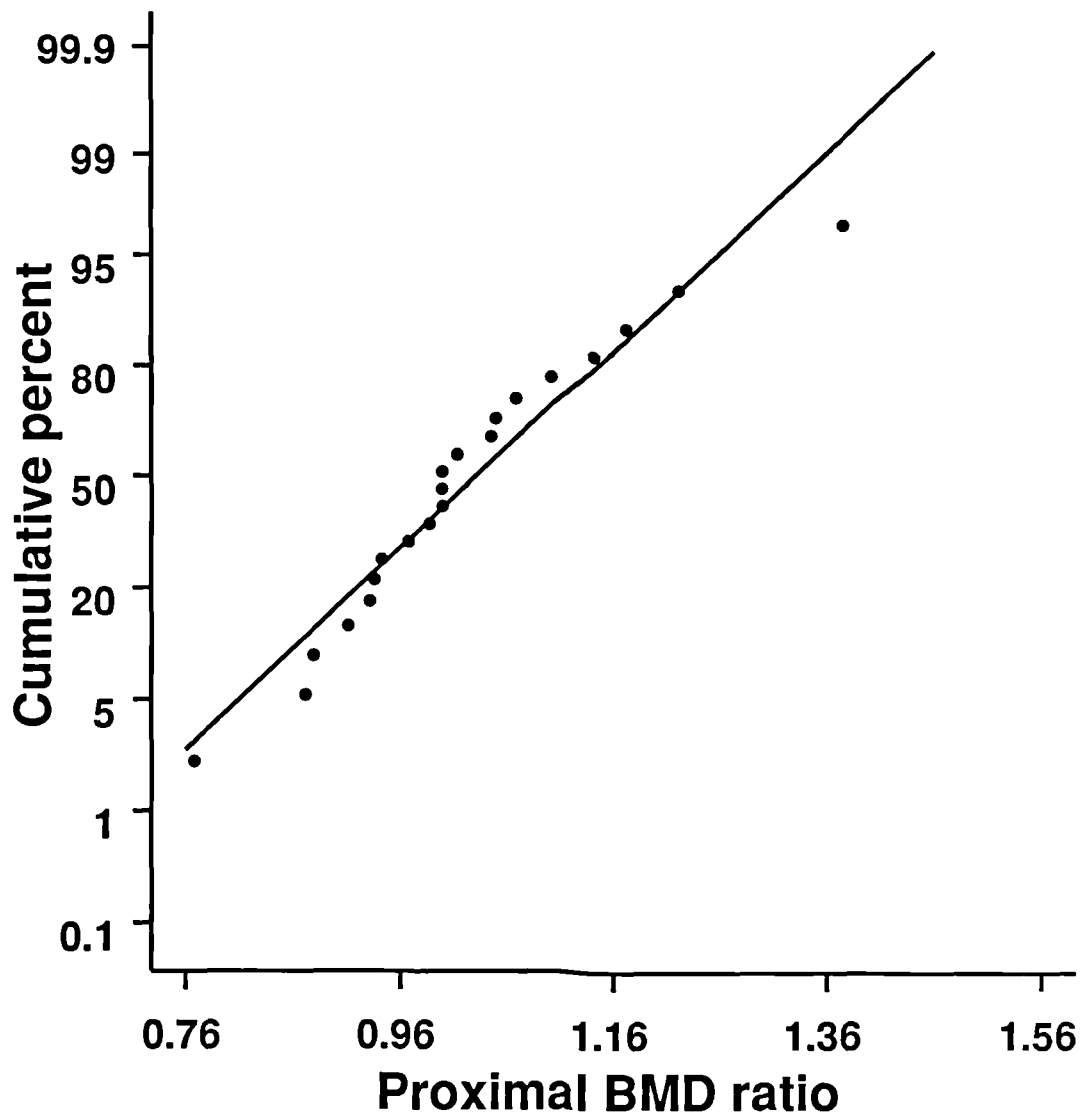
Fig 12.6. Probit analysis was performed on the proximal BMD ratios in 21 patients who had no evidence of algodystrophy or recent distal radial fracture. Since the ratios, which were expressed as the dominant divided by the non-dominant hand, were normally distributed, the 95% confidence interval was used to calculate the normal range.

<u>iii) Discussion</u>

This technique was developed to study the decrease in bone mineral that occurs following algodystrophy and it's evolution with time. In longitudinal studies however, the measurement precision is critical if the method is to be sensitive enough to monitor clinically significant rates of change of bone density. The consequences of poor precision are that individuals must be studied over longer periods to establish a true change, or that larger numbers of subjects must be studied in order to demonstrate a given change (Kanis *et al.* 1983).

The short-term reproducibility of this technique is approximately 4% which is greater than the 1-3% described by Christiansen *et al.* (1975) at the forearm. This 4% reproducibility applies to measurement of BMD which was only slightly less than measurements based on BMC. The better reproducibility with BMD was unexpected however as this measurement relies on two variables, BMC and bone width, rather than BMC alone. The difference in reproducibility between the technique described and forearm scanning and that described to measure metacarpal density was probably due to positioning errors since the width of the metacarpal varies markedly at the site measured. The hook grip used in this technique when positioning the hand is less replicable and is more likely to allow slight rotation of the hand than the full grip used in measurements of the distal forearm. Changes in orientation are unlikely however to cause major problems with reproducibility (Christiansen *et al.* 1975). The main source of error was probably variation in the starting point of the scans. In distal radial scans, the starting point is found automatically by the computer soft-ware and is therefore not operator dependant. It was not possible to program the scanner to find a smaller interosseous gap and therefore the starting point relied on optically aligning the scanning arm on the distal palmar crease.

SPA is usually used to evaluate changes in mineralisation due to generalised osteoporosis which occurs slowly over a long time period rather than the rapid onset of

demineralisation apparent radiographically in algodystrophy. Although this technique needs to detect an 8% change in BMD to be significant (mean +2SD), it may still be sufficiently reproducible to detect the more marked changes seen in algodystrophy.

The radiographic scoring system described in Chapter 10 was based on changes seen in trabecular bone which change markedly in algodystrophy. Trabecular bone has a higher rate of turnover than cortical bone due principally to the greater surface area available for active resorption and formation. For this reason the results of increased resorption in algodystrophy are more likely to be apparent and seen at an earlier stage in trabecular bone rather than at a cortical site. In the forearm 85% of bone mass is trabecular in both bones at 1 cm from the ulna styloid tip; this proportion falls to 10% within the next 2 cm proximally (Sclenker and VonSeggen 1976). The distal and proximal scan sites at the forearm are mainly through trabecular and cortical bone respectively. Although these proportions will not be identical for metacarpals, in view of the starting point for the scans at the metaphyseal/diaphyseal junction, the distal scan is through the mainly trabecular metaphysis and the proximal scan through the mainly cortical diaphysis. Indeed, BMD was 24% less at the distal site. Consequently differential losses and recovery in BMD in the two different areas scanned are likely to reflect in part the differing response of trabecular and cortical bone.

CHAPTER 13: BIOCHEMISTRY

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Radiographically there is a generalised loss of bone which is indicative of a net increase in bone resorption. No comment can be made of the change, if any, in bone formation. These changes however occur locally and consequently may not markedly influence the overall rate of skeletal bone turnover. There have been reports however, claiming that systemic indices of bone resorption and formation change, particularly in the early stages of the disease (Eisinger *et al* 1974; Schiano *et al* 1976).

In this section the techniques used for the biochemical assessment are described and the laboratory normal ranges defined. The findings in algodystrophy are described in chapters 21 and 25.

i) Methods and Normal ranges.

Serum and urine samples were taken after an overnight fast. The serum was used to measure calcium, phosphate, alkaline phosphatase, creatinine, urea and electrolytes using a Technicon SMAC. Serum calcium was adjusted for variations in serum albumin by the addition or subtraction of 0.02 mmol/l for each g/l that albumin was above or below 42 mg/l. A portion of the serum was also frozen for later determination of parathyroid hormone (PTH), using chicken antiserum directed at the mid portion of the PTH molecule (Immuninnuclear Corporation), and osteocalcin, using a radioimmunoassay (Hauschka *et al* 1989). To minimise interassay variability in the PTH and osteocalcin assays, the stored serum samples were analysed over a three week period.

After voiding the bladder following an overnight fast, urine was collected over a 2 hour period before breakfast. Urinary calcium and hydroxyproline were expressed as ratios of urinary creatinine, which in the fasting state provided indices of net calcium release from bone and bone resorption (Paterson *et al* 1983). Urinary hydroxyproline

was measured using a modification of Stegemann's method (Stegemann and Stalder 1967). The laboratory reference ranges are shown below.

Measurement	Laboratory normal range
Serum calcium (mmol/l)	2.26 - 2.63
Alkaline phosphatase (IU/l)	35 - 105
Parathyroid hormone (pg/l)	30 - 130
Osteocalcin (ng/ml)	8 - 32
Urinary calcium mol/mol creatinine	< 0.30
Urinary hydroxyproline mmol/mol creatinine	< 30.0

RESULTS

CHAPTER 14: PREDISPOSING CHARACTERISATION OF ALGODYSTROPHY

Despite numerous studies, the aetiology of post-traumatic algodystrophy

remains unknown. Although Kleinert *et al.* (1973) in their large series of 506 cases did

not comment on the severity of the trauma preceding algodystrophy, Serre *et al.* (1973)

thought that 50% suffered only minimal trauma and that there was no correlation

between the severity of trauma and the subsequent severity of algodystrophy. A

number of authors ((Herrman *et al.* 1942; Weil and Gerard-Marchant 1954; Fontaine *et*

al. 1957; Beasley 1964; Ivins *et al.* 1969; Serre *et al.* 1973; Bernstein *et al.* 1978; Kim *et*

al. 1979; Goldner 1980; Fam and Stein 1981) have claimed that immobilisation rather

than the initial trauma may precipitate algodystrophy or aggravate the condition. The

aim of this study was to examine the predisposing features attributable to the patient or

the fracture management and their bearing on the development of algodystrophy.

Methods.

Two hundred and seventy-four patients with Colles' fractures were reviewed

prospectively over an 18 month period begining in December 1987 upon completion of

their period of immobilisation. All presented to the orthopaedic fracture clinics at the

Royal Hallamshire Hospital, Sheffield. As will be shown in Chapter 15 discrete

populations were identified based on the presence of abnormal pain or tenderness,

vascular instability, swelling or stiffness. Any patient with all these symptoms and

signs was assumed to be suffering from algodystrophy. The data collected (including

age, sex, side fractured, time from fracture to manipulation *etc.*) on the 274 Colles'

fracture patients has been explained in Chapter 8 and is detailed in Table 8.1.

The results were expressed as mean $\pm$ one standard error of the mean (SEM).

Differences between groups were calculated using Student's t test for unpaired data and

the Chi-squared test (with Yates correction for 2 x 2 contingency tables) for frequency of

observations.

Results.

There was a peak prevalence of Colles' fractures during the winter months

(October - March; Fig 14.1b), reaching a peak in December and January.

Algodystrophy however, appeared to be more prevalent during Spring and, to a lesser

extent, Autumn (Fig 14.1a).

a) Patient characteristics

Of the 274 patients studied, 77 (28.1%) had features of pain/tenderness,

vascular instability, stiffness and swelling. The mean age at presentation of the

population as a whole was 63.7 years (SD 14.2) with a female to male ratio of 4.5:1

(Table 14.1). The mean age of female patients sustaining a Colles' fracture was 65.8

years $\pm$ 0.9 compared with 54.2 years $\pm$ 2.3 in males (Fig 14.2a; p < 0.0001). From 40

years, the age prevalence rose steadily to it's peak at 65 years in female patients, no

such increase in incidence was seen in the male patients (Fig 14.2a). This post-

menopausal peak in Colles' fractures was confirmed by estimating the incidence based

on the population statistics for Sheffield Area Health Authority (HMSO 1987; Table

14.2). As there were two hospitals with emergency services serving this area, the

population was divided by two to give an approximate estimate of the number served by

each hospital. There was no significant difference between the mean age of the

algodystrophy and control patients (Table 14.1; Fig 14.2b). Similarly there was no age

difference in male (algodystrophy 54.3 years $\pm$ 3.4; control 54.2 years $\pm$ 2.9) and female

(algodystrophy 66.3 years $\pm$ 1.09; control 65.6 years $\pm$ 1.1) patients.

Fracture of the left side (58.8%) was significantly more common than the right

(41.2%) (X^2 = 16.12; p < 0.0001) with the overwhelming majority of patients being right

handed (95.3%). There was no significant differences in the side fractured or the hand

dominance between those patients who developed algodystrophy and the remainder (Table 14.1).

Table 14.1. Mean (± SEM) and ratios of sex distribution, handedness and side affected in 274 patients with a Colles' fracture. Those in the algodystrophy group had symptoms of abnormal pain/tenderness, vascular instability, swelling and stiffness.

	ALGODYSTROPHY	CONTROL	TOTAL (SD)
Age (years)	64.7 ± 1.3	63.5 ± 1.1	63.7 (14.2)
Sex(F:M)	62:11	162:39	224:50
Handed (R:L)	71:2	190:11	261:13
Side (R:L)	28:45	85:119	113:161
Time from fracture (hrs)	7.4 ± 0.8	6.8 ± 0.4	7.02 ± 0.4
Time in plaster (days)	38.9 +0.9	37.1 + 0.6	37.5 + 0.5

Table 14.2. The apparent incidence of Colles' fractures were calculated for male and female patients based on the 1977 population census for Sheffield Area Health Authority. Above the age of 45 years, there is approximately a 10 fold increase in the incidence of Colles' fracture.

Age	Incidence of Colles' fractures (per 1,000 population)	
	Male	Female
15 - 29 years	0.00005	0.00006
30 - 44 years	0.0002	0.0002
45 - 59 years	0.0003	0.001
60 - 74 years	0.0003	0.002
>75 years	0.0006	0.002
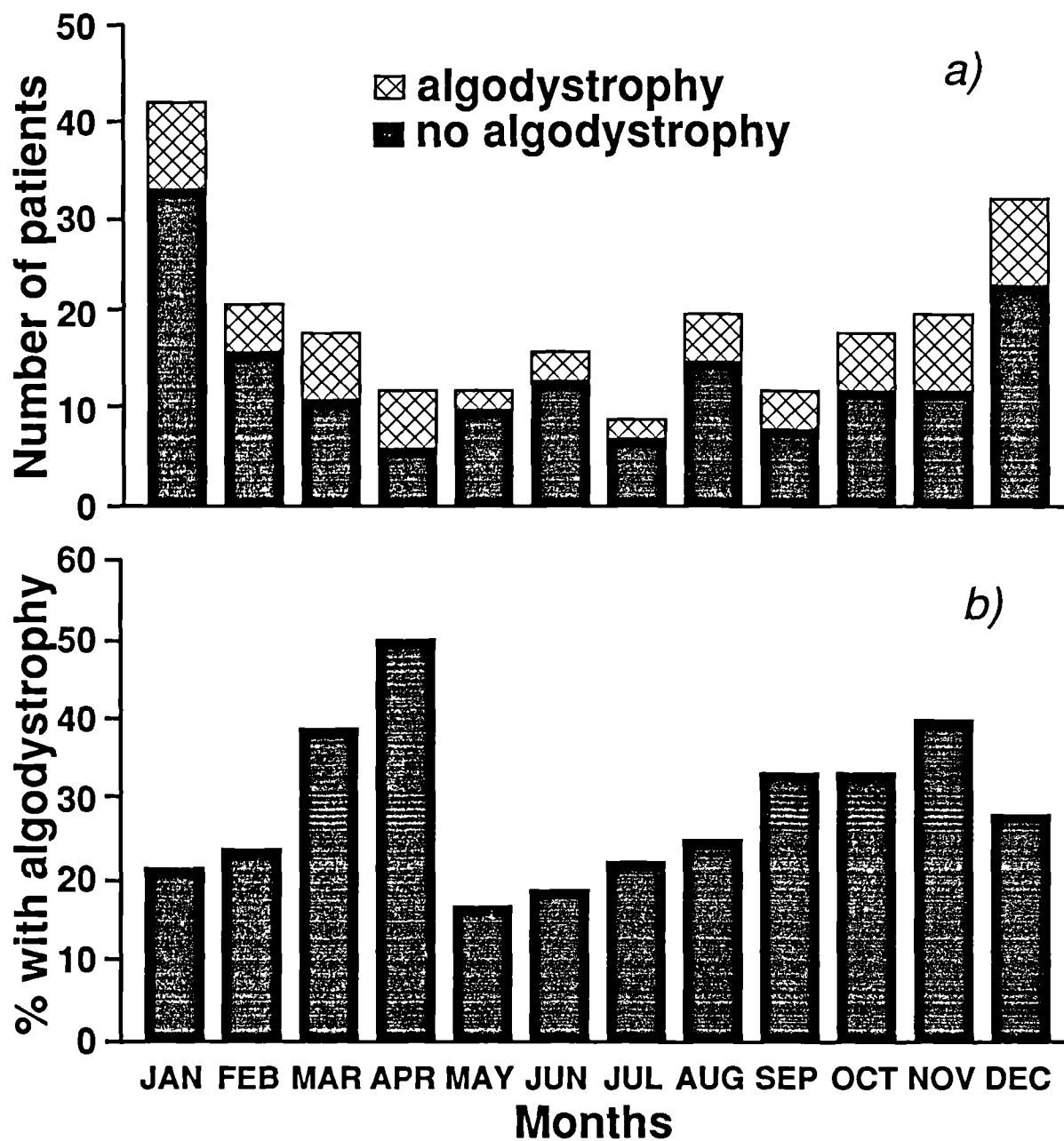
Fig 14.1 a and b. All the patients who sustained Colles' fractures over an 18 month period between December 1987 and May 1989 were reviewed in orthopaedic out-patients. The prevalence of fracture for the months during 1988 (a) was higher in winter, with a peak in December and January. The incidence of algodystrophy (b) did not follow this distribution, with peaks in April and, to a lesser extent, November.
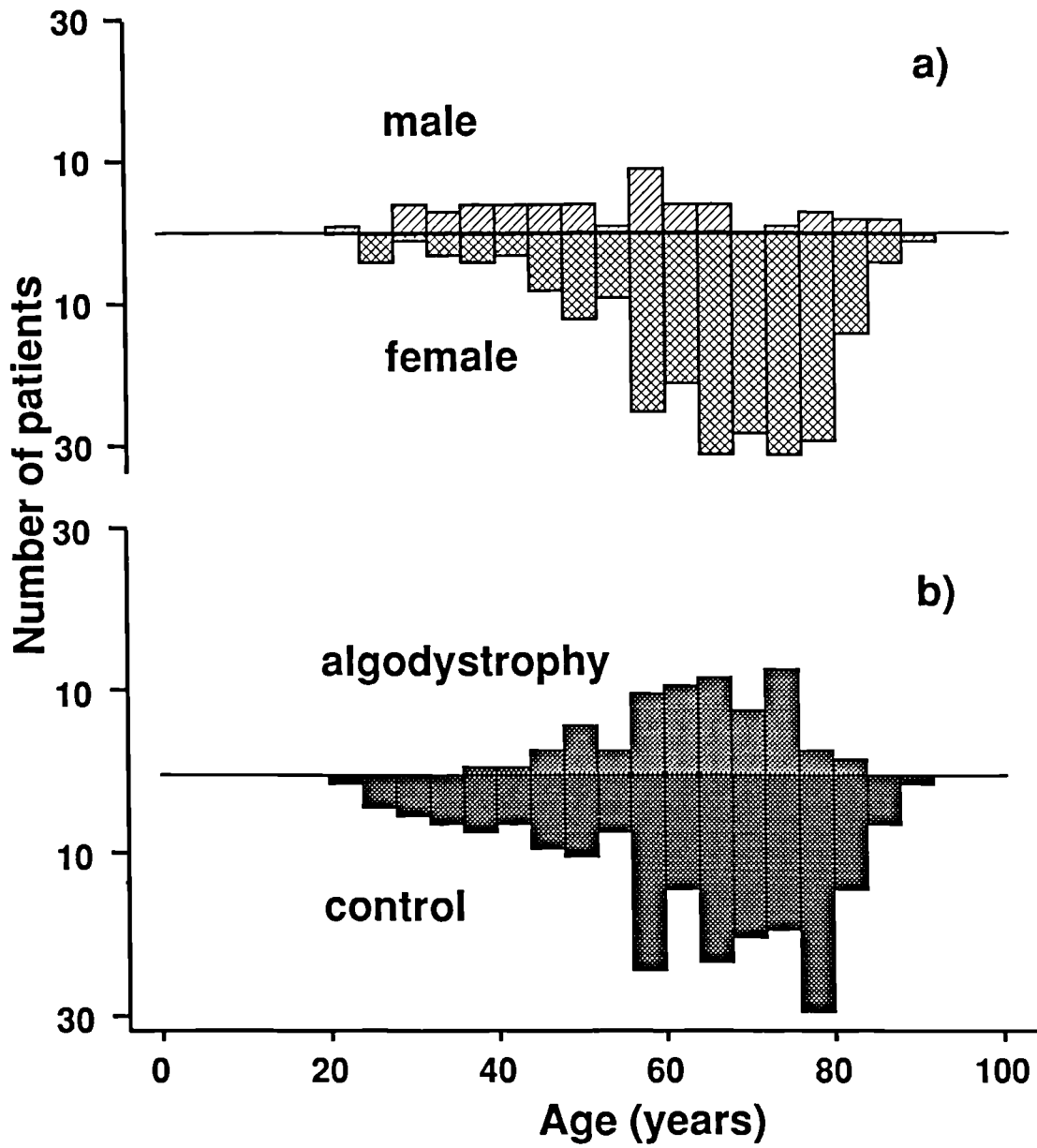
Fig 14.2 a and b. The age distribution of patients with Colles fracture divided
on the basis of a) sex and b) the presence or absence of algodystrophy.
There was a post-menopausal peak in females whereas the incidence in men
remained constant. There was no significant difference in age or sex between
the patients with or without algodystrophy.

b) Fracture type and management.

Frykman type. The distribution of Frykman types showed peaks at the upper and lower ends of the scale (Fig 14.3). Thus fractures usually occurred without joint involvement or, if there was joint involvement, both the radio-carpal and distal radio-ulna joints were affected (Table 8.2). In general the more severe fractures occurred in the algodystrophy group ((Fig 14.4; compare Frykman I with Frykman VIII). Involvement of the ulna styloid (Frykman II, IV, VI and VIII), was also associated with a higher incidence of algodystrophy (X^2 = 29.03; p < 0.0001). The only fracture type which was associated with a higher incidence of algodystrophy but did not involve fracture of the ulna styloid was the Frykman VII. This fracture however is inherently severe with fracture lines extending into the radio-carpal and distal radio-ulna joints.
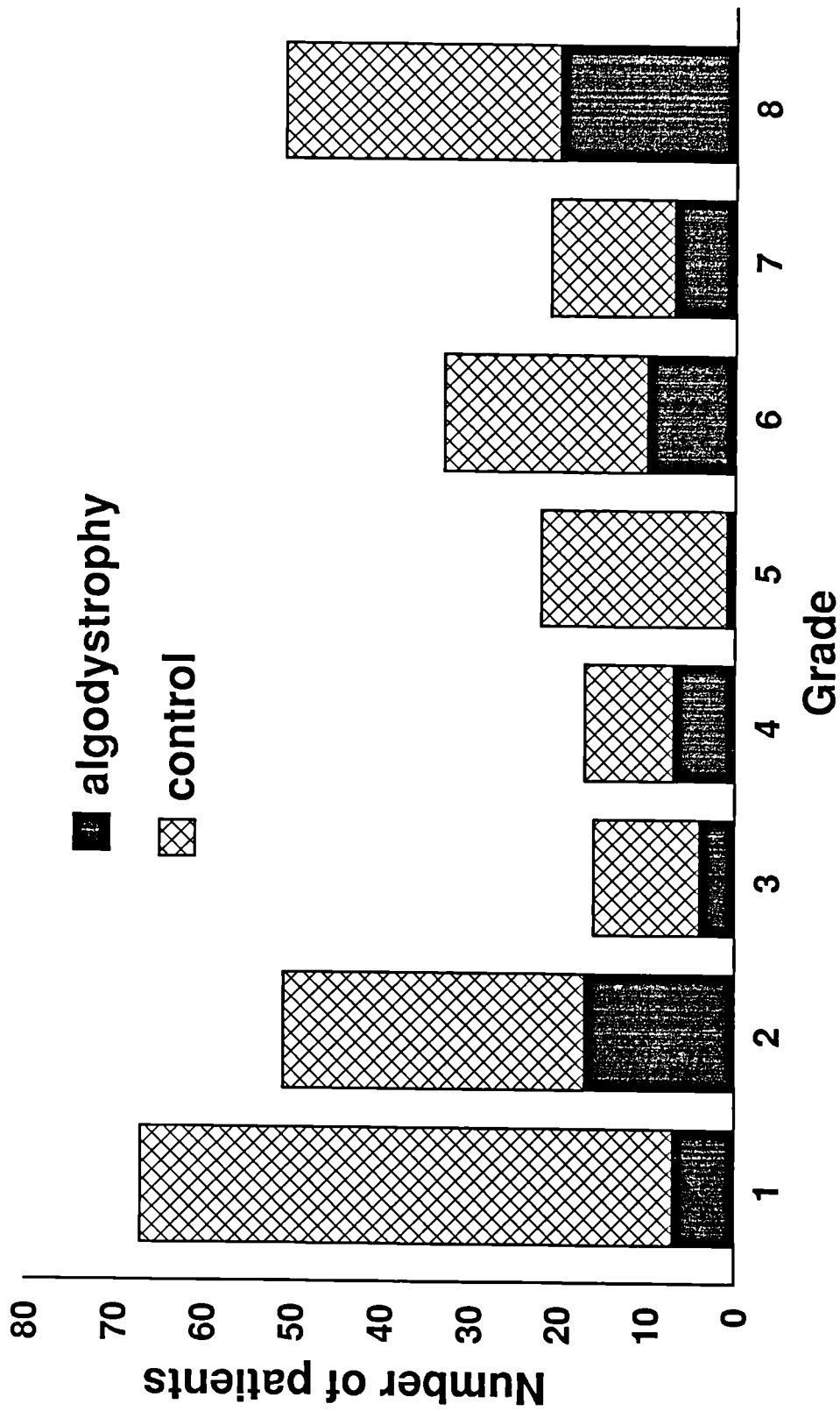
Fig 14.3. The Colles' fractures were graded with Frykman's classification which is based on the fracture involving the radio-carpal and/or radio-ulna joints with or without fracture of the ulna styloid (Table 8.2). The majority of fractures (I and II) did not involve either the radio-carpal or radio-ulna joint. There was however a further peak incidence with the more severe complex fracture affecting both joints and ulna styloid (VIII).
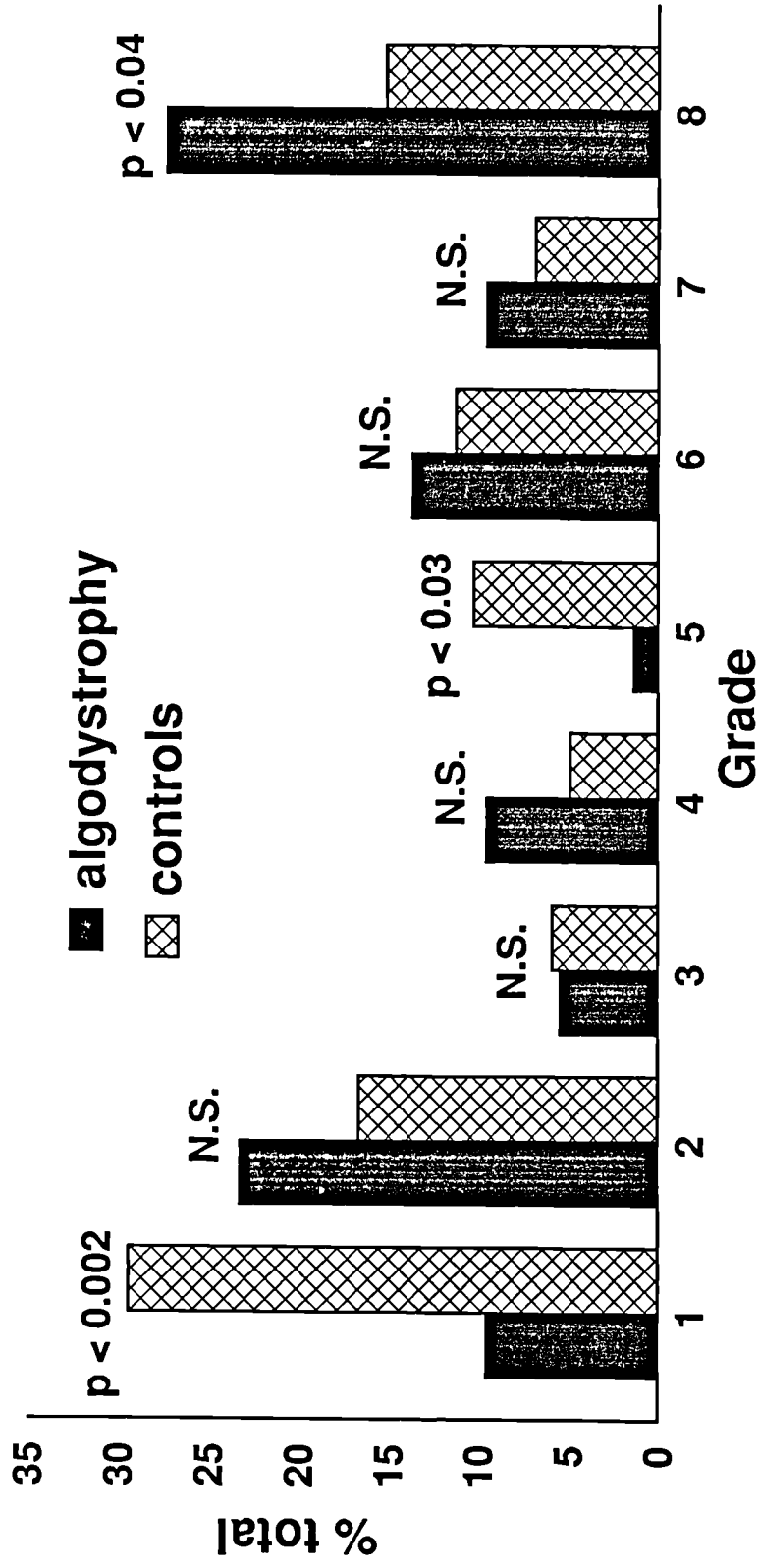
Fig 14.4. The percentage distribution of fracture pattern using Frykman's classification was calculated based on the presence or absence of algodystrophy. There were significant differences at each end of the spectrum with a higher incidence of algodystrophy in the more severe fracture. In addition, fracture of the ulna styloid (Frykman 2, 4, 6 and 8) predisposed to a higher incidence of algodystrophy (p < 0.0001).

Fracture management. One hundred and sixty-six fractures (61.0.%) required

manipulation. This included 62/73 (85%) patients with algodystrophy and 104/201

(52%) without algodystrophy, which was significantly different (X^2 = 4.70; p = 0.03).

The majority (86.2%) of the fractures, however required only one manipulation (Table

14.2). In those patients who needed manipulation, there was no significant difference

in the number of manipulations required between the two groups

Table 14.2. Manipulations of Colles' fracture in patients divided by the presence or

absence of algodystrophy. There was a significantly greater proportion requiring

manipulation in the algodystrophy group (X^2 = 4.70; p < 0.03).

	Number of Manipulations				
	0	1	2	3	One or more
Algodystrophy	11	54	8	-	62
Control	97	89	13	2	104

Although the time interval from fracture to manipulation was slightly greater in

the algodystrophy group (algodystrophy 7.4 ± 0.84 hours; control 6.8 ± 0.40 hours;

Table 14.1), the difference was not significant with the majority of patients treated

within 10 hours from the time of injury (Fig 14.5). Most patients were immobilised in a

radial slab (81.8%), with the remainder in half-arm plasters or full-arm plasters (Table

14.3). There was no significant difference in the method of immobilisation between the

two groups. Similarly there was no difference in the period of immobilisation

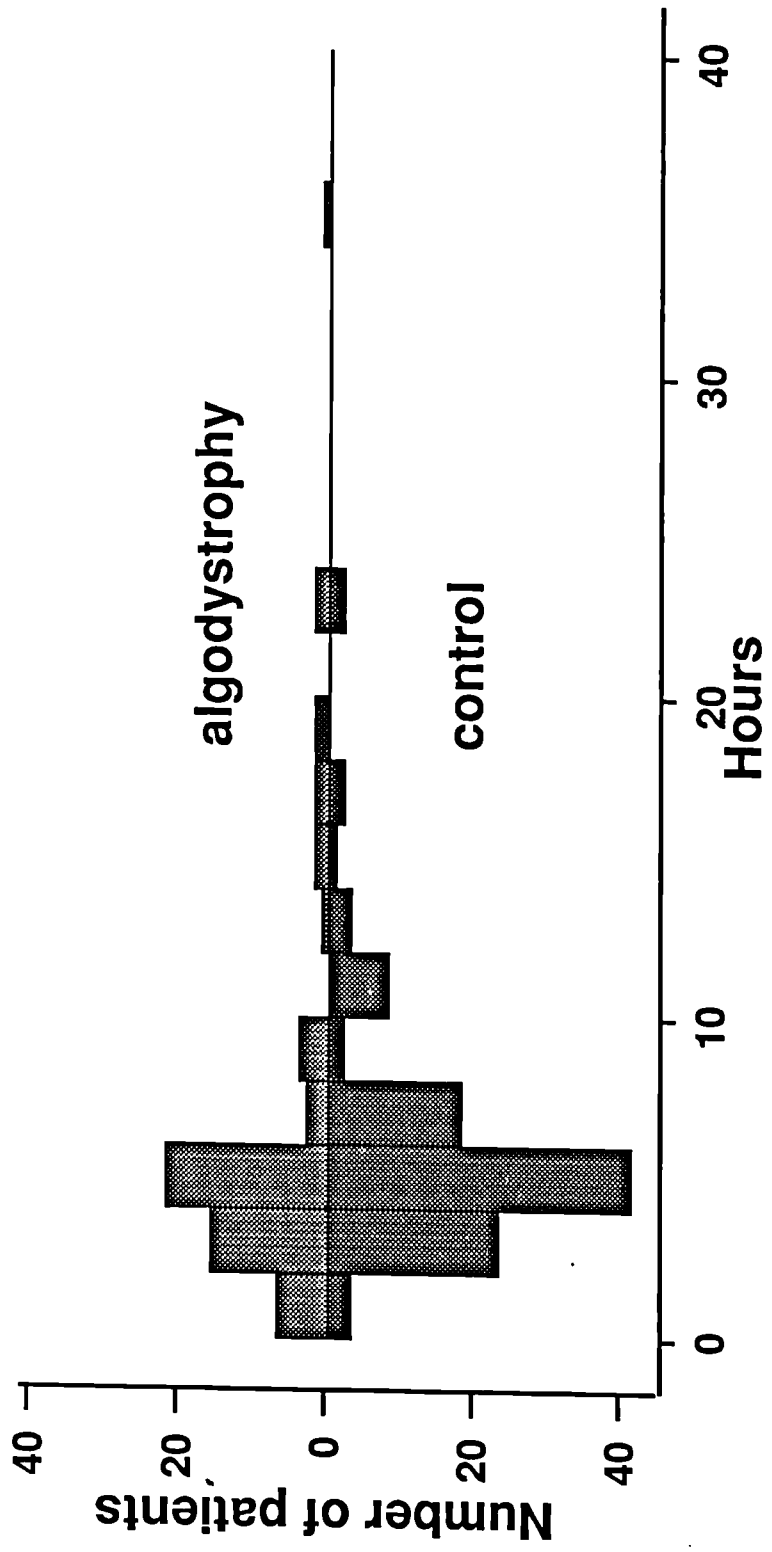(algodystrophy 38.9 ± 0.9; control 37.1 ± 0.6; Fig 14.6; Table 14.1).

Fig 14.5. The time between fracture and manipulation was recorded in 166 patients who required manipulation. There was no significant difference between patients with or without the subsequent development of algodystrophy.
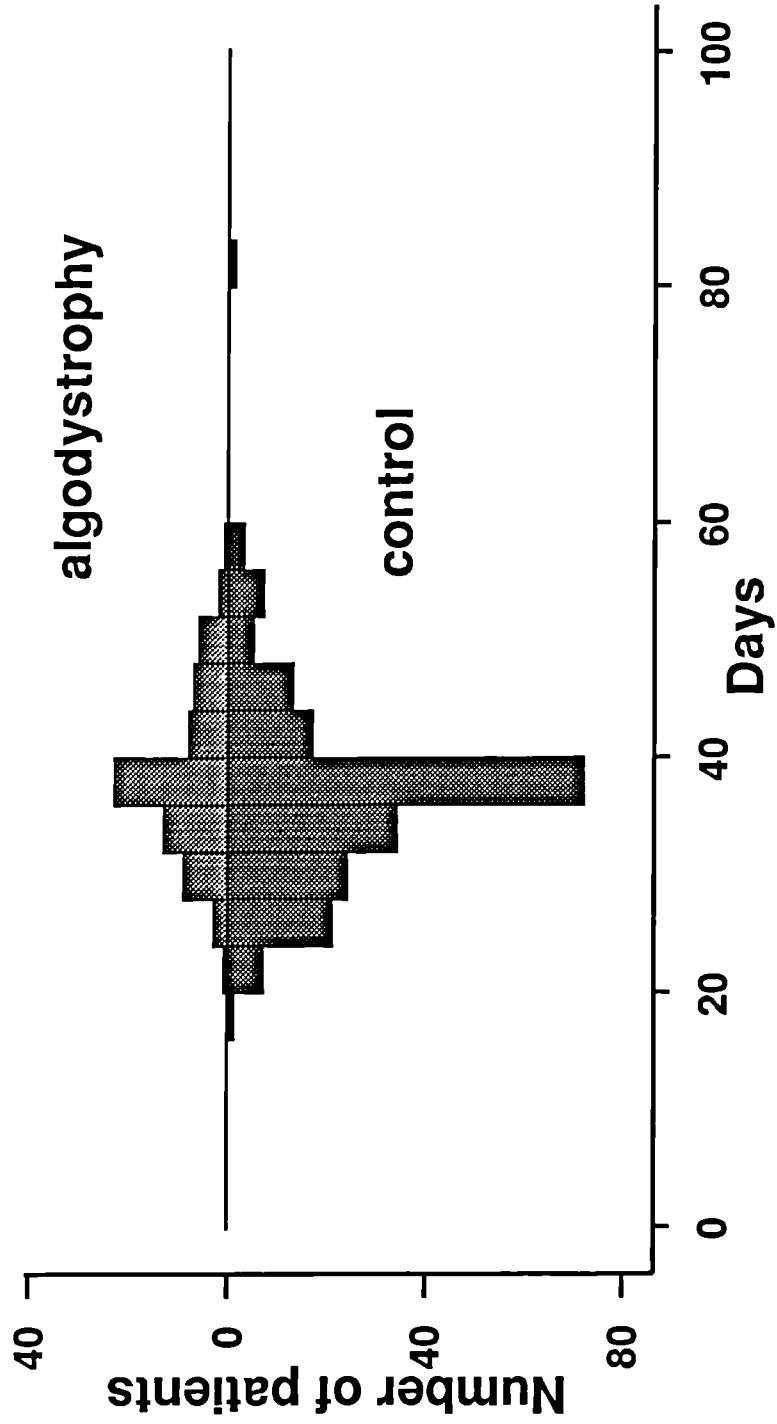
Fig 14.6. The duration of immobilisation was recorded in the 274 Colles' fractures. There was no significant difference between patients with or without the subsequent development of algodystrophy.

Table 14.3. The majority of patients in both groups were immobilised in a plaster back slab.

	Radial slab	Half-arm cast	Full-arm cast	Total
Algodystrophy	61	11	1	73
Control	163	37	4	204

Discussion.

The distribution of Colles' fracture recorded over a one year period (1988) demonstrated a higher incidence in winter. Although not recorded, it was my impression that most of the injuries took place outside, contrary to fractures of the femoral neck which usually occur after falls in the home. This may explain the higher incidence in winter with falls due to icy or wet conditions. The higher prevalence of algodystrophy during Spring, and to a lesser extent, Autumn was surprising and contrary to Aubert's (1980) findings of an increased prevalence during winter.

The higher incidence of Colles' fracture following menopause in females is well known and was reflected in these data (Fig 14.2a). There was no similar increase in incidence in males with advancing age. Indeed the incidence of Colles' fractures remained relatively constant between 30 years upto retirement age at 65 years (Fig 14.2a). Therefore in males, rather than the ageing process, which results in more porotic bones and poorer coordination, leading to Colles' fracture, it appears that trauma sustained during the working years may be as important in the aetiology of this fracture in men. From an epidemiological point of view, these fractures in men therefore appear discrete and it has been suggested (McMurtry, personal communication) that their treatment should also differ from that of the post-menopausal Colles' fracture. He recommends more aggressive treatment with open reduction and internal fixation of the fracture.

The left side was fractured more often despite the majority of patients being right handed. It is unlikely that this is due to a conscious effort to protect the dominant hand. Therefore, if one assumes that falls should at least occur equally on either side, there must be another factor which results in the non-dominant hand fracturing more frequently. In an age and sex matched population of patients without fracture or algodystrophy there is no difference in bone mineral between the dominant and non-dominant hand (Chapter 12). Therefore there is no inherent weakness in the non-dominant hand to account for a higher fracture rate.

The Frykman classification of Colles' fractures determines the presence of joint involvement, and consequently increasing force expended at the time of injury, with or without fracture of the ulna styloid. Although the classification does not directly assess the degree of fracture comminution, with a higher Frykman grade, it is more likely that comminution would ensue as the degree of energy being expended increased. The data on the Frykman classification indicate that the more severe the fracture, the higher is the probability of developing algodystrophy. The incidence of algodystrophy was low a Frykman I fracture and became higher with a Frykman VIII fracture. Involvement of the ulna styloid is also a measure of the force expended at the time of injury. Therefore in the Frykman classification, for a given joint involvement, more force is involved if the ulna styloid is fractured. Although the association between fracture of the ulna styloid and algodystrophy reached significance only in the Frykman VIII fractures, in all grades where the styloid was involved (Frykman II, IV, VI and VIII), there were more patients with algodystrophy (Fig 14.4). This difference became highly significant when they were compared as a group without fracture of the ulna styloid ($p < 0.0001$).

