OSTEOPOROSIS IN RHEUMATOID ARTHRITIS

BY

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DEDICATION.

THIS WORK IS DEDICATED TO

MY WIFE ZULEIKHA

MY DAUGHTERS RABIA AND RIFQA

MY LATE FATHER SULEIMAN

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PREFACE.

The terms osteoporosis and osteopaenia will be used interchangeably in order to avoid confusion. The literature abounds with reports of osteoporosis in rheumatoid arthritis (RA). However, close scrutiny shows that several questions remain unanswered. It is not clear whether the osteopaenia of RA is due to a generalised defect in collagen synthesis or a result of excessive bone resorption. The main reason for this continuing controversy appears to be related to inadequate control for age and the menopause in the subjects studied. Since the exact mechanisms for age-related (Type II) and post-menopausal (Type I) idiopathic osteoporosis are not known, it is clear that any attempts at separating these effects from the additional multi-factorial basis of bone loss in RA could only add to the confusion. The analysis is compounded by the fact that many of the kinetic markers of bone metabolism may behave as acute phase reactants in RA, making their evaluation difficult in the absence of information about disease activity, physical activity, drug therapy and nutritional status. The age-related prevalence of RA adds to the difficulties in evaluating an adequate sample of young patients. For all these reasons, it would seem appropriate to embark on a systematic analysis of the factors possibly related to bone loss in RA. The ideal group of patients would be young and premenopausal. This creates a further technical difficulty in that current evidence suggests that RA patients in this age group rarely show significant differences in bone mass when compared with normal subjects. Several reasons could possibly explain this. They include the lack of a definition of osteoporosis; insensitivity of the Vernier caliper technique in detecting

small changes over time; predominantly cortical bone loss, usually at the metacarpals; and limited availability of the sophisticated nuclear techniques. Costs can also be prohibitive. South Africa is a vast country with a population of several million subjects. The most sophisticated method of bone mass measurement available is the single photon absorptiometer. In Cape Town, where this study was undertaken, the only objective measure of bone mass is radiogrammetry. Despite its limitations, radiogrammetry has great potential value as a measure of radiological events in the hands of patients with RA, where the greatest damage from the disease is generally seen. Osteoporosis is usually the earliest radiological feature (apart from soft-tissue swelling - which is usually clinically apparent). The need for a quantitative measure of early radiological change has been highlighted in a number of recent editorials. Unfortunately, the Vernier caliper technique of radiogrammetry is poorly reproducible, between different observers and the same observer at different times. The method is tedious and subject to a number of potential sources of error. The earlier innovations of computer-assisted techniques has done relatively little to improve the technical speed of the procedure, and the error has remained unchanged. Reports of single photon absorptiometry have been unable to show significant correlations with disease activity in young subjects (small samples). The same can be said about studies using neutron activation analysis. Dual photon absorptiometry measures trabecular bone and its application to measurements in the hand and wrist is encouraging. It is against this background that I undertook to study a group of 100 young subjects with RA who were premenopausal and independently ambulant. They were to be compared with 100 young normal subjects. Exact age and sex matching was considered inappropriate since statistically significant changes have been generally difficult to

detect in this age group. Males usually have a higher bone mass, and RA is generally a disease of females, so the groups were marginally matched for these important factors. The protocol was designed to evaluate as many of the confounding variables as possible, in the limited scope of a cross-sectional analysis. A computer-assisted technique using a digitiser interfaced with a personal computer was designed and evaluated. Patients with systemic lupus erythematosus were included in the analysis, provided they fulfilled the selection criteria for age, menopause and disability. Bone mass in SLE has not been previously systematically studied and the frequent use of corticosteroid therapy in these patients makes them an ideal group for comparison with RA. The fact that the diseases are pathogenetically and clinically similar strengthens their possible role in adding to the knowledge regarding the mechanism of osteoporosis in rheumatoid arthritis.

CONTENTS.

ABBREVIATIONS.

25 OH-D	25 hydroxy vitamin D.
A1AT	alpha 1 anti-trypsin.
ADA	anti-DNA antibody
ADL	activities of daily living.
AHI	arthritis helplessness index.
AI	area index.
ALT	alanine transaminase.
ANF	anti-nuclear factor.
AP	alkaline phosphatase.
APP	acute phase proteins.
ARA	American Rheumatism Association.
AS	ankylosing spondylitis.
ASCII	American Standard Code for Information Interchange.
AST	aspartate transaminase.
B1	beta 1.
B2	beta 2.
BMC	bone mineral content.
BMD	bone mineral density.

BMDP	statistical software.
BME	biomedical engineers.
BMI	body mass index.
BRS	bone resorption stimulation.
C3	3rd component of complement.
C4	4th component of complement.
CA	cortical area.
CA%	percent cortical area.
CA/SA	cortical area / surface area.
Ca^{2+}	ionised calcium.
CAI	cortical area index.
CCT	clavicular cortical thickness.
CCW	combined cortical width right 2nd metacarpal.
CH50	total haemolytic complement.
CIC	circulating immune complexes.
CMR	carpo - metacarpal ratio.
CRP	C' Reactive Protein.
CS	corticosteroid.
cv	coefficient of variation.

d	inner diameter.
D	outer diameter.
DHEAS	dehydroepiandrosterone.
DIP	distal inter phalangeal.
PIP	proximal inter phalangeal.
DM	diaphyseal mass.
DMA	disease modifying agent.
DNA	deoxyribo nucleic acid.
DOD	duration of disease.
DPA	dual photon absorptiometry.
DQ	disability questionaire.
EMS	early morning stiffness.
ESR	Erythrocyte Sedimentation Rate (Westergren).
FC	functional class.
FCW	femoral cortical width.
FDA	Food and Drug Administration.
FI	femoral index.
FNF	femoral neck fracture.
FPR	false positive ratio.

GAG	glycosaminoglycans.
GGT	gamma glutamyl transpeptidase.
GLA	bone glutaric acid.
GSH	Groote Schuur Hospital.
HAQ	Health Assessment Questionaire.
Hb	haemoglobin.
HCl	hydrochloric acid.
HFI	hand functional index.
HLA	human leucocyte antigen.
IAI	intra articular injection.
IBM	International Business Machines.
IDA	index of disease activity.
IL-1	interleukin 1.
IU	internationa units.
JAOP	juxta articular osteoporosis.
JSN	joint space narrowing.
KFT	Keitel function test.
L	length of metacarpal.
LBM	lean body mass.

LBW	lean body weight.
LE	lupus erythematosus.
LSI	Lansbury systemic index.
M6CA%	6 metacarpal cortical area percent.
M6HS	6 metacarpal hand score.
MBD	metabolic bone disease.
MCP	metacarpo phalangeal.
MCTD	Mixed Connective Tissue Disease.
MI	metacarpal index.
MM	metaphyseal mass.
MP	methylprednisolone pulse.
MRC	Medical Research Council.
MVA	multi - variate analysis.
MW	medullary width right 2nd metacarpal.
NAA	neutron activation analysis.
NSAID	Non Steroidal Anti Inflammatory Drug.
OA	osteo arthritis.
OAF	osteoclast activating factor.
OH-P	Hydroxy - Proline.

OI	osteoporosis index.
OM	osteomalacia.
OP	osteoporosis / osteopaenia.
OT	occupational therapist.
PA	postero-anterior.
PAOH	Princess Alice Orthopaedic Hospital.
PC	personal computer.
PG	Prostaglandin.
PIP	proximal inter-pahalangeal
Plt	platelets.
POP	plaster of Paris.
PTH	Parathormone.
PV	plasma viscosity.
PVAS	pain visual analogue scale.
QC-T	quantitative computerised tomography.
RA	Rheumatoid Arthritis.
RAI	Ritchie articular index.
RBG	retinol binding globulin.
RDU	Rheumatic Diseases Unit.

RF	Rheumatoid factor.
RID	remission inducing drug.
ROC	receiver operating characteristic.
rr	relative risk.
RSA	Republic of South Africa.
SAARD	slow acting anti rheumatic drug.
SAMRC	South African Medical Research Council.
SAS	statistics software.
SCAT	sheep cell agglutination tests.
Σ CCW	sum of combined cortical widths.
SD	standard deviation.
SFT	skinfold thickness.
SH	sulphydryl.
SI	Systems International.
SLE	Systemic Lupus Erythematosus.
SPA	single photon absorptiometry.
SVAS	severity visual analogue scale.
TA	total area.
TBBM	total body bone mineral.

TBCa	total body calcium.
TBCa p	predicted total body calcium.
TBPA	thyroxine binding prealbumen.
TBV	trabecular bone volume.
Tc99	Technetium 99.
TPR	true positive ratio.
TW	total width right 2nd metacarpal.
UCT	University of Cape Town.
UK	United Kingdom.
USA	United States of America.
VAS	visual analogue scale.
WB-1	Willmore Behnke - 1.
WB-2	Willmore Behnke - 2.
WBA	whole bone ash.
WBCa	whole bone calcium.
WBD	whole bone density.
WBR	whole body retention.
WCC	white cell count.
WHO	World Health Organisation.

ABSTRACT.

The literature is replete with reports of osteoporosis in rheumatoid arthritis, but the mechanism of bone loss remains obscure. This is probably due to the overlap with bone loss of aging and the menopause, whose exact mechanisms are also poorly understood. Against this background, a study was designed to evaluate generalised bone loss in young, premenopausal (if female), patients with rheumatoid arthritis. The protocol was designed to record demographic data, as well as information pertaining to the disease. Cortical bone mass was measured at the metacarpals and left femur, using an automated, computer-controlled technique. Trabecular bone was evaluated at the left femur (Singh index) as well as at the 3rd lumbar vertebra (Saville index). Bone kinetics were studied by the measurement of urinary excretion of calcium, phosphate and hydroxy-proline (resorption) and serum alkaline phosphatase (formation). Disease activity was measured clinically and with laboratory indices. Physical activity was indirectly measured by quantitating the disability, using the Keitel function test as well as a modified health assessment questionnaire (HAQ). The radiograph of the right wrist was scored by the Larsen index. The carpometacarpal ratio was also calculated from the radiograph. Numerous statistical techniques were applied in the analysis of the data. Healthy volunteers were used as controls. Patients with SLE were also studied, in order to compare the 2 inflammatory diseases. Patients with RA had generalised cortical bone loss (metacarpal and femur) ($p < 0.001$). Trabecular bone measurements were not significantly different from normals, using the crude radiographic techniques. Duration of disease was the most im-

portant clinical determinant of this bone loss. The relative contributions of disease activity and lack of physical activity to the loss of bone could not be adequately separated using conventional statistical techniques. Corticosteroid therapy did not promote metacarpal bone loss in these subjects, but may have contributed to thinning of the femoral cortex. Nonsteroidal anti-inflammatory drugs and disease modifying agents did not seem to influence the extent of the bone loss. Nutritional status and skinfold thickness did not correlate with bone mass. Dietary factors played no role in the genesis of bone loss, but may have had some effect on disease activity. Metacarpal measurements showed a sensitivity of 80% and specificity of 85% in discriminating between osteopaenic and normopaenic groups with RA. Osteopaenia could not be adequately predicted in the absence of metacarpal measurements. Metacarpal bone loss in RA was due to endosteal resorption, while in SLE it was due to periosteal resorption. The semi-automatic technique for measurement of metacarpal bone mass showed good reproducibility among 5 observers and at 2 different centres. The pathogenesis of bone loss in RA was multifactorial, the largest contribution probably coming from a humoral factor in the circulation, closely related to disease activity. Ionised calcium was elevated in 55% of RA patients, but only 5% of SLE patients. Serum PTH levels were normal in 99% of the RA subjects. Elevations in alkaline phosphatase (25%) probably reflected disease activity rather than increased bone formation. Factor analysis of 27 variables showed that disease activity was central to the development of OP in RA. CS therapy tended to be used in the presence of active disease. Disability was not an important determinant of bone loss in RA, but may be a useful measure of activity of the disease. This study did not evaluate the relationships with sex hormonal status or vitamin D metabolism. Future research should

aim at cohort analysis at 2 different periods, in order to improve our understanding of the pathogenesis of bone loss in RA.

INTRODUCTION.

A BRIEF OVERVIEW.

Over the last 20 years, more has been written about osteoporosis (OP) in rheumatoid arthritis (RA), than any other extra-articular manifestation of the disease. In the last few years, this has been related to the development of more refined, reproducible and accurate non-invasive techniques for the *in-vivo* measurement of bone mass (Johnston 1982). When used in patients with RA, these support the concept that generalised OP is a frequent feature of the disease (McConkey 1965). More recently, Sambrook *et al* (1987) have shown with dual photon absorptiometry (DPA), that RA patients have similar bone mass to normal post-menopausal subjects. Juxta-articular OP is a well recognised manifestation of RA and is one of the radiological criteria in the American Rheumatism Association (ARA) criteria for classification of RA (Ropes *et al* 1958). Its exact definition is not clear, but Larsen (1977) seems to compare it with the bone density at the metacarpal midshaft.

Controversy revolves around the mechanism for the localised and generalised bone loss in RA. The importance of defining predicting factors has recently been reviewed (Sambrook *et al* 1987). It is generally agreed that in RA several important associated features, *confounders*, may contribute significantly to the loss of bone mass. Among these, the most strongly implicated is immobilisation, but disease activity, nutrition, drug therapy, menopausal status and age also make a con-

tribution. Some work (Kennedy *et al* 1976; 1979) has shown that hypercalcaemic serum from patients with RA induces bone resorption *in vitro*. Prostaglandins (PG) E2 and F2 are implicated. It has recently also been suggested (Ralston *et al* 1986) that interleukin 2 may have an effect of stimulating *osteoclast activating factor* (OAF), to cause bone resorption in these patients, as in patients with certain malignant diseases.

Osteopaenia is defined radiologically and osteoporosis, histologically. Osteopaenia is the radiological impression of bone loss, and the *osteoporotic syndrome* is the association of osteopaenia and structural bone failure (fracture). Barnett and Nordin (1960), separate the definition of osteoporosis into *simple* and *accelerated* depending on whether the apparent density of representative bone is normal or low, after correction for age and sex, respectively. Bone is osteoporotic when its apparent density falls below the *young normal* lower limit. This depends on objective measurement. The author favours Barnett and Nordin's concept, despite its inherent weakness of including some patients with osteomalacia (OM). The terms osteoporosis and osteopaenia will henceforth be used interchangeably in order to avoid confusion. The mechanisms of post-menopausal OP are not known.

There are various ways of diagnosing osteopaenia, but it is usually done by radiography (Genant *et al* 1988a). Pathogenetic mechanisms other than normal aging need to be sought only when dealing with accelerated OP. The clinical syndrome characterised by vertebral and/or femoral neck fractures represents a late stage in the diagnosis. In order for treatment to be effective, it is imperative that

the diagnosis is made at a much earlier stage, using the numerous new non-invasive techniques which have been developed (Cameron and Sorensen 1963; Cameron *et al* 1968; Mazess 1987; Recker 1982).

Single photon absorptiometry (SPA) (Wahner *et al* 1977; Nicoll *et al* 1987a; Gupta *et al* 1984), neutron activation analysis (NAA) (Kennedy *et al* 1982; Eastell *et al* 1983; Tothill *et al* 1986; Nicoll *et al* 1987b), whole body retention (WBR) of calcium (Kennedy *et al* 1982) and Tc-99m labeled phosphates (Fogelman *et al* 1978; Holmes 1978), quantitative computed tomography (QC-T) scanning (Genant *et al* 1982; Genant 1988) and dual photon absorptiometry (DPA) (Schaadt and Bohr 1982; Smith *et al* 1983; Tothill *et al* 1983; Nuti *et al* 1988; Mazess *et al* 1988) studies are largely limited to highly specialised centres and are useful for serial evaluations. Mazess (1983) suggested that DPA and/or QC-T scanning would become the non-invasive standards for evaluating metabolic bone disease (MBD). Smith *et al* (1983) compared different energy sources for DPA and found that ^{241}Am and ^{137}Cs could be used as practical alternatives to ^{153}Gd. In South Africa, there are very few single photon absorptiometers and no dual photon absorptiometry apparatus at the moment. Radiogrammetry remains the only objective method for non-invasive evaluation of OP in the western Cape.

In RA, measurement of bone mass in the hands has potential for the evaluation of disease progression. However, hand deformities may influence the reproducibility of the measurement, making changes difficult to interpret. Nicoll *et al* (1987a) designed an apparatus to apply the technique of SPA (with its established potential for precision and low radiation dosage and its simple nucleonic require-

ments) to the measurement of hand bone mineral. They found that hand measurement was not unduly influenced by a 3 cm limit proximal to the ulna styloid. Errors introduced in the result by repositioning the marker band are incorporated in the precision measurement. Hutton *et al* (1988), reported the use of DPA of the hand in evaluating early RA. They concluded that this was a potentially useful objective measure of bony change in RA.

Bone biopsy remains the most important diagnostic investigation for generalised OP. Malluche *et al* (1982a & b), using more recent techniques, have improved its quantitative use. It remains the most critical marker of bone turnover, which is essential if one is to relate reduced bone mass to Frost's (1963, 1973a, 1973b, 1979), concept of coupling between formation and resorption as a dynamic, controlled process. It is the only way to exclude OM. However, it is limited by its invasive nature.

Only when expressed in morphological terms, does coupling and uncoupling become sufficiently concrete to be amenable to further analysis. The piecemeal character of the lamellar bone turnover implies the activation, in specific location, of new sites of bone resorption or formation. This relates to separate aspects of the precursor cells' activities : first, discrete location and number of these activities (activation frequency) and second, their subsequent local rate and duration. While little is known about the activation of these sites, several agents have been implicated in the onset and maintenance of local osteoclast proliferation (Avioli 1987). Similar recently identified factors, usually a byproduct of bone matrix degradation, have been implicated in the onset and maintenance of osteoblast pro-

liferation, and have been proposed as a coupling factor (Raisz and Kream 1983; Raisz 1988).

Jaworski (1984), in a comprehensive review of the concept of coupling and uncoupling, remarked that the ultimate reduction of bone physiology and pathology to its molecular biology is unavoidable and a necessary condition for further progress in this field. This descent to the *ultimate* should be balanced by the awareness of the integrating mechanisms so obvious in the making and maintenance of the skeleton. This means that direct inferences and applications from the molecular level to the normal or diseased whole skeleton, without taking into account the hierarchy of its intermediate levels of organisation, may fail to enhance understanding.

Raisz (1988) presented a comprehensive overview of the local and systemic factors in the pathogenesis of osteoporosis. He re-iterated the difficulties in definition and diagnosis. He also emphasised the difficulties in predicting subjects who were likely to develop fractures. The potential local regulators of bone metabolism have only begun to be identified. He introduces Eriksen's (1986) concept of the regulation of the normal sequence of bone remodeling and the possible pathologic alterations in that sequence. The first step is activation. Inactive bone surfaces are covered by lining cells, possibly of osteoblastic lineage, which can respond to bone resorbing hormones. The next step is bone resorption , which involves replication of osteoclast progenitors and their differentiation, migration and fusion into mature osteoclasts under the control of both local and systemic hormones. Once the osteoclasts have resorbed most of the mineral and matrix,

there is a reversal phase during which macrophages may appear on the resorbing surface. The next stage of the remodeling cycle is the formation phase, in which the osteoblasts replace resorbed bone. A number of factors influence the extent and rapidity of the replacement. The systemic hormones (growth hormone, glucocorticoids, thyroid hormones, insulin and oestrogen) as well as local substances (PG E2, IL-1, interferon alpha, insulin-like growth factor and transforming growth factor beta) exert their effect through the calcium regulating hormones to produce resorption or formation.

Although it is generally accepted that osteoclasts (OC) are the cells responsible for bone resorption, Rodan and Martin (1981) presented interesting evidence to support their hypothesis that osteoblasts may have a pivotal role in the hormonal regulation of bone resorption. It is clear that these cells have an intricate *communications network* which regulates the coupling process in favour of bone formation up to a certain critical stage when the balance is disturbed in favour of resorption. Relatively little is known about the factors controlling this important change in skeletal dynamics.

Adams (1981) pointed out that there was no evidence that the persons with the least amount of bone at the start of adult life are those destined to lose the most bone with advancing age. None the less, they could form the group likely to develop structural failure of the skeleton in old age. Persons with low bone mass seem to manifest the OP syndrome earlier than those with better mass; females have lower bone mass than males and they develop OP more readily. Solomon (1979), showed results which differ from those of Stewart *et al* (1972), in that

Caucasians, despite higher bone mass than blacks in South Africa, developed far more complications of the osteoporotic syndrome with age, especially females.

Studies of bone mass in osteoporotic patients who develop fractures (Aitken 1984b) emphasised the concept of a numeric definition of OP. This is the only way to identify *at risk* subjects, in whom prophylactic therapy may be a feasible option. Mazess (1987) in an editorial, questioned the practice of defining OP numerically, since most of the attributable risk of hip fracture occurs in subjects with the lowest 10% of femoral neck density (90% specificity), whereas most of the attributable risk of crush fracture occurs in the lowest 30% of spine density (70% specificity). He pointed out that public health attention needs to be directed toward these low-density minorities to be cost-effective.

Peck (1987) provides a perspective of the medical and social implications of osteoporosis. About 1.5 million fractures, usually of the spine, wrist and hip, are attributable to OP in the USA annually, at a total cost of $7 to $10 billion. The prevalence of OP in the USA is 20 million. Over 200,000 hip fractures each year are attributable to OP, and hip fracture is a dominant cause of morbidity, mortality and cost to society. He re-iterated the importance of a reduction in bone mass as a risk factor and drew attention to the importance of early diagnosis. The local and systemic factors responsible for bone resorption were also reviewed in this paper. Similar costs are incurred in Finland annually (Simonen 1986).

In the same issue, Lindsay (1987) reviewed the non-invasive techniques for measuring bone mass. He emphasised the need for screening, but pointed out

that the current techniques (SPA, DPA and C-T scanning) were not cost-effective. This is in agreement with the recommendations of Hall *et al* (1987). Radiogrammetry is still recommended by the FDA for drug trials, and the precision of the technique is comparable to that of SPA and DPA (Dequeker 1972; 1982). Although low bone mass is a risk factor for fracture, it does not predict fracture for an individual patient.

A number of factors are implicated in the risk for fracture. Low bone mass seems to be the common denominator. Other important risk factors include female sex, caffeine intake, Caucasian race and a susceptibility to falling (Cummings 1985; Cummings *et al* 1985).

CORTICAL BONE.

The development of new non-invasive methods for determining whole bone mass and total body calcium have not only simplified the process, but have also considerably improved the sensitivity of these measurements (Wahner *et al*, 1984a and 1984b). These generally use radioactive absorptive and retention techniques and are technically highly sophisticated. Since these are financially available only at specialised centres interested in MBD research, the more easily obtained radiogrammetric methods continue to be the most practical method of determining bone mass. The other advantage of radiological methods is that differential evaluation of the skeleton is possible at little extra cost or inconvenience, allowing simultaneous assessment of cortical bone and trabecular bone in the same patient. Different radiological scoring methods have been devised to enable researchers to quantitate bone mass. The methods generally in use include single photon absorptiometry and radiogrammetry. Dual photon techniques, QCT scanning and neutron activation analysis are available for research only. They are not currently recommended for screening.

RADIOGRAMMETRY.

Barnett and Nordin (1960), reported a method for objective measurement of the cortical bone at the 2nd metacarpal midshaft of either hand and the midshaft of the femur, as well as a measurement of the biconcavity of the third lumbar vertebra as a measure of trabecular bone. The metacarpal index (MI) was calculated as the ratio of the thickness of the cortex in the shaft of the metacarpal (d) to the

total width of the bone (D) { MI = d/D }. Their study was unable to demonstrate any correlation between peripheral and spinal scores, suggesting to them that there may be 2 types of OP - spinal and peripheral. Only the hand scores were found to fall with age in normal subjects. They concluded that their method may prove useful in the routine screening of suspected cases until a satisfactory method of measuring vertebral density could be evolved. This study was carefully conducted and has served as the basis of a number of subsequent studies, aimed at improving the sensitivity of the method.

Meema and Meema (1969), questioned the relationship between porosity and cortical thickness, suggesting that measurements of cortical thickness may not reflect reduced mineral density, if such a disparity should exist. Using SPA and radiogrammetry at the distal radius, they showed that cortical thickness measurements were not sufficiently sensitive for determining the degree of osteopaenia, since they failed in the diagnosis of bone mineral loss which frequently manifested itself as intracortical porosity.

Exton-Smith *et al* (1969a), tested this hypothesis by comparing the ash content of the left third proximal phalanx with the measurement on X-Ray, in 29 selected patients. They calculated a third index - the cortical area index (CAI), for correlations with dry ash weight of bone. Comparing various calculations of bone mass, they found a significant correlation only with the CAI ($r = 0.85$). They concluded that no special advantage was obtained by dividing cortical thickness by external diameter. They showed that estimates of the cross-sectional area of the cortex made from X-Rays were directly related to chemical measurements of ash con-

tent. Moreover, this calculation was based on the same simple measurements of the hand X-Ray that were used to estimate cortical thickness.

Albright *et al* (1941) and later Albright (1947), described the clinical syndrome of OP which is almost physiological after the menopause. Albright and Reifenstein (1948) described the syndrome of metabolic bone disease in patients with hyperparathyroidism. Newton-John and Morgan (1968), supported the concept that the clinical syndrome of OP could result solely from the loss of bone with age. Exton-Smith *et al* (1969a), further suggested that variations in skeletal size invalidated comparisons between the bones of different individuals. They found that the product of length and external shaft diameter (D X L), correlated with cortical area ($r = 0.86$). They concluded that the dimensionless ratio, cortical area/ surface area [CA/SA = $(D^2 - d^2) / D \times L$]), minimised the effect of differences in skeletal size between men and women.

Horsman and Simpson (1975), pointed out that in those longitudinal morphometric studies which had used the 2nd metacarpal index, the results had thus far been severely limited by measurement error. They developed a simple method involving morphometric measurements on radiographs of the diephysis of the metacarpals of both hands, (the six metacarpal hand score) (M6HS), by which sequential changes in bone geometry, and by implication bone mass, may be observed. Their method was simply implemented, requiring only conventional diagnostic X-Ray facilities and relatively inexpensive measuring calipers. They concluded that the method had a precision comparable to that of SPA.

Two disadvantages of the above method were the subjectivity and tedious nature of the measurement procedure, both of which may be eliminated by the development of an automated measurement system. These authors expressed the opinion that such objectivity would only be achieved at the expense of simplicity. The application of the technique to normal premenopausal females showed that within the limits of measurement error and group size, premenopausal women on the whole neither gained nor lost bone from the endosteal surface.

Dequeker (1976), observed that the multiplicity of metacarpal indices proposed suggested that none had been really satisfactory. The difficulty of differentiating pathological from physiological bone loss is linked to the large variability of bone mass within one age group. This variability in bone mass is almost constant and not influenced by age or sex.

He suggested that the cortical area ($CA = D^2 - d^2$) was the most suited to be grouped according to outer diameter (periosteal bone). Normal values have to be obtained for each population separately. X-Ray determination of periosteal and endosteal surface changes in long bones in different populations or in the same population over a period of time provides information on skeletal dynamics. As both processes may represent responses to different mechanical and chemical stimuli, they have to be considered separately in studies of OP.

Horsman *et al* (1977), described a semi-automated technique for measuring the diameters at the midshaft, using a computer-controlled morphometer. This device has replaced the Vernier calipers. The error remained the same, and the

midpoint was still determined manually prior to measurement. They showed that the medullary width increases with age after the menopause, reaching a plateau in some patients. Total width also increases, suggesting that this may be the reason for the subsequent decrease in cortical thinning. The combined cortical width decreases progressively as well. These authors proposed that OP results from the inability to increase total width and arrest resorption, particularly in the absence of a protective effect from oestrogens.

Fredensborg and Nilsson (1977), introduced a further index, the femoral cortical index, as a guide to the selection of persons likely to develop fractures of the femoral neck. Cortical thickness was measured immediately proximal to the lesser trochanter. The measure of the thickness of the medial cortex was divided by the width of the femoral neck in its most narrow part. The ratio was referred to as the cortical index of the femoral neck. There was no right / left difference. The index did not significantly decrease with age, but it was significantly decreased in individuals with fracture of the upper end of the femur. They concluded that the cortex of the femoral neck was probably not a useful variable for morphometric valuation of bone mass. However, it may have some use in predicting the risk of femoral neck fracture from routine films of the hips. These authors did not simultaneously measure the metacarpal indices in their patients.

Aitken (1984a), introduced further formulae for calculations of bone mass using measurements at the 2nd metacarpal. These derived values provide different expressions of the same data and all have their uses. He pointed out that all the calculations assume that the metacarpal at its midpoint is a perfect hollow cy-

linder and that this assumption is quite erroneous. Other expressions have been derived to relate the physical and chemical properties of bone. Hence with the knowledge of the gravimetric density of bone (2.0 g.ml-1) one can calculate the whole bone density (WBD), whole bone ash (WBA) and the whole bone calcium (WBCa).

The use of a digitiser in radiogrammetry was first undertaken by Evans *et al* (1978). They performed measurements on X-Ray pictures projected on a paper with a twelvefold enlargement by an overhead projector. They introduced the concept of *corrected cortical area*, which was a correction of the CA to a mean total area (TA) of 782 mm^2. They believed that measurement of the metacarpals in this manner had several advantages over other metacarpal measurements. It expresses a defined area and does not make the assumption that the bone is tubular. However, a further error variable is introduced in the magnification process.

Buckland-Wright (1983 a & b; 1986) extended the concept in its application to microfocal radiological diagnosis in RA. This involves the use of the microfocal X-Ray unit, characterised by an extremely small X-Ray source overcoming many of the limitations of the conventional units. This X-Ray unit produces projection radiographs at high magnification (x 10 or more), obtained by placing the object close to the X-Ray source and the film at some distance away. It provides high resolution and penumbral blurring is minimal. However, the method is more useful in the detection of erosions than in the measurement of bone mass.

REPRODUCIBILITY OF THE RADIOGRAMMETRY METHOD.

One important drawback of the radiogrammetry method is that errors are introduced at both the observer level and the level of the radiology. Horsman and Simpson (1975) pointed out that only the total error is usually measurable. Each of these errors is a compounded error consisting of sub-errors at each level. With respect to measurement, the observer error is related to the recording of one's measurements as well as the subsequent calculation of bone mass. Such calculations are computerised in equipment using photon absorptiometry.

Several of the above authors (Barnett and Nordin 1960; Saville 1967; Horsman and Simpson 1975; Dequeker 1976), who have performed inter- and intra-observer analyses of variance, have found it imperative that the same observer perform all the measurements, due to the coefficient of variation (cv) of 2% - 18%, using Vernier calipers. It seems that this is the major limitation of the radiogrammetric method. Also, when applied to interpretation of therapeutic efficacy, bias is unavoidable if the observer knows what therapy is being given to the patient, particularly if the same observer is involved in both the clinical and radiological evaluation.

Double-blind studies are limited by the expertise required in doing radiogrammetry on a number of X-Rays to improve reproducibility. This usually means that the same observer is involved in both the clinical and radiological evaluation. Computer-assisted methods of bone measurement have the added advantage of removing this important subjective element which contributes to the total error.

Dequeker (1976) and Exton-Smith *et al* (1969a), drew attention to several additional limits of the radiogrammetry approach. It had failed to give information on the bone status at an individual level due to the large variability in each sex-age group even when it was corrected for skeletal size. On an individual and short-term basis the static radiographic picture does not necessarily coincide with direct measurements of bone dynamics.

Those who have reported findings of radiogrammetry have not been consistent in their methods for testing reproducibility. Barnett and Nordin (1960) studied measurement error by randomly selecting ten sets of X-Rays (normal and abnormal) measured by nine independent radiologists, who had been briefly instructed in the technique of measurement. Saville (1967) found a cv of 7%. However, inter- and intra-observer differences of 0.02 mm were statistically significant. Adams *et al* (1969) compared measurements of 3 observers, measuring cortical width at the midshaft in 86 X-Rays on 2 occasions. The coefficient of variation (cv = SD/mean x 100) was 8 - 11 %. The standard deviation of 0.2-0.3 mm between observers was statistically significant. Naor *et al* (1972) randomly selected 10 of 806 X-Rays which were read on 2 occasions. They also measured the two cortices separately, rather than calculating it as the difference between outer and inner diameters (D-d). The SD was accurate to within 0.037 mm. The intra- and inter-observer differences were statistically significant.

Bloom (1980) measured various bone sites and compared the reproducibility. He found a cv of 13.9 - 17.4 % at the metacarpals. However, at the humerus, the cv was reduced to 9.1%, suggesting that the wider diameters were probably more

reproducible. Horsman and Simpson (1975), who report on serial measurements of the six metacarpal hand score (M6HS) defined the midpoints of the metacarpals on the first set of X-Rays and superimposed subsequent pictures on this original, as a marker of the point for measuring inner and outer diameters. The additional potential sources of error introduced by this method make it relatively unsuitable, although Horsman suggested that the reproducibility was improved. They later described a semi-automated technique, which probably reduced the mathematical error but did little to improve the errors of measurement. Dequeker (1976), used 2 sets of X-Rays and measured a reference metacarpal. The study showed that it is possible to obtain a coefficient of variation of 1.9%, which is comparable with that reported with the use of DPA (Sambrook *et al* 1987). This is the only report of such a low cv using this technique. The inter-observer differences remained statistically significant.

The mean measuring error of 8% for cortical thickness with calipers suggests that an interval of many years is necessary to find a longitudinal difference in a normal aging individual with certainty. Another limitation of the radiogrammetry method is the occurrence of local disorders of bone as occur after fractures and RA. There may also be a permeative type of cortical bone loss which may be apparent on observation, but which affects the cortical measurements only slightly eg thyrotoxicosis.

The most serious limitation of radiogrammetry is that it does not measure trabecular bone. Nevertheless, as observed by Dequeker (1976), the measure-

ment of cortical bone certainly has added to the knowledge of changes in bone mass in aging and disease.

Aitken (1984a), pointed out that the errors with the caliper method have led to radiogrammetry methods being labelled a *guestimate* of bone mass. The inter-observer differences are unacceptable and it is again strongly recommended that a single observer perform the test. The method is tedious and in consecutive X-Rays, Horsman and Simpson (1975) have superimposed X-Rays rather than repeat the measurements of the midpoints of the shafts of the metacarpals. The additional errors introduced by this method leave much to be desired, even though they claim that this would not be the case.

A preset mould of a metacarpal bone embedded in wax or similar substance could serve as a fixed object against which comparisons are made between X-Rays and between observers. Using this latter method, it would be possible to design a study which would allow simple evaluation of inter-observer differences as well as inter-centre differences; where more than one hospital is involved in the recruitment of patients and controls. The M6HS and 2nd metacarpal index, as well as some sites of the skeleton using SPA, essentially measure cortical bone. The 6 metacarpal index has not been previously evaluated in patients with RA, although one group have devised a score using 3 metacarpals of the right hand only (Virtama *et al* 1968).

Aitken (1984a), warns in his book that irregularities on the endosteal outline often lead to indecision as to where exactly the cortex ends and the medullary

cavity begins. The investigator must adopt a set of rules which he follows slavishly to help with measurement strategy.

TRABECULAR BONE.

Among the methods used for measuring OP in trabecular bone, bone biopsy is probably the most sensitive, followed by DPA, NAA, WBR of calcium, QC-T scanning and SPA. Magnetic resonance imaging has not been applied to the study of OP and it is not known whether the fat-rich marrow of osteoporotic patients is demonstrable by this technique. It has been used successfully in the measurement of localised OP at the femur and is the most useful method for the diagnosis of avascular necrosis of the femoral head. Mazess (1982) provided a useful back-ground to the non-invasive methods for quantitating trabecular bone.

Lost mineral in bone is replaced by marrow fat. A 50% increase in marrow fat will appear as a 25% bone loss to single energy quantitative spinal C-T; a 12% bone loss with Compton scattering; a 7% loss to dual energy QC-T; and a 3% loss to DPA (Cohn 1982). OP is detected on radiographs of the lumbar spine when 30-50% of the bone mass has been lost, making this a late diagnostic feature.

HAND AND WRIST.

The presence of juxta-articular OP is sometimes regarded as evidence of trabecular bone involvement. Studies using SPA (Mazess 1979) consider the proximal radius as trabecular bone while the junction of the lower and middle

third of the shaft represents cortical bone. Dequeker (1972), however, regards all measurements at the radius as cortical measures. The most reliable method of trabecular bone measurement is DPA at the hip or vertebra, with reported coefficients of variation of 1.5-2% (Sambrook *et al* 1987).

FEMUR.

Singh *et al* (1972), showed that an index based on the changes in the trabecular pattern of the upper end of the femur could distinguish between persons with and persons without spinal crush fractures. The method is based on the fact that, as trabecular bone loss occurs, those trabeculae that are subjected to less mechanical stress are lost first. The radiological femoral trabecular pattern was characterised by a 7 - point scale -- grade 7 (normal) to grade 1 (severe osteopaenia). The grading correlated well ($r = 0.81$) with the histologic grading of trabecular bone in iliac crest biopsy specimens of the same patients. In a detailed methodologic description, the same authors (1973), outlined some difficulties which may occur. Occasionally, radiographs showing transitional stage between one grade and the next may be difficult to grade. Where there was an actual difference of one grade between the left and right hips, the higher grade was arbitrarily used. Other conditions which might interfere with the trabecular pattern grading are arthritic conditions of the hip and abnormalities of the neck-shaft angle. They emphasised that, unless the radiograph is taken with the hips in 15^{o} internal rotation, accurate grading was not possible. They concluded that persons with a femoral trabecular pattern index of grade 4 or lower have a pathologic degree of bone

loss and have a higher risk of fracture. They recommend that consideration should be given to prophylactic treatment of individuals with a skeletal grade of 4 or less, even if they do not have spinal or femoral neck fractures. Metacarpal bone measurements were not performed in the same patients, so it is not clear if the patients with a low Singh index also had less metacarpal bone. One would expect this to be the case, since vertebral fracture incidence has been correlated with decreased metacarpal bone mass (Barnett and Nordin 1960; Aitken 1984). Dequeker *et al* (1974) confirmed the clinical value of the Singh index in evaluating asymptomatic spinal OP and femoral neck fracture.

VERTEBRAE.

Jensen and Tougaard (1981), evaluated a simple X-Ray method for monitoring the progress of OP. The method for measuring vertebral height is a three-stage process. The method is valid for the body heights of the sixth thoracic to the fifth lumbar vertebrae in all patients with a scoliosis of less than 15^{o}. It took them about 15 minutes to measure the vertebral heights of one patient. They found the mean vertebral body height to be lower in OP subjects than in normal controls. They concluded that the ability of the method to register changes in vertebral body heights even when no fracture had occurred, made it valuable for monitoring the progress of OP. The method has not been applied in RA. The Saville index (Saville 1967), has been generally used in RA. It is a grading of the 3rd lumbar vertebra according to the trabecular and cortical pattern. Grades 1 and 2 are normal, while grades 3 and 4 are osteopaenic and associated with fracture. Verti-

cal trabeculations remain until the latest stage. Kovarik *et al* (1981), showed that poor consensus can be achieved when 3 different radiologists interpret routine X-Rays of the spine for the diagnosis of osteoporosis. Reading of the Singh index was associated with a learning effect. The lumbar spine index, Singh index and photon absorptiometry were unable to differentiate males who had crush vertebral fractures from those who did not. In females, however, these semi-quantitative methods were able to discriminate significantly, irrespective of age in decades. They concluded that the lumbar spine index is a subordinate test for the diagnosis of senile OP.

The method used by an investigator is largely determined by the facilities available at the institution performing the study. Also, non-invasive methods are preferred by both the investigators and subjects. Aitken (1984a), reminds us that the accuracy and reproducibility of histomorphometry for assessing bone mass (bone biopsy), even with the most sophisticated methods available, is inferior to that of radiographic morphometry, in the hands of some workers. Bergaoui *et al* (1987) showed significant correlations between cortical thickness and iliac crest biopsy at the humerus and radius, but not at the second metacarpal. This difference is possibly due to the fact that the larger bones have a higher content of trabecular bone, but may also relate to the greater variation in measurement at the second metacarpal, as shown by Bloom (1980).

RELEVANCE OF RADIOGRAMMETRY.

Differential changes in the axial and peripheral skeleton correlate with each other in RA, as shown by Saville (1967) and Reid *et al* (1982). Bjelle and Nilsson (1970), showed changes in the metacarpals, but were unable to demonstrate changes in the femoral cortex and lumbar spine of RA subjects. Peripheral changes predominate in RA, so that the major contribution of objective measurement would relate to the quantification of juxta-articular OP.

In postmenopausal females, it seems that trabecular loss proceeds at half the rate of cortical loss (Riggs *et al* 1981), and trabecular loss is clinically more significant in its relation to the vertebral crush syndrome. Each of the presently available methods used to determine the nature and degree of changes in skeletal metabolism has significant limitations. However, numerous studies have shown statistically significant correlations between the different methods at the different sites in postmenopausal OP (Cohn 1982). Age-related changes can also be demonstrated by radiogrammetry of the metacarpals in normal subjects (Smith *et al* 1969; Solomon 1979; Meyers 1982).

Radiographic techniques can be applied to the whole skeleton, but they lack the sensitivity required for quantifying levels of change associated with the development of pathological conditions. Radiogrammetry, with quantitation of cortical thickness of the appendicular skeleton, is useful but not always indicative of the

status of the axial skeleton. Photon absorptiometric techniques, although highly quantitative and precise, provide information on only a localised portion of the appendicular or trabecular skeleton.

Finally, total body calcium measurements by NAA permit the direct in vivo measurement of total calcium content of the body, and hence skeletal mass, with a high degree of precision.

Cohn *et al* (1978), commented that metacarpal measurements were insensitive to small decreases in bone mass since cortical thinning usually denoted an advanced stage of generalised OP. They suggested that total body calcium measurements were probably the most accurate technique for measuring the absolute and relative loss of bone mass. Mazess (1979), concluded that suitably normalised (standardised) measurements of peripheral bones could give discrimination better than that of unnormalised total body measurements and equal to that of unnormalised spine measures. Horsman *et al* (1983) showed that total body calcium could be estimated from peripheral bone measurements. Kovarik *et al* (1981) pointed out several limitations of the semi-quantitative methods for measuring bone mass, but concluded that they have definite clinical relevance.

Aitken (1973) showed a surprisingly good correlation ($r = 0.7$) between vertebral medullary WBD and metacarpal mineral content in 13 female cadavera. In 1974, Aitken *et al* showed that there are also statistically significant correlations between *in vitro* measurements at the metacarpal and the distal femur, distal radius and distal midshaft. The radiation dosage to the patient's hands, derived

from direct output measurements made with an electrometer and ionisation chamber, is about 40 mrem. The time spent by the patient in the X-Ray room is less than 1 minute, and the technician time involved in estimating the M6HS will be about 10 minutes. This is highly suitable for epidemiologic studies.

Despite the difficulties with the use of radiogrammetry, Horsman *et al* (1977) were able to show significant sequential changes in bone mass in postmenopausal females receiving oestrogen replacement or calcium therapy. They devised a computer-assisted technique for radiogrammetry, but were unable to demonstrate a significant reduction in the total error compared with Vernier calipers.

BONE LOSS IN RHEUMATOID ARTHRITIS.

The literature is replete with studies of OP in RA. Guyatt *et al* (1984), pointed out that several factors contribute a *confounding bias* to any study of this nature. The effects of age, menopausal status, polypharmacy, immobilisation, diet, malabsorption of calcium, bone resorption stimulating factors, corticosteroid (CS) and second line drugs on bone metabolism are difficult to separate from those of disease activity as a composite parameter. It is, therefore, not surprising that in 1988 there is still no resolution of *the conflict between those who think osteoporosis is due to a calcium drain and those who think it has primarily to do with collagen*, Wright (1965). Since the pathogenesis of primary OP is not known (Kruse and Kuhlencordt 1980), overlapping factors need to be excluded if meaningful conclusions are to be derived from studies on RA subjects.

LITERATURE REVIEW.

Among the earliest studies of OP in RA is a report by McConkey *et al* (1965). They studied 102 females of mean age 58.4 years and duration of RA 11.8 years. Skin transparency was subjectively assessed as being transparent, opaque or doubtful. Vertebral OP was also subjectively graded at the thoracic and lumbar spine according to vertical trabeculation, fractures of the end plates and biconcavity of the vertebral bodies. They reported a 38% incidence of OP, and in those patients who also had transparent skin the incidence was as high as 76%. They concluded that OP is probably not one disease but an accompaniment of a num-

ber of disorders with different causes; one type associated with transparent skin. They suggested that when OP is accompanied by transparent skin a disorder of connective tissue underlies both phenomena.