The main disadvantage of the classification is that it provides no information about the degree of angulation or displacement. Although there was no direct evidence of displacement or angulation, manipulation of the fracture, and consequently the degree of displacement, was associated with a higher incidence of algodystrophy ($p =$

0.03). It is unlikely that the act of manipulating the fracture itself resulted in the higher incidence of algodystrophy as multiple manipulations did not increase this further (Table 14.2). Other features of the treatment such as time to manipulation, type of immobilisation and period of immobilisation were not related to the development of algodystrophy.

Algodystrophy following minimal trauma is well recognised (Bouvier *et al.* 1973; Kleinert *et al.* 1973; Patman *et al.* 1973 and Doury *et al.* 1981). Indeed seven of our patients developed algodystrophy following a Frykman I fracture. Nevertheless, these data suggest that the increased force involved at the time of fracture resulting in distal radial comminution, fracture of the ulna styloid and displacement were associated with the increased likelihood of developing algodystrophy.

DIAGNOSTIC FEATURES

CHAPTER 15: CLINICAL FEATURES AND THEIR ASSOCIATION

Atkins *et al.* (1990) demonstrated the presence of a discrete population of

patients with abnormal tenderness, stiffness and vascular instability based on a study

of 60 patients with Colles' fracture seen two to six weeks after removal of plaster. They

found a significant association between these features (p < 0.0001). The aim of this

study was to investigate the nature and distribution of the four classical clinical

features of algodystrophy, namely pain and tenderness, vascular instability, swelling

and stiffness. In addition, it was intended to confirm Atkins *et al.* (1990) previous work

that the presence or absence of these features occurs in discrete populations.

Methods.

All 274 patients were reviewed clinically following Colles' fracture (Appendix I).

The clinical techniques used to assess the four features of algodystrophy have been

described in detail (Chapter 9). They were the subjective presence of pain, vascular

instability, swelling and stiffness. In addition, dolorimetry was used as an assessment

of tenderness.

The same method of statistical analysis was used in this and subsequent

chapters. The values were expressed as mean $\pm$ one standard error of the mean (SEM)

and normality of distribution assessed using Probit analysis. The significance of the

difference between means was calculated using Student's t test or one way analysis of

variance (ANOVA) for unpaired data. Wilcoxin's paired or unpaired test was used for

non-parametric data and Chi-squared (with Yates' correction for 2 by 2 contingency

tables) for frequencies. Correlations between data were identified using simple

regression analysis for parametric data and Spearman's rank correlation for non-

parametric data.

Results.

a) Features.

Pain and tenderness. The mean dolorimetry score for all the patients was 0.91 (SD

0.14) but with a large range from 0.34 to 1.08. Probit analysis demonstrated that the

population was not normally distributed (Fig 15.1a). If however, the total population

was split into two groups based on the lower limit of the 95% confidence interval (0.92)

for dolorimetry scores in the control population, each population became normally

distributed (Fig. 15.1b and c) which suggests the presence of two populations based on

the presence or absence of abnormal tenderness in the fingers.

Eighty-two patients (30%) complained of pain in their hands, 65 of whom also

had abnormal tenderness. There were 54 patients who complained of shoulder pain

which was not related to trauma at the time of injury, 45 of whom also had abnormal

tenderness. The relationship of hand and shoulder pain to the algodystrophy group will

be dealt with later.
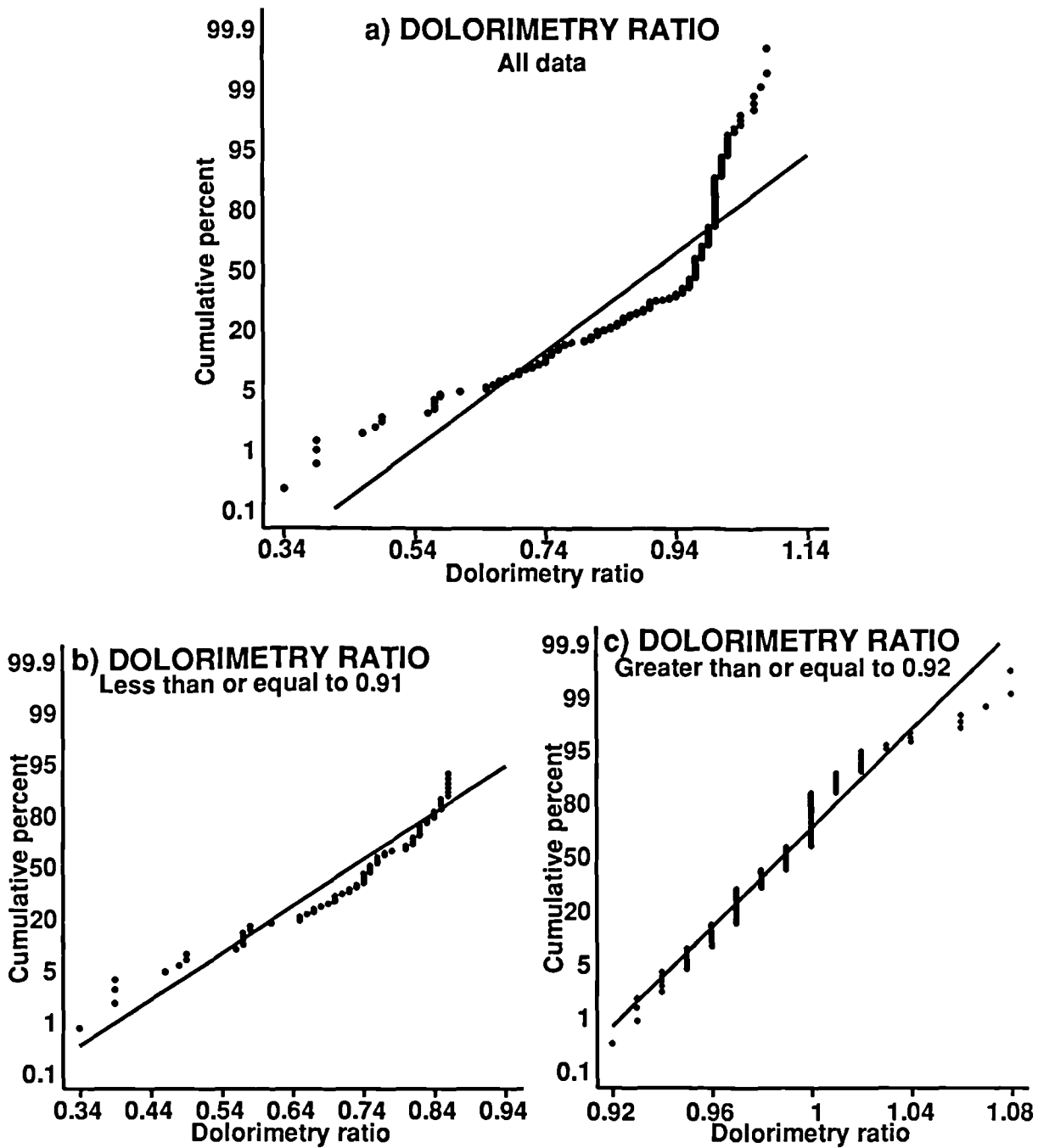
Fig 15.1. Dolorimetry was used to assess finger tenderness in 274 patients with Colles' fracture and their distribution plotted using Probit analysis (a). This demonstrated that the population was abnormally distributed. When Probit analysis was performed in patients with abnormal (b) or normal (c) dolorimetry ratios, the distribution for each group became normal.

Vascular instability. One hundred and twenty out of the 274 patients studied (43.8%) exhibited signs of vascular instability in the fractured hand. Of these 120 patients, 101 (84%) had alteration in temperature and 88 (73%) alteration in colour of the hand. Sixty-nine (58%) patients complained of both. Ninety of the patients with an alteration in temperature complained of warmth (89%), the remainder claiming their affected hand felt cool. Of the 88 patient who complained of a change in colour of their hand, 66 (75%) thought it was red and 22 (25%) blue. Table 15.1. depicts the inter-relationship between the patients with temperature and colour changes. There was a statistically significant difference in the distribution of temperature and colour change between the groups (X^2 = 16.25; p < 0.003) suggesting that the hand tended to feel warm regardless of the colour.

Thirty-three (27.5%) of the patients who had an alteration in temperature or colour thought that, although the there was always a difference, the intensity altered with changes in the environmental temperature. In cold weather the hand would be abnormally cold and blue and in hot weather warm and red. In addition 5 of these patients noticed a difference dependant on mood. Two notable examples were patients who, having returned to work later in the course of the disease, noticed alteration in colour, temperature and pain in stressful situations.

Table 15.1. Vascular instability, based on the presence of abnormal colour or temperature, was present in 120 of the 274 Colles' fracture patients studied. The number of patients with alteration in colour have been cross-tabulated with alteration in temperature. The majority of patients have hot hands regardless of the colour change.

TEMPERATURE	COLOUR			
	Blue	Red	No change	Total
Cold	5	4	2	11
Hot	11	49	30	90
No change	6	13	0	19
Total	22	66	32	120

There were some differences between the history of temperature and colour changes and clinical examination. In 73 of the 101 patients who reported a difference in temperature, an increase in skin temperature was clinically apparent (Table 15.2). A further six patients had a warm hand unnoticed by the patient. Twenty-eight patients who reported a change in temperature had no change on clinical examination. Ninety-one patients had clinical evidence of a change in colour of the affected hand but only 80 gave a history of colour change, the remaining 11 gave no such history (Table 15.2). There were also 8 patients who reported a colour change which was not evident on examination.

Table 15.2. Of the 274 Colles' fracture patients studied, 101 reported or had clinical

evidence of a change in temperature of the hand with 99 reporting a change in colour

providing a total of 120 patients with evidence of vascular instability. A proportion of

patients reported vascular instability without any clinical evidence which may support

evidence for a sub-clinical form of algodystrophy.

History	Clinical evidence	No clinical evidence
Change in temperature	73	28
No change in temperature	6	167
Change in colour	80	8
No change in colour	11	175

The reports of temperature and colour change with no clinical features may

reflect the variable nature of the instability in that it was not evident at the time of

examination. More importantly however, it may provide evidence for a trend towards a

sub-clinical form of algodystrophy. Using dolorimetry as a measure of disease activity,

patients with and without clinical evidence of temperature and colour changes were

compared. There were significantly lower dolorimetry scores in the patients with

clinical and historical evidence of a change in colour or temperature but, even in the

absence of clinical evidence, the dolorimetry scores were still below the lower limit of

normal (0.92; Table 15.3) This lends support to the presence of a sub-clinical form of

algodystrophy.

Table 15.3. Dolorimetry scores (mean ± SEM) in patients with and without clinical evidence of temperature or colour change but who claim such changes on questioning.

	Clinical evidence	No clinical evidence	
Temperature change	0.76 ± 0.02	0.90 ± 0.02	p < 0.0001
Colour change	0.77 + 0.02	0.91 + 0.05	p ≤ 0.03

Forty-three patients complained of hyperhidrosis, all of whom exhibited other features of vascular instability. Although the majority complained of increased temperature and warmth (90%), 10% had cool, blue, clammy hands. As with the changes in temperature and colour, sweating also seemed to related to external factors. Thirty of the 43 patients with hyperhidrosis exhibited an increase in sweating as compared to the unaffected hand when undergoing dolorimetry. This was never seen in patients who had not complained of hyperhidrosis.

Finger stiffness. One hundred (36.5.%) of the patients complained of stiffness in the fingers with or without clinical evidence of loss of movement. In none of the cases was this attributable to concomitant trauma to the fingers at the time of injury.

Swelling. One hundred and twenty four patients (45.3%) complained of swelling in their fingers and hand regardless of clinical evidence of swelling. Of the 124 patients with a history of swelling, 106 also had clinical evidence of oedema in the hand. Only 12 had evidence of oedema but denied swelling. This leaves 18 people who claim to have swelling which was not clinically evident. This may indicate a sub-clinical form of algodystrophy which is supported by the difference in dolorimetry scores between the two groups:

Clinical evidence of swelling 0.80 ± 0.16

No clinical evidence of swelling 0.94 ± 0.08

                               $p < 0.002$

b) Association of features.

In total there were 77 (28.1%) patients with a dolorimetry score lower than 0.92 (control population 95% confidence interval; 0.92-1.08) and evidence of vascular instability, finger stiffness and hand swelling, 125 (45.6%) patients without any features and a borderline group of 71 (26.3%) with a variety of features (Table 15.4; Fig 15.2).

If the probability of each of the features being displayed was independent of the occurrence of any of the other features, and occurred randomly with a probability level of 0.5, then the distribution of the number of features, between 0 and 4, displayed by the patients would follow a binomial distribution. On this assumption, the expected frequencies were calculated and compared in relation to the observed frequencies:

Table 15.4. The observed incidence of patients with all, some or none of the features of

pain/tenderness, vascular instability, swelling and stiffness were compared with the

expected binomial distribution.

Feature	Observed	Expected
0	125	17.12
1	36	68.50
2	14	102.75
3	22	68.50
4	77	17.12
Total	274	273.99

By looking at the frequencies in Table 15.4 it can be seen that the frequencies

observed do not follow the distribution expected. This was confirmed by testing the

goodness-of-fit using Chi-squared techniques (X^2 = 1012.88; p < 0.0001). There was an

excess number of patients observed displaying either none or all four of the features,

and much smaller numbers of patients displaying one, two or three of the features.
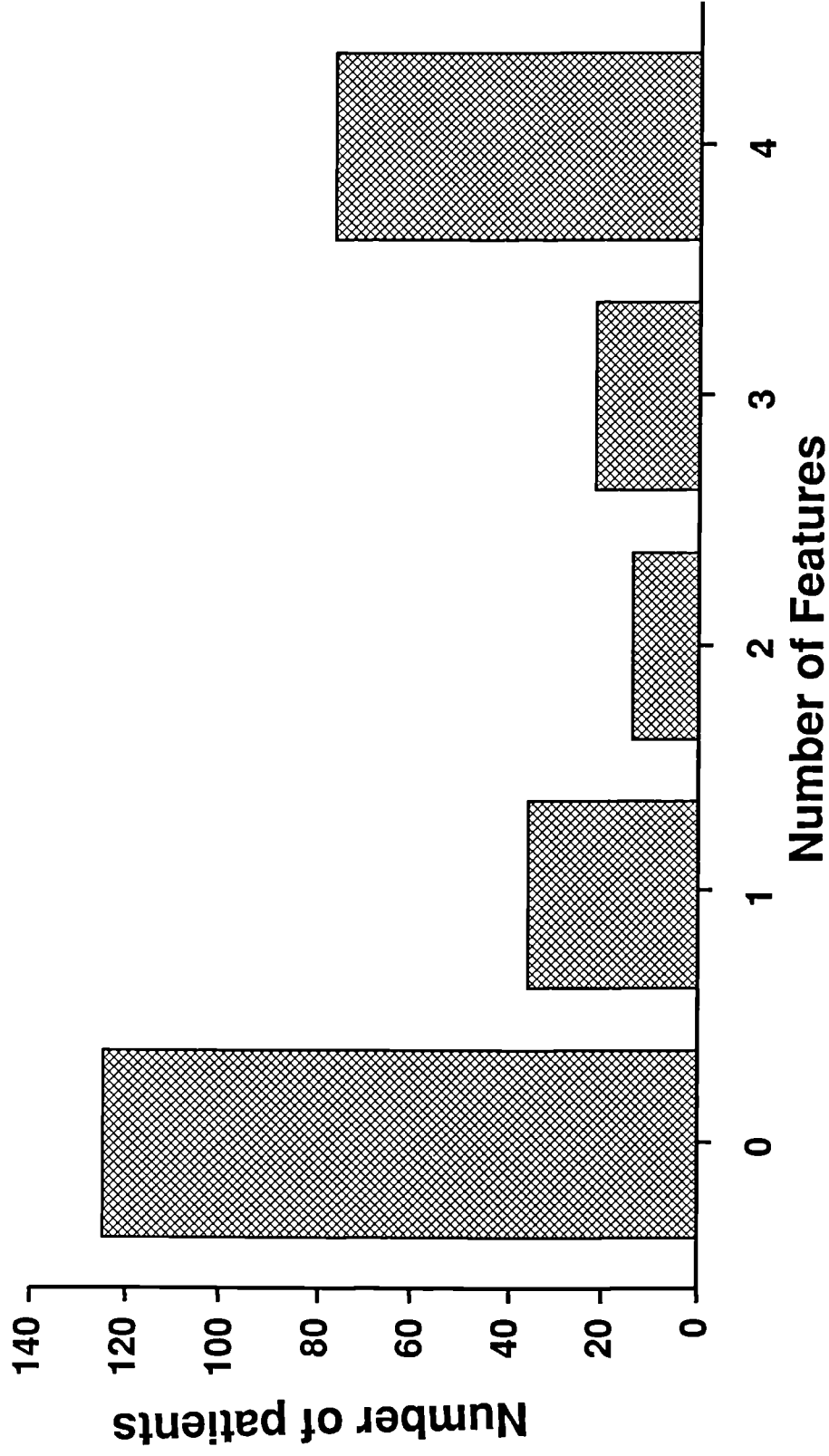
Fig 15.2. *The 274 Colles' fracture patients were classified on the presence of all, some or none of the features of tenderness, vascular instability, swelling or stiffness. There was a higher incidence of patients with all or none of the features which is significantly different from the expected binomial distribution (p < 0.0001).*

<u>Discussion.</u>

Analysis of the distribution of the features demonstrated that if a patient displayed one of the features there was a high probability that all four would be displayed, and similarly, if a patient did not display one of the features it is unlikely that others would be seen. Consequently there was a discrete population of patients who exhibited all the classical signs and symptoms of algodystrophy, pain and tenderness, vascular instability, swelling and stiffness, amounting to 28% of patients following a Colles' fracture in this study. The presence of two distinct populations was further confirmed by the normal distribution of dolorimetry ratios in those patients with ratios above or below 0.92, the lower limit of normal. Therefore there were two populations, one with and one without abnormally tender fingers.

Patients predominantly presented with a warm, red hand. Indeed, the hand felt warm even in the presence of blue skin discolouration in the majority of patients. This is keeping with the classically described features of stage I algodystrophy (Chapter 4). Thirty-three percent of patients who had evidence of vascular instability claimed that the type or intensity of the changes was affected by changes in environmental temperature or mood. In addition 70% of those with hyperhidrosis had a further increase in sweating in the affected hand when undergoing dolorimetry. These environmentally dependant changes in vascular instability and hyperhidrosis demonstrate the influence of cerebral function on the spinal levels involved in the algodystrophic process and consequently on the clinical presentation of the condition.

There was a discrepancy in the number of patients with a history of vascular instability or swelling and the clinical signs they displayed. As mentioned in the methodology, the wording of the questions concerning the presence of features such as vascular instability and swelling were structured to avoid suggesting changes to the patient. Therefore, the reports of temperature and colour change and the presence of hand swelling with no clinical features may reflect the variable nature of the condition

In that it was not evident at the time of examination. More importantly however it may provide evidence for a trend towards a sub-clinical form of algodystrophy. This was suggested by the significant difference in the dolorimetry scores between those with and without clinical evidence of vascular instability or hand swelling. The question of sub-clinical algodystrophy will be dealt with in more detail in a later chapter. This includes an analysis of the 72 patients who had some but not all of the features of algodystrophy and may represent a sub-clinical group.

Despite numerous papers on Colles' fracture in the English literature, the incidence of algodystrophy is generally regarded to be low (upto 2%; Bacorn and Kurtzke 1953; Plewes 1956; Lidström 1959; Frykman 1967; Pool 1973; Stewart *et al.* 1984). In contrast, in a study designed specifically to investigate algodystrophy, Aubert (1980) recorded an incidence of 29%. This was recently confirmed by Atkins *et al.* (1990) using similar diagnostic criteria to those used in this study. The high incidence is probably accounted for by the detection of a greater number of milder cases which may nevertheless cause morbidity.

In conclusion there is statistically significant evidence for the presence of two distinct patient populations following Colles' fracture, one of which displays all the clinical features of algodystrophy and amounts to 28% of patients studied. It is therefore valid to use this population for further studies into the natural history of the condition.

CHAPTER 16: QUANTITATIVE CLINICAL MEASUREMENTS.

      Having confirmed the presence of two discrete population based on the presence

or absence of abnormal pain and tenderness, vascular instability, swelling and

stiffness, it was appropriate to extend the analysis to examine the differences in the

quantitative clinical measurements between the two groups and to what extent these

measurements might contribute to a diagnosis of algodystrophy.

Methods.

      The quantitative measurements used to assess the 274 Colles' fracture patients

have been described in Chapter 9. They were measurements of tenderness

(dolorimetry), hand volume and grip strength. In addition the subjective presence or

absence of pain in the hand and shoulder was examined further in relation to the

presence of the four features of algodystrophy; abnormal tenderness, vascular

instability, swelling and stiffness. In the dolorimetry assessment the presence of the

latter three were used as criteria for the diagnosis of algodystrophy.

      The statistical analysis used was the same as described in the previous chapter.

Results.

Dolorimetry. Using Probit analysis, the distribution of dolorimetry scores was studied

in patients with or without evidence of vascular instability, stiffness and swelling. In

the population without any of these features, the dolorimetry score was 0.99 ± 0.002

which was not significantly different from the control population 1.00 ± 0.008 but was

normally distributed (Fig 16.1b). Similarly the dolorimetry scores for patients with all

the features (mean 0.77 ± 0.02) were normally distributed (Fig 16.1a). In addition,

there was a highly significant difference between these two populations (Fig 16.2; p <

0.0001). It is interesting to note that the distribution of dolorimetry scores in the group

of patients who displayed some of the features was not normally distributed (Fig 16.1c),

and indeed the pattern of distribution is similar to that seen in the population as a

whole (Fig 15.1a). In addition, the mean dolorimetry score for the borderline group

(0.94 ± 0.01) lies in between, and is significantly different from the group with no

features $(p < 0.0001)$ and those with all three features $(p < 0.0001)$ (Fig 16.2).
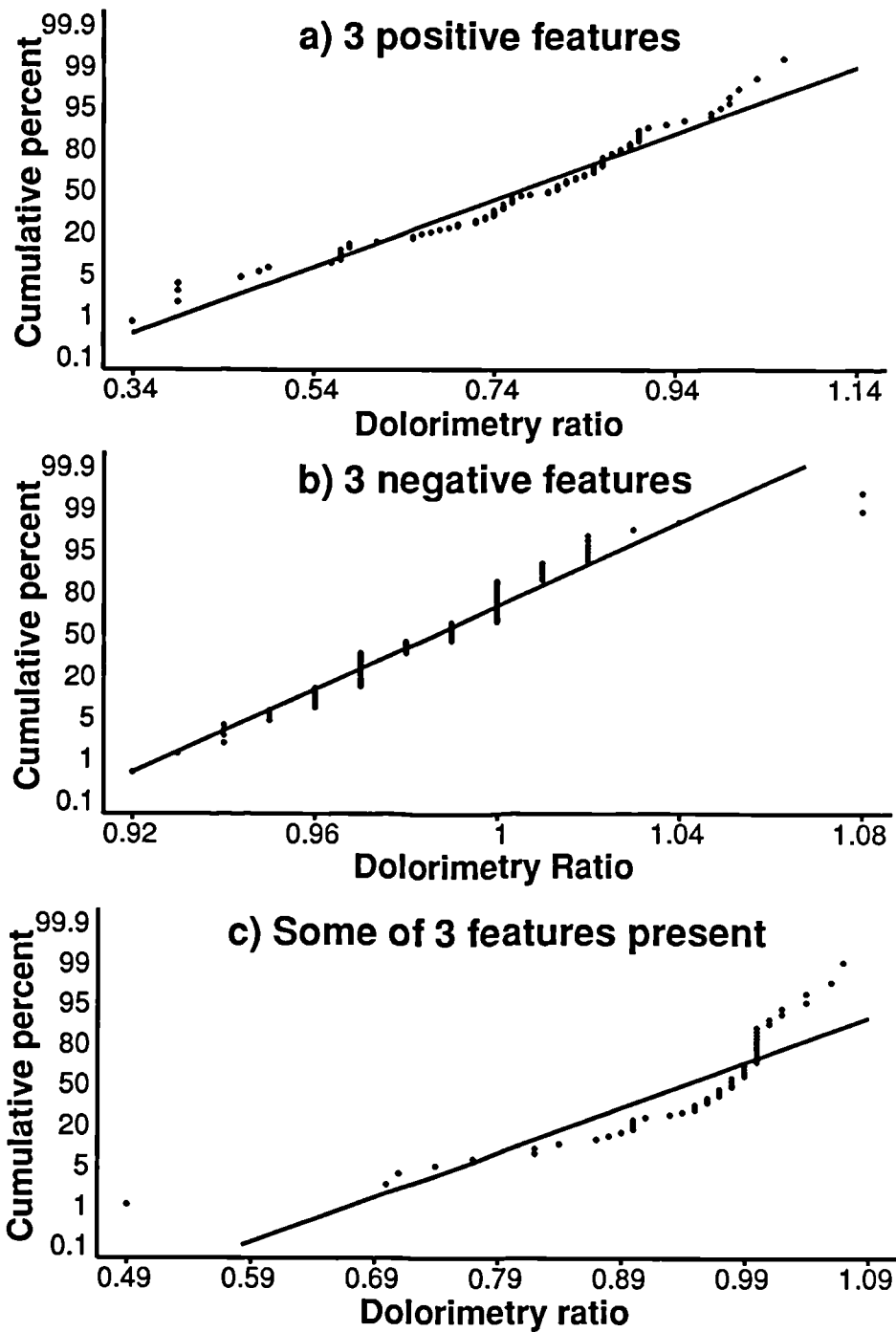
Fig 16.1. Dolorimetry was used to assess finger tenderness in 274 patients with Colles' fracture and there distribution plotted using Probit analysis. The distribution was normal in those patients with (a) and without (b) the presence of vascular instability, swelling and stiffness. In those patients who displayed one or two of the features (c), the distribution was abnormal. This implies the existence of two distinct populations based on the presence or absence of these three features.
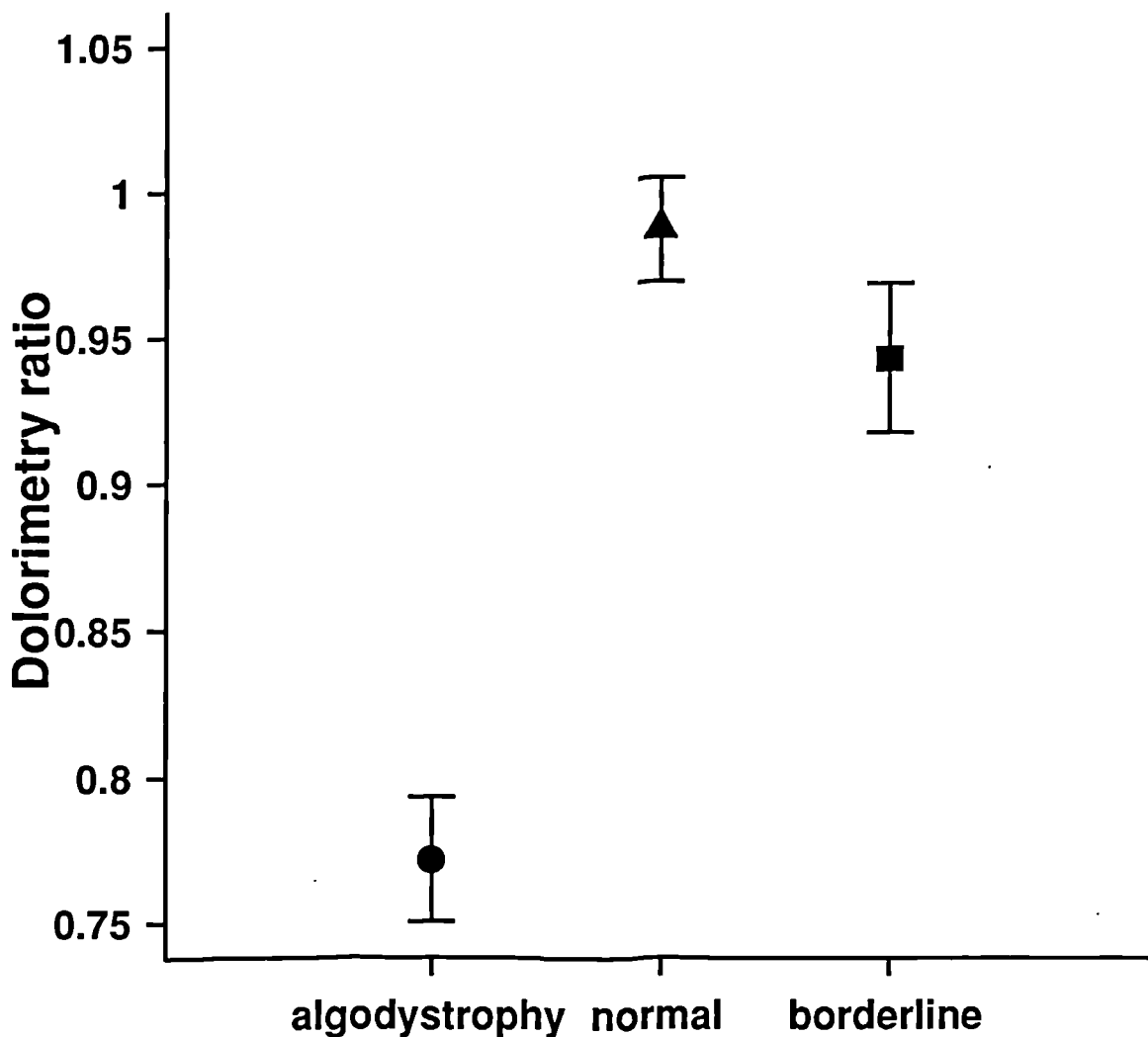
Fig 16.2. The dolorimetry ratios (+/- SEM) were calculated in three groups of patients. Those with all the features of vascular instability, swelling and stiffness were considered to be suffering from algodystrophy. The normal group had none of the features and the borderline either one or two. The mean ratio in the algodystrophy group was significantly different from the normal group (p < 0.0001). In addition, the mean ratio for the borderline group lay between the algodystrophy and normal ggroups and was significantly different from both (p < 0.0001).

There was a significant association (X^2 = 105.3; p < 0.00001) between the presence of pain in the hand and the presence of the four features (Table 16.1). If the patients in the borderline and normal groups are considered in isolation, this significance disappears confirming there is an abnormally increased proportion of patients with hand pain in the algodystrophy group. In the borderline group, 7 also had abnormally tender fingers. Therefore 65 (79%) patients with pain in their hands also had abnormal tenderness. Of the 77 patients with all the features of algodystrophy, all but 19 had pain in their hand. There was also a significant association (X^2 = 67.7; p < 0.00001) between the presence of pain in the shoulder and inclusion into one of the three groups (Table 16.1). Again this was due to a higher incidence of shoulder pain in the algodystrophy group. Six patients developed the classical features of "frozen shoulder". There were a further 12 patients excluded from this analysis who reported pain in the shoulder but who also gave a history of trauma to the shoulder at the time of the Colles' fracture.

Table 16.1. Distribution of patients with hand or shoulder pain based on the presence of abnormal tenderness, vascular instability, swelling and stiffness.

	Algodystrophy	Normal	Borderline	Total
Hand pain	58	8	16	82
Shoulder pain	40	5	9	54

Hand volume. Probit analysis of the distribution of hand volume ratios showed that they were not normally distributed (Fig 16.3a). If, however the population was subdivided into patients with and without the four features associated with the diagnosis of algodystrophy, the distributions were normal (Fig 16.3b and c), again suggesting two distinct populations of fracture patients. Also a highly significant

difference in hand volume was found between the algodystrophy (1.09 ± 0.009) and the

normal group (1.007 ± 0.003; p < 0.00001; Fig 16.4). There was no significant

difference between the normal group and the control population or borderline group.

Grip strength. The distribution of grip strength measurement also conformed to the

pattern seen with the dolorimetry score and hand volume ratios. The distribution of

data became normal when patients were divided based on the presence or absence of

the four features (Fig 16.5). The patients with algodystrophy were significantly weaker

(0.20 ± 0.02) than the normal population (0.42 ± 0.03; p < 0.00001; Fig 16.6) but there

was no difference between the latter and the borderline group (0.34 ± 0.03).
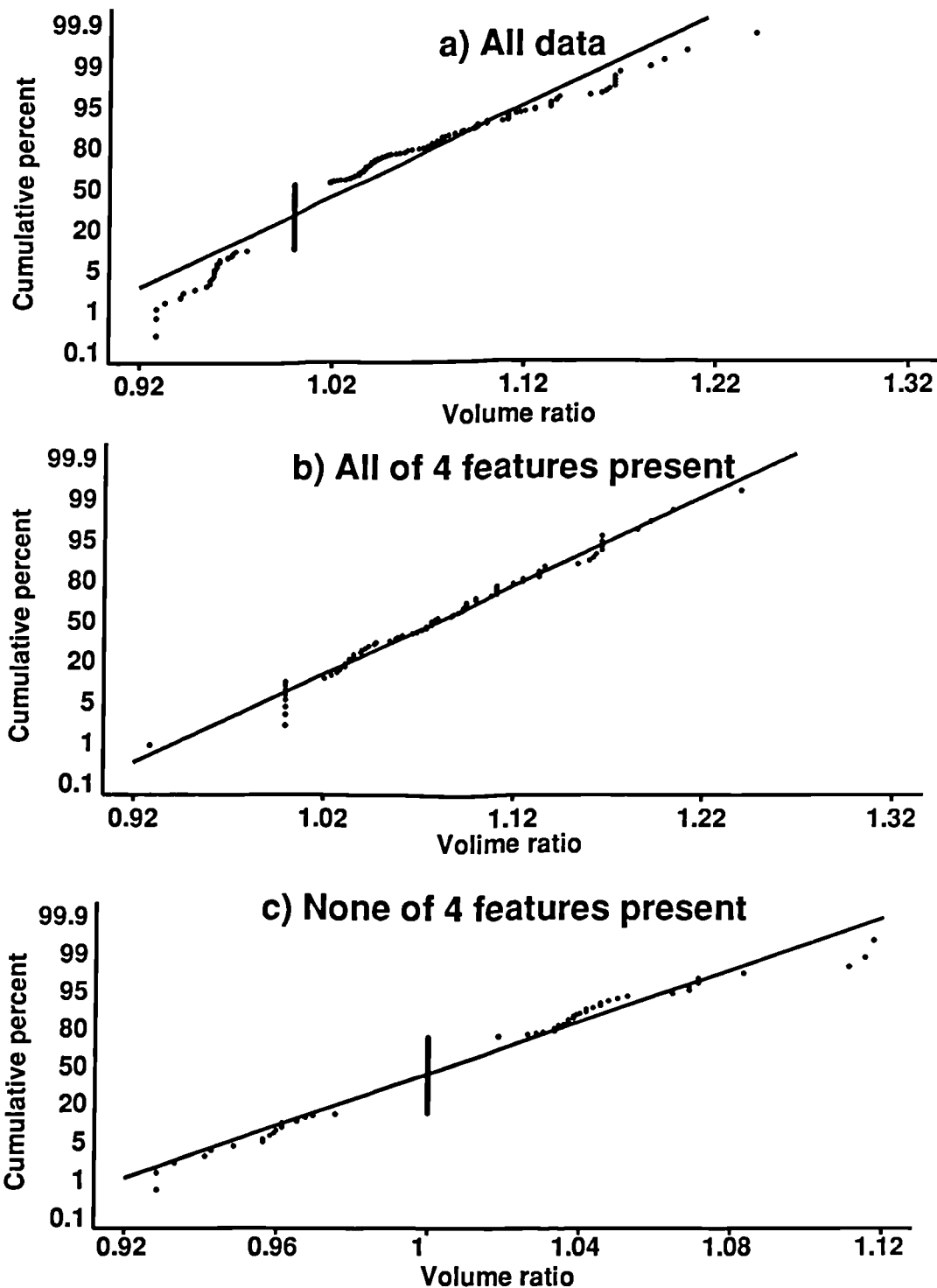
Fig 16.3. The hand volume was expressed as the ratio of affected to unaffected hand in 274 patients with Colles' fracture and their distribution plotted using Probit analysis. The distribution was abnormal when all patients were included (a) but was normal when performed on patients with or without the features of tenderness, vascular instability, swelling and stiffness. This implies the presence of two distinct populations.
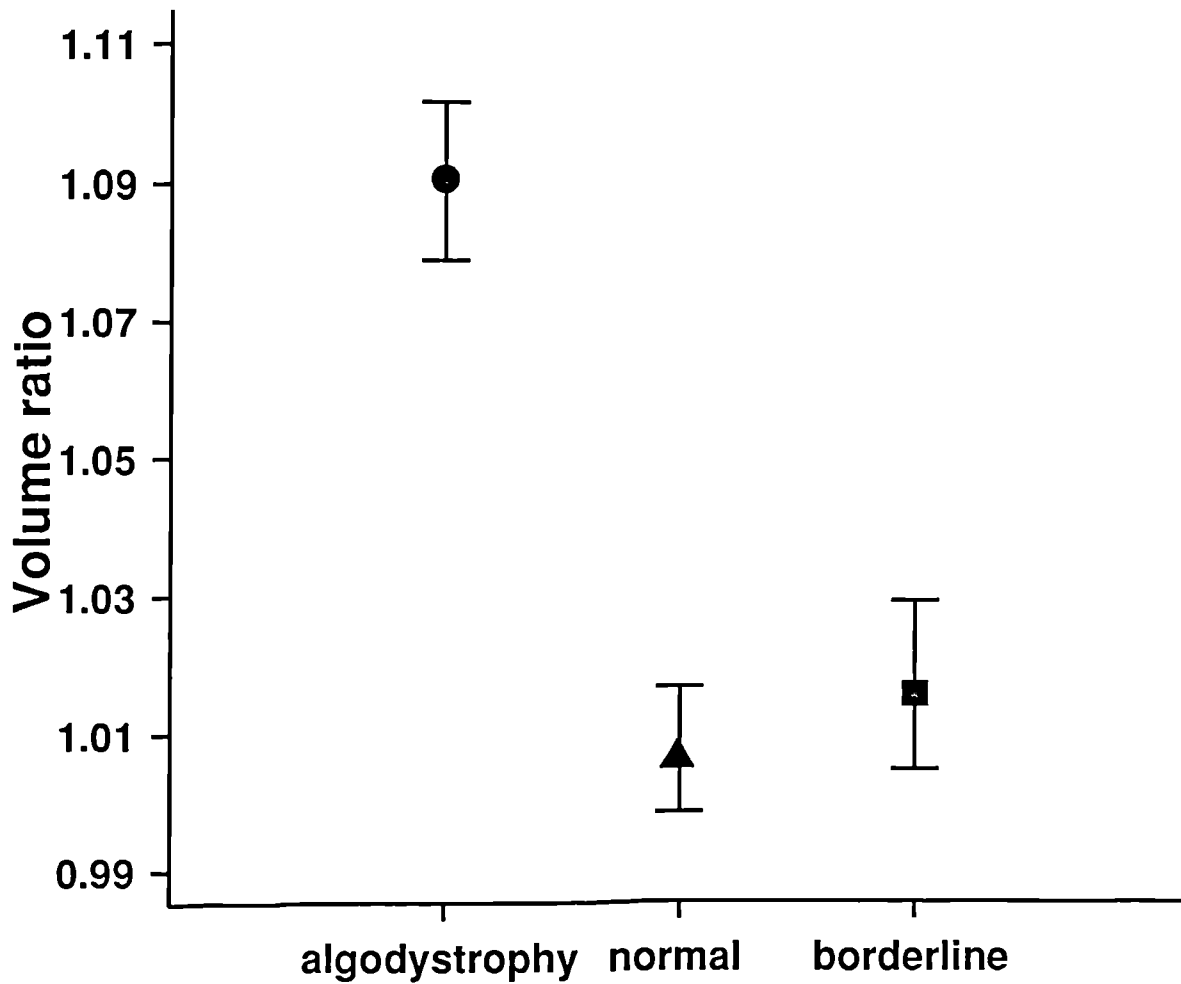
Fig 16.4. The volume ratio mean (+/- SEM) was calculated in those patients with all the features of tenderness, vascular instability, swelling and stiffness (algodystrophy), none of the features (normal) and the presence of one to three of the features (borderline). The volume ratio was significantly greater in the algodystrophy group (p < 0.0001).
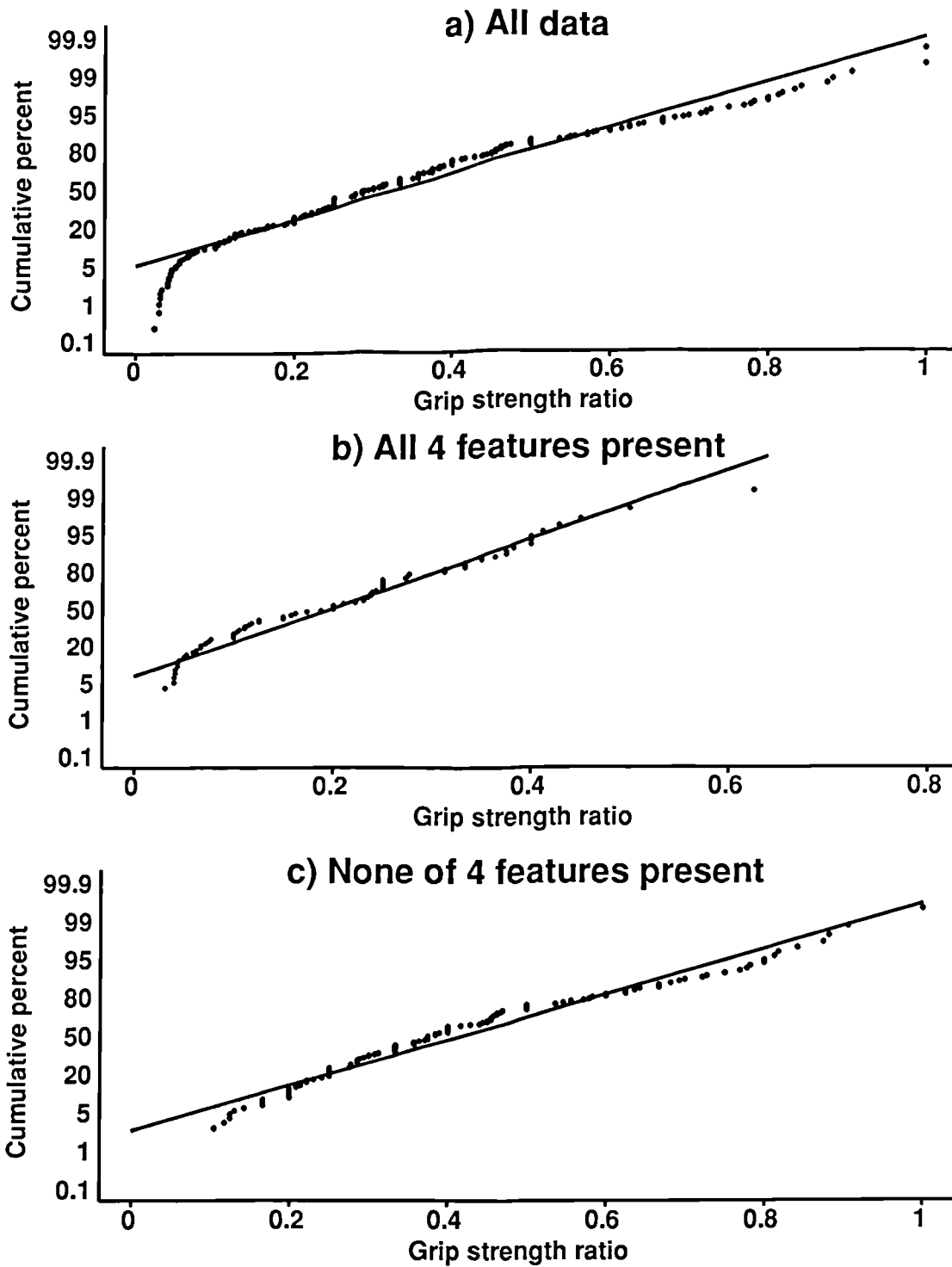
Fig 16.5. The grip strength ratio was expressed as the ratio of the affected to unaffected hand in 274 patients with Colles' fracture and their distribution plotted using Probit analysis. The distribution was abnormal when all patients were involved (a) but was normal when performed on patients with or without the features of tenderness, vascular instability, swelling and stiffness. This implies the presence of two distinct populations.
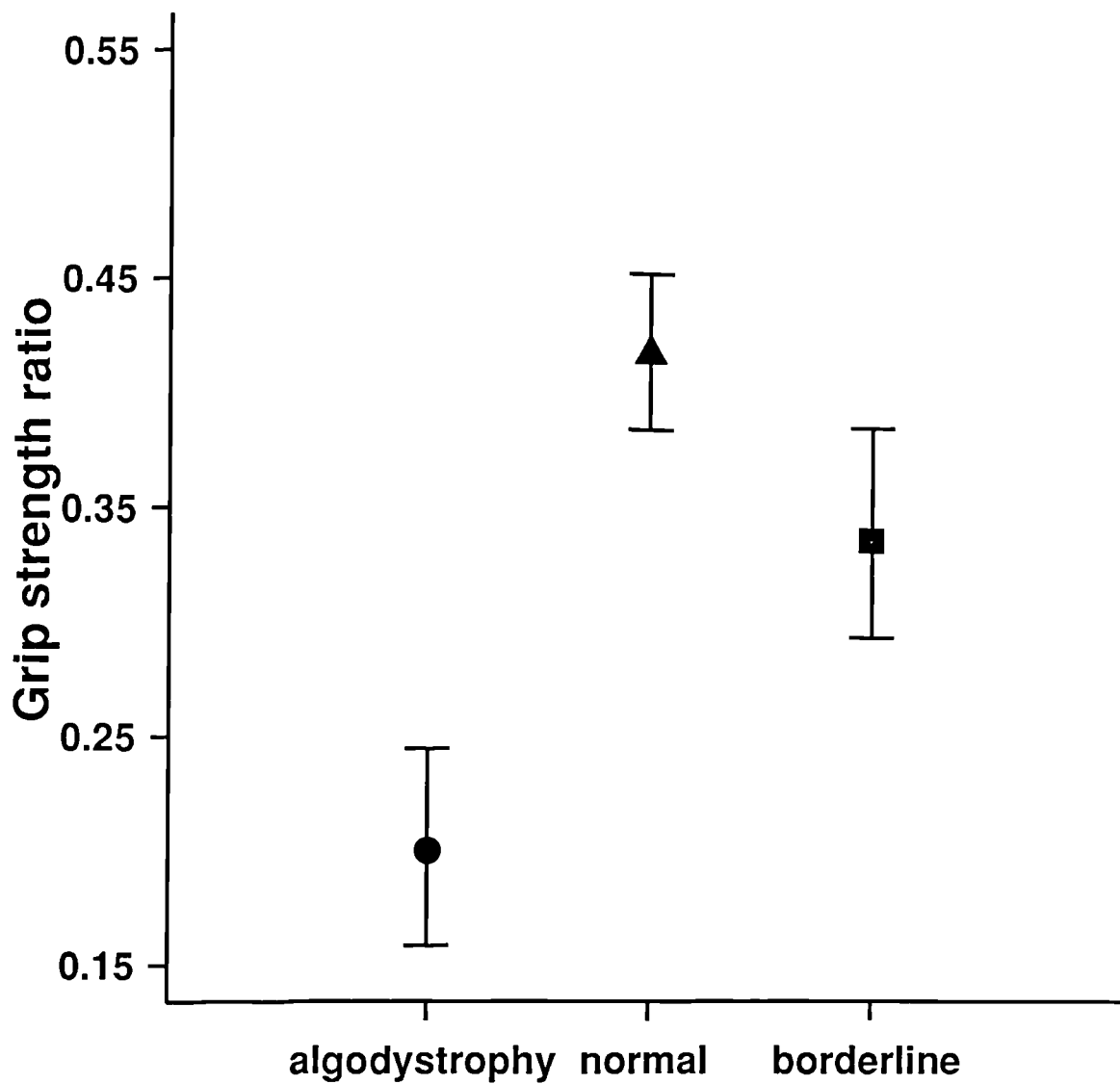
Fig 16.6. The grip strength ratio (+/- SEM) was calculated in those patients with all the features of tenderness, vascular instability, swelling and stiffness (algodystrophy), none of the features (normal) and the presence of one to three of the features (borderline). The grip strength ratio was significantly less than the algodystrophy group (p < 0.0001).

Due to the non-uniform distribution of dolorimetry score, hand volume and grip strength, correlations between these parameters were performed using the Spearman Rank test for non-parametric data. There were significant correlations between the dolorimetry score and hand volume (R_S = -0.54; p < 0.00001) and dolorimetry score and grip strength (R_S = 0.46; p < 0.00001). Although the correlation between hand volume and grip strength was poor, there was still a significant association (R_S = -0.29; p < 0.00001). In this three way analysis however, it is not clear to what extent the parameter that was excluded from the calculation influenced the correlation between the remaining two. For example, to what extent does a change in volume of the hand affect the correlation between tenderness (dolorimetry) and grip strength. To investigate this, partial correlations were calculated which take into account this factor. This showed that the correlations, though slightly reduced, still existed between dolorimetry and hand volume (R_S = -0.41) and dolorimetry and grip strength (R_S = 0.38). The weak correlation between hand volume and grip strength however, completely disappeared (R_S = -0.02).

Discussion.

This study has shown that the three quantitative clinical measurements, dolorimetry, hand volume and grip strength, are capable of differentiating between groups of patients with and without algodystrophy following a Colles' fracture.

In the previous chapter, two distinct populations were identified on the basis of a dolorimetry score greater or less than 0.92, the lower limit of normal. This analysis was carried further with the distribution of the dolorimetry scores calculated on the presence of all, some or none of the features of algodystrophy. Again, in those patients with all or none of the features, the dolorimetry scores were normally distributed. In addition, patients who exhibited all three features had significantly greater tenderness in their fingers than those with none of the features. In those with no features of

algodystrophy, their dolorimetry scores were no different from a control population who had no previous fracture. Therefore finger tenderness is likely to be solely related to the presence of algodystrophy.

The presence of pain in the hand and shoulder was significantly associated with algodystrophy. There were however 19 of the 77 patients who displayed all the features of algodystrophy who did not complain of hand pain. The presence of pain in the hand was on occasions difficult to assess as the patient concentrated on the fracture site rather than distally in the hand. It was my impression that patients who exhibited the features of algodystrophy also complained of abnormally increased pain from the fracture site but this was not specifically recorded. Excessive pain from the fracture site may well have masked pain in the hand in some cases and accounted for the 19 patients who reported no pain but were abnormally tender. Nevertheless, there were a significantly greater number of patients with tender hands in the algodystrophy group.

The presence of a greater number of patients with shoulder pain in the algodystrophy group, with no history of trauma to the shoulder at the time of injury, is of interest. They may represent patients with mild forms of shoulder-hand syndrome, indeed six of them went on to develop the classical features of a "frozen shoulder". The spread of symptoms to sites distant to that originally injured demonstrates the patho-physiological concept of involvement of spinal levels above or below those serving the dermatomes of the injured part.

As with the dolorimetry scores, Probit analysis of the hand volume and grip strength demonstrated non-gaussian distributions. When the distributions were calculated on the presence or absence of the four features of algodystrophy, they were normal. Furthermore there was a significant difference in the mean values for the two measurements between the algodystrophy and normal group. These investigations are able therefore to identify, on a population basis, those patients with algodystrophy.

Although originally there seemed to be a correlation between hand volume and

grip strength, this disappeared when the influence of tenderness in the hand was excluded. The loss of grip strength therefore was not secondary to the hand swelling but was associated with the degree of tenderness in the hand. The change in grip strength however, did not influence the correlation between hand volume and tenderness which suggested that the latter two may be causally related.

This study has demonstrated that in the absence of any of the features of algodystrophy, there was no difference in the degree of tenderness or hand volume compared with a control population with no recent fracture. The use of these measurements with the addition of grip strength were able to identify a population of patients with algodystrophy.

CHAPTER 17: THE DIAGNOSTIC POWER OF QUANTITATIVE MEASUREMENTS.

The diagnosis of algodystrophy in the previous chapters was based on the presence of abnormal tenderness (dolorimetry), vascular instability, swelling and stiffness. The only quantitative measurement was dolorimetry, and although this test in isolation is able to differentiate between populations of patients, it's ability to diagnose algodystrophy on an individual basis was unknown. Although the measurement of hand volume and grip strength are not fundamental to the diagnosis of algodystrophy, it was of interest to compare the diagnostic accuracy of these measurements with dolorimetry. For these reasons estimations of diagnostic precision were performed on the three quantitative measurements.

Methods.

The dolorimetry, hand volume and grip strength techniques used to assess the 274 Colles' fracture patients have been described in Chapter 9. The diagnosis of algodystrophy was based, as in previous chapters, on the presence of abnormal tenderness, vascular instability, swelling and stiffness. In the dolorimetry assessment the presence of the latter three were used as criteria for the diagnosis of algodystrophy.

The ability of the quantitative measurements to discriminate between algodystrophy and disuse was evaluated by categorising patients according to the presence or absence of clinical evidence of algodystrophy and a measurement value greater or less than a chosen cut-off value. Thus patients fell into four categories for any chosen cut-off value:

a: algodystrophy with an abnormal score (true positive)

b: algodystrophy with a normal score (false negative)

c: disuse atrophy with a normal score (true negative)

d: disuse atrophy with an abnormal score (false positive)

The sensitivity of each feature (ability to detect patients with algodystrophy) was calculated as a/a+b, and the specificity (ability to exclude patients without disease) c/c+d. The relative power of the different techniques in the diagnosis of algodystrophy was evaluated using Receiver Operated Characteristics (ROC) curve analysis which is based on the relationship between specificity and sensitivity at different cut-off values. The nearer the curve approaches the ideal curve (Fig 17.1), the more powerful the technique. The optimal predictive power of each value ({a+c}/{a+b+c+d}) to discriminate between algodystrophy and disuse was also calculated for each type of measurement.
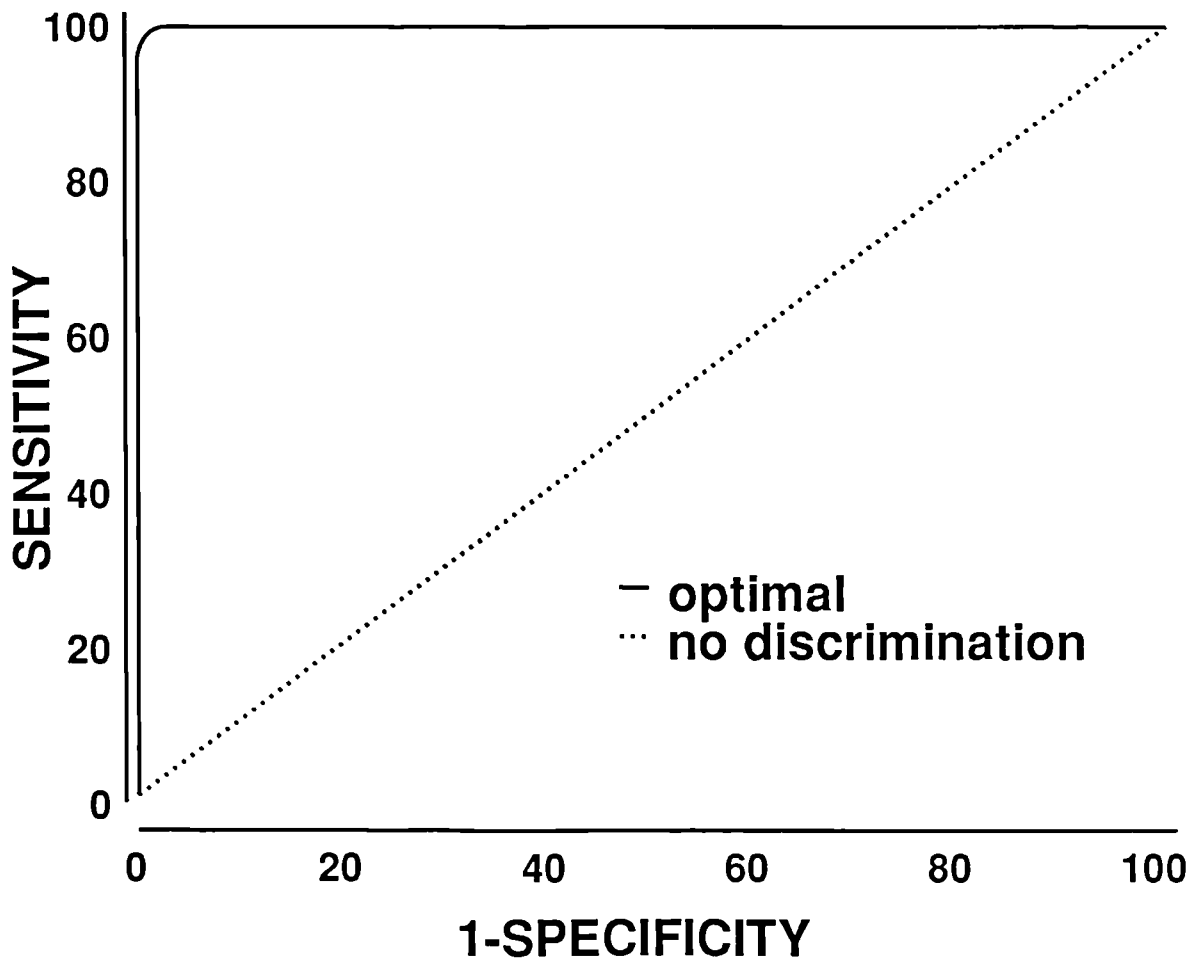
Fig 17.1. Two hypothetical ROC curves, one with 100% sensitivity and 100% specificity, and the other with no discriminant value.

Results.

ROC analysis of the dolorimetry data produced a curve approaching ideal (Fig 17.2). The maximal predictive value of dolorimetry was 90% at a score less than or equal to 0.91 which corresponds to the cut-off value defined by the control population (lower limit of normal using the 95% confidence interval - 0.92). At this score there was a sensitivity of 89% and specificity of 91%. Therefore, of the 87 patients with a diagnosis of algodystrophy based on the above criteria, 77 would have been diagnosed by dolorimetry alone, with 10 falsely diagnosed as having no algodystrophy. Of the remaining 196 patients only 17 were thought to have algodystrophy. Dolorimetry therefore appears to be a highly discriminating factor in the diagnosis of algodystrophy and it's inclusion with the other three features seems justified.

ROC analysis on the other two parametric variables, hand volume and grip strength, demonstrated them to be of less discriminant value. Hand volume performed better but the curve fell short of ideal (Fig 17.2). The maximal predictive value was only 82% with a low sensitivity of 63% but a reasonably high specificity of 89%, based on a ratio of 1.06 or greater (affected to unaffected hand). It would appear therefore that the hand volume ratio was able to accurately categorise those with no algodystrophy (high specificity) but was less able to identify those with algodystrophy.

Grip strength was of even less diagnostic ability in isolation. The curve was little better than that expected with no discriminant value (Fig 17.2). The highest predictive value was only 77% at a grip strength ratio of 0.12 (affected to unaffected hand). At this value there was a low sensitivity (38%) but again a high specificity (93%). Therefore as with hand volume measurements, the technique was able to categorise the normal patients, but was a poor discriminant of those with algodystrophy.
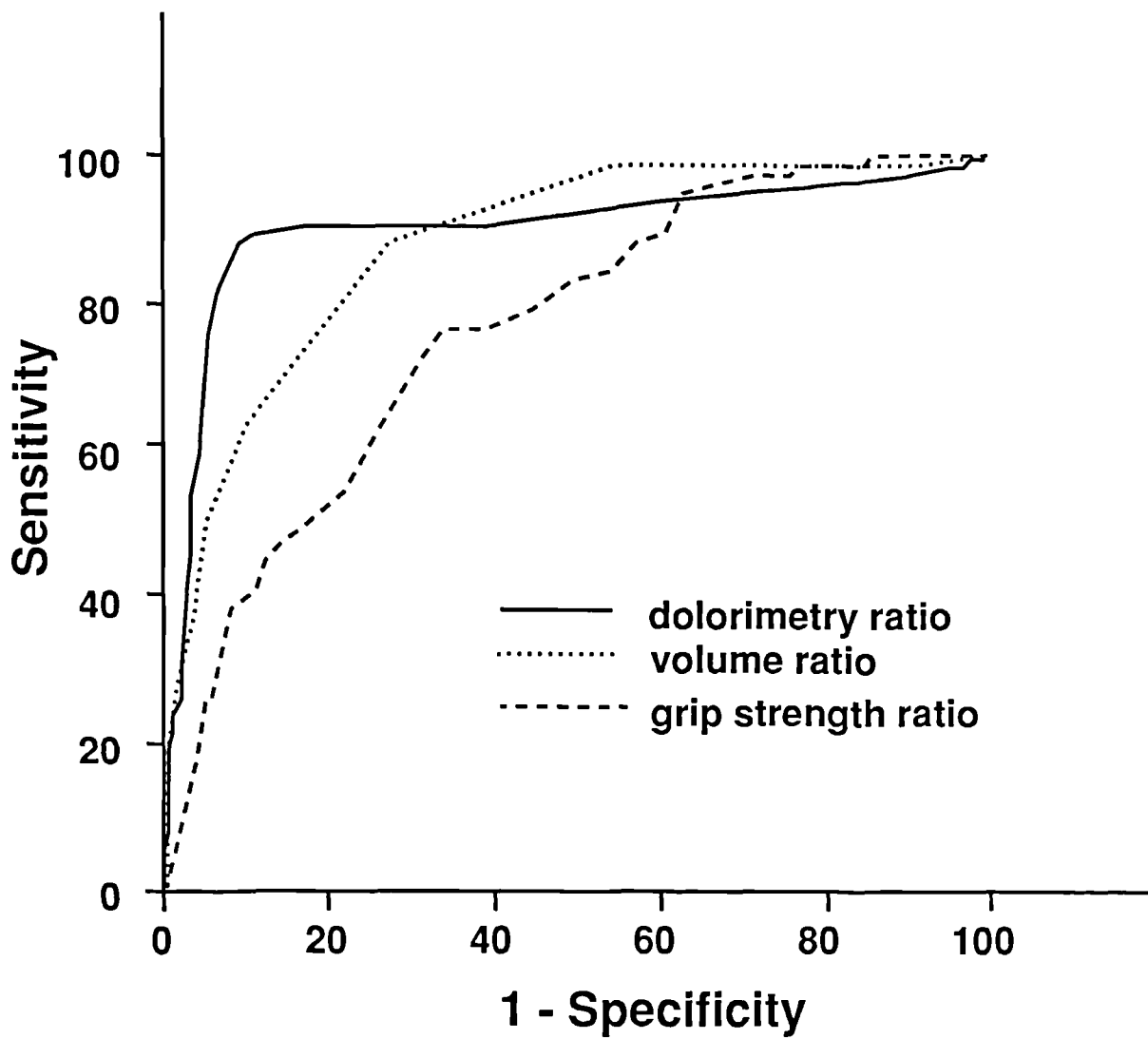
Fig 17.2. The ability of the dolorimetry, hand volume and grip strength ratios to identify patients with algodystrophy was analysed by ROC analysis on 274 patients with a Colles' fracture. Dolorimetry was the most sensitive and specific technique for diagnosing algodystrophy with the curve approaching ideal. The measurement of grip strength was of little diagnostic value.

Discussion.

Dolorimetry as a measurement of tenderness proved to be an accurate method of detecting patients with vascular instability, swelling and stiffness. This was further confirmed by it's maximal predictive value corresponding to a score of less than or equal to 0.91, a score previously defined in a control population as being the lower limit of normal (95% confidence interval).

The measurements of the hand volume ratios was not a sensitive method of identifying patients with algodystrophy. However, although it may be of poor discriminant value in individual cases, it was still capable of differentiating between the groups and may therefore be of use in a longitudinal study. The same applies to the measurement of grip strength which, as a measure of morbidity, may be of use in defining the degree and rate of recovery of function in the patients with algodystrophy.

CHAPTER 18: SUB-CLINICAL ALGODYSTROPHY.

Although two distinct patient populations were defined based on the presence or absence of tenderness, vascular instability, swelling and stiffness (Chapter 15), there still remained a number of patients who displayed some, but not all, of these features. These patients therefore occupy a middle ground between no disease and outright algodystrophy and may represent a sub-clinical form of the condition. To determine whether they were a discrete group or the features of the condition occurred at random, the quantitative clinical measurements were used to further characterise this borderline group.

Methods.

There were 72 patients who had either one, two or three of the four features of algodystrophy (abnormal tenderness, vascular instability, swelling or stiffness). Each group was assessed using the quantitative clinical techniques (dolorimetry, hand volume and grip strength) described in the previous two chapters and the presence of pain in the hand and shoulder. This group was further analysed by dividing it into the number of features displayed from one to three (Table 15.4). The statistical analysis used was the same as in previous chapters.

Results.

There was a significant difference in the dolorimetry score between those with one feature (0.98 ± 0.01) and those with two features (0.91 ± 0.03; p < 0.02). Patients with three features had spuriously high dolorimetry scores (0.92 ± 0.02) as a low dolorimetry score (< 0.92) would have automatically excluded them from the borderline group (Fig 18.1).

The increasing tenderness in the borderline group was mirrored by complaints

of increasing pain in both the hand and shoulder. Of the 16 patients who complained of pain in the hand in the borderline group, three had one feature, five had two features and eight had three features (X^2 = 8.0; p < 0.02). This significant difference disappeared if the analysis was carried out on those with only one or two features. There was therefore a significantly greater number of patients with three features who complained of pain in the hand. Of the 5 patients who complained of shoulder pain in the borderline group, three were in the group with three features and one in each of the remaining two groups. Due to the few numbers, no statistical analysis was carried out on this data.

The hand volume in the borderline group also increased with increasing numbers of associated features (Fig 18.2). There was however no significant difference between the groups.

Although there was a decrease in grip strength between patients with one and two features, this trend was not significant and did not continue when patients with three features were considered (Fig 18.3).
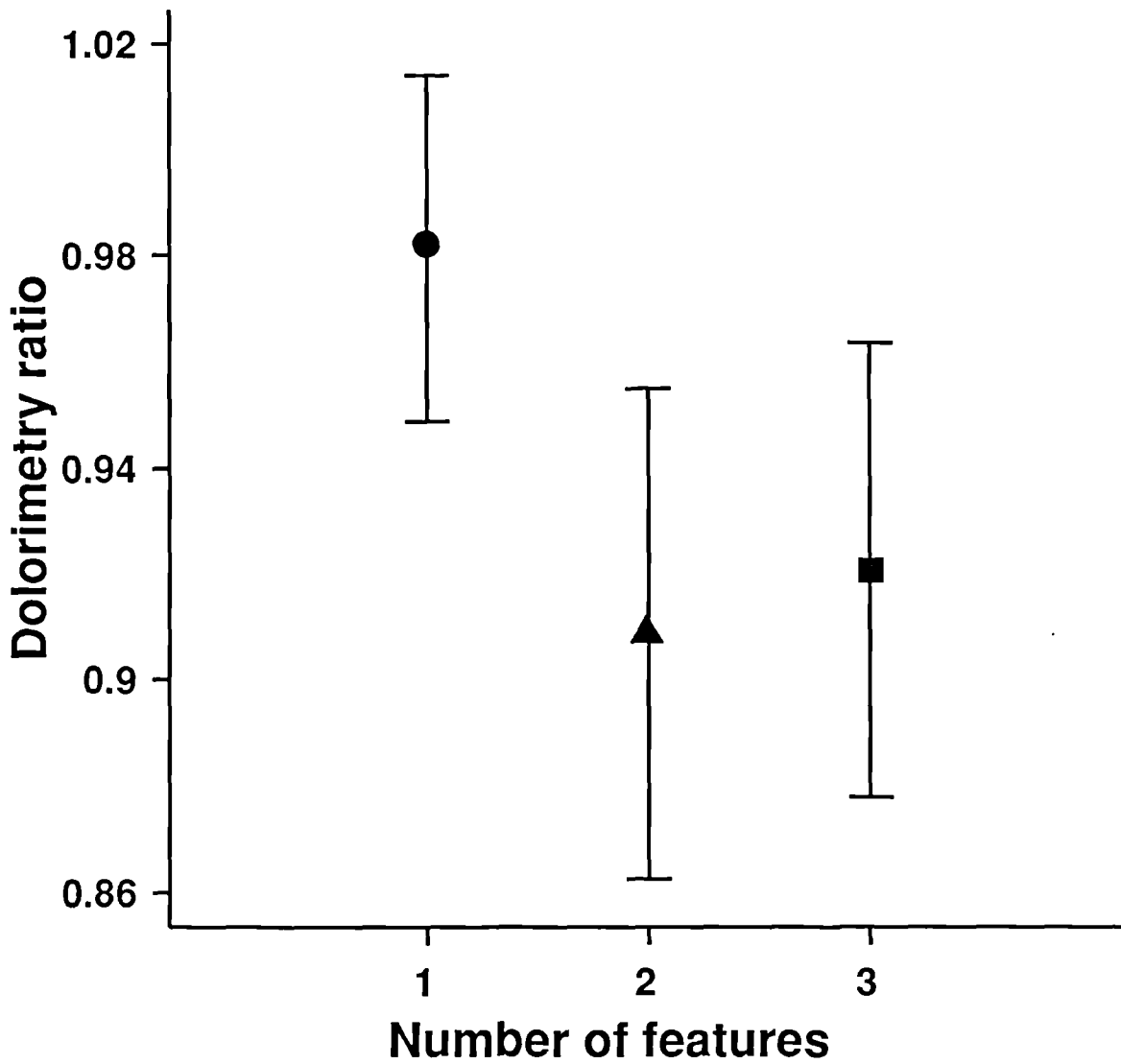
Fig 18.1. The mean (+/- SEM) dolorimetry ratio was calculated in 72 patients who displayed either one, two or three features of abnormal tenderness, vascular instability, swelling and stiffness. There was a significant difference (p < 0.02) in the dolorimetry ratio between patients displaying one or two of the features. The value for three features is spuriously high as a dolorimetry ratio of less than 0.92 would have excluded them from the borderline group.
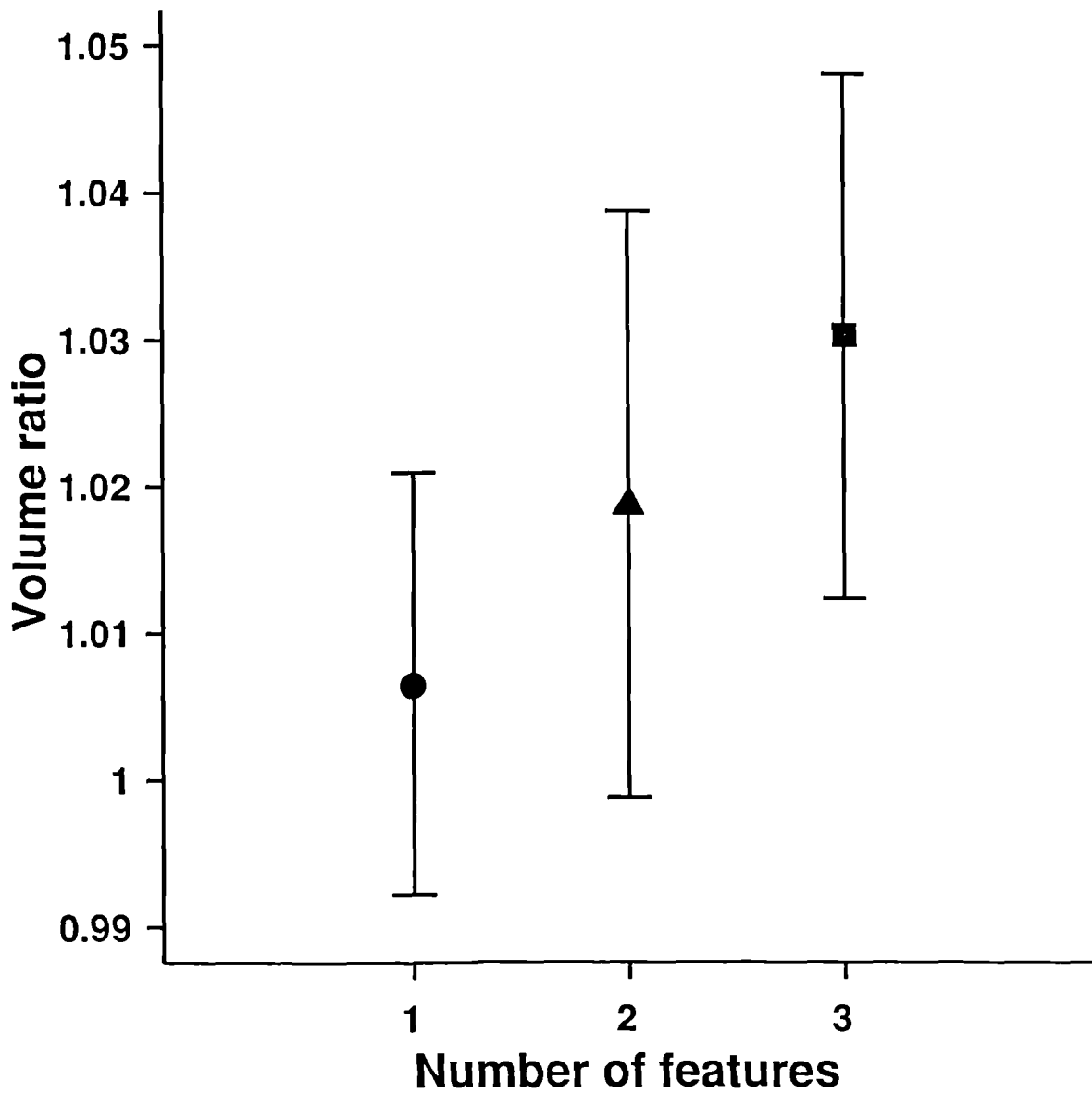
Fig 18.2 The mean (+/- SEM) volume ratio was calculated in the 72 patients who displayed either one, two or three of the features of abnormal tenderness, vascular instability, swelling and stiffness. There were no significant differences between any of the groups but there was a trend towards increasing hand volume as the number of features increased.
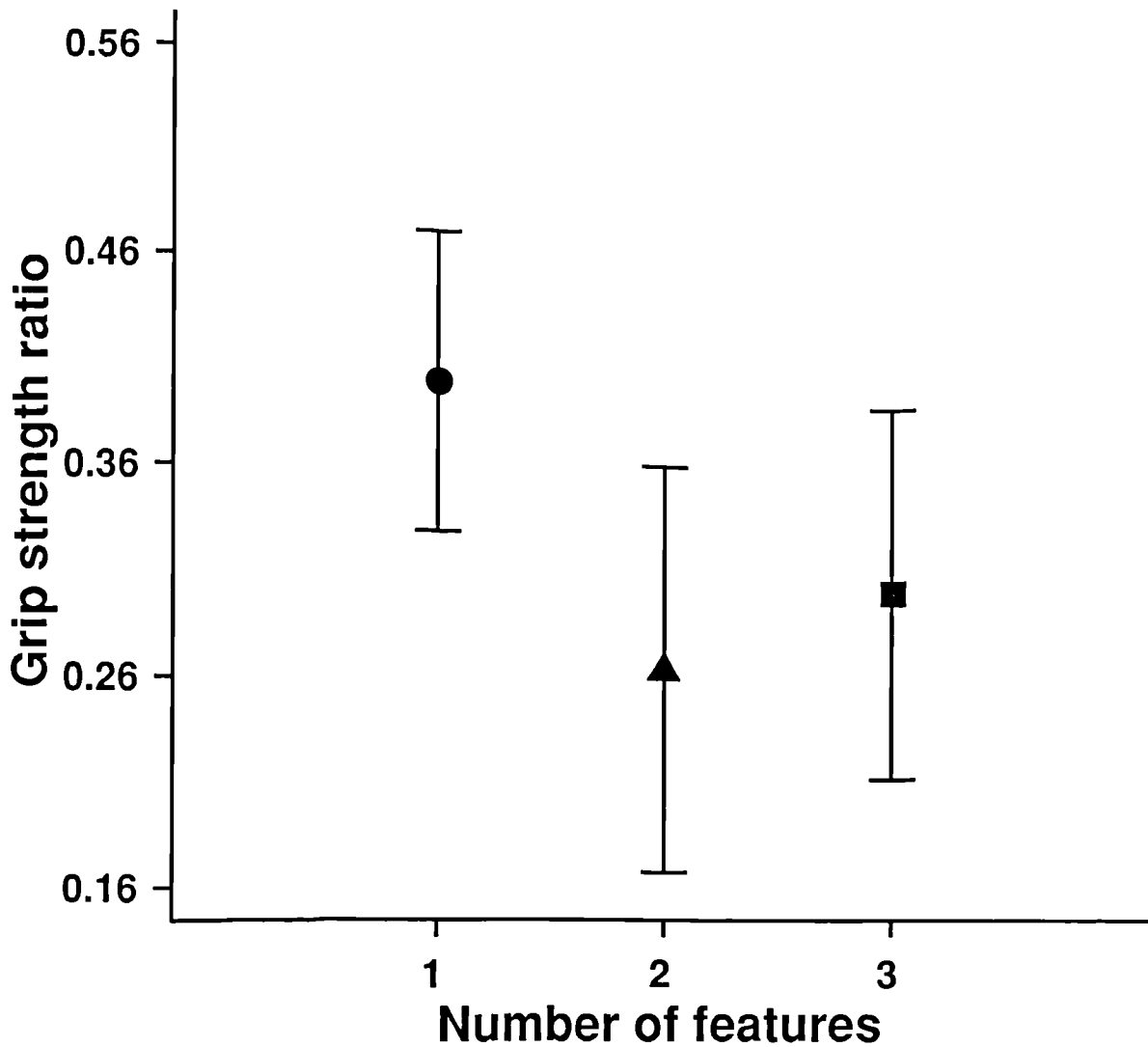
Fig 18.3. The mean (+/- SEM) grip strength ratio was calculated in 72 patients who displayed either one, two or three features of abnormal tenderness, vascular instability, swelling and stiffness. Again there were no significant differences but the trend in the towards a greater loss in grip strength in the patients with more features was still apparent though less convincing than with the measurement of the dolorimetry and hand volume ratio.

Discussion.

Although a discrete population can be identified on the basis of the four main features, there was a definite trend in the borderline group, particularly with the data concerning pain and tenderness, towards more morbidity in the patients with three of the four possible features needed for a diagnosis of algodystrophy. Therefore, there was a spectrum of morbidity associated with these features which increased as the number of features increased. In view of this trend, the absence of a feature was unlikely to be due to inaccuracy inherent in the assessment technique used as these would have been expected to occur at random. There would accordingly have been no definite trend in morbidity seen in this borderline group.

These patients therefore represent a sub-group who do not manifest all the symptoms which have been arbitrarily defined as required for the diagnosis of algodystrophy. The reason why they failed to develop all the features of the condition remains unknown.

CHAPTER 19: SKELETAL ARCHITECTURE

The characteristic radiographic features of algodystrophy, first reported by Sudeck in 1900, are a general loss in trabecular bone density with a patchy appearance. Changes in cortical bone, comprising of endosteal, intracortical and periosteal resorption of bone, have also been reported by Genant *et al* (1975) and Kozin *et al* (1976). These reported changes in trabecular and cortical bone, however, have been largely subjective.

Although the radiographic changes seen in post-traumatic algodystrophy have been described, it is unclear to what extent they are due to the condition itself, or disuse atrophy following trauma. This may lead to diagnostic confusion in the early stages if the clinical picture is equivocal. Also the pathophysiological mechanism causing disuse atrophy and the extent with which this is altered in algodystrophy is unknown. A more effective method of differentiating the radiographic changes in algodystrophy from disuse and more information on the pathophysiology of the changes would benefit not only the diagnosis, but also the formulation of future treatment regimes.

For these reasons, having defined algodystrophy on the basis of clinical features, the radiographic characteristics of bone were examined in patients with algodystrophy using the scoring system and metacarpal morphometry described in Chapter 10, and compared with a control group of Colles' fracture patients who did not have algodystrophy.

Methods.

a) Radiographic features.

The radiographic techniques of a scoring system and metacarpal morphometry have been described in Chapter 10. Radiographs were performed on 77 patients with a Colles' fracture two weeks after removal of the plaster cast, 44 of whom demonstrated abnormal pain/tenderness, vascular instability, swelling and stiffness and were thus considered on clinical grounds to have algodystrophy.

b) Single photon absorption (SPA)

The technique has been described in Chapter 12 and was performed on the same day the radiographs were taken on 29 patients with algodystrophy and 23 controls.

The statistical methods used were the same as that described in the previous chapter on clinical features.

Results.

There was no difference in the age, sex and duration of immobilisation between patients with algodystrophy or control. Nor was there any difference in the radiographic score, combined cortical width (CCW) or bone mineral density (BMD) at the unfractured side (Table 19.1).

Table 19.1. Details of patients and findings (mean ± SEM) at study entry on the unfractured side.

	ALGODYSTROPHY n = 44	CONTROL n = 33	p<
Age (years)	65 ± 1	64 ± 1	NS
Sex M:F	6:38	3:30	NS
Duration of immobilisation (days)	39 ± 1	37 ± 1	NS
Combined cortical width (mm)	9.5 ± 0.3	9.4 ± 0.4	NS
Metacarpal diameter (mm)	23.2 ± 0.3	23.8 ± 0.3	NS
Radiographic score	0	0	NS
*BMD_{cort} (g/cm^2)	0.83 ± 0.16	0.80 ± 0.17	NS
*BMD_{trab} (g/cm^2)	0.60 + 0.11	0.59 + 0.12	NS

* measured in 29 algodystrophy patients and 23 controls.

At the affected (fractured) side all the measurements were lower at first review approximately seven weeks after fracture compared to the unaffected side, with the exception of the metacarpal diameter which did not change. On the assumption that these measurements would have been similar before fracture between sides, and that no bone loss had occurred on the unfractured side, the rate of change was calculated for each patient with and without algodystrophy (Table 19.2). Bone loss and radiographic changes occurred in all patients but the changes were more marked in patients with algodystrophy and more marked at the trabecular (radiographic score and BMD_{trab}) rather than cortical sites.

Table 19.2. Rates of change ± SEM in bone measurements at the first assessment 7 weeks after fracture. Values are expressed as the percentage difference between the affected and unaffected hand.

	ALGODYSTROPHY	CONTROL	$P_1 \le$
Metacarpal diameter (mm)	100.6 ± 1.2	98.5 ± 0.9	NS
Combined cortical width (mm)	96.2 ± 1.1	97.2 ± 1.7	NS
Radiographic score	59.4 ± 3.6 **	20.7 ± 2.9 **	0.0001
BMD_{cort}	85.8 ± 2.8 *	94.3 ± 2.5	0.05
BMD_{trab}	76.8 + 2.9 **	89.7 + 1.8	0.001

P_1 signifies the significance of difference between patients with and without algodystrophy.

Asterisks signify the significance of difference from the control (unfractured side).

* p < 0.05; ** p < 0.001

The radiographic score for each individual feature was significantly greater in patients with algodystrophy (Table 19.3). There was no significant difference between the mean values for each of the four features within the group of patients with algodystrophy (ANOVA; p >0.05). This was not true of the patients with no evidence of algodystrophy. The mean value for the density was greater than those of other features (Table 19.3) and analysis of variance of the four groups confirmed there was a significant difference in the means (p < 0.01). The difference disappeared when the scores for lucencies, subchondral lysis and loss of trabecular pattern were taken in isolation (ANOVA; p > 0.05). Therefore, although all the features were apparent with

disuse, a generalised loss of density was the most prominent.

Table 19.3. Mean score ± SEM for each individual feature and the total for the groups with algodystrophy and the control population.

	ALGODYSTROPHY	CONTROL	
Number	44	33	
Density	2.0 ± 0.1	1.2 ± 0.1	p < 0.001
Lucency	1.9 ± 0.1	0.6 ± 0.2	p < 0.001
Erosion	1.6 ± 0.2	0.4 ± 0.1	p < 0.001
Trabeculae	1.7 ± 0.2	0.5 ± 0.2	p < 0.001
Total	7.1 + 0.2	2.6 + 0.5	p < 0.001

Using simple regression analysis there was a significant association between measurements of trabecular bone (BMD_{trab} and radiographic score; $R = -0.46$, $p > 0.05$) and measurements of cortical bone (BMD_{cort} and CCW; $R = 0.47$, $p < 0.05$) in patients with algodystrophy seven weeks after fracture. There was however no correlation between measurements of cortical and trabecular bone.

ROC analysis.

Radiographic score. ROC analysis of each individual feature produced curves which overlapped, but indicated that each feature examined could contribute significantly to the diagnosis. When the total score was used the curve (Fig 19.1) was of more predictive value than the individual scores taken in isolation. At a score of 4 or greater, the positive predictive value was maximal (83%), with a sensitivity of 87.5% and specificity of 75%. The positive predictive value at this score was also greater than for

any of the features assessed individually. This meant that 39 of the 44 algodystrophy
patients were positively identified with only 8 of 33 controls falsely identified.