The prevalence of OP in relation to CS therapy was not significantly different between treated and untreated patients. Although the findings in this study are significant, the pathogenetic inferences about the disease are difficult to separate from those of age. Also, no mention was made of the menopausal status of the patients. Finally, the subjective assessments of OP and skin transparency should have been evaluated in relation to observer differences. Guyatt *et al* (1984) argue that the small daily dose is scarcely sufficient to have an effect on the physiology of bone.

The role of physical activity in the genesis of OP in RA was questioned in the same year. Castillo *et al* (1965), studied hand radiographs from 153 unselected patients with RA. Cystic erosions and OP were subjectively graded as being mild, moderate or severe. They reported a significant inverse relation between cystic changes and OP in the hands ($x^2 = 44.3; p < 0.001$). A significant positive correlation was found between cystic erosions and physical activity, while OP correlated inversely with physical activity. They concluded that, because the men in their group dominated the *cystic* group and females dominated the *osteopaenic* group, the cystic changes were due to increases in intra-articular pressures related to tasks performed with the hands.

Several difficulties are encountered in the interpretation of this data. The authors did not present the age or menopausal status of their patients, no tests of hand strength were carried out between the groups, physical activity was inferred from Steinbrocker's classification (1949) of functional disability only, and the methods of evaluating OP and cystic erosions were not analysed for observer differences. This study added little to the understanding of the pathogenesis of OP in RA.

Probably the most significant contribution to some of our understanding of OP in RA was made by Saville (1967). They studied 164 patients (128 female, 36 male), measuring the cortical thickness of the left radius just below the tuberosity, using the method of Meema and Meema (1969). Spinal porosity at the lumbar spine was graded from 0-4 according to strict criteria. The inter-observer correlation for spinal porosity grading was 0.69, while that of measurement of the radial cortex was 0.95. The intra-observer difference was 0.2 mm., but this was highly significant and suggested that this technique was unsuitable for paired measurements in individuals radiographed at different times. They recommended that, in a clinical study, the radiographs should be measured by one observer.

They found that the tendency for cortical thickness to diminish as grade of spinal porosity increases, was highly significant both for men suffering from RA and for women. This finding supports the suggestion that there is a surprisingly good correlation between clinical assessment of radiographic bone density and mineral measurements from autopsy material. They concluded that these 2

simple clinical techniques are suitable for assessing differences in bone density between groups of individuals.

Later, Saville and Kharmosh (1967) evaluated the influence of age, sex and CS therapy on OP in the same group of 164 patients with RA. They found that in women taking CS, cortical thickness remained the same in treated and untreated groups until the 6th decade; after which time there was a decrease in both groups, the decrease being greater in treated females.

In men taking CS, there was a decrease in cortical thickness in both groups during the 6th decade; tending to rise again in both groups in subsequent decades. They concluded that age greater than 50 years had a more profound effect on bone mass than CS therapy. This study included 45 patients younger than 30 years of age. Adding all the males and females less than 50 years of age failed to show a relationship between CS therapy and OP. They suggested that *the insufficiency of cases of OP among the younger age group is thus a natural one, and makes it necessary to combine mild, moderate and severe grades in order to compare men and women under 50 years with respect to treatment with steroids.*

The study confirmed an inverse relation between porosity and functional ability. They concluded that while small doses of CS had been shown to play a role in the development of OP, age, sex and physical disability were more important. They also suggested that CS may have a protective effect on cortical bone in younger women! The only defect in this study was the small number of patients under 50 years of age and the small daily dose of CS.

The following year, Virtama *et al* (1968), studied OP in 33 patients with RA. The study group consisted of 7 males and 26 females, the ages of whom are not indicated. They introduced the osteoporosis index (OI), which is the mean cortical index of the 2nd, 3rd and 4th proximal phalanges or metacarpals of the right hand only. They studied their patients at 2 intervals, 4 years apart. Measurements were not simultaneously carried out on the left hand. They found that the fall in OI was more rapid in the old age groups than in the young ones.

Duration of disease had no influence. There was a parallel between destructive changes and OP. No correlation was found with rheumatoid factor (RF) titre, but those with a higher erythrocyte sedimentation rate (ESR) seemed to have a lower bone mass. Power of grip showed a high correlation with bone mass at the proximal phalanx of the right hand, but none with the metacarpals. According to this study, *quantitative estimation of the mineral content of bones in RA seemed not to be as important as suggested. Even if it has a great theoretical interest, such simple tests as grip strength and radiographs reflected the degree and development of the disease giving an appropriate basis to therapeutic measures*. CS therapy for more than 1 year did not increase the pace of demineralisation of the hand bones. The flaws in this study include the lack of an assessment of physical activity, omission of the age of the patients in the report and the measurement of grip strength only at the end of the study. It is, therefore, difficult to comment on the significance of this study in relation to the pathogenesis of the bone loss reported.

Bjelle *et al* (1970), quantitated the bone mass in 37 female patients with RA using several different methods, and attempted to define the role of CS therapy

in producing OP. Radiogrammetry measurements were performed at the lower radius, right 2nd metacarpal and midshaft of the femur. Photon densitometry was done at the distal end of the femur using the method of Nilsson (1966) and the lumbar spine was graded according to the recommendations of Saville (1967).

They found that, overall, there was a decrease in bone mineral content (BMC), CA, and cortical width at the femur in RA patients compared with age-matched normals. Spinal OP occurred no more frequently than in controls. In CS treated patients, the values of bone mass were significantly lower in the upper limb, but the differences were of doubtful significance in the lower limb and lumbar spine. The duration of disease could not be shown to influence any of the parameters of bone mass. Duration could also not explain the difference between CS-treated and non-treated patients. They concluded that RA produced OP and that CS therapy contributed to this loss. However, the lack of effect on the skeleton of the lower limb probably reflected the effects of weight-bearing and activity in the patients who could and did walk.

A detailed review of OP in RA was presented by Duncan (1972). He discussed normal bone physiology, illustrating the close relationship between osteoblasts, osteoclasts and synoviocytes. He makes a strong case for a vascular basis to OP, quoting angiographic studies (from their unit), which showed increased vascularity in areas close to bone erosions. He observed that no clear relationship existed between bone mass and tendency to fracture, suggesting that there may be an inhibitor to repair which is the predominant factor. He considered that the evidence for steroid bone loss was substantial, but that the mechanism for this

loss was not known. Finally, he recommended that the prevention of bone loss was extremely important, since the evidence showed that bone lost after the menopause was essentially irreplaceable.

Kennedy *et al* (1974), studied 420 patients with RA; 295 females, of whom 109 were on CS therapy and 26 were under 45 years of age. The onset of menopause in the females was 45.2 years. The 2nd metacarpal index (MI) was measured with Vernier calipers. Under 45 years of age, there was no statistical difference between the groups taking CS and those who were not. In males over 45 years, MI was inversely related to duration of disease. With respect to CS therapy, the MI was significantly lower in females irrespective of age, while in males this only reached significance after the age of 55 years. The findings of this study are significant, but the interpretation is hampered by the small number of patients under 45 years of age, absence of trabecular bone measurements, the mean age of the study groups being over 50 years and the absence of data regarding physical activity.

The above authors later corrected some of the defects in their study by reporting the findings of the femoral index (FI) and clavicular cortical thickness (CCT), in the same patients (1975). They found the CCT to be lower in all patient groups, but this difference reached significance only in males between 55 and 65 years of age. They reported a good correlation between MI and FI, and also that bone mass was lower at both the metacarpal and femur than at the clavicle. They concluded that RA caused generalised OP. The majority of their patients were menopausal and the functional ability was not indicated.

An abstract of a histological study presented by Muirden (1976) at an Australian meeting is quoted by several authors. The area of bone adjacent to articular cartilage and the synovial reflection was studied in 15 patients with RA. In 5 patients tetracycline labelling was performed, and in 2 patients a double label was given. Even in early disease, where there was no macroscopic evidence of cartilage or bone damage, a marked cellular reaction in the periosteum deep to the synovial layer was noted. Vascular changes were prominent. Absorption of bone was active around numerous osteoclasts along the periosteal surface of bone. These areas were detached from synovial and sub-synovial granulation tissue. More surprisingly, osteoclastic and osteoblastic reactions were seen on the marrow surface of trabeculae. Tetracycline was deposited here, indicating active remodeling and repair of bone side by side with destruction.

The findings conflicted with the popular concept of eroding rheumatoid granulation tissue as the sole primary event in the periarticular bone lesion. A spectrum of change was also apparent at the pannus-cartilage junction where eroding cells may or may not be separated by a layer of fibrous tissue. He concluded that vascular changes, leading to ischaemia and dilatation of vessels resulting in activation of osteoclasts and bone absorption, were likely to be important factors. He remarked that the pathological resemblance in extreme cases to Paget's disease may have therapeutic implications. This was the first histological evidence of active bone loss in RA. However, the ages and physical abilities of the patients were omitted, so that it is difficult to establish the roles of age, menopause and immobilisation in the genesis of the changes described.

Robinson *et al* (1975), evaluated the possibility of prostaglandin (PG) stimulated bone resorption as the possible mechanism for bone destruction in RA. Synovia from 2 patients with classical RA were incubated in a culture medium which was assayed for purified PG E2. Bone resorption stimulating (BRS) activity was evaluated using an ether extract of the medium incubated with mouse calvaria. Separate experiments were performed in the presence of Indomethacin (PG E2 inhibitor) and Colchicine (PG E2 stimulant). They found that RA synovial culture contained tenfold higher concentrations of PG E2 than normal synovial culture and concluded that this was the basis for the BRS activity in RA synovial cultures. They confirmed that Indomethacin inhibits BRS while Colchicine stimulates BRS.

They remarked that the extraction of BRS activity by ether was significant. Parathormone (PTH) and osteoclast activating factor (OAF) are not extractable by organic solvents, so that they are unlikely to have been responsible for the BRS activity seen here. They concluded that PG E2 was the bone resorbing factor in RA and suggested that their findings supported a retarding role for non steroidal anti-inflammatory drugs (NSAID). The numbers are also too small for meaningful conclusions.

These authors had omitted the age, menopausal status and functional ability of their patients. Since the mechanisms of menopausal and immobilisation OP include an unidentified resorption stimulating factor in some instances, these facts need to be known in order to place the above findings in perspective.

Kennedy *et al* (1976), presented a conflicting report on the bone resorbing activity in the sera of patients with RA. They studied 2 groups of RA patients divided on the basis of the level of the ionised calcium so that there were 8 normocalcaemic and 6 hypercalcaemic patients. These sera and a group of normal sera were then incubated with rat calvaria labelled with Ca^{45}. BRS activity was measured as the ratio between Ca^{45} released by treated and control numbers of the bone pair (test/control Ca^{45} ratio). They found that the hypercalcaemic group of patients had a significantly higher ratio than those who were normocalcaemic. The BRS activity was found to be equivalent to 0.5 U/ml. of PTH. This was inhibited by the addition of calcitonin, suggesting that the resorption was a cell-mediated phenomenon. These authors discounted the suggestion that the BRS activity is PG E2 mediated because it is so easily degraded.

They postulated that OAF was likely to cause the erosion in RA and suggested that the idea was supported by Muirden's findings (1976). They remarked on the therapeutic implications of the inhibitory effect shown by calcitonin. This study is marred severely by the omissions of similar well-intentioned attempts at deducing the pathogenesis of bone resorption in RA : they did not indicate the age, menopausal status and functional status of the patients in the study.

The role of CS therapy in the genesis of OP in RA is further addressed in a study by Mueller (1976), comparing RA patients with a group of patients with asthma. Bone mass was measured at the distal and midshaft radius using single photon absorptiometry (SPA). It was found that females with RA treated with CS showed severe and dramatic demineralisation while patients with asthma showed

no detectable bone mineral loss whether or not CS had been used in the therapy. The loss in RA was equally severe at distal and midshaft radius, suggesting similar rates of cortical and trabecular loss. They concluded that RA had a unique catabolic effect on the skeleton. They further suggested the alternative hypothesis, that asthma or its treatment protects against bone loss. The author omitted to report the age, menopausal status or functional status of the patients, so the results are difficult to interpret.

Trabecular bone mass measurement has been facilitated by the introduction of total body neutron activation analysis (NAA). Zanzi *et al* (1976), compared bone mineral content (BMC) using a Norland analyser and NAA for measuring total body calcium (TBCa). Nineteen patients with RA, 12 of whom were on CS therapy equivalent to 13 mg for a mean of 3.7 years, were studied. There was a highly significant correlation between TBCa and BMC in the total population under study. Significantly lower values were found only in postmenopausal females taking CS therapy. This study confirmed the positive correlation between cortical and trabecular bone changes in RA, and emphasised the need for further studies on larger numbers of premenopausal patients.

Kennedy *et al* (1977), presented a further review of the literature, dealing at great length with the evidence that RA causes generalised OP through a BRS factor. They questioned the role of the menopause in the genesis of this bone loss. No substantial contribution to our understanding of the pathogenesis of OP in RA was provided in this paper.

One of the first studies to evaluate the effect of therapy in modifying the OP of RA was presented by Hahn and Hahn (1976). They interpreted the evidence to be strongly in support of CS-induced bone loss in children and in females over the age of 50 years. They found that patients with RA treated with non-steroid drugs who had stage 3-4 disease, had significantly less forearm bone mass (using SPA), than did patients with stage 1-2 disease. Vitamin D and calcium supplements did not increase the BMC in these patients. They concluded that patients with rheumatic diseases were subject to the same genetic, environmental, and age-sex related determinants of OP that affect the general population as a whole.

They are much more prone to an accelerated development of severe OP as a result of decrease in the level of physical activity, disease-related alterations in Vit D metabolism, and toxic side-effects of the agents required to control their disease. The authors emphasised that the most effective means of managing skeletal complications in rheumatic disease patients was early detection and prevention.

Hancock *et al* (1978), reported an absorptiometry study using SPA at the lower end of the femur. The findings were then correlated with disease activity, body weight, knee circumference and mobility, among other things. Forty-two patients with RA (of whom 16 were under 50 years of age), were compared with 27 patients who had osteoarthritis (OA). They found the bone mass in both patient groups to be lower than a control group of 554 normal subjects. This finding conflicted with the general concept that OA is associated with increased bone mass. This study also found a positive relationship between muscle weight and bone

mass. Albumen also correlated with bone mass, suggesting a causal link between these 2 variables. They concluded that the only significant finding from this study was the negative correlation between muscle function and bone mass. The numbers of subjects in this study were extremely small, and the effects of aging are difficult to separate entirely. This study supports the concept that studies of OP in RA should be restricted to subjects who are functionally independent.

Kennedy *et al* (1979), presented yet another comprehensive review on the implications of hypercalcaemia in RA and the investigation of its causes. They reported on the ionised calcium in a random group of 50 patients with RA. Twenty-three (46%) had elevated corrected total serum calcium and 8 (16%) had elevated ionised calcium. The average age was 51.6 years. No patients had elevated levels of PTH, despite biochemical evidence of PTH-like activity. They also found a significant correlation between the erosion score and the metacarpal index. They suggested that this indicated similar events at the joint margin and the midshaft of the metacarpal. They also suggested that the MI provided a reasonably simple guide to the extent of bone damage occurring in the hands of the rheumatoid patient. No correlation was found between hypercalcaemia and disease activity. Urinary D-glucaric acid (GLA-protein) levels were elevated.

They concluded that hypercalcaemia was a not uncommon feature of RA and that BRS activity was responsible for this state. Calcitonin and hydrocortisone (both of which block in vitro resorption), may have therapeutic roles in preventing or diminishing this loss. Again, omission of age and menopausal status confuse the interpretation of these important findings.

In a study involving a larger sample, Scott *et al* (1981) contradicted the above findings of hypercalcaemia in RA. Three groups were studied, consisting of :

a) 201 ambulant outpatients with RA (mean age 52.3 years);

b) 155 in-patients with non-rheumatic diseases (mean age 59.2 years) ; and,

c) 38 inpatients with RA (mean age 57 years).

There were 2 control groups; one of 4490 healthy subjects and another of 2609 inpatients at a general hospital. Patients with any possible associated cause of altered calcium metabolism were excluded. Disease activity was assessed by the early morning stiffness (EMS), Ritchie articular index (RAI), Hb, ESR, CRP, and haptoglobin.

They found that calcium levels were lower in RA patients as well as hospital inpatients, compared with healthy controls. Inpatients with RA had lower calcium levels than all the other groups in this study. There were no significant differences between RA inpatients using vitamin D and calcium supplements, and those who were not. RA outpatients on CS therapy had levels which were lower than normal, but higher than those not on CS therapy. This study emphasises the need for controls to be matched for the presence or absence of disease. The contradictory findings are difficult to interpret in relation to the pathogenesis of bone loss in RA. The role of age and menopause are not addressed by the authors.

Osteomalacia always needs to be considered as a cause of bone loss in RA. Bird *et al* (1982) compared serum 25-OH vitamin D concentrations in RA and OA, and found no significant differences. They were unable to show any correla-

tions between 25-OH D concentrations and duration of arthritis or the articular index in the RA group.

Buchanan *et al* (1982), in a review of some metabolic effects of arthritis, considered OP to be one of the commonest systemic complications of RA. They commented on the association of hypergastrinaemia and hypercalcaemia in some patients with RA. It is not clear whether the bone resorbing substance is gastrin or whether it has similar radio-immunological properties. They supported the concept of chemical stimulated bone resorption in RA.

Reid *et al* (1982), reported on the effects of disease activity and CS therapy on TBCa measurement in RA. 63 patients with RA (mean age 34 years), comprising of 4 groups divided on the basis of menopausal status and CS therapy, were compared with normal controls matched for age, sex and menopausal status. Total body calcium (TBCa) was not correlated with any single measure of disease activity. However, when a composite index of an articular index (AI), EMS, ESR, functional class (FC) and rheumatoid factor (RF) was evaluated, a weak inverse relationship was found. In patients receiving steroids, TBCa was closely correlated with mean daily dose but not with mean duration of treatment or with total cumulative dose. They concluded that the finding of reduced TBCa in non-steroid treated patients strongly suggested that *the reduction in bone mass is an integral feature of the disease*. They interpreted the significant correlation with CS therapy to favour an implication of this drug in the pathogenesis.

They also drew attention to the need for epidemiological studies into fracture incidence in order to establish the pathological basis of bone loss in RA. Despite the methodological care taken in this study, several important associated factors needed to be controlled. This study confirmed the body of circumstantial evidence that RA causes OP. However, the pathogenesis of this loss had not been adequately evaluated in this study.

Steven *et al* (1982), added to the controversy in a report of whole body retention (WBR) of diphosphonate in RA. WBR of diphosphonate (*the most accurate measure of skeletal metabolic activity*), was measured in 3 groups of rheumatic disease patients (29 RA; 10 OA; 9 AS) and age and sex-matched normal controls. This study showed significantly increased uptake in RA patients compared with OA patients only. The major component of this RA group consisted of inpatients and patients on CS therapy. The difference between steroid and non-steroid patients was highly significant. All patients had normal PTH levels and no correlation was found with ionised calcium (Ca2+) levels.

A negative correlation was found with disease duration but not disease activity. The significance of these findings is not clear, since the ages of the patients were not stated and the physical activity had not been evaluated at all. Despite this, they concluded that *the elevated WBR levels seen in RA patients taking corticosteroids are unlikely to be the result of synovial inflammation and may reflect a non-specific effect.*

Rajapakse *et al* (1983), using Tc-99m as a measure of WBR, studied 21 patients with RA (mean age 51 years). They excluded patients with renal disease, CS therapy and biochemical evidence of MBD. In addition to WBR, urinary hydroxy proline (OH-P), ESR and radiological grades of RA were also recorded. WBR and urinary excretion of OH-P were both higher in RA patients than in controls. WBR correlated with OH-P excretion, AI and global assessment of activity, but not with ESR, radiological grading or disease duration.

Inpatients and outpatients had similar results, suggesting to the authors that mobility played an insignificant role in the genesis of the bone losing state in RA. No further assessment of physical activity is provided and in-vitro studies of bone were not done. The conclusion that OH-P excretion may be a useful measure of disease activity in RA supports the finding by Mbuyi *et al* (1982), that glycosaminoglycans (GAG) and OH-P excretion is increased in RA.

Earlier research seems to have concentrated on the negative effects of rheumatoid disease and CS therapy on bone mass. It is reasonable to assume that disease modifying drugs such as gold sodium thiomalate (Myocrisin), triethyl phosphate gold (Ridaura/Auranofin), D - Penicillamine, Chloroquine and Sulphasalazine should have a positive effect on bone mass. The earliest study, by Schorn (1983), looked at 2nd metacarpal bone mass in 172 RA patients, of whom 42 were on penicillamine and 17 on ridaura (mean age 46 years for males and 50 years for females). Radiographs were measured 3 years apart. The 2nd metacarpal area index fell in RA patients irrespective of CS therapy.

Patients on Ridaura showed a fall despite 12 months of therapy. The penicillamine group was most interesting; over a 3 year period the area index fell from 62.2 to 58.2, whereas in the year that they were continuously on penicillamine therapy, the area index increased from 58.2 to 63.5 ($p < 0.01$). This is surprising, since penicillamine, which is thought to work by inhibiting collagen cross linking and synthesis would be expected to hasten OP by suppressing collagen maturation in bone. The author concluded that RA is associated with progressive loss of bone mineral content, irrespective of disease duration.

He also believes that the reversal of bone loss in the penicillamine group was the result of improved hand function due to a reduction in joint swelling and synovitis. The findings of this study suggested that penicillamine probably had more *anti-rheumatoid activity* than oral gold. The importance of these findings is marred by the absence of tests of hand function in the patients at the times of bone mass measurement, but the finding with respect to penicillamine therapy was very interesting and worthy of more intensive investigation.

Fam *et al* (1983), in a review of stress fractures in RA, presented their experience with 4 patients (mean age 61.5 years). All presented with pain in the lower limbs and all showed diffuse osteopaenia. They found that stress fractures resulted from muscular activity rather than from direct impact. A number of factors contributed to the insufficiency fractures in RA, including generalised OP, angular joint deformities and increased activity following reconstructive surgery. Three patients had been on CS therapy and one was found to have osteomalacia (OM) on histology. They believed that stress fractures may be missed early on,

and the role of scanning was emphasised. Healing of RA stress fractures proceeded normally.

Wordsworth *et al* (1984), in a report of MBD among inpatients with RA, studied 25 consecutive RA patients admitted to their hospital (age range 50-70 years). Fourteen had been on less than 10 mg/day CS therapy. The evaluation included dietary assessment of calcium and vitamin D intake, sunlight exposure and articular index (AI). The spinal OP score was calculated by summing the total number of wedge fractures (= 1), and crush fractures (= 2) in the thoracolumbar spine. Bone biopsy at the iliac crest was done on all patients. Plasma and urine biochemistry were measured before and after 50,000 IU of vit. D daily. Seven patients (5 on CS therapy) had sustained pathological fractures in the preceding 5 years. Radiological evidence of OP was present in 14 of the 25. Spinal OP tended to increase with age and CS therapy and the scores were also higher in those who sustained limb fractures. The 10 patients who showed histological evidence of OP also had the highest spinal score. Dietary levels of vit. D and calcium were below required levels and 10 patients had low excretion of D-xylose. There was a close correlation between X-Ray and histology, and CS therapy appeared to be a potent association with limb fractures. No cases of OM were found in this study.

Hajiroussou *et al* (1984), studied 32 consecutive outpatients with RA (mean age 59.4 years), to see the effects of oral prednisone (5mg daily) on the axial and appendicular skeleton. These were matched with 31 RA patients who had never received CS therapy (mean age 58.5 years). Radiogrammetry was measured at the right 2nd metacarpal and the lower femur, while the spine was subjectively

graded according to the trabecular pattern at the vertebrae. The difference between treated and untreated patients was not statistically significant, and the authors concluded that the risk of developing OP should perhaps not be considered a definite contra-indication to low-dose CS therapy. In female patients, the central skeleton appeared to be more sensitive than the peripheral skeleton to the effects of CS therapy.

Ng *et al* (1984), evaluated bone biopsy specimens from 45 RA and 41 OA patients (average age 55 years), who came to total hip replacement (THR). Detailed biochemical analysis and a detailed dietary history were also obtained. Trabecular bone volume (TBV) resorption surface were significantly lower in RA females than normal females, and lower in OA males than in normal males. Histological OP was judged to be more common among patients thought to have skin transparency. There was a significant reduction in mean PTH in RA males compared with OA. No patients had definite hypercalcaemia. No cases of OM were found in this study. The overall prevalence of OP was 27%.

Katz *et al* (1984), studied the pathogenesis of OP in RA using in-vitro effects of copper (Cu^{2+}) on PG mediated bone resorption. They found that the inhibitory effect of Cu^{2+} was greater than that of indomethacin alone, suggesting that copper may have more than one locus of action. In a similar experiment, PTH mediated bone resorption was unaffected by the addition of Cu^{2+} to the system. They concluded that Cu^{2+} not only impeded the action of exogenous PG on bone, but may also inhibit resorption mediated by lysosomal enzymes or other as

yet undefined mechanisms. Cu^{2+} may *uncouple* the resorptive response to PG, but its exact mechanism of action cannot be deduced from these experiments.

Tannebaum (1984), in a review of the literature on the pathogenesis of OP in rheumatology practice, concluded that prolonged immobility and disease duration were important factors. CS therapy could be expected to hasten the process due to a direct effect of decreasing osteoblast function, as well as an indirect reduction in calcium absorption from the intestine. Elevated PTH levels resulted, followed by bone resorption. The author also states that there is evidence that supplemental calcium and vitamin D may be beneficial in retarding this process, but does not indicate the source of his reference. PTH levels were not measured, and no reference was made to the lack of studies showing elevated PTH levels in patients with RA.

Reid *et al* (1984a), studied NAA in RA and found a 5.3% loss in men and 6.8% loss in females with RA not on CS therapy. They also found a correlation with disease activity and disease duration. When patients on CS therapy were added to the analysis, it seemed that loss of bone was exaggerated early and then equilibrated with the *normal* rate. Patients with polymyalgia rheumatica (PMR), showed no loss in bone mass, suggesting that RA patients may be more sensitive to CS therapy. They observed that calcium and vitamin D did not increase bone mass in the longterm, fluoride is contra-indicated in RA and trials of anabolic steroids in the treatment of bone loss in RA are in progress. They concluded that a mild degree of generalised OP occurred in RA, but the loss was significantly increased when CS therapy (6.25 mg daily) was given. The age and functional status

of the patients were not described, making these results difficult to interpret with respect to pathogenesis of bone loss in RA.

Reid *et al* (1984b) also studied bone mass in nodal primary generalised osteo arthritis (OA) using NAA. They were unable to confirm the earlier suggestions (Foss *et al* 1972; Roh *et al* 1974) that patients with OA had an increased bone mass.

The effects of calcium and vitamin D treatment on bone mass were further studied by Dykman *et al* (1984), using SPA measurements. Measurements were done at metaphyseal (MM) and diephyseal (DM) sites. Serum PTH, 1,25 OH-D and 25 D cholecalciferol were measured. Radiographs of the hands, femur and spine were assessed for fracture and all patients had iliac crest bone biopsy. The study included 30 ambulant patients with rheumatic diseases who were on more than 5 mg. CS for longer than 6 months. Twenty-three completed the study, of whom 12 had RA, 8 had SLE, one had scleroderma, one had seronegative RA and one had mixed connective tissue disease (MCTD). The results showed an overall mild but insignificant increase in bone mass at both areas in treated and placebo groups. They concluded that vitamin D and calcium supplementation did not increase appendicular bone mass in RA, nor did it reduce the fracture incidence to any significant extent. Since the age range and functional status of the patients were not indicated, these results need to be interpreted with great caution.

In a population-based study of fractures after RA, Hooyman *et al* (1984) found that aging, reduced ambulation and relative weight were significant predictors of proximal femur fracture occurrence. Age and relative weight were independent predictors of risk for pelvic fractures, while aging was the only significant variable in the final proportional hazards models for proximal humerus, distal forearm and vertebral fractures. They concluded that a causal relation between RA and fracture incidence was unlikely. They also proposed that it was not necessary to invoke a generalised inhibiting factor in the genesis of bone loss in RA.

Bone biopsy remains the most critical investigation in understanding the mechanisms of bone turnover in RA. Ishikawa *et al* (1984), reported on light microscopy and electron microscopy changes in 7 patients with RA. Although light microscopy showed that bone resorption was mediated by macrophages and osteoclasts, electron microscopy suggested phagocytosis by macrophages. Osteoclasts contained vacuolated material. Osteoblasts were also seen, suggesting that repair and resorption co-existed. Resorption exceeded formation, but the greater the resorption, the greater the formation. They concluded that multiple factors contributed to the pathogenesis of OP in RA. No information was provided on the age and functional status of their patients.

Dykman *et al* (1985), further analysed the factors associated with glucocorticoid induced osteopaenia in rheumatic diseases. They previously reported their findings of reduced MM and DM in OP, using SPA. They pointed out that in CS-induced OP the MM falls to a greater extent than the DM, so that the DM:MM

ratio rises. This trend was found by multivariate analysis to be independent of age. Increased ratios, similar to age older than 50 years and menopause, were associated with a higher incidence of fractures. There were 82 patients with RA and 41 with SLE. They concluded that longterm CS therapy had a cumulative effect, occurred in all patient groups, was as common in males as females, and resulted in fractures in patients older than 50 years who were post-menopausal and had had large cumulative doses of this drug.

The influence of the menopausal state on the effect of CS therapy was further questioned in a study by Als *et al* (1985a). 97 patients were categorised into 4 groups based on steroid use and menopausal status. Bone mineral content (BMC) was measured using SPA and total body bone mineral (TBBM) using DPA measurements. They found that RA males treated with CS had lower TBBM than normal controls and RA patients on penicillamine. RA females had lower TBBM than normal irrespective of CS or penicillamine therapy. On the other hand, BMC was lower in all the RA patients compared with normal controls. In premenopausal RA females, both TBBM and BMC were significantly lower in patients receiving CS therapy. In postmenopausal females, however, there was no detectable difference due to treatment. The results in premenopausal females suggested that CS therapy caused bone loss in RA. The findings with respect to post-menopausal females receiving CS therapy are difficult to understand from the data provided.

Sambrook *et al* (1985a), in a 3-part study on 17 patients with RA of recent onset, evaluated bone turnover in early disease (average age 54 years; duration 3

years). They found that although RA patients had a trend towards lower indices of bone formation and higher indices of resorption, these differences were not statistically significant. Measures of disease activity did not correlate with any index of bone formation. Physical activity was quantitated using the Framingham activity index, but the finding of reduced muscle mass in this sample did not allow this effect to be totally excluded. Osteocalcin, a measure of bone formation, was reduced in these patients.

They concluded in this first part, that no skeletal abnormalities could be found in patients with RA of recent onset. These findings seemed to support the idea that the effects of disease duration are more likely to be due to aging than prolonged disease. The effects of age and menopausal status are not addressed.

In a 2nd paper (1985b), the same authors report on serial measurements of bone density in the distal radius, mid-shaft of radius and lumbar spine. At the distal radius, some patients showed a rapid fall in a stepwise fashion. Joint count and CRP correlated with bone loss at the lumbar spine, but not at the radial mid-shaft. The annual loss was calculated to be 2.5%. They concluded that predominantly local factors were responsible for bone loss in early disease. They postulated that fluctuation in disease activity may have contributed to the stepwise loss at the distal radius.

Calcium absorption in RA was studied by the same group of authors (1985c) on the same 17 patients as above. They found no significant differences in mean values of serum calcium and plasma creatinine compared with controls. Frac-

tional absorption of calcium was significantly reduced in the patients, but did not correlate with any index of disease activity. Levels of calcitriol were significantly increased in patients with RA. There was no significant difference in calcium intake between RA patients and controls. They suggested that the impaired calcium absorption in these patients may have been due to either a vasculitis or Sjogren's syndrome, or even secondary to NSAID's. They concluded that impaired calcium absorption would increase the risk of OP in RA.

Reid *et al* (1985), in a further analysis of the effects of CS therapy in RA, compared 39 RA patients receiving CS therapy (25 low dose; 14 high dose), with 41 patients who had asthma and 12 who had PMR. Longitudinal bone studies were also available on 57 RA patients (30 on regular CS therapy) and 19 patients with OA over 18 months. They found that the mean measured TBCa in the low dose CS group was slightly but significantly lower than predicted. TBCa was not correlated with duration of therapy or total dose taken. There was, however, a strong correlation between the mean daily dose of prednisolone and TBCa in the RA patients. The RA patients treated with moderate doses of CS had significantly less TBCa than all the other groups. In the longitudinal study, the patients treated with CS did not appear to lose any bone, while those patients who did not receive CS had a marked loss.

Patients receiving moderate doses of CS had significantly lower bone mass than those receiving low dose CS, suggesting a bone loss *threshold* slightly in excess of 5mg daily. Patients with RA receiving CS therapy lost more bone than patients with asthma or PMR, and the longitudinal studies supported the concept

that CS-induced bone loss occurred early in the course of the disease. The age and functional class, which may have been important confounders, are not indicated for the study groups.

Als *et al* (1985b), studied the role of disease duration and functional impairment in determining bone loss in RA in 105 patients using SPA measurements. The mean age was 57.2 years, and the group comprised of 29 patients receiving myocrisin, 61 receiving penicillamine and 15 receiving either cytotoxics, chloroquine or NSAID's only. They found that patients whose disease had been present longer than 8 years had a significantly lower functional ability than those with duration 0-3 years. Functional class 2,3 and 4 had significantly lower bone mass than functional class 1, measured by SPA. Duration of disease for 4 years or more was associated with a significantly lower BMC than with duration less than 4 years. A functional impairment corresponding to FC 1 or duration of RA less than 3 years implied less than 10% reduction in BMC compared with normal. If the FC changed to 2 or the disease was present longer than 4 years, the BMC could be as low as 85%. Progression from FC 2 to 3 or duration from less than 3 years to greater than 8 years did not seem to have any substantial effect on the BMC.

The data in this study did not clarify which of the two, functional class or duration of disease, carries the principal load on bone mass. They concluded that a high degree of functional impairment implied a low BMC. The greatest loss occurred in the first 3 years. Also, the effect of a long duration was simply one of adding more years of disability. The major importance of this study was that CS-

treated patients were excluded. No comments were made regarding the effects of disease modifying drugs on bone mass.

D'Angelo *et al* (1985), in another study of the effects of CS therapy on bone mineral metabolism, studied 41 patients with a mean age of 54.5 years. The mean Ca^{2+} was at the lower normal limit. Mean alkaline phosphatase (AP) was at the upper limit of normal, but was much higher in CS-treated patients. Prolonged, high-dose CS therapy was associated with higher fasting creatinine/calcium ratios. Urinary phosphate was lower in CS-treated patients. PTH was within normal limits. Urinary OH-P levels were higher in patients not treated with CS. BMC was reduced in all patients.

The significant reduction in BMC of patients who had never received CS therapy suggested to the authors that the bone loss was disease-mediated. CS dosage of 10 mg was considered to be a critical level above which a significant decrement of BMC may occur in RA patients. Calcitonin levels were at the lower normal level in all cases. The authors suggested that this was due to a reduction in synthesis or release of calcitonin in RA. The calcitonin deficiency was not corrected by CS therapy. This study did not adequately evaluate the effects of immobility and the results were confounded by the average age of the patients.

Shimuzu *et al* (1985), using histomorphometric studies on 12 patients with RA and 6 with OA, found almost equal total bone volume (TBV) in both groups of patients. In the RA group, percentage active osteoid was increased and inactive osteoid decreased. RA patients showed a significant increase in resorption com-

pared with formation. They concluded that periarticular OP was chemically mediated. The age and physical activity of the patients are not indicated by the authors, making the results difficult to interpret with respect to pathogenesis.

Fogelman (1986), remarked in an editorial that despite abundant evidence showing that RA patients lose bone at an accelerated rate, the reason for the bone loss was not established. In the same edition Gevers *et al* (1986), reported on a study of osteocalcin in 56 patients with classical or definite RA. They found a significant increase in osteocalcin level in RA. Alkaline phosphatase (AP) activity was also increased in the RA patients. The significant correlation with osteocalcin indicated that the AP arises from bone and was further evidence that bone turnover was increased in RA. There was also a good correlation of osteocalcin with OH-Proline, implying that there is also a link between osteocalcin, bone resorption and disease activity. They concluded that overall bone turnover was increased in RA and that serum osteocalcin appeared to be a useful investigation of bone metabolism in this disease. The interpretation of AP levels is confounded by the fact that the liver is a potential source of AP as an acute phase reactant in RA. Isoenzymes are crucial to accurate interpretation. The level of gamma glutamyl transferase (GGT) may provide additional support for liver origin of this enzyme in some instances.

Reid (1986), using TBCa measurements at 18 month follow up of their earlier cases, found that bone loss occurred to the same extent in patients using 5.1 - 10 mg/day of CS as in patients using NSAID's or penicillamine. No significant loss occurred in females using less than 5 mg/day. This finding was interesting, and

suggested that CS therapy might limit the degree of local bone damage at periarticular sites by reducing disease activity. They hypothesised that CS could induce bone loss early in the course of therapy, perhaps at an axial site, and thereafter prevent destructive bone loss at appendicular bone sites. Longitudinal studies are needed to test this hypothesis. This report reflects a change in this group's ideas about the effects of CS therapy on bone loss in RA.

Pitt *et al* (1986), used an isotope (methylene diphosphonate) to study the metabolic activity of erosions by scanning the joints of 10 patients with RA. They were unable to confirm that erosions always showed increased uptake of isotope. They also found that erosions could appear within 12 months without any preceding bone isotope changes. An additional feature emerging from this study was the well known difficulty in clearly defining criteria for erosions which would satisfy a number of observers. Internal consistency was high, but cross observer reproducibility was much lower. Metabolic activity of erosions was not compared with bone mass in this study.

Ekenstam *et al* (1986), reported their finding of reduced osteocalcin levels in serum from 36 patients with classical or definite RA. This finding contradicted the increased levels reported by other workers (Gevers 1986). They found that all patients with RA had significantly lower mean values for serum osteocalcin than a group of age matched patients with ankylosing spondylitis.

The effects of therapy were interesting. Penicillamine and chloroquine caused the levels to rise significantly over a nine month period, while CS caused the le-

vels to fall even lower. Withdrawal of CS therapy was accompanied by a rise in levels. NSAID's had no effect on osteocalcin levels. This study found no correlation between serum osteocalcin and duration or activity of the disease defined by ESR and acute phase reactants. They offered several interesting explanations for their observation of lowered osteocalcin levels, but concluded that it was premature to define the possible value of osteocalcin as a marker of the deleterious effects of CS on the skeleton.

Bijlsma *et al* (1986) studied the effects of methylprednisolone pulse (MP) therapy on bone metabolism in RA. Twenty patients (19 female) with a mean age of 60.6 years and mean duration of disease of 14 years were studied. Subjects were given 1G MP infusions. They concluded that changes in bone metabolism during MP therapy were only minor and transient. They suggested that the sustained fall in OH-Proline levels in the urine at 3 days after the last MP infusion, may reflect a fall in juxta-articular bone resorption, and that the effects of CS on bone differed with duration and dosage of therapy. Since the mean age of the patients exceeded 55 years and the mean duration of disease was 14 years, it is possible that the bone mass of the subjects in this study had stabilised by the time of the study.

Verstraeten and Dequeker (1986) reported on the effects of low dose CS on vertebral and peripheral bone mineral content and fracture incidence in postmenopausal patients with RA. BMC was measured by SPA at the radius and by DPA at the lumbar vertebra. In the control group, BMC at the radius was significantly correlated with BMC at the vertebra, while in the RA group this correla-

tion was found only in the CS treated group. The percentage of patients in the CS treated group who sustained fractures was greater than the percentage in the non-CS treated group. They concluded that RA did not alter the BMC in the spine, but that CS even in low dose affected the spine and fracture incidence. They postulated that this effect of CS in postmenopausal females was due to suppression of the hypothalamic-pituitary axis, resulting in smaller amounts of androstenedione from the adrenal for conversion to oestradiol in the subcutaneous fat. It is difficult to explain the apparent discrepancy between vertebral BMC and fracture incidence when a case control study was made in the RA group with comparable disease duration.

Sambrook *et al* (1986), in a study of 84 patients with RA (mean age 56 years), compared a group receiving CS (n = 40) with a group (n = 44) not receiving CS therapy. Bone mineral density (BMD, g/cm2) in the lumbar spine and femoral neck was measured with a dual photon absorptiometer (DPA). They concluded that low dose oral CS do not result in significant axial bone loss in RA. They also commented that fear of inducing osteoporosis should not influence the decision to use these agents.

Kaplan (1987), in an editorial, discusses the possible chemical mechanisms for bone resorption in Rheumatic diseases. The responses are largely dependent upon the interaction of bradykinin with cellular receptors. Two types of receptors have been defined thus far, B2 and B1. The most ubiquitous is the B2 receptor, which is stimulated by lysyl-bradykinin as well as by bradykinin. The B1 receptor is stimulated by desArg9-bradykinin to a greater degree than by the above-men-

tioned kinins. It appears to be inducible in some tissues as a result of an inflammatory response.

Lerner *et al* (1987) present evidence that desArg9-bradykinin and bradykinin are capable of stimulating bone mineral mobilisation and matrix degradation that is dependant upon interaction with osteoclasts. This suggests that kinins activate the osteoclast and that the reaction is dependent upon endogenous prostaglandin production.

Avioli (1987) summarised the current knowledge regarding the possible basis of osteopaenia in RA. He suggests that the mast cell may prove to be pivotal in inducing both the periarticular and generalised osteopaenia. In addition, IL-1 (interleukin 1) may have a local regulating effect on bone resorption through its action on macrocyte - monocyte interaction.

The evidence for generalised bone loss in RA is strengthened by a report from Sambrook *et al* (1987). They reported DPA measurements in the lumbar spine and femoral neck in 111 patients with classical RA. The study showed a significant correlation between bone mass and physical activity, as measured by the Framingham index (Kannel *et al* 1979), with a predictive value of 18.5%. A significant correlation was also found with markers of disease activity. Corticosteroid therapy was not significantly correlated with bone mass and spinal fractures were not increased in patients receiving such therapy. Age and menopausal status were not considered to have any significant added effect in RA. Smoking and alcohol were also not significant factors in this study. Although parity was not a significant

predictor of lumbar BMD, they felt that multiparity may have had a protective effect in RA.

Mellish *et al* (1987), studied bone biopsies in 48 patients with definite or classical RA. The mean trabecular bone volume volume was significantly reduced in females aged 34 - 50 years, but not in males in the same age group. Older patients of both sexes were similar to the controls. The mean trabecular plate thickness was significantly reduced in all the females, but not the males. The mean trabecular plate density and separation showed no age related change in either male or female patients. They conclude that the basis for increased fracture in RA is most likely to be trabecular thinning.

In 1988, Alwan *et al* provided further evidence for bone resorbing activity in the synovial fluid of patients with RA and destructive OA. Using the mouse calvarial system, they showed that synovial fluid from destructive OA and RA patients had significantly higher resorptive capabilities than fluid from simple OA and pyrophosphate arthropathy. These effects were shown to be largely due to IL-1 activity. However, other undetermined factors were also responsible, since IL-1 activity was higher in RA subjects, while bone resorptive activity was greater in patients with destructive OA. The bone resorbing activity was reduced by dialysis of the fluid.

Cooper *et al* (1988) reported on alterations in appendicular skeletal mass in patients with rheumatoid, psoriatic and osteoarthropathy. 50 patients were studied using SPA at the distal forearm. Distal forearm BMC was reduced in pa-

tients with RA and psoriasis and increased in those with OA. The increase in bone mass in patients with OA was confined to those with isolated large joint disease and was not found in those with primary generalised OA.

Ralston *et al* (1988) reported a high prevalence of unrecognised OM in 31 hospital patients with RA. The study was conducted in Glasgow. All affected patients were elderly women who had a poor diet and were virtually housebound. Additional risk factors in 2 patients were partial gastrectomy and occult coeliac disease. Biochemical screening was of limited value in differential diagnosis. Diagnosis was based on iliac crest biopsy.

Compston *et al* (1988) using quantitative computed tomography in 88 patients, presented further evidence for vertebral bone loss in RA, especially in younger subjects. They were unable to demonstrate any relationship with nutritional status, disease duration or disability index. The prevalence of OP was 7%, as defined by a bone mass greater than 2SD below the normal mean.