Combined cortical width. This proved to be of little discriminant value with a linear ROC
curve (Fig 19.2).

Bone mineral density. There was little difference in discriminant ability between the
proximal (cortical) scan and the distal (trabecular) scan (Fig 19.3). Comparison with Fig
19.1 showed that these techniques were less powerful in discriminating algodystrophy
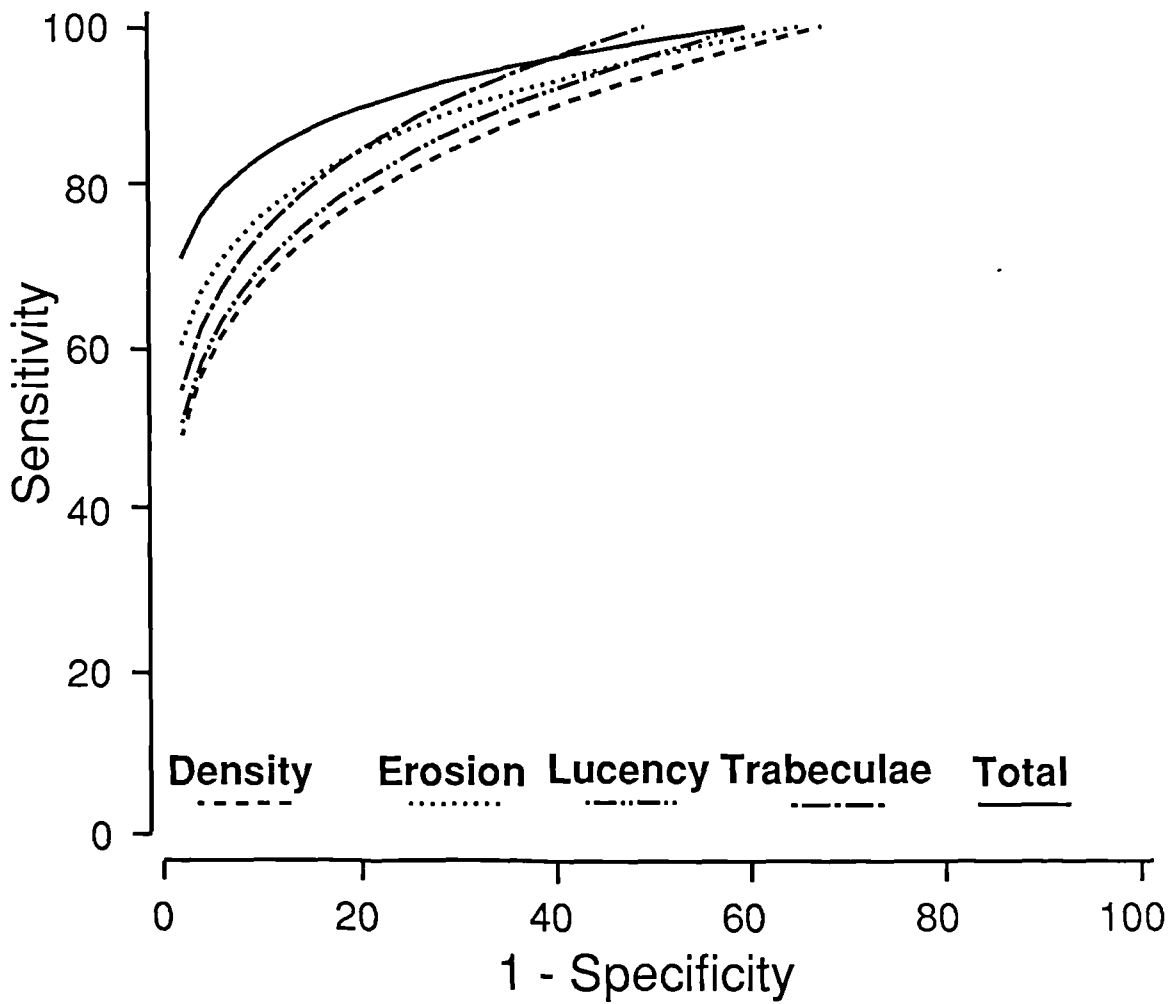from disuse than the radiographic score.

Fig 19.1. The ROC curves for the individual radiographic features and total
score combined. The greatest sensitivity and specificity was achieved using the
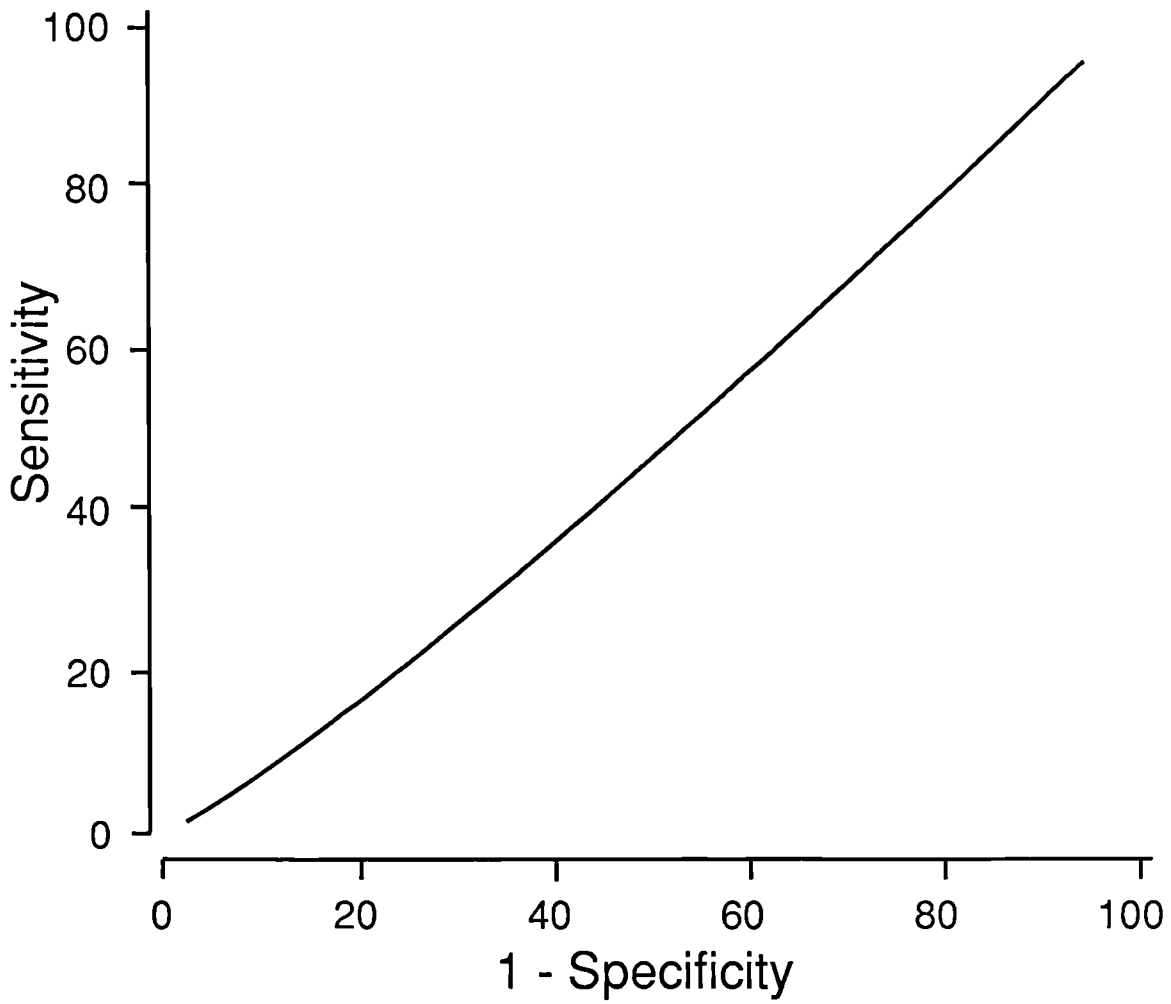combined score.

Fig 19.2. The combined cortical width ratio was measured in 77 patients with a Colles' fracture but proved to be of no value in the diagnosis of algodystrophy as assessed by ROC analysis.
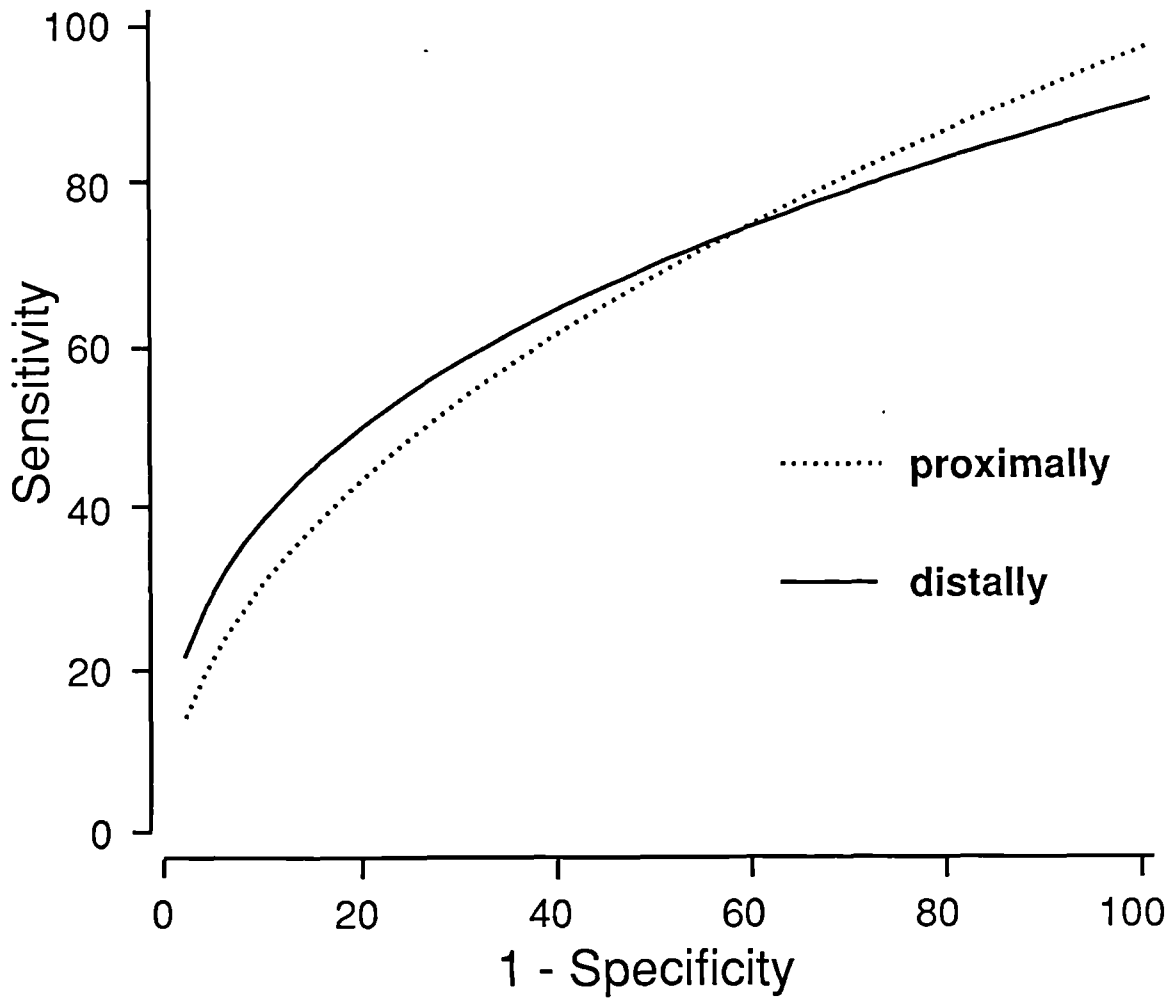
Fig 19.3. There was little difference in diagnostic ability between the distal and proximal BMD ratios assessed by ROC analysis on 52 patients.

Discussion.

This study indicates that the radiographic appearances, as measured by the radiographic score, of algodystrophy are not specific for the disorder but are qualitatively similar to those which follow fracture and immobilisation. It is not possible from the present study to determine to what extent such changes are secondary to fracture or to the immobilisation. Nevertheless our findings are of some importance since traditionally investigators rely on the radiographic changes to diagnose algodystrophy even in the presence of a fracture. Not withstanding, the present study also indicates that the radiographic changes in patients with Colles' fracture are significantly more marked in those patients who developed algodystrophy. The differences between patients with and without algodystrophy are sufficiently large to discriminate albeit imperfectly between disuse and the radiographic changes due to algodystrophy following trauma. Regarding the measurement of cortical width, there was a greater decrease in the algodystrophy group two weeks after immobilisation but this did not reach statistical significance.

Kozin *et al* (1976) and Genant *et al* (1975) demonstrated loss of bone density and cortical width in both the affected and unaffected hands in patients with algodystrophy as proof of the bilateral nature of the condition. Unfortunately they had few patients and did not use a control population for comparison. Within the sensitivity of our techniques, we were unable to demonstrate any changes in the unaffected hand in the patients with algodystrophy or control population and consequently cannot support their findings.

This difference between measurement of cortical and trabecular bone was reflected in the results of the bone mineral density. Unlike the measurement of cortical width, there was a significant decrease in the cortical BMD when compared with the unaffected side ($p < 0.05$), but the rate of change was greater in trabecular bone ($p <$

0.001). Thus the semi-quantitative assessment of bone density and increased porosity, seen on the radiographs was confirmed by a quantitative assessment of trabecular BMD. This relationship was further confirmed by the significant correlation between the radiographic score and trabecular BMD. It is interesting to note that, although there was no significant decrease in cortical width between the two groups, there was a good correlation between the cortical BMD and measurement of cortical width. This may suggest that the lack of cortical changes evident on metacarpal morphometry was due to increased porosity of the cortex due to intracortical resorption of bone from around the Haversian canals. This feature was examined in more detail relating to the natural history of the skeletal changes in algodystrophy (Chapter 24).

Regarding the scoring system we devised, the total score provided a more powerful discrimination than each radiographic feature alone in distinguishing patients with and without algodystrophy. A cut-off value of four gave the maximal predictive value (83%) which is nevertheless short of 100%. It is not suggested therefore that radiography alone can be used to diagnose algodystrophy nor to screen a population, but it can provide an adjunct to diagnosis alongside other clinical and investigative indices. There was no difference in the predictive capabilities of cortical and trabecular BMD but they were both of less discriminant value than the radiographic score. As expected, the measurement of cortical width was of no diagnostic value this early in the evolution of the condition.

Although loss of bone density was the most prominent radiographic feature of disuse atrophy in this study (Table 19.3), as confirmed by the measurements of bone density, the other features (lucencies, subchondral lysis and loss of trabecular pattern) were also detected. This produced a "patchy" peri-articular appearance comparable to that seen in algodystrophy. The radiographic similarity between disuse and algodystrophy has been described previously (Steinbach 1964; Jones 1969), but as demonstrated in this study, the severity of the demineralisation distinguishes

algodystrophy from disuse. There may therefore be a common pathogenesis which is ,
accelerated in algodystrophy. In both conditions there is decreased mechanical stress
on the bone which is thought to be an important factor (Trueta 1954; Geiser and Trueta
1958). The reduction in movement causing this alteration in stress however, is
generally equal in both groups or may even be more pronounced in disuse. Therefore
this cannot account for the more marked radiographic findings in algodystrophy.
Trueta (1954) did notice however, a marked increase in vascularity following disuse.
Increased bone blood flow is a feature of algodystrophy reflected in the increased uptake
of technetium labelled diphosphonate into bone (Doury *et al* 1981, MacKinnon and
Holder 1984). The uptake seen in algodystrophy is in excess of that seen in simple
disuse (Chapter 20) at an identical time after fracture, and therefore increased bone
blood flow may well be implicated in the excessive bone resorption seen in
algodystrophy.

In conclusion, algodystrophy is associated with radiographic abnormalities in
trabecular bone early in the condition which is greater than those following
immobilisation alone. These semi-quantitative assessments were confirmed by
measurements of bone mineral density. The significant difference in radiographic
abnormalities between disuse and algodystrophy may help differentiate between them
in cases which are not clinically obvious, particularly early in the course of the
condition.

CHAPTER 20: SCINTIGRAPHIC FEATURES.

Technetium isotope scans are recommended in the early diagnosis of algodystrophy before radiographic changes become apparent (Doury *et al.* 1981). They provide information not only on the metabolic activity of bone in late scans but also on the regional blood flow in the blood pool phase. These patterns of activity are altered in algodystrophy (Doury *et al.* 1981; Mackinnon and Holder 1984) but have not been directly compared with a control group following trauma. Therefore the reported increase in tracer uptake has not been adequately differentiated from disuse alone which may lead to diagnostic confusion. In addition, an alteration in local bone blood flow and metabolism would have implications with regard to the cause of the excessive bone loss seen in algodystrophy when compared with a control population (Chapter 19). There may therefore be an association between tracer uptake and the measurements of bone loss detailed in the previous chapter.

In order to define the isotope uptake in algodystrophy and disuse shortly after trauma, the activity seen on Technetium isotope scans was compared in post-traumatic algodystrophy and a control population following Colles' fracture.

Methods.

Technetium ^{131}I scans were performed on 43 patients with pain/tenderness, vascular instability, swelling and stiffness and 10 patients with none of these features. The scans were taken two weeks after plaster cast removal, when both the radiographic and densitometric assessments were made. In addition isotope scans were performed on three patients with a dense hemiplegia seven weeks after a cerebro-vascular accident (CVA). The uptake in the delayed phase is expressed as a ratio of affected to unaffected side (metacarpal score), details of which are given in Chapter 11.

The statistical analyses used were the same as in the previous two chapters.

Results.

There was no difference in the age, sex distribution and duration of immobilisation between the patients with algodystrophy and the control group (Appendix I).

There was increased uptake in the blood pool phase in 38 out of 43 scans on patients with algodystrophy with normal uptake in a further two. Due to technical failure, there was no information available on the remaining three. Increased uptake was seen in only four of the 11 scans on the control patients, a significant difference $(X^2 = 16.58; p < 0.0001)$.

The distribution of metacarpal scores within each group was normal but with control patients occupying the lower end of the range (Fig 20.1a). The mean metacarpal score in the algodystrophy group was 2.06 ± 0.10 which was significantly greater (p < 0.0002) than the control group (1.14 ± 0.04). The mean score for the three patients with hemiplegia was 1.73 ± 0.17 which, although less than the score for the algodystrophy patients, was not significantly different. It was however, significantly greater than the score for the control group (p < 0.0001).

Using linear regression analysis there was a good correlation between the metacarpal score and the bone mineral density of trabecular bone (BMD_{trab}) defined in the previous chapter (Fig 20.2). This was not apparent when the metacarpal score was compared with $BMD_{cort}(R = -0.36)$, combined cortical width (R = -0.18) or radiographic score (R = 0.24).

ROC analysis of the metacarpal score (Fig 20.3) demonstrated that it was of less discriminant value than dolorimetry (Fig 17.2). At a metacarpal score of 1.3, the positive predictive value was maximal (88%) with a sensitivity of 91% and specificity of 82%. This meant that 39 of the 43 algodystrophy patients were positively identified with only one of 10 controls falsely identified.
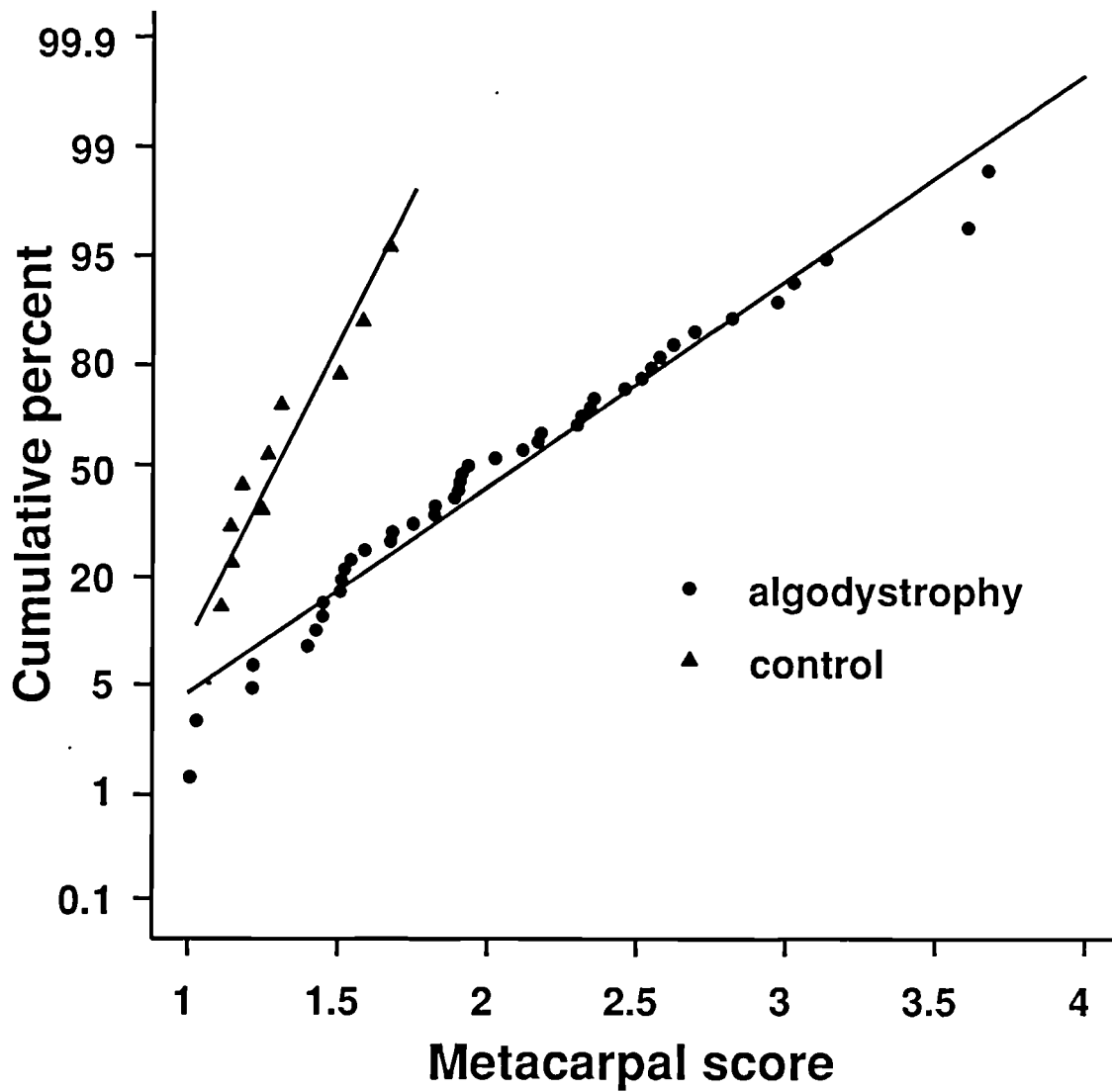
Fig 20.1. The distribution of the metacarpal scores was examined using Probit analysis in 43 algodystrophy, and 10 control patients who had a Colles' fracture but no evidence of algodystrophy. The values in both groups were normally distributed with the score in control patients occupying the lower end of the range.

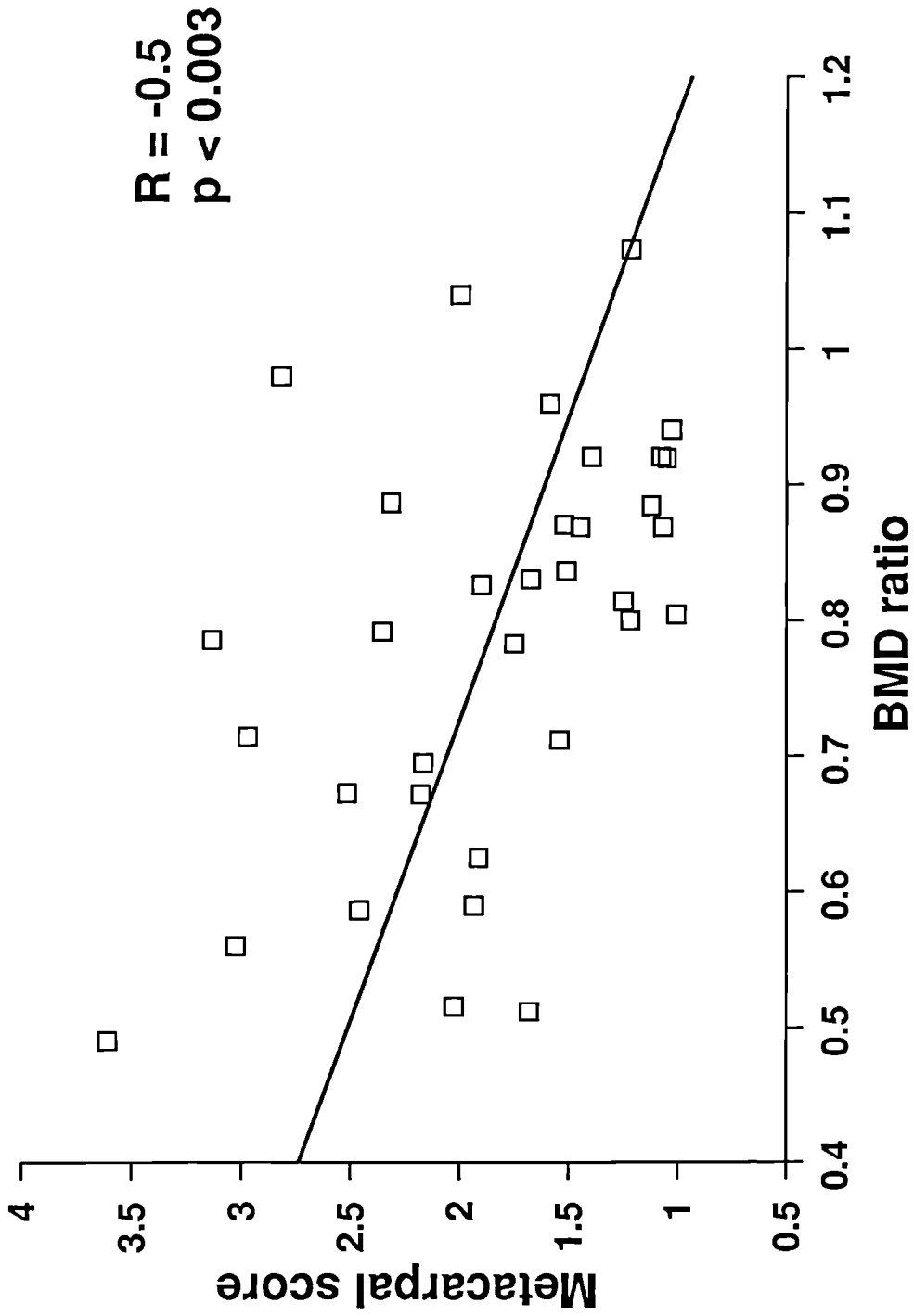R = -0.5
p < 0.003

Metacarpal score

BMD ratio

Fig 20.2. There was a significant correlation between the metacarpal score and distal bone mineral density (BMD) in the 33 patients who had both measurements performed.
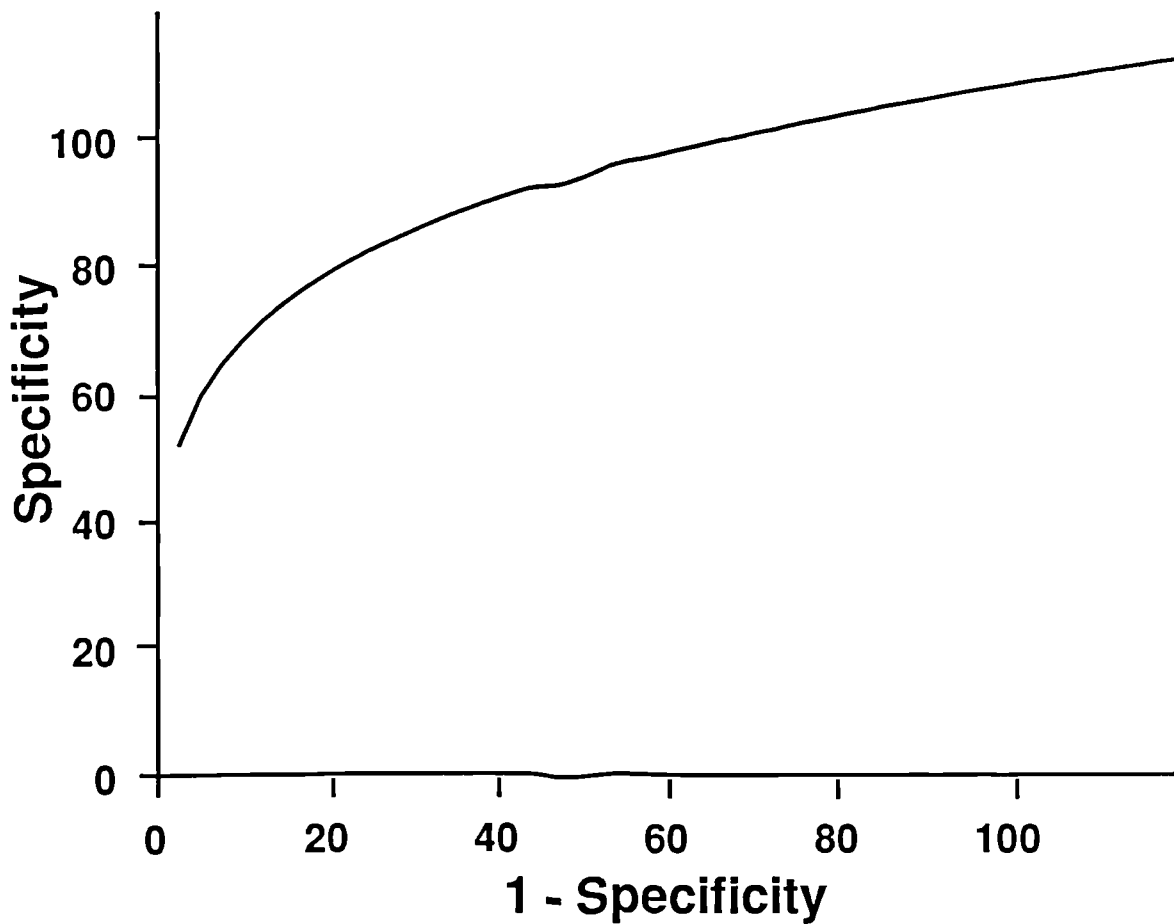
Fig 20.3. The ability of the isotope metacarpal score to identify patients with algodystrophy was analysed by ROC analysis in 43 patients with algodystrophy and 10 controls. Though of more discriminant value than radiographic scores or photon absorptiometry indices, the metacarpal score was still of less value than dolorimetry.

<u>Discussion.</u>

This study has shown that the increase in uptake of Technetium in disuse atrophy following trauma is significantly less than that in post-traumatic algodystrophy and demonstrates that isotope scans can identify post-traumatic algodystrophy at an earlier stage than we had previously reported (Atkins *et al* 1990).

Isotope scanning was of more discriminant value than the radiographic score, which had a positive predictive value of 83%, and consequently was a more useful investigation for the diagnosis of algodystrophy than radiography or photon absorptiometry. A cut off value of 1.3 gave the maximal predictive value (88%) which is nevertheless short of 100%. Therefore isotope scanning alone cannot be used to diagnose algodystrophy nor screen a population, but it can provide an adjunct to diagnosis alongside other clinical indices particularly in the early stages of the condition.

The early images may be of use in differentiating disuse from algodystrophy, as in only four of the 10 control patients was there any detectable increase in the vascular phase. Originally, there was some confusion as to the significance of the early images in algodystrophy as the response was often variable (Mackinnon and Holder 1984). Desai and Intenzo (1984) however, have demonstrated the reactional hyperaemia following tourniquet release would account for a spuriously high uptake in the unaffected limb, if, as is usually the case, the injection was given in this limb. In this study an intravenous cannula was inserted without the use of a tourniquet thus removing this source of error. Vascular instability is one of the criteria for the diagnosis of algodystrophy and in the early stages of the disease is usually red and warm (Chapter 15). The increased uptake in the blood pool phase, which indicates a generalised increase in blood flow, is therefore reflected in the clinical picture. In four control patients there was also an increase in blood flow but this was not

complemented by an increase in the delayed phase indicating an increase in bone

metabolic activity.

The degree of uptake in the CVA patients was rather surprising considering

there was no evidence of algodystrophy. The degree of uptake however, probably

represents the maximal uptake possible in the hand due to immobility alone and as

such emphasizes the scintigraphic abnormalities seen in disuse. The scans were

performed seven weeks following a CVA, and therefore the period of immobilisation, if

anything, was greater than in our patients with algodystrophy, but despite this, the

degree of uptake is still more marked in the algodystrophy group (2.06 ± 0.10), though

not significantly. It should also be noted that although the algodystrophy patients will

have stiffness and swelling of the hand, the joints are by no means completely immobile

and patients were encouraged to actively mobilise their fingers both during

immobilisation and after cast removal. In addition the algodystrophy group includes

patients with a milder disease process than is typically envisaged by the early

descriptions of Sudeck's atrophy. There is therefore an as yet undefined factor in

algodystrophy which results in the more marked uptake of isotope seen in excess of

disuse.

There was a significant correlation between the trabecular bone mineral density

and metacarpal score which suggests that they may have been causally related. The

loss in bone density was likely to be due to an increase in osteoclast activity and

therefore bone resorption. This is coupled with an imbalanced increase in bone

formation resulting in an increase in the uptake of Technetium but a net loss of bone.

The cause of the increased bone turnover, although in some way related to increased

blood flow is unknown. Burkhart and Jowsey (1967) found that excessive bone

resorption failed to develop in rats following parathyroidectomy, even though complete

immobilisation and secondary hypervascularity of the extremity was induced. They

concluded that circulating parathyroid hormone is the essential effector in disuse

atrophy and local factors such as hyperaemia induce greater sensitivity to the

circulating hormones in the immobilised part. It is interesting to note that in one of the

control patients, who proved to have primary hyperparathyroidism, there was an

unusually high radiographic score and low BMD. This patient was excluded from the

main study group. It may be therefore that the skeletal effects of algodystrophy are

simply a consequence of an alteration in local blood flow.

CHAPTER 21: BIOCHEMICAL FEATURES

Traditionally one of the hall-marks of algodystrophy has been the absence of any measurable biochemical changes in bone metabolism. This is not surprising considering the regional nature of the condition. There have been recent reports however, notably by Eisinger *et al.* (1974) and Schiano *et al.* (1976), claiming changes in the rates of bone resorption and formation which alter as the disease progresses. Unfortunately, other authors have not been able to report these findings in as consistent a fashion. In addition, the normal metabolic response to trauma may hamper use of the parameters of bone turnover as a diagnostic aid in post-traumatic algodystrophy.

The aim of this study was therefore firstly to determine the effect of algodystrophy, a regional osteoporosis, on systemic skeletal homeostasis. Secondly, if there were any systemic markers of bone metabolism, their ability to differentiate post-traumatic algodystrophy from disuse.

Methods.

Forty seven patients with algodystrophy and 29 control patients with a Colles' fracture but no evidence of algodystrophy were examined 2 weeks out of plaster. The biochemical parameters measured were corrected serum calcium, parathyroid hormone (PTH), serum alkaline phosphatase and osteocalcin (markers of bone formation) and urinary calcium and hydroxyproline (markers of bone resorption); the measurement techniques have been detailed in Chapter 13. The statistical analysis was the same as in previous chapters.

<u>Results.</u>

Both groups were matched for age and sex (Table 21.1.). There was a significant

difference in the osteocalcin between the two groups (p < 0.0002; Table 21.1) at

presentation but this was not matched with a similar difference in alkaline

phosphatase, the other marker of bone formation. There was no correlation with

between the alkaline phosphatase and osteocalcin using simple regression analysis.

Table 21.1. Biochemical parameters (mean ± SEM) at presentation. The only

significant difference between the algodystrophy and control group two weeks after

removal of plaster, was a lower osteocalcin. The normal ranges shown are the

laboratory reference range.

	Algodystrophy	Control	Normal range
Age (years)	64.2 ± 1.5	64.4 ± 1.9	
Sex (F:M)	39:8	27:2	
Serum calcium (mmol/l)	2.43 ± 0.01	2.43 ± 0.02	2.12 - 2.63
Serum phosphate (mmol/l)	1.05 ± 0.01	1.05 ± 0.01	0.60 - 1.50
Creatinine (umol/l)	82.0 ± 2.1	81.2 ± 2.4	60 - 120
Parathyroid hormone (pg/l)	51.4 ± 2.4	51.4 ± 2.5	30 -130
Alkaline phosphatase (IU/l)	93.5 ± 7.4	91.4 ± 4.0	35 - 105
Osteocalcin (ng/ml)	5.09 ±0.60*	11.43 ± 1.69	8 - 36
Urinary calcium mol/ mol creatinine	0.28 ± 0.03	0.32 ± 0.03	<0.4
Urinary hydroxyproline mmol/ mol creatinine	28.3 + 2.1	28.8 + 3.1	< 30

* - p < 0.0002.

Although both the urinary calcium and hydroxyproline levels were at the upper

limit of normal (Table 21.1), there was no significant difference between the two groups.

The urinary calcium/creatinine did however, correlate well with urinary hydroxyproline

in the algodystrophy group (R = 0.39; p < 0.007), unlike the control group (R = 0.25; p >

0.05). There appeared to be no correlation between the urinary

hydroxyproline/creatinine and alkaline phosphatase in either group (algodystrophy R =

0.14; control R = 0.12).

In both groups, the serum calcium was maintained well within the normal range

with a normal PTH level. There was no correlation between the PTH and osteocalcin as

might be expected if there was an increase in bone formation.

ROC analysis was performed on the only significant biochemical parameter,

serum osteocalcin. The calculated maximal predictive value was 84% at a level of 4

ng/ml or less but this was mainly due to a high specificity (75%). The sensitivity at this

level was only 36% and correspondingly, the ROC curve was only marginally better than
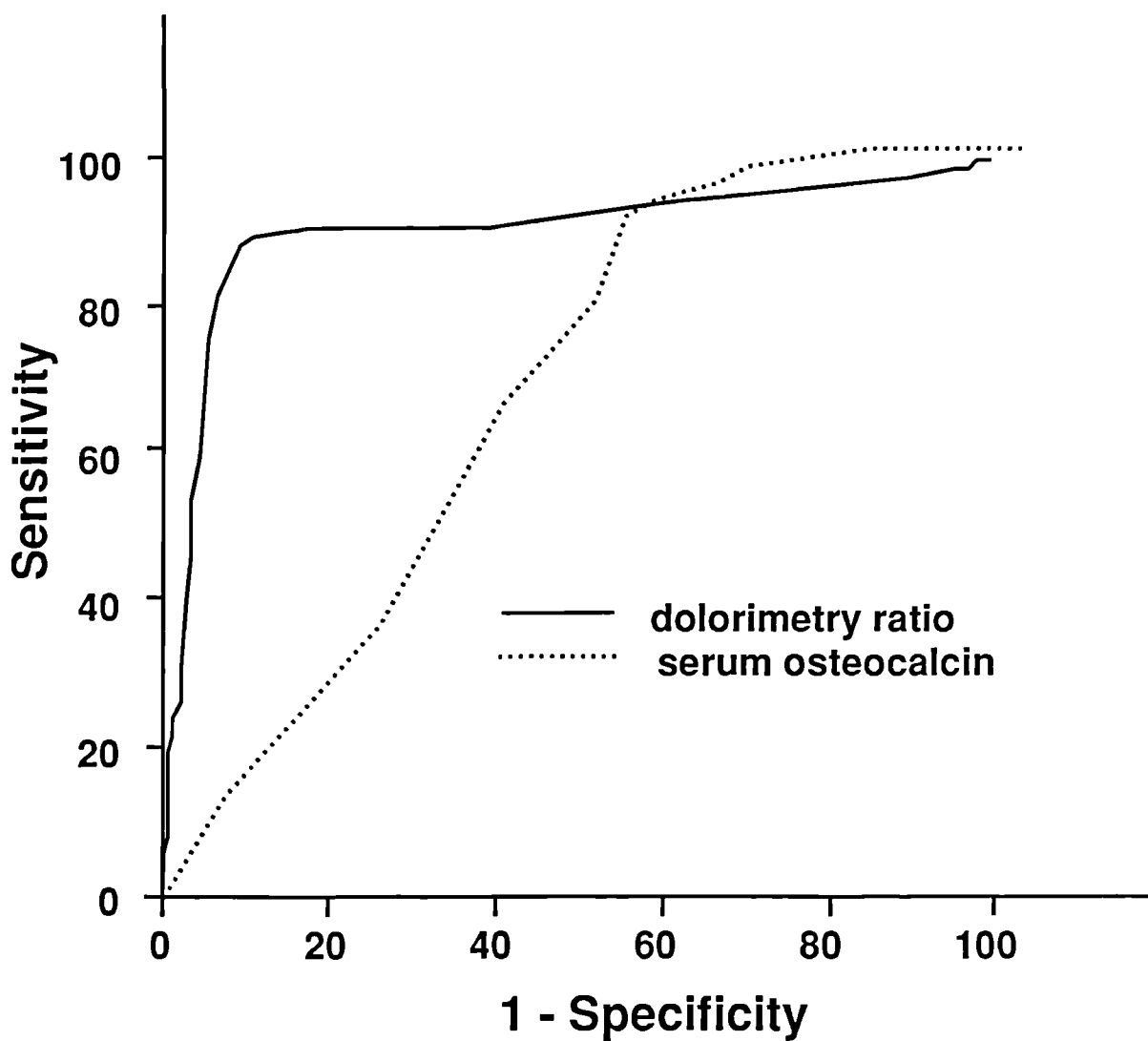
that of no discriminant value (Fig 21.1).

Fig 21.1. The ability of the serum osteocalcin to identify patients with algodystrophy was analysed using ROC analysis on 47 algodystrophy anf 29 control patients. The measurement of serum osteocalcin was of minimal discriminant value and of less value than the measurement of finger tenderness by dolorimetry.

Discussion.

Eisinger in 1967, reported significant increases in urine hydroxyproline, a marker of bone resorption, in eight cases of algodystrophy. He elaborated on these findings in a later study (Eisinger *et al.* 1974) on 67 patients demonstrating hydroxyprolinuria in the early stage of the disease, gradually falling to within the normal range as the disease entered it's latter stages. The main criticism of this paper is that increased bone resorption occurs secondary to immobilisation alone, and therefore the changes they observed may have been due to this rather than the algodystrophic process. In addition, the site and precipitating cause of the algodystrophy was variable. It is perhaps not surprising therefore that the results of the present study differ considerably from that of Eisinger *et al.* (1974). In both groups the urinary calcium and hydroxyproline were at the upper limit of normal as one would expect following immobilisation, but there was no evidence of a greater increase in bone resorption in algodystrophy.

In the absence of any difference in renal function between the two groups (Table 21.1), the significant decrease in osteocalcin in the algodystrophy group does indicate a reduction in bone formation. This was not mirrored by a similar decrease in alkaline phophatase which is also a marker of bone formation though not bone specific. This decrease in formation at a local rather than skeletal level was not sufficient to cause an alteration in serum or urine calcium and consequently there was no change in PTH. This local decrease may also account for the absence of any change in the serum alkaline phosphatase. The imbalance in bone turnover in algodystrophy would lead to a net loss of bone mineral which explains the significantly greater decrease in the bone mineral density in cortical and trabecular bone (Chapter 19) at the same time following fracture. It would be of interest to monitor the progression of bone formation, as measured by serum osteocalcin, and the recovery of bone mass. This will be addressed in a later chapter.

NATURAL HISTORY.

CHAPTER 22: CHANGES IN CLINICAL FEATURES

The late sequelae of algodystrophy, chronic causalgic pain, atrophy and stiffness, are well documented but occur relatively infrequently following trauma, accounting for the 1-2% incidence quoted in the English literature (Bacorn and Kurtzke 1953; Plewes 1956; Lidström 1959; Frykman 1967; Pool 1973; Stewart et al. 1984). The discrepancy between this incidence and the 28% found in this study (Chapter 15) was probably due to the identification of a milder form of the condition which was not documented in the retrospective studies. The clinical significance of this milder condition however, is unclear. There are no prospective studies examining the local clinical response to trauma, in particular with regard to the development of pain and tenderness, vascular instability, swelling and stiffness, the fundamental clinical features of algodystrophy. The time period over which these symptoms progress and resolve and the degree of morbidity associated with them remains unknown. The lack of knowledge of the early natural history has particular implications with regard to the evaluation of therapeutic measures aimed at preventing or speeding recovery of the condition. In view of the fact that there is such a large discrepancy between the quoted incidence and the incidence in this study, a large proportion of the cases must resolve spontaneously. A failure to recognise this fact may lead to falsely attributing the resolution of the condition to the therapeutic intervention.

In order to study the resolution post-traumatic algodystrophy and define the morbidity it causes, the clinical progression of algodystrophy following Colles' fracture was evaluated using the techniques described in previous chapters.

Methods.

The clinical techniques used to identify pain and tenderness, vascular instability, swelling and stiffness, the four basic features of algodystrophy, have been

described in detail in Chapter 9. They were based on dolorimetry, the measurement of .

hand volume, and direct questioning. In addition, a functional assessment of the

degree of morbidity was made using measurements of grip strength which were

incorporated into a functional scoring system, again described in Chapter 9 (Table 9.3).

The scoring system was based on patients complaints, ability to do everyday tasks,

signs and symptoms, and cosmesis. They were first reviewed two weeks after plaster

removal and then at monthly intervals upto a maximum of six months in patients with

no algodystrophy. Patients with algodystrophy were reviewed monthly until their

symptoms resolved or when they declined any further visits.

The statistical analysis used was the same as in previous chapters with the

addition of actuarial analysis to study the progression in various features of the disease.

This took into account patients withdrawing from the study because the feature

resolved or they were lost to follow-up. Life-tables were calculated using the Kaplan-

Meier technique and the difference between survival curves assessed using Gehan's

method which is a modification of the Wilcoxin Rank test.

Results.

Two hundred and seventy four patients were studied prospectively of whom 77

had pain and tenderness, vascular instability, swelling and stiffness and were thus

considered to have algodystrophy. Of the remaining 197 patients, 72 were considered

to be a borderline group displaying some of the features and 125 had no features.

Pain and tenderness. The significant difference in the dolorimetry scores (ANOVA p <

0.0001) between the three groups at presentation, seven weeks after fracture, (Fig 22.1)

has previously been shown (Chapter 16). There was however a gradual resolution in

finger tenderness such that the difference between the borderline group and those with

no features of the disease had become insignificant by 19 weeks after the fracture.
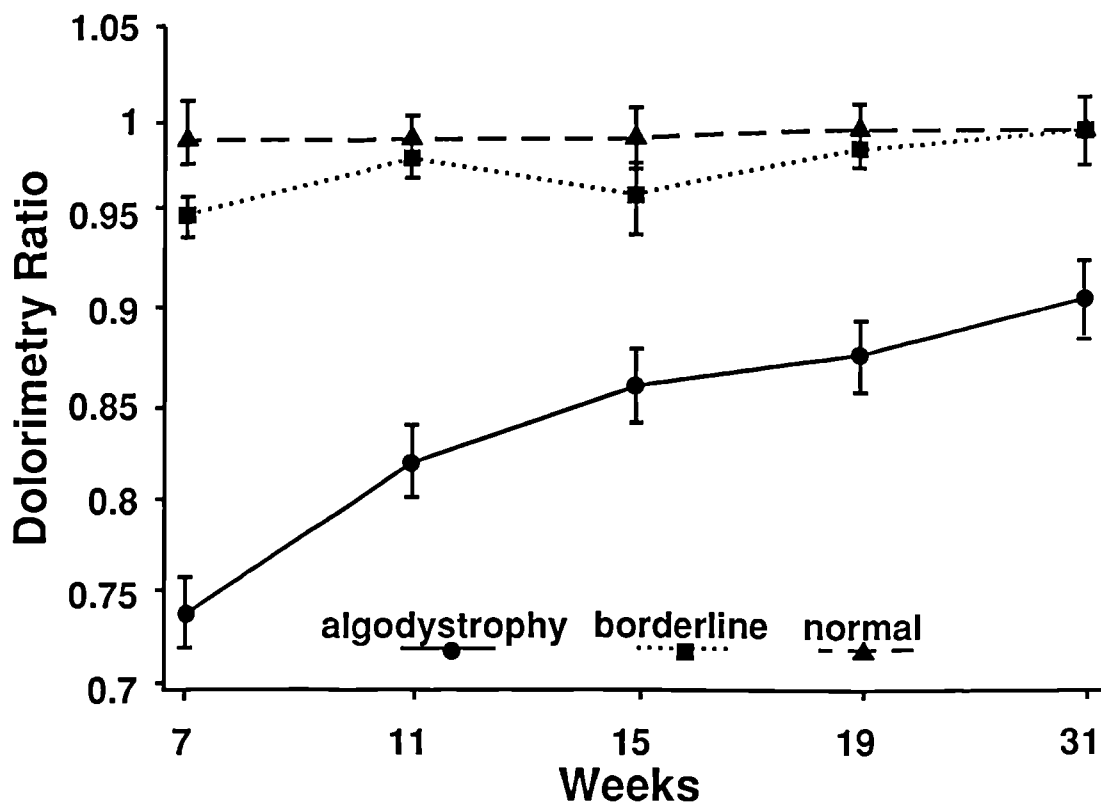
Fig 22.1. The mean (+/- SEM) dolorimetry ratio was recorded in 274 patients
with a Colles' fracture divided into algodystrophy, borderline and control
groups. The dolorimetry ratio remained significantly lower in the algodystrophy
group and was below the normal range (0.92 - 1.08) at 31 weeks after fracture.
Although initially significantly lower, the dolorimetry ratio in the borderline
group were indistinguishable from controls by 11 weeks after fracture.

The same was true of the algodystrophy group but the dolorimetry score remained significantly lower than the other two groups such that at 31 weeks after the fracture, it was still below the normal range (0.92-1.08).

Kaplan-Meier life tables were calculated for the algodystrophy (Table 22.1) and borderline groups (Table 22.2) to examine the resolution of abnormal finger tenderness between the two groups as only 16 of the 72 patients in the borderline group had abnormally low dolorimetry scores. A patient was deemed to have resolved when the dolorimetry score was within the normal range. The internal probability was the percentage probability of patients entering that interval surviving to the end and the conditional probability was the percentage probability of those entering the study surviving to the end of the interval. The variance was that of the conditional probability.

In the borderline group there was a 12.5% probability that patients, entering the study with an abnormal dolorimetry score, would have abnormal dolorimetry at to 31 weeks, with 50% resolving by 15 weeks. By comparison, there was a 50% probability that algodystrophy patients would have abnormally tender fingers at 31 weeks, with only 23% resolving by 15 weeks. Indeed, at one year there were still two patients with low dolorimetry scores. A comparison of the survival curves (Fig 22.2) demonstrated a significant difference (p < 0.03) in the rate of resolution of tenderness between the borderline and algodystrophy group.

Pain appeared to resolve quicker than tenderness in both groups. In patients with algodystrophy, there was a 25% probability that pain would persist to 31 weeks in those who initially complained of painful fingers (Table 22.3), with 40% of patients resolving by 15 weeks. In the borderline group, only 17 patients complained of pain, with the majority resolving by 15 weeks (Table 22.4). There was only one patient complaining of painful fingers in this group after 23 weeks. Although pain settled in the borderline group at a faster rate and lasted a shorter duration, there was no

significant difference between the slopes (Fig 22.3).

Table 22.1. Kaplan-Meier life table for the continuation of algodystrophy patients with abnormal dolorimetry scores.

Interval (weeks after fracture)	At risk	Resolved	Lost	Int. prob (%)	Cond. prob (%)	Variance
8-9	77	2	0	97.3	97.3	0.0004
9-10	75	3	0	95.8	93.2	0.0009
10-11	72	3	2	97.1	90.5	0.0012
11-15	67	9	1	86.4	77.0	0.0024
15-19	57	6	0	89.1	68.9	0.0029
19-23	51	6	14	88.2	60.8	0.0032
23-27	31	3	3	90.3	54.9	0.0037
27-31	25	2	0	92.0	50.5	0.0040
31-35	23	8	2	65.2	33.0	0.0042
35-39	13	1	0	92.3	30.4	0.0042
39-43	12	2	0	83.3	25.4	0.0040
43-47	10	2	0	80.0	20.3	0.0036
47-51	8	1	2	87.5	17.8	0.0033
51-55	5	2	1	60.0	10.7	0.0027
55-55	2	0	0	100	10.7	0.0027

Int. prob. - internal probability

Cond. prob. - conditional probability.

Table 22.2. Kaplan-Meier life table for the continuation of borderline patients with abnormal dolorimetry scores.

Interval (weeks after fracture)	At risk	Resolved	Lost	Int. prob (%)	Cond. prob (%)	Variance
11-15	16	8	0	50.0	50.0	0.0156
15-19	8	2	0	75.0	37.5	0.0146
19-27	6	2	2	66.7	25.0	0.0117
27-31	2	1	0	50.0	12.5	0.0107
31-31	1	0	0	100	12.5	0.0107

Int. prob. - internal probability
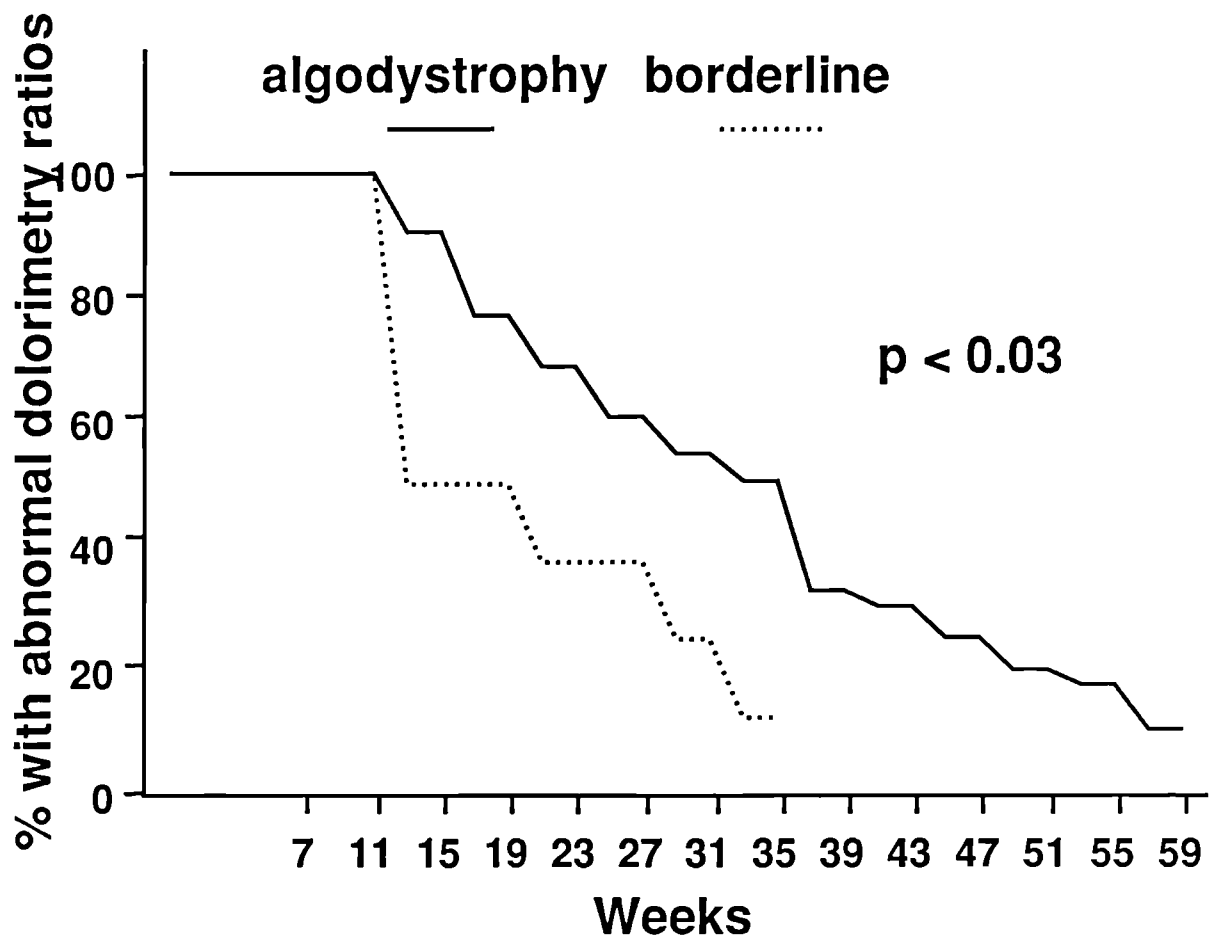
Cond. prob. - conditional probability.

Fig 22.2. Actuarial analysis was performed on the 77 algodystrophy and 16 borderline patients who had abnormally low dolorimetry ratios at presentation. There was a rapid and significant resolution in the number of patients with abnormally tender fingers.

Table 22.3. Kaplan-Meier life table for the survival of algodystrophy patients with abnormal pain in the hand.

Interval (weeks after fracture)	At risk	Resolved	Lost	Int. prob (%)	Cond. prob (%)	Variance
8-9	77	8	0	89.2	89.2	0.0012
9-10	69	7	0	89.4	79.7	0.0022
10-11	62	5	2	91.5	73.0	0.0027
11-15	55	9	1	83.3	60.8	0.0032
15-19	45	5	0	88.9	54.1	0.0034
19-23	40	11	3	72.5	39.2	0.0032
23-27	26	6	1	76.9	30.2	0.0030
27-31	19	3	0	84.2	25.4	0.0027
31-35	16	3	3	81.3	20.6	0.0024
35-55	10	3	7	70.0	14.4	0.0021

Int. prob. - internal probability

Cond. prob. - conditional probability.

Table 22.4. Kaplan-Meier life table for the continuation of borderline patients with

abnormal pain in the hand.

Interval (weeks after fracture)	At risk	Resolved	Lost	Int. prob (%)	Cond. prob (%)	Variance
11-15	17	11	0	35.3	35.3	0.0134
15-19	6	1	0	83.3	29.4	0.0122
19-23	5	2	2	60.0	17.7	0.0085
23-23	1	0	0	100	17.7	0.0085

Int. prob. - internal probability

Cond. prob. - conditional probability.

Fig 22.3. Actuarial analysis was performed on the 77 algodystrophy and 17 borderline patients who had pain in the hand at presentation. Although not significant, the pain resolved more rapidly in the borderline group.

Vascular Instability. Symptoms of vascular instability were slower to resolve than

tenderness resulting in a 29% probability that symptoms would persist one year after

the fracture. In particular, resolution early in the course of the condition was slow

(Table 22.5) with 91% of patients persisting with symptoms of vascular instability at 15

weeks compared to 77% with tenderness. By 31 weeks after fracture the respective %

probabilities were more comparable (vascular instability - 61%; tenderness - 51%).

There therefore appeared to be a more gradual resolution in the symptoms of vascular

instability compared with tenderness.

Over half the patients in the borderline group complained of vascular instability

(Table 22.6). There was a rapid decrease in symptoms by 15 weeks with only 45%

persisting, far less than the algodystrophy group (91%). By 31 weeks there were no

patients complaining of vascular instability in the borderline group. The rapid

resolution of this symptom resulted in a significant difference (p < 0.0001) between the

actuarial curves (Fig 22.4).

Table 22.5. Kaplan-Meier life table for the continuation of algodystrophy patients with ·

symptoms of vascular instability in the hand.

Interval (weeks after fracture)	At risk	Resolved	Lost	Int. prob (%)	Cond. prob (%)	Variance
8-9	77	1	0	98.7	98.7	0.0002
9-10	76	6	2	97.3	96.0	0.0005
10-11	74	2	2	97.2	93.2	0.0009
11-15	70	2	1	97.1	90.5	0.0012
15-19	67	4	0	94.03	85.1	0.0017
19-23	63	10	10	84.1	71.6	0.0027
23-27	43	4	3	90.7	65.0	0.0033
27-31	36	2	0	94.4	61.4	0.0035
31-35	34	8	5	76.5	46.9	0.0041
35-39	21	2	4	90.5	42.5	0.0042
39-43	15	2	2	86.7	36.8	0.0046
43-47	11	1	2	90.9	33.4	0.0048
47-55	8	1	5	87.5	29.3	0.0052
55-55	2	0	0	100	29.26	0.0052

Int. prob. - internal probability

Cond. prob. - conditional probability.

Table 22.6. Kaplan-Meier life table for the continuation of borderline patients with

symptoms of vascular instability in the hand.

Interval (weeks after fracture)	At risk	Resolved	Lost	Int. prob (%)	Cond. prob (%)	Variance
11-15	38	21	1	44.7	44.7	0.0065
15-19	16	1	0	93.8	41.9	0.0065
19-27	15	7	5	53.3	22.4	0.0048
27-31	3	1	2	66.7	14.9	0.0058

Int. prob. - internal probability

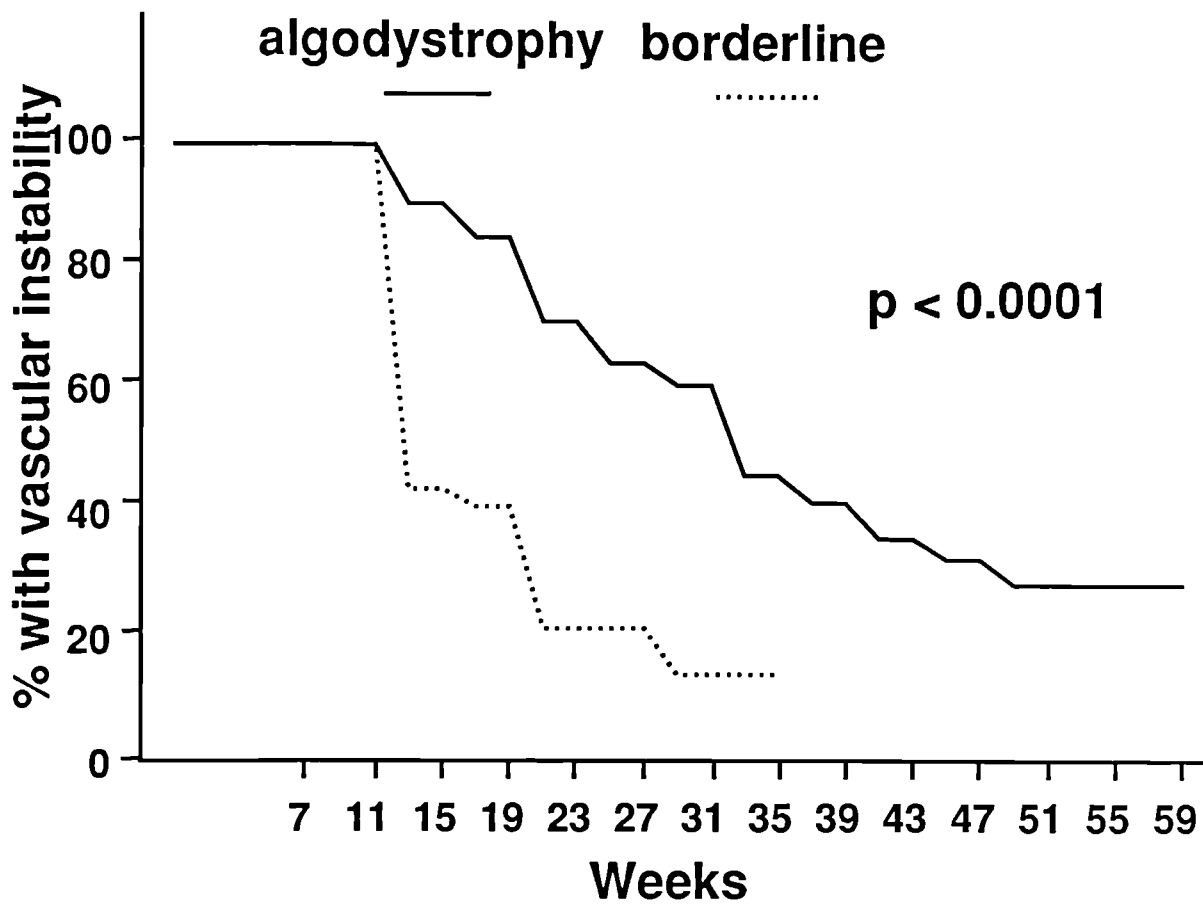Cond. prob. - conditional probability.

Fig 22.4. Actuarial analysis was performed on the 77 algodystrophy and 38 borderline patients who had vascular instability at presentation. There was a significant difference in the rate of resolution between the groups with vascular instability persisting in 30% at one year in those with algodystrophy.

There was no change in the type of vascular instability described by the patients. with algodystrophy. The warm, hot hand predominated and, at least upto 26 weeks after fracture, there did not appear to be a transition to the cold, blue hand described in the later stages of the condition (Table 22.7).

Table 22.7. Vascular instability was defined as an alteration in colour or temperature of the hand as experienced by the patient. The change in colour was categorized into a red or blue hand and temperature into a hot or cold hand. The percentage distribution of change in colour and temperature are given in time points upto 31 weeks after fracture. There was no difference in the proportions of red/blue or hot/cold hands for the duration of the study.

Weeks after fracture	Alteration in colour		Alteration in temperature	
	% Red	% Blue	% Hot	% Cold
7	78	22	93	7
11	84	16	96	4
15	76	24	90	4
19	77	23	88	12
31	91	9	90	10

Hand swelling. There was a significant difference in mean hand volume between the algodystrophy, borderline and normal patients at first presentation (ANOVA p < 0.0001), 7 weeks after fracture. This difference was due to the larger hand volume in the algodystrophy group, there was no difference between the borderline and normal patients (Fig 22.5). The greater hand volume in the algodystrophy group gradually resolved such that at 15 weeks after fracture, there was no difference in volume between any of the groups. Hand volume in the patients with algodystrophy continued to decrease steadily until, at 31 weeks after fracture, the volume was significantly less than the other two groups (ANOVA p < 0.02). At no point was there any difference in hand volume between the borderline and normal group, nor was there any obvious trend in change in volume as shown in the algodystrophy group.

Kaplan-Meier life tables were also calculated for the patients perception of swelling of the hand. There were 44 (62%) patients who complained of swelling in the borderline group. The degree of swelling was minimal however as there was no detectable difference in hand volume between this and the normal group who had no symptoms of hand swelling. Indeed the probability of the swelling persisting at 15 weeks after the fracture in the borderline group was only 20% (Table 22.9), the number complaining having fallen to nine. There was no further follow-up on those patients with swelling after 19 weeks.

In contrast, in the patients with algodystrophy there was a gradual decline in the number complaining of swelling and only two were still symptomatic at one year after the fracture. The probability of the symptom persisting to 15 weeks after the fracture was 87% (Table 22.8), greater than the probability at the same time point in the borderline group. There was consequently a significant difference between the survival curves (Fig 22.6; p < 0.0001).
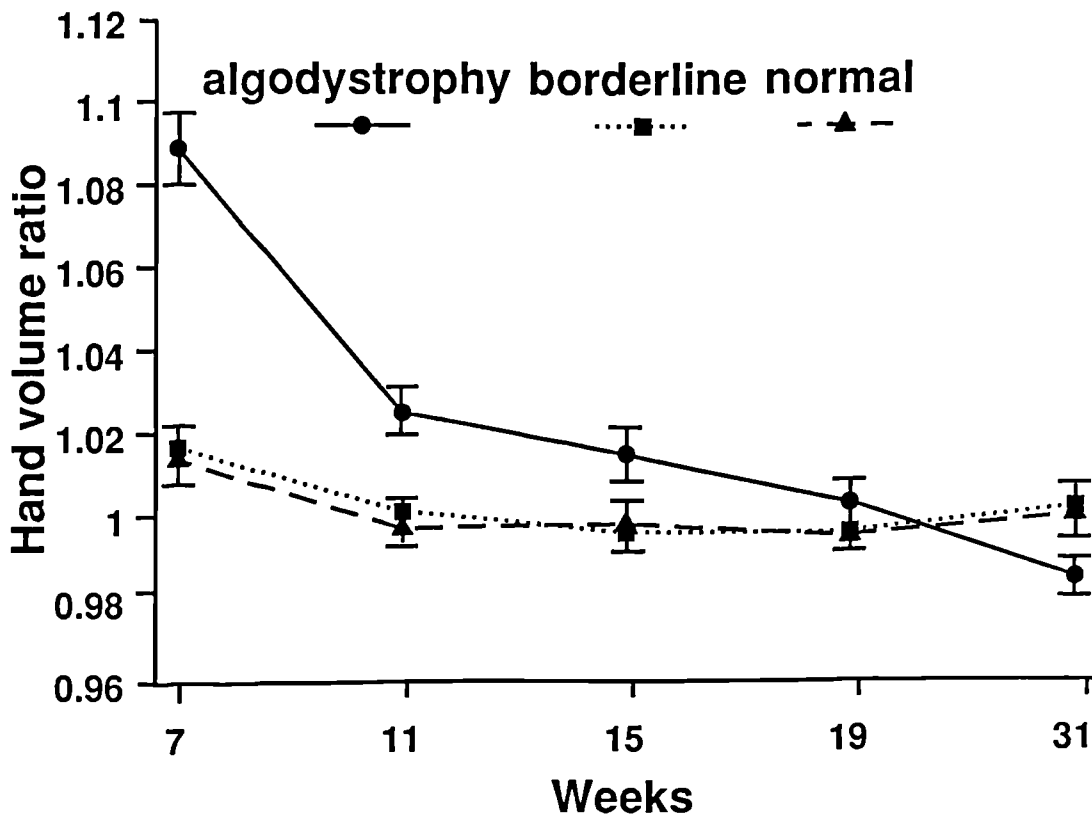
Fig 22.5. The mean (+/- SEM) hand volume ratio was recorded in 274 patients
with a Colles' fracture divided into algodystrophy, borderline and control
groups. The hand volume ratio was significantly greater in the patients with
algodystrophy upto 19 weeks after fracture. Following this the mean hand volume
ratio was significantly lower than the borderline or control groups. A smaller
hand was consistant with the atrophic appearance of the hand which is seen in
the later stages of algodystrophy.

Table 22.8. Kaplan-Meier life table for the persistence of hand swelling in patients with algodystrophy.

Interval (weeks after fracture)	At risk	Resolved	Lost	Int. prob (%)	Cond. prob (%)	Variance
8-10	77	2	0	97.3	97.3	0.0004
10-11	75	2	2	97.2	94.6	0.0007
11-15	71	6	1	91.4	86.5	0.0016
15-19	64	14	0	78.1	67.6	0.0030
19-23	50	14	0	72.0	48.7	0.0034
23-27	28	7	1	75.0	36.5	0.0035
27-31	20	4	0	80.0	29.2	0.0033
31-35	16	8	3	50.0	14.6	0.0022
35-51	5	1	2	80.0	11.7	0.0021
51-51	2	0	0	100	11.7	0.0021

Int. prob. - internal probability

Cond. prob. - conditional probability.

Table 22.9. Kaplan-Meier life table for the persistence of hand swelling in the

borderline patients.

Interval (weeks after fracture)	At risk	Resolved	Lost	Int. prob (%)	Cond. prob (%)	Variance
11-15	44	35	0	20.5	20.5	0.0037
15-19	9	4	0	55.6	11.4	0.0023
19-19	5	0	0	100	11.4	0.0023

Int. prob. - internal probability

Cond. prob. - conditional probability.
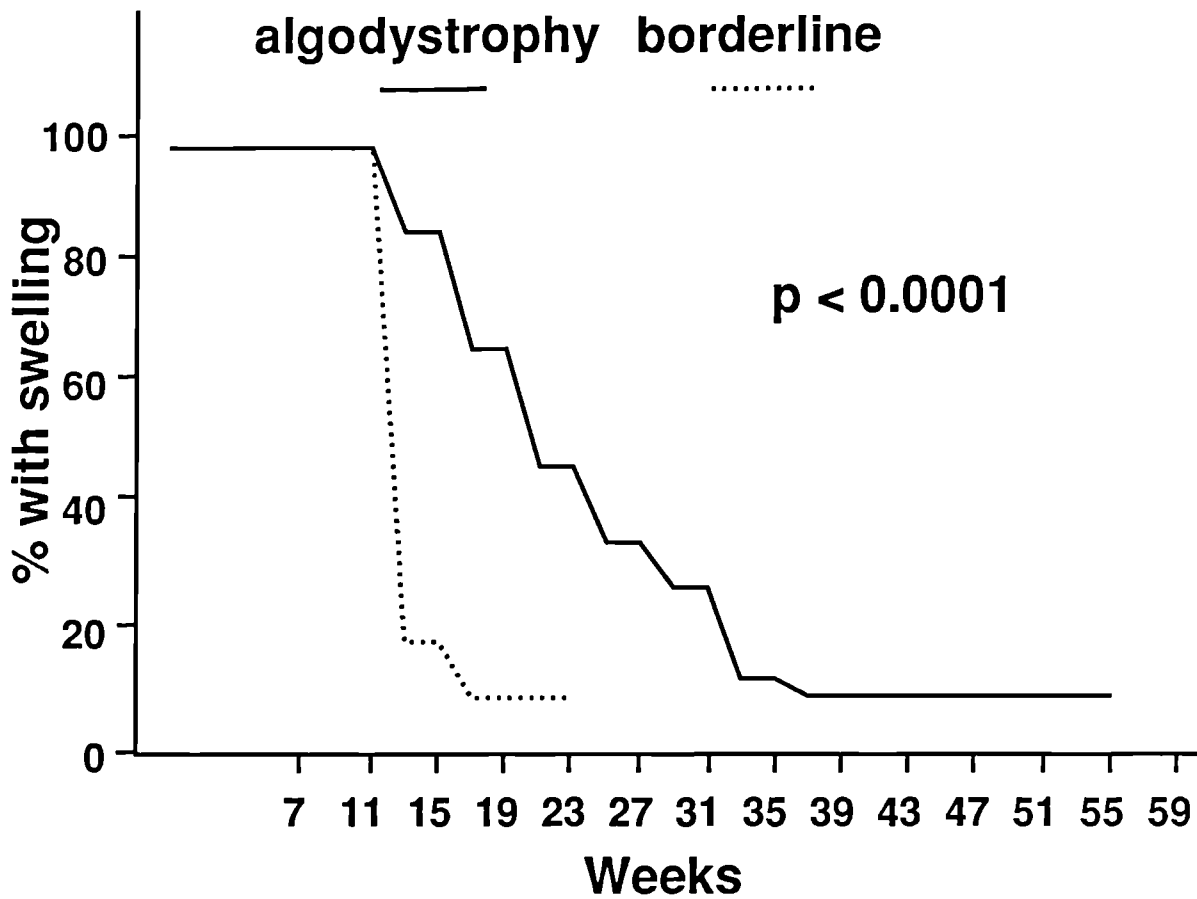
Fig 22.6. Actuarial analysis was performed on the 77 algodystrophy and 44 borderline patients who had hand swelling at presentation. There was a rapid and significant resolution in hand swelling in the borderline patients. Swelling resolved at a slower rate in the algodystrophy group with 11% still demonstrating the symptom one year after fracture.

Stiffness and function. A sensation of stiffness in the fingers was the most permanent feature of algodystrophy with a 66% probability of the symptom persisting for one year (Table 22.10), that is 25 of the original 77 patients still complained of stiff fingers. Although ranges of movement were not specifically measured, 14 of these patients also had clinical evidence of a limitation in movement, particularly fixed flexion deformities of the proximal inter-phalangeal joints. As with other features of the condition, there was a gradual decrease in the number of patients with stiffness, unlike the borderline group in whom stiffness resolved rapidly (Fig 22.7). Twenty-four patients complained of stiff fingers in the latter group, but only 11 remained stiff by 19 weeks (a 46% probability; Table 22.11).

Stiffness was therefore the most persistent of the four features of algodystrophy. To examine whether persistent stiffness was associated with the other features of algodystrophy or occurred at random, the patients examined at six months were divided into those with or without stiffness (Table 22.12). Of the 37 patients available, 28 (76%) complained of stiffness in their fingers. These patients also had significantly greater finger tenderness ($p < 0.03$) and weaker grips ($p < 0.05$). Although not significant, their hand volume was less than those patients with no evidence of stiffness which was similar to the earlier finding that patients with algodystrophy had a smaller hand volume six months after fracture than controls (Fig 22.5). There was no significant difference in the proportion of patients with vascular instability or swelling in patients with or with out stiffness.

Table 22.10. Kaplan-Meier life table for the persistence of finger stiffness in patients ·

with algodystrophy.

Interval (weeks after fracture)	At risk	Resolved	Lost	Int. prob (%)	Cond. prob (%)	Variance
9-10	77	2	0	97.3	97.3	0.0004
10-11	75	4	2	97.2	94.6	0.0010
11-15	69	2	1	97.1	89.2	0.0013
15-19	66	1	0	98.5	87.8	0.0014
19-23	65	6	14	90.8	79.7	0.0022
23-31	43	2	4	95.5	76.0	0.0026
31-35	37	1	5	97.3	74.0	0.0029
35-43	31	1	5	96.8	71.6	0.0033
43-50	25	2	23	92.0	65.6	0.0043

Int. prob. - internal probability

Cond. prob. - conditional probability.

Table 22.11. Kaplan-Meier life table for the persistence of finger stiffness in borderline.

patients.

Interval (weeks after fracture)	At risk	Resolved	Lost	Int. prob (%)	Cond. prob (%)	Variance
11-15	24	13	0	45.8	45.8	0.0103
15-19	11	3	0	72.7	33.3	0.0093
19-23	8	3	4	62.5	20.8	0.0069
23-23	10	0	0	100	20.8	0.0069

Int. prob. - internal probability

Cond. prob. - conditional probability.

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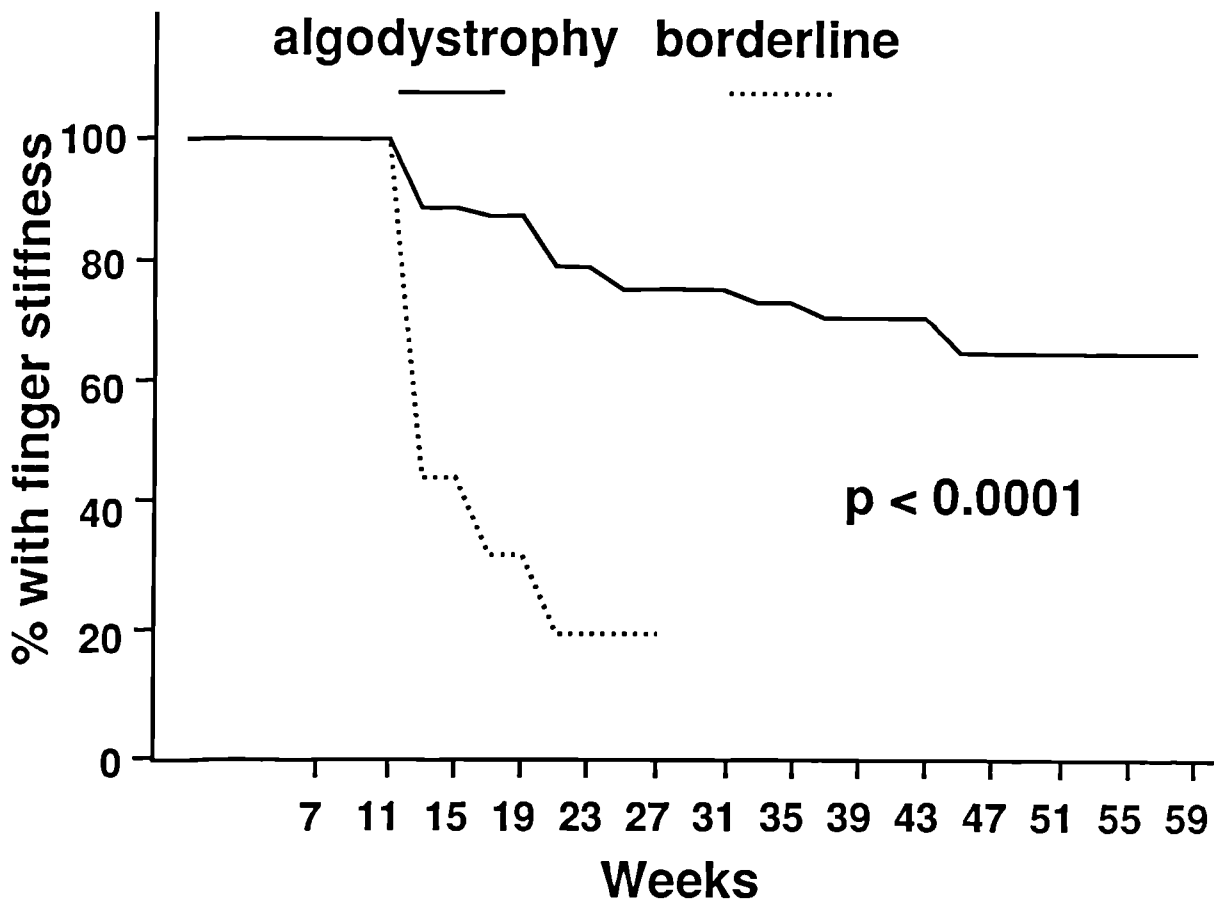
Fig 22.7. Actuarial analysis was performed on the 77 algodystrophy and 24 borderline patients who had hand stiffness at presentation. Stiffness quickly resolved in the borderline patients but remained a persistent problem in patients with algodystrophy. At one year, 65% of patients with algodystrophy continued to complain of a sensation of stiffness.

Table 22.12. The mean value (± SEM) of the dolorimetry, hand volume and grip

strength ratios and the proportion of patients with evidence of vascular instability and

hand swelling were calculated in patients with and without finger stiffness six months

after fracture. There was a significant difference in the dolorimetry and grip strength

ratios. Although not significant, the hand volume was reduced in the patients with

finger stiffness.

	Stiffness	No Stiffness	
Number of patients	28	9	
Dolorimetry ratio	0.88 ± 0.02	0.99 ± 0.01	**
Grip strength ratio	0.49 ± 0.04	0.64 ± 0.07	*
Hand volume ratio	0.98 ± 0.01	1.00 ± 0.01	NS
Vascular instability	15	2	NS
Hand swelling	7	1	NS

** $p < 0.03$; $p < 0.05$; NS not significant.

There are many reasons for a functional loss after immobilisation for a fracture ·
and it was not surprising to find a reduction in grip strength ratio (affected/unaffected
side) in the group with none (0.42 ± 0.03) or some of the features of algodystrophy (0.34
± 0.03) at presentation. The difference in grip strength between these two groups was
not significant. There was however, a significant difference between these groups and
patients with algodystrophy (0.20 ± 0.02; ANOVA p < 0.0001). There was a steady
improvement in grip strength in all groups (Fig 22.8) but the significant differences
between the algodystrophy and other two groups remained. By six months the grip
strength in the control population had almost reached parity (0.85 ± 0.03) but was still
approximately 50% reduced in the algodystrophy group (0.54 ± 0.03). Indeed at one
year, in five patients still being followed, the ratio was still reduced at 0.62 ± 0.05).

From the point of view of grip strength alone therefore there was a significant
reduction in functional ability in patients with algodystrophy. This was further
examined using a functional scoring system which takes into account loss of grip
strength (Chapter 9; Table 9.3). Thirty-seven patients with algodystrophy and 32
normal controls were picked at random and reviewed six months following their Colles'
fracture. There was no difference in the age, sex or duration of immobilisation between
the two groups (Table 22.13). In all three sections, complaints, function, and signs and
symptoms, there was a significant difference between the algodystrophy and control
groups. No attempt was made to categorize patients who had some but not all the
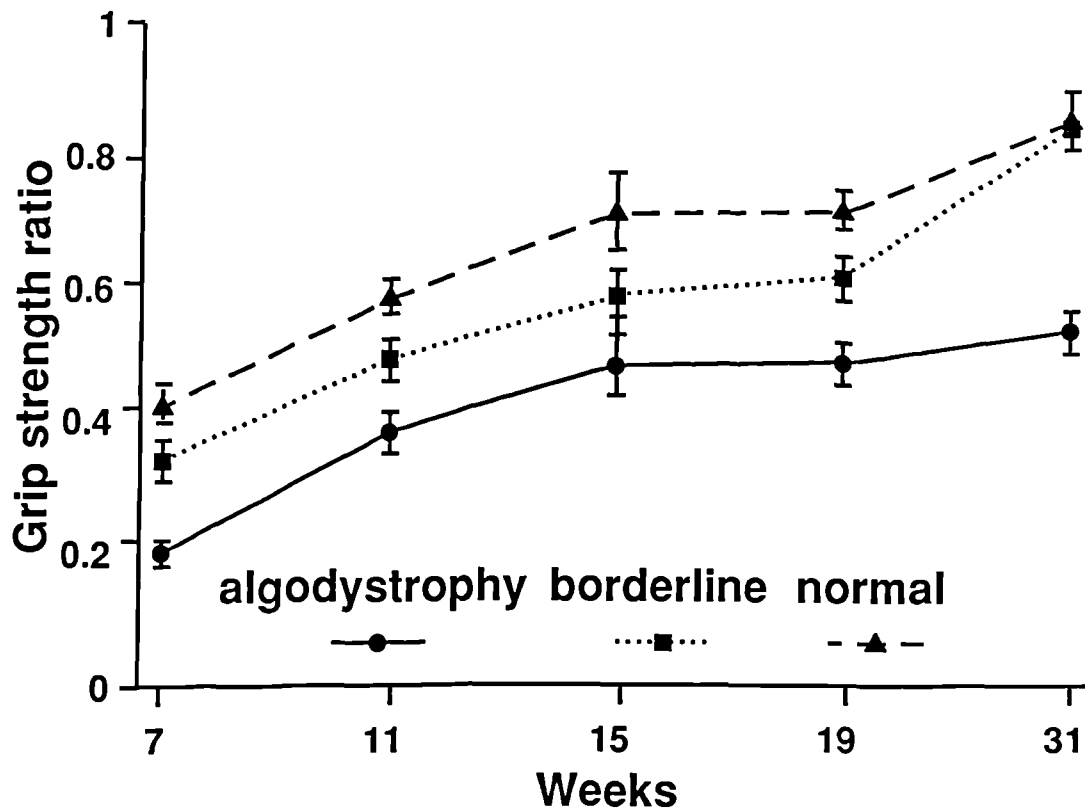features of algodystrophy.