In summary, several studies of OP in RA have been reported over the years. Table 1 shows that the majority of these otherwise well constructed studies are severely limited by the difficulty in differentiating age related changes from those due to disease. It is surprising to find that the more recent studies (1985 / 1986) also failed to control for this most important risk factor in the pathogenesis of bone loss. A study of the age range with respect to the mean suggests larger numbers of older subjects.

Table 1.**Summary of earlier studies of OP in RA, showing the year, sample size and age ranges of each. Where the range was not available, the mean age is shown.**

Authors	Year	Sample Size		Mean Age / Range	
		Control	RA	Control	RA
McConkey et al	**1965**	--	102	--	40-78
Saville	**1967**	92	164	21-76	20-70
Virtama et al	**1968**	--	33	--	25-65
Bjelle et al	**1970**	74	37	40-70	20-65
Kennedy et al	**1974**	629	420	26-75	26-75
Kennedy et al	**1975**	221	307	21-79	25-78
Scott et al	**1981**	155	201	59.2	52.3
Reid et al	**1982**	40	63	54	54
Rajapaksi et al	**1983**	--	21	--	51
Schorn	**1983**	--	172	--	46
Ng et al	**1984**	41	45	58	59
Sambrook et al	**1985**	19	17	--	55.4
Als et al	**1985**	--	105	--	53
D'Angelo et al	**1985**	--	41	--	54
Verstraeten et al	**1986**	43	104	58.6	59.2
Bijlsma et al	**1986**	--	20	--	36-77
Sambrook et al	**1986**	--	84	--	56.1

DIFFERENTIAL SKELETAL CHANGES IN RA.

Bjelle and Nilsson (1970), in a study of patients with RA, showed that changes in the hands were not necessarily associated with vertebral changes. This study suggested that possibly two types of bone loss occur in RA. However, it is also possible that changes in the vertebrae were not detectable because of the insensitivity of the visual method in detecting changes in trabecular bone mass. This finding was in contrast to the earlier finding by Saville (1967), who found a tendency for cortical thickness to decrease as spinal porosity increased. Kennedy *et al* (1975), found a good correlation between the metacarpal cortical index and the femoral cortical index. They also found that bone mass in their patients with RA was lower at the metacarpal and femur than at the clavicle. Zanzi *et al* (1976), comparing total body calcium using NAA with bone mineral content using SPA, found a good correlation between the methods. These findings suggest that RA is a cause of generalised bone loss, similar to the loss reported in diseases such as hyperparathyroidism and the humeral mediated bone loss of malignancy reported by Ralston *et al* (1986). However, it is possible that changes in the hands are far in excess of changes in other areas in patients with RA. Reid *et al* (1982), in a study reporting measurement of TBCa, speculate that the reduced TBCa seen in RA is attributable to the disproportionate bone-losing effect of RA in the hands.

RADIOLOGICAL ASSESSMENT OF RA.

Radiography provides an important method for evaluating RA. A variety of evaluation systems, practically all based on conventional radiography, have been used in clinical and epidemiological studies of RA. Radiological changes in RA may be reported in descriptive form, which is used routinely to give an overall view of the status of a joint or of a patient. For scientific purposes, however, this is insufficient and some form of staging or scoring is required to permit numerical analysis of the degree of joint destruction.

A radiological evaluation, suitable for both clinical trials and routine follow-up of patients during treatment of RA, should fulfill the following criteria:

1. It should be objective, reproducible and accurate.
2. The changes recorded should be relevant to the long-term progression of the arthritic process and should be independent of acute exacerbations.
3. The degree of severity of joint destruction assessed by the radiological method, should correspond (as closely as possible) to the clinical status of the joint.
4. It should be possible to record changes in separate parameters (for example erosion and joint space narrowing) as well as the overall result

of these parameters in a single joint, a group of joints, or in the patient as a whole.

5. The method should be based on standard projections of plain films for use in multi-centre studies.

LITERATURE REVIEW.

STANDARD

The most widely used radiological classification of RA was presented by Steinbrocker and colleagues in 1949, who proposed a standardised evaluation based on four stages. Although used for several decades, this system had obvious disadvantages. The staging depended on the worst affected joint. Several pathological changes may develop between examinations, without qualifying the joint for progression from one stage to the next. This meant that the sensitivity of the system was low. The vague descriptions qualifying for each stage also meant low reproducibility. Although stages 1-3 corresponded with chronic progression of the disease and roughly with the clinical status, stage 4 did not. Ankylosis (stage 4) may reflect a reparative process in arthritis. Sievers (1965) and Larsen (1973), confirmed poor reproducibility using this method. Of the above ideal criteria, therefore, only number 5 was fulfilled by this system.

In 1963, Kellgren *et al* published an *Atlas of Standard Radiographs of Arthritis* with reference films, representing stages 2-4 as defined by Steinbrocker (1949), for the hand, wrist, forefoot and cervical spine. Similar objections are raised with respect to the second, third and fourth ideal criteria referred to above.

In 1971, Sharp *et al* designed a scoring system for erosion and joint space narrowing in the hand and wrist. This system fulfilled most of the above criteria, but included only 2 of the parameters which constitute arthritic change and was limited to the hand and wrist.

Larsen (1973; 1974) and later Larsen *et al* (1977), presented a 6-graded system based on standard reference films, describing all the large joints as well as the hand and foot. Although this system has been widely accepted in clinical research, it does have some disadvantages. De Carvalho *et al* (1981), concluded that the Larsen system fails to detect progression of joint changes over short observation periods. It is clear, therefore, that radiological evaluation in RA is subject to differences related to different observers as well as the interval between observations. Larsen *et al* (1983) compared radiological changes with auranofin and myocrisin and showed sensitivity of the method.

Brook and Corbett (1977) studied the radiographic changes in early rheumatoid disease. They found changes in the feet more commonly than in the hands. Erosions preceded joint space narrowing. In 71.3%, changes occurred within 2 years of the onset of disease. They graded OP of the hands subjectively as absent, definite or severe. 77.6% of those with definite OP developed diagnostic erosions. In 8 patients with severe OP, progression was rapid. They concluded that frequent X-Ray examinations in the first 2 years after presentation were required if we are to identify patients at risk for serious joint damage. The study suggests that OP may be a useful predictor of severe disease. These features are import-

ant, since the radiographs were measured by a single observer who followed the patients prospectively.

De Carvalho *et al* (1980), addressed the question of the joints which could be grouped in the radiological evaluation. They found that the wrist and carpus could be regarded as a single unit, as well as the 2nd to 5th MCP, PIP, DIP joint of the hands and feet. De Carvalho (1981), in a prospective evaluation of 188 patients, found that the Larsen index was unable to express progression in up to 42%. He concluded that for shorter periods of observation a more detailed system of evaluation was required.

Mewa *et al* (1983), evaluating observer differences in detecting erosions in radiographs of RA, compared 3 radiographic views (postero-anterior (PA); Norgaard 1965 and Brewerton 1967) of the hands. They found that the observer agreement was uniformly poor with all views and the number of erosions detected was similar in all 3 views, though slightly lower in the Norgaard view. They concluded that no advantage could be demonstrated in choosing the Brewerton or Norgaard views over the standard PA view for detecting erosions at the MCP joints.

Gofton (1983), in an editorial on the problems associated with the measurement of radiologic progression of disease in RA, pointed out (amongst other things) that no study had compared the sensitivity of scoring methods on the same sets of films. Practically, one is faced with the problem of determining if a small difference in the appearance of an erosion is due to advance of disease, to dif-

ference in contrast between 2 films or to minor differences in projection. Film quality is of greatest importance in this comparison.

Iannuzzi *et al* (1983), in an exhaustive review of the literature reporting the effects of drug therapy on radiological changes in RA, emphasised the many methodologic flaws in such reports. These related to the small number of observers evaluating X-Rays, randomisation of treatment groups, duration of follow-up, sample size and radiological techniques. They also commented on the lack of correlation between clinical responses (as judged by signs and symptoms of disease activity) and radiographic changes. It is possible that some of the disparity was due to the lack of sensitivity of the radiological method in assessing progression or improvement in RA. Genant (1983) provided further guidelines on the assessment of radiographic changes in RA.

Buckland-Wright (1983a & b; 1985; 1986), recognising the limitations of conventional diagnostic radiology, reported on the development of microfocal radiography as a more accurate means of quantifying disease activity. In a detailed presentation of the technique, its limitations and advantages, the author concluded that microfocal radiography provided a precise method of qualitative and quantitative assessment of changes in bone structure and was a technique which could be applied in the evaluation of the effectiveness of disease-modifying drugs.

Scott *et al* (1985), in a re-evaluation of the methods of radiological assessment of RA, concluded that there was good correlation between the Larsen system (1977) and Sharp's scoring system (1971), using joint space narrowing, erosions,

and loss of allignment in the evaluation. This was an important study since it compared the different methods on the same set of radiographs. They found good reproducibility between observers. In addition, joint space narrowing correlated with erosive change. They also pointed out that cartilage loss rather than erosive change may be of critical importance and that the relationship required further investigation.

Sharp (1985), in a discussion of X-Ray analysis of outcome in RA, concluded that radiological evaluation of outcome was an attractive method of representing disease at a given time and measuring its progression. He expressed the opinion that a better understanding of how to measure radiological progression, including defining the sensitivity of measurement and the reproducibility of detecting change, could be expected to make possible wider and more successful use of radiological evaluation in future.

Sharp *et al* (1985a), in a carefully conducted study, clarified a number of misconceptions introduced by earlier studies. Four different radiological methods for assessing RA were used by 13 observers on X-Rays from the same 49 patients with classical or definite RA. Intra-observer variance was assessed by single observers reading the same films 2 or 3 times without knowing the prior readings. Repeated radiographs of the same patients were studied in sequence. They found that 2 observers, reading the same films on multiple occasions, were quite consistent in scoring abnormalities; absolute scores of multiple observers, using the same or different methods, were quite divergent; correlation coefficients between total scores of multiple observers were 0.85 in approximately 2 of 3 comparisons;

individual observer rankings of films agreed within 10% of the median rank of all observers in 2 of 3 instances; there was agreement on progression of disease in approximately 92% of sequential film comparisons when the difference between the films was 15 units of standardised score; and, no statistically significant differences were detected between different methods or different observers.

Pullar and Capell (1985), in an editorial on the influence of treatment on radiological progression of RA, emphasised the need for more sensitive radiological techniques in detecting change with therapy. They recommended that other avenues be looked at. Radiogrammetry measurement of bone mass is an attractive alternative, but the Vernier caliper technique is limited by similar unacceptable observer differences.

Sharp *et al* (1985b) provided a useful approach to the scoring of hand X-Rays, particularly with respect to the number of joints to be included in the radiological evaluation of RA.

Scott (1986), presenting an analysis of the long term progression of joint damage in RA, re-iterates the relative importance of cartilage loss, which can be difficult to separate from erosive change using Larsen's grading technique. The relative importance of cartilage loss is further reflected in changes of the carpometacarpal ratio, as referred to by Trentham and Masi (1976).

Fries *et al* (1986), extending some of the earlier points made by Sharp (1985), conducted a randomised controlled trial of the assessment of radiological progression in RA. A number of important conclusions emerged. Erosions and joint

space narrowing contribute different information, and both should be evaluated separately. There is little difference between global erosion estimates and weighted erosion counting. The use of trained, experienced readers is critically important to the identification of disease progression. Evaluating either a more comprehensive or a more selective number of joints makes little difference in either reliability or validity. Averaging the scores of 3 or more readers greatly increases the reliability of progression scores. Films should be read in pairs rather than separately. With optimal reading techniques, the required number of patients in a study could be greatly reduced; such reading techniques could reduce costs by at least one-half and could achieve high study power with reasonable numbers of patients.

Kaye *et al* (1987) reported a technique of measuring joint space narrowing (JSN), erosion and malalignment at specific sites in the hand and wrist. Using this schema, a total score is derived for the right and left hands respectively. They concluded that bony ankylosis in RA was often associated with longer duration and greater severity of disease.

In one of the few studies relating clinical changes to radiological scores, Fuchs *et al* (1988) showed that joint scores for limitation of motion and deformity were strongly correlated with the total scores derived with the technique of Kaye *et al* (1987). The correlations with joint swelling scores were much lower. Radiological scores were not correlated at all with joint count tenderness scores, using a modified Ritchie index. This raises important issues related to the design of drug trials

evaluating disease modifying drugs. It also supports the idea that adequate evaluation of function may serve a useful purpose in the monitoring of disease activity.

In addition to the monitoring of therapy and or disease progression, radiographs in RA have been used in diagnosis. Symmetry of involvement is considered characteristic of RA, However, Halla *et al* (1986), in a systematic roentgenographic study of small joint involvement in RA, found that absolute symmetry was the exception rather than the rule. Unilateral involvement (complete asymmetry) was more common than previously found. DIP joint involvement was found in 16%. There was no significant right handed predominance of erosions. Although Burns and Calin (1983) found that erosions and global symmetry were strongly correlated with seropositivity in a blinded study, this study was unable to confirm the finding.

In a comprehensive review of radiological assessments of outcome in RA, Dawes (1988) re-iterated the methodological difficulties. He concluded that the advent of new technology should improve our knowledge further and may establish imaging of joints as the assessment of choice in inflammatory joint disease. Even now the use of an established scoring method, appropriate radiographic technique, careful timing of films and appropriate study groups should allow a better judgment of therapeutic effects and assessment of disease outcome by radiographs.

The question of frequency of radiological evaluation and the differentiation between erosion score and damage score is addressed in a paper by Larsen and

Thoen (1987). They concluded that disease duration was a critical feature for therapeutic studies. They suggested that patients with disease duration less than 36 months only were suitable for therapeutic trials of RA and that the follow-up time should be at least 18 months if radiological assessment is used.

Young *et al* (1988), reported a very interesting study of a prognostic index for erosive changes in the hands, feet and cervical spine of patients with early RA. Clinical, laboratory and radiological changes were evaluated over a 3 year interval. The strongest association with the presence of peripheral radiological damage was the rheumatoid factor. Subluxation of the cervical spine was associated only with HLA Dw 2 and HLA B27. Discriminant function analysis predicted the development of erosive damage in 79% (RA latex titre, SCAT, Hb and platelet count). Radiological outcome in the cervical spine was successfully predicted in 82% using HLA Dw2, HLA B27 and age at onset of disease. They concluded that the best predictors of erosive disease were standard laboratory features measured at onset, but that more powerful discriminant factors are needed if these are to influence clinical practice.

Mottonen (1988) evaluated the factors which predict erosiveness and the development of new erosions in RA. He found that the feet were more useful than the hands; that joint swelling was a better predictor than tenderness; that the ESR was more closely related to progression than the CRP; and there was equal progression in seropositive and seronegative disease.

Resorptive arthropathy may occur in 5% of patients with RA (Mody and Meyers 1988). The mechanisms are not known, but vascular defects have been suggested. There are very few reports of the association with RA and no reports of the markers of metabolic bone disease in this situation. The study of Mody and Meyers (1988) report the lack of any association with serology or subcutaneous nodules. Ionised calcium, calcium excretion and PTH levels were not measured. It is clear that this sub-group of patients with RA suffer a unique *uncoupling* of the metabolic process in bone. They need to be more carefully evaluated as a source of information regarding bone loss in RA.

The need for an objective measure of bone loss in the hands of RA patients has been discussed. Hutton *et al* (1988) recently reported the use of DPA of the hand in early RA. They concluded that the technique may be superior to conventional radiography in the evaluation of early disease. However, the expense of the equipment makes it prohibitive for routine use in RA.

CARPO - METACARPAL RATIO.

Trentham and Masi (1976) introduced the carpo-metacarpal ratio (CMR) as a measure of radiological progression at the wrist in RA. The ratio was determined by dividing the right carpal length by the right third metacarpal length. The longitudinal length of the carpus was measured from two distinct points on plain films of the wrist and hand, ie, the distance from the dense volar-ulnar margin of the distal radius to the base of the third metacarpal bone at its cortical midpoint. This carpal length was divided by the greatest length of the third metacarpal bone to determine the CMR. All measurements were carried out to the nearest millimeter and the ratio was quickly derived using a hand calculator. The CMR was found to be independent of age, and did not correlate with degree of mineralisation, osteoarthritis or handedness.

The ratio was abnormally low in 19% of male RA patients without erosions and in all with multiple erosions and deformity. Similar trends were seen in RA females. All increases from a pre-erosive to an erosive stage showed a fall in the CMR. The fall in the ratio with progressing RA appears to be explained by its ability to detect degrees of cartilage loss and bone compaction at the radio-lunate, lunate-capitate, and capitate-third metacarpal articulations.

They concluded that the ratio may prove to be more sensitive than conventional radiologic procedures in detecting progression of disease in some patients. It may have particular value in longitudinal studies of RA patients in setting long-term drug evaluations, by providing data suitable for objective analysis. The ratio

is proposed as an adjunct to careful, experienced, radiographic description, which is undoubtedly of great diagnostic value.

Alarcon and Koopman (1985), using both cross-sectional and longitudinal approaches, validated the CMR initially described by Trentham and Masi (1976). They found that the CMR clearly distinguishes between early and advanced disease. They suggested that the changes in CMR reflect progressive loss of cartilage and/or bone mass, although it is not possible to distinguish these two processes. Their finding that the ratio could be determined rapidly, offers a clear advantage over the more cumbersome and time-consuming methods of Larsen *et al* (1977) and Sharp *et al* (1971) and Sharp (1983). These authors concluded that the CMR is a useful, reproducible and simple measurement of disease progression in RA.

The relationship between bone loss at the metacarpals and loss of carpal length has not been evaluated in normal aging, or in patients with RA. Similarly, no information is available regarding the relationship between the femoral bone and CMR. One might expect that inflammatory arthritides such as RA and SLE would show a similar effect on bone and cartilage loss. These relationships need to be evaluated in longitudinal and cross-sectional studies.

Dawes (1988) provided a comprehensive review of the methods used for assessing radiological outcome in RA. He also provides useful insights to the relationships between function and radiological change, differentiation between inflammatory and mechanical progression and measuring the effects of treatment on radiological progression. He concluded that the use of an established scoring

method, appropriate radiographic technique, careful timing of films and appropriate study groups should allow a better judgment of therapeutic effects and assessment of disease outcome by radiographs.

FACTORS CONTRIBUTING TO OP IN RA.

AGE, SEX and MENOPAUSAL STATUS.

Age, sex and menopausal status make vital contributions to the development of OP in the non-arthritic population. Numerous reports have confirmed the observation of age-related bone loss, which seems to be accelerated in the menopausal female (Cohn *et al* 1978; Saville & Kharmosh 1967). It is also known that males have a higher bone mass than females (Garn 1967a). Idiopathic juvenile osteoporosis is a rare condition (Evans 1983), which seems to differ from osteogenesis imperfecta. The mechanisms of age-related bone loss are poorly understood, but the pathogenesis is likely to be multifactorial. Physiological changes in the metabolism of parathormone (PTH) may be important (Parsons 1979).

Evans *et al* (1983) reviewed the syndrome of juvenile OP, which introduces the possible lower limit of adult-based studies as 18 years of age. In addition, epidemiological studies show that bone loss occurs slightly later in males, and the rate of loss is slower. Newton-John and Morgan (1968), confirmed the observation by Albright *et al* (1941) that the clinical syndrome of OP can result solely from the bone loss of age, which usually commences around the age of 35-40 years. In males, the calculated loss is 4.5% per decade, while in females this loss is 10% per decade, as found by Newton-John and Morgan (1968; 1970). Bone loss is rarely detectable by standard techniques before the age of 45 years. It can be as-

sumed that these physiological effects are operative in the aging patient irrespective of whether or not disease is present.

Marcus *et al* (1983) have shown that trabecular bone volume of iliac crest decreases in women across the span of reproductive life. The predicted annual loss of bone represents a change of 0.04%-0.08% total bone volume (TBV), and the cumulative effect over 30 years might amount to a loss of 25% of original trabecular bone volume before the age of menopause is reached. If loss of bone were to continue at this same rate, even without a menopausal acceleration, 50% of original bone mass would be lost by age 80, half of which would have occurred before the menopause.

Trabecular bone is lost prior to the withdrawal of oestrogen which accompanies the menopause, suggesting that oestrogen withdrawal is not the only reason for the accelerated loss in postmenopausal women. Factors operating during adolescence or earlier may have an important bearing on skeletal integrity in later life.

Garn *et al* (1967a & b) suggested that the best natural protection against the sequelae of bone loss was a large skeletal mass at maturity. Newton-John and Morgan (1968) and Stewart *et al* (1972) make a similar claim regarding the pattern of bone loss with aging. Seeman *et al* (1988) studied the effect of early menopause on bone mass in normal women and patients with osteoporosis. They concluded that patients with OP have lower bone mass, which is independent of the

age at menopause. The risk of early menopause is probably related to the duration of exposure to minimal trauma at low bone mass.

The effect of aging on bone mass has been demonstrated with the use of radiogrammetry (Barnett and Nordin 1960; Exton-Smith *et al* 1969; Smith *et al* 1969), single and dual photon absorptiometry, NAA and whole body retention (WBR) studies (Avioli 1984a & b). Similar effects of aging have been shown in RA, emphasising the need for studies in large groups of *young* subjects. Poor control for this important factor severely reduces the interpretation of statements regarding pathogenesis. The importance of age (Saville and Kharmosh 1967) and menopausal status (van Soesbergen *et al* 1986) in the OP of RA are well recognised.

Earlier studies in RA have compared individuals whose mean age is in excess of 50 years. They have assumed the suggestion by Saville and Kharmosh (1967), that the *natural selection of the disease results in fewer young people being eligible for study*. There is clearly a need for a carefully conducted study of subjects in whom age-related effects present no confusion in interpreting the results.

Osteopaenia needs to be detected long before the clinical syndrome manifests itself in the form of vertebral and femoral neck fractures. Therapeutic measures will only be effective in the prevention the clinical syndrome if started at the age of peak bone mass.

PHYSICAL ACTIVITY.

Numerous studies have shown that immobilisation causes OP. Paraplegic patients have been shown by Wright *et al* (1965), using osteodensitometric techniques, to start losing bone mass within 6 months of paralysis. The loss is accelerated over the next two years and then slows down to a plateau by 4 years. Similarly, Jenkins and Cochran (1969) have demonstrated localised OP in the humerus of an arm immobilised in a plaster cast (POP) for a fracture. In this situation, bone loss begins as early as 3 weeks after the application of the cast. In addition, the bone loss of immobilisation, although generalised, tends to be rather patchy. Peacock and Francis (1982) have compared this with the patchy OP of Sudeck dystrophy.

Although loss of bone with reduced mobility has been easily demonstrated, the reverse is more difficult to prove scientifically.

Donaldson (1933; 1935) long ago showed that physical activity increases bone mass in animals. The difficulty lies in defining the degree of physical activity necessary to stimulate bone formation. An additional difficulty lies in finding a suitably sensitive method of measurement to detect these changes, as shown in the study by Aloia *et al* (1978). The important question in a rheumatoid population is also one of comparability between an ambulant normal population and a group of ambulant patients who have the additional burden of joint pain, swelling

and stiffness to contend with. There is no clear definition as to the degree of physical inactivity necessary to produce a critical imbalance of *coupling*.

Three theories have been proposed to explain the possible effects of muscle activity on bone. The first is a neural effect on bone; the second suggests that vascular and blood flow changes are associated with physical activity; and the third relates it to mechanical stress and strain resulting from weight bearing and muscle tension.

Dalen and Olsson (1974) concluded that it was impossible to obtain a rapid increase in the amount of bone mineral in the skeleton of healthy normal male subjects by physical training. Aloia *et al* (1978), explained the failure to demonstrate an increase in bone mass in 9 postmenopausal females with exercise, by suggesting that SPA is either insensitive at detecting the changes or that the appendicular skeleton does not reflect changes in the whole skeleton. Nilsson and Westlin (1971) showed that top rank athletes had significantly denser femora than non-athletes. White *et al* (1984), investigating the effects of exercise on the bones of postmenopausal women, found that walking and aerobic dancing caused a significant increase in bone width and cross sectional moment of inertia compared with a program of no physical activity. Krolner *et al* (1983) also recommended physical exercise as a prophylaxis against involutional vertebral bone loss.

Johnell and Nilsson (1984) evaluating the factors associated with OP in perimenopausal females, found that late menarche and early menopause were asso-

ciated with lower bone mineral content while the life-style parameters such as smoking and physical activity were not.

Dalsky *et al* (1988), in a study of weight-bearing exercise training and lumbar bone mineral content (DPA) in postmenopausal women, showed significant increases above baseline. These were maintained with continued training in older, postmenopausal women. With reduced weight-bearing exercise, bone mass reverted to baseline levels. Further studies are needed to determine the threshold exercise prescription that will produce significant increase in bone mass.

In a comprehensive review of the literature, Falch (1982) points out the various difficulties in these studies. The relationship with aging must always be considered. They conclude that immobilisation osteopaenia is largely reversible when mobilisation is re-instituted. They also express the opinion that it is uncertain whether physical activity can increase maximal bone mass or limit the bone loss due to aging. This is contrary to the findings in astronauts, whose bone mass rarely returns to normal over a prolonged period, even with exercise.

In an editorial, Burry (1987) pointed out that exercise does not usually accelerate arthritis. Recently, there has been renewed interest in the association between physical activity and disease activity in RA. Nordemar (1976; 1981a; 1981b), Ekblom *et al* (1974; 1975) and Lyndberg *et al* (1988) have all shown beneficial effects of exercise in patients with RA. Beals *et al* (1985), in a measurement of exercise tolerance in patients with RA and OA, showed that there were no statistically significant differences between the groups, although both groups

were significantly weaker than controls. Strenuous ergometer exercise did not exacerbate joint symptoms in these patients. The effects of exercise on bone mass in patients with RA are not known. These relationships are worthy of more careful evaluation.

In RA, functional assessment is probably the closest indirect measure of physical activity. Disability in RA is difficult to quantify, and detailed evaluation of physical activity is required when evaluating its possible effects on bone mass. The development of disability in RA is a progressive phenomenon which is influenced by numerous related and unrelated factors (Sherrer 1986).

The methods for functional assessment in RA have been extensively reviewed by Liang and Jette (1981), and are essentially designed as a measure of outcome. The oldest is the method of Steinbrocker (1949).

Burton and Wright (1983) outlined the difficulties in designing a *functional index*. They concluded that the measures of function currently available were inclined to be too lengthy, too complex or suffered from cross-cultural difficulties. They suggested that it may be better to move away from seeking a *general* functional index and concentrate on the needs of particular groups of patients.

Helewa *et al* (1982) described an independent measurement of functional capacity in RA based on the Mc Master Study of Medical Care Utilisation. The questionnaire is completed within a mean of 18 minutes and is reproducible between 2 observers. Meenan (1982) provided a conceptual background and dis-

cussed the measurement properties of the AIMS (arthritis impact measurement scales) approach to health status assessment.

The Keitel functional test (1972) (KFT), is an observed measure of function in distal and proximal joints throughout the body. It consists of 24 standardised tasks performed by the individual and rated by trained observers. The test can be performed in 10-15 minutes and does not require special props. The Keitel instrument demonstrates high inter- observer agreement ($r=0.85$), and Eberl *et al* (1976) demonstrated good test-retest ability (coefficient of generalisability $=0.96$).

Lee *et al* (1973), described a functional status instrument based on self-report data. This ordinal index measures whether an activity is performed and the degree of difficulty perceived in performing the activity. The Lee instrument produces statistically significant correlations with walking time ($r=0.47$), grip strength ($r=0.57$), and the Ritchie Articular Index (RAI) for joint tenderness ($r=0.62$). The Lee index demonstrated significant changes in RA patients who had undergone total hip surgery, but not in patients on a drug study. Whether this lack of difference was due to the ineffectiveness of the drug or the instrument's lack of precision is not known.

Badley *et al* (1984), argued that critics of the methods of assessment of function had been obsessed with evaluating reproducibility, to the virtual neglect of validity or biological significance. They derived a mobility score for activities of daily living using a standardised questionnaire of 24 activities selected from the

41 recommended in the Health Assessment Questionnaire of the World Health Organisation.

Convery *et al* (1977), described an almost perfect relationship between their method (based on a detailed questionnaire) and the ARA functional classification. However, there is no appropriate score for each class. They concluded that it is difficult to relate the ARA classes to overall function. These measures of disability are more relevant to a rheumatoid population than a physical activity index such as the Framingham index (Kannel 1979), which is highly subjective and poorly reproducible.

Durham *et al* (1985) compiled the MDR index of function in RA which comprised of a ten item list of activities which were considered most essential to independence in modern, western, urban living. They concluded that their index fulfilled the urgent need for a functional index which was easy and economical to apply and which was reliable and valid. The method needs to be tested in drug trials before valid conclusions can be drawn about its sensitivity in detecting change with time. Thompson (1987) reviewing the various techniques for evaluating functional outcome in RA concluded that the modified Stanford HAQ is suitable for evaluating function in RA. However, there is a need for long-term studies of changes in HAQ scores in normal and arthritic populations.

Nicassio *et al* (1985) drew attention to the psychological contribution to learned disability in RA. They pointed out that the learned helplessness model described by Miller *et al* (1979) and Garber *et al* (1980) appears to have signifi-

cant relevance to the analysis of the relation between psychological variables and health outcomes in RA. They developed the Arthritis Helplessness Index (AHI), which is a fifteen item scale to assess patients' perceptions of helplessness in coping with arthritis. It is a measure of perceived helplessness and not a measure of actual helplessness.

The measure is correlated with self-reported cognitive, affective, and behavioral dimensions of RA and with changes in health status. Therefore, the AHI may be helpful in the clinical evaluation and screening of patients who may benefit from psychosocial interventions that would complement their medical regimens.

Yelin *et al* (1980), document the high probability of work loss among patients with RA. Sixty percent of their sample was disabled at the time of study, which was an average of 10 years after onset of disease. They were unable to show any positive effects on work of the drug, medical or surgical therapies which respondents received perhaps outlining the importance of learned helplessness in the disability of RA.

Fries (1983a), in a comprehensive review on the assessment of disability, points out that in RA, disability cannot be considered apart from other dimensions such as mortality, pain, iatrogenic problems and economic impact. He recommended the use of the more reliable and more valid instruments such as self-administered patient questionnaires.

The evaluation of sexual activity is a useful indirect measure of physical activity. Brown *et al* (1987), in an evaluation of the impact of RA on patients daily

lives, found that sexual difficulties were present in 40% of their subjects. Although the reasons are numerous, disease activity may play a vital role. A recent editorial (Cohen 1987) highlights this issue in RA subjects.

Although most of these indices revolve around the ease of performance of activities of daily living, none of them consider the patient's attitude to sexual activity. Psychological factors often contribute, but impairment of physical function or activity of disease may make a significant contribution to poor sexual performance.

Despite the clear clinical impression that functional disability may bear a relationship with diseases activity, there have been surprisingly few reports of correlations between functional class and the RAI or Lansbury systemic index. Since functional disability (KFT) may be more reproducibly measured than the RAI (Eberl *et al* 1976), it is important that this relationship be more carefully evaluated (Thompson 1980).

The relationship between functional impairment and disease activity requires careful evaluation. Kirwan and Reeback (1986) developed the modified HAQ and found a significant correlation with disease activity. Bombardier *et al* (1986) showed that the KFT improved with auranofin therapy. Recently, Thompson *et al* (1987) derived a computer-based articular index which showed significant correlation with the CRP. They also found that findings in a restricted set of joints were equivalent to those in a more complete set. However, the system appears complicated and difficult to administer. Eberhardt *et al* (1988) reported a method

of functional assessment for early RA, but did not evaluate the relationship with disease activity. Thompton *et al* (1988) compared 28 articular indices to detect an induced flare of joint inflammation, but the report was based on a short-term evaluation only. They were able to detect a flare with moderate accuracy if tenderness and swelling of joints were simultaneously present. When a *weighting* for joint size was included, these were the most sensitive indices.

SEROLOGY.

The rheumatoid factor (RF) differentiates the polyarticular syndrome due to RA from that of conditions like psoriasis and Reiter's disease. Serological tests for RA are based on the determination of the sheep cell agglutination test and the latex fixation test. These are capable of determining immunoglobulin (Ig) G, Ig M and Ig A RF. In practice, only the Ig M RF tends to be evaluated. The ARA criteria (Ropes *et al* 1959; Arnett *et al* 1988) regard a test as significant if it is present in less than 5% of a normal population. Others have defined seropositivity on the basis of a latex greater than 320 (Alarcon *et al* 1982). The exact role of RF in the pathogenesis of the disease is not clear, but numerous studies have demonstrated that seropositive patients have more severe disease (Duthie *et al* 1964; Cats *et al* 1970; Feigenbaum *et al* 1979). In an analysis of therapeutic intervention based on a case-controlled comparison of seronegative and seropositive disease, Reilly *et al* (1988) concluded that seronegative disease in females may be

as severe as seropositive disease in a referral-centre population and should be treated with similar vigor. Similar conclusions were reached by Tuomi *et al* (1988) in an eight-year longitudinal study.

Calin and Marks (1981) present a very strong argument against the diagnosis of seronegative RA, an recommend that such patients be labelled as *undifferentiated seronegative arthritis*. Masi and Feigenbaum (1983) conclude that seronegative RA is a valid clinical diagnosis. They point out that for research purposes it is important to segregate patients according to the presence or absence of RF, erosions, HLA DR4 or other notable immunologic or clinical variants. In a later editorial, Masi (1988) warns that criteria for seronegative RA may be premature and that the 1987 revised ARA criteria (Arnett *et al* 1988) need to be evaluated. There is also the possibility that RF is an epiphenomenon which has little to do with disease progression (Levinson and Martin 1988).

BIOCHEMISTRY OF METABOLIC BONE DISEASE.

Nordin (1978) reviewed the diagnostic procedures in disorders of calcium metabolism He outlines the investigations which are mandatory. Jowsey (1977), in a textbook on bone metabolism, expanded on some of the practical precautions and theoretical background to these measurements.

The first step is to obtain plasma and urine from the patient in the fasting state. Blood measurements are calcium, phosphate, creatinine, alkaline phosphatase, blood urea, electrolytes and bone GLA-protein. If the facilities are available, blood should be taken for measuring ionised calcium, PTH, calcitonin, 25-hydroxy cholecalciferol (25-OHD3) and other vitamin D metabolites. Urine measurements are calcium, phosphate, creatinine and OH-proline. Urine can be collected over 2 hours or 24 hours and findings can be related to creatinine clearance.

Alkaline phosphatase and GLA measure bone formation, while urinary OH-Proline, calcium and phosphorous excretion are a measure of bone resorption. It is a general observation that resorption always precedes formation (Frost 1963).

The methods for evaluating MBD have several drawbacks when applied to a population of patients with RA. Mbuyi *et al* (1982), showed that urinary excretion of OH-Proline was higher in RA patients with higher grades of disease activity, probably due to the greater tissue destruction and inflammatory response. Kennedy *et al* (1979) found elevated levels of total calcium in some RA patients with normal levels of PTH.

Scott *et al* (1981), reported hypocalcaemia in their patients with RA. They did not measure PTH. D'Angelo *et al* (1985) found all biochemical variables in RA patients to be within normal limits, although ionised calcium levels were at the lower limit, AP was at the upper limit and PTH was at the upper borderline. Sambrook *et al* (1985a & b), found a trend for RA patients to have lower indices of

bone formation and higher indices of bone resorption, but the differences were not statistically significant. Obviously, some controversy exists in this regard.

Bird *et al* (1982) were unable to demonstrate differences in 25-OH vitamin D concentrations in RA patients compared with age-matched patients with osteoarthritis (OA). Schnitzler and Solomon (1984) found osteomalacia (OM) in 11.25% of white South African females beyond 60 years of age who presented with femoral neck fractures (FNF). They postulated that this was due to reduced sun exposure, but no dietary or treatment history was available in those patients. No similar study has been reported on RA patients in South Africa.

Alkaline phosphatase (AP) may arise in bone and liver, so that measurement of isoenzymes is critical. Concomitant rises in gamma glutamyl transpeptidase (GGT) usually imply liver disease, which is not infrequent in RA (Roberts and Coblyn 1983). Elevations in AP may also be part of the acute phase response, so that it has limited value as a marker of bone metabolism in RA.

Gevers *et al* (1986), found a significantly increased osteocalcin (GLA) level in RA. This finding suggested that bone loss in RA is unlikely to be due to an absolute decrease in bone formation. They also found a good correlation of osteocalcin with fasting urinary OH-Proline and mucopolysaccharide excretion, suggesting that there is also a link between osteocalcin, bone resorption and disease activity in RA. Butler *et al* (1988) found increased levels of osteocalcin in men and postmenopausal females with RA who had reduced BMC measured by SPA in

the distal forearm. This suggests that bone formation is normal or accelerated, but the role of osteocalcin in the acute phase response is not known.

Ekenstam *et al* (1986), compared serum osteocalcin levels in patients with RA and other inflammatory arthritides with those in controls matched for age, sex and factors influencing osteocalcin. The acute effects on serum osteocalcin due to CS therapy and NSAID's was studied, and serial measurements were performed in a number of RA patients receiving remission inducing drugs (RID's). Contrary to the findings of Gevers (1986), they found that osteocalcin was reduced in males and females with RA or other of the inflammatory arthritides. Acutely, CS therapy lowered the levels further, while NSAID's had no effect. In the longitudinal study, RID's caused a gradual rise in the levels of osteocalcin. No correlation was demonstrated with biochemical markers of disease activity in RA.

Verstraeten and Dequeker (1986), found that total calcium levels in active RA normalised when adjusted for albumin, when compared with age, sex and menopausal age-matched controls. Serum phosphorous and alkaline phosphatase were elevated in the RA subjects. Urinary OH-P was elevated, but calcium excretion was normal. PTH levels were normal. They concluded that active RA was associated with increased metabolic activity of bone.

DISEASE ACTIVITY.

CLINICAL.

Clinical evaluation of disease activity in RA is based on subjective, semi - objective and objective variables which form the basis of *weighted* scales (Wright 1983). The systemic nature of the disease demands that any index of disease activity comprise of features related to the local effects of joint inflammation (early morning stiffness, night pain, articular index, number of warm or swollen joints, grip strength, functional status), as well as the systemic effects of inflammation (hours to onset of fatigue, anaemia, elevated ESR, CRP and plasma viscosity, and reduced SH-groups) (Lansbury 1958; Wright *et al* 1985). Pain is a useful feature of disease activity in RA. Its objective measurement has been considerably improved by the visual analogue scales (VAS) recommended by Huskisson (1974; 1982) and Dixon (1981). However, psychological factors may contribute significantly to the perception of pain. Parker *et al* (1988) draw attention to these related psychosocial problems, which may need to be treated separately in the pain management strategy in RA. Anderson *et al* (1987) reported the validity of a behavioral observation method for the objective assessment of RA pain. Callahan *et al* reported a pain scale based on activities of daily living (ADL) and a VAS. Scott and Huskisson (1979) showed differences in the reporting of pain when vertical and horizontal VAS were compared.

The number of warm and swollen joints also reflect inflammation. This subjective evaluation is improved when taken in conjunction with isotope studies

(1982). Pinals *et al* (1981) developed preliminary criteria for clinical remission in RA. They considered night pain to be an additional feature of active disease in RA and emphasised the importance of the duration of early morning stiffness (EMS) as a symptom of disease activity. The mechanisms of EMS in RA are not clearly understood (Magder *et al* 1986). However, they did not evaluate functional impairment in any detail.

Wright *et al* (1985) introduced the concept of the patient model system, where the patient serves as his/her own control. Seven clinical and six biochemical variables were evaluated, including CRP, PV, SH-groups and serum histidine levels. The model is extremely useful for research on the effects of disease modifying agents in RA.

A number of studies (Eberl *et al* 1976; Hart and Huskisson 1972; Joyce *et al* 1983; Kirwan *et al* 1983a & b) have demonstrated clinicians' inconsistencies when evaluating disease activity. Kirwan *et al* (1988) further showed that analysis of clinical judgment helps to improve agreement in the assessment of RA. In RA, it is pertinent to ask *what are we measuring ?* Is disease activity a measure of process or outcome ? Should we measure short-term or long-term effects of the disease ? How do we select these measures ? (Dixon and Wright 1986; Smythe *et al* 1982; Fries 1983).

LABORATORY.

Laboratory tests are subject to misinterpretation, variation with age and sex (Shearn *et al* 1986), smoking (Larkin *et al* 1984) and fasting (Palmblad *et al* 1977). Chlud (1986) reviewed the limitations of the ESR as a measure of inflammation. However, he concluded that - in its standardised form - it is still a valid method for objective assessment of RA inflammatory activity, provided it is carried out within 4 hours of obtaining the sample. He points out that the acute phase proteins (APP) are not more valid in reflecting disease activity, prognosis or outcome. They do, however, reflect possible changes sooner and are less prone to disturbances. Kelly *et al* (1987) found that ESR correlated with clinical parameters better than did serum or plasma viscosity. Mielke *et al* (1985) also showed the ESR to be the best indicator of inflammatory activity in RA. Rowe *et al* (1987) compared CRP levels in the synovial fluid (SF) and in the serum of patients with RA, OA and psoriatic arthropathy. They found that SF CRP levels were significantly reduced compared with serum levels. Changes in SF CRP reflected closely changes in serum CRP. They conclude that possible consumption of CRP in the SF may be playing an important part in the inflammatory process in RA. Van der Heidje *et al* (1988), in a review of the literature of prognostic features on the final outcome of RA, conclude that female sex and a positive RF are variables indicating a poor prognosis. Long-standing increased ESR and CRP values, decreased Hb, or the appearance of subcutaneous nodules are indicators of a less favorable clinical course. Other factors are difficult to evaluate due to in-

complete and heterogeneous study designs. Thompson *et al* (1987) developed a computer-based articular index and related this to the acute phase response. They found that findings in a restricted set of joints was equivalent to those in a more complete set; that the simultaneous presence of joint tenderness and swelling yielded higher correlation than did either variable alone; and that joint *weighting* for size yielded higher correlations than simple counts.

Dawes *et al* (1987) showed that alpha-1-anti-trypsin may behave as an acute phase reactant in RA. Pickup *et al* (1981) demonstrated the value of plasma viscosity (PV) as an index of disease activity in RA. Larkin *et al* (1984) showed several advantages of PV over ESR in RA. Circulating immune complexes (CIC) can be measured by various techniques. Westedt *et al* (1986) showed that CIC containing IgA appear to predict erosive arthritis. Measurement of CIC may add to the predictive value of multiple variables. Sukenik *et al* (1988) showed that serum and synovial fluid (SF) levels of serum amyloid A protein correlated significantly with CRP levels from these sites. It would seem that little advantage is gained in adding yet another biochemical variable to the evaluation of diseases activity. The bone resorption states are closely linked to the synergistic action of interleukins and growth factors and may be susceptible to control with biological response modifiers (Stanshenko *et al* 1987; Scheinberg 1988). Thompson (1988) puts the various laboratory in perspective in a useful review of the literature.

RADIOLOGY.

The radiograph represents destructive effects of the disease which are largely irreversible (joint space narrowing, erosions, dislocation and ankylosis). Buckland-Wright (1985), using microfocal radiography, suggests that radiographs are valuable in monitoring RA disease activity.

Pullar and Capell (1986) pointed out in an editorial questioning the effect of treatment on radiological progression in RA, that inexpensive, time-saving, objective methods need to be sought to monitor radiological change. Bone metabolism is a dynamic process and could be subject to alterations in disease activity. The current methods of bone mass measurement using Vernier calipers are insensitive, tedious and poorly reproducible.

The above subjective, semi-objective and objective measures of disease activity are often weighted and summated to comprise a systemic index as described by Lansbury (1958). The Lansbury systemic index (LSI) needs to be modified for current purposes, since the use of salicylates is being rapidly replaced with newer NSAID's.

Liang *et al* (1982) provide useful insight into the problems in their review of the search for a more perfect mousetrap (health status or quality of life instrument). They conclude that obsession with statistical soundness of instruments may cloud the objective of finding measures that are patient orientated and clinically useful.

The Ritchie articular index (RAI) (1968), based on a record of the graded pain response to pressure over selected joints has gained worldwide acceptance

as a test of disease activity. However, the reproducibility has recently been questioned and a modification suggested (Hart *et al* 1985). They showed that reproducibility was improved by grading the pain response as present or not, while the clinical value was maintained. Lewis *et al* (1988) reported close agreement within and between observers in an evaluation of the RAI. This was the first study to address the question of a significant Ritchie score. They emphasise the importance for each centre to determine its own 95% confidence intervals for these important errors. The need for an all-encompassing articular index of disease activity is further outlined in a paper by Klinkhoff *et al* (1988), who reduced the inter-observer variability by modifying the joint count of the Co-operating clinics of the ARA (1965). The value of standardisation in reducing variability is clearly demonstrated. They conclude that such a reduction may allow a reduction in the sample size required for RA clinical trials.