Fig 22.8. The mean (+/- SEM) grip strength ratio was recorded in 274 patients with Colles' fracture divided into algodystrophy, borderline and control groups. All groups had evidence of decreased grip strength at presentation but the algodystrophy group were significantly weaker. Strength improved at a comparable rate in all groups upto 15 weeks after fracture, after which there was little further improvement in the algodystrophy group.

Table 22.13. The functional scoring system assessed patient complaints, the ability to perform everyday tasks and symptoms and signs. Each detail was given a value which increases as the severity of the disability increased. There was a significant increase in the score for each individual section and in total for patients with algodystrophy.

	Algodystrophy	Normal	p≤
Complaints	20.5 ± 1.8	14.3 ± 1.3	0.01
Function	25.7 ± 2.1	11.0 ± 1.2	0.0001
Signs and symptoms	7.32 ± 0.9	2.56 ± 0.2	0.0001
TOTAL	53.5 + 4.3	27.9 + 2.9	0.0001

Discussion.

This study has shown that there is a gradual resolution of symptoms and signs in algodystrophy but still sufficient to cause short-term morbidity in a greater number of cases than has been previously recognised. The rate of resolution was greatest in the patients perception of swelling and pain in the hand with a probability that there would be approximately a 40% decrease in patients with these symptoms at three months after the fracture. The decrease in swelling mirrored a similar decrease in the direct measurement of hand volume in that by 15 weeks after fracture, there was no significant difference between algodystrophy and the other groups. Nevertheless, despite the relatively rapid initial resolution of swelling, there was still a significant difference in the patients perception of hand swelling from the borderline group.

The absence of any difference in pain between the algodystrophy and borderline groups may have been due to pain from the fracture site masking the pain in the hand and fingers. Indeed, although not specifically recorded, it was my impression that

patients with algodystrophy complained of more pain from the fracture site and may therefore have ignored pain from other sites. It was not thought possible to further quantify this in view of the problems encountered with linear analogue scales or pain questionnaires (Chapter 9).

The resolution of tenderness and vascular instability was less rapid than that of pain with a 20% remission at three months. Stiffness was the most persistent feature with only a 10% remission by three months. It is interesting to note the difference between the rate of resolution of stiffness and swelling in light of the persistence of poor grip strength in the algodystrophy patients. It would appear that grip strength is not dependent upon swelling which confirms earlier findings (Chapter 16).

Overall there was approximately a 30% rate of resolution of symptoms three months after a fracture. This has important therapeutic implications in the treatment of post-traumatic algodystrophy in that early recovery may wrongly be attributed to the treatment. In therapeutic trials therefore, in order to demonstrate treatment efficacy, it is essential that the study is adequately controlled and that a large number of patients are enrolled.

By six months after fracture, the proportion of patients complaining of hand pain and swelling had fallen to 20-30%, vascular instability and tenderness to 50%, and stiffness to 80%. These factors, along with decreased grip strength, are also associated with a significant loss of function. For these reasons there was an appreciable short-term morbidity in patients who exhibited signs of algodystrophy at presentation. This would be missed in retrospective studies of Colles' fractures which rarely assess morbidity earlier than one year. In this study, at one year after fracture, pain and tenderness, vascular instability and swelling had decreased appreciably which may account for the quoted 1-2% incidence of algodystrophy reported in most studies. Stiffness however was still apparent in 50% of cases but in the absence of the other features, would not necessarily be noted or attributed to algodystrophy. This stiffness

may account, at least in part, for the 24% permanent loss of hand function seen following Colles' fracture (Bacom and Kurtzke 1953). It should be remembered however, that stiffness in this study was based on the patients perception of the recovery of normal movements of the fingers. It does not always imply clinical evidence of stiffness although 14 patients, half those at one year, had fixed flexion deformities of the proximal inter-phalangeal joints.

The existence of a borderline group of patients, who had some of the features of algodystrophy, was described in Chapter 18. They had signs and symptoms which were of intermediate severity between the algodystrophy and control group and may thus have formed a sub-clinical form of algodystrophy. In this group, apart from the perception of hand pain, the symptoms resolved more quickly than in algodystrophy. Although function was not formally assessed in this group using the scoring system, the grip strength was less than the normal group upto six months.

The existence of a borderline group suggests that there was a spectrum of disease which may have become apparent with more sensitive methods of assessment. This spectrum ranges from the normal physiological response to trauma, to the florid examples of algodystrophy which are well recognised. The point at which the physiological response became pathological was unclear. If the development of morbidity is taken as an indication of a pathological process, then patients who developed the four features of algodystrophy (28% of patients following a Colles' fracture) fall into the latter category, though this may well be an underestimation.

The majority of patients with vascular instability presented with warm, red hands and persisted with this abnormality until the instability settled or they were lost to follow-up. There was no significant difference in the type of vascular instability for the duration of the study upto six months. At this point however, the hand volume in *algodystrophy was significantly lower than in the other groups which implies* a degree of atrophy. It would appear therefore that, at least in the initial stages, atrophy is not

necessarily associated with a cold, blue hand. Accordingly, although there is great variation in the progression of the condition, the development of Steinbrocker's second stage (Ravault's stage 1; Doury's stage 1 and 2), which describes a cold, cyanotic atrophic hand with fixed flexion contractures, occurred later than usually recognised (Chapter 4).

In conclusion this study has described a spectrum of disease activity which gradually resolved over the period of a year, leaving a small percentage of patients remaining with all the features of algodystrophy. The resolution of algodystrophy accounts in the past for the low incidence quoted in other series. There was however, significant morbidity associated with the milder and largely unrecognised form of transient algodystrophy. In addition, finger stiffness, in the absence of the other features, persisted and must contribute to the late morbidity following Colles' fracture. The features of pain and tenderness, vascular instability, swelling and stiffness after a fracture should therefore alert the clinician to the likelihood of there being a delay in rehabilitation and prompt treatment at the earliest opportunity.

CHAPTER 23: CHANGES IN THE VASOMOTOR SYSTEM.

Conventionally, the circulation is divided into two types, the macrocirculation and the microcirculation. The macrocirculation is amenable to non-invasive methods of investigation such as Doppler ultrasound (Kempczinski and Yao 1982) but until recently, probes used to measure the microcirculation disrupted blood flow giving spurious results. The logical extension of ultrasound Doppler angiography is the optical analogue, laser Doppler angiography which has been developed to examine red-cell flux in the microcirculation (Nilsson et al. 1980a and b).

Although vascular instability is one of the fundamental features of algodystrophy it is difficult to quantify. Doury et al. (1981), using Doppler ultrasound, had inconsistent results when examining 25 patients with algodystrophy. They attributed this to examining different stages of the disease but if, as we believe, the sympathetic system is responsible for the clinical vascular changes, any alteration is likely to occur in the microcirculation rather than the macrocirculation.

The blood pool phase of the Technetium isotope scan gives a static image of the blood flow to a region incorporating both bone and soft-tissue. Although a less precise method, it does have the advantage of being more readily available in a clinical setting unlike laser Doppler angiography which should be considered a research tool.

Quantifying changes in vascular instability would be of value, not only in investigating the pathophysiology of algodystrophy but also as a measure of therapeutic response. For these reasons, laser Doppler angiography and the blood pool phase of Technetium isotope scans were used to investigate the natural history of vascular instability in algodystrophy.

Methods.

Laser Doppler angiography. The laser Doppler system used was the Perimed Periflux

PfII system (Gambro Ltd, Sidcup, Kent). The technique can only be applied to a limited

number of micro-vascular beds because of the shallow penetration depth of the laser

light in tissue (about 1 mm at the low power levels used in laser Doppler flow meters).

Fortunately, the human skin is rich in microvessels and therefore the back of the hand

provided a suitable site for measurement.

Many factors, psychological, neural, metabolic, humoral and physical, influence

blood flow in the micro-circulation (Weideman *et al.* 1981). Consequently a stimulus-

response measurement was made where the effects of the selected stimulus, heat in

this study, would outweigh all other factors influencing blood flow in the selected

region. In addition, the vascular instability in algodystrophy responds to alterations in

the environment such as changes in temperature, and therefore any change in red-cell

flux should be maximised. The system therefore incorporated a small thermostatic

heater element which allowed skin temperature in the region of the laser probe tip to be

raised over a short range. The skin temperature was monitored by a small thermistor

incorporated in a digital thermometer. The heater element was set to increase skin

temperature to 44^0C though, due to heat dissipation by circulating blood, the skin

temperature does not in practice reach this level.

Ten patients with features of algodystrophy were examined using laser Doppler

angiography. In view of the influence of external factors on the microcirculation, the

examinations were carried out in a standardised manner. Patients were requested to

abstain from smoking, and drinking alcohol, tea or coffee prior to the examination. The

same room was used for the test at each visit, in which they rested in bed at least 30

minutes before the examination started. In addition, all examinations took place in the

morning. The probe was applied to the dorsum of both hands between the 2nd and 3rd

metacarpals just proximal to the metacarpo-phalangeal joints. This site was used at

each visit as variations in microvasculature can occur over short distances. Once the patient was relaxed with a steady baseline measurement, the heater element was switched on and the response recorded continuously on a heat sensitive plotter. The first examination was performed, as with the other investigations, two weeks after plaster removal. Two further examinations were made at four weekly intervals.

The microvasculature response to a heat stimulus has been well characterised in normal subjects (Cochrane *et al.* 1986). After an initial delay following switching on the heater, the red-cell flux rises sharply to reach a broad peak and thereafter declines to a steady state. The various parameters reflecting microvasculature response were measured on the thermal response curve (Fig 23.1). Two further parameters were derived from the basic parameters. The total perturbation caused by heating the skin was calculated as the area under the curve from time of application of the stimulus to the time of reaching the steady state. The rate of change of flux was defined as the total perturbation divided by the time taken to reach a new steady state.

Technetium isotope scan blood pool phase. The methodology for the isotope examination has been described in Chapter 11. Blood pool phase scans were available on 36 of the original 43 patients described in Chapter 20. The repeat scan was performed after a 12 weeks interval. As before, a qualitative assessment was made as to whether there was increased, normal or decreased uptake in the blood pool phase. The presence or absence of vascular instability was also assessed at the time of the repeat scan.

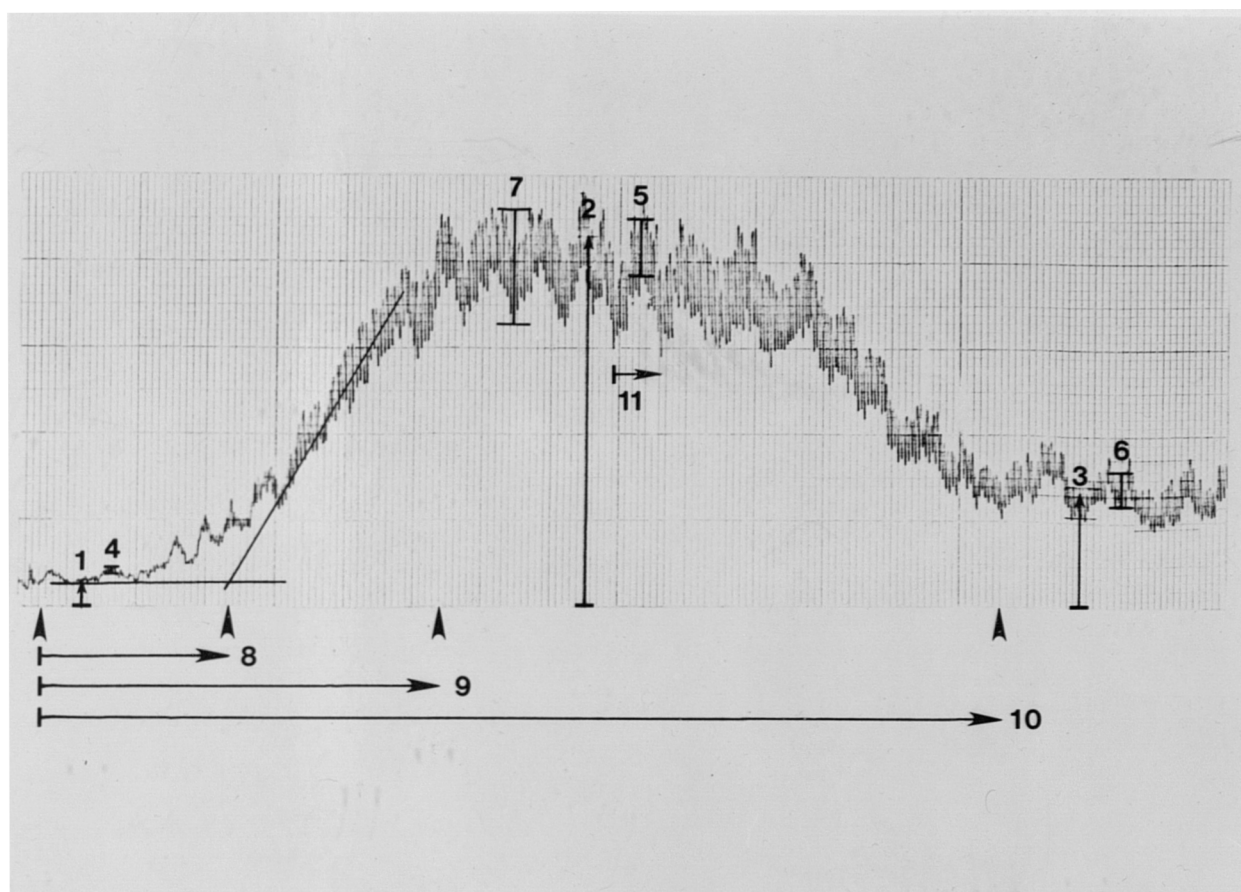The statistical analysis was the same as that used in previous chapters.

Fig 23.1. Schematic diagram showing the parameters measured from each of the local heating response curves. 1, baseline flux; 2, mean peak flux; 3, steady-state flux; 4, peak-to-peak flux at baseline; 5, peak-to-peak flux at peak response; 6, peak-to-peak flux at steady state; 7, peak-to-peak depth of vasomotor activity; 8, time to start of response; 9, time to start of maximum plateau; 10, time to reach steady state; 11, period of vasomotor activity.

Results.

Laser Doppler angiography. All the patients studied were female with a mean age of 63 $\pm$ 2.05 years. The room temperature during the examinations was fairly constant (23.3 $\pm$ 0.28^{0}C).

In all but one patient there was some form of abnormality on the angiogram at presentation (Table 23.1). Five patients had a poor thermal response with a low peak and increased time to response (Fig 23.2). Of these patients, two complained of a cold hand but with red discolouration, the remainder had warm, red hands. Therefore the response to thermal stressing, although causing some form abnormality, was unpredictable and did not always accurately correlate with the type of vascular instability displayed.

Consequently it was not surprising to find no significant difference between the affected and unaffected hand in any of the parameters (Table 22.2). This is with the exception of the time to peak flux which was longer on the affected (199 $\pm$ 15.7 seconds) than the non-affected side (125 $\pm$ 23.6 seconds; p < 0.02).

In view of the potential variation between sequential measurements, the parameters were expressed as the ratio of the affected to unaffected side to examine the progression of the changes in red-cell flux. Inspite of this however, there were wide variations in most of the parameters such that no coherent information was available though all the traces appeared to demonstrate a trend towards a normal thermal response by 15 weeks after fracture. In four parameters (time to peak, time to steady state, ratio of perturbation and rate of change of flux), although not significant, there was a definite trend towards recovery (Fig 23.3).

Table 23.1. Abnormalities of red-cell flux detected at presentation in the ten patients·
studied. There appeared to be no close correlation with the temperature or colour of the
affected hand.

Patient	Abnormality	Vascular instability	
		Temperature	Colour
1	Increased peak	Hot	Red
	Increased peak flux		
	Increased time to peak		
	Increased time to steady state		
	Increased steady state flux		
2	Increased peak flux	Hot	Red
	Increased time to peak		
	Increased steady state		
	Increased steady state flux		
3	No abnormality	Hot	Red
4	Increased peak flux	Hot	Red
	Increased steady state		
	Increased steady state flux		
5	Increased peak flux	Hot	Red
	Increased time to steady state		
6,7,8,9 & 10	Decreased peak	3 Hot/2 Cold	5 Red
	Decreased time to peak		
	Poor thermal response		

Table 23.2. The parameters used to measure the red-cell flux (mean ± SEM) in response to a heat stimulus. The only significant difference between the affected and unaffected side seven weeks after fracture was in the time to peak response.

	Affected	Unaffected
Baseline flux (mm)	13.0 ± 1.97	9.4 ± 1.15
Peak flux (mm)	52.0 ± 10.23	41.3 ± 6.37
Steady state flux (mm)	37.5 ± 7.54	30.0 ± 5.31
P/P flux at baseline (mm)	1.83 ± 0.44	1.50 ± 0.21
P/P flux at peak (mm)	7.33 ± 1.52	7.40 ± 0.49
P/P flux at steady state (mm)	5.00 ± 1.05	5.10 ± 0.41
P/P depth vasomotor activity (mm)	12.0 ± 1.99	13.2 ± 1.05
Time to response (secs.)	34.7 ± 8.67	63.9 ± 12.4
Time to peak flux (secs.)	125 ± 23.6	199 ± 15.7 *
Time to steady state (secs.)	313 ± 19.1	336 ± 17.3
Perturbation (mm^2)	5737 ± 828	4637 ± 776
Rate of change of flux (mm^2/secs)	19.0 + 3.34	13.9 + 2.05

* - $p < 0.002$
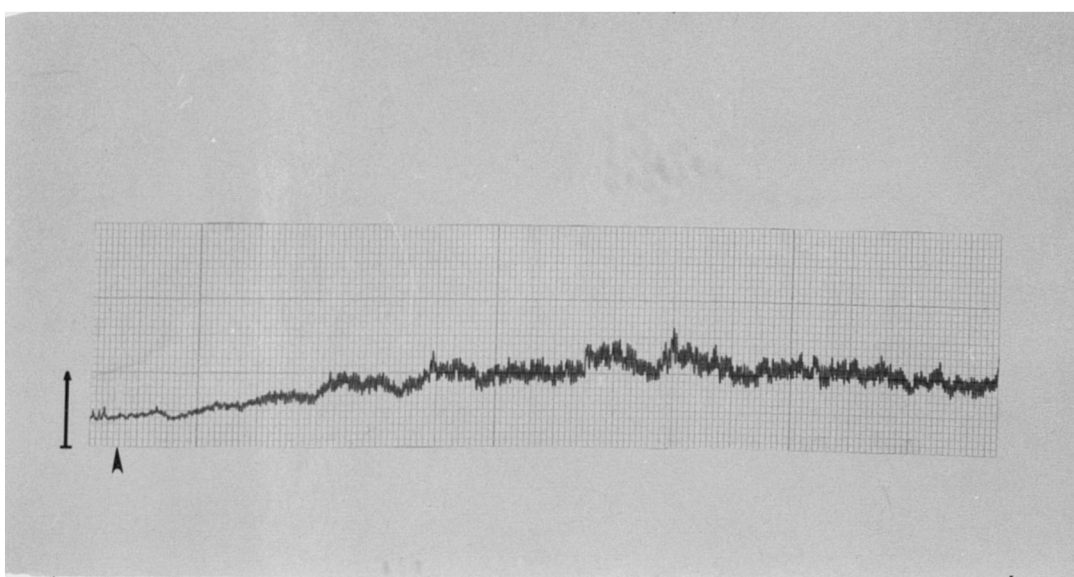
Fig 23.2. In five patients there was a poor thermal response to local heating measured with laser Doppler angiography.
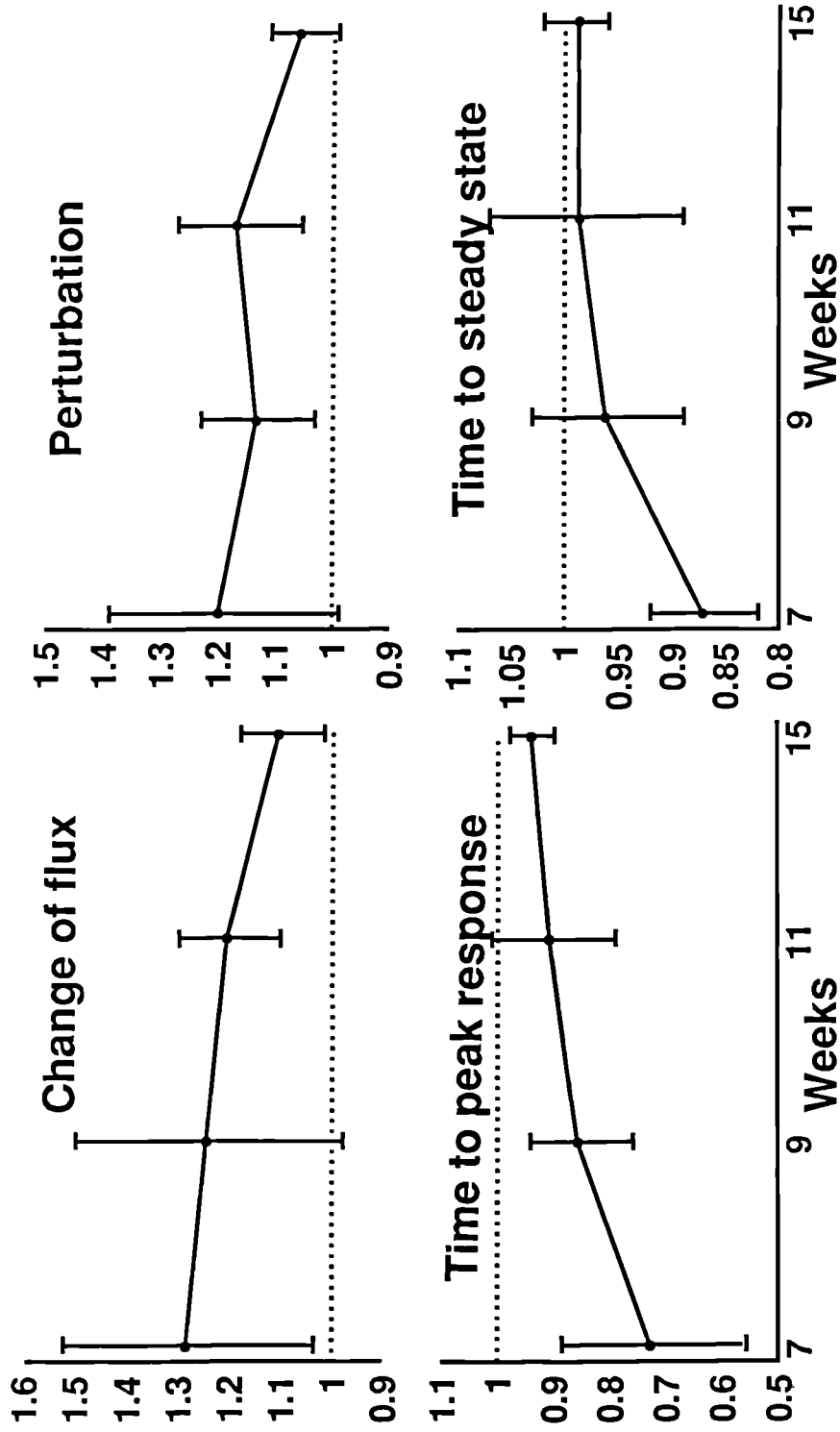
Fig 23.3. The mean (+/- SEM) ratio of affected to unaffected hand was calculated for four of the parameters measured on the thermal response curve following thermal stressing. Although not significant, there was a trend towards complete recovery by 15 weeks in 10 patients with algodystrophy following fracture.

Blood pool phase. The age and sex distribution of the patients is given in Appendix I.

Of the 36 scans available, 13 demonstrated increased uptake, 19 were normal and 4

were considered to have decreased uptake. The distribution of the type of uptake had

significantly altered (X^2 - 29.89; $p < 0.0001$) from the scans taken seven weeks after

fracture due to an increase in normal and, to a lesser extent, scans with decreased

uptake:

Weeks after fracture	Uptake		
	Increased	Normal	Decreased
7	38	2	0
19	13	19	4

Although there was no increased uptake in the blood pool phase in 23 patients,

this was not reflected in a resolution in symptoms of vascular instability. There was no

significant difference in the distribution of vascular instability between the three types

of scan (X^2 - 0.21; $p > 0.05$):

	Uptake		
	Increased	Normal	Decreased
Vascular instability	9	12	3
No vascular instability	5	7	1
Total	13	19	4

Similarly there was no difference in the type of vascular instability between the different

groups.

Discussion.

This study has demonstrated the difficulty in quantifying the vascular changes seen in algodystrophy. Qualitatively all but one of the responses demonstrated some form of abnormality. Generally, there appeared to be two types of response; a flat curve with little thermal response, and a normal looking but more exaggerated curve with a higher peak and steady state, and increased peak flux. Only one curve looked completely normal. Theoretically one might assume that the flat curves would be seen in cold, blue atrophic hands and the exaggerated curves in a warm hot hand, but this did not appear to be the case. This suggests that even though there may be increased vascularity on clinical grounds, cutaneous blood flow is not necessarily increased. There may be alternate episodes of increased blood flow and stasis which would explain the abnormal thermal responses without correlation to the clinical picture. Indeed, in all of the patients with flat curves, and therefore stasis in the micro-circulation, there was increased uptake in the blood pool phase which suggests an overall increase in blood flow at least to bone.

It was hoped that there may have been a fundamental difference in the thermal response that was common to all patients regardless of the type of curve. Apart from the time to peak response, there was no significant difference in any of the parameters measured. This may in part be due to the effect external factors had on red-cell flux despite measures taken to decrease environmental effects on the microcirculation, and use of a thermal response test. Nevertheless, the time to response, may prove to be a useful parameter in the assessment of vascular instability. Indeed, although no significant difference was seen, there was a definite trend towards normality when the ratio of the affected to unaffected side was measured upto 15 weeks after fracture (Fig 23.3).

In all, four parameters (time to peak, time to steady state, ratio of perturbation

and the rate of change of flux) demonstrated trends towards normality but at 15 weeks ·
after fracture there were still detectable abnormalities. This was in accordance with the
90% probability that the clinical features of vascular instability had persisted to 15
weeks (Chapter 22). By 19 weeks after the fracture this probability had fallen to 85%
and yet in over half the blood pool phase scans, the uptake was normal or decreased.
Considering the rate of resolution of the laser Doppler features, it was likely they would
still have been abnormal at this stage. This suggests that by 19 weeks, although still
apparent clinically and on laser Doppler angiography, the vascular instability had
resolved to such an extent that the increase in blood flow was insufficient to cause a
qualitative increase on the blood pool phase of an isotope scan. A radionuclide
angiogram, the first of the three-phase bone scan described by Maurer *et al* (1983), is a
more accurate assessment of blood flow than the blood pool phase and may well be
sensitive enough to demonstrate an abnormality in blood flow at this stage.

In conclusion, although there are changes in the thermal response test using
laser Doppler angiography, quantitation is difficult due to the variation in response
caused by external factors on the microcirculation. Similarly, there was little statistical
evidence of improvement though the type of curve produced by the thermal response at
15 weeks after fracture approached normal. The increase in uptake on the blood pool
phase of an isotope scan evident at presentation did not persist in over 50% of cases at
19 weeks after fracture despite continuing vascular instability. The sensitivity of this
phase of the scan as a criterion for diagnosis of algodystrophy at this stage must be
questioned.

CHAPTER 24: CHANGES IN SKELETAL ARCHITECTURE.

Focal and patchy radiotranslucency of bone is a characteristic feature of algodystrophy on radiographs, but similar features are seen after fracture, a common predisposing factor in it's aetiology. Although the radiographic features of trabecular bone in algodystrophy and disuse atrophy following Colles' fracture are qualitatively similar, it is possible to accurately differentiate between the two, using a semi-quantitative scoring system, due to the more pronounced features present in algodystrophy (Chapter 19). In addition single photon absorptiometry can be used to differentiate between trabecular and cortical bone and, as seen earlier (Chapter 19), there is a more pronounced loss of bone, particularly trabecular, in algodystrophy patients seven weeks after fracture. The purpose of the present study was to examine prospectively the natural history of bone loss and particularly the focal changes in trabecular and cortical bone in algodystrophy after Colles' fracture.

Methods

The radiographic scoring system and the metacarpal morphometry technique have been described in Chapter 10. The results at presentation in the 44 algodystrophy and 33 control patients, and the diagnostic ability of the techniques have been discussed in Chapter 19. The scoring system was used to assess changes in trabecular bone and is in arbitrary units. The metacarpal morphometry measured combined cortical width (CCW) and metacarpal diameter and were expressed in mm or as the ratio of the affected to unaffected side. After the initial radiograph taken at presentation seven weeks after fracture, they were repeated at three monthly intervals for six months, and for a further six months in 9 patients with algodystrophy (Table 8.3).

The technique of single photon absorptiometry has been described in Chapter 12. The results seven weeks after fracture in the 29 algodystrophy and 23 control

patients demonstrated that it was possible to differentiate between trabecular and cortical bone. The results were expressed as bone mineral content (BMC; g) and bone mineral density (BMD; g/cm^2) or as the ratio of affected to unaffected side. Scans were performed at the same time as the radiographs.

The statistical analysis used was the same as in previous chapters.

Results.

There was no significant difference in age, sex, duration of immobilisation between patients with algodystrophy and controls (Appendix I).

Bone loss and radiographic changes had occurred in all patients at presentation but the changes were more marked in patients with algodystrophy and more marked at trabecular (radiographic score and BMD_{trab}) rather than cortical sites (Chapter 19).

During the subsequent follow-up cortical bone width continued to decrease in patients with algodystrophy whereas it had recovered by 19 weeks in control patients (Fig 24.1a). Thereafter, there was no further bone loss in the patients with algodystrophy, but the cortical width remained significantly lower at 31 weeks than that of the unaffected hand or that of control patients. No changes were observed in the metacarpal diameter. A similar pattern of events was observed in cortical BMD (Fig 24.1b).

At trabecular sites the radiographic score and BMD were significantly lower in patients with algodystrophy than in controls at the first assessment (Fig 24.1c and d). In control patients these measurements returned towards normal by 31 weeks but the rate of recovery was slower than that seen at cortical sites. In contrast, no subsequent recovery of trabecular BMD was noted in patients with algodystrophy and radiographic improvements were incomplete (Fig 24.1c and d).

The decrease in bone density at the cortical site was associated with a decrease in cortical width. Indeed at 19 weeks there was a significant correlation between these

measurements (R = 0.51; p < 0.05). In order to determine whether the decrease in

BMD_{cort} was due solely to a decrease in the width of bone cortex, the change in

calculated cortical area on metacarpal morphometry (Fig 24.2) and the change in

cortical bone mineral content (BMC) was examined. Since no loss of bone occurred on

the unaffected side, the cortical area and BMC measured at this site were assumed to

represent the values which were present at the fractured side before fracture had

occurred. The change in apparent BMD of cortical bone was calculated from the

change in BMC divided by the change in cortical area. In both control and

algodystrophy groups there was a significant loss in apparent BMD which was more

pronounced in the patients with algodystrophy (Table 24.1), suggesting that metacarpal

osteoporosis was due to an increase in cortical porosity as well as a decrease in cortical

width. The relationship between change in cortical area and change in bone mineral

content was similar in patients with and without algodystrophy (Fig 24.3).

In nine patients with algodystrophy who were reassessed at one year, no further

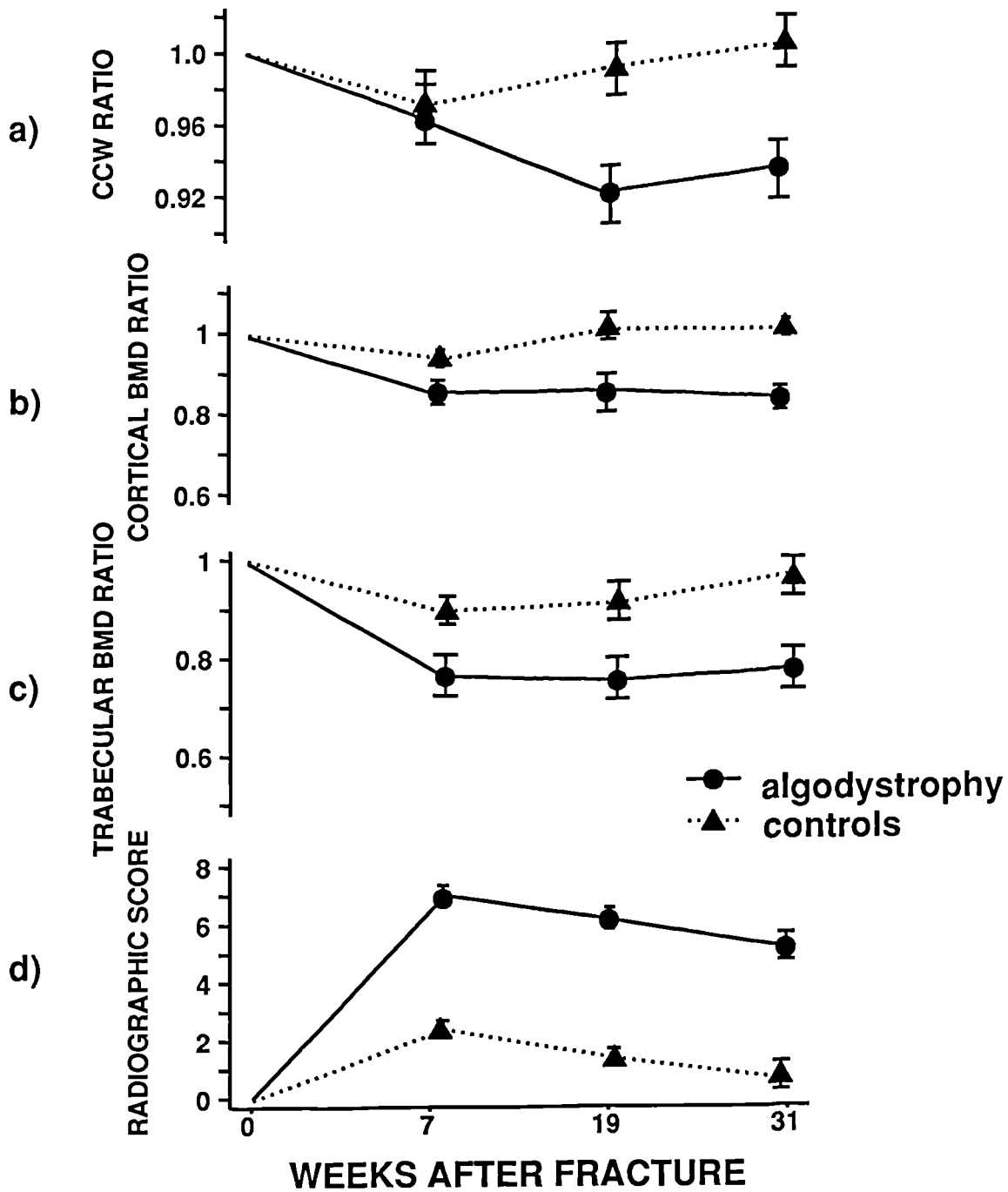recovery was observed in cortical BMD, trabecular BMD or radiographic score (Fig

24.4).

Fig 24.1 a -d. Sequential changes (mean +/- SEM) in indices of cortical (a and b) and trabecular (c and d) bone. The mean change in CCW and BMD was expressed as the ratio of affected to unaffected side in patients with algodystrophy and in controls. A higher radiographic score indicates more marked radiographic abnormalities.
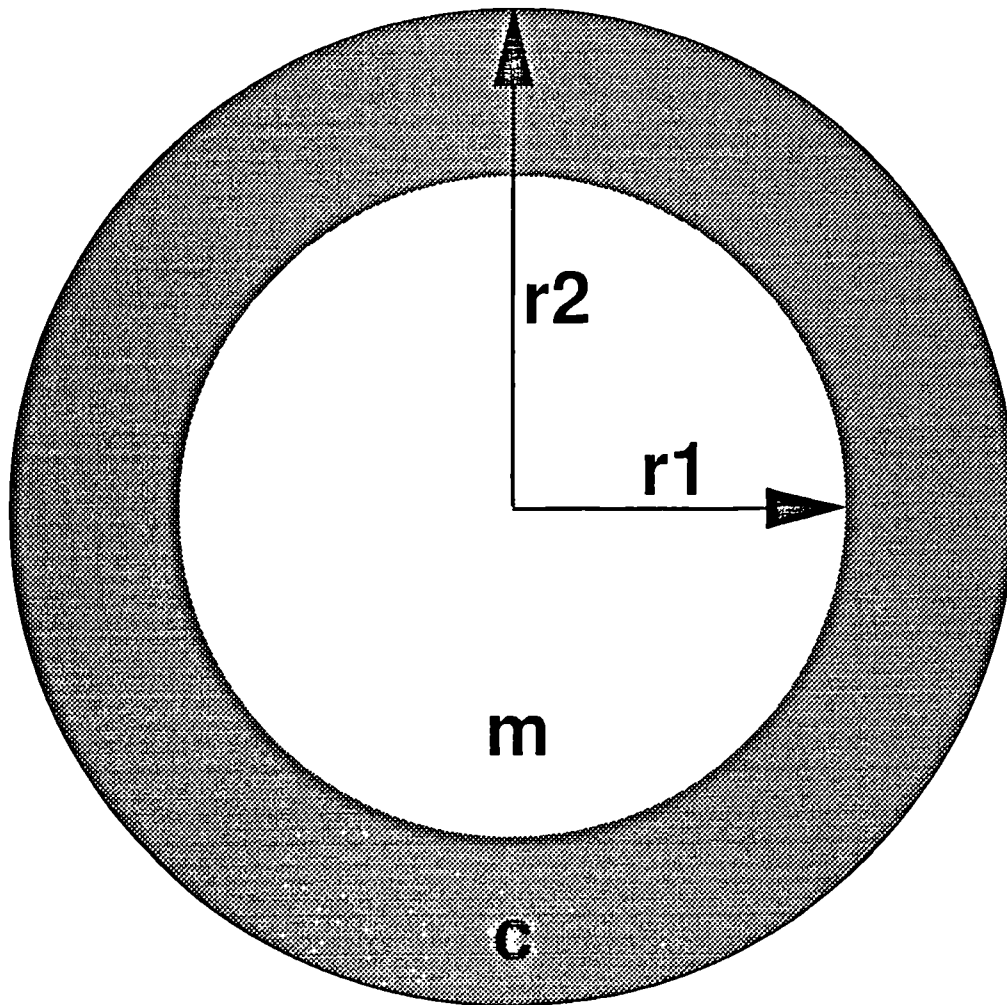
m - medullary cavity
c - cortex
r - radius

Fig 24.2. Method of calculating the area of cortex measured at the
diaphysis with metacarpal morphometry:

$r2$ = metacarpal diameter/2

$r1 = r2 - CCW/2$

area $= \pi r2^2 - \pi r1^2$

Table 24.1. Cortical area and bone mineral content (BMC) ($\pm$ SEM) in algodystrophy and controls in the unaffected side, assumed to be pre-fracture values and at 19 weeks after fracture. There was a greater percentage change in bone density in algodystrophy.