Evaluation of functional impairment as a marker of disease activity needs more careful study in RA. Pincus *et al* (1987) recently showed that such evaluation was able to predict mortality in a group of RA subjects. McGuire and Wright (1971), in recommending a statistical approach to indices of disease activity in RA, found that factor analysis and a maximisation of statistical significance were two mathematical techniques which produced clinically significant results. Mallya and Mace (1981), found that a multivariate analysis (MVA) seems to provide a rapid and easy way of producing an index of disease activity (IDA) that correlates well with the facets used. Hart and Huskisson (1972) set out an important series of recommendations regarding measurement in RA. Their recommen-

dation of a *top six* include a pain scale; duration of EMS; patient preference; articular index and digital joint size. They point out that further work must be directed at reducing the number of tests needed by improving their quality. Radiological changes were not included in these statistical analyses.

Recently, attention has focused on alternative biochemical measures of disease activity. Among these, serum sulphydryl groups have been a source of attention. Lorber *et al* (1964) and Hall *et al* (1982) showed that reduced levels are characteristic of active RA. Grimaldi (1980) showed the potential for change in the levels in a patient treated with cyclophosphamide. Helliwell *et al* (1984a & b) showed that thyroxine binding prealbumen was altered by changes in disease activity, making it less useful as a test of nutritional status in RA. Forster and McConkey (1986) showed that circulating immune complexes (CIC) reflect disease activity in a manner analogous to the ESR and CRP. They also found that CIC levels fell with high dose CS therapy, but not with doses lower than 20 mg daily.

Reibnegger *et al* (1986) measured urinary neopterin levels in 106 patients with RA and in 45 patients with OA. (Neopterin is a marker for activation of cellular immunity). Levels were significantly higher in RA than in OA patients and were strongly dependant on stage and activity of RA. Correlations with other laboratory parameters were weak. MVA demonstrated that urinary neopterin levels reflected clinical activity better than did other laboratory findings. Thus, neopterin determinations might be useful in monitoring RA patients.

Berliner *et al* (1985) reported on the usefulness of the leukergy test in evaluating disease activity in RA. This leucocyte adhesiveness/aggregation (LAA) correlates well with severity in rheumatic patients (Berliner *et al* 1988). In a subsequent comparison with other laboratory markers such as CRP, albumin, Hb, etc, they found the LAA to be the best laboratory variable for the grading of disease activity. Correct grading was achieved in 63% of the patients with LAA, compared with 48% with CRP. They suggest that LAA of the peripheral blood during inflammation may be used as a reliable marker of disease activity in RA.

Spiegel *et al* (1987) showed that walking time and grip strength measured function rather than disease activity over time. They suggested that these be used as objective functional measures in studies primarily directed towards changing functional ability, but appeared to be poor major outcome measures for trials aimed at altering disease activity.

Hancock *et al* (1978) were unable to demonstrate a correlation between bone mass and disease activity. Reid *et al* (1982), however, showed a weak inverse relationship when a composite index of AI, EMS, ESR, FC and rheumatoid factor (RF) was evaluated. The observation by Sambrook *et al* (1985b), that bone loss in RA occurs in a stepwise fashion, supports the concept that these periods of loss may represent exacerbations of disease.

Radiological change in RA is a progressive phenomenon, as is indicated from the scoring system of Larsen and Dale (1977). Although this grading system is practical and useful in routine analysis, De Carvalho (1981) has shown that it fails

to describe the progression in a considerable percent of examinations. Scott *et al* (1985) showed that, although changes in the hands and wrists were unable to predict large joint disease, significant correlations ($r = 0.85$, 0.79, 0.74) were found between total scores at the PIP, MCP and wrist joints compared with the total score in other joints.

Fletcher and Rowley (1952) and Scott and Bacon (1985), have shown that an erosion is an irreversible event with very limited repair observed very rarely. Shipley (1985), in an essay on the natural history of erosions, concluded that it was doubtful whether we could regard the natural history of erosions as a single entity. He suggested that, probably, we should think in terms of several different potential historical courses and try to distinguish between them at an earlier stage.

In an comprehensive review of clinical and laboratory markers of outcome in RA, McKenna (1988) concluded that several parameters of disease activity appear to remain remarkably constant: grip strength, duration of EMS, ESR, haemoglobin, PV and serum histidine all appear to be stable indicators of disease activity when compared with the articular index. A suitable articular index would be a good indicator of prognosis, particularly if combined with a measure of the acute phase response. Larsen (1988) showed that CRP and orosomucoid were the most valuable markers for severe RA, since they showed a significant correlation with radiographic changes, ADL index and Drug index. They conclude that the ESR and RF (SCAT) are not suitable measures of disease activity on their own.

The interpretation of reports in the literature is confounded by the overlap between measures of activity, severity and outcome. In a series of publications (Fries 1983b; Bird *et al* 1983; Potts *et al* 1987), recommendations were made for the measurement of outcome. Distinction is drawn between *process* and *outcome* on the basis of potential for change with time. The Stanford health assessment questionnaire (HAQ) is currently regarded as the most suitable measure of patient status in Europe and the UK. Spiegel *et al* (1988) in an attempt to answer the question *what are we measuring*, undertook to examine self-reported functional measures. They found that mental and physical health perceptions were significant predictors for each self-reported functional measure. They concluded that the relationships among mental health and self-reported functioning should be considered when interpreting studies that use functional status questionnaires. The status of patient status measures is reviewed in an excellent editorial by Meenan and Pincus (1987). In a long-term study extending over a period of 20 years, Scott *et al* (1987) pointed out the aggressive nature of RA and its effect on patients' lives. They question the concept of *remission* in RA, suggesting that the beneficial effects of DMA extend only over a few years and that they do not influence long-term outcome. These negative conclusions may be related to the late introduction of these agents in the group under study. Meyers (1984) addressed several several difficulties related to the definition of *remission* in RA. However, *remission* is proposed as the goal of rheumatic disease therapy (Roth 1982).

INFLAMMATION MEDIATED OSTEOPAENIA.

Erosions occur when the cortex of the bone has been breached. In a review of the pathogenesis of the erosion, Kennedy and Lindsay (1977) showed that there was conflicting evidence favoring the presence of a resorption stimulating factor. Robinson *et al* (1975) postulated that PG E2 was responsible. Krane (1974), in a similar experiment, also showed bone resorptive activity in the sera of patients with RA, but concluded that PG E2 was unlikely to be the factor responsible. It is important to note that NSAID's (potent inhibitors of prostaglandin synthetase) have not been shown to alter significantly the progression of bone involvement. However, Khokher and Dandona (1988) showed inhibitory effects of indomethacin and salicylate on osteoblast activity in subjects with OA. It seems, therefore, that NSAID may inhibit formation without interfering with resorption.

Pitt *et al* (1986), in an attempt to study the metabolic activity of erosions in RA using the bone seeking isotope methylene diphosphonate, were unable to always show increased uptake in erosions. Radiological evidence of erosion could occur within 12 months, without any preceding bone isotope changes. In many cases the presence of a positive scan was associated with healing of an erosion rather than radiological deterioration. They also confirmed the well known difficulty in clearly defining criteria for erosions which would satisfy a number of observers.

Perhaps the erosion is a late stage of disease and that the serial measurement of osteoporosis accurately and consistently may serve a more useful endpoint for analysing the effects of RID's on radiological progression in RA. Abendroth *et al* (1988) in a histomorphological and immunological study of the mechanism of joint destruction in RA, conclude that autoantibodies to altered membrane structures of connective tissue cells is the primary development in the pannus. This stimulates the proliferation of cells and the transformation of connective tissue, bone and cartilage.

In the studies of OP in RA, there has been no attempt at comparing the total Larsen score in the hand and wrist with the 2nd or six metacarpal indices. Certainly there seems a need for a reproducible method for evaluating Larsen grades 1 and 2 in the pre-erosive stage (De Carvalho 1981). Kennedy *et al* (1979), showed concordance between erosion score and metacarpal index, suggesting that whatever is happening at the joint surface is also being reflected at the midpoint of the shaft of the metacarpal.

The pathogenesis of the erosion is not known. In addition to the postulate by Kennedy *et al* (1976), there is the alternative suggestion that erosions represent the effects of raised intra-articular pressure, as shown by Castillo *et al* (1965). The erosion may also conceivably be an extension of the juxta-articular OP commonly described in RA. Harris (1976), reviewing insights into the pathogenesis of the proliferative lesion in RA, concluded that with availability of experimental systems in which the proliferative response of synovial cells and macrophages to certain stimuli can be measured, there existed means for establishing conditions es-

sential for inhibiting part of the proliferative response and repressing some of the destructive potential of RA. No such studies seem to have been done.

Histopathological studies of the synovial-cartilage-bone junctions are hampered by the pluri-potential nature of the osteoblast, osteoclast and macrophage, all of which arise from the same stem cell. In an excellent essay on joint and bone metabolism, Peacock and Francis (1982), explored these fascinating inter-relationships. The tissues have a common origin embryologically, they have a similar biochemical profile and the various cell types in each tissue have an analogous pattern of organisation and inter-communication. Blair *et al* (1985) showed that macrophage mediated bone resorption occurs in an acidic environment

In an electron microscopic study of the synovial-bone junction in RA, Ishikawa *et al* (1984) concluded that there was a strong likelihood that articular bone resorption depends upon the local host response to the macrophage and osteoclast in the rheumatoid joint. Bromley and Woolley (1984 a & b) and Crisp *et al* (1984) found mast cells at sites of cartilage erosion in some of their patients. Wasserman (1984), reviewing the relationship of the mast cell to inflammation, concluded that the mast cell provides a homeostatic function in the joint. Mast cells have been reported by Taylor *et al* (1986) to stimulate angiogenesis, probably through the release of heparin. This may encourage the spread and overgrowth of invasive rheumatoid pannus tissue. As heparin has also been shown, by Sakamoto *et al* (1975), to stimulate the release of collagenase from cultured bone tissue, it might have an important function in regulating proteinase physiology at the rheumatoid lesion.

The presence of mast cells at sites of cartilage erosion suggests that they can regulate the microenvironmental physiology by the production of various vasoactive, chemotactic, spasmogenic, and proteinase-modulating factors in response to certain local stimuli. The mast cell product most likely to influence bone remodeling is heparin.

Goldhaber (1965) has shown that heparin can potentiate, while Johnston *et al* (1970) have shown that protamine can inhibit, PTH-mediated bone resorption in vitro. PTH has been shown by Crisp *et al* (1983), to potentiate bone resorption in RA. Shiozawa *et al* (1984) suggested that fibronectin on the surface of articular cartilage was responsible for promoting pannus extension. Blauss *et al* (1985) strengthened the arguments favoring inflammation mediated osteopaenia (IMO) by demonstrating bone resorption in rats given intra-abdominal injections of inflammatory substances. The reaction was associated with bone resorption at distal sites.

Crisp *et al* (1986) used a quantitative mouse calvarial bone resorption assay to investigate the effects of the mast cell products, heparin and histamine, and of salmon calcitonin. *Amorphous* heparin, containing a range of molecular weight fractions, inhibited resorption by 15-20% at concentrations of 0.75-5.0 mg/ml. A *defined* heparin species of molecular weight 13,500 inhibited resorption by 14-28% at 10^{-5}-10^{-4} mol/l. Histamine inhibited resorption by 19-55% at 10^{-3}-10^{-2} mol/l. It was proposed that heparin and histamine depress coupled bone resorption and formation and may lead to net loss of bone. Salmon calcitonin inhibited resorption at concentrations as low as 10 pg/ml. *Amorphous* (but not *defined*) he-

parin blunted calcitonin-induced inhibition of bone resorption and may depress osteoclasts.

Little is known of the properties of the human mast cell heparin released in vivo. Mast cell heparin release adjacent to osteoclasts in the rheumatoid joint could impair the effect of circulating calcitonin and indirectly stimulate osteoclastic resorption. Even if this indirect catabolic effect of heparin can be confirmed, however, it is unlikely to be as important as its primary antianabolic role.

Taylor *et al* (1986) found that histamine stimulates PGE production by RA synovial cells and human articular chondrocytes in culture. They propose that the mechanism of action is related to H_1 receptor activation and subsequent arachidonic acid liberation.

Tan *et al* (1988) studied the effects of aminobisphosphonate (APD) in the inhibition of interleukin-induced bone resorption in mouse calvaria. The positive effects cause the authors to conclude that these in vitro observations may have relevance to the use of APD in bone and joint diseases in which inflammation and bone resorption are prominent. The most likely candidates would probably be those diseases associated with arthritis mutilans (severe resorptive arthropathy). The metabolic bone events in this interesting clinical situation have not been adequately addressed in the literature.

Rooney *et al* (1976) and De Witte *et al* (1979), have reported elevated levels of gastrin in some patients with RA. The source of elevated gastrin in RA is not known. Preliminary immunofluorescent studies by Buchanan *et al* (1982) suggest

that an as yet unidentified synovial cell may be responsible for gastrin production, and that this may reflect disease activity. Yorke *et al* (1986), confirm these findings. Henriksson *et al* (1986), also confirming these findings, suggested that disturbances in gastric flora may influence the course of the disease. This is also the postulated mechanism of the effect of Salazopyrine in RA. La Montagna *et al* (1987) reported a low incidence of hypergastrinaemia in their patients with RA. It is possible that gastrin increases inflammation, thereby accelerating bone resorption.

DISEASE DURATION.

Several studies have attempted to show a relationship between disease duration and loss of bone mass. Such a relationship could be expected if one considers that aging causes a loss in bone mass. Menopause could also conceivably accelerate such loss in RA. In a study of the right 2nd metacarpal, Schorn (1983) found a statistically significant reduction in the area index of non-CS treated patients according to duration of disease. Reid and Nuki (1984a), using NAA, showed a negative correlation between disease duration and total body bone mineral (TBBM).

Sambrook *et al* (1985b), in an analysis of osteocalcin and urinary OH-proline, concluded that no skeletal abnormalities could be found in RA patients with less than 3 years of disease. Als *et al* (1985b), found that patients with RA longer than 4 years had lower bone mass than those with a shorter duration of disease. The interest of this study was the finding that functional impairment also deteriorated with prolonged disease, so that it was difficult to differentiate the respective contribution of disease duration and immobilisation to the bone loss. They concluded that in RA, maximum bone loss occurred in the first 3 years. The effect of a long duration was simply one of adding more years of disability.

These relationships have not been fully evaluated in young, premenopausal females.

DRUG THERAPY.

NON STEROIDAL ANTI-INFLAMMATORY DRUGS.

Despite the experimental evidence of the inhibitory effect of NSAID on bone resorption (Klaushofer 1988), there is little clinical evidence that these drugs prevent bone loss in RA (Reid 1986; Cooper *et al* 1988). Klaushofer *et al* (1988) evaluated the biopotency of various NSAID in inhibiting PG mediated bone resorption, in a neonatal mouse calvaria organ culture medium. Diclofenac was the most potent, while salicylates showed the least potency. In practice, most patients with RA require regular NSAID. Perhaps the osteopaenia of RA would be more significant if such agents are not being used. Since studies of OP in RA emanate from specialised centres dealing with relatively severe cases, it is unlikely that a large enough group of subjects with RA not receiving NSAID would be available for study. More recently, however, Khokhler and Dandona (1988) showed that aspirin and indomethacin inhibit osteoblast function *in vitro*. These relationships are obviously important and require study, but protocols would be difficult to design. The role of NSAID in the management of RA is not regarded as disease modifying.

DISEASE MODIFYING AGENTS.

Few studies have documented intake of disease modifying agents (DMA's) in relation to bone mass. Als *et al* (1985b), who compared these regimens, showed that penicillamine may offer some protection against loss, myocrisin offers none and NSAID's probably have no effect at all. Schorn (1983), showed that penicillamine therapy showed a definite increase in area index over a 3 year period.

Robinson *et al* (1975), using in vitro studies, have shown indocid to inhibit PG E2 mediated bone resorption, while colchicine stimulates bone resorption in this experimental situation. One would expect that a reduction of the *inflammatory load* with RID's would prevent resorption mediated by interleukin 2 or OAF. Also, better disease control could lead to improved function, as suggested by Schorn (1983). Penicillamine therapy (Schorn and Mowat 1977) has been shown to result in improved bone mass, despite its effect of altered collagen metabolism. However, the effect on wound healing was equivalent to that of giving CS therapy for 3 years. This finding is significant, since objective measurement of these changes using a sensitive device would be a useful means of evaluating radiological progression in RA.

Situnyake (1988) in a comprehensive review of the literature evaluating disease modifying effects of therapy in RA, concludes that these drugs are capable of altering the disease in the short-term only. Large-dose corticosteroid therapy

may influence progression of erosions, but the effects on metacarpal bone mass are controversial.

There is obviously controversy in this area as well, and the role of immobilisation in this situation needs to be more carefully evaluated. Ideally, young subjects need to be studied. Comparisons between groups should enable one to evaluate the effects of therapy. Treated and untreated groups should not only be compared with one another, but also with normal controls.

CORTICOSTEROIDS.

In the clinical situation, there is controversy as to the mechanism whereby CS-related bone loss is mediated (Guyatt *et al* 1984). It is not known whether it is the total daily dose, total duration or total dose of CS which is important. McConkey *et al* (1965) found that OP was most common in RA patients with transparent skin who had received CS therapy. Saville and Kharmosh (1967) concluded that age greater than 50 years had a more profound effect on bone mass than CS therapy. They believed that duration of CS therapy was extremely important. They also suggested that CS therapy may have a protective role on bone mass in women under 45 years of age. Duncan (1972) concluded from a review of the literature that CS therapy in RA definitely caused OP, but that the mechanism whereby this effect was mediated remained unclear. Suda *et al* (1983) studied the effects of hydrocortisone on osteoclasts generated in cat bone marrow cultures,

and found that osteoclast numbers and size were reduced. These findings are compatible with the suggestion that CS may act directly on osteoclasts, which in vivo may result in decreased resorption of bone. However, it is not clear to what extent these findings can be extrapolated to the mechanisms in man. Rickers *et al* (1984) concluded that high-dose prednisone therapy has an effect on cortical and trabecular bone.

Kennedy *et al* (1974) found that CS therapy significantly reduced bone mass only in patients over 45 years of age. In males, this loss became statistically significant only after the age of 55 years. Mueller (1976), comparing RA patients with asthma patients taking CS therapy, found that only patients with RA showed a loss of bone mass with such treatment. Hahn and Hahn (1976), concluded that CS related OP is more common in children and in women over the age of 50 years. Reid *et al* (1982), found that in RA patients using CS therapy, total body calcium was closely correlated with mean daily dose but not with duration of treatment or mean cumulative dose.

Schorn (1983) showed that area index was reduced in RA patients irrespective of CS therapy, but comparisons were not made between treated and untreated patients. Wordsworth *et al* (1984), found that spinal OP tended to increase with age and CS therapy (less than 10 mg. daily), often leading to pathological fractures. Hajiroussou *et al* (1984), in a study of prolonged low dose CS therapy in RA, found no significant differences when compared with matched patients not given CS therapy. They concluded that the risk of developing OP should perhaps

not be considered a definite contraindication to the use of low-dose CS therapy in RA.

Dykman *et al* (1984) showed that oral 1,25 dihydroxy-D3 and calcium supplementation did not significantly increase bone mass. These same authors (1985) showed subsequently that CS therapy reduces metaphyseal mass (MM) to a greater extent than diephyseal mass (DM), causing the DM:MM ratio to increase. The implications of this finding are not clear, but seem to point to a specific diagnostic pattern of bone loss with CS therapy.

In a comprehensive essay on determining causation, Guyatt *et al* (1984), concluded that the evidence that exogenous CS cause clinically important OP was weak and unproven. The review of the literature on bone loss in RA showed that a similar statement could be made about this association in RA. Byron and Mowat (1985), studying the pattern of CS prescribing in their unit, were surprised to discover that 24% were receiving CS therapy for articular disease, with a mean duration of therapy of 8.3 years. De Deuxchaisnes *et al* (1986) showed that the menopausal state had a synergistic effect on the bone-losing process accompanying low-dose CS therapy.

Zerwekh *et al* (1984) studied 34 patients with RA to see the effects of CS therapy on vitamin D metabolism. The patients were initiated into a double-blind trial that lasted 32 weeks. There were no significant differences between the treated (5 mg daily for 24 weeks) and untreated groups in serum levels of vitamin D or its metabolites.

The suspected effects of prednisone on bone mass have led to the evaluation of other forms of corticosteroid. Deflazacort, a oxazolino derivative of prednisone, has been compared with prednisone in a number of recent studies. Lo Cascio *et al* (1984) showed that trabecular bone was lost to a lesser extent with Deflazacort than prednisone in 2 groups of subjects matched for age, sex and underlying disease. The dose of prednisone or deflazacort is not stated. Gennari *et al* (1984) compared the effects of 20 mg prednisone with that of 30 mg deflazacort in 10 patients. They found that both these agents caused an elevation in serum PTH levels, but that prednisone had a more profound effect. Reduction in bone mass was also less in the deflazacort group. They propose that CS induced bone loss is mediated by an elevation in PTH secondary to increased urinary excretion of calcium as well as decreased intestinal absorption of calcium. Balsan *et al* (1987) showed a similar effect of deflazacort in the treatment of 9 children requiring varying doses of prednisone. They concluded that these results warrant the extension of clinical trials with this new glucocorticoid for the management of the acute, active phase of paediatric diseases requiring steroid therapy.

Bijlsma *et al* (1988a) re-evaluated the effect of oral calcium and vitamin D on CS-induced OP. BMC measurements of the spine were prospectively studied, comparing the preventive effect of calcium (500 mg a day) and calcium plus vitamin D (4000 IU on alternate days) during long-term treatment (2-161 months). 40 patients (mean age 45.5 years) with a variety of rheumatic disorders requiring more than 10 mg a day of CS were evaluated. They concluded that a small increase in BMC was noted in both groups, but no differences between preventive

calcium and calcium plus vitamin D became evident. It was suggested that patients receiving prednisone should be advised to use supplemental calcium.

The same authors (1988b) report on the acute changes in calcium and bone metabolism during MP pulse therapy (1000 mg alternate daily for 3 doses) in RA. The effects could be divided into those which occur within 24 hours and those secondary effects arising after 24 hours. The primary effects (24 hrs) include a decrease in bone resorption and formation; a decrease in renal excretion of calcium; and an increase in serum 1-25 dihydroxy cholecalciferol. The secondary effects (after 24 hrs) include a decrease in serum calcium due to the decrease in intestinal Ca absorption and the decrease in renal tubular reabsorption of Ca; and an increase in serum PTH concentrations. In a previous study it was found that these changes normalise within a few days after completion of the CS treatment.

Despite these warnings about the possible effects of CS therapy in RA, these drugs continue to be used in the clinic (Barraclough 1986). Byron and Kirwan (1986) reported that 25% of the patients attending their clinic were receiving regular systemic CS therapy. Ianuzzi (1987) concluded from a review of the literature that CS therapy has a definite place in the treatment of RA. They have not been proven to be disease modifying, but adequate trials are lacking. In recognition of this, Byron and Kirwan (1986), questioned the feasibility of a trial to see the disease-modifying capabilities of CS therapy. They concluded from a review of the literature that a trial of low-dose CS therapy for the prevention of erosion development was feasible and should possibly be undertaken. Buchanan *et al* (1988) showed that reduction of the dose of prednisone from a mean of 3.5

mg daily to placebo caused an almost immediate flare in the arthritis. They concluded that *homeopathic* doses of oral CS are effective in RA. Such doses are unlikely to interfere with bone resorption.

HAND EVALUATION.

SIMPLE HAND FUNCTION.

In a systematic, radiological study, Halla *et al* (1986), showed that the small joints in the hand and wrist are the commonest sites of Rheumatoid involvement. In studies of radiological evaluation of progression, Larsen and Dale (1977) have shown that these joints contribute to approximately 50% of the total score. It is, therefore, incumbent on the researcher to correlate bone changes in the hand with changes in hand function and strength.

Hand function can be evaluated in several ways, each aimed at demonstrating some aspect of dysfunction. Since hand function can be impaired by extra-articular disease as well as articular disease, it is desirable to try to study several components in a single test. Grip strength is such a test, since it uses a combination of function and strength in the PIP's, MCP's and wrists, respectively. De Choisy (1973) introduced the concept of the *functional grip*, which is measured with the Winthrop torquometer. It has an advantage over the sphygmomanometer test because it measures wrist and arm movement as well as the usual grip strength.

The KFT (Keitel 1972) evaluates some aspects of hand function, which can be monitored serially. In addition, Clawson *et al* (1971), devised a test of hand function using 4 simple procedures performed during a monitored period of time. The tests were designed to evaluate the results of hand surgery in RA.

HAND STRENGTH.

One would expect that bone mass would correlate with loss of function or strength in the hand. Virtama *et al* (1968), in a study involving 33 patients, found that power of grip in the right hand showed a high correlation with bone mass in the proximal phalanx but not in the metacarpal. It is important to note that grip strength is often a component of systemic indices of disease activity such as the Lansbury systemic index (1958). McGuire and Wright (1971), Mallya and Mace (1981) and Rhind *et al* (1980) recommend grip strength as an integral component of an index of disease activity in RA, for application in drug trials. These generally use the sphygmomanometer.

De Choisy (1973), designed the Winthrop torquometer for measurement of *functional grip* in RA. The torquometer measures both the ability to grip and also the ability of the wrist and elbow to rotate. The study showed that there was very good and statistically significant correlation between grip strength as measured by the conventional sphygmomanometer and functional grip as measured by the torquometer. This study did not measure bone mass in relation to grip strength.

Myers *et al* (1980), evaluated hand grip function using a dynamometer. The device was able to relate power and work. The physical features of the device (standard clinical inflated cuff bag) offer several advantages over the use of a solid-handle torsion dynamometer. Long *et al* (1970), defined power grip as forcible activities of the fingers and thumb acting against the palm. Flexion, abduction and adduction of the phalanges are involved in adjusting to the shape of the object. All the extrinsic and some intrinsic muscles of the hand are involved in normal power grip.

In a study of bone mass in relation to hand strength, a group of workers (Dickson *et al* 1972) measured forces in individual digits using a cybernometer. They were unable to show any relationship between flexion force and 2nd metacarpal bone mass (Dickson *et al* 1973). However, finger extension, adduction and abduction were not measured. The relationship between bone mass and hand grip was also not studied, although the earlier study showed a significant correlation between grip strength and cybernometer readings.

Agre *et al* (1987) evaluated the reproducibility of dynamometer measurements of muscle strength in the upper and lower limbs respectively. They found that although the dynamometer was reliable for measuring upper extremity muscle groups, it was unreliable for measuring lower extremity muscle groups. They outline the need for further work to evaluate muscle strength quantitatively in the clinical setting in an accurate, valid and reliable manner.

There is a need for a careful evaluation of finger strength in relation to metacarpal bone mass. It is very likely that patients with RA lose bone in the hands as a result of weakening of grip secondary to inflammatory arthritis.

NUTRITIONAL STATUS AND DIET.

In a comprehensive review of current techniques of nutritional assessment, Grant *et al* (1981), suggested that, to aid in nutritional assessment, the body could be divided into six compartments, namely, fat; skin and skeleton; extracellular mass; plasma protein; visceral protein mass; and skeletal muscle or somatic protein mass. No anthropometric or biochemical tests are available as a measure of bone mass, although inferences can be made from the difference between lean body mass and fat mass. The fat component can be measured by a summation of triceps and subscapular skinfold thicknesses (SFT's) (Sloan 1967), while the visceral protein mass is represented in serum albumen, transferrin, prealbumen and skin antigen delayed hypersensitivity.

Skeletal muscle body cell mass is measured by arm muscle circumference (Frisancho 1974), creatinine height index and weight. Baker *et al* (1982) showed that general clinical assessment is a reproducible and valid technique for evaluating nutritional status. Measurement of thyroxine binding prealbumen (TBPA) is considered by Keyser (1979) to be the most accurate and sensitive biochemical

index in the assessment of nutritional status. Serum half-life is 2 days and its body pool is quite small. It is best measured by radial immunodiffusion.

Watters *et al* (1985), in a study of nutritional assessment by hand grip dynamometry, found that hand grip strength measured this way was reduced in severely malnourished males. However, dynamometry correlated very poorly with most nutritional tests studied in the same patients. Hand grip strength also fell with increasing age. They suggest that dynamometry is not a substitute for nutritional tests but rather another of an already long list of nutritional measurements. The poor correlation with these nutritional parameters precludes its use as a single test. Blackburn and Thornton (1979) provided valuable guidelines for the nutritional assessment of the hospitalised patient.

Retinol binding protein (RBP), is the specific protein for vitamin A alcohol transport and is linked with prealbumen in a constant molar ratio. The serum half-life is only 10 hours, so that acute changes in protein malnutrition are best reflected in this measure.

McConkey *et al* (1965), in one of the earliest studies of OP in RA, related bone mass to skin transparency and found that RA patients who were on corticosteroids had transparent skin as well as lower bone mass than their non-treated cohorts. They postulated that a common defect of collagen metabolism in bone and skin was responsible for this association. No relationship could be demonstrated between bone mass and skinfold thickness of the dorsum of the hand in this study. Few subsequent studies have attempted a similar analysis.

Hancock *et al* (1978), found that osteoporotic RA patients tended to have lower serum albumen levels. They offered the suggestion that this may represent a defect in bone glycoprotein formation. A recent study by Sambrook *et al* (1985c), in patients with short duration of RA, demonstrated that calcium absorption was abnormal. The reasons for this are conjectural at present. The patient population studied had an average age of 55.4 years. This is significant, since calcium absorption has been shown to be reduced in post-menopausal OP by Bullamore *et al* (1970). Age may have been a significant factor in the pathogenesis of the calcium malabsorption in this group of RA patients.

Lean body mass (LBM) is a measure which excludes the fat component. Willmore and Behnke (1970) showed that lean body mass can be predicted almost equally well from either skin folds, circumferences and diameters, or a combination of these. The method has been validated by Tcheng and Tipton (1973). None of the previous studies of OP in RA have attempted to correlate bone mass with anthropomorphic measurements of LBM, although McConkey (1965) and Schorn and Mowat (1977) were unable to show correlations with SFT at the dorsum of the hand. Reid *et al* (1982), measuring LBM by the retention of potassium, were unable to demonstrate a relationship between LBM and bone mass.

Helliwell *et al* (1984a) in a study of nutritional status in 50 patients with RA, using the anthropometric body mass index and triceps SFT measurements, found evidence of malnutrition in 26%. Upper arm circumference was significantly reduced in male but not female subjects with RA. Malnourished patients had more active disease. They concluded that in RA, severity of disease adversely affects

the nutritional status. In another report (1984b), the same authors show that the biochemical markers of disease activity (ESR, CRP, A1 antichymotrypsin) showed a negative correlation with TBPA as a marker of nutritional status. It may behave as a negative acute phase reactant in these patients and is, therefore, a poor guide to nutritional status.

Peacock and Francis (1982), pointed out that vitamin D deficiency was still a significant factor in the low bone mass of RA patients in places such as the UK. This emphasises the need for biopsy confirmation of OP in patients with radiological evidence of osteopaenia, since this is the only way to differentiate OM from OP. The incidence of OM in RA patients in RSA is not known.

Serum albumin is a useful estimate of visceral protein status (Bistrian *et al* 1975). Bistrian *et al* (1976) have also shown a good correlation between changes in serum albumen and changes in upper arm circumference. In addition, it is inexpensive and easy to determine. Anderson and Wochos (1982), showed that the hospital stay was prolonged, and the postoperative complication increased, in hospitalised patients who had low serum albumen levels. Low albumen is not directly involved in the pathogenesis of protein calorie malnutrition, but depression of lymphocytes, anergy and reduced antibody responses are restored when albumen levels are repleted.

The dietary contribution to bone formation is well known. Seftel *et al* (1966) showed that in middle-aged South African Blacks with OP, 69% were scorbutic, or had been scorbutic in the past. The reasons for this have been reviewed, iron

overload being suggested as the most likely explanation. They pointed out that there are at least 3 ways in which iron overload may lead to OP. It might damage organs or tissues concerned with bone formation; it might impede calcium absorption; or it might interfere with the metabolism of ascorbic acid.

Richman *et al* (1979) considered diet to be the major reason for the differences in intracortical bone remodeling seen in three Aboriginal American populations. It is well known that a high protein diet causes metabolic acidosis which is associated with bone loss and hypercalciuria (Sauberlich 1972; Lemann 1966 Mazess and Mather 1974). On the other hand, Ellis *et al* (1972) have shown that vegetarians demonstrate less cortical bone loss than omnivores, by radiographic examination. Investigators have also noted diminished formation of osteoid by osteoblasts in protein deficiency, a decrease in the number of osteoblasts, and slowed mineralisation (Follis 1957; Ramalingaswami and Deo 1968 and Stewart 1975).

Lukert *et al* (1987) studied the relationship between nutritional factors, calcium regulating hormones and bone density in 3 groups of normal subjects. In perimenopausal females, significant correlations were found between bone density and dietary Ca:P ratio, iPTH and 25 OH D. In elderly women, significant correlations were found between change in bone density and initial bone density; change in bone density and serum 25 OH D; and serum calcium and age. In elderly men, significant correlations were found between serum 25 OH D and dietary vit D; iPTH and 25 OH D; and iPTH and serum phosphorous. They concluded that the more adequate the state of vit D nutrition, the lower the serum

iPTH in perimenopausal women and elderly men and the less bone loss in elderly women. They suggested that the dietary Ca:P ratio may be important in maintaining bone density in perimenopausal women.

Since dietary intake is a vital aspect of bone metabolism, it is pertinent that some measure of dietary analysis be related to bone mass. Several methods of dietary evaluation are available, and the sensitivity is obviously improved by the degree of detail recorded. Reshef and Epstein (1972), concluded that the Burke-type interview (1947) is reliable and reproducible. In a review of validations of dietary assessment methods, Block (1982), comments that a seven-day record of actual intake should give a reasonably accurate measurement. Also, a seven-day record is more representative of usual intake than a single day.

The seven-day record is a standard measure of dietary intake used by the dietitians at our hospital and consists of a 7-day record of all foods taken orally. These records are then analysed in a variety of ways. Socio-economic and other factors will obviously influence individual dietary habits. Computer programmes have been devised to quantitate the daily intake of calcium, phosphorous and vitamin D at the SAMRC in Cape Town.

Bone turnover can only be fully evaluated if dietary intake is correlated with urinary, faecal, blood and bone calcium studies. With respect to RA, dietary factors may influence bone mass indirectly through modifying disease activity. It is interesting to note that Palmblad *et al* (1977) demonstrated that fasting may reduce levels of acute phase reactants, although there is no significant improvement

in disease activity. These findings were confirmed by Skoldstam *et al* (1979; 1983), and they may be important when considering the relationship between disease activity, diet and bone mass in RA. The effects of dietary manipulation on disease activity in RA have been shown in a number of studies (Kremer *et al* 1975; Stroud 1983; Uden *et al* 1983; Magaro *et al* 1988).

SMOKING.

Previous studies have not considered the role of smoking in the pathogenesis of the OP in RA. Jensen *et al* (1985), in a recent study in postmenopausal females, have shown that smoking reduces the effects of exogenous oestrogens on bone mineral metabolism. This may be an area in which prophylactic measures may serve a major role in preventing age-related bone loss or postmenopausal OP. Larkin *et al* (1984) have shown that smoking reduces the ESR, but has no effect on plasma viscosity. This lack of dependence of the plasma viscosity on smoking habits may be advantageous in sequential studies of disease activity in RA. The relationship between smoking and bone mass in RA has not been evaluated in any of the earlier studies.

GENETICS.

Inheritance could affect the development of OP in 2 ways. Genetic factors could influence the amount of bone mass attained at maturity and subjects with genetically determined lower bone mass might be more susceptible to develop OP after entering the period of age-dependant bone loss. Alternatively, or in conjunction with the above, genetic factors could influence the rate of bone loss.

Dykman *et al* (1985), in a study of factors influencing CS induced osteopaenia, remark that although US blacks have a higher bone mass throughout life than whites, there is no difference in the fracture rate between the 2 races. In South Africa, Dent *et al* (1976), showed that severe degrees of vertebral deformity were commoner in Caucasians than in blacks. Solomon (1979) in a study in Johannesburg, showed that bone mass in Blacks was lower than Whites for all ages in the 2 sexes. He also showed that Caucasians lost bone more rapidly, discounting the suggestion by Stewart *et al* (1972) that a lower bone mass at onset of maturity precipitates bone loss later in life. However, black patients are subject to the same age and presumed steroid related losses, so it would seem that environmental factors are also important. Mayor (1976) also pointed out the need for differential bone mineral standards for Blacks. Wagener and Hough (1987) evaluated metacarpal bone mass in 559 White and 582 Coloured subjects aged 10-80 years. They showed significant differences between males and females in the 2 groups. Coloureds had a lower metacarpal bone mass, underlining the need for *normal* values appropriate to the individual. No previous studies have evaluated the

genetic profile which predisposes to the development of OP in the aging, menopausal or rheumatoid populations.

Smith *et al* (1973), in a study of 71 juvenile and 80 adult monozygotic (MZ) and dizygotic (DZ) twin pairs, found a definite genetic element. However, gene transmission is not of the Mendelian type. HLA studies were not performed in the groups. The intrapair variance was greater in the dizygotic pairs. Because the tendency to OP was greater in the adult twins, they concluded that environmental factors were likely to be important. The exact genetic factors for osteoporosis are not known. No previous studies of post - menopausal (or other) OP have evaluated the HLA antigens in affected and unaffected subjects. The interpretation of genetic factors in RA subjects with OP would be difficult to separate from the disease - susceptibility genes. It is possible that the same genetic factors may predispose subjects to the development of both RA and OP. Prockop (1988) reviewed the genetic mechanisms in osteogenesis imperfecta. The genetic defect may reside at a number of steps in the intra- and extracellular synthesis of type I collagen from procollagen. The primary aetiology of OP might be in *minor* mutations within genes whose correct expression is required to assemble and maintain normal cartilage and associated joint structures.

In RA, HLA DR4 has been shown to increase the relative risk (rr) (Woodrow 1986; Sachs and Kirwan 1986; Tiwari and Terasaki 1985). There is also some evidence that this leucocyte antigen may be a marker for more severe disease (Gran *et al* 1984). The studies are controversial (Silman *et al* 1988), but this is an area that is likely to develop further. Gran and Husby (1987) point to the need for

criteria to clearly define the group of seronegative RA, who may have milder disease and a different genetic predisposition to RA. The immunogenetics of RA are adequately reviewed in 2 recent editorials by Woodrow (1988) and Mc Cusker and Singal (1988). Caution is expressed in interpreting HLA data.

Khan *et al* (1987) suggest that a significant relationship can be found between RA and HLA B27. They found that patients with RA who had the B27 antigen were more likely to develop atlanto-axial subluxation. Dahlqvist (1986) showed a strong association between B27 and RA in Swedish subjects with RA. It is likely that this high prevalence is related to the higher frequency of this gene in the general Swedish population. Quite clearly, these relationships need further evaluation, since the genes are not known to be in linkage disequilibrium and the clinical significance remains obscure. Lanchbury (1988) and Mc Cusker and Singal (1988), in comprehensive editorials on the molecular genetics of the HLA-D region component of inherited susceptibility to RA, reviewed the developments over the last ten years. The field is exciting and in a state of flux as new facts become available. The past, present and future trends in research are reviewed in this very useful essay.

SEASONAL VARIATION.

The seasonal variation of calcium balance has been known for some time (Malm 1958; Smith *et al* 1964; Stamp and Round 1974; Robertson *et al* 1974). Aitken *et al* (1973) showed that metacarpal bone mass of 38 postmenopausal females was 3.4% higher in the period May-August than in November-February. Krolner (1983a) similarly reported an increase of 1.7% in the lumbar spine bone mineral content of 26 normal women during July-September compared with January-March.

Tothill *et al* (1986), however, were unable to demonstrate any seasonal variation in TBCa using whole body measurements in patients with rheumatic diseases. They point out that the mechanism for this seasonal variation is not known. The differences in their findings may also be related to the fact that they studied a different group of subjects.

CONTROLS.

The selection of controls for comparison in any study of OP is extremely important. Scott *et al* (1981) have shown that not only is bone mass lower in hospitalised RA patients but that inpatients with other diseases also had a lower bone mass than normal. They also showed that bone mass was lower in RA hospitalised patients than it was in RA outpatients. Most studies in the past have used only a

single control group for comparison, consisting of normal individuals matched for age and sex. The majority of such studies report findings on patients and controls whose average age is in excess of 50 years, making it very difficult to separate the effects of age-related bone loss in the pathogenesis of the OP in RA (Table 1). In a recent critical analysis of CS-associated OP, Guyatt *et al* (1984) drew attention to this and remarked that *in the majority of studies the important 'confounders' outlined had not been adequately excluded for valid conclusions to be drawn about the effects of steroids on bone mineral metabolism*. Reid *et al* (1985) compared RA patients with patients who had polymyalgia rheumatica (PMR) (n = 19) as well as patients with asthma (n = 19). The PMR group is suitable for comparison with post-menopausal (elderly) subjects, but not with younger patients suffering from RA. Asthmatic subjects generally do not have disability related to joint stiffness and deformity, making them relatively unsuitable for comparison with patients who have RA. Systemic lupus erythematosus (SLE) appears to be ideal for comparison with young RA subjects. Although the arthropathy is generally much milder than that of RA (Labowitz *et al* (1971), it can be deforming in some patients (Alarcon-Segovia *et al* 1988). In addition, the inflammatory nature of the disease is similar to that of RA (Seitz and Hunstein 1985). Finally, corticosteroid therapy is often used in treatment, making this an ideal group for evaluating the effects of CS therapy in the 2 diseases. There is no known relationship between SLE and hyperparathyroidism (Gordon and Isenberg 1987). Bone mass evaluation in SLE also has some bearing on the aetio-pathogenesis of avascular necrosis (AVN) of the femoral head in this disease (Zizic *et al* 1985). The mechanism is unknown, but micro-fractures due to OP have been postulated as a patho-

genetic factor. Lindsay *et al* (1976) demonstrated the value of bone density measurement in predicting the risk of developing AVN following renal transplantation.

Several reports have compared RA patients with a group of subjects suffering from OA (Burr *et al* 1983). This is obviously undesirable, since OA is generally a disease of elderly subjects who may have age-related bone loss prior to the development of their disease (Voss and Byers 1972). It is usually characterised radiologically by features of bone hypertrophy (Dequeker 1983; Verstraeten *et al* 1986). The age-related factors are difficult to separate. Recent evidence suggests that some patients with OA have reduced bone mass.

SEX STEROIDS.

The effects of the postmenopausal state on bone metabolism are though to be largely related to the removal of a protective effect of oestrogens (Lindsay 1978; 1987; Nordin *et al* 1970). Hormonal replacement therapy (HRT) is being more forcefully recommended for all postmenopausal females (Nordin *et al* 1979; 1980; 1985). In RA, there is evidence that oestrogen therapy may have a beneficial effect on clinical and laboratory manifestations of the disease (Bijlsma, 1987). Some improvement during oestrogen treatment was found in 30m walking time, Hb concentration, and thrombocytosis. ESR and CRP deteriorated in both these periods (of the double blind cross-over study), but less in the oestrogen treated

period. Grip strength improved during both periods. The number of swollen joints decreased whereas the joint tenderness score increased during the oestrogen period. The sample is small and the period of therapy short, but the findings are exciting and require further investigation. The effects of pregnancy on disease activity in RA are also well established (Ostensen *et al* 1983).

The importance of androgens in maintaining bone was demonstrated by the finding of OP in men with idiopathic hypogonadotropic hypogonadism (Finkelstein *et al* 1987; Seeman *et al* 1983). Low levels of androgenic anabolic steroids have also been reported in women with RA (Masi *et al* 1984). Sambrook *et al* (1988) recently reported the relationship between sex hormone status and osteoporosis in postmenopausal females with RA. Compared with the controls, postmenopausal RA patients had significantly reduced levels of oestrone, dehydroepiandrosterone sulphate (DHEAS), testosterone and femoral BMD. They conclude that reduced DHEAS levels in postmenopausal females with RA may increase their risk of osteoporosis. Premenopausal females were not studied, again diminishing the potential contribution of an excellent study. Spector *et al* (1988) have also reported low free testosterone levels in RA.

STATISTICAL METHODS.

A basic knowledge of statistical methods is essential to the correct interpretation of results. Clinical epidemiology introduces statistical concepts such as specificity, sensitivity and prevalence. Williams (1979), in his book on reasoning with statistics, provides excellent guidelines on the application of statistical methods and the interpretation of results.

Research in MBD involves several potential sources for invalidation of results, as exemplified in the review of the perplexing pathogenetic factors. A further source of error is introduced in the selection of a control group, in terms of age, sex and physical activity. The probability of disproving the null hypothesis is also greatly influenced by the sensitivity of the measuring instrument and the X-Ray technique. As Horsman *et al* (1975) have pointed out, it is often impossible to separate the components of this total error.

Virtama and Helela (1968), Adams *et al* (1969) and Dequeker *et al* (1972) studied observer error by expressing measurement differences as a percentage of the overall mean value. Dequeker (1976), reminds us that the inter-observer error also depends partially on the difficulty in defining the exact margins of the cortical layer. It is advisable to define the inner limit of the cortical layer as the border of the solid cortical layer without separate trabeculae in the vicinity. These dif-

ferences provide reason to believe that one observer working according to certain defined rules obtains the most reliable results.

Barnett (1969), in a study of simultaneous pairwise linear structural relationships, provided a series of mathematical equations which have been adapted for computerisation. The work in that study was based on the relative merits of 3 or mare instruments designed to measure certain aspects of lung function. The method is designed for performing triplet comparisons. Analyses of variance and paired t-tests are also useful under these circumstances, but they are limited in that they do not separate the potential sources of observer error in the same way that the method of Barnett (1969) does.

Where multiple variables are compared in more than two groups, a professional statistician is often required for guidance on the appropriate tests for regression and factor analyses. Frequency distributions need to be critically evaluated for possible bias and validation of comparisons and correlations. In other instances, non-parametric tests of rank order may need to be applied (Fleiss 1981). Consensus analysis (Bull *et al* 1986) enables one to eliminate less valuable tests using the mean of the correlation coefficients (r values) of a group of tests relative to a dependant variable. This technique has been usefully applied in evaluating 17 independent markers of disease activity in RA.

Stepwise multiple regression analysis enables one to predict the variation in the dependent variable. Cluster analysis provides a means of grouping common variables. Discriminant analysis allows the calculation of specificity and sensitivity

of a test, using true and false positive and negative results. Fleiss (1981) provides useful guidelines on the use of applied probability. The above concepts are also explained in some detail.

The recent introduction of the Receiving Operator Characteristic (ROC) curve (Lusted 1972) to clinical statistics (Swets 1979) has provided a major tool in detectability (Simpson *et al* 1973). A ROC curve demonstrates the relationship between the true positive ratio (TPR) and the false positive ratio (FPR) as the definition of a positive test is varied. ROC curves free us from the constraint of a predetermined definition of positivity. Hessel (1979), in an editorial, provides a useful perspective on the use of ROC analysis. The application of this statistical technique to a personal computer was facilitated by Centor (1985), who introduced a *Visicalc* program for estimating the area under a ROC curve. The area under the ROC curve is similar to the Mann-Whitney U test, which is equivalent to the Wilcoxon rank-sum test (Hanley 1985). The ROC curve has the advantage that the standard error of the area can be calculated, confidence intervals for the area can be worked out and tests can be constructed to compare two curves. This technique has not been applied to the radiological evaluation of RA. However, 2 recent reports evaluate these concepts in relation to the osteopaenia of aging, comparing TBCa with BMC at the wrist (SPA) and bone density at the spine (DPA) (Ott *et al* 1983; Cohn *et al* 1986).

Ott *et al* (1983), reported that ROC curve analysis showed TBCa to be a better discriminant than BMC in determining osteoporosis. The prevalence of OP in their sample was 25%. The posttest probability of disease was 90% if the TBCa /

TBCa P ratio was less than 0.84. Cohn *et al* (1986), in a similar study, found that TBCa was correctly able to classify 86% of OP subjects, while BMC was correct in 31% compared with 56% using spinal bone density. In a serial study, they were able to predict normal individuals at risk for developing OP. The application of this statistical technique in Rheumatology was recently reviewed by Lequesne (1988), who illustrated the concept with HLA B27 in the diagnosis of ankylosing spondylitis.

Where numerous related variables are considered, factor analysis (Gorsuch 1974) may be a useful means of reducing variables by grouping related variables into factors. The purpose of using factor analysis is scientific. Usually the aim is to summarise the interrelationships among the variables in a concise but accurate manner as an aid in conceptualisation. The result is based on *principal components analysis.*

Graphical methods need to be carefully selected. Useful recommendations are provided by Chambers *et al* (1983). Further developments in the field of sensitivity and specificity include the derivation of likelihood ratios, post-test positivity and the development of decision-making trees. These are reviewed in a chapter (Fletcher *et al* 1982) on the interpretation of diagnostic data, which is recommended for reading to all interested in developing and using diagnostic information in clinical practice.

In the final analysis of the vast literature on this controversial subject, it seems that *the pathogenesis of the OP in RA is multifactorial*. The osteoporotic syndrome is most likely to manifest itself in the susceptible individual who develops the added problems of immobilisation due to severity of RA. Several other environmental factors such as diet, drug intake, disease activity and smoking may accelerate the process in that individual. The role of inflammation mediated osteopaenia in the pathogenesis of bone loss in RA needs further investigation. The nature of the effects of corticosteroid therapy are not clearly established.

NUMERICAL DEFINITION OF OSTEOPOROSIS.

Previous studies of OP (Dequeker 1976; Evans *et al* 1978) had arbitrarily defined subjects as osteopaenic if the cortical area was less than two standard deviations below the mean for a young normal group of subjects (*fracture threshold*). The earlier studies of OP in RA as well as those looking at bone loss of aging, have been unable to demonstrate statistically significant differences in premenopausal subjects using a variety of different techniques. This is probably due to the small numbers of premenopausal subjects included in those studies. The numerical definition of OP is subject to wide variation, dependant on the technique used and the characteristics of the control subjects used for comparison.

CLINICAL SIGNIFICANCE OF OSTEOPOROSIS.

The financial implications of idiopathic OP have recently been reviewed for the USA (Peck 1987). These implications for the OP of RA are not known, but would probably be much smaller than this. The most serious complication of OP is the development of fractures and a reduced bone mass is the dominant risk factor, even though the relationship is not strictly linear. The lack of consensus re-

garding the definition of OP (Mazess 1987) causes great difficulty in the development of prophylactic or therapeutic strategies. Carlsson and Nilsson (1980) reported the relationship of bone mass and loosening of the femoral component in total hip replacement. They studied 83 patients with OA, so their conclusions may not necessarily apply to patients with RA. They were unable to demonstrate a relationship between pre-operative films and subsequent loosening of the femoral component of the prosthesis. Haider and Storey (1962) reported a small number of RA patients who developed spontaneous fractures. Fam *et al* (1983) also reported spontaneous fractures in 4 patients with RA, 3 of whom had osteoporosis. They drew attention to the importance of considering stress fractures in the differential diagnosis in patients with RA presenting with painful lower limbs. Hooyman *et al* (1984) reported a rr of 1.5 for developing fractures after RA. Univariate analyses indicated increased risk associated with increasing age, earlier age at onset of RA, disability, impaired ambulation, steroid use and thinness. There was a decreased risk associated with obesity and oestrogen use. Multivariate analysis identified aging, impaired ambulation and thinness as independent risk factors. Lowthian and Calin (1985) reported the association between geode development and multiple fractures in RA. Verstraeten and Dequeker (1986) showed that vertebral and peripheral bone mass was significantly reduced in RA patients who develop fractures. Patients with RA had significantly reduced bone mass compared with normal controls, even in the absence of CS therapy. There were no significant differences in biochemical markers of bone turnover between RA groups. Konttinen *et al* (1988), in a review of the pathogenesis of the rheumatoid cervical spine, pointed out the importance of inflammation mediated osteo-

paenia in the genesis of vertebral subluxation of the dens in RA. This lesion is usually caused by a bilateral collapse of atlanto-axial facet joints, although collapse of atlanto-occipital joints may also contribute to this end. The first stage of the pathological processes underlying this type of change involves ligamentous destruction, followed by diffuse loss of cartilage, erosions of facet joints progressing centripetally, and the growth and advance of pannus as well as juxta-articular osteoporosis.

Numerous epidemiologic studies have demonstrated a non-linear relationship between bone mass and fracture incidence (Cummings *et al* 1985; Melton and Riggs 1982). In an extensive review of the literature, Cummings (1985) concluded that there was insufficient objective evidence that patients with hip fractures are more osteopaenic.

TREATMENT OF OSTEOPOROSIS.

The pathogenesis of idiopathic OP is not clearly understood, nor is the definition of the disorder uniformly accepted. It is not surprising, therefore, that there is such controversy regarding the treatment of age-related bone loss (Milhaud *et al* 1983). The issue is further compounded in the patient with RA, particularly when the age-factor is not excluded. Some authorities have tried to standardise

for age after the menopause (Sambrook *et al* 1987; Reid *et al* 1986). However, in the individual subject, important factors may be responsible for the rapid bone losing state which are unrelated to the amount of oestrogens present. A number of therapeutic approaches have been tried, with varying degrees of success. This variation is partly related to the heterogeneity of idiopathic OP.

Calcium supplements are generally recommended at doses greater than 1.5 G daily (Keyler and Peterson 1985; Riis *et al* 1987). Vitamin D supplements are generally recommended where there is seasonal variation in the amount of sunlight and sun exposure (Schnitzler and Solomon 1983; Tasi *et al* 1987). It is usually given together with calcium supplements. The use of 1,25 dihydroxy vitamin D is restricted to those individuals with evidence of decreased activation in a minority of patients with idiopathic OP (Johenssen *et al* 1982; Lindholm *et al* 1977; Lund *et al* 1975). There is also some evidence that it may improve the myopathy associated with the disorder in some patients (Sorensen *et al* 1979). Fluoride is a potent stimulus to bone formation (Riggs *et al* 1982; Schnitzler *et al* 1987). It has the severe drawback that it is unpalatable, but is probably the only significant bone forming agent available. The role of exercise has been clearly shown, but one needs to avoid the development of amenorrhea in some females. Inhibitors of bone resorption, such as the diphosphonates and calcitonin are currently experimental in the treatment of OP (Stevenson *et al* 1979). Coherence therapy combines the intermittent use of bone stimulation followed by inhibition followed by a period of resting. It may prove to be the superior approach to treat-

ment (Aloia *et al* 1987). Vitamin C supplements are useful in some unusual cases of osteopaenia (Seftel *et al* 1966).

There is a large body of evidence favoring the prophylactic use of oestrogens in the perimenopausal female (Adlin 1979; Nachtingall *et al* 1979; Nordin 1979). Although oestrogens do not generally increase bone mass, they do retard the rate of bone loss in the female predisposed to developing OP. Hormone replacement therapy (HRT) is now standard practice in several overseas countries (De Fazio *et al* 1985). Cigarettes interfere with the metabolism of oestrogens in this situation and should be avoided (Jensen *et al* 1985).

Many of the above statement would apply equally to the menopausal patient with RA. However, they have usually been applied to those patients receiving CS therapy, so that these effects in RA patients receiving NSAID alone or together with DMA's is not known. When calcium supplements and vitamin D were used in patients with RA, no protective effect was shown (Dykman *et al* 1984; Bijlsma *et al* 1988). If vitamin D deficiency is clearly related to the pathogenesis (Maddison and Bacon 1974; Ralston *et al* 1988), supplementation of the diet with vitamin D must clearly be effective. The effect of 1,25 dihydroxy vitamin D is probably better (Lund *et al* 1977). Recent evidence of improvement in some of the markers of disease activity in patients receiving oestrogen replacement (Bijlsma *et al* 1987), suggests that this group of hormones may be effective in this situation as well. These findings argue against the long-held belief that oestrogens are responsible for the female preponderance of this disorder. Another potentially useful finding is that of a reduced level of DHEAA in patients with RA (Sambrook

et al 1988; Spector *et al* 1988). Perhaps the answer to the treatment of OP in RA is a restoration of the premenopausal hormonal status.

Many of the difficulties in evaluating the effects of therapy have been hampered by poor reproducibility of the measurement techniques. Cohn (1982) reviewed the techniques for determining the efficacy of treatment of OP and concluded that TBCa was the most accurate non-invasive measure of bone mass.

THE IDEAL STUDY.

The review of the literature addressing the evaluation of MDB in RA, suggests that a study which may contribute further to our understanding of the mechanisms involved in the causation of OP in RA would need to meet the following requirements:

1) It would need to select patients who are not menopausal and could, therefore, be presumed to have normal ovarian function. These should include as many female patients with RA under the age of 45 years as possible. Males under 50 years of age should also be included for study.
2) The study should be on an ambulant group of outpatients, so that all patients in Steinbrocker's (1949) functional classes 3 & 4 should be excluded. A measure of mobility or function would need to be selected to overcome the limitations of the ARA measure of function. Combining a mobility index with a functional test would probably suffice.
3) A dynamometer should be used to evaluate grip strength as well as flexion, extension, abduction and adduction of a single finger. These findings could then be tested against bone mass values using the corresponding single, and six metacarpal scores as a measure of bone mass. Correlation coefficients would establish the relationship between strength and bone mass.
4) The 7-day record to evaluate dietary intake, is highly suitable.

5) Patients who have either been on corticosteroids or are currently receiving this therapy should be included. A detailed drug history should be obtained and quantified as accurately as possible.

6) Radiographic interpretations should be designed in such a way that the observer is not aware of the type of therapy being taken by the patient, so that objective evaluations may be achieved. The X-Rays should be graded according to the recommendations of Scott (1984) and Larsen and Dale (1977) for grading severity of radiological progression in RA.

7) Biochemical measurements of ionised calcium, inorganic phosphate, alkaline phosphatase, GLA, vitamin D metabolites, PTH, oestrogens and calcitonin may help in clearing some of the controversy.

8) Bone mass should ideally be measured by radiogrammetry, photon absorptiometry, neutron activation analysis and WBR of calcium. The development of an objective, quick, simple, accurate, reproducible computer-assisted method of applying radiogrammetry principles would be a major advance in the study of bone mass at institutions where radiology is the only method of measurement. The various methods should then be correlated with each other. Correlations should be carried out between bone mass measurements and the other scores of radiological progression in RA.

9) Controls should consist of two groups: one of normal age and sex matched subjects, and the other of age and sex matched patients attending outpatients for another chronic illness. Preferably, this second group

of controls should have a rheumatological disease, but they should also be ambulant.

10) Statistical methods are very important in an analysis of this nature and univariate as well as multivariate analyses should be performed by trained statisticians.

Strict principles such as these need to be applied to the design of protocols for research, so that meaningful conclusions can be drawn about pathogenetic mechanisms in the OP of RA.

MATERIAL AND METHODS.

The ideal study requires an ideal environment. The University of Cape Town (UCT), where this study was carried out, is reasonably equipped with the techniques for basic biochemical evaluations, but severely limited in facilities for the measurement of bone mass by SPA, DPA, NAA, or WBR studies. It was hoped that attention to detail in performing the simplest of the available methods for measuring osteoporosis would compensate for these deficiencies. The methods for this study included detailed clinical examination, measurement of as many serum and urine variables as were possible in our laboratories, and radiological examination at three different sites of the skeleton. A personal computer-assisted alternative to the Vernier calipers in radiogrammetry measurements was assessed. It was hoped that the reproducibility of X-ray measurements in the hand would be improved with the use of a digitiser. This is vital, since serial studies are totally dependant on the repeatability, precision and sensitivity of the technique employed.

The objectives of this study included the following:

i. to define the factors involved in the pathogenesis of bone loss in RA;

ii. to improve the intra- and inter-observer reproducibility of radiogrammetry measurements of metacarpal combined cortical width.

The study was commenced after the protocol had been accepted by the Ethics and Research Committee at UCT. It was completed over twelve months from 1st April, 1985 to 31st March, 1986.

PATIENT SELECTION.

The Rheumatic Diseases Unit (RDU) at UCT is the referral centre for patients with rheumatic diseases throughout the Western Cape. Two hospitals are involved with patient care, providing the unique availability of an acute and chronic hospital environment. Groote Schuur Hospital (GSH) is the acute care centre with all the modern investigations easily available. The Princess Alice Orthopaedic Hospital (PAOH) is a much smaller centre with limited radiological facilities, but a highly sophisticated physiotherapy and occupational therapy department. These sources were ideally suited to the recruitment of volunteers and patients for study. Outpatient followup facilities are available at both centres.

SELECTION CRITERIA.

A. **Age** - Males under 50 years; Females under 45 years.

B. **Function** - ARA Functional Classes 1 and 2.

C. **Disease** - Classical or Definite Adult RA

D. **Residence** in the Cape Peninsula.

E. **Consent** for study.

EXCLUSION CRITERIA.

A. **Age.** - Males over 50 years; Females over 45 years or early menopausal.

B. **Function** - ARA functional classes 3 and 4.

C. **Disease** - Less than 5 ARA Classification Criteria.

D. **Pregnancy.**

E. **Residence** outside the Cape Peninsula.

F. Recent **bedrest** exceeding 14 days.

G. Recent (previous 6 months) **surgery** of any nature.

SELECTION CRITERIA FOR CONTROLS.

A. Normal, healthy volunteers.

B. **Age** - Males under 50 years; Females under 45 years.

C. **Function** - ARA Functional Classes 1 and 2.

D. **Residence** in the Cape Peninsula.

E. **Consent** for study.

EXCLUSION CRITERIA FOR CONTROLS.

A. **Age.** - Males over 50 years; Females over 45 years or early menopausal.

B. **Function** - ARA functional classes 3 and 4.

C. **Disease** - Any disease requiring regular medical therapy.

D. **Pregnancy**.

E. **Residence** outside the Cape Peninsula.

ADDITIONAL CONTROLS.

Patients with SLE meeting the selection and exclusion criteria were used as a 2nd group of controls, because :

i) the disease is generally more common in young females;

ii) they have multisystem manifestation of the disease;

iii) they are generally mobile and less incapacitated than with RA;

iv) corticosteroids are often used as an adjunct to therapy;

v) the pathogenesis is likely to be closely related to that of RA;

vi) they are easily accessible from the RDU Lupus Clinic of UCT;

vii) they are often on multiple therapies simultaneously.

viii) the hands are often involved and up to 5% may develop severe deformities (Alarcon-Segovia *et al* 1988).

Informed consent was obtained from all subjects at the time of study.

The protocol was approved by the Ethics and Research committee at UCT.

STUDY DESIGN.

A detailed protocol was designed to record the relevant data on a computer. It was constructed in sections, aimed at capturing a wide range of data relating to:

i) demography;

ii) disease duration and criteria for diagnosis;

iii) disease activity;

iv) global functional assessment;

v) mobility;

vi) hand function;

vii) hand strength;

viii) movement at other joints;

ix) treatment;

x) biochemical changes of MBD;

xi) serology and biochemical markers of RA activity;

xii) dietary intake;

xiii) nutritional status;

xiv) X-rays at 3 skeletal sites;

xiv) Genetic markers (HLA antigens).

Details of the protocol are provided in Appendix A.

DEMOGRAPHY.

AGE, RACE, SEX.

The date of birth, age, marital status, race and sex were recorded. Patients and controls were asked about their state of employment, work record, absence from work, time spent in the sun and also about a family history of arthritis. They were also questioned about smoking habits in the preceding 6 months, and a similar history of alcohol consumption was also obtained. A menstrual history was taken and information about the use of the contraceptive pill was also elicited.

DISEASE DURATION

Age at onset of disease was recorded as the time at which the first acceptable symptoms of disease (RA, SLE), became manifest. Duration of disease was calculated in months. The criteria for the diagnosis of RA were recorded in the interview and the patient classified according to the ARA criteria into classical and definite RA groups (Ropes *et al* 1958). Previous surgical procedures were also recorded. Patients with SLE were classified according to the revised ARA criteria for classification of SLE into definite or probable SLE (Tan *et al* 1982).

DISEASE ACTIVITY.

The patient was asked to grade the severity of his/her disease on a 10 cm. horizontal visual analogue scale (SVAS). Pain was similarly graded by the patient (PVAS), as recommended by Huskisson (1974; 1982). The duration of morning stiff-

ness was selected from a choice of 6 options, viz. less than 45 mins = 0; 46 min - 90 mins = 1; up to 2 hrs = 2; up to 3 hrs = 3; up to 4 hrs = 4; up to 6 hrs or more = 5. Hours to onset of fatigue was similarly selected from 5 options ranging from less than 2 hrs = 1; to 8 hrs = 4. The presence or absence of night pain was recorded, as well as the patient's working capacity.

The number of individual warm and swollen joints were counted and a Ritchie articular index (RAI) (1968) was calculated. The author then recorded his global assessment of the patient's disease activity, based on the clinical findings as nil, mild, moderate or severe. The Lansbury systemic index (1958) needed to be modified, since salicylates are no longer in use at our clinic. The index was calculated using the grip strength, duration of EMS, hours to onset of fatigue and ESR, scoring as defined by Lansbury *et al* (1958).

PHYSICAL ACTIVITY.

GLOBAL FUNCTION.

Since there is no single, universal measure of functional disability in RA (Liang 1981), the Keitel function test (KFT) (Keitel 1972), which relies on observed performance, was performed in addition to the ARA functional classification (Steinbrocker *et al* 1949) and the UK classification of function (Joint Committee 1954). The Keitel Function Test (KFT) was selected because it is reasonably quick to administer, extremely reliable, very sensitive and highly reproducible (Eberl *et al* 1976). It involves observing the patient perform a series of movements, aimed at providing a global as-

sessment of functional status. The components of the test are shown in table 2. These were all evaluated by a single observer.

At the time of statistical analysis, the test was arbitrarily divided into 3 basic components, namely hand and wrist, shoulder and lower limb. The hands feature most strongly, lower limbs slightly less and shoulders least in this test. It should be noted that the lowest possible total score is 4, due to items 6 and 7. The maximum score is 100. The combined hand and wrist score can be obtained in less than *one minute*, compared with 12 minutes for the total score. The hand and wrist score will be referred to as the hand functional index (HFI). Table 2 outlines the complete test. The higher the score, the greater the disability.

Table 2. **Components of the Keitel Function Test. The test evaluates function in the hands, wrists, shoulders and lower limbs. It is conveniently divided into 3 major groups, where the hand and wrists are evaluated as a group.**

Test Items	Grading		Criteria
	Right	Left	
1. Tip of thumb touches hypothenar of 5th finger	0	0	Test performed fully and with no delay
	1	1	Test performed Fully but with effort/or delay
	2	2	Tip of thumb touches proximal phalanx 3 and4
	3	3	Neither realised.

2. Bending of 2nd finger	0	0	Clutched normally
	1	1	Cannot be bent fully; tip reaches palm
	2	2	Fingertip does not reach palm
3. 3rd finger			As Above
4. 4th finger			As Above
5. 5th finger			As Above
6. Forearm held horizontal palmar surfaces pressed together point upward.	1	1	Test performed fully and no delay.
	2	2	Test performed fully with effort &/or delay
	3	3	Volar and dorsal flexion of wrist 45°
7. Forearm held horizontal volar surfaces pressed together point downward.	1	1	Fully; no delay
	2	2	Fully; with effort &/or delay
	3	3	palmar and ventral flexion of wrist 45°

8. Both backs of hands simultaneously on the table; elbows held rectangularly; ulnar margin of hand lifted.	0	0	Performed full
	1	1	Back of hands on table; margin cannot lift
	2	2	Backs of hands not fully on table.
9. Radial margins of hands simultaneously placed on table; thumb points downward before table edge; planes of hand inclined inward; no lateral bending of trunk.	0	0	Performed full
	1	1	Planes of hand perpendicular; cannot be inclined inward
	2	2	Planes of hand not vertical
10. Both hands simultaneously on ipsilateral shoulder	0	0	Normally
	1	1	Fingertips approach shoulder up to 5 cm.
	2	2	Greater distance.
11. Both hands simultaneously behind the neck (below ear level)	0	0	Performed full
	1	1	Fully with effort &/or delay
	2	2	Fingertips touch neck
	3	3	Fngertips do not touch neck

12. Rising from resting position (examination couch).	0	Quickly;hands extended
	1	Effort with hands extended
	2	Reinforcement of hands
	4	Extraneous assistance
	6	Impossible.
13. Active spreading of legs in resting position	0	More than 50cm condylar distance
	1	More than 20 cm
	2	Less than 20 cm condylar distance.
14. Rising from chair	0	Quickly; hands extended
	1	Effort; hands extended
	2	Reinforcement of hands
	4	Extraneous assistance
	6	Impossible.
15. Standing tip-toed 15 sec	0	Possible 15 sec support with one hand permitted
	1	Less than 15 sec
	2	Impossible
16. Standing on heels 15 sec	0	Possible 15 sec
Must stand straight	1	Less than 15 sec
Support with one hand OK	2	Impossible

17. Knee-bending exercise gluteal region almost touches heels; support with one hand permitted		0 1 2	Normal test Partial test Impossible
18. Standing on one leg 15 sec; support with one hand permitted; must stand straight.	0 1 2	0 1 2	Possible 15 sec Less than 15 sec Impossible
19. External rotation of hip heel of test leg placed on supporting leg; support with one hand permitted; must stand straight	0 1 2	0 1 2	Normal test Angle of foot axes 90° Angle of foot greater than 90°
20. Plantar surface of foot placed on chair; knee bent; patient stands very close to chair; support with one hand permitted.	0 1 2	0 1 2	Normal test Leg lifted from floor Lifting leg impossible.
21. Heel placed on chair; knee extended; patient distance from chair 1m support with one hand permitted.	0 1 2	0 1 2	Normal test or delayed Leg lifted from floor Lifting leg impossible.

22. Walking 30m in hospital corridor; standard time of 20 sec	0	No difficulty; standard time
	1	Visible difficulty;20sec
	2	25 sec
	3	30 sec
	4	40 sec
	5	Few steps with assistance
	6	Impossible
23. Walking 10 steps upstairs; standard time of 7 sec	0	No use of rails; 7sec
	1	Up to 14sec with use of rails
	2	More than 14sec; some effort
	3	No steps.
24. Walking 10 steps downstairs; standard time of 7 sec	0	No use of rails; 7sec
	1	Up to 14sec with use of rails
	2	More than 14sec; some effort
	3	No steps.

MOBILITY.

Mobility was scored using a different functional assessment test (Badley *et al* 1984). The mobility score was derived from a disability questionnaire (DQ), which graded difficulties in performing activities of daily living.

The method is based on the Stanford Health Assessment Questionnaire (HAQ) (Fries 1982) recommended by the WHO. 24 questions replaced the original 41 in the HAQ. This test allows scores to be obtained for mobility, bending down, dexterity, bending the arm and reaching up. The difficulty with which each of a series of tasks is performed was graded on a Guttman scale of 0-7, where 0 = no difficulties encountered and 7 = activity impossible. A total score of mobility could thus be obtained from the responses to a series of simple questions. Table 3 shows the areas evaluated, and details of the questionnaire are included in appendix 1.

Table 3. **Questions pertaining to modified Stanford HAQ for evaluating global mobility in patients with RA.**

	Functional Group.		**Constituent Activities.**
1.	Mobility	*	Walk to toilet;
		*	get on and off toilet;
		*	get in and out of bed
		*	turn side to side in bed
		*	go up and down stairs;
		*	get in and out of a bath
2.	Bending down	*	Put on shoes, tie laces;
		*	pull on socks/stockings;
		*	wash below waist and towel dry;
		*	cut toe/finger nails.
3.	Dexterity	*	Unscrew lid from 1in. jar
		*	prepare vegetables;
		*	carve meat;slice bread;
		*	cut toe/finger nails.
4.	Bending arm	*	Drink from full cup or beaker;
		*	shave/apply cosmetics;
		*	wash face and neck and towel dry;
		*	wash trunk and arms and towel dry.
5.	Reaching up	*	Clothes over head;
		*	brush/comb hair;
		*	wash hair;
		*	put in electric plug at shoulder height;
		*	peg out washing;
		*	use shelves above shoulder height;
		*	open/clean high window.

HAND FUNCTION.

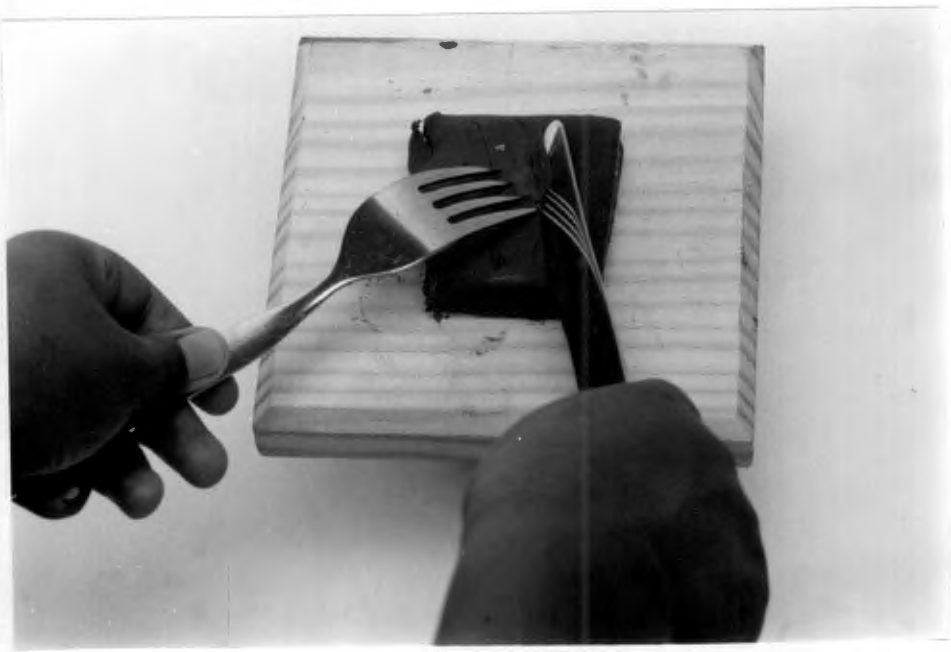
Hand function was further evaluated by an occupational therapist (OT), who recorded the ability of the patient to perform 4 standardised tests of hand function (Clawson *et al*, 1971), using the instruments depicted in Figure 1.

Figure 1. Composite picture showing the instruments used by the occupational therapist (OT) for evaluation of simple hand function.

These consisted of:

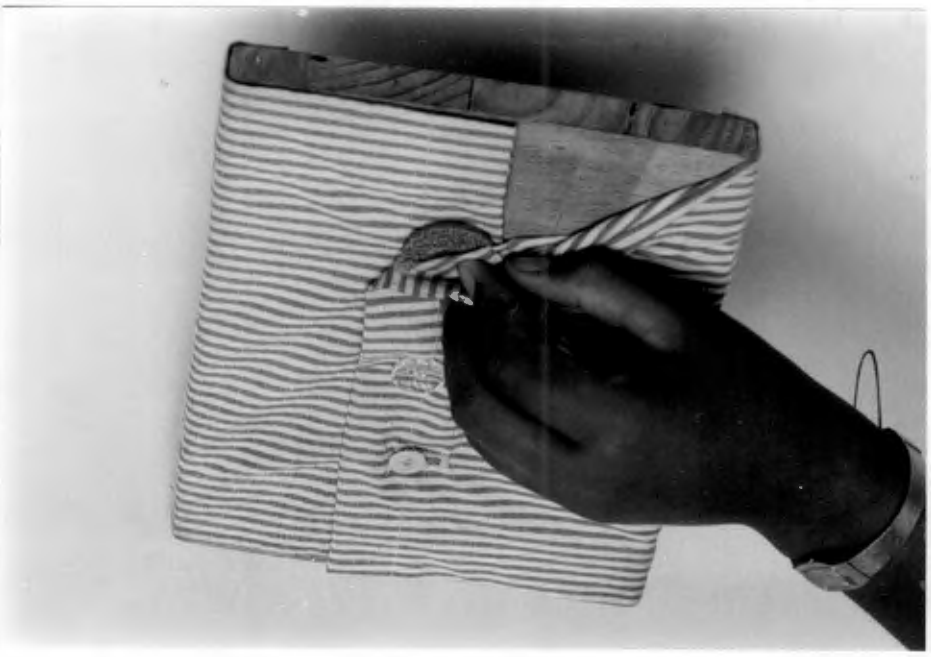
i) the time taken to cut through a 1cm mould of putty, (the consistency of which was designed to maintain a constant firmness) (Fig 2);

Figure 2. Knife and fork used to cut through a 1 cm thick mould of putty. The time taken to complete this task was recorded with a stopwatch.



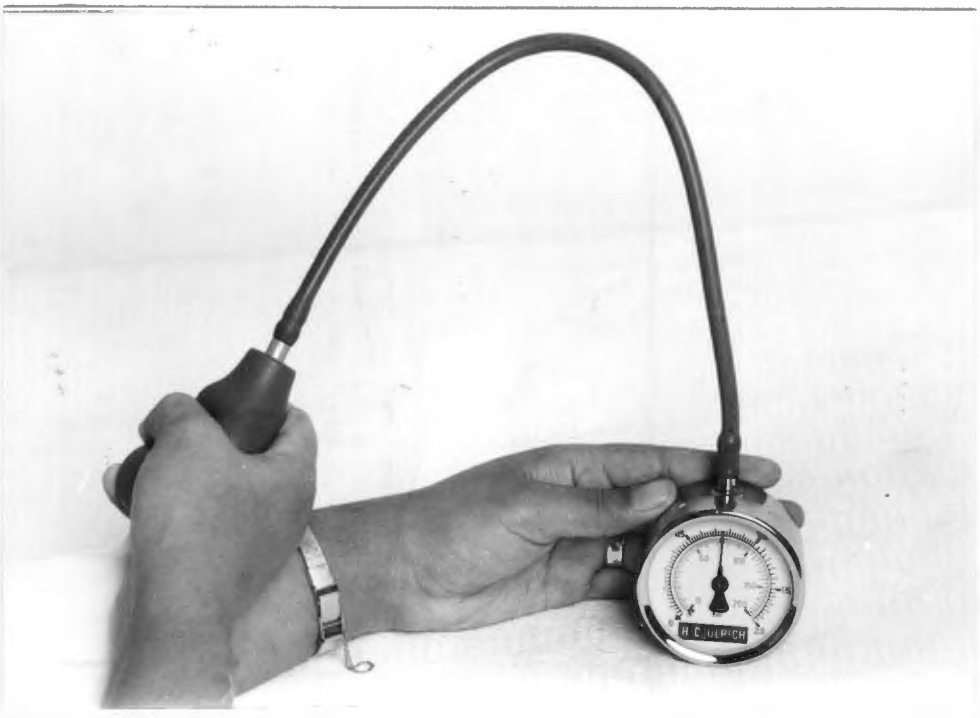
ii) The time taken to button 3 buttonholes on a piece of material fixed to a board (Fig 3);

Figure 3. *The buttonhole test, measuring the time taken to do and undo 3 buttons.*



iii) grip strength using a barometer with a medium-sized cuff, designed by Mannerfelt (Fig 4); and

Figure 4. Mannerfelt instrument for testing grip strength. 3 sizes of bulb are available, of which the medium-sized was used for this study. Measured in mm Hg.



iv) three point pinch was measured as shown in figure 5.

Three readings were obtained for each test and the average was used in the statistical analysis.

The mean of 3 readings was used because its numerous statistical advantages. The 3 readings were compared with each other as a measure of reproducibility.

Figure 5. Pinch grip measurement, using a guage designed by Mannerfelt. Measurements are recorded in Kilo Pascals (Kp).

VALIDATION.

The scatter plots shown in figure 6a and b represents measurement of 3-point pinch by the OT, but similar correlation coefficients were obtained for the other measurements (grip strength, knife and fork and buttonhole test) done by the OT (see table 4).

Figure 6a. Scatter plot showing the relationship between serial measurements of pinch grip. The figure shows the relationship between the 1st and 3rd attempt with the instrument.

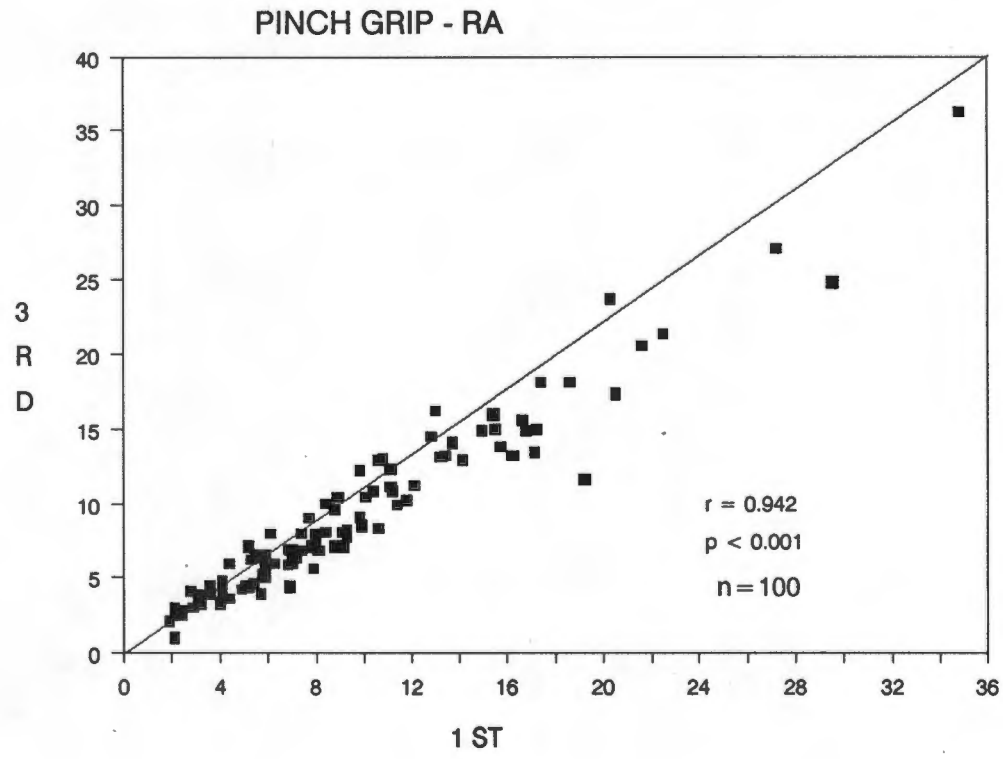


Figure 6b. Scatter plot showing the relationship between serial measurements of pinch grip. The figure depicts the relationship between the 1st and 2nd attempt with the instrument. The mean of 3 readings was used in the analysis of the results.

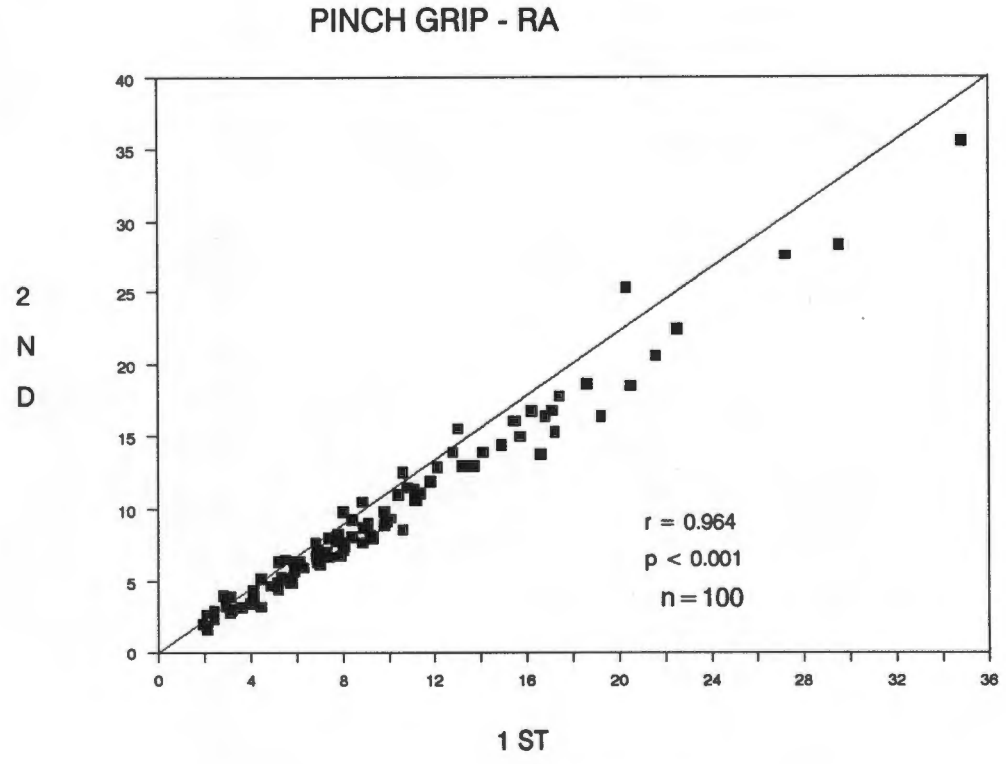


Table 4 summarises the results for the various tests in the different groups tested. It is interesting to note that the correlations were better in the RA group ($r > 0.9$), particularly with the knife and fork test, suggesting a wider variation among the normal subjects. This was confirmed by the univariate sample distributions.

Table 4. Comparison of 3 readings from which the mean was calculated as a measure of hand function and grip strength. Measured by an occupational therapist (OT).

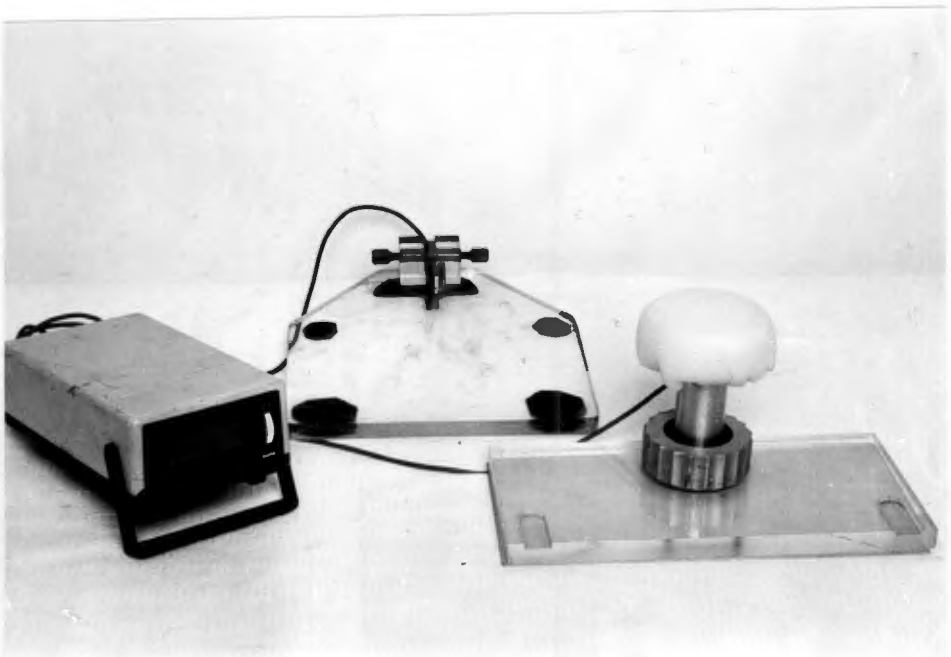
Test	Group	Correlation Coefficient Comparing Readings		
		1vs2	1vs3	2vs3
3-Point Pinch	Normal	0.942	0.925	0.944
	RA	0.964	0.943	0.98
Knife and Fork	Normal	0.65	0.5	0.67
	RA	0.963	0.958	0.97
Buttonhole Test	Normal	0.801	0.824	0.77
	RA	0.887	0.909	0.91
Grip Strength	Normal	0.939	0.902	0.94
	RA	0.922	0.983	0.92

These findings are important, since they mean that valid conclusions can be based on the readings obtained with this set of instruments. As it turns out, in this study, each of the 3 readings was valid and the measurements were reproducible for a single observer, with coefficients of correlation ranging from 0.77 to 0.98. The mean is, therefore, a good reflection of the measurement.

HAND STRENGTH.

A dynamometer (Fig 7), was used to measure i) adduction, ii) abduction, iii) flexion and iv) extension strength in the right middle finger, as well as v) torque strength in the right hand.

Figure 7. The dynamometer used for measuring force of finger flexion, extension, abduction and adduction. A separate component was used for measuring torque force in the right hand. The instrument was designed at the biomedical engineering department, UCT.