	ALGODYSTROPHY	NORMAL
DAY 0		
Cortical area (mm^2)	31.8 ± 2.0	33.0 ± 1.6
Cortical BMC (g)	13.7 ± 0.9	13.2 ± 0.5
Apparent cortical Density (g/cm^2)	0.43 ± 0.01	0.40 ± 0.01
WEEK 19		
Cortical area (mm^2)	29.2 ± 1.7	32.2 ± 1.5
Cortical BMC (g)	11.2 ± 0.9	12.0 ± 0.6
Apparent cortical density (g/cm^2)	0.38 ± 0.01	0.37 ± 0.01
% CHANGE		
Cortical area	7.4 ± 2.1 *	1.9 ± 1.1
Cortical BMC	18.5 ± 2.5 **	9.6 ± 2.6
Apparent cortical density	$11.6 + 1.8$ *	$7.8 + 1.1$

Asterisks denote significance of differences from control patients (* $p < 0.05$; ** $p < 0.02$).
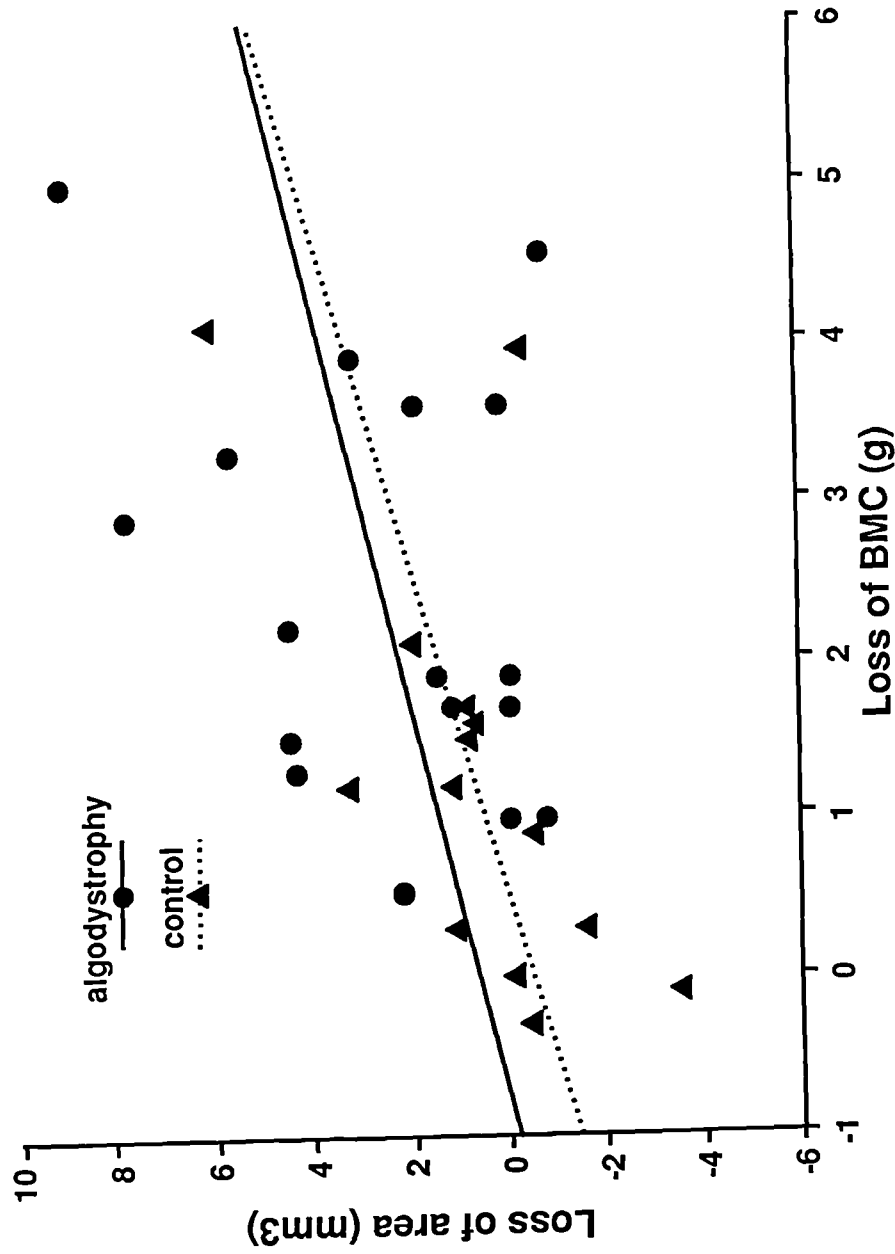
Fig 24.3. The relationship between the loss in cortical area with the loss in bone mineral content (BMC) in patients with algodystrophy and controls 19 weeks after fracture. There was a similar loss in BMC per unit change of cortical area in both groups and no significant difference between the slopes.
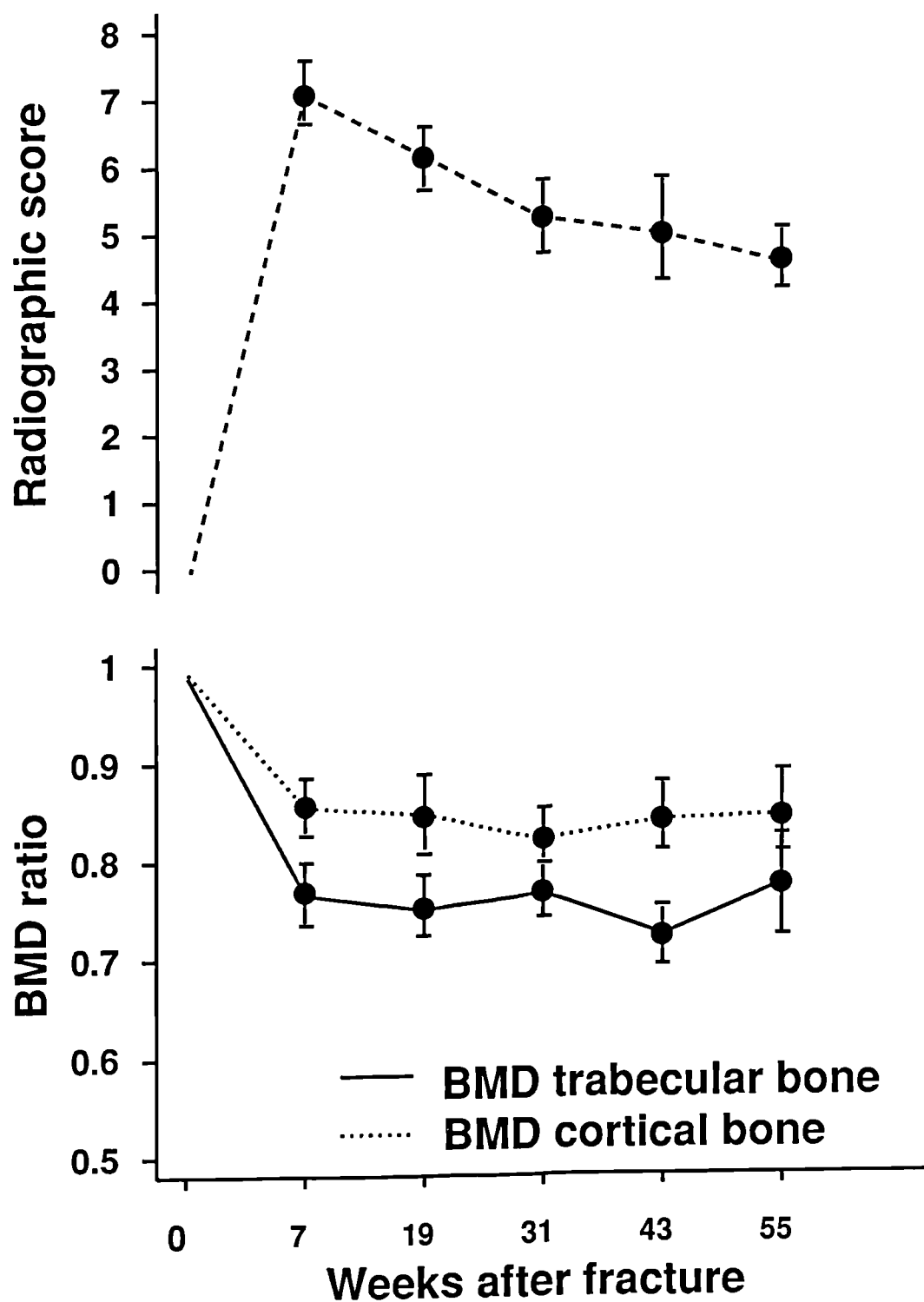
Fig 24.4. Mean (+/- SEM) change in BMD ratio and radiographic score in nine patients with algodystrophy followed for a year. There was no recovery of bone loss throughout the one year period of observation.

Discussion.

Bone loss is a well recognised feature of immobilisation and of fracture,

particularly at the immediate fracture site (Steinbach 1964; Jones 1969; Feist 1970).

The present study indicates that bone loss also occurs after Colles' fracture at the

carpals and metacarpals. It is not possible, however, to distinguish the components of

loss due to fracture and it's metabolic consequences from that due to immobilisation.

The bone loss in uncomplicated Colles' fracture was however transient and at six

months indices of bone mass were comparable to those measured at the unfractured

side.

Algodystrophy is also characterised by bone loss. Indeed the patchy osteolysis

evident on radiographs is thought by some observers to be diagnostic of the disorder.

The present study indicates that algodystrophy following Colles' fracture is associated

with significantly greater degrees of skeletal losses than that expected in the

uncomplicated fracture.

It might be argued that the greater losses in algodystrophy were due to a

limitation in finger movement caused by swelling and stiffness. This may have resulted

in changes in the BMD of the distal metacarpal, but it is difficult to explain how

immobility of the fingers could result in increased bone resorption in the mid-

metacarpal and, in particular, the carpus. This suggests a factor inherent to the

algodystrophic process which results in more accelerated bone loss than normally seen

after fracture.

The distal SPA scans measured metacarpal bone which is mainly trabecular and

the proximal scan measured predominantly cortical bone. There was a significant

correlation between the radiographic score (at trabecular carpal sites) and BMD at the

trabecular bone of the metacarpal. There was also a significant correlation between

cortical BMD at the metacarpal and CCW of the diaphysis. There was no correlation

between measurements made at cortical and trabecular sites (Chapter 19). There was

also a similarity in the pattern of recovery between the two methods of measuring trabecular bone (Fig 24.1 c and d) and cortical bone (Fig 24.1 a and b). These observations cross validate the techniques used to asses skeletal losses and indicate that the pattern of loss differs at cortical from trabecular bone.

In both groups there was greater trabecular bone loss immediately after immobilisation which was demonstrated by the difference in the BMD_{trab} and BMD_{cort} seven weeks after the fracture (Fig 24.1 b and c). This difference was significant ($p < 0.05$) in the algodystrophy group. The earlier and more marked loss of BMD in trabecular bone is probably caused by more the greater availability of resorption surfaces and the higher surface to volume ratio of cancellous bone.

The resorption surfaces available in cortical bone are confined to the endosteal and periosteal surfaces, and intracortically within the Haversian canals. Kozin *et al.* in 1976 using microradiography suggested that changes at all three sites contributed to the loss in cortical BMD but not to what extent. In this study we have shown that there was increased cortical porosity and endosteal resorption in both groups, and both these features were more marked in algodystrophy compared with controls. Indeed, the relationship between the change in bone mineral content and change in cortical area was similar in the two groups. Since there was no change in the diameter of the metacarpal, it is reasonable to assume that the loss in cortical area is due to endosteal resorption of bone. These observations indicate that the nature of the bone loss is similar in controls and algodystrophy, but more marked in the latter.

The recovery of bone loss at both trabecular and cortical sites in uncomplicated Colles' fracture is in marked contrast to that seen in algodystrophy. In the patients with algodystrophy there was no recovery at six months and cortical and trabecular losses persisted in all the nine patients that we followed for one year. The reason for the failure of recovery in algodystrophy is unclear but may be due to increased blood flow which is also a feature of disuse atrophy (Trueta 1954). Increased blood flow has

been demonstrated in algodystrophy by the uptake of technetium labelled
diphosphonate into bone (Doury *et al.* 1981; MacKinnon and Holder 1984). This uptake
is greater than that seen in simple disuse and increased uptake persists for longer than
19 weeks after fracture (Chapter 25). It is possible that increased bone blood flow could
contribute to the excessive bone resorption seen in algodystrophy.

The clinical implications of the failure to recover bone loss in algodystrophy are
unknown. It is relevant to note that the decrease in cortical bone density was greater
than 10% and that of trabecular bone greater than 25%. This degree of bone loss might
be expected in 10 years during the natural history of uncomplicated osteoporosis. If
similar deficits were to be present at the wrist then the risk of refracture are likely to be
proportionately increased. Microscopic analysis on bone taken from areas that had
been affected by algodystrophy for greater than a year, has shown that the loss of
trabecular bone is not only due to a decrease in trabecular width but also to the
complete disappearance of trabeculae (unpublished data). Even if there were to be
recovery of the BMD to normal in algodystrophy, this could only be achieved by
hypertrophy of the remaining trabeculae. This would explain the persistence of
abnormal trabecular architecture assessed by the radiographic scoring system even in
patients with relatively mild disease. This suggests that early treatment with agents
that decrease bone resorption, such as calcitonin, may be worthy of trial to prevent the
irreversible loss of trabecular structure.

In conclusion, algodystrophy is associated with a more marked and prolonged
loss of bone than is found following immobilisation alone. This bone loss occurs more
markedly at trabecular bone but increased endosteal resorption of cortical bone is also
a feature. Bone loss may result in irreversible changes in the structure and strength in
the bony architecture.

CHAPTER 25: CHANGES IN SCINTIGRAPHY.

An increase in bone activity greater than that seen in a control population has already been demonstrated with ^{131}I Technetium isotope scans in patients with algodystrophy approximately seven weeks after fracture (Chapter 20). The increase in skeletal metabolism however, was not reflected in biochemical evidence of increased bone turnover. Nevertheless, the increase in uptake on the delayed phase of the scans provided good diagnostic accuracy in the early stages of post-traumatic algodystrophy. It remains to be seen for how long this increase in activity persists.

There appeared to be no difference in the degree of bone resorption between simple disuse atrophy and the addition of algodystrophy (Chapter 21). Bone formation however, did appear to be suppressed in algodystrophy. A hypothesis was proposed which explained the greater bone loss, as demonstrated radiographically and with single photon absorbtiometry, to be secondary to a failure to reform bone in algodystrophy resulting in a greater net loss of bone at seven weeks after fracture. As described in chapter 24, the decrease in bone density continued for at least a year, and therefore if this hypothesis is correct, there should be continued biochemical depression of bone formation.

For these reasons, the progression of bone metabolic changes have been prospectively studied using biochemical and scintigraphic indices of measurement.

Methods.

The technique used for the Technetium isotope scan and the calculation of the metacarpal score (ratio of uptake in affected to unaffected hand) has been described previously (Chapter 11). The 43 patients, whose initial results were described in Chapter 20, had repeat isotope scans 12 weeks later.

The biochemical parameters measured were serum corrected calcium,

parathyroid hormone (PTH), serum alkaline phosphatase and osteocalcin (markers of bone formation) and urinary calcium and hydroxyproline (markers of bone resorption); the measurement techniques have been detailed in Chapter 13. The study included 46 patients with algodystrophy, followed monthly upto 6 months, and 26 control patients followed for three months after removal of the plaster (Table 8.3).

The statistical analysis used has been described previously.

Results.

There was a significant decrease in bone turnover 19 weeks after fracture (p < 0.0001; Fig 25.1), as measured by Technetium uptake in the delayed phase of the scan compared with the scan at seven weeks. The metacarpal score at 19 weeks (1.45 $\pm$ 0.06) was however still significantly greater (p < 0.008) than the score in the control population (1.14 $\pm$ 0.04), seven weeks after fracture. The rate of decrease in the metacarpal score was 0.05 per week which, if it decreased in a linear fashion would mean the uptake becoming normal 24 weeks after the fracture (Fig 25.1).

The only biochemical parameter which appeared to be of value was the serum osteocalcin which continued to be significantly lower in algodystrophy (Fig 25.2). No control patients were examined later than 19 weeks after fracture, but in the 23 algodystrophy patients followed to 31 weeks, the osteocalcin level continued to be lower than the normal range (8-36 ng/ml; Fig 25.5) upto 19 weeks, gradually returning to normal. This apparent depression of bone formation was not reflected in changes in alkaline phosphatase (Fig 25.2) or urinary hydroxyproline and calcium, the markers of bone resorption (Fig 25.3). There was no change in serum corrected calcium or parathyroid hormone level (Fig 25.4).
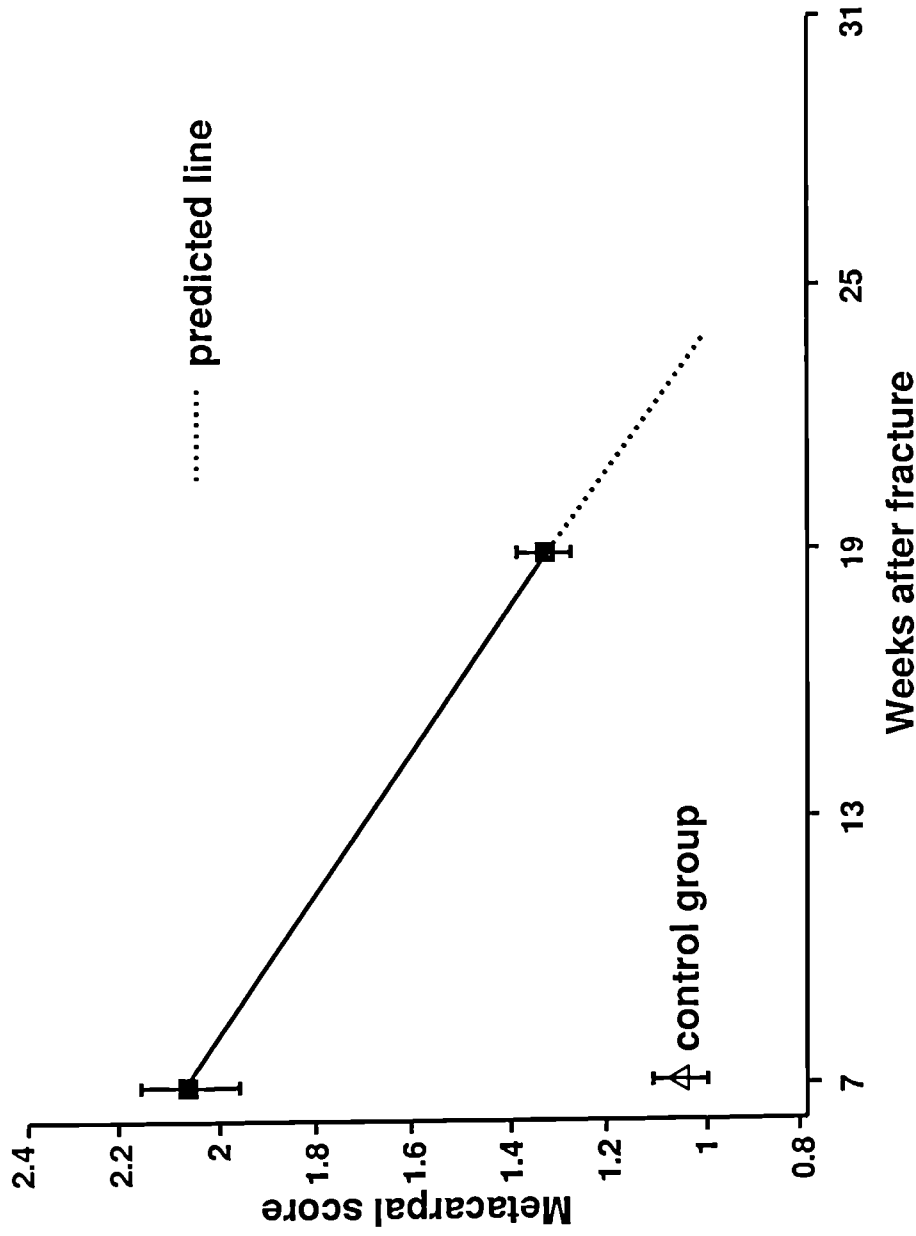
Fig 25.1. There was a significant decrease in the mean (+/- SEM) metacarpal score in patients with algodystrophy between 7 and 19 weeks after a Colles' fracture. The score at 19 weeks however, was still significantly greater (p < 0.008) than in the control group 7 weeks after fracture. Assuming a linear decrease in activity, there would have been no difference between the affected and unaffected hand by 24 weeks.
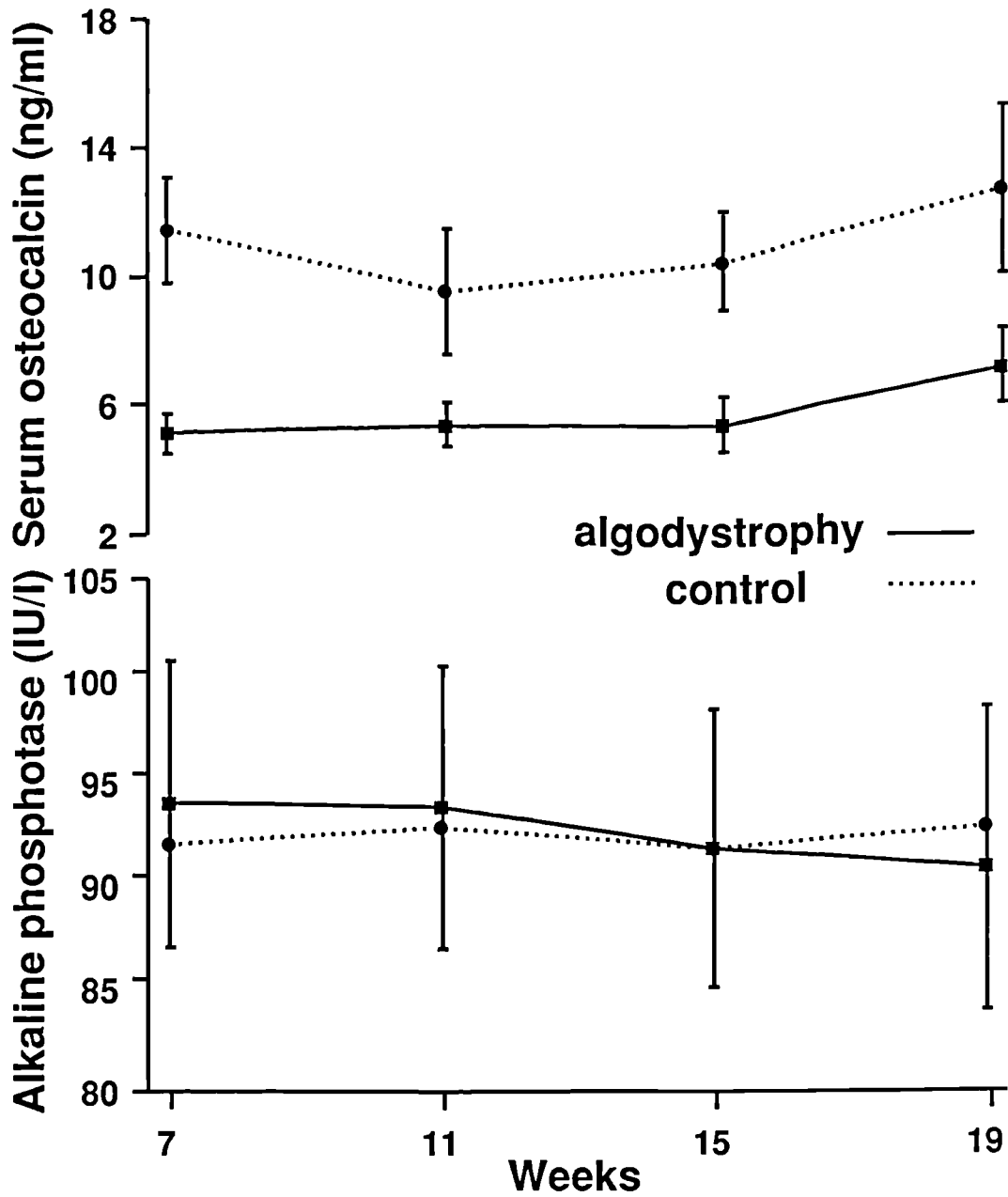
Fig 25.2. Serum osteocalcin and alkaline phosphatase, markers of bone formation were measured in 46 patients with algodystrophy and 26 controls patients following a Colles' fracture. Serum osteocalcin was significantly lower in algodystrophy than in controls throughout the period of observation but there was no difference in the alkaline phosphatse.
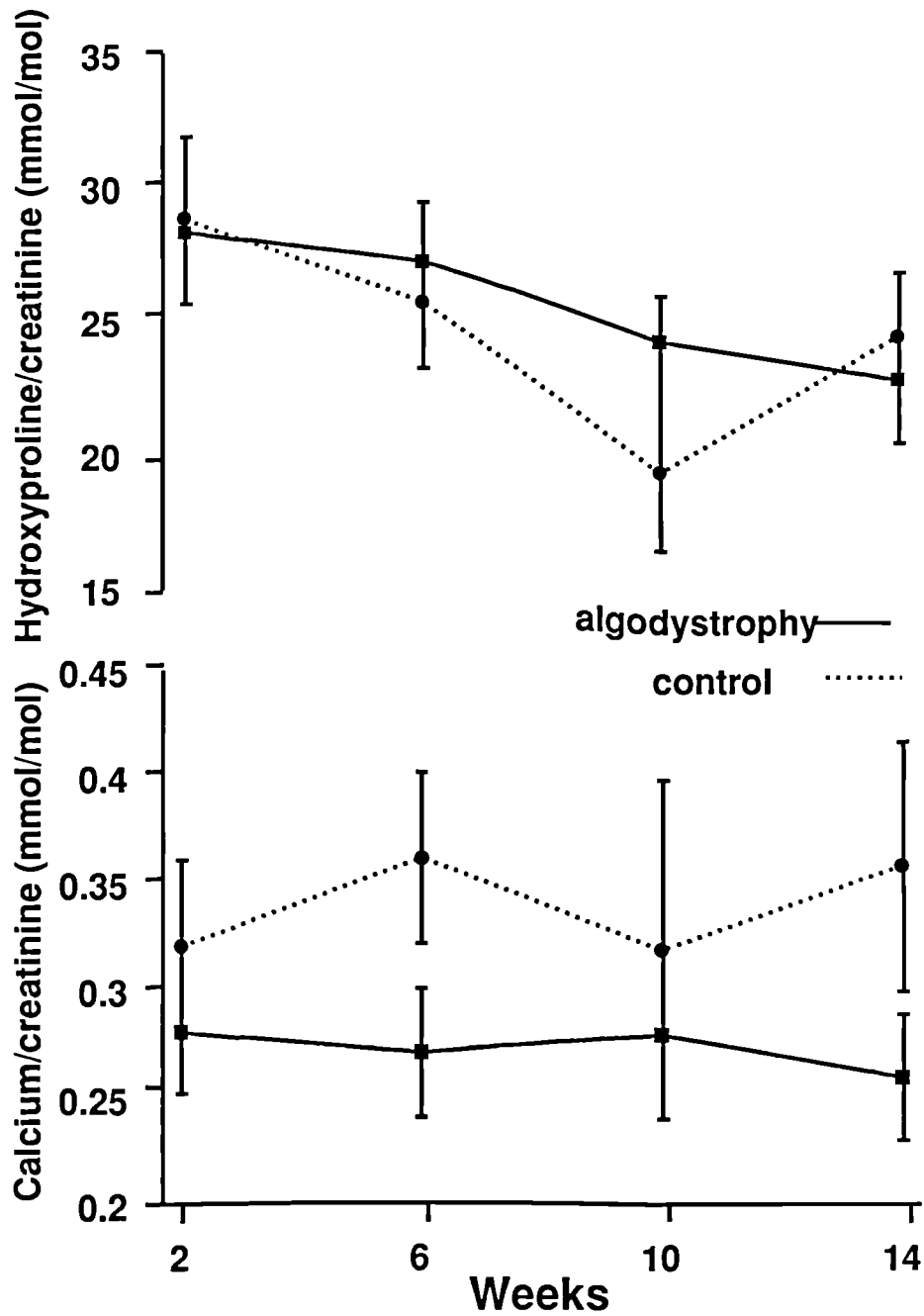
Fig 25.3. There was no significant difference in the mean (+/- SEM) urinary hydroxyproline/creatinine and calcium/creatinine ratios, which are markers of bone resorption, between the 46 algodystrophy and 26 control patients over the study period.
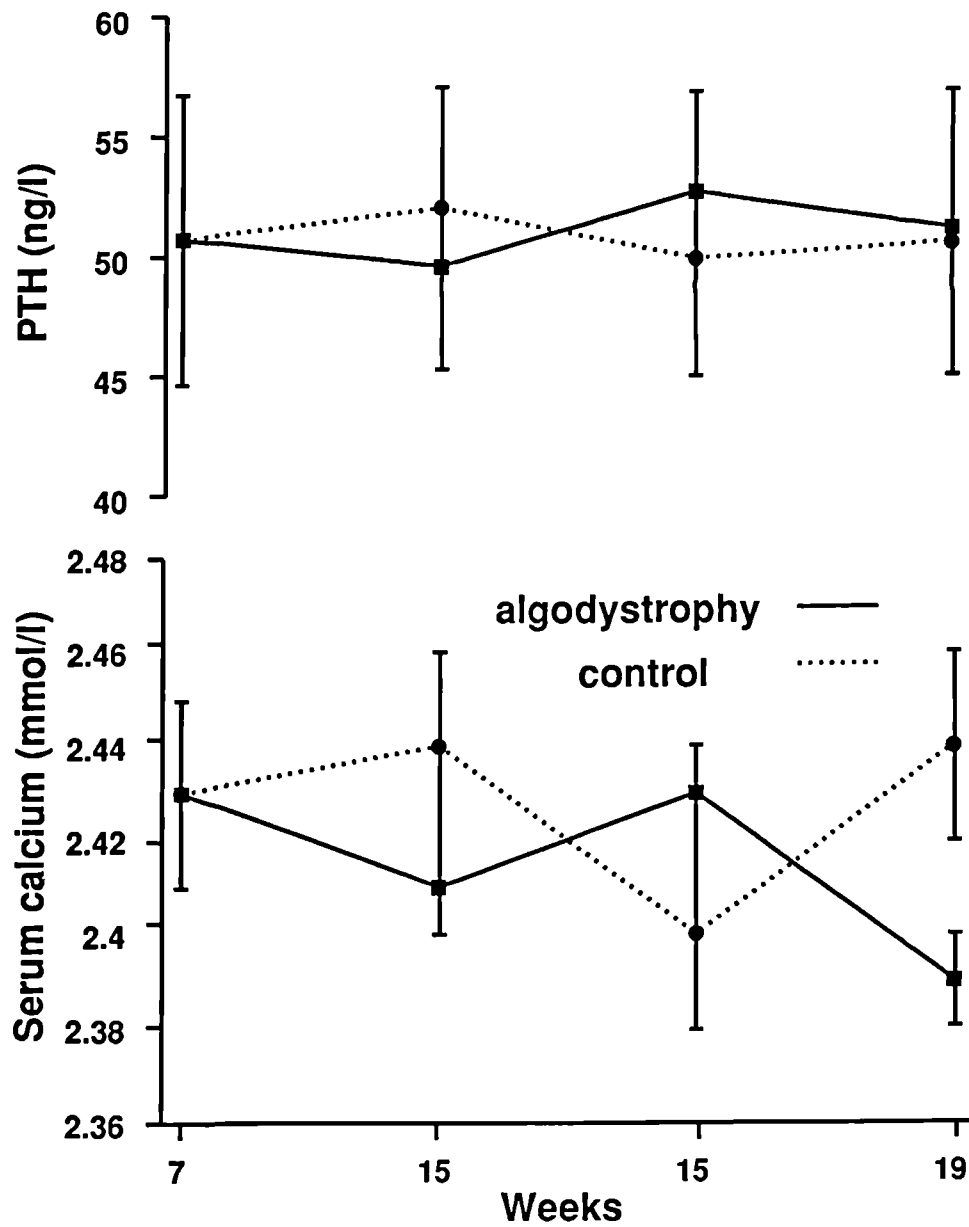
Fig 25.4 There was no significant difference in the mean (+/- SEM) serum calcium and parathyroid hormone (PTH) in the 46 algodystrophy and 26 control patients upto 19 weeks after a Colles' fracture.
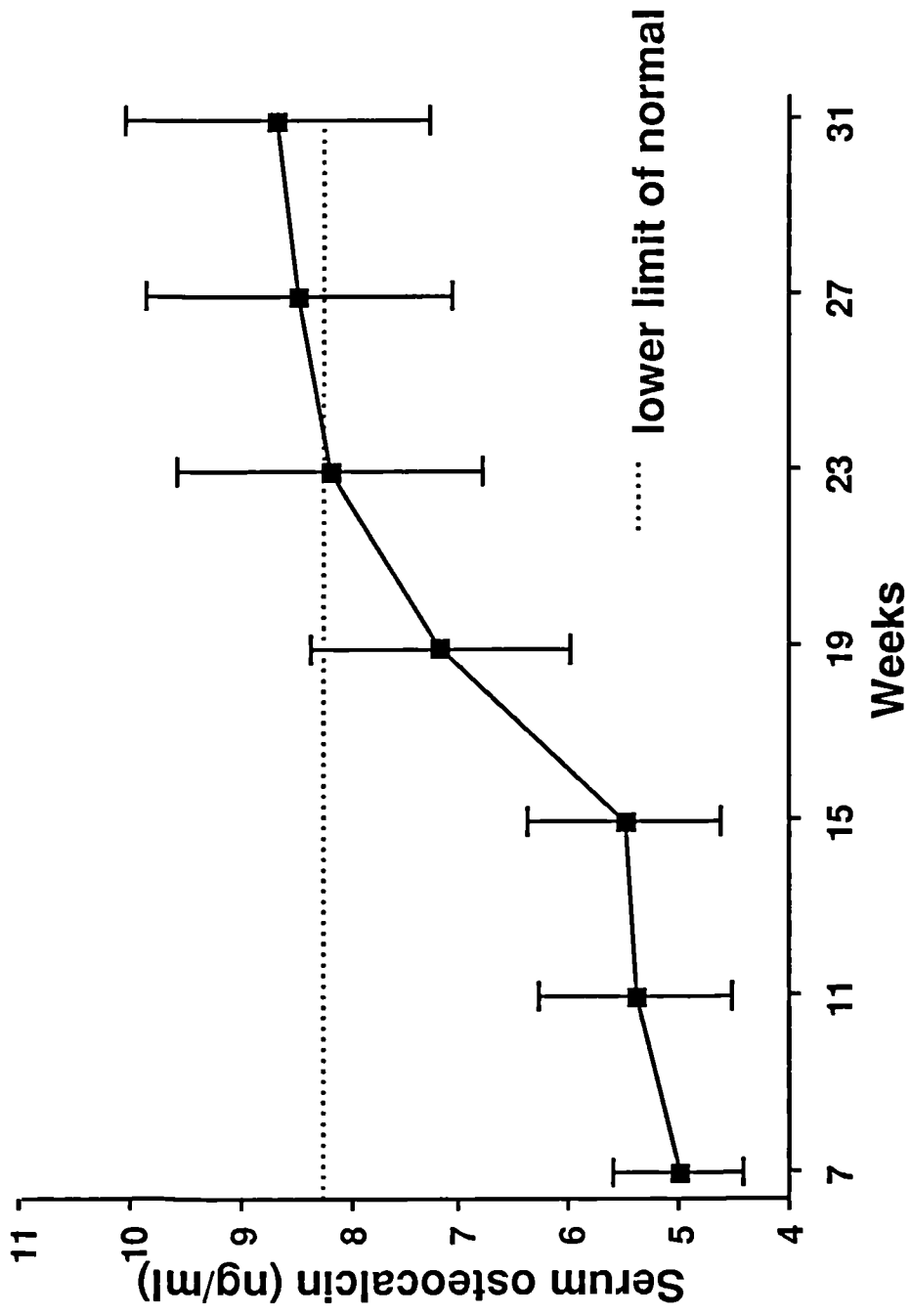
Fig 25.5. The mean (+/- SEM) serum osteocalcin measured in 46 patients with algodystrophy had returned to normal by 23 weeks after Colles' fracture.

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Discussion.

This study has shown that the increased metabolic activity, and presumably bone turnover, following algodystrophy gradually resolved as the condition progressed to the latter stages. The predicted time at which there would be no scintigraphic evidence of an increase metabolic rate was 24 weeks after fracture, provided the decrease was linear. The rate of change however was 0.05 per week which is five times greater than the weekly decrement seen in the control patients (0.01; Chapter 20). This suggests that the rate of change may not be linear. It may be high in the initial stages of the condition and later decrease as the score approaches normality. The consequence of this is that the increased metabolic activity of the bone, as measured by bone scans would continue for longer than the 24 weeks originally predicted. Regardless of this, the delayed phase of the scan would continue to be a useful diagnostic tool in identifying algodystrophy at least upto 19 weeks following a Colles' fracture.

The increased activity on isotope scans probably reflects an increase in bone turnover, although this cannot be detected biochemically. If true, increased turnover must be associated with net resorption resulting in a net loss of bone. There is recovery of trabecular bone by 31 weeks after fracture in the control group. There must therefore have been a reversal of the imbalance in bone turnover originally seen in this group, favouring net formation of bone. This may be explained by two factors. Firstly, the rate of bone formation was probably only slightly depressed in the control population as, although low, the serum osteocalcin was always within the normal range (Fig 25.2). Therefore, although the rate of resorption was initially greater, bone formation continued to prevent too great a loss of bone. Secondly, the increase in bone resorption was probably transient. If so, bone formation must have taken place at a relatively greater rate achieving normal coupling and balance of bone turnover and consequently normal bone density by at least 31 weeks.

In algodystrophy, although there was not a continued loss of bone density, there ·
was similarly no recovery of the bone mass initially lost over the period of study
(Chapter 24). The mechanism for this is uncertain but the low osteocalcin values
suggest that for any given rate of resorption, bone formation may be more suppressed
in algodystrophy than in controls. As turnover decreased with the evolution of the
disease, lower formation rates would delay recovery. In addition, the loss of trabecular
structures may be an inevitable event in that once they are destroyed there is no bone
surface available for new bone formation.

NASAL CALCITONIN.

CHAPTER 26: BIOAVAILABILITY OF NASAL CALCITONIN

Most studies use 80-100 units of salmon calcitonin subcutaneously for the treatment of algodystrophy (Chapter 6). However, this amount appears to have been arrived at purely empirically and there are few dose-response data available. Similarly, little known about the bioequivalence of nasally administered calcitonin as compared with the subcutaneous route. Before studying nasal calcitonin as a treatment for algodystrophy, the question of it's bioequivalence was first considered. With this data it was hoped to make a rational decision as to the amount of nasal calcitonin appropriate to use in the treatment of algodystrophy.

To address this problem the acute hypocalcaemic response to calcitonin was studied. As hypocalcaemia induced by calcitonin is primarily related to its inhibitory effect on osteoclasts (Singer 1976) it was considered appropriate to study patients with increased bone turnover, and therefore patients with Pagets' disease of bone were chosen for investigation. In the patients studied, a standard dose of intranasal calcitonin (400 units salmon calcitonin) was compared to varying doses of calcitonin administered subcutaneously.

Methods

Forty patients with active Paget's disease of bone were studied. These patients were divided into five treatment groups, which were matched for disease activity. Nine patients received, sequentially, and in a random order 1, 10, and 100 units of salmon calcitonin subcutaneously. These tests were separated in time by at least two weeks. For the 1 and 10 unit tests, standard salmon calcitonin solution was diluted with normal saline containing albumin, to minimise its adsorption to the plastic syringe. Nine further patients were given a subcutaneous injection of normal saline. These two groups were compared with a third group of 22 patients, who received 400 units of

intranasal salmon calcitonin, administered as a nasal spray of 200 units into each nostril.

All patients were admitted to a metabolic ward for the period of the test. After an overnight fast and after voiding the bladder, the urine produced over the subsequent hour was collected and saved. Halfway through this period a venous blood sample was taken for serum estimations. At the end of the first urine collection calcitonin or saline was administered to the patients, and hourly urine and blood collections made for the next six hours. The patients remained fasting throughout the six hours of the test, but were allowed to drink distilled water.

Serum was analysed for calcium, phosphate, alkaline phosphatase, creatinine, hepatic transaminases, urea and electrolytes as previously described. The urine was assayed for calcium, phosphate, hydroxyproline and creatinine.

The significance of differences between treatments were assessed using one way analysis of variance, and Student's t-test for unpaired data. Changes in biochemical values during each treatment were studied using the t-test for paired observations. In the case of hydroxyproline and alkaline phosphatase statistical comparisons were made on log-transformed values, but were antilogged for presentation. Results are expressed as the mean ± SEM, unless otherwise indicated.

Results

Before the start of this study there were no significant differences between the groups in any of the measured variables. In particular, the prevailing rates of bone turnover, as judged by the urinary excretion of hydroxyproline and serum activity of alkaline phosphatase, were well matched in the placebo and each of the test groups (Table 26.1).

a) Changes in Serum Calcium

A decrease in serum calcium was observed after the injection of one hundred units of subcutaneous calcitonin, which was evident by the end of the first hour (p=0.002), and maximal from 4 to 6 hours (Fig 26.1). The summated change in serum calcium at 4 to 6 hours was calculated and used as a measure of the maximal hypocalcaemic response in further analyses.

No significant changes in serum calcium were seen in the placebo group, and intermediate responses observed with the lower doses of parenteral calcitonin and with nasal calcitonin. When the summated calcium drop from 4 to 6 hours was plotted for each group a significant obvious dose-response was evident (ANOVA, p<0.01; Fig 26.2).