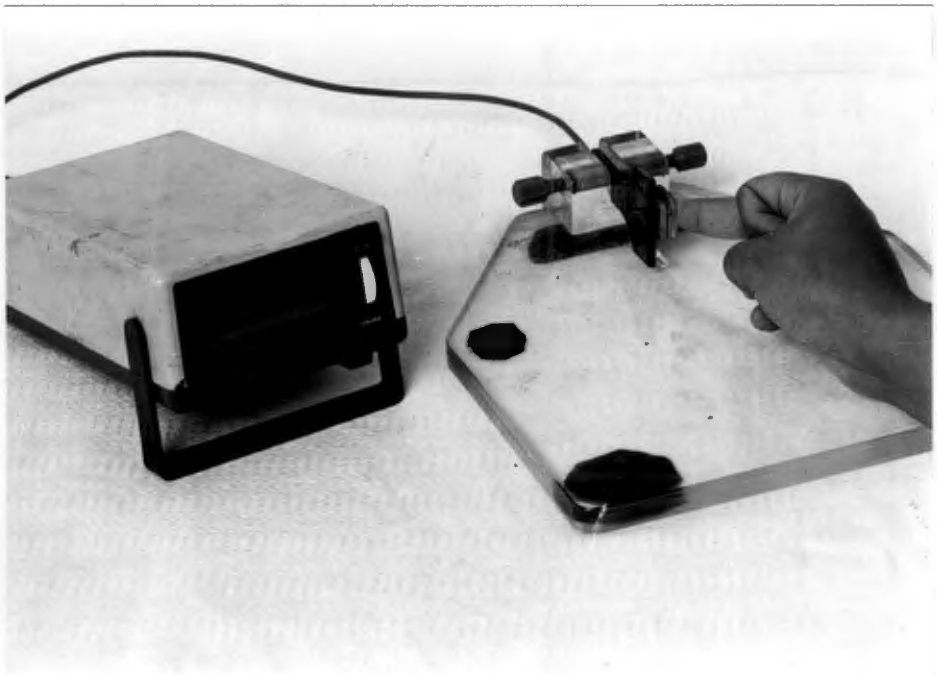
The instrument was designed by the Department of Biomedical Engineering (BME) at UCT. The base remains firm and the transducer causes the dynamometer to display the force as a measure of strength. The highest reading attained on each of 3 attempts was recorded.

Adduction and abduction were measured with the right arm in a comfortable position, wrist in a neutral position and fingers extended with the palm down. The middle finger applies pressure against a cushion attached to the transducer (Fig 8).

Figure 8. Measurement of abduction and adduction in the right middle finger. Three readings were recorded. The transducer is turned in the opposite direction to measure adduction.

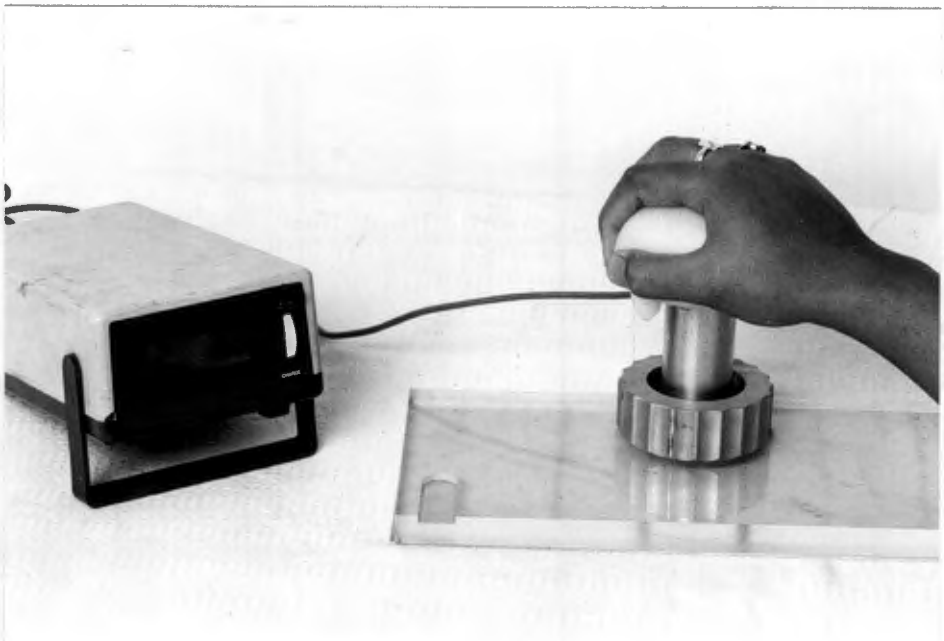
Flexion and extension were tested with the hand clutched prone, little finger against table, and pressure exerted against the cushion by the middle finger (Fig 9). The transducer can be detached and reversed for the measurement of flexion.

Figure 9. Measurement of flexion and extension in the right middle finger. Three readings were recorded. The transducer is turned in the opposite direction to measure flexion.



Torque was measured using the same instrument, except that a torquometer was designed for measurement of grip (Fig 10). A sponge cushion was glued to provide comfort and improved grip.

Figure 10. Measurement of torque foce in the right hand. A sponge cushion was used to improve the comfort of grip. Three readings were recorded.



VALIDATION.

Reproducibility of the dynamometer was shown by the comparison of 3 readings. The scatter plots depicted in figure 11a + 11b, show that the machine performed adequately between readings. The mean of these readings was used in comparisons between groups, in order to minimise errors due to reproducibility. The scatter plots show good precision with the instrument.

Figure 11a. Scatter plots showing the reproducibility of the dynamometer in measuring force in the finger. Only the abduction values are shown, but the technique was highly reproducible for a single observer measuring adduction as well.

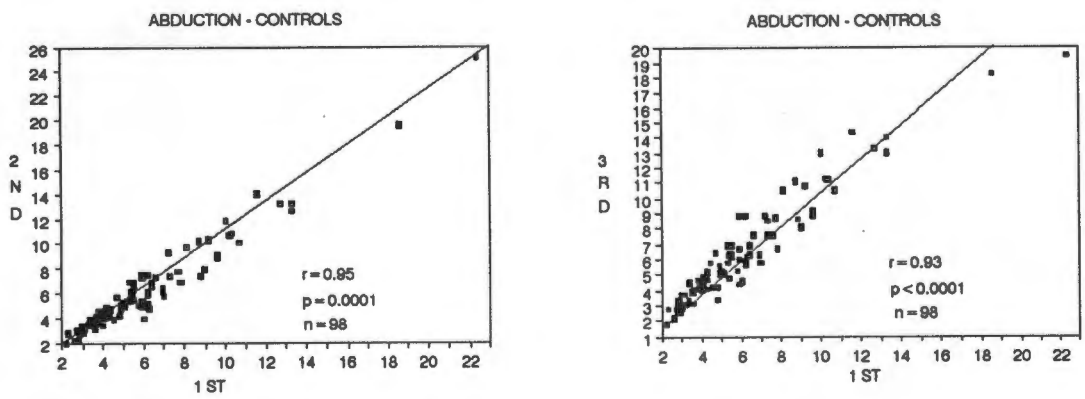


Figure 11b. Scatter plots showing the reproducibility of the dynamometer in measuring torque force in the hand. Only the RA values are shown, but similar findings were shown in the control group.

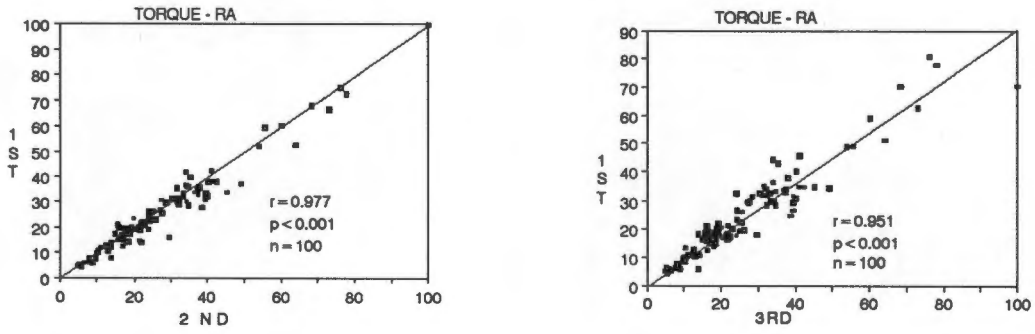


Table 5a shows the coefficients of correlation for some of the readings.The table includes some of the tests of hand strength only, but similar results were obtained for the tests of adduction and extension strength in the right middle finger. These results show that the dynamometer was reproducible between readings. The results show

that the dynamometer measurements were more reproducible than the OT instruments.

Table 5a. Comparison of 3 readings of finger strength and hand torque strength using a dynamometer. The mean of 3 readings was used in all correlations involving hand strength. Some of the results (abduction, flexion and torque) are shown in the 3 groups of subjects.

Measure.	Group	Correlation Coefficient Comparing Readings		
		1vs2	1vs3	2vs3
Abduction	Normal	0.954	0.928	0.963
	RA	0.967	0.893	0.892
Flexion	Normal	0.972	0.928	0.929
	RA	0.986	0.967	0.983
	SLE	0.934	0.913	0.959
Torque	Normal	0.957	0.925	0.972
	RA	0.977	0.951	0.973
	SLE	0.956	0.905	0.941

Since the study was confined to subjects with RA and SLE who were independently mobile, the range of movement in the various joints was not recorded. The KFT and DQ are specifically designed for global assessment of function in RA.

DRUG THERAPY.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS.

Treatment was recorded as accurately as possible. Non- steroidal anti-inflammatory drugs (NSAID's) are used routinely in the treatment of RA. These were often used in combination at our clinic. Use of these agents in the 12 months preceding the study was recorded. NSAID's have totally replaced aspirin in our clinic. The commonest agents used were diclophenac, indomethacin, naproxyn and piroxicam. Frequent changes were sometimes indicated for side - effects or lack of effect. The dosages and durations are, therefore, not absolutely accurate.

DISEASE MODIFYING AGENTS.

Disease modifying agents (DMA's) were recorded for their total duration, so that total doses up to the time of study could be calculated. If these agents were stopped, the reason for stopping was also recorded. Details were obtained for penicillamine, myocrisin, ridaura (Auranofin - oral gold), chloroquine, salazopyrine and immunosuppressive agents. Patients were often uncertain of dosage and duration, so their hospital records were analysed to make calculations more accurate. Despite this attention to detail, some of the values obtained are at best an estimate of total therapy. Patients were not necessarily on these drugs at the time of study and the period for which they were discontinued was not recorded.

CORTICOSTEROID THERAPY.

Corticosteroid therapy was similarly recorded. Several routes of administration are applied in RA; intra-articular injection (IAI) is the commonest. Although it is generally accepted that insignificant amounts are absorbed systemically, there is

some evidence that frequent IAI's over a period of time may lead to adrenal suppression. For this reason all forms of CS administration were recorded in detail. Hospital records were again consulted when necessary, to improve and to check on the reliability of the calculations. Past and present usage was recorded. Cumulative dose was calculated as an approximation of total dose. The period for which CS therapy had been discontinued was not recorded. Patients with SLE usually used much higher doses of CS than those with RA, whose total dose was more difficult to approximate. RA patients currently receiving CS were compared with those not receiving CS at the time of study. SLE patients also took CS for longer periods as shown in Table 5b.

Table 5b. Duration of corticosteroid (CS) therapy in patients with RA and those with SLE.

	RA (mths) $n=27$	SLE (mths) $n=50$
Total	659	1569
Mean	24	31
Range	2 - 108	2 - 108

ORAL CONTRACEPTIVES.

The type of contraceptive used and the date of the last menstrual period were also recorded. Detailed menstrual and obstetric histories were not obtained. Females who had had a hysterectomy with oophorectomy and who were not receiving hormonal replacement therapy were excluded from the study.

LABORATORY INVESTIGATIONS.

BIOCHEMISTRY OF METABOLIC BONE DISEASE.

Biochemical tests of metabolic bone turnover were selected using the recommendations of Nordin (1978), Jowsey (1975) and Aitken (1984c). Serum was separated for measurement of renal function, calcium, phosphorous, alkaline phosphatase (AP), ionised calcium, parathormone (PTH), albumen and uric acid. Liver enzymes such as gamma glutamyl transpeptidase (GGT), aspartate transaminase (AST) and alanine transaminase (ALT) were also measured. Haematological indices such as haemoglobin (Hb), ESR (Westergren), white cell count (WCC) and platelets (Plt) were also recorded. Calcium, phosphorous, albumen, urea, creatinine and enzymes were measured in the Department of Chemical Pathology using the Technicon SMAC 12 Autoanalyser. Haematological measurements were performed by the Haematology Department with the Coulter S-plus automated counter.

Ionised calcium was measured in the renal laboratory, using the ICAI ionised calcium analyser. CRP was also measured in the renal lab using rocket immunoelectrophoresis (mg/ml) [antibody from Hoechst]. Two 24 hr urine specimens were obtained for the measurement of urinary calcium and phosphorous excretion, as well as hydroxy-proline (OH-P). The patient was issued a set of instructions for the urine collections and warned to avoid gelatin containing foods for the duration of the OH-P collection. Toluene (10ml) was added to the OH-P bottle, and HCL (10ml) was added to the calcium and phosphate specimens, as preservatives. Creatinine clear-

ance was not calculated in the patients with RA, but was done on the patients with SLE. Urinary calcium and OH-proline was not assessed in the SLE subjects.

Additional serum was stored at -70° for later analysis of thyroxine binding prealbumen (TBP) and retinol binding globulin (RBG). A limited number of these tests were performed on the normal controls, and the patients with SLE.

Since PTH requires expensive kits for accurate results, this investigation was confined to the group of patients with RA. Blood was collected in an EDTA tube and stored on ice. The N-terminal was measured in the renal laboratory, using a radioimmunoassay. Local laboratory normals were used as reference values for comparison of the range of results.

SEROLOGY.

RA diagnosis was evaluated by the sheep cell agglutination test (SCAT; slide agglutination technique: Rheumaton supplied by Wampole laboratories) and the Latex fixation test (slide agglutination technique: Ortho diagnostics). A latex titre of 1/40 or higher and a SCAT of 1/16 or higher were considered to be positive for our laboratory. Antinuclear factor (ANF) (Johnson and Holborow 1973) was measured by the indirect immunofluorescence technique. In the group of patients with SLE, additional samples were submitted for double stranded anti-DNA antibody activity (ADA) using the millipore filtration technique (Ginsberg and Keiser 1973).

DISEASE ACTIVITY.

Disease activity was evaluated by measurements of C reactive protein (CRP) (rocket electrophoresis), ESR (Westergren), sulphydryl (SH)-groups, retinol binding globulin (RBG), thyroxine binding prealbumen (TBP) and plasma viscosity (capillary viscometer; cP).

DIET AND NUTRITIONAL STATUS.

DIET.

All patients and controls completed a 7-day record of dietary intake. This was then analysed for food constituents and coded according to a computer program used by the Medical Research Council (MRC). This data was entered onto a computer and the mineral and food content calculated per 100 grams of foodstuff or fluid.

NUTRITIONAL STATUS.

Nutritional status was measured by several different anthropometric methods using body diameters (Willmore and Behnke 1970) skinfold thicknesses (Sloan 1967; 1973), height and weight (body mass index). The height was measured without shoes and the patient was weighed with the minimum of clothing. The bi-acromial, bi-iliac, bi-trochanteric, bi-ankle and bi-wrist diameters were measured using a body calipers designed in the BME department at UCT. Subscapular, thigh, upper arm and abdominal skinfold thickness was measured using a Harpenden caliper. The upper arm

diameter was measured using a tape measure.The anthropometric and skinfold measurements were performed by the research sister.

The measurements were standardised according to the following landmarks and principles in all subjects:

i) **Standing Height.** The subject stands, head back, hands on hips and takes a deep breath at the time of measurement. Read to nearest cm.

ii) **Body Weight.** The subject stands in the centre of the scale platform wearing only underwear and a light examination gown.

iii) **Bi-acromial Diameter.** With the subject standing or sitting with arms hanging freely, record the distance between the most lateral projection of the biacromial processes. Record to the nearest mm.

iv) **Bi-iliac Diameter.** Locate the crests of the ilium. Place the calipers on these sites and press firmly. Record to the nearest mm.

v) **Bi-trochanteric Diameter.** Place the calipers over the most lateral projections of the trochanters. Press firmly. Record to the nearest mm.

vi) **Bi-ankle Diameter.** Place one foot on a platform. Measure distance with the calipers placed at an angle of 45o and with the calipers on the widest point of the malleoli. Measure both ankles. Record to the nearest mm.

vii) **Bi-wrist Diameter.** Place calipers over styloid processes at their most lateral projection site. Measure both wrists. Record to the nearest mm.

viii) **Chest Width.** Take at end of expiration. Calipers must avoid the pectoralis muscles and be placed in axillary region near the 2nd or 3rd rib. Pressure should be firm. Record to the nearest mm.

ix) **Chest Depth.** Locate the end of the sternum and place the caliper tips on the sternum site and on the back near the spinal cord. Read at the end of expiration and record to the nearest mm.

All Skinfolds were measured from the right side. Grasp the skin between the thumb and index finger. Grasp 2 skin thicknesses but avoid the muscle and fascia. Take all measurements in the vertical plane.

i) **Subscapular.** Subject stands erect with shoulders relaxed and arms by the sides. The skinfold is raised with the thumb and forefinger of the left hand lateral to the inferior angle of the right scapula, the skinfold running downward and outward in the direction of the ribs.

ii) **Abdominal.** Subject stands in normal erect posture. The skinfold is raised with the thumb and forefinger of the left hand in a position 1 - 2 inches above the right anterior superior iliac spine so that the fold runs forward and slightly downward.

iii) **Triceps.** Taken at the midposterior midpoint between the tip of the acromion and the tip of the olecranon with the arm hanging in an extended position.

All skinfold measurements taken 3 times, and the mean of the 3 readings was used in calculation of lean body mass (weight) by 3 different anthropometric techniques (Sloan; Willmore-Behnke and body mass index).

VALIDATION.

The following scatter plots show the correlations between skinfold measurements. The precision of the measurement was not influenced by the presence of disease, as shown in figure 12a and 12b respectively.

Figure 12a. Scatter plots showing the reproducibility of measuring skinfold thickness at the subscapular region in normal subjects.

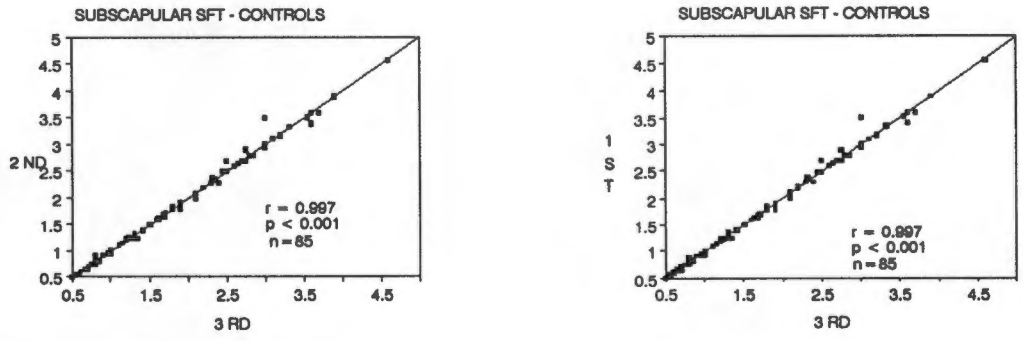


Figure 12b. Scatter plots showing the reproducibility of measuring abdominal skinfold thickness in subjects with RA. The measurements were highly reproducible.

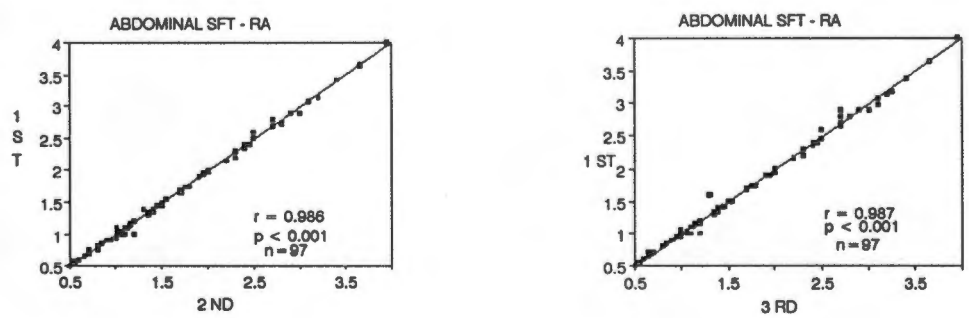


Table 6 summarises the coefficients of correlation between measurements of skinfold thickness for the 3 groups of subjects (RA, SLE, controls) at the different sites. The results show that repeated measurements at the same site were redundant ($r > 0.9$).

Table 6. Skinfold measurements were used in calculating lean body mass (LBM). The mean of 3 readings was used in the calculations of LBM. Reproducibility of the measurements is shown.

Skinfold	Group	Correlation Coefficient Comparing Readings		
		1vs2	1vs3	2vs3
Subscapular	Normal	0.997	0.997	0.999
	SLE	0.997	0.998	0.998
Triceps	Normal	0.999	0.947	0.944
	SLE	0.998	0.916	0.924
	RA	0.997	0.938	0.941
Abdominal	Normal	0.999	0.998	0.999
	RA	0.986	0.998	0.987

The relevant values were substituted in the following formulae for the calculation of lean body mass (LBM):

A. SLOAN :

X1	=	1.1043	- (0.001327 X2)	- (0.001310 X3)

WHERE X1 = Density (G/ml)

X2 = thigh skinfold (mm) and

X3 = subscapular skinfold (mm)

B. WILLMORE-BEHNKE.

LBW1	=	D^2	x	Height (dm),

AND

LBW2	=	D^2	x	Height $^{0.7}$ x 0.263

WHERE

D	=	1.12569	-	0.001835	x triceps SFT	(mm)
			-	0.002779	x hip girth	(in)
			+	0.00549	x flexed biceps girth	(in)
			-	0.0007167	x scapula SFT	(mm).

C. BODY MASS INDEX :

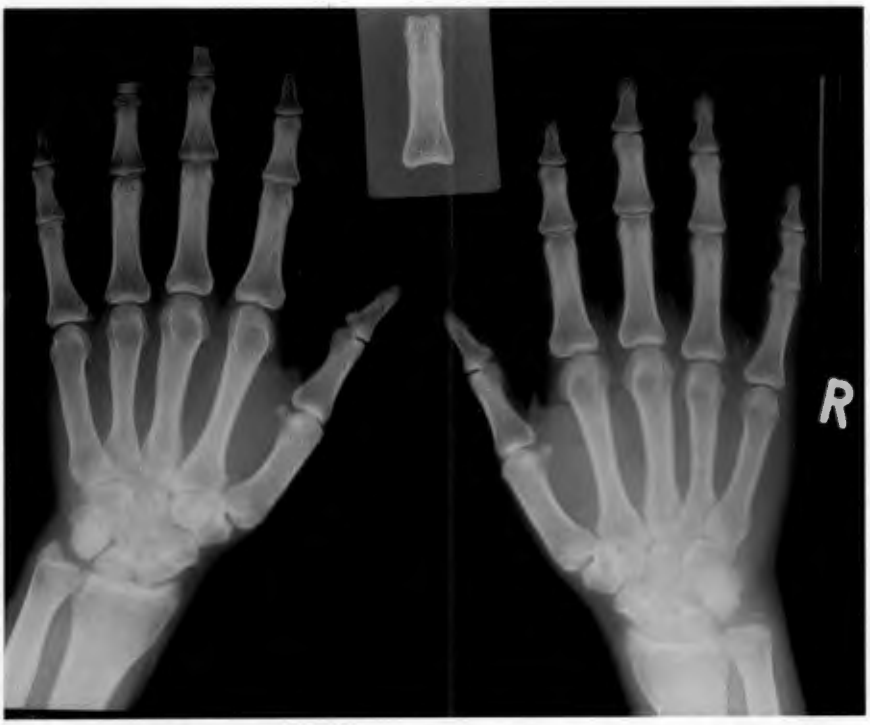
BMI	=	Mass /	Height ^{2}	

Biochemical assessment of nutritional status was based on measurement of serum albumen RBG and TBP measurements.

RADIOLOGY AND RADIOGRAMMETRY.

X-rays were standardised for the purpose of this study. These were performed at 2 different centres. Three skeletal sites were selected for comparison with other published series. The hands were radiographed at a tube distance of 100 cm, with exposure time standardised as recommended by Dequeker (1976) and others (Barnett and Nordin 1960). A *phantom phalanx* embedded in wax was included on the picture for tests of reproducibility (Fig 13).

Figure 13. Radiograph of the hands, showing the phantom embedded in a rectangle of wax. The phantom digit was used in the analysis of reproducibility of the technique.

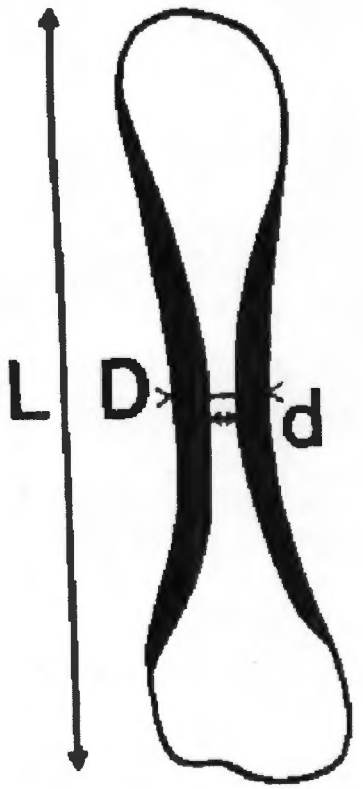


The left hip was internally rotated to 15°, as recommended by Singh *et al* (1973). Finally, the lumbar spine was examined in a lateral view centered on the 3rd vertebra.

These views allowed the measurement of the right 2nd metacarpal index as described by Barnett and Nordin (1960), the 6 metacarpal index as described by Horsman *et al* (1975), the carpo- metacarpal ratio using the landmarks of Trentham and Masi (1976), the Singh index (1970; 1972; 1973) at the left hip, left femoral cortical thickness proximal to the lesser trochanter, the femoral index at the left hip by dividing the cortical width by the narrowest width of the femoral neck (Fredensborg and Nilsson 1977), and the lumbar spine index according to the method of Saville (1967). Several modifications have been made to the basic formula proposed by Barnett and Nordin (1960), in an attempt to *normalise* for variations in body habitus and structure between individuals. These complex calculations depend on the basic measurements of the outer (TW) and inner (MW) diameters at the midshaft of the metacarpal. These diameters were used to calculate the combined cortical width (CCW), which is the basis of the metacarpal bone mass calculations.

In the application of the radiogrammetric method, the landmarks suggested by Barnett and Nordin (1960) and Dequeker (1976) were used (Fig 14). Horsman *et al* (1975), use slightly different landmarks, making comparisons of results difficult to interpret. The Vernier caliper method, which has been extensively studied and validated, was not used in this study.

Figure 14. Diagramatic representation of landmarks used for measurements at the metacarpals. Combined cortical width (CCW) is calculated as the difference between total width (D) and medullary width (d) at the midshaft (L/2).



In order to evaluate a newer, more reliable method for measurement of bone mass by radiogrammetry, the techniques of Evans (1978) and Horsman *et al* (1977), were modified for the interpretation of standard X-rays using a digitiser. In consultation with the Department of Information Technology at the University of Cape Town, computer software was designed for use with a Houston Hipad digitiser interfaced with an IBM PC (Fig 15).

Figure 15. Houston Hipad Digitiser, showing grid markings as well as cursor for plotting co-ordinates. The cursor has ten times magnification and a cross in the centre, facilitating accurate measurement.

The computer programme written for this study was designed to calculate all the radiogrammetric measures of bone mass recommended by Aitken (1984a). The programme was used to measure the inner (MW) {d}, and outer (TW) {D} diameters, after being directed to the midpoint of the metacarpal shaft (L/2). The carpal length, femoral cortical width and narrowest diameter of the femoral neck trabeculations were also measured as recommended by the respective authors. The right wrist was graded for severity according to the modified Larsen index (1979). All measurements

for radiogrammetry were done on a standard antero-posterior radiograph of the hands at a tube distance of 100 cm. No magnification techniques were applied.

Formulae were entered for the simultaneous calculation of the right 2nd metacarpal index, whole bone ash (WBA), density (WBD) and calcium content (WBCa), the 6 metacarpal indices (M6CA% and M6HS), carpo-metacarpal ratio (CMR) and femoral index (FI) (Figure 16).

Figure 16. Formulae for calculation of bone mass using measurements at the right 2nd metacarpal.

$$\text{Area Index (AI)} = D^2-d^2 = TW^2-MW^2$$

$$\text{Metacarpal Index (MI)} = \frac{D^2-d^2}{DL} = \frac{TW^2-MW^2}{TW \times L}$$

$$\text{\% Cortical Area (\%CA)} = \frac{100(TW^2-MW^2)}{TW^2}$$

$$\text{WBD} = \%CA \times 2.0 \ (g\ ml^{-1})$$

$$\text{WBA} = \%CA \times 1150 \ (mg\ ml^{-1})$$

$$\text{WBCa} = \%CA \times 450 \ (mg\ ml^{-1})$$

$$\text{CA} = \frac{\pi}{4}(TW^2-MW^2)$$

$$\text{CA/SA} = \frac{TW^2-MW^2}{4L \times TW}$$

Intra-observer reproducibility was tested by measuring the phantom digit 6 times on 6 randomly selected radiographs (Figure 13). The coefficient of variation (cv) was calculated for 6 measurements as well as a single measurement.

Table 7 shows that the readings were reproducible for a single observer. It would seem from the table that the margins of the metacarpal were more easily defined than those of the phantom used in this study. Our findings confirm earlier suggestions (DeQueker 1976, Aitken 1984a) that medullary width (MW) shows the greatest variation in measurement.

Table 7. Intra - observer analysis of variance, using digitiser for measuring length, total width (TW) and medullary width (MW) at the midshaft of the phantom used in this study, as well as the right 2nd metacarpal of 6 subjects. Measurements were performed 6 times on 6 reference radiographs, giving a total of 36 readings.

Measure	Coefficient of Reliability.	
	Phantom	Metacarpal
Length	0.8	0.9945
TW (D)	0.8462	0.9758
MW (d)	0.7222	0.8175

Inter-observer reproducibility was evaluated for 5 different observers with varying experience with radiogrammetry. Observer 1 was familiar with the digitiser technique and was responsible for its development. Observer 2 was familiar with the Ver-

nier caliper technique and had never previously used the digitiser. The remaining 3 observers were not at all familiar with radiogrammetry or use of the digitiser. The results represent a single encounter with the digitiser by observers 2-5.

Table 8 summarises the measurements for the 5 observers. Applying the method of Barnett (1969) we were able to show that the differences between the measurements of the 5 observers was negligible.

Table 8. Measurements of phantom by 5 different observers. Inter-observer differences were not statistically significant ($p > 0.05$).

Measure	Observer Reading -- Mean (SD)				
	1	2	3	4	5
Length	4.48	4.51	4.47	4.48	4.49
	(0.02)	(0.05)	(0.03)	(0.04)	(0.02)
TW (D)	1.15	1.09	1.10	1.08	1.12
	(0.02)	(0.03)	(0.02)	(0.02)	(0.02)
MW (d)	0.66	0.69	0.68	0.71	0.60
	(0.02)	(0.02)	(0.02)	(0.02)	(0.02)
CCW	0.49	0.44	0.42	0.37	0.52
	(0.02)	(0.03)	(0.03)	(0.02)	(0.03)

The *inter-centre* reproducibility was tested with the same phantom used at the 2 centres where the patients were seen. Six measurements each on six X-rays from the respective centre were measured by one observer. The 36 measurements obtained

are shown in table 9. The paired *t-test* showed that there was no statistically significant difference between measurements of the mould between centres ($p > 0.05$) for the diameters, even though the length was significantly different ($p < 0.05$).

Table 9. Measurement of phantom at 2 different centres. Although the differences in length is statistically significant ($P < 0.05$), TW and MW were not significantly different. This suggests that inter-centre comparisons were valid.

Mean Measure	Centre 1 (SD)	Centre 2 (SD)	*p* value
Length	4.493 (0.027)	4.426 (0.072)	0.001
TW (D)	1.119 (0.018)	1.092 (0.031)	NS
MW (d)	0.604 (0.025)	0.607 (0.028)	NS

In order to further evaluate the error (particularly for longitudinal studies), 6 controls and 10 patients with RA were X-rayed on 2 separate occasions, 1-4 weeks apart. The RA controls were recruited from the remission induction clinic at GSH, where patients were seen at regular intervals to monitor side-effects of therapy. They were selected because this is the group in whom one would expect disease modifying effects of therapy over a period of time. Randomisation was hopefully achieved by

studying the first 3 consecutive patients at the clinic over a month. Seven sets of radiographs were analysed (2 patients had only one set of X-Rays while 1 patient had had surgery to the MCP joints). The right 2nd metacarpal was measured 6 times on each set of X-Rays.

In the control group, the metacarpal length was statistically significantly different in the 2 sets of radiographs. However, the cortical diameters at the midshaft were not significantly different on the 2 occasions. In the patients with RA, randomisation tests showed no significant differences in length, TW, MW or CCW in the 2 sets of radiographs.

The results of the validation studies show that the measurements made with the instruments in this study were reliable. They show that the dynamometer is perhaps better than the cuff for measuring hand strength (see tables 5 and 6), supporting the suggestion by (De Choisy 1973).

The digitiser is a marked improvement on the Vernier caliper technique, particularly with respect to multiple observer analysis. The digitiser technique is ideally suited to multi-centre, multi-observer studies. This is particularly important to South Africa, where resources are limited and facilities sparsely distributed.

The 6 metacarpal bone mass was calculated from the formula provided by Aitken (1984a), depicted in figure 17. It is derived from the right 2nd metacarpal indices.

Figure 17. Formulae for calculating bone mass from measurements at the midshaft of 6 metacarpals.

$$6MHS = \frac{100\,([TWa-MWa]+[TWb-MWb]+\dots+[TWf-MWf])}{TWa+TWb+TWc+TWd+TWe+TWf}$$

$$6M\%CA = \frac{100\,([TWa^2-MWa^2]+[TWb^2-MWb^2]+\dots+[TWf^2-MWf^2])}{TWa^2+TWb^2+TWc^2+TWd^2+TWe^2+TWf^2}$$

The output of the data was in a computer format (ASCII), which allowed it to be read into a standard database management system (eg *CONDOR 3; DBASE 3*). Selected fields could then be subjected to graphical (eg *Lotus 123*) and statistical analyses using the appropriate computer software. This method removed the errors introduced while entering data for calculations when using the Vernier calipers. In this way the total error was likely to be reduced considerably. Details of the digitiser technique are provided in Appendix B.

The authors of other studies do not indicate the amount of time spent in measuring and subsequently calculating the indices, but the impression created is that the method is extremely time-consuming. It would seem that Horsman's method requires at least 10 minutes of technical time, which does not include the time for making the complex calculations (Aitken 1984a). The author was able to show that the digitiser method is more accurate, reproducible and simple to administer. It was also found that, contrary to the suggestion (Horsman *et al* 1975), the 2nd metacarpal bone mass could be calculated in less than 1 minute, while the 6 metacarpal bone mass was calculated in less than 5 minutes. Records were available for comparison at different time of radiography. Therefore, time element was considerably reduced using the new technology.

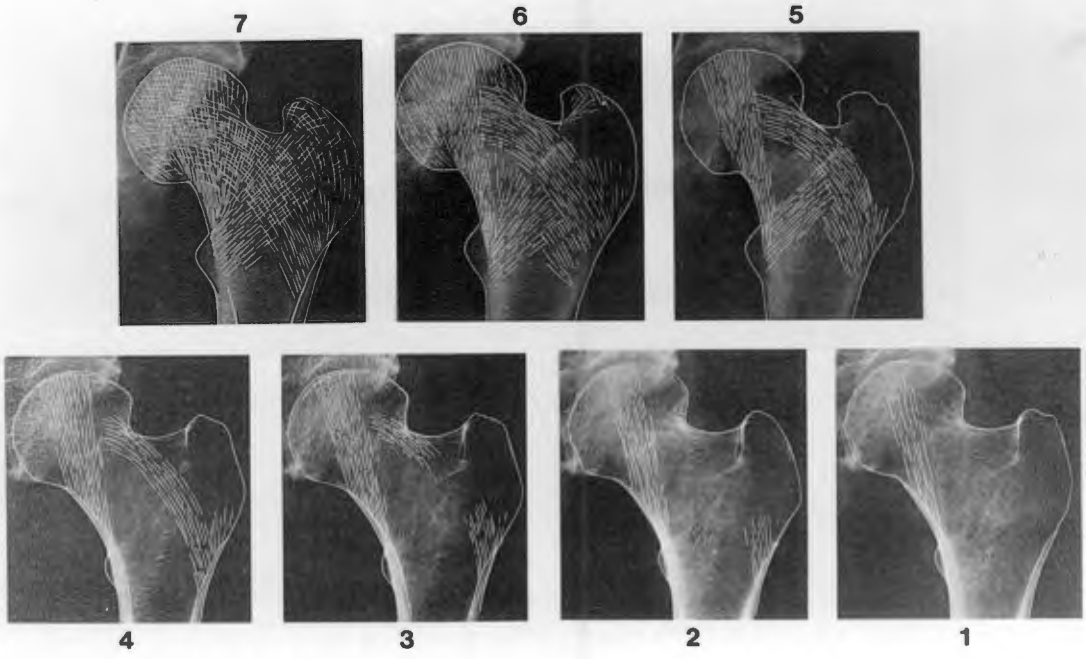
The sensitivity of the method would be illustrated by its ability to differentiate between the three groups in this study, using discriminant analysis.

It was hoped that this modified method would be an improvement on the previous techniques (Barnett and Nordin 1960; Horsman *et al* 1977), especially with respect to speed, precision and reproducibility.

The landmarks for measurement of carpal length were those of Trentham and Masi (1976). The femoral cortical and trabecular measurements were based on the recommendations of Fredensborg and Nilsson (1977).

The Singh index was scored as suggested by Singh *et al* (1970; 1972; 1973). This was based on the trabecular pattern as depicted in Figure 18.

Figure 18. Reference pattern at the left hip from which the Singh index was derived and graded according to the trabecular pattern.



The 3rd lumbar vertebra was also graded for trabecular porosity, using the method of Saville (1967). The following grades were recorded:

0 = Normal bone density.

1 = Minimal loss of density; end plates begin to stand out, giving a stenciled effect.

2 = Vertical striation is more obvious; end plates are thinner.

3 = More severe loss of bone density than grade 2, end plates becoming less visible.

4 = Ghost-like vertebral bodies.

GENETICS.

Alloantisera were obtained both locally and by international exchange for use in the standard microlymphocytotoxicity assay for HLA-typing (Terasaki *et al* 1974). 180 antisera were used to type 17 A-locus, 31 B-locus and 8 C-locus antigens. The nylon wool technique was used to obtain the B lymphocyte fraction (Danilovs *et al* 1980) and 95 antisera were used for the typing of 10 DR and 3 DQ locus antigens.

STATISTICAL METHODS.

The Institute of Medical Biostatistics, SAMRC was responsible for statistical analyses. Calculations were made using an IBM mainframe computer. A multitude of computer-based statistical methods were used in the final analysis of the data. These included univariate as well as multivariate techniques. The data was carefully scanned for data errors and true outlies (unexpected values). Sample distributions

were inspected for skewness, platykurtic or leptokurtic characteristics. Relationships between variables were investigated. In the case of nominal variables, contingency tables were used. In the case of continuous variables, Pearson and Spearman correlations were used. The Bonferroni technique (*in* Neter and Wasserman 1974) was applied when the 3 groups were being compared, as well as Duncan's multiple range test. Every large study of this nature, should aim at recommending a programme of data reduction for future researchers. A *correlation matrix* allows the researcher to reduce groups of variables to smaller sets without losing information. Tests such as the Keitel Functional Test and the mobility test measure a number of related variables. Also, radiogrammetry combines a series of variables of bone mass, which are not all necessary to draw meaningful conclusions. A series of correlation matrices were constructed with the goal of data reduction in mind, using Pearson and Spearman correlations.

The correlation coefficients were applied to the concept of *consensus analysis* (Bull *et al* 1986), which is the mean of the correlation coefficients of a group of independent variables. Calculations were done with *Lotus 123*. The spreadsheet was used in deriving histograms to illustrate important differences. *Stepwise multiple regression* and *discriminant analyses* were used where appropriate. *Factor analysis* (Gorsuch 1974) was used to evaluate 27 variables representing disease activity, disability, biochemical and radiological markers of OP. The measurements of finger strength were combined in a composite *strength* index. The tests of simple hand function were combined in a composite *hand* index, in order to maximise the factor analysis of the 27 variables. Further statistical techniques included the use of *receiver operating characteristic* (ROC) curve analyses (Centor 1985) in evaluating the detectability of OP in

RA, as well as disease activity in RA, using clinical, laboratory and radiological variables. The IBM PC was used for this purpose, applying the spreadsheet of Centor (1985) in calculating the true positive ratio (TPR) and false positive ratio (FPR). The sample size per range of abnormality was derived with the *CONDOR 3* database management system.

In applying these techniques, the RA group was divided into 2 subgroups, based on the CA% below that of 90% of the normal control group (< 10 percentile). ROC curves were derived for the Σ CCW, CCW, CA% and M6HS, comparing ranges for the normal control group and patients with RA. In the RA group, the 2 subgroups were compared with the use of ROC curves for different measures of bone mass. The RA group was also subdivided into 2 groups based on the physician's assessment of disease activity. ROC curves were derived for clinical and laboratory variables in these groups.

PRESENTATION OF THE THESIS.

Several guidelines are available for the presentation of the thesis. Hawkins (1976) discusses a number of important features in a comprehensive outline of the problems. In this presentation, the results and discussion will be combined. This deviation from the conventional method was chosen in order to maintain continuity of thought. It was hoped that the reader would obtain a clearer understanding of the multifactorial mechanisms of bone loss in rheumatoid arthritis. Caution was exercised in order to avoid the use of speculation in the presentation of the results.

Data was collected and stored on the IBM PC using the *CONDOR 3* database management system. This was then transferred to the mainframe computer at the SAMRC for statistical analysis. The scatter plots were derived with the use of the *Lotus 123* spreadsheet. ROC curves were constructed with *Lotus 123* using the computer programme reported by Centor (1985). The graphs were enhanced with the *Lotus Freelance* software. The manuscript was written with *Microsoft WORD*. Images were scanned with the *DFI HS 2000* hand scanner. The final product was printed on the *HP Laserjet II* printer, using *Ventura*, the desktop publishing software for the IBM PC.

RESULTS AND DISCUSSION.

CLASSIFICATION CRITERIA OF DISEASE.

CLASSIFICATION OF RHEUMATOID ARTHRITIS.

Table 10 shows the prevalence of the criteria for classification of RA (ARA) (Ropes *et al* 1958). These compare with those of other series (Mitchell and Fries 1982), suggesting that the patients with RA in this study were representative. Since most patients fulfilled more than 5 ARA criteria, it can be inferred that very few patients required the more sophisticated diagnostic procedures, such as histology or synovial aspiration, for classification. These findings concur with those of the ARA revising committee (Arnett *et al* 1988) who have recently reduced the total number of criteria to 7.

Table 10. Classification criteria for Rheumatoid Arthritis in 100 patients under 50 years of age.

ARA Criterion	Present Series %	Mitchell & Fries %
Morning Stiffness	95	66
Pain on motion of at least one joint	100	91
Swelling in at least one joint	100	82
Swelling in at least one other joint	99	75
Positive Serology	87	74
Symmetrical, Simultaneous joint disease	96	68
Subcutaneous Nodules	20	19
Poor Mucin Clot	4	-
Characteristic Histology in Synovial Membrane	18	-
Characteristic Histological changes in Nodules	7	-
X - Ray changes Typical of RA	100	47

The same table shows that all the patients in this study were considered to have radiological changes of RA (Ropes *et al* 1958) at the time they were seen for this study. The radiological assessment was performed by the same person who subsequently performed bone mass measurements. The features in Mitchell's series were recorded at the time of presentation, while the present series includes patients with varying clinic follow-up. Patients with RA often develop further criteria as the disease progresses. This may explain some of the differences in the 2 groups of subjects.

Table 11 shows that 85% of the patients had classical RA. There were no patients with probable RA in this group of subjects. The revised criteria (1987) no longer differentiate *classical* and *definite* groups. They also obviate the need for the long list of exclusions. Four criteria are now recommended for the diagnosis.

Table 11. Summary of RA Classification according to ARA Criteria in 100 subjects with RA.

ARA Classification	No. of Criteria	%
Definite RA	5 - 6	15
Classical RA	6	85

CLASSIFICATION OF SYSTEMIC LUPUS ERYTHEMATOSUS.

Table 12 shows the criteria for classification of SLE (ARA), compared with 2 other studies (Taylor and Stein 1986, Tan *et al* 1982).

Table 12. Criteria for classification of SLE, comparing the present series of subjects (72) with other reported studies.

Criterion	Present Series $n=72$ %	Taylor & Stein $n=31$ %	Tan et.al $n=177$ %
Arthritis or Arthralgia	93	81	86
Butterfly Rash	47	61	57
Discoid L E	15	19	18
Photosensitivity	25	16	43
Mucosal Ulcers	19	19	27
Serositis	32	23	56
CNS Lupus	21	13	20
Renal Changes of SLE	42	71	51
Positive ANF	99	96	99
Haematological Abnormalities of SLE	74	61	59
Positive ADA / Sm / WR	90	65	84

The antinuclear factor (ANF) was present in 99% of our patients with SLE. History of joint disease was the commonest clinical manifestation of the disease, confirming the findings of these workers. Immunological abnormalities were seen in 90%. Auto-immune haemolytic anaemia, leucopaenia, lymphopaenia or thrombocytopaenia occurred at some stage of the disease in 74%, while the characteristic butterfly rash was seen in less than 50%. Urinary protein, casts, or biopsy evidence of renal disease was recorded in 42%. This is considerably less than in Taylor and Stein's (1986) series, which was confined to Blacks from Zimbabwe. Serositis was seen at some stage in approximately one-third of our patients with SLE (32%). Discoid LE and mucosal ulcers were the least common clinical features in the present group. Approximately 1 in 5 patients had neurological features in the course of their illness.

The table shows that the patients in this series were comparable with those seen in other parts of the world. There are minor differences in the distribution of individual criteria, but they need to be interpreted with respect to the actual classification of the disease, as shown in the table which follows. There is no relationship between the number of criteria at diagnosis and severity of disease.

Table 13 shows that 3 of the patients in this series fulfilled less than 4 of the revised ARA classification criteria for SLE (Tan *et al* 1982). They were included in the analysis of bone mass, since corticosteroid therapy had been commenced for the presumed diagnosis of SLE.

Table 13. Summary of Classification criteria in 72 patients with SLE.

ARA Classification	No. of Criteria	Sample size *n*	%
Definite SLE	> 3	69	95
Probable SLE	< 4	3	5

DEMOGRAPHY.

AGE AND MENOPAUSAL STATUS.

This is one of few studies of bone mass in RA, where the analysis has been confined to an age-group where differences have generally been difficult to demonstrate with radiogrammetry (Saville and Kharmosh 1967). Causal relationships can be inferred only when such stringency is applied to the selection of the study sample.

The patients with RA were older, while the patients with SLE were younger than the controls, as shown in table 14. However, these differences were not statistically significant ($p > 0.05$).

Table 14. The demographic features such as the mean, median and range of the subjects' ages is shown. All groups had a mean age less than 40 years.

	NORMAL	RA	SLE
Number	100	100	72
Mean	33.47	38.08	31.75
Median	34	39	32
Range	(21 - 50)	(18 - 50)	(19 - 45)

Each group of subjects had a mean age less than 40 years. Since RA is generally a disease of older females, it is not surprising that the mean age of the patients with RA was higher than that of the controls. Patients with SLE were younger than the controls, confirming the clinical impression that SLE is a disease of young females.

Numerous epidemiological studies have shown that the physiological changes in bone mass are usually not detectable by radiogrammetry before the age of 45 years (Barnett and Nordin 1960; Meyers 1983; Solomon 1979). In addition, studies in premenopausal subjects with RA have failed to show significant differences when compared with premenopausal normal subjects (Saville and Kharmosh 1967). Therefore, any significant differences which may be demonstrated could be regarded to be due to some effect of the disease. Such differences may also be a reflection of the sensitivity (precision) of the digitiser technique compared with the Vernier calipers.

For this reason, the groups were only approximately matched for age. The mean age of the subjects with RA was not significantly different from that of the normal controls (Table 14), and a comparison between bone mass and age in the 3 groups showed that age did not contribute significantly to the differences in bone mass in this study.

RACE AND SEX.

Table 15 shows that the groups were adequately matched for race and sex, particularly in the Coloured group, who dominated in all 3 groups of subjects. The reason for this is related largely to the fact that the RDU at GSH sees a greater proportion of Coloured patients in comparison with other race groups, rather than a higher prevalence of RA in this ethnic group.

Table 15. Frequency distribution of race and sex of the subjects under study.

	NORMAL	RA	SLE
Number	100	100	72
White Male	3	5	-
White Female	27	16	5
Coloured Male	24	16	4
Coloured Female	45	48	56
Indian Male	-	-	1
Indian Female	1	2	2
Black Male	-	3	-
Black Female	-	10	4

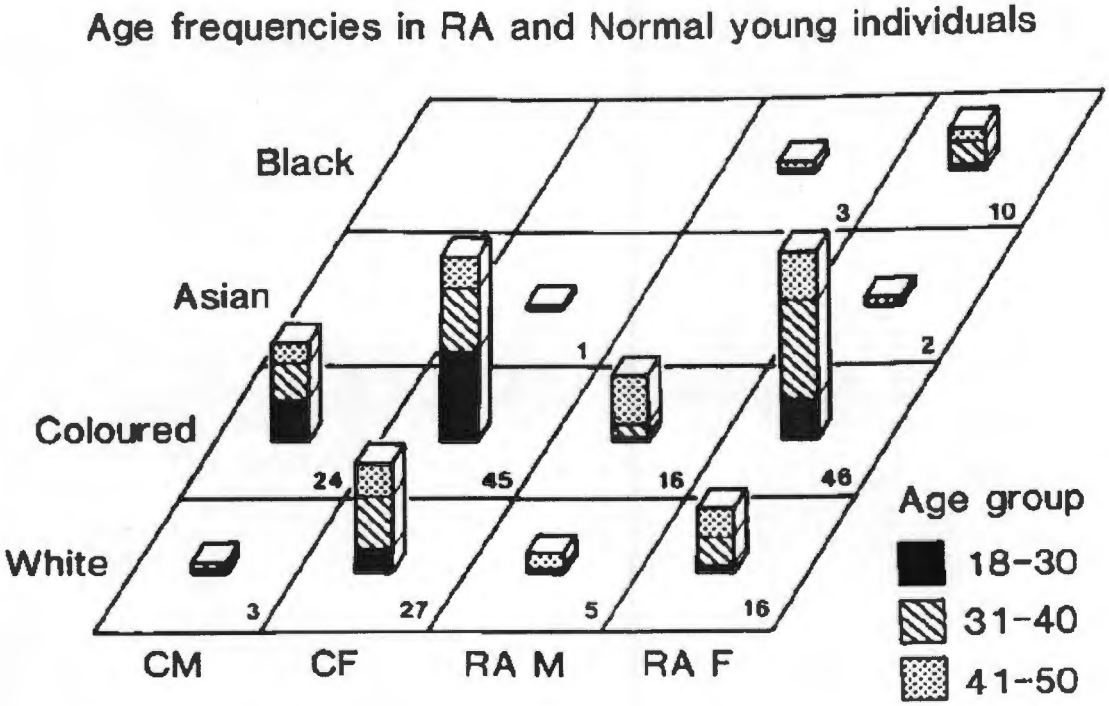
Overseas work (Mayor 1976) has shown that Negroes have a higher bone mass than age matched Whites. Solomon (1979), on the other hand, has shown that Blacks in Johannesburg (SA) have a lower bone mass than their White counterparts of com-

parable age and sex. In a study of Coloureds in Rietpoort (RSA), no comparison was made with age - matched subjects of other race groups (Meyers 1983), but the fall in bone mass showed trends which were comparable with those of the Johannesburg study, as well as other studies in Caucasians. Wagener and Hough (1987) showed that Coloureds had lower bone mass than Whites, but the differences were not statistically significant (n = 582; n = 559).

The present study was not aimed at comparing the race groups with respect to bone mass, and table 15 clearly shows that some groups were too small for statistical analysis. There is no evidence that the Cape Coloured is genetically predisposed to RA, SLE or osteoporosis.

Figure 19 is a 3-dimensional histogram of the RA and normal control groups, showing the sex per study group (X-axis), racial distribution (Y-axis) and frequency (Z-axis) for the 2 groups. The age range is depicted by the height of each bar, as shown in the legend. The Coloureds, who formed the largest group, were comparable for age and sex distribution in the groups. The younger group of subjects with SLE is not shown.

Figure 19. Histograms showing the age, race and sex distribution of the groups under study. Coloured females predominated. The subjects with SLE are not shown (CM = Control Males; CF = Control Females; RA M = RA Males; RA F = RA Females).



BONE MASS IN RA.

METACARPAL RADIOGRAMMETRY.

It can be seen from the review of the literature, that there are 2 major limitations of radiogrammetry. The first is due to the fact that the method only measures cortical bone, and the second is related to poor reproducibility. In order to overcome the first limitation, multiple areas were X-rayed. The preceding reliability studies showed that the digitiser technique used for the measurement of bone mass in this study was reproducible, overcoming the second limitation of the radiogrammetry method.

The precision of the method needs to be tested by a longitudinal study in the same study group at a subsequent stage. However, if we assume that changes of bone mass in subjects below 45 years of age are generally small, a technique capable of detecting significant differences between such age matched diseased and normal individuals would need to be highly sensitive and precise. Since our measurements were found to be reliable, valid conclusions can be drawn about bone mass changes in the study subjects with RA and these can be assumed to be due to the disease.

The selection of subjects for study has also proved a limiting factor in the interpretation of earlier reports of bone mass in RA. The most significant confounding factor is age, often associated with a change in sex hormonal status. These have been comprehensively addressed in the introductory chapter.

There is controversy about the use of controls for comparative analyses. Some have suggested the the reference group for comparisons consist of young normal individuals (Barnett and Nordin 1960), while others have argued that the comparisons be made with age matched normal controls of all ages. Some of the studies in RA are summarised in Table 1 (pg 61). It can be seen that the subjects were generally of an elderly population (mean age > 50 years), making the interpretation of the results difficult to separate from age-related events.

The literature is replete with studies showing that measurable bone loss begins after 45 years of age, irrespective of race (Exton-Smith *et al* 1969; Horsman *et al* 1976; Solomon 1979; Wagener and Hough 1987). Postmenopausal females are known to show an accelerated loss, which is seen in males a decade or more later. Therefore, the subjects in this study represented a group of individuals in whom physiological bone loss is generally detected with great difficulty (Saville and Kharmosh 1967). The reasons for the careful selection of these subjects have been outlined. The review by Guyatt *et al* (1984), adequately summarises the defects in earlier studies of bone mass, particularly in corticosteroid treated patients. The criticisms apply to many of the studies of subjects with RA as well.

Several calculations have been recommended for the determination of bone mass (fig 16; pg 191). Since the early studies of Barnett and Nordin (1960), workers such as Meema and Meema (1969), Dequeker (1972), Exton-Smith *et al* (1969a), Horsman and Simpson (1975), and Aitken (1984a) have addressed the limitations of the method and proposed modifications to overcome some of them. The calculations are

complex and there is no study in which all the various computations have been compared with each other in the same individuals.

Table 16 shows an unpaired comparison (*t-test*), taking into account unequal variances where necessary, between patients with RA and a group of normal controls. The table includes several of the different formulae which have been introduced by the various authorities for the purpose of *normalisation* of bone mass for body stature. The changes in the patients with SLE will be discussed separately, but reference will be made to the changes when related to possible pathophysiological mechanisms in the RA group.

Table 16. Bone mass calculations in RA, using the standard techniques recommended for normalisation of bone mass.

Measurement	Mean Control (SD)	Mean RA (SD)	*p* value
AI	0.5893 (0.089)	0.5406 (0.127)	0.0027
MI	0.1077 (0.014)	0.0978 (0.021)	0.0002
CA	0.4630 (0.069)	0.4247 (0.099)	0.0027
CA%	85.1880 (6.872)	76.5957 (10.14)	0.0001
CA / SA	0.0280 (0.002)	0.0252 0.003	0.0001
6 MHS	62.5261 (7.959)	55.4786 (8.733)	0.0001
6 % CA	85.1085 (5.711)	79.0184 (8.037)	0.0001

The table shows that patients with RA have a significantly lower metacarpal bone mass than normal controls ($p < 0.0001$). The table also shows that in this group of patients, the differences remain significant at the most basic level of bone mass calculation (Barnett and Nordin 1960). However, the alternative hypothesis is strengthened by the corrections for body habitus, as is shown in the comparison of CA%, CA/SA and M6HS, as suggested by Dequeker (1972), Exton-Smith *et al* (1969a) and Horsman and Simpson (1975), respectively.

Since previous methods used the Vernier caliper to measure inner and outer diameters at the midshaft, it would seem that the method was not sensitive at detecting small changes. The digitiser method overcomes a number of the limitations previously described and it is obviously more precise. In this study, 2nd metacarpal scores were comparable with 6 metacarpal scores in the RA patients.

The various hand scores were correlated with each other using the Spearman rank correlation as a non-parametric test. The normal control group served as a basis for correlating different skeletal sites, as well as different calculations at the same skeletal site, in a non-pathological environment. Differences resulting from disease would change the basic correlations found in the control group. Table 17 shows the r value in the upper triangular matrix and the p value in the lower triangular matrix, for the control group.

Table 17. Spearman correlation of right second and six metacarpals in 98 normal control subjects. The r value is shown in the upper and p value in the lower triangular matrix. Which 2nd metacarpal measure correlates best with the 6 metacarpal score?

	AI	MI	CA	CA%	CA/SA	M6HS	M6CA
AI		0.908	1.0	0.239	0.431	0.024	0.023
MI	0.0001		0.908	0.193	0.99	0.153	0.156
CA	0.0001	0.0001		0.024	0.431	0.024	0.023
CA%	NS	NS	NS		0.458	0.879	0.88
CA/SA	0.0001	0.0001	0.0001	0.0001		0.479	0.479
M6HS	NS	NS	NS	0.0001	0.0001		0.998
M6CA	NS	NS	NS	0.0001	0.0001	0.0001	

Table 17 shows that in normal subjects, measurements at the right 2nd metacarpal do not all correlate with those using 6 metacarpals of both hands. However, the CA% explained over 75% of the variation in M6HS and M6CA% (the square of r = 0.88). The CA/SA, on the other hand, showed significant correlations with all the other variables. This finding is in agreement with the suggestion by Exton-Smith *et al* (1969a), that it is the most representative measure of metacarpal bone mass using radiogrammetry.

In addition, the table shows that in normal subjects, calculation of separate 6 metacarpal hand scores is a redundant exercise (r = 0.998). These findings suggest that many of the recommendations previously suggested by other authors are, indeed, also pertinent to a young group of normal subjects.

Table 18 shows the same correlations in 97 young patients with RA. As in the previous table, the *r* value is depicted in the upper triangular matrix, while the *p* value is depicted in the lower triangular matrix.

Table 18. Spearman correlation of second and and six metacarpals in 96 patients with RA showing r value in upper and p value in lower triangular matrix.

	AI	MI	CA	CA%	CA/SA	M6HS	M6CA
AI		0.915	1.0	0.32	0.739	0.236	0.247
MI	0.0001		0.915	0.534	0.99	0.441	0.448
CA	0.0001	0.0001		0.325	0.739	0.236	0.247
CA%	0.0011	0.0001	0.0011		0.663	0.896	0.899
CA/SA	0.0001	0.0001	0.0001	0.0001		0.553	0.567
M6HS	0.0192	0.0001	0.0192	0.0001	0.0001		0.998
M6CA	0.0144	0.0001	0.0144	0.0001	0.0001	0.0001	

Several differences become apparent on inspection of the table. The first observation is that CA is a linear function of AI. In addition, the correlations between the right 2nd metacarpal and 6 metacarpal scores are all significant ($p < 0.02$) in this group of patients with RA. The table also shows that the calculation of a host of 2nd metacarpal scores may be important. The variation in AI explained over 80% of the variation in MI ($r = 0.92$), and CA ($r = 1$). However, the variation in AI explained less than 10% of the variation in CA% ($r = 0.325$), M6HS ($r = 0.236$) and M6CA% ($r = 0.247$). The table shows that of the 2nd metacarpal scores, the CA% ($r = 0.896$)

best explains the variation in M6HS and M6CA%. Also, the effect of RA on bone mass is such that the calculation of CA/SA does not appear to improve the sensitivity of the test relative to the CA%, even though the correlation with 6 metacarpal indices is greater than with AI, CA or MI.

The changes in correlations seen in the patients with RA confirm an osteopaenic process in the hands. Since the loss involves both hands equally (see later), no advantage is gained by repeating 6 measurements, except with respect to accuracy of measurements. This was borne out in the reliability studies discussed earlier, where it was shown that the accuracy of inner diameter measurement was considerably improved by six measurements compared with a single measurement. Horsman and Simpson (1975), have suggested that the index derived by 6 metacarpals is as sensitive as the bone mineral content (BMC) measured by single photon absorptiometry (SPA).

Dequeker (1976) suggested that the differences must eventually be related to changes in periosteal (TW) and endosteal (MW) bone. Table 19 shows the rank correlations (Spearman) between these diameters and combined cortical width (CCW) of the right second metacarpal as well as the sum of the six cortical widths, and calculated bone mass for the control group.

Table 19 shows that in normal subjects, CCW correlates significantly ($p < 0.01$) with the bone mass derived by CA, CA%, CA/SA and M6HS. The outer diameter (TW) correlated significantly ($p < 0.0001$) with CA and M6HS, but the variation in

TW explained 23% of the variation in CA ($r=0.48$) compared with 8% of the variation in M6HS ($r=0.28$).

Table 19. Comparison of correlations of inner and outer diameters as well as combined cortical width of right 2nd metacarpal with bone mass in normal controls. Also shown is the correlation with the sum of the cortical widths of 6 metacarpals. The r value is depicted in the upper row and the p value in the lower row of the respective cross-correlation.

		TW	MW	CCW	Σ (CCW)
CA	(*r*)	0.49	0.25	0.27	0.45
	(*p*)	0.0001	0.02	0.013	0.0001
CA%	(*r*)	-0.22	-0.71	0.61	0.65
	(*p*)	0.04	0.0001	0.0001	0.0001
CA / SA	(*r*)	-0.12	-0.38	0.32	0.46
	(*p*)	0.09	0.0001	0.0002	0.0001
M6HS	(*r*)	-0.28	-0.01	0.65	0.74
	(*p*)	0.005	0.0001	0.0001	0.0001

The inner diameter (MW) correlated significantly ($p<0.0004$) with CA%, CA/SA and M6HS. The variation in MW explained 14% of the variation in CA/SA ($r=0.38$), compared with 48% of the variation in CA% ($r=0.69$) and 69% of the variation in M6HS ($r=0.83$). This shows that the inner diameter is the most significant measurement for bone mass calculation in normal, young individuals. In addition, CCW is more important in the evaluation than either measurement alone.

Table 20 shows the rank correlations (Spearman) between the diameters and cortical width of the right second metacarpal as well as the sum of the six cortical widths for the group of RA patients. Negative correlations in the table correspond to situations where MW has a greater influence on the *normalisation* process (see formulae in Fig 16).

Table 20. Comparison of correlations of inner and outer diameters as well as cortical width of right 2nd metacarpal, with bone mass in patients with RA. Also shown is the correlation with the sum of the cortical widths of 6 metacarpals. The r value is depicted in the upper row and the p value in the lower row of the respective cross- correlation.

		TW	MW	CCW	Σ (CCW)
CA	(*r*)	0.52	0.02	0.44	0.63
	(*p*)	0.0001	NS	0.0001	0.0001
CA%	(*r*)	-0.1	-0.69	-0.67	-0.79
	(*p*)	NS	0.0001	0.0001	0.0001
CA / SA	(*r*)	0.11	-0.37	0.49	0.71
	(*p*)	NS	0.0002	0.0001	0.0001
M6HS	(*r*)	-0.2	-0.83	0.72	0.79
	(*p*)	0.044	0.0001	0.0001	0.0001

It can be seen from table 20 that patients with RA exhibit a significant change in CCW. The variation in the sum of the cortical widths of 6 digits explained 40% of the variation in CA ($r = 0.63$). Variation in outer diameter (TW) explained 27% of the variation ($r = 0.52$) in CA, while variation in inner diameter (MW) hardly explained

any of the variation in CA ($r = 0.02$). Similar to the normal subjects, patients with RA showed the most significant correlations with the cortical width of the right 2nd metacarpal as well as the sum of the cortical widths of 6 metacarpals.

In fact, the sum of the cortical widths explained 62% of the variation in M6HS ($r = 0.79$), compared with the cortical width of the right 2nd metacarpal, which explained only 52% of the variation in M6HS ($r = 0.72$). Again, negative correlations are interpreted as being due to the influence of MW. In both groups of subjects, MW makes a greater contribution to bone mass calculation than TW. This table (Table 20) confirms that metacarpal bone loss is significant in RA, and is largely related to loss of endosteal bone. However, cortical thinning at the metacarpals in RA is due to a combination of periosteal and endosteal resorption, although endosteal resorption predominates. This loss is similar to that seen in post-menopausal OP (Horsman *et al* 1977).

When the above tables are seen in conjunction, they highlight several features about the radiogrammetric detection of bone loss using metacarpal measurements. Although the statements would apply strictly to the patients under study, one might extrapolate to bone loss in other clinical situations, such as in post-menopausal OP, hyperparathyroidism, renal osteodystrophy, and osteomalacia, to name only a few.

The following points need to be emphasised, regarding the investigation of bone loss from hand X-rays in young patients with RA :

1. TW plays a greater role than MW in determining CA ($r = 0.5$). However, the sum of multiple cortical widths is the most sensitive index of cortical area (CA).
2. Calculation of the CA% amplifies the influence of MW (increased endosteal resorption) on the bone loss of Rheumatoid Arthritis.
3. The sum of multiple cortical widths is a much stronger predictor of change in CA/SA, a modification made to the basic formula, introduced for *normalisation* (standardisation).
4. In RA, the 6 metacarpal hand score is virtually entirely predictable from the measurement of MW. This finding supports the suggestion that multiple measurements of the inner diameter improve the sensitivity of the radiogrammetry technique.

Muirden (1976) has suggested that the histological features of the bones in RA patients may resemble those seen in severe hyperparathyroidism and Paget's disease of bone. However, in those diseases the outer diameter is more significantly reduced, suggesting a discrepancy with our findings. Perhaps these discrepancies are due to differences between trabecular and cortical bone, since Muirden's report is based on biopsy changes at the iliac crest.

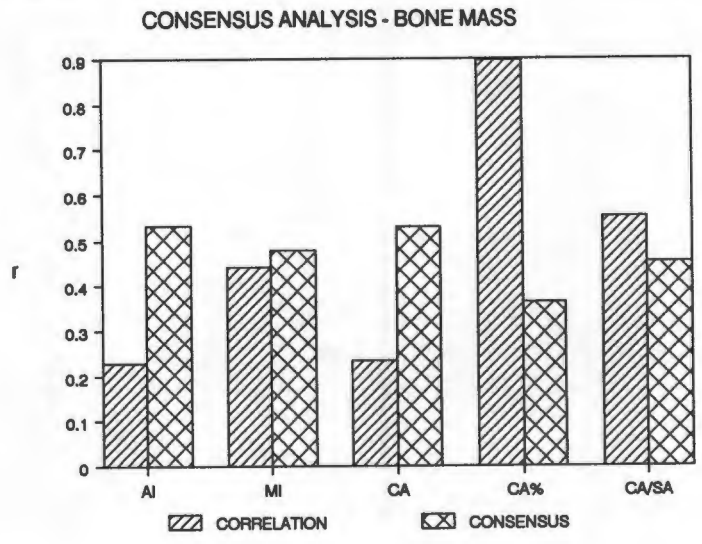
Normal females had significantly lower values for inner diameter than normal males ($p < 0.01$), while the presence of disease reversed the difference considerably ($p < 0.0001$). In RA, the differences were not influenced by comparisons for gender.

The presence of disease had a greater effect on bone mass than the difference in gender.

Dequeker (1976), remarked that determinations of periosteal and endosteal changes over a period of time provides information on skeletal dynamics. The endosteal surface enlarges throughout life faster than the periosteal surface. Morgan *et al* (1967) found a poor correlation between cortical width and the width of the shaft in healthy individuals aged between 20 and 40 years. Dequeker (1972), found that cortical area (D^2 - d^2) correlated best with outer diameter. This finding is confirmed above.

In order to decide which of the 2nd metacarpal scores best represents the 6 metacarpal index, we performed consensus analysis (Bull *et al* 1986) using the correlation coefficients of the comparison between AI, MI, CA, CA%, CA/SA, and M6HS. The results are depicted in the form of a histogram (Figure 20), showing that the CA% was the most suitable calculation of bone mass at the right 2nd metacarpal, closely representing the 6 metacarpal index.

Figure 20. Histogram showing the effect of consensus analysis. The consensus represents the mean of the r value of the comparison between the remaining variables and the 6 metacarpal hand score (M6HS).



Stepwise multiple regression analysis was used to determine which of the measures on X-ray best predicted the variation in CA%. The independent variables consisted of MW, TW and CCW at the midshaft of the right 2nd metacarpal, sum of inner and outer diameters of 6 metacarpals and sum of cortical thicknesses. Carpal length, CMR and Larsen index at the right wrist were included in the analysis. Both the RA group and the normal controls were evaluated. In the control subjects, the sum of inner diameters was able to predict 72% of the variation in CA%. Outer diameter at the 2nd metacarpal improved the predictive value to 80%, but none of the other variables were of any predictive value. In the RA group, on the other hand, 63% of the variation in CA% was predicted by the sum of the cortical thicknesses and the sum of inner diameters improved this to 83%. The other variables did not feature. This confirms the osteopaenic effects of RA. When the regression analysis was applied to CA% in SLE, the sum of inner diameters predicted 61% of the variation in CA% while the sum of outer diameters increased the predictive value to 68%. These findings suggest that the pathogenesis of bone loss in these 2 inflammatory diseases is significantly different.

WHOLE BONE PARAMETERS.

Exton-Smith *et al* (1969a) showed that dry ash weight of bone correlates best with the cortical area. It can, therefore, be inferred that patients with RA have a significant fall in the dry ash weight of bone. Aitken (1984a) has indicated that WBD, WBA and WBCa relate the physical and chemical properties of bone. Applying the knowledge that the gravimetric density of bone is 2.0 $G.ml^{-1}$, these variables were calculated, using the measurements at the right 2nd metacarpal. Since these values are direct multiples of the CA%, the differences and correlations can be expected to be identical to those seen when comparing the CA% with the other variables. These comparisons were, therefore, omitted in the present analysis.

It is clear from table 21 that the bones of patients with RA had significantly lower chemical content than those of normal controls matched for age and sex. The findings of this study are consistent with those of previous workers (McConkey 1965; Saville and Kharmosh 1967; Kennedy 1975), who have shown that bone mass is lower in patients with RA. However, this is the first study to demonstrate these differences in a group of premenopausal subjects under the age of 50 years by radiogrammetry, as discussed earlier.

Table 21. Whole bone density (WBD), whole bone ash (WBA) and whole bone calcium (WBCa) in normal subjects (n = 98) and patients with RA (n = 96).

Measurement	Mean Control (SD)	Mean RA (SD)
WBD	170.3 (13.81)	153.91 (20.28)
WBA	97924 (7940)	88085 (11660)
WBCa	38318 (3107)	34468 (4563)

These results show that the patients with RA have *accelerated OP* as defined by Barnett and Nordin (1960). It becomes important to establish the pathogenesis of this bone loss. The further contributing factors which may have amplified this loss will be discussed later.

NUMERICAL DEFINITION OF OSTEOPOROSIS.

The numerical definition of osteoporosis is based on the finding of a higher rate of fractures among subjects with metacarpal bone mass below the 10 th percentile of a normal control group. Table 22 shows that the prevalence depends on the reference bone mass for comparison as well as the measure of bone mass used.

Table 22. Prevalence of Osteoporosis in RA using the Mean - 1SD, Mean - 2SD and the 10 percentile value of the control subjects as the respective cut-off points.

Measurement	Prevalence of Osteopaenia		
	Mean - 1SD	Mean - 2SD	10 percentile
CA	42.9 %	17.3 %	33.7%
CA%	53 %	30.6 %	39 %
CA/SA	61.2 %	37.8 %	58.2%
M6HS	45.9 %	16.3 %	32.7%
M6CA	48 %	23.5 %	33.7%

It can be seen from table 22 that the CA/SA was the most sensitive measurement of bone mass in RA, conflicting with our earlier observation that CA% is the most useful predictor of M6HS. If one accepts the *fracture threshold* as a bone mass less than 2SD below the normal mean, 37.8% of our patients could be expected to sustain a fracture if they should have a significant fall in the course of their disease.

HANDEDNESS AND BONE MASS.

The following discussion will relate to the symmetry of changes in RA, and will also reflect the bone changes seen at other sites. In addition, the radiological features associated with RA will also be addressed in relation to the changes in metacarpal bone mass and the carpo-metacarpal ratio.

Analysis showed that 98% of the normal controls were right handed while 10% of the patients with RA were left handed. The right 2nd metacarpal was selected to enable comparison with other studies (Barnett and Nordin 1960). It has been shown that involutional bone loss is symmetrical (Dequeker 1976). Similar studies in RA have been neglected. Therefore, the groups were compared using the diameters at the left 2nd metacarpal as well. There were no significant differences between the 2 sides ($p > 0.05$). Similar comparisons using the other metacarpals on either side also showed symmetrical changes. This would suggest that the osteopaenia detected in this study was not due to the left-handedness of some of the subjects.

The following scatter plots (Fig 21 - Fig 23) were constructed from the comparisons of the different measurements between right and left sides using the 2nd metacarpal of each hand.

Figure 21. Scatter plots showing the symmetry of changes in cortical thickness resulting from RA. The figure demonstrates that measurements of one hand closely reflect those of the other.

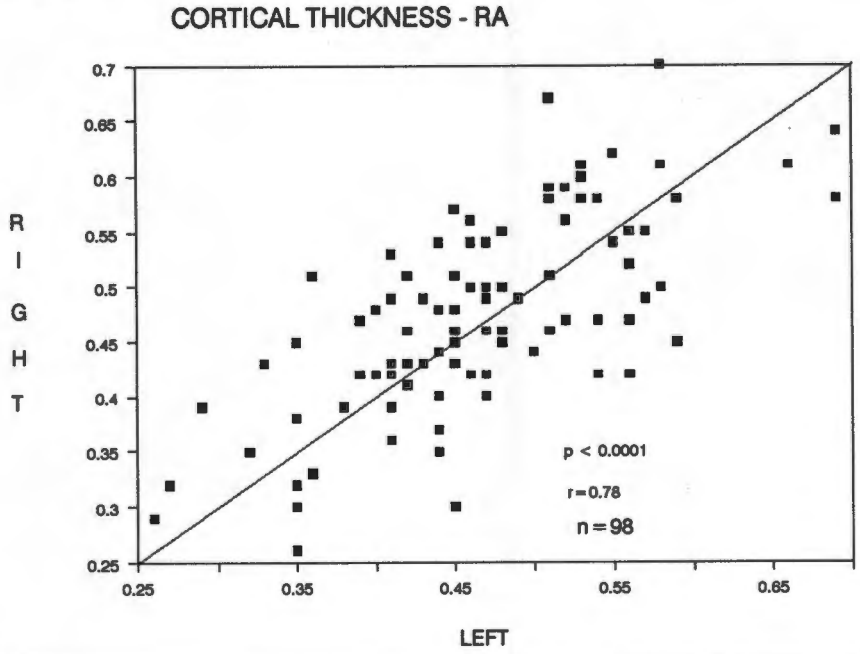


Figure 22. Scatter plots showing the symmetry of changes in total width resulting from RA.

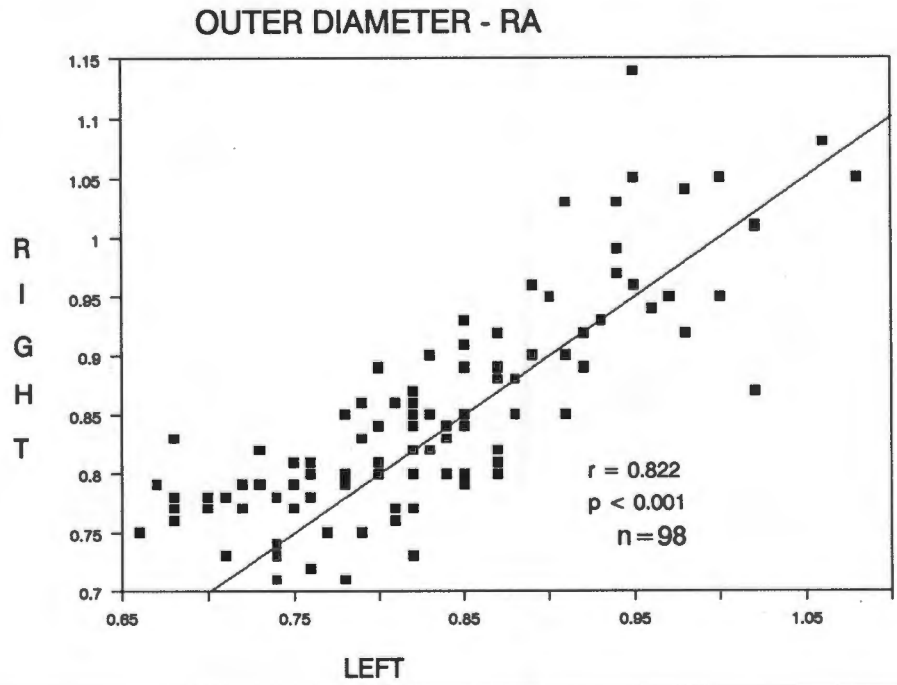
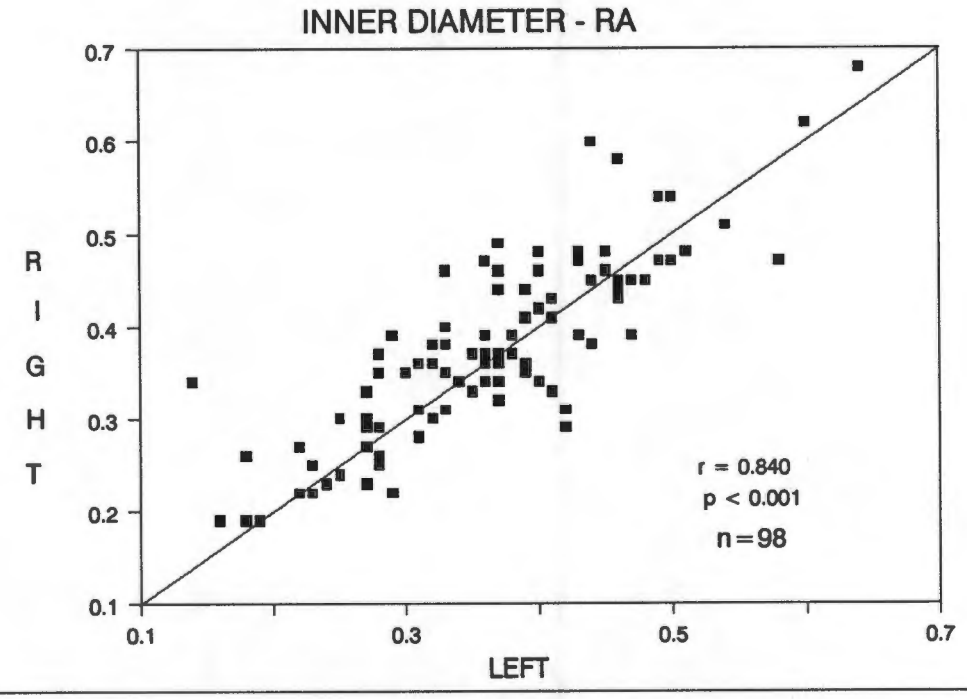


Figure 23. Scatter plots showing the symmetry of changes in medullary width resulting from RA. The figure shows that measurements of one hand closely reflect those of the other.



These findings confirm the symmetry of radiological changes in the hands of patients with RA (Ropes *et al* 1958; Pitt 1986). The differences between the 2 sides were not statistically significant ($p > 0.05$).

RADIOLOGICAL CHANGES OF RA.

These included an analysis of erosions, joint space narrowing (JSN), loss of allignment and ankylosis. The methods used in this study have been reviewed. Difficulties related to reproducibility were not tested, but were overcome by confining the analysis to a single observer, who read all the X-rays.

MODIFIED LARSEN INDEX AT RIGHT WRIST.

The Larsen Index at the wrist has been modified (Larsen 1983), since it was first described (Larsen 1972). Several scoring methods have been described for measurement of radiological changes in RA (Scott *et al* 1985, Larsen 1972, 1974, 1977, 1979). These have been shown to be reliable and reproducible (Sharp *et al* 1985). The changes in the wrists have been shown to correlate with changes in the periphery (Scott *et al* 1986), and for this reason the right wrist was the only area graded by the Larsen index (1977).

The author scored the wrist according to the modified Larsen index (1983), recording the global impression of changes at the right wrist. These are shown in Table 23. The standard radiographs of Larsen were used for the evaluation. The intra-observer error was not studied.

Table 23. Modified Larsen index at the right wrist in 96 subjects with Classical or Definite RA.

Larsen Grade	Features	Number
1	JAOP	30
2	JSN	10
3	Erosions	21
5	Ankylosis	37

It can be seen from table 23 that 37% of our patients had severe destructive disease (erosions with ankylosis). Thirty percent of the radiographs showed juxta-articular-osteoporosis (JAOP), while 10% showed joint space narrowing (JSN) as well (Larsen grade 1 & 2), giving a total of 58% with severe radiological change (grades 3-5). This is an important point, since it shows that more than a third of this group of patients with RA had mild radiological disease, comprising the group in whom the Larsen index is least reproducible (De Carvalho 1981). This is the group in whom more reproducible radiological measures (such as radiogrammetry) might have a useful role in RA (Pullar and Capell 1985 and 1986). This is particularly significant with respect to longitudinal studies, where a change from one grade to another may be important in management (De Carvalho 1981).

The correlation matrix depicted in table 24 shows that the modified Larsen index at the right wrist correlated significantly with the CA% as well as the 6 metacarpal hand scores ($p < 0001$). In fact, 20% of the variation in bone mass is explained by

variation in the Larsen index ($r = 0.45$; 0.43). This suggests that the 2 groups of variables (disease severity and bone mass) are a reflection of a related pathogenetic mechanism. However, the correlation is far from perfect, suggesting that the basic mechanisms responsible for these changes are sufficiently different to be monitored separately. This finding needs to be interpreted with caution, since the the Larsen index represents a 5 point scale, whereas the bone mass represents a continuous variable. The use of a rank correlation (non-parametric test; Spearman), makes the finding statistically acceptable and important. As expected, patients with more severe Larsen grades at the wrist had a lower bone mass.

Table 24. The modified Larsen index at the right wrist was correlated with the metacarpal bone mass, using a single metacarpal and the sum of six metacarpals. The r value is depicted in the upper triangular matrix and the p value in the lower triangular matrix.

	Larsen	CA%	M6HS
Larsen		-0.45	-0.43
CA%	0.0001		0.9
M6HS	0.0001	0.0001	

Other studies have related bone mass changes in the metacarpals to erosive changes in the PIP and MCP joints, but not at the right wrist. One study (Castillo *et al* 1965), showed that cystic bone changes were seen more commonly in males, who generally had a higher bone mass. Osteopaenia was more common in females, who generally had less severe changes and were thought to be less active, physically. However, no attempt was made to substantiate their claim by relating the changes to ac-

tual differences in strength in the fingers and wrists. Another study (Reid *et al* 1988), showed good correlation between erosive change (at the PIP and MCP joints) and metacarpal bone loss. Trentham and Masi (1976) and Alarcon and Koopman (1985) compared the CMR to the Larsen index at the wrist, but not with metacarpal bone mass, so these results cannot be compared with the other reports.

The Larsen index reflects a combination of bone loss and loss of cartilage. There is some suggestion that these processes occur independently of each other (Scott 1985), so that both need to be measured separately. If metabolic processes control erosions, loss of bone mass *may* represent the earliest detectable stage of such a process. This suggestion is confirmed by our finding of statistically significant negative correlations between the Larsen index at the right wrist and the CA% of the right 2nd metacarpal. However, erosions are seen in the early stages at the margins of bone, yet our patients showed a more significant change in medullary width. It is possible that the correlation between Larsen index, erosions and outer diameter are more significant in comparisons at the respective sites, ie, MCP and PIP joints. These need to be evaluated in future studies. Radiogrammetry techniques for evaluating bone mass at the wrist have not been devised.

In an attempt at further evaluating the relationship between the Larsen index at the wrist and metacarpal bone mass, pairwise comparisons were performed between the Larsen groups and between each Larsen grade and the normal controls, with respect to medullary, total and combined cortical width at the right 2nd metacarpal; sum of 6 metacarpal diameters and cortical widths; CA% and M6HS (Table 25). The total width (right 2nd) was not significantly different across groups or in comparison

with the normal controls. Patients in the milder grade 1 had significantly smaller medullary widths than those with a more severe grade 5. Only the patients with grade 5 Larsen index had a significant increase in MW compared with the controls. The combined cortical width (right 2nd) was significantly different between the groups. Only groups 2 and 5 were significantly different from the normal controls. Identical findings were seen in the comparisons with the sum of 6 diameters.

Table 25. Mean bone mass of various Larsen grades as well as normal controls. Comparisons were made between groups and against the normal control subjects.

Measure	Larsen 1	2	3	5	Control
TW_D	0.34	0.37	0.36	0.42	0.32
CCW	0.53	0.47	0.52	0.41	0.54
CA%	81.57	76.27	78.54	71.55	85.15
M6HS	59.96	55.87	57.91	50.36	62.46

When the same groups were analysed with respect to metacarpal bone mass (CA%, M6HS), slightly different results were seen. Compared with the normal group, Larsen grades 2-4 had a significantly lower CA%, but only grade 4 had a lower M6HS. Grades 1 and 4, as well as grades 3 and 4 had significant differences in CA% and M6HS.

CARPO-METACARPAL RATIO.

The carpo-metacarpal ratio (CMR) has been recommended as a useful measure of severity in RA. Trentham and Masi (1976) showed that the ratio falls as a result of a shorter carpal length in patients with RA (n = 123). This fall in carpal length is probably due to a loss of cartilage between the carpal bones. Table 26 is a summary of the carpal length, metacarpal length and CMR in RA patients compared with normal controls.

Table 26. Comparison of carpal length, metacarpal length and CMR in RA and normal controls.

Measure	RA Mean (SD)	Control Mean (SD)	*p* value of Difference
Carpal Length	2.99 (0.54)	3.44 (0.26)	0.0001
Metacarpal Length	6.356 (0.47)	6.298 (0.41)	NS
CMR	0.46 (0.08)	0.55 (0.04)	0.0001

The findings in this study confirm that the CMR is significantly reduced in RA. The table also shows that cartilage loss is a significant component of the radiological change in RA. It can be seen from the table that the carpus is shorter in patients with RA. This is most likely due to the loss of joint space. The table also shows that the carpal length is the main determinant of the difference in the ratio between the 2

groups, although the metacarpal length was slightly increased in the RA group. The reason for the apparent differences in metacarpal length is surprising and difficult to explain adequately. It may have been due to difficulties in defining the ends of the bone in those patients with severe erosive change, or resorptive arthropathy (Mody and Meyers 1988).

In the studies of Trentham and Masi (1976) and Alarcon and Koopman (1985), it was shown that the CMR was a useful monitor of disease progression in RA. They have also claimed it to be a more objective and reproducible measure than the Larsen index. The mean ratio for our normal controls was comparable to that of Trentham's control group. The patients in Alarcon's report had a mean CMR which was higher than that of our subjects. These 2 radiological methods measure similar events, since the variation in the Larsen index at the wrist explained 25% of the variation in CMR ($r = 0.495; p < 0.0001$), in the patients under study.

The other studies have not measured bone mass, so that the relationship between the CMR, Larsen index at the right wrist and bone mass in the hands has not been previously explored. Table 27 shows these relationships.

Table 27. Correlation matrix showing a comparison of the relationship between the Larsen index at the right wrist, CMR and metacarpal bone mass (CA%).