As expected there was a significant correlation between hydroxyproline excretion before the test and the fall in serum calcium in patients given 100 units of subcutaneous calcitonin (r = 0.7; p = 0.038). No significant correlation was observed however at any other dose, since the hypocalcaemic response appeared to be blunted particularly in those patients with the more marked disease activity. In order to explore this further the relationship between initial disease activity and the hypocalcaemic response was computed by bivariate regression in those patients given 100 units of subcutaneous calcitonin. In this way the expected maximal hypocalcaemic response (E) in the other tests was calculated from the initial urinary hydroxyproline. The observed (O) and expected hypocalcaemic responses for each patient were then compared by plotting:
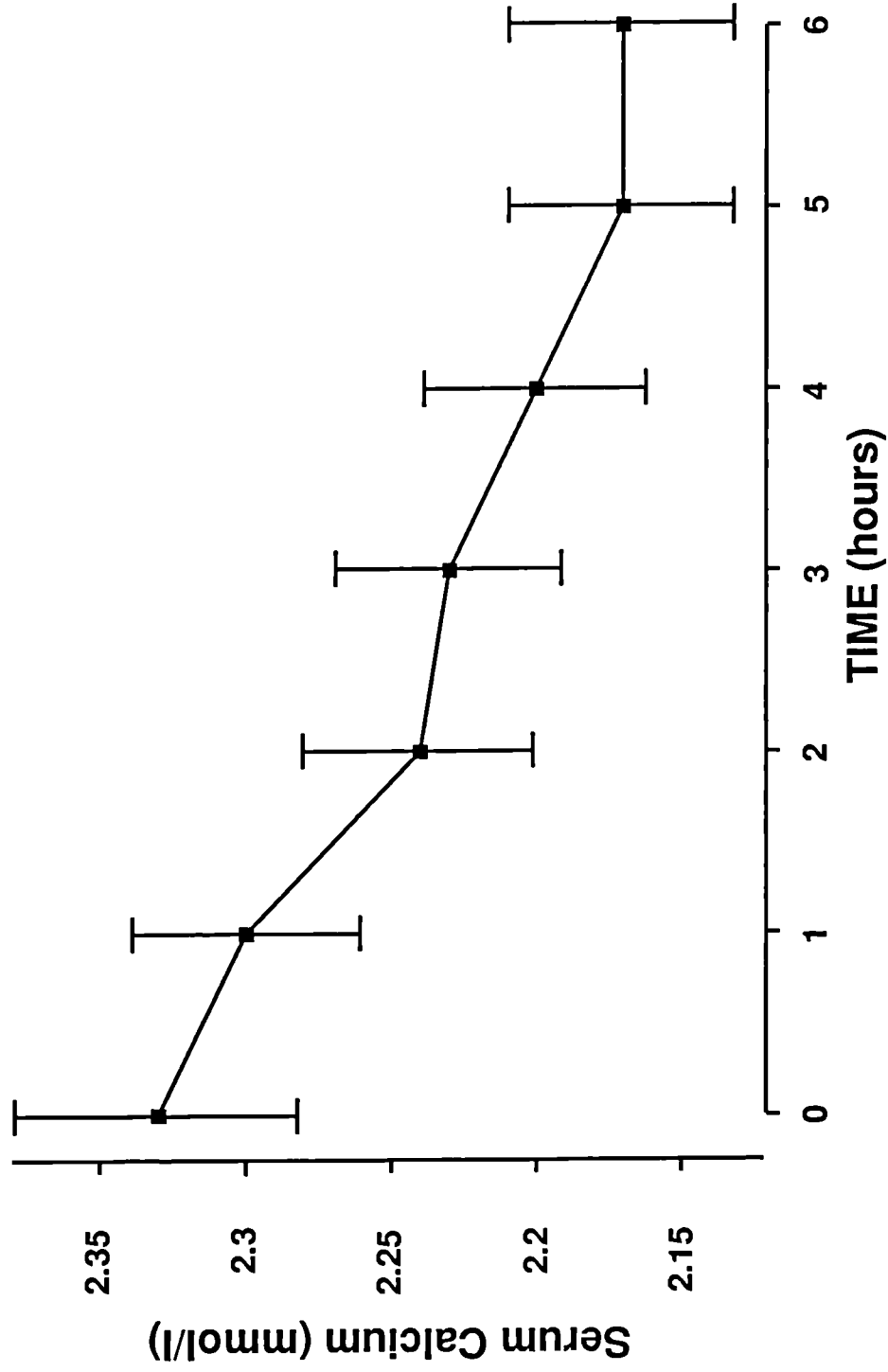
$$(O - E) / E.$$

Fig 26.1. Serum calcium concentration (mean +/- SEM) following subcutaneous injection of a single dose of 100 units of salmon calcitonin in 9 patients with Paget's disease of bone.
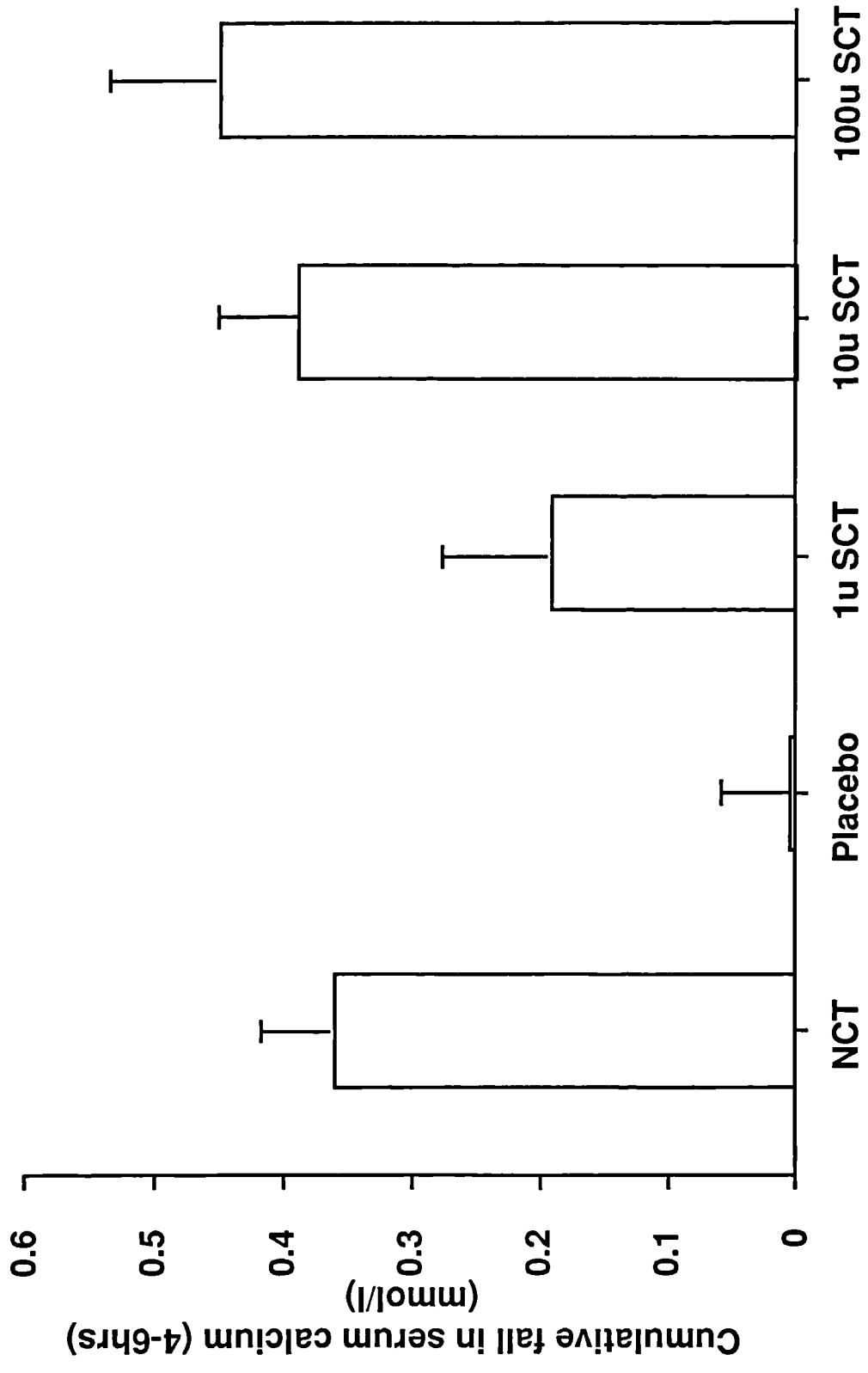
Fig 26.2. Cumulative fall in serum calcium after nasal calcitonin after nasal calcitonin (NCT), placebo and 3 doses of parenteral calcitonin (SCT). The fall in serum calcium was calculated from the summed decrement in values observed between 4 to 6 hours.

b) Other Effects

After the administration of 100 units of subcutaneous calcitonin there was an initial increase in the urinary hydroxyproline excretion (p=0.049 at 2 hours), and this was followed by a significant fall decrease to below starting values from 4 to 6 hours (p<0.05). During this period (4-6 hours), as with the serum calcium, there was little further change in the observed values.

A similar pattern was seen with 10 units of calcitonin. No significant changes in hydroxyproline excretion were observed with either the 1 unit of calcitonin or placebo. Nasal calcitonin induced a fall in the urinary hydroxyproline excretion that was significant by 3 hours (p=0.042) and had reached a steady state by 4 hours. The cumulative fall from 4 to 6 hours (58.4 ± 14.2 mmol hydroxyproline/mol creatinine) was less than that seen with both 10 and 100 units of subcutaneous calcitonin (75.9 ± 34.2 and 67.2 ± 29.6 mmol hydroxyproline/mol creatinine).

Serum activity of alkaline phosphatase did not change significantly throughout the test in any group.

Discussion

In this study, we have shown that surprisingly low doses of calcitonin appeared to have acute effects qualitatively similar to those observed with the highest dose used (100 IU) which are commonly recommended for the treatment of bone disease. The daily endogenous secretion rate for calcitonin has been estimated at 20 IU, but this is almost certainly an overestimate (Kanis 1985). It therefore seems possible that such doses as 10 IU might be exerting pharmacological effects. The physiological role of calcitonin in man is still speculative (Kanis et al. 1985), but the small responses evoked with only 1 unit of calcitonin suggest it may still have a role in extracellular calcium homeostasis.

In this study 400 units of intranasal calcitonin, given as a single dose, appeared to have biological effects similar to those observed with the use of subcutaneous calcitonin. The activity of the nasal spray was however low, since the hypocalcaemic effect of 400 units of intranasal calcitonin was similar to that of 10 units subcutaneously. The dose-response of nasal calcitonin was not studied, but the sub-optimal response in serum calcium suggests a bio-equivalence of approximately 2.5%. The efficacy of small doses of calcitonin suggest that at low rates of bone turnover the nasal spray, even with it's low bioavailability, might be suitable for the treatment of either generalised or, as in algodystrophy, regional osteoporosis.

CHAPTER 27: THE USE OF NASAL CALCITONIN IN THE TREATMENT OF POST-TRAUMATIC ALGODYSTROPHY.

Calcitonin, as a therapy for algodystrophy, has received widespread interest because of it's analgesic action (Pecile *et al.* 1975; Fraioli *et al.* 1982), effects on the microvasculature and bone resorption (Freidman and Raisz 1965; Chapter 6) properties which would be expected to be of value in the treatment of algodystrophy. Several controlled trials of parenteral calcitonin report a beneficial action (Doury *et al.* 1981; Martin 1985; Gobolet *et al.* 1986) and are mentioned in detail in Chapter 6. The need for parenteral administration may be overcome by formulations which are absorbed through the nasal mucosa. The use of the nasal spray has had some encouraging results in the treatment of Pagets' disease (Reginster *et al.* 1984) and osteoporosis (Reginster *et al.* 1987; Christiansen 1988) and for this reason a prospective double-blind controlled study to evaluate it's use in algodystrophy was performed.

Methods.

Two weeks after their plaster had been removed (as in the study design for the natural history of algodystrophy), any patients who exhibited features of algodystrophy were asked if they would participate in a trial of treatment of nasal calcitonin. The clinical techniques and investigations (including radiography, bone scintigraphy, photon absorptiometry and biochemical assessment) used in evaluating the response to treatment were identical to those used in the assessment of the natural history of the condition (Table 8.3) and are described in detail in earlier chapters. During the treatment period however (weeks 7 to 11 after fracture) clinical and biochemical data were recorded weekly.

Exclusion criteria included:

1)   A history of unstable cardiovascular disease or uncontrolled hypertension.

2)   Any medical or surgical condition which would be likely to compromise nasal absorption, subsequent distribution, metabolism or excretion of calcitonin.

3)   A history of alcohol or drug abuse.

4)   Known hypersensitivity to salmon.

5)   Current treatment with diphosphonates, sodium fluoride, mithramycin, phosphates or glucagon.

6)   Pregnant or lactating.

The trial was designed as a randomised double-blind placebo controlled study. Forty patients were studied; 20 with the active drug and 20 placebo. The active drug was given as a daily dose of 400 units of salmon calcitonin (Sandoz, Basle) intranasally for four weeks. The canisters containing the active drug (Fig 27.1) gave a metered dose of 100 units of salmon calcitonin in a normal saline carrier. The placebo canister provided the equivalent amount of normal saline only. After the pre-treatment data had been recorded, patients were instructed to insert the nozzle of the canister into the nostril as far as was comfortable and then depress the lever twice to deliver the two standard doses. This was then repeated in the other nostril providing a total dose of 400 units at one sitting. This procedure was performed every morning for the four weeks of the study period.

The patients were reviewed weekly during the period of drug administration and any side-effects noted. At the end of the treatment period, their review continued according to the protocol specified for the study into the natural history (Table 8.3). Patients were not formally referred to the physiotherapy department but were given general instructions on mobilising the upper limb.

The values were expressed as mean ± one standard error of the mean (SEM) and the significance of difference between means calculated using Student's t test. Differences in proportions were calculated using the Chi-squared test with Yates correction were appropriate. Kaplan-Meier actuarial analysis was also performed on the

dolorimetry data and any difference between groups calculated using Gehan's modification of the Wilcoxin Rank test.

Fig 27.1. The canister used to administer the nasal calcitonin.

Results.

There was no difference in the mean age, sex distribution or duration of immobilisation at study entry between the two groups (Table 27.1). Both groups were matched for disease activity as judged by clinical, biochemical and skeletal methods of assessment (Table 27.1). Two patients withdrew from the study, both from the placebo group. One developed acute cholangitis and the other did not wish to continue treatment for personal reasons. There were no local or systemic side-effects from the treatment in any patients.

In both wings of the study there was a progressive and significant improvement in patient assessment of pain, stiffness, hand swelling and vascular instability (Fig 27.2). This was matched by a progressive decrease in bony tenderness, hand volume and an increase in grip strength so that values for the ratios (affected to unaffected side) changed towards unity (Fig 27.3).

There was no significant difference between the calcitonin and placebo group, with regards to tenderness (dolorimetry), hand volume or grip strength over the study period (Fig 27.3). Nor were there differences between groups in the perception of pain, vascular instability, swelling and stiffness between the two groups (Fig 27.2).

There was a trend however, towards a greater improvement in the dolorimetry ratio and perception of stiffness in patients given calcitonin. At the end of the study period, 70% of placebo treated patients had abnormally tender fingers, compared to 60% in those who received calcitonin. Stiff fingers persisted in 90% in the placebo and 80% of the calcitonin group, but actuarial analysis showed no significant difference between the treatment wings at the end of treatment or at the end of the study.

A small but significant decrease in serum calcium occurred in the calcitonin treated patients during treatment which reversed when treatment stopped (Fig 27.4). Mean serum calcium also fell in placebo treated patients but the decrement was smaller

and the difference not significant. There was no significant change in urinary hydroxyproline and calcium excretion in either wing of the study.

Tracer uptake on scintigraphy decreased significantly ($p < 0.001$) in the affected hand and the ratio approached unity in calcitonin and placebo treated patients. The improvement was the same in both groups (Table 27.2). The measurements of trabecular and cortical bone mineral density, and radiographic score remained low in both groups throughout the study period.

There were no local or systemic side-effects in either the calcitonin or placebo group.

Table 27.1. Clinical, biochemical and physical findings (mean ± SEM) of patients with algodystrophy at randomisation. There was no significant difference in the pre-treatment values between the two groups. Where no units of measurement are given, with the exception of the radiographic score which has arbitrary units, the value expressed is the ratio of the affected to unaffected hand.

	Calcitonin	Placebo	Normal range
Age (years)	60.8 ± 2.7	65.5 ± 1.8	
Sex (F:M)	15:5	19:1	
Time immobilised (days)	38.1 ± 1.8	40.6 ± 1.9	
Dolorimetry score	0.73 ± 0.03	0.68 + 0.04	0.92 - 1.08
Hand volume	1.12 ± 0.02	1.11 ± 0.02	0.90 - 1.10
Grip strength	0.21 ± 0.03	0.20 ± 0.03	0.76 - 1.24
Serum calcium (mmol/l)	2.43 ± 0.02	2.43 ± 0.02	2.26 - 2.63
Urinary calcium (mol/ mol creatinine)	0.28 ± 0.04	0.26 ± 0.05	< 0.30
Urinary hydroxyproline (mmol/mol creatinine)	27.9 ± 2.89	28.5 ± 3.60	< 30.0
Alkaline phosphatase (IU/l)	93 ± 4.95	96 ± 19.19	35 - 105
Osteocalcin (ng/ml)	6.5 ± 1.14	4.8 ± 0.77	8 - 32
BMD$_{trab}$	0.72 ± 0.06	0.69 ± 0.04	-
BMD$_{cort}$	0.86 ± 0.06	0.84 ± 0.06	-
Combined cortical width	0.97 ± 0.02	0.96 ± 0.02	-
Radiographic score	6.81 ± 0.87	8.20 ± 0.72	-
Isotope score	2.01 + 0.19	2.07 + 0.19	-

Table 27.2. Changes in radiographic, densitometric and scintigraphic assessment after

treatment with calcitonin or placebo. The change (mean ± SEM) is shown as a

percentage change of initial value (± SEM). There was no significant difference in the

change between groups nor, with the exception of isotope score, between the pre-

treatment and end of study values. Improvement in values towards normal are

indicated as a positive change.

	Percentage change			
	Calcitonin		Placebo	
	mean + SEM	n	mean + SEM	n
BMD$_{trab}$ (g/cm^2)	+3 ± 5	10	0 ± 10	10
BMD$_{cort}$ (g/cm^2)	+3 ± 8	10	-6 ± 6	10
Combined cortical width (mm)	0 ± 1	20	-1 ± 2	20
Radiographic score	+3 ± 10	20	+18 ± 10	20
Isotope score	+33 + 5 *	14	+25 + 5 *	13

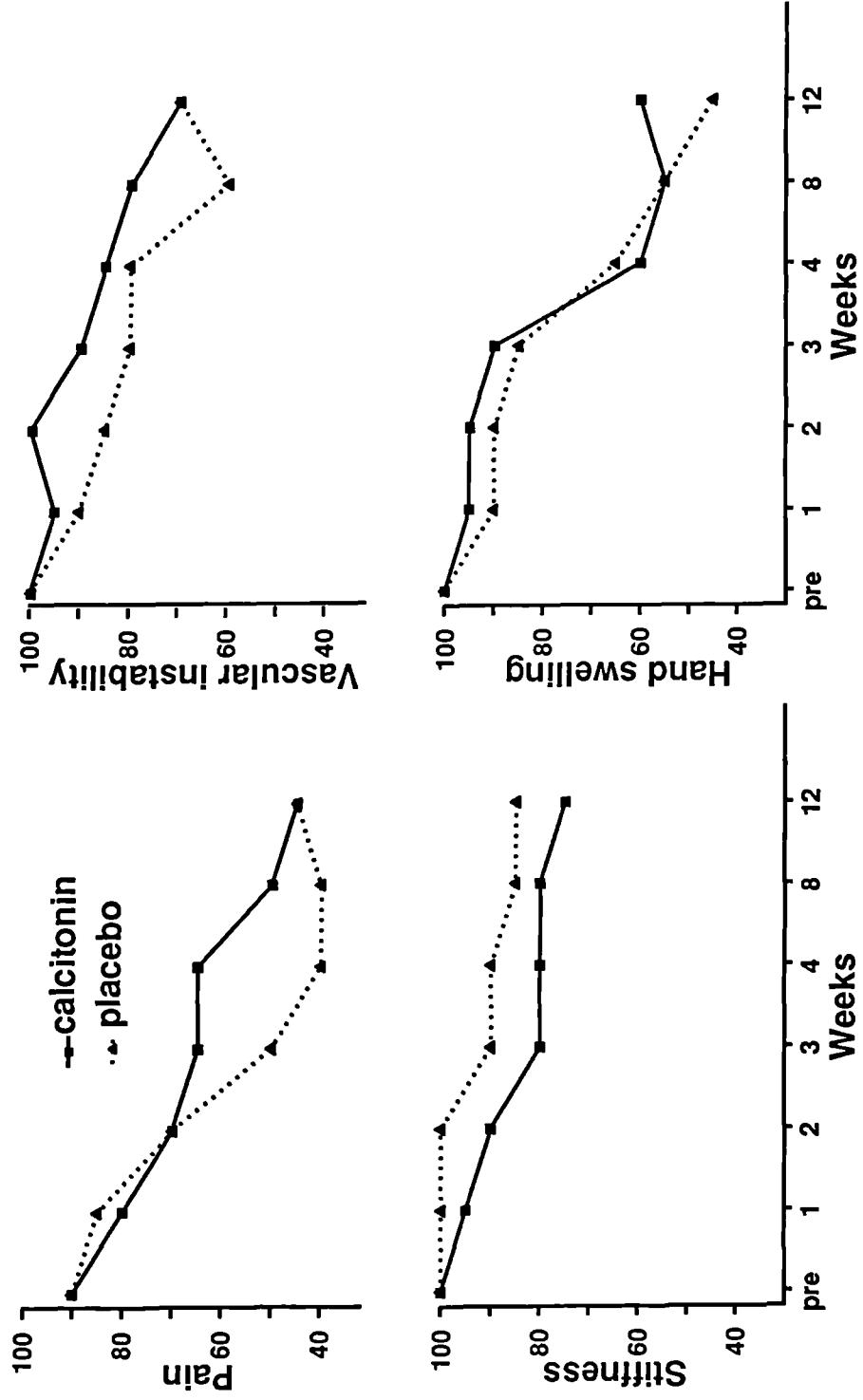* - significantly different from pre-treatment value; p < 0.001.

Fig 27.2. *The proportion of patients (%) complaining of pain, vascular instability, swelling and stiffness throughout the study period. There was a gradual resolution in both groups, although stiffness resolved more slowly.*
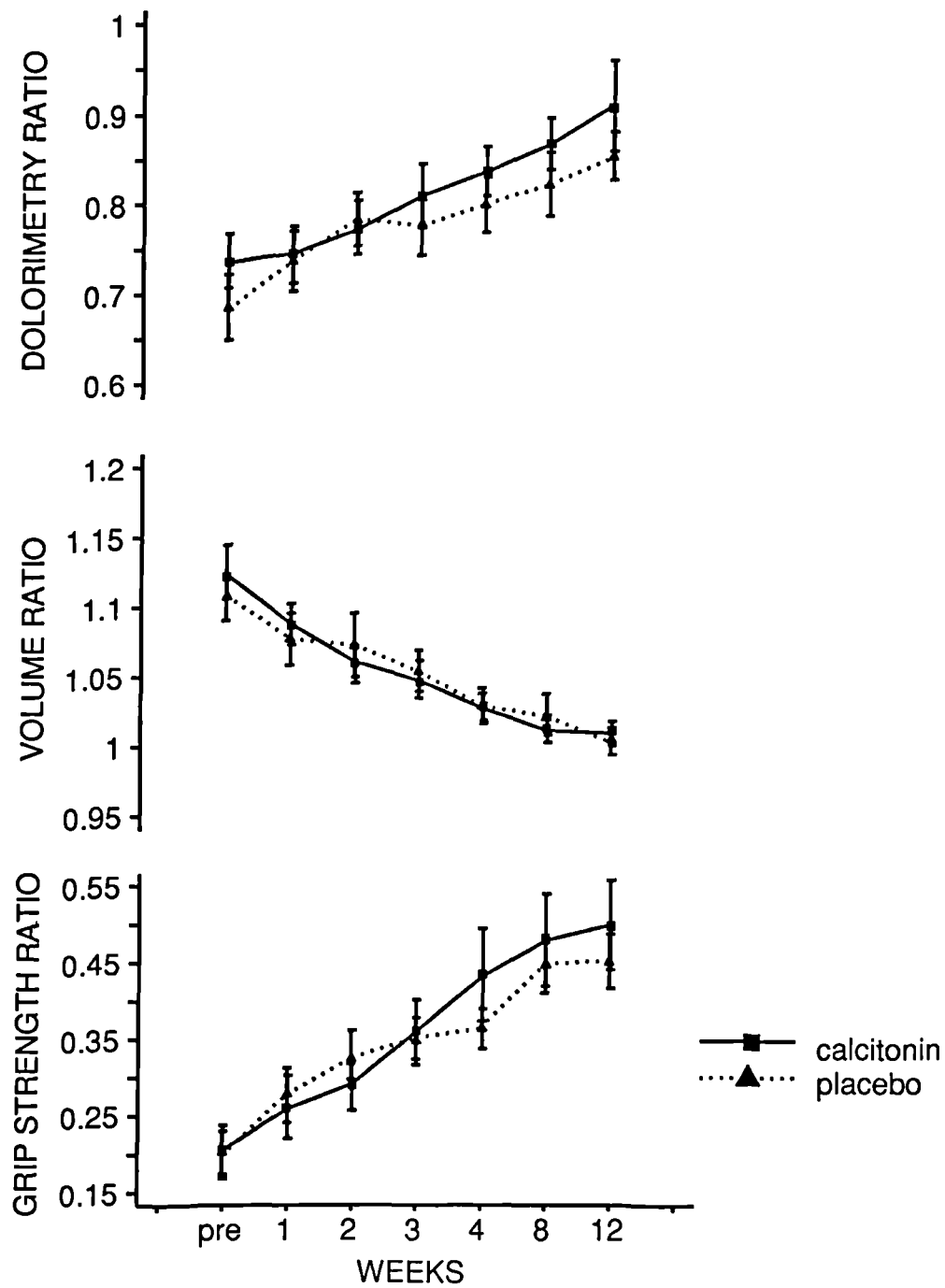
Fig 27.3. The mean ratio affected to unaffected (+/- SEM) for the three quantitative clinical methods of assessment, dolorimetry, hand volume and grip strength, throughout the study period. In all three parameters the ratios changed progressively with time towards normal (a ratio of 1). There was no significant difference between the two treatment groups.
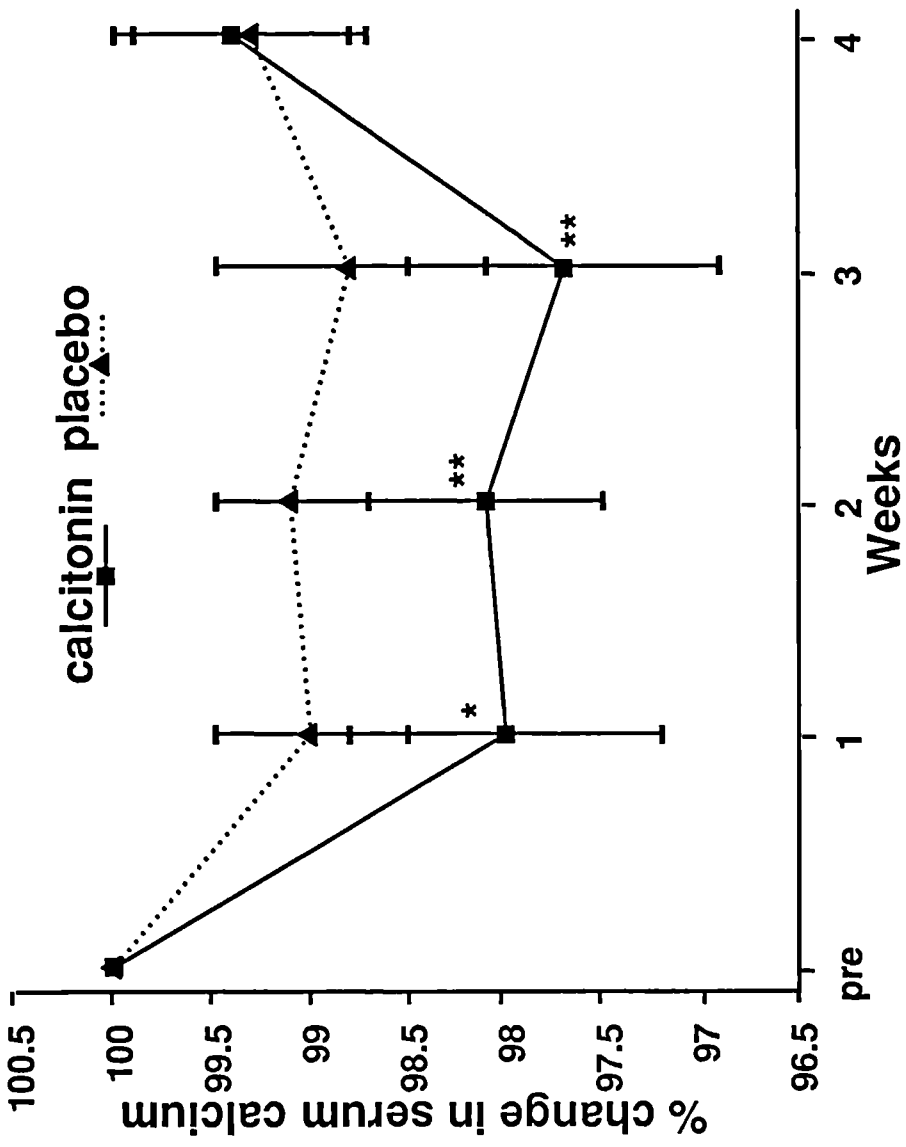
Fig 27.4. Mean serum calcium (± SEM) in patients given calcitonin (■) or placebo (▲). Mean serum calcium fell significantly in the calcitonin treated patients (* p < 0.05; ** p < 0.001, paired t test).

Discussion.

Since the first report by Eisinger *et al.* (1973) on the use of calcitonin in algodystrophy, the beneficial effects of it's parenteral injection have been documented in several studies (Acquaviva *et al.* 1976; De Bastiani *et al.* 1978; Ginsberg *et al.* 1978; Doury *et al.* 1981; Martin 1985; Gobolet *et al.* 1986). Calcitonin appears to have a marked effect on signs and symptoms, particularly in the early stages of the disorder, but many of these claims have been based on open and uncontrolled studies. In one controlled randomised double-blind study of 28 patients with algodystrophy of the lower limbs reported by Doury *et al.* (1981), there was an appreciable improvement in pain in 64% of those receiving calcitonin 100iu daily compared with 25% in the placebo group after 14 days (p < 0.001). By 28 days there was however, no significant difference in pain between the two groups. Although this study demonstrates a rapid effect of calcitonin, it also confirms that spontaneous resolution of symptoms occurs commonly in algodystrophy. Consequently, open studies evaluating the use of calcitonin should be interpreted with caution.

In the study reported here, calcitonin given as a nasal spray was shown to have no significant effect on the clinical progression of post-traumatic algodystrophy compared to that noted with a placebo spray. The methods used to assess algodystrophy have been shown in previous chapters to be sufficiently reproducible to discriminate effectively between algodystrophy and a control population following Colles' fracture. These considerations suggest that the failure to detect a more rapid or complete response in calcitonin treated patients is unlikely to be due to inadequate methodology.

A possible, and perhaps the most likely, explanation for not finding a difference between the treated and placebo wing is that the bio-availability of the nasal formulation was too low. Although there was a small decrease in serum calcium during the treatment period, the response was not associated with changes in the indices of

bone turnover. In particular, the fasting urine excretion of calcium did not change.

This suggests that the decrease in serum calcium was due to a decrease in renal

tubular reabsorption of calcium, a known effect of calcitonin. The absence of clinical

and skeletal effects suggest that, although small amounts of calcitonin were absorbed,

they were insufficient to affect these indices of bone turnover. In addition, there were

no systemic side-effects reported which are a dose - dependent effect of calcitonins.

In studies of the acute calcium lowering effect in patients with Pagets' disease,

400 iu given by nasal spray induces effects similar to those induced by 10-20iu

subcutaneously (Chapter 26). If acute effects can be used to predict long term

responses, and if calcitonin is effective in algodystrophy of the hand, then the minimum

effective daily dose in algodystrophy is likely to lie between 10 and 100 iu. An

alternative to increasing the dose administered would be to add a promoter to enhance

it's nasal absorption. A number of such formulations are currently undergoing

evaluation.

In conclusion, 400 iu of nasal calcitonin in the formulation used is inadequate

for the treatment of post-traumatic algodystrophy though does exert a biochemical

effect. Further studies using higher doses of calcitonin or formulations which enhance

it's absorption will be required to evaluate it's potential use in this condition.

CHAPTER 28: CONCLUSIONS

The main criticisms of previous studies into algodystrophy have been the variation in the subject data and methods of assessment. Although the majority of studies concern post-traumatic algodystrophy, there was often great differences in the type and time from trauma and the initial management, all factors which may influence expression of the condition. In addition, the assessment techniques were commonly subjective and therefore open to observer bias. It was hoped to overcome these problems by selecting a relatively uniform population with regards to age, sex, type of trauma and initial management. In addition they were reviewed at identical periods after fracture using techniques with good reproducibility and precision.

The presence of the classical features of algodystrophy, pain and tenderness, vascular instability, swelling and stiffness, were used to identify patients with the condition. This amounted to 28% of patients who displayed all four features. In addition, the distribution of the features throughout the whole population was highly significant. This implied that in the presence of one feature, the patient was highly likely to display all four features, and if one feature was absent, it was likely that none of the features would be present. Thus it was possible to distinguish two populations, one with and one without algodystrophy, and also confirmed the high incidence of algodystrophy detected in a previous study (Atkins *et al.* 1990). Therefore, given this high incidence of algodystrophy and the uniform nature of the patient population, it seemed appropriate to use this clinical model in further studies.

It appeared that the degree of trauma sustained did predispose to algodystrophy in that patients with a higher Frykman score or displacement of the fracture (necessitating manipulation) were more likely to develop algodystrophy. Therefore, although algodystrophy does occur after minimal trauma, as confirmed in this study, those with more extensive injury should be considered a higher risk. There was no

association between the time from injury to treatment, time in plaster or type of plaster, and the development of algodystrophy.

The most reproducible and accurate method of diagnosing algodystrophy was dolorimetry. Although the technique is easily learnt and relatively quick to perform, it is unlikely to be adopted in the clinical setting. It's high precision however does indicate that part of the general examination of patients suspected of having algodystrophy should include the presence of tenderness distant from the site of trauma. This can easily be performed by digital pressure. The other two clinical quantitative techniques, hand volume and grip strength measurements, were of less diagnostic value. All three however, were used to document the resolution of symptoms with time. Although the therapeutic trial used in this study did not demonstrate any alleviation in symptoms, due to the poor bio-availability of nasal calcitonin, it is hoped that these techniques will be useful in assessing the resolution of symptoms using more effective treatment regimes.

The most precise diagnostic investigation was scintigraphy with a maximum predictive value of 88%. This however was only slightly better than using the radiographic scoring system on plain radiographs of the hand and wrist (maximum predictive value - 83%) despite potential problems due to simple disuse atrophy. It is often quoted (Doury *et al.* 1981) that scintigraphic changes precede radiographic however this was not true in this study in the presence of disuse atrophy at approximately seven weeks after fracture. This study did demonstrate that scintigraphy remained highly specific for the diagnosis of algodystrophy at a stage earlier than has been reported (Atkins *et al.* 1990). It is possible that a scan earlier than seven weeks will identify patients with algodystrophy however a complicating factor may be confusion caused by increased uptake secondary to disuse atrophy which would reduce specificity.

The late sequelae of algodystrophy, chronic causalgic pain, atrophy and stiffness, are well documented but occur relatively infrequently following trauma, accounting for the 1-2% incidence quoted in the English literature. The discrepancy between this incidence and the 28% found in this study became clear after studying the progression of the condition. There was resolution of pain and swelling in 40%, tenderness and vascular instability in 20% and stiffness in 10%, three months after fracture. These symptoms disappeared spontaneously in approximately 30% of patients. This has obvious implications in the interpretation of uncontrolled therapeutic trials in that symptomatic improvement may be attributed to the efficacy of a treatment rather than the normal expected spontaneous improvement.

One year after fracture, the point at which most retrospective papers review Colles' fractures, there was an appreciable decrease in the number of patients who still demonstrated tenderness, swelling or vascular instability. Fifty percent however, still complained of a sensation of stiffness with 14% demonstrating contractures in the inter-phalangeal joints. In the absence of the other features, stiffness may be assumed to be a complication of the fracture itself and not the end stage of algodystrophy. This therefore accounts for the discrepancy between the incidence of algodystrophy in this study and that reported in other series. It may also explain the 24% with functional disability reported by Bacorn and Kurtzke (1953) in their large study of Colles' fractures.

Regardless of the exact percentage of patients who remain with problems due to algodystrophy one year after fracture, those who had settled spontaneously still suffered significant morbidity during this period. At six months after fracture, 80% of patients with algodystrophy complained of finger stiffness which contributed to the significant difference in the functional scores between algodystrophy and control patients. Therefore the incidence of algodystrophy following trauma, at least after a Colles' fracture, is far higher than had previously been supposed and, although many

may be milder, settling by one year after fracture, they still cause appreciable short term morbidity. Accordingly, a more careful appraisal of patient's symptoms following trauma would identify those patients with algodystrophy at an earlier stage and allow appropriate management to prevent this short term morbidity.

In addition to the patients who displayed all the clinical features of algodystrophy detailed earlier, there was a population who displayed some but not all of these features. This borderline group again had an abnormal distribution of features, either having three or one of the signs which means that the features did not occur at random. It may be that with more sensitive methods of clinically assessing algodystrophy, the patients at either end of this spectrum would merge into the groups with or without algodystrophy, thus increasing the incidence of the condition. Indeed, although there was no formal functional assessment made in this group, stiffness did persist for 19 weeks after fracture in 20% of patients. It may be inferred from this that they did suffer a degree of morbidity.

Although this study used patients with Colles' fracture as the clinical model, it is reasonable to suppose that the incidence of algodystrophy is also high at other sites of trauma. Again, there is not likely to be permanent morbidity as the recorded incidence of algodystrophy is generally low regardless of the site. This is not to say however, that these milder cases would not cause short-term morbidity as seen in the Colles fracture.

The clinical changes demonstrated in the 28% of patients with algodystrophy, using the clinical criteria detailed earlier, were associated with a greater and more persistent loss of bone mineral density than seen after uncomplicated fracture. This study demonstrated that changes in skeletal mass occurred more rapidly in patients with algodystrophy than in controls during the period of immobilisation and failed to recover seven months after fracture. In nine patients followed for one year, there was still no evidence of the restoration of normal bone mass.

The loss of bone mineral density occurred in both cortical and trabecular bone,
but was more apparent in the latter due to it's higher rate of bone turnover. The
pathogenesis of the skeletal changes is unclear but may have been due to an increase
in blood flow which was demonstrated by the correlation between the isotope scan
metacarpal score and bone mineral density of trabecular bone. These vascular changes
were also seen following simple disuse atrophy but to a significantly lesser degree.
Even after a hemiplegia, where there was complete immobility of the limb, the degree of
uptake was less than that seen in algodystrophy. The clinical implications of these
skeletal changes remain unknown. However, there were losses of 10% in cortical and
25% in trabecular bone over a six month period, changes normally seen after ten years
in post-menopausal osteoporosis. Accordingly there may be a higher than normal risk
of refracture or of stress fractures.

The skeletal changes measured by radiological, densitometric and scintigraphic
techniques which to be highly reproducible. However, it was not envisaged that they
would become routine in clinical practice but would provide useful tools to measure
serial changes in skeletal mass and architecture, and response to treatment in
controlled therapeutic trials.

In view of the evidence that parenteral calcitonin had beneficial effects on the
evolution of algodystrophy, a controlled randomised study was performed with nasal
calcitonin. It was hoped that the use of this formulation would increase patient
compliance though there were doubts about it's bioavailability. For this reason, dose
response studies were performed prior to the clinical trial, comparing the hypocalcaemic
effect of subcutaneous with nasal calcitonin. This demonstrated an acute
hypocalcaemic response with 400 units of nasal calcitonin but with an efficacy
equivalent to 10 units of subcutaneous calcitonin. Previous studies of subcutaneous
calcitonin had not identified the optimum dose required to alleviate symptoms, and
therefore, despite it's low bioavailability, 400 units of nasal calcitonin were used in the

clinical trial. As expected there was a small hypocalcaemic response during the treatment period, but no significant difference in the resolution of symptoms between the active and placebo group. It is therefore evident, based on the results in this study and those of others, that the optimum dose for the treatment of algodystrophy lies between 10 and 100 units of calcitonin. In it's present formulation, nasal calcitonin has no role in the treatment of algodystrophy.

In conclusion, the work in this thesis has shown that algodystrophy is common, resolves spontaneously but causes morbidity in the short-term and results in changes in skeletal architecture and mass which may not be reversible. Research in the future into this condition should be directed to other sites of trauma to determine whether the incidence, natural history and morbidity are comparable to that found in Colles' fracture. In addition, although the condition does resolve spontaneously in the majority of patients, the morbidity suffered does warrant treatment. Efforts should therefore be made to firstly identify the condition early, and secondly tailor the treatment to the degree of morbidity expected. This might require the identification of various features at presentation which correlate with a poor outcome. Those with the worst prognosis may need sympathetic ganglion blocks from the outset whereas milder states may require simple physiotherapy with or without calcitonin. Research should also be directed towards prophylaxis for the condition. If this is contemplated, the Colles' fracture model and methods of assessment used in this study would be suitable material. Indeed any therapeutic study would benefit from such a controlled population and reproducible methods of assessment.

Appendix I.

The age (mean ± SEM) and sex distribution of the patients in the algodystrophy and control groups for each individual investigation. In all cases the groups were well matched.

		ALGODYSTROPHY				CONTROL		
	No:	Age	Period of Immobilisation	Sex % Female (F:M)	No:	Age	Period of Immobilisation	Sex % Female (F:M)
Clinical	73	64.5 ±1.15	39 ± 0.9	62:11 85%	201	63.4 ±1.09	37 ± 0.6	162:39 81%
Radiography	44	65.1 ±1.32	39 ± 0.9	39:6 85%	33	64.0 ±1.01	37 ± 0.6	29:4 86%
Densitometry	29	63.2 ±1.85	39 ± 0.9	22:7 76%	23	63.1 ±2.20	37 ± 0.6	22:1 95%
Scintigraphy	43	63.4 ±1.52	39 ± 0.8	35:8 81%	10	62.6 ±3.18	36 ± 0.7	8:2 80%
Biochemistry	47	64.2 + 1.47	40 + 0.9	39:8 83%	29	64.4 + 1.92	38 + 0.6	27:2 93%

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ADDENDUM

A number of points have been raised which need further clarification.

Chapter 8.

Although there is no sentence stating that a Colles' fracture is a fracture of the distal radius with or without a fracture of the ulna styloid, this is detailed in the description of Frykman's classification (page 71 and Table 8.2). In addition the age prevalence, incidence, predisposing factors and mechanism of injury are discussed on page 69.

Chapter 9; page 77-81.

The methodology has been described before in detail and was referenced in the text (page 80; Atkins *et al.* 1989). The tip of the dolorimeter was applied to the dorsum of the MCPJ, PIPJ, DIPJ, proximal and middle phalanx from the index to little finger, a total of 20 measurements per hand. The tip of the examiners left index finger and thumb were used to *steady* the tip of the dolorimeter and did not apply pressure. This point is made in the text (page 80; paragraph 2).

Chapter 11; page 134; paragraph 2.

The ten patients in the uncomplicated Colles' fracture group were picked at random. Their age and sex prevalence was similar to that found in the algodystrophy group. Therefore they were comparable groups, though they were not age and sex matched in a prospective sense.

Chapter 11; page 137; paragraph 2.

There was no intention to draw firm conclusions from these data as to the exact timing of the resolution in bone scintigraphy after uncomplicated Colles' fracture, particularly in view of the small numbers and different investigators. The time to resolution was calculated on the *assumption* that resolution was linear. Because there were only two points, there was no intention to infer that the resolution *must* be linear. The reason for including this graph was to compare with the resolution found in the algodystrophy group on repeat scintigraphy (Fig 25.1; page 298). The basis on which this assumption rests can only be tested by prospective studies.

Chapter 12; page 151; paragraph 2.

Intra-observer reproducibility of the single photon absorptiometry technique was carried out on paired measurements (page 146). This demonstrated a coefficient of variation of 4.2% for proximal scans and 4.4% for distal scans. This compares favourably with estimates of density and content errors when single photon absorptiometry is used at other sites. The long-term reproducibility was not performed on my patients but is well established for mono-chromatic studies and is 1% or less. The long-term reproducibility errors depend on changes in fat content within patients and on the deterioration of the isotope source. These considerations apply equally to measurement of the forearm as it does to the metacarpal but changes of fat are less likely in the soft tissues of the metacarpal. In any event these errors are substantially less than the errors of repositioning which I have reported.