	CMR	Larsen	CA%	M6CA
CMR		0.49	0.2	0.17
Larsen	0.0001		-0.45	-0.43
CA%	0.045	0.0001		0.9
M6CA	NS	0.0001	0.0001	

The finding of a significant correlation between the Larsen index and the CMR has already been referred to above. There was no significant correlation between the CMR and the 6 metacarpal hand score (M6CA%) ($p > 0.05$). The CA% just attained significance at the 5% level ($p < 0.045$), but explained only 4% of the variation in CMR. This is easy to understand, since the metacarpal indices reflect bone metabolism and the CMR reflects both cartilage and bone metabolism. It is likely that the effect of RA at the wrist manifests cartilage loss to a greater extent than bone loss. Not surprisingly, there was a good correlation between carpal length and CMR ($r = 0.88$). It is also possible that the effects of the disease were disproportionately greater at the wrists than at the metacarpals (Sharp 1985). This is reflected in the significant correlation between CMR and the modified Larsen at the right wrist.

FEMORAL CORTICAL WIDTH and FEMORAL INDEX.

Two of the patients with RA had bilateral hip prostheses inserted for hip failure. Their measurements were excluded from the calculation of the mean and SD (n = 96). Table 28 shows the differences between the normal controls and the patients with RA.

Table 28. Femoral cortical width (cm) and femoral index in RA and normal controls.

Measure	Mean Control SD	Mean RA SD	*p* value
Femoral Width	1.137 (0.28)	0.998 (0.27)	0.001
Femoral Index	0.88 0.24	0.84 0.21	NS

The table shows that although the cortical width at the femur was significantly lower in patients with RA, the femoral index was not significantly different between the 2 groups. Fredensborg and Nilsson (1977), suggested that the index was a useful predictor of femoral neck fracture. This may be one reason why none of the patients in the present study demonstrated fractures of the femoral neck at the time of study. A longitudinal study is needed to evaluate this relationship more carefully. Perhaps

the patients with significantly reduced femoral bone mass are the ones who would fracture or experience complications from their prosthetic implants at a later stage in the disease.

Patients with RA are known to be more susceptible to stress fracture (Fam *et al* 1983). It has been suggested that this increased risk is related to bone loss in the femur. However, since the factors leading to fractures are not entirely understood (Cummings 1985; Cummings *et al* 1985), a prospective study would be required to ascertain whether the fall in femoral cortical width plays a significant role in fracture incidence in RA. There is still controversy regarding the relationship between bone mass and femoral neck fracture in post-menopausal subjects (Cummings 1985).

It has been suggested that the bone loss of RA is generalised (Kennedy *et al* 1975). Therefore, the changes at the right second metacarpal, right wrist and both hands were compared with changes in bone mass at the left femur, using a correlation matrix.

The correlations in the normal controls were first tested to establish a baseline. The inner (MW) and outer (TW) diameters as well as the combined cortical width (CCW) at the right 2nd metacarpal, showed no significant correlations with femoral cortical width or the femoral index. The sum of these diameters in six metacarpals also failed to show any significant correlation. When bone mass (CA, CA%, CA/SA, M6HS) in the hands was correlated with the femur, again no significant correlation could be demonstrated in these normal subjects.

In patients with RA, as shown in table 29, the femoral cortical width showed significant correlations with TW and CCW at the right 2nd metacarpal, as well as the sum of the cortical widths of 6 metacarpals. However, the correlation with MW was not statistically significant. Since the inner diameter (MW) was the most significantly affected in the RA group, it is not surprising that a negative correlation existed between femoral width and medullary width. This suggests that an increase in medullary width at the right 2nd metacarpal (cortical thinning) is accompanied by a fall in femoral cortical width, lending support to the concept that generalised bone loss is seen in RA (Kennedy *et al* 1975). These findings suggest that the same mechanism causing periosteal resorption is responsible for femoral cortical resorption, but is different from that causing endosteal resorption in RA.

Table 29. Correlation matrix (Spearman) of metacarpal midshaft diameters and femoral cortical width measurements, showing r value in the upper and p value in the lower row, in patients with RA (n = 96).

Metacarpal Measure		Femoral Width	Femoral Index
TW	(*r*)	0.24	0.21
	(*p*)	0.018	0.039
MW	(*r*)	-0.03	-0.02
	(*p*)	NS	NS
CCW	(*r*)	0.2	0.2
	(*p*)	0.05	0.05
Σ (CCW)	(*r*)	0.22	0.2
	(*p*)	0.03	NS

The comparison with bone mass at the metacarpals and radiological changes at the right wrist are shown in table 30. Although the metacarpal bone mass calculations (CA%,CA/SA,M6HS), showed no significant correlation with femoral bone mass in RA, the Larsen index at the right wrist showed significant correlation with the left femoral cortical width ($p < 0.003$). However, the variation in the Larsen index explained only 9% of the variation in femoral width ($r = 0.29$). The negative correlation confirms that the femoral width is significantly lower in patients with severe wrist disease. The femoral index, on the other hand, correlated less significantly with the Larsen index ($p > 0.05$), and explained only 4% of the variation in the Larsen index ($r = 0.2$) at the right wrist.

Table 30. Correlation matrix of calculated metacarpal bone mass and femoral cortical width, showing r value in the upper and p value in the lower row, in patients with RA (n = 96).

Metacarpal Measure		Femoral Width	Femoral Index
CA %	(*r*)	0.16	0.01
	(*p*)	NS	NS
CA / SA	(*r*)	0.06	0.12
	(*p*)	NS	NS
M 6 HS	(*r*)	0.02	0.01
	(*p*)	NS	NS
Larsen	(*r*)	-0.3	-0.1
	(*p*)	0.00	NS
Carpal Length	(*r*)	0.22	0.23
	(*p*)	0.02	0.02
CMR	(*r*)	0.01	0.08
	(*p*)	NS	NS

The carpal length correlated significantly with both the femoral cortical width and the femoral index. This finding supports our earlier suggestion that bone and cartilage loss occurs concurrently in RA. An alternative explanation for these correlations would be that severe disease in the wrists was a reflection of generalised severity, resulting in reduced weight-bearing activities in such patients.

The CMR, unlike the Larsen index or carpal length at the right wrist, showed no correlation with the femoral cortical width or femoral index ($p > 0.05$). The result shows that the generalised bone losing effect seen in these patients is reflected to some degree in the severity of the changes observed at the right wrist. Scott *et al* (1986), indicate that examination of the hands and wrists alone gives a good overall indication of both the extent of overall joint damage in any given time and the rate of progression of damage. The wrists are also often the most severely affected area in other series (Sharp 1985). Our findings support these suggestions.

The practical implications of this finding are of potential importance in RA. They show that the Larsen index at the right wrist and metacarpal bone loss may be used to infer cortical changes further away in the skeleton, particularly the left femur. The implications regarding the prediction of femoral neck fractures and loosening of prostheses needs to be evaluated in longitudinal studies.

TRABECULAR BONE MASS MEASUREMENT.

METACARPAL (JUXTA-ARTICULAR OP.)

Juxta-articular osteoporosis (JAOP) is defined as the loss of bone adjacent to the joint capsule. The radius is considered to have trabecular bone at its proximal end at the carpus, and cortical bone more distally at the midshaft or one third up. This has been the basis of a number of SPA studies comparing cortical and trabecular changes (Dykman 1984), and probably applies to the metacarpal as well. The radiological definition is largely subjective. Larsen *et al* (1977) regarded osteoporosis as the earliest change and used reference films in the assessment. They commented that compatible appearances may occur without arthritis in old age, Sudeck's atrophy, etc. The subjective nature of such a method of diagnosis of osteoporosis in the hand was shown by De Carvalho (1981). In the present study, JAOP was regarded as that stage which was abnormal, but no erosions or JSN was present. It was thought to be present at the metacarpals in all the RA subjects (Table 4), but at the right wrist in only 30% (Table 23).

There is no objective method of measuring JAOP radiologically. Horsman *et al* (1977) reported the use of a semi-automated computerised technique for 6 metacarpal bone mass measurement, but were unable to improve the observer error. Our study has shown that the metacarpal bone mass is highly reproducible using a digitiser. A comparison between metacarpal diameters in normal controls and RA subjects considered to have JAOP at the right wrist, as defined above, showed that CCW

was significantly lower in the group with JAOP. This suggests that bone mass in the patients with JAOP was significantly lower than in normal controls and that it can be objectively measured. One might infer from this that cortical and trabecular bone loss occurs concurrently in the hands of patients with RA. Since metacarpal bone mass measurement is objective and reproducible, it could serve as an important measure of disease status in patients with early disease. Digitised radiogrammetry *may* fulfill the need addressed by Pullar and Capell (1986).

FEMUR.

THE SINGH INDEX.

The Singh index at the left femur has been shown to correlate with vertebral changes in patients with postmenopausal OP (Singh *et al* 1972). Surgery obviously produces changes in bone structure, so the patients with surgery to both hips were excluded. In the case of surgery to the left hip only, the right hip was used for measuring the Singh index, as described earlier. The grades of porosity are shown in table 31. This index in our patients was above the level which Singh associated with an increased risk of spinal fractures, suggesting that none of the patients had detectable trabecular bone loss. The significance of this finding needs to be interpreted against the background that 30-50% of trabecular bone needs to be lost before it is detected visually.

Table 31. Singh index at the left hip in 96 patients with RA and 72 with SLE.

GRADE	RA	SLE	NORMAL
7	91	55	98
6	2	11	0
5	1	6	0
4	1	0	0

The Singh index is not useful in patients with OA due to the severe changes from the disease (Dequeker 1983). In the current group of RA patients, this did not prove to be a major problem. This is likely to be due to our selection of ambulant patients, most of whom were unlikely to have major hip pathology.

The correlation between CMR and the Singh index did not reach statistical significance ($p > 0.05$). The Larsen index also showed no significant correlation with the Singh index of trabecular bone loss, suggesting that the metabolic effects on cortical bone are probably more significant in RA than on trabecular bone. However, since the responses of cortical bone cells are identical to those of trabecular bone cells *in vitro* (Kaplan 1987), these apparent differences are likely to be due to differences in the relative sensitivities of the measuring techniques used.

LUMBAR VERTEBRA.
VERTEBRAL INDEX.

The vertebral index of Saville was also not significantly different in the groups, as shown in table 32. Again, the patients in this study were found to have an index which was above that associated with increased risk of spinal fractures. As discussed earlier with respect to the Singh index, these findings may reflect the insensitivity of the method rather than indicating differential rates of bone loss in trabecular and cortical bone. However, the different metabolic rates in the 2 areas of bone may explain some of these findings.

Table 32. Vertebral index of Saville at L3 in 96 patients with RA, 72 with SLE and 98 control subjects.

GRADE	RA	SLE	NORMAL
1	76	31	91
2	14	25	8
3	6	6	0

It has been previously shown that vertebral bone loss needs to exceed 30% before it is detectable on X-ray. In the absence of DPA, which is possibly the most sensitive method for detecting early vertebral loss, no further comments are possible regarding changes in trabecular bone.

Saville and Kharmosh (1967) showed that vertebral porosity increased as cortical thickness decreased. The correlations reached significance in patients over the age of 50 years (n = 164). Bjelle *et al* (1970), measuring multiple sites such as the metacarpal, radius, femur and lumbar spine, found a decrease in bone mass at all sites except the vertebrae, in patients with RA. Although the femoral cortex was thinner than in age-matched normal controls, the difference was not statistically significant. Their study included subjects over 50 years of age (range 20-65; mean 47 years). They concluded that weight-bearing and physical activity were important determinants of this difference, but did not quantitate the degree of physical activity in their patients or normal controls.

Kennedy *et al* (1975), measured cortical thickness at the metacarpal, clavicle and femur. They found that the clavicular cortical thickness was lower in all age groups,

but that statistical significance was attained only in males between 55 and 65 years of age. They found a good correlation between metacarpal (MCI) and femoral cortical indices (FCI). The MCI and FCI were both lower than the clavicular cortical thickness; this study confirming the suggestion by Saville and Kharmosh (1967), that age is an important factor in the genesis of bone loss in RA. Perhaps our finding of grade 3 vertebral changes in 6 subjects each with RA and SLE is highly significant, particularly if one considers the age group of the subjects. This group is too small for further statistical analysis.

Studies after this period have used the more sophisticated techniques for measurement of bone mass (SPA, DPA, NAA). They are, therefore, not suitable for comparison with the findings in this thesis. In the present study, metacarpal bone mass did not correlate significantly with trabecular bone changes at the hip or the third lumbar vertebra.

These later studies of trabecular bone using DPA (Sambrook *et al* (1987) have generally been marred by the lack of control for age and menopausal status. In the post-menopausal female with RA, disease does not seem to significantly influence the effects of age and the menopause on normal bone loss. Larger groups of pre-menopausal subjects with RA need to be evaluated using DPA, in order for these relationships to be more carefully analysed. Studies in RA using DPA must ultimately be related to metacarpal measurements, since the hand radiograph is probably the single, most useful investigation in the evaluation of patients with RA. Reid *et al* (1986) observe that the differences in TBCa measurements between RA subjects and

normal controls, matched for age and menopause, is largely due to the disproportionate metacarpal loss associated with RA.

BONE LOSS IN SLE.

This study was carried out at 2 different hospitals. Patients with SLE were seen regularly at the Lupus clinic at GSH. The normal controls and the patients with RA had their X-rays at PAOH. Since the major discussion revolves around the radiological changes, it was important to establish that the methods were comparable in the 2 centres. In order to test reproducibility, the phantom phalanx was included on most X-rays. The same mould was used at both institutions and comparisons were made between six X-rays from each centre. The analysis of variance showed that the differences between the measurement of CCW at the 2 centres was not significant, as previously shown in Table 13.

Involvement of the musculoskeletal system in SLE is one of the earliest and most frequent manifestation of the disease (Labowitz and Schumacher 1971). The degree of involvement may range from minor arthralgias or soft-tissue calcification to severe deforming arthritis (Alarcon-Segovia *et al* 1988) with multiple ruptured tendons (Cooney *et al* 1980). Although any joint can be involved, the knees, wrists and small joints of the hands are most common. Usually there is symmetrical involvement but up to 25% have asymmetrical disease. Deforming arthritis occurs in up to 30% of cases of SLE with arthritis, but hand deformities are rare and seen in 4-8% of patients (Bywaters 1975; Harvey *et al* 1954). Surprisingly, the development of these deformities most often occurs with little evidence of inflammation and may occur with

relatively little pain. This pattern of non-erosive, deforming disease has been referred to as Jaccoud's syndrome (Bywaters 1975).

Sometimes, hook-like erosions of the metacarpal heads are seen late in the disease. Radiologic findings are usually few. There may be periarticular or diffuse OP. Soft-tissue swelling may be present, but typically there are no erosions, even when severe deformities are present (Weissman *et al* 1978).

Despite these disabling effects of SLE and the increasing use of CS therapy for the control of this disease, systematic measurements of bone mass in SLE are lacking. Textbooks (Dubois 1966; Schur 1983) contain empirical statements that OP is rare in SLE and usually associated with CS therapy. The need for objective evaluation of bone mass in SLE becomes important with improved outcome of this disease (Studenski *et al* 1987), since more of these patients are likely to reach the menopause. Avascular necrosis of the femoral head is seen in 7% (Kalla *et al* 1986) and Lindsay *et al* (1976) have shown the importance of bone mass measurement in predicting this complication in renal transplant subjects.

METACARPAL BONE MASS IN SLE.

Pairwise comparisons between the normal controls and patients with SLE showed that these patients are also significantly osteopaenic, as shown in table 33.

Table 33. Bone Mass in 72 patients with SLE, showing significant differences compared with normal controls.

Measurement	Mean Control (SD)	Mean SLE (SD)	*p* value
CCW	0.59 0.089	0.552 0.092	0.01
AI	0.5893 0.089	0.5522 0.092	0.01
MI	0.1077 0.014	0.1062 0.012	NS
CA	0.4630 0.069	0.4339 0.072	0.01
CA%	85.1880 6.872	82.7149 7.569	0.04
CA / SA	0.0280 0.002	0.026 0.003	NS
6 MHS	62.5261 7.959	61.411 7.828	NS

The reason for introducing this second group of controls was to ensure that the differences found in the RA group were not necessarily due to a chronic disease. The degree of bone loss was much less than in patients with RA (see Table 16). Normalisation of bone mass removed the statistical significance of these differences. Since the CCW is significantly reduced in SLE, it needs to established whether the fall is due to periosteal or endosteal resorption (Dequeker 1972; Horsman *et al* 1977).

When multiple groups are compared, the *p* value needs to be adjusted accordingly. Duncan's multiple range test corrects for this Bonferroni effect. Table 34 was constructed by this statistical method, and showed that the two patient groups (RA,SLE) were similar with respect to CA, but they were significantly osteopaenic compared with the normal controls ($p < 0.01$). However, CA%, M6HS and M6CA% were similar between the normal controls and subjects with SLE, but the patients with RA had significantly lower values ($p < 0.001$).

Table 34. Duncan's multiple range test for comparing 3 groups. The probability (p value) is appropriately adjusted for multivariate comparisons (Bonferroni). The symbols (A, B, C) relate to significant differences between the means ($p < 0.05$).

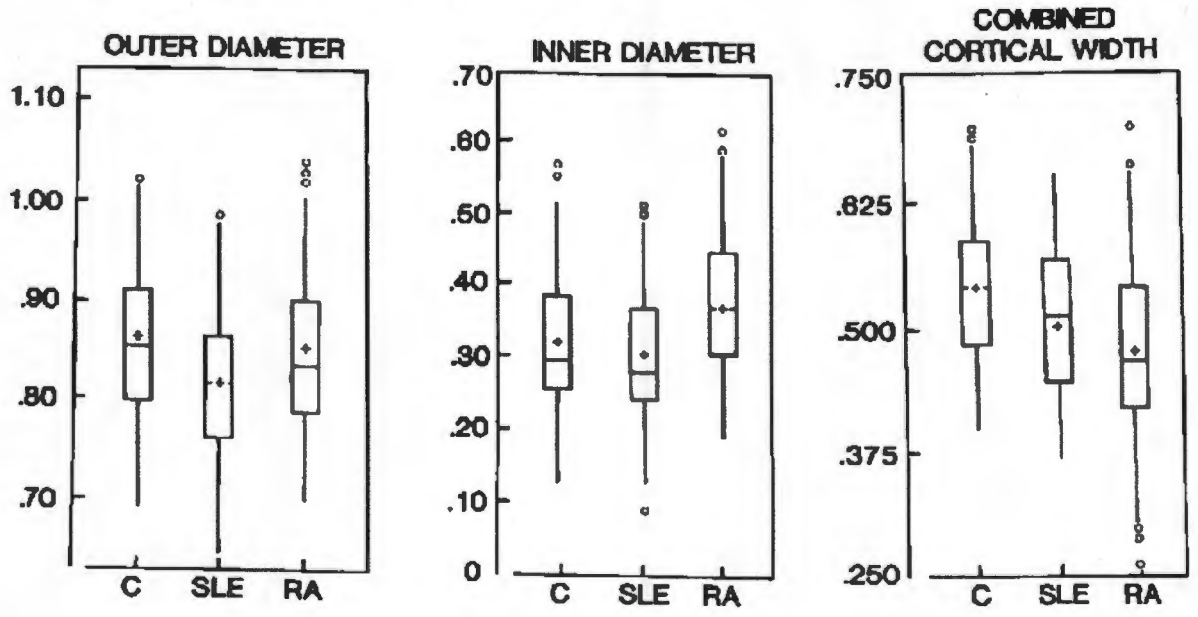
Measure	Control	RA	SLE
Σ TW^2	A	A	B
Σ MW^2	B	A	B
Σ CCW^2	A	B	B
AI	A	B	B
MI	A	B	C
CA	A	B	B
CA%	A	B	A
CA/SA	A	B	C
M6HS	A	B	A
M6CA	A	B	A
Carpus	A	B	C
CMR	A	B	C

The area index (AI) was also comparable between the RA and SLE groups, but significantly lower than the normal controls ($p < 0.01$). The right 2nd metacarpal index (MI), was significantly different between the 3 groups ($p < 0.001$). The ratio of the cortical area to the surface area (CA/SA) was also significantly different between the 3 groups ($p < 0.001$).

These findings show that, although RA and SLE both cause a fall in combined cortical width (CCW), the pathogenesis is different in the 2 diseases. Dequeker (1983) has shown that RA, similar to post-menopausal OP, causes an increase in MW. The fall in TW is usually a feature of diseases like hyper-parathyroidism and CS therapy. In the current study, PTH levels were not measured in the subjects with SLE. Ionised calcium Ca^{2+} levels were elevated in 49% of the RA group (normal PTH) and only 10% of the subjects with SLE. The mechanism of the elevated calcium in RA is likely to be multi-factorial and will be discussed later. The significance of the marginally elevated Ca^{2+} in SLE is not known.

When TW and MW are evaluated with regard to their respective contributions to cortical thinning in the 2 diseases, it can be seen from the box plots depicted in figure 24 that SLE causes periosteal resorption while RA causes endosteal resorption. Both diseases are associated with significant cortical thinning.

Figure 24. Box plots of the inner diameter (MW), outer diameter (TW) and combined cortical width (CCW) in 3 groups of subjects. The box represents 75% of the readings and is divided at the mean, while the cross represents the median for that group. The lines complete the representation of the range of values.



Our findings suggest that the pathogenesis of bone loss (MBD) in SLE needs to be more carefully evaluated. Hyperparathyroidism is said to be uncommon in SLE, so it is possible that a PTH-like substance is responsible for the changes described. The small number of patients with elevated Ca2+ in this series mitigates against this mechanism. Perhaps IMO exerts its effects through IL-1 and other local mediators of bone resorption in this disease. These hypotheses need to be more carefully studied. There is experimental evidence that synovial cells from patients with these 2 diseases behave similarly *in vitro* (Seitz and Hunstein 1985). These findings become important in the light of the evidence that survival of these patients is considerably improved (Studenski *et al* 1987).

CARPO-METACARPAL RATIO.

Table 35 shows that the CMR was also significantly reduced in patients with SLE. This is the first study where the ratio has been measured in SLE, so the significance of the changes is not clear. Although the arthritis of SLE is considered to be less severe than in RA (Cronin 1988), wrist involvement is probably a significant component of the joint disease in SLE. This was corroborated by our finding that although 93% of the SLE patients complained of joint symptoms, the Keitel score was much lower than in RA. In fact over 80% of the variation in total KFT could be explained by disease of the hands and wrists (see Table 49).

Table 35. Comparison of carpal length, metacarpal length and CMR in SLE and normal controls.

Measure	SLE Mean (SD)	Control Mean (SD)	*p* value of Difference
Carpal Length	3.17 (0.25)	3.44 (0.26)	0.0001
Metacarpal Length	6.28 (0.43)	6.298 (0.41)	NS
CMR	0.51 (0.04)	0.55 (0.04)	0.0001

Table 36 shows the comparison between CMR and metacarpal diameters. In the group with SLE, the CMR showed significant correlation with the MI at the right 2nd metacarpal ($r = -0.3$; $p < 0.02$), but not with any of the other bone mass calculations. However, the CMR showed significant correlations with TW and CCW at the right 2nd metacarpal.

Table 36. Relationships between carpo - metacarpal ratio (CMR) and metacarpal diameters in 98 normal controls, 72 patients with SLE and 96 patients with RA.

Bone Mass Measure.		CMR (Control)	CMR (SLE)	CMR (RA)
MW^2 (d)	(*r*)	0.14	0.14	0.07
	(*p*)	NS	NS	NS
TW^2 (D)	(*r*)	-0.02	0.26	0.19
	(*p*)	NS	0.04	0.05
TW^2 - MW2	(*r*)	-0.07	0.26	0.27
	(*p*)	NS	0.04	0.009
Σ (TW^2 - MW^2)	(*r*)	-0.04	0.11	0.29
	(*p*)	NS	NS	0.004

The carpal length, on the other hand, showed significant correlation with all the metacarpal midshaft diameters in SLE (Table 37) ($p < 0.001$). Since the major contribution to the change in CMR is due to a change in carpal length (Table 35), one might infer that bone and cartilage loss occur simultaneously in SLE. This would support the earlier suggestion that bone resorption in SLE is a manifestation of inflammation.

Table 37. Relationships between carpal length and metacarpal diameters in 96 patients with RA, 72 with SLE and 98 normal controls.

Bone Mass Measure.		Carpal Length (Control)	Carpal Length (SLE)	Carpal Length (RA)
MW (d)	(*r*)	0.28	0.38	-0.02
	(*p*)	0.01	0.003	NS
TW (D)	(*r*)	0.43	0.45	0.39
	(*p*)	0.0001	0.0003	0.0001
$TW^2 - MW^2$	(*r*)	0.41	0.36	0.49
	(*p*)	0.0001	0.005	0.0001
$\Sigma (TW^2 - MW^2)$	(*r*)	0.53	0.39	0.54
	(*p*)	0.0001	0.001	0.0001

In RA, where the destructive effect on the carpus is usually extensive, there was a significant correlation between carpal changes and endosteal resorption. It would seem that unrelated mechanisms govern the bone and cartilage loss seen in these 2 diseases, since the cortical thinning in SLE was entirely due to periosteal bone loss.

Future analysis of these findings may confirm the close relationship between the chondrocyte, osteoclast and fibroblast, particularly in IMO.

Table 38 shows the comparison of the correlation between carpal length and CMR, with metacarpal bone mass. It shows that in SLE (as in RA), bone and cartilage metabolism are affected to differing degrees. Although it is said that radiological changes in SLE are few, it would seem that the carpal length may have some value as a measure of radiological change in SLE. Osteopaenia is probably the result of the systemic nature of the disease and should be included among the systemic complications of SLE.

Table 38. Comparison of the correlation between metacarpal bone mass and carpo - metacarpal ratio in 72 patients with SLE, depicted in a standard correlation matrix.

	Carpus	CMR	CA%	M6CA
Carpus		0.64	-0.27	-0.36
CMR	0.0001		0.06	0.09
CA%	0.04	NS		0.88
M6CA	0.004	NS	0.0001	

It is clear from our findings that RA has a much more profound effect on the carpus than SLE. It would appear, therefore, that the mechanisms leading to loss of bone and cartilage are similar to, but less severe than, in patients with RA. This is the first evidence of cartilage changes in SLE. The arthropathy of SLE is usually non-erosive (Tan *et al* 1982), but ligamentous laxity is common. Jaccoud arthropathy is

well described in SLE (Bywaters 1975), and may be aggravated by hypermobility (Liote *et al* 1987). The mechanisms for subluxation and tendon rupture are not known, but it is possible that cartilage loss explains some of the ligamentous laxity seen clinically.

FEMORAL CORTICAL WIDTH.

The femoral cortical width in SLE was not significantly different from that measured in the normal controls. However, the outer diameter of the right 2nd metacarpal showed a significant correlation with femoral cortical width ($r = 0.3; p < 0.02$). The area index ($r = 0.3; p < 0.02$) and metacarpal index (MI) ($r = 0.33; p < 0.008$) also showed significant correlations with femoral width. Normalisation of bone mass (CA,CA%,CA/SA,M6HS) reduced the correlation between these areas. The statistical significance of the correlation was considerably lower than in the RA group, indicating that patients with SLE lose less femoral bone than patients with RA. However, these findings suggest that the bone loss in SLE is also generalised.

TRABECULAR BONE MASS.

The Singh index and Saville index were not significantly different in the patients with SLE. compared with both the RA group and the normal controls. As in the case of patients with RA, these differences in metabolic events in trabecular and cortical bone may be due to several explanations. These could be due to effects of the disease, or may be a reflection of the sensitivity of the radiological method in detecting early trabecular changes.

Osteoporosis has not been an area of systematic research in SLE. Textbooks gloss over it as an insignificant consequence, usually related to CS therapy. It is generally believed that vertebral fractures are uncommon; that the OP is mild and reversible. Our findings show that bone loss in SLE requires more careful evaluation. The relationship with renal disease (2^{o} hyperparathyroidism), inflammation mediated osteopaenia and CS therapy needs systematic evaluation. The mortality has improved over the years and many more subjects are likely to reach the menopause. The impact of OP in this disease is likely to gain prominence. There is a clear need for a search into the mechanisms of bone and cartilage loss in SLE.

FACTORS CONTRIBUTING TO OP IN RA.

DEMOGRAPHY.

RACE.

The effects of race on bone mass are controversial. Reports from America have shown that bone mass in Blacks is significantly higher than in Whites in the USA (Garn 1967a & b; Mayor 1976). South African (SA) studies have shown the reverse; Whites in Johannesburg have a higher bone mass than Blacks of all ages (Solomon 1979). In a study of Coloureds in Rietpoort (SA), no comparison was made with age-matched subjects of other race groups (Meyers 1982), but the bone loss with age showed trends which were comparable with those of the subjects in the Johannesburg and overseas studies.

Coloured females predominated the present study, most probably because the Cape has the largest population of Coloureds in the country. There is no evidence that Coloured females are genetically predisposed to the development of RA. The groups under study were matched with respect to the proportion of Coloured females (Table 15). This study was not aimed at showing differences between the various racial groups, hence the smaller numbers of Black and White subjects. As a group, the two sets were found to be marginally comparable for race, sex and age, for meaningful conclusions to be drawn about differences in bone mass.

This study confirmed the need for *normalisation* of bone mass, as previously reported (Dequeker 1976; Exton-Smith *et al* 1969a). The findings in Table 39 show that even in premenopausal subjects, the AI and CA are significantly different between the sexes. The results of *normalisation* techniques are shown in table 40.

Table 39. Right 2nd metacarpal bone mass in males and females with RA, showing mean and result of comparison of the sexes in the various groups.

Bone Mass	Sex	Mean Control (SD)	Mean RA (SD)	*p* Value of Diff. (M vs F) Control	RA
AI	Male	0.6 (0.09)	0.64 (0.12)		
	Female	0.57 (0.08)	0.51 (0.1)	0.0002	0.0001
MI	Male	0.11 (0.008)	0.1 (0.012)		
	Female	0.11 (0.008)	0.09 (0.014)	NS	NS
CA	Male	0.52 (0.07)	0.51 (0.09)		
	Female	0.45 (0.06)	0.39 (0.08)	0.0002	0.0001

The statistical significance of the difference is diminished by normalisation techniques (Table 40).

Table 40. Effect of normalisation on differences in bone mass between males and females.

Bone Mass	Sex	Mean Control (SD)	Mean RA (SD)	*p* Value (M vs F) Control	RA
CA%	Male	83.56 (7.95)	77.06 (9.41)		
	Female	85.71 (6.48)	76.44 (10.42)	NS	NS
CA/SA	Male	0.027 (0.001)	0.026 (0.003)		
	Female	0.027 (0.002)	0.024 (0.003)	NS	NS
M6HS	Male	59.66 (7.97)	54.3 (8.48)		
	Female	63.44 (7.82)	55.86 (8.83)	NS	NS
M6CA	Male	82.55 (3.1)	78.15 (7.49)		
	Female	84.41 (6.16)	79.3 (8.23)	NS	NS

The M6HS and M6CA were slightly higher for the females in both groups, but the differences were not statistically significant ($p > 0.05$). Similar findings were reported by Wagener and Hough (1987), while others (Solomon 1979) found higher values for males of all ages. The group with SLE had too few males for a valid comparison between the sexes. It is known that patients with SLE are a highly selected group, since the disease has a predeliction for younger females. Coloured females predominated in this group as well, the mean age of the 72 subjects being 31.4 years. This is significantly lower than the RA group but not the normal controls.

When an age and sex-matched comparison was done, the RA females (n = 73) and males (n = 27) remained significantly different from the normal females (n = 63) and males (n = 37; $p < 0.001$), irrespective of the radiogrammetric formula for bone mass calculation. However, when the females with SLE (n = 58) were compared with the normal females (n = 63), only the CA% showed a significant difference ($p < 0.05$).

It would seem, therefore, that age and gender do not make a significant contribution to metacarpal bone loss in RA. Perhaps other factors, such as disease activity (inflammation) and duration contribute to this loss to a greater extent. In post-menopausal subjects with RA, Saville and Kharmosh (1967) showed that age contributed significantly to bone loss. This is not surprising, since the bone loss after the menopause is multi-factorial and is likely to be aggravated by some of the effects of RA (Als *et al* 1985b).

DURATION OF DISEASE.

Duration of disease is generally calculated according to the time of the first acceptable symptoms of a disease. Studies in auto-immune diabetes mellitus, have shown that the immunological process is detectable some time before the onset of symptoms. There must also be a pre-clinical stage in the development of auto-immune diseases such as RA and SLE. It is obvious that attempts at quantitating the duration of disease are often inaccurate, dependant largely on the ability of the patient to recall the exact date at onset of symptoms and patients generally have great difficulty in recalling such events with accuracy.

Table 41 shows that patients with RA had a longer mean duration of disease than patients with SLE. This difference may be largely due to the fact that the RA patients were older at time of study.

Table 41. Some demographic features in 72 patients with Systemic Lupus Erythematosus (SLE) and 96 patients with RA.

	RA Mean (Range)	SLE Mean (Range)	
Age	38.2 (18-50)	31.8 (17-45)	yrs.
Age at Onset	30 (17-49)	25 (10-42)	yrs.
Duration of Disease	96 (6-336)	74 (3-408)	mths.

It has been suggested that the bone loss in RA occurs early in the course of the disease (Sambrook *et al* 1985b). When the present RA group was subdivided at the median duration of disease (78 months), the group with duration less than the median (n = 50) showed a significantly higher CA/SA than the group with duration greater than the median (n = 48; $p < 0.005$). Sambrook *et al* (1985b), showed that bone loss occurred within the first 3 years in their subjects with RA (n = 17). When the present group was subdivided at a duration of disease of 36 months, the CA/SA and the M6HS were significantly higher in the group with duration less than 36 months (n = 26). However, when the CA/SA and M6HS of the patients whose disease had been present for less than 36 months were compared with those of the normal subjects, the difference was not statistically significant. Those with duration less than the median had significantly lower bone mass than the normal controls.

This would suggest that bone loss in RA is progressive, and is significantly influenced by disease duration. In our patients with RA, bone loss became significant only after the disease had been present for more than 3 years. This is in contrast to the findings of Sambrook *et al* (1985b) and Als *et al* (1985b). These findings also contradict earlier suggestions that most of the bone loss in RA occurs early and reaches a plateau, since the loss in our patients was progressive after 3 years. Perhaps these differences are related to the differences in menopausal status of the patients from earlier studies.

The patients with SLE showed no difference when subdivided at the median duration of disease of 54 months (n = 30; $p > 0.0001$). These differences may be related to the fact that disability in SLE is usually not as progressive as in RA.

The following line graphs (Fig 25a,25b, 25c) show the relationship between disease duration radiological changes at the metacarpal, wrist and femur. Figure 25a shows a significant downward trend ($p < 0.05$) in metacarpal bone loss.

A similar downward trend is seen in the loss of carpal length ($p < 0.0001$) in patients with long-standing RA, as shown in figure 25b. The same relationship is shown with respect to the femoral cortical width (Figure 25c) [$p < 0.0001$].

Figure 25a. Line graph showing that there was a significant downward trend in metacarpal bone mass with increasing disease duration.

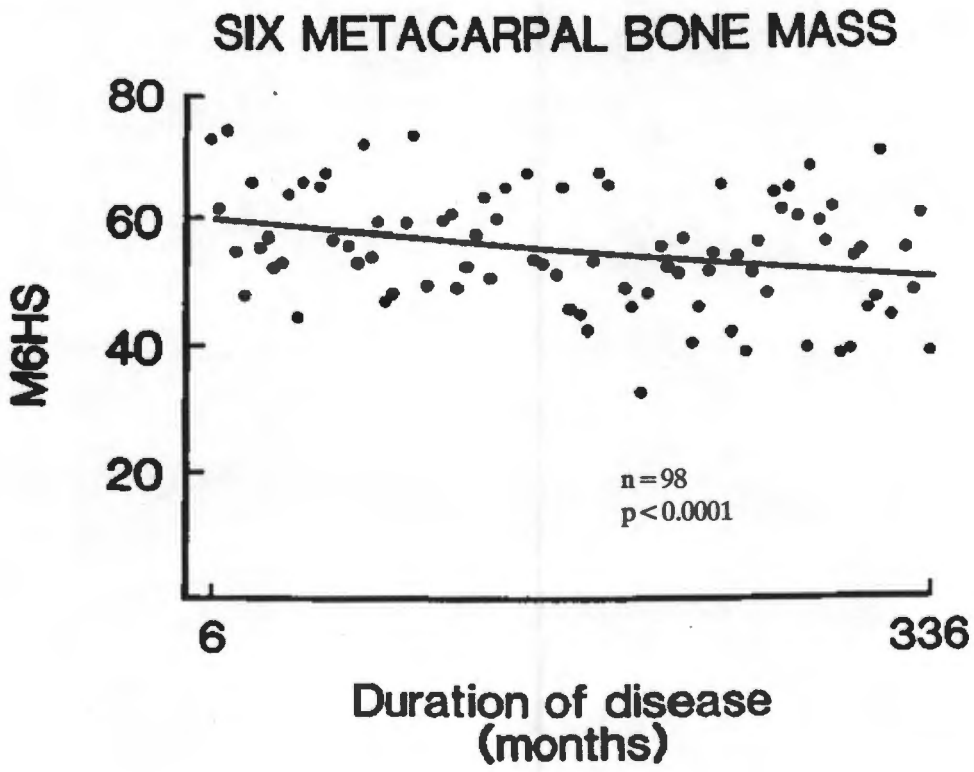


Figure 25b. Line graph showing that there was a significant downward trend in carpal length with increasing disease duration.

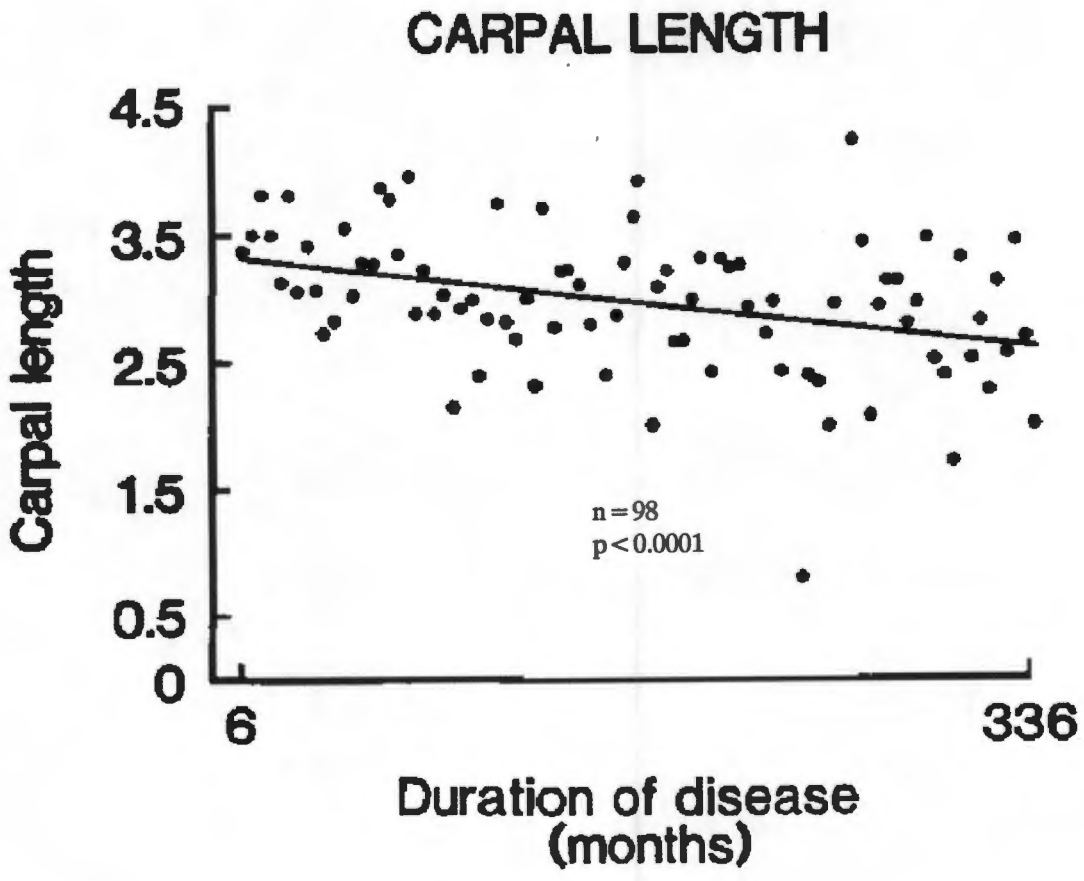
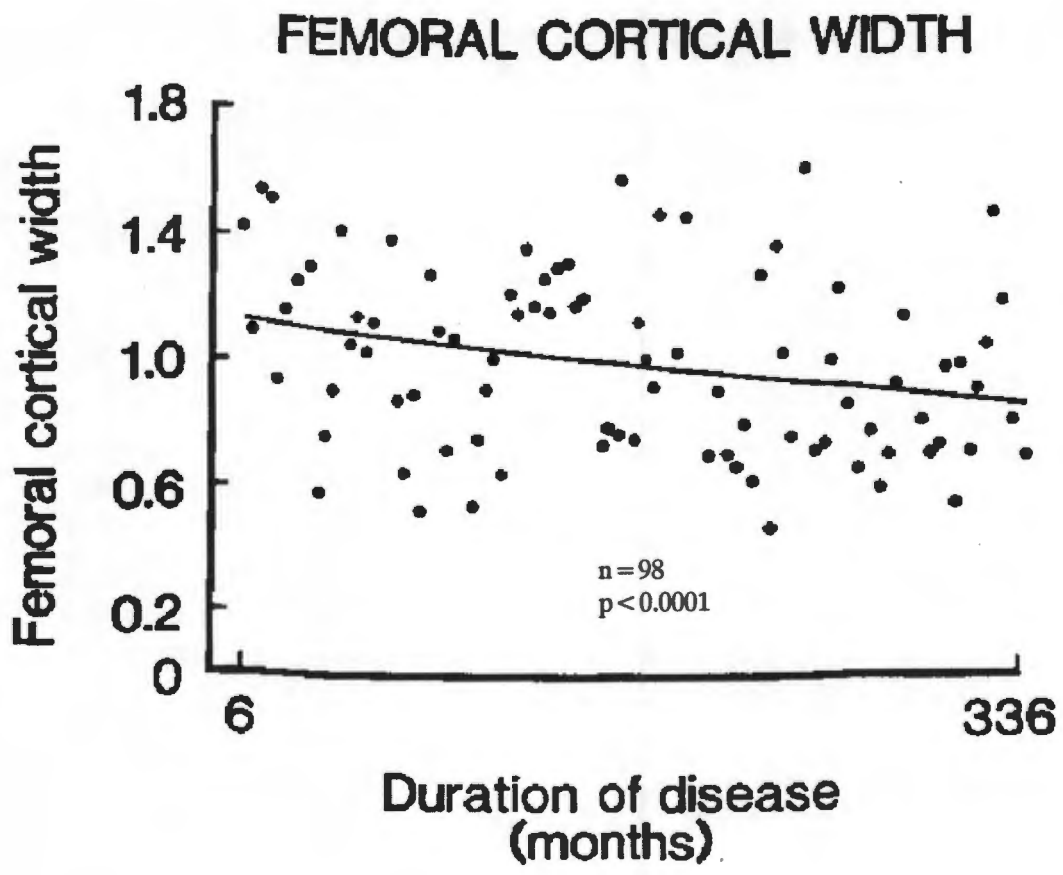


Figure 25c. Line graph showing that there was a significant downward trend in femoral cortical width with prolonged disease.



SOCIAL IMPACT OF RHEUMATOID ARTHRITIS.

RA is known to have far-reaching effects on the activities of daily living. It has been shown that the effects of disability erode the patients' personal relations as well as their work capacity (Brown *et al* 1987; Mody *et al* 1988).

Table 42 shows a comparison of the RA group with the normal controls, showing the marital status and work capacity of the subjects under study.

Table 42. Social characteristics of 100 young subjects with Rheumatoid Arthritis.

		RA	Normal Control
Marital Status			
	Single	27	24
	Married	57	68
	Divorced	15	7
	Widowed	1	1
Employment			
	Full Time	35	100
	Part Time	10	-
	Unemployed	55	-

The control subjects were all employed at the time of study (for obvious reasons). It can be seen from table 42 that more than 50% of the patients with RA were unemployed at the time of study. This is interesting, since the subjects were functionally independent (ARA FC 1 & 2). It is also interesting that twice as many RA patients

were divorced. Details of unemployment and reasons for divorce were not recorded in all cases. Some of the patients volunteered that reasons other than arthritis were responsible for the divorce or unemployment. This value is higher than the 40% of patients unemployed in a study by Brown *et al* (1987), who studied 254 patients of all ages with RA. However, the value is lower than the 76% of unemployed RA subjects reported by Mody *et al* (1988). The differences in these values may be related to inherent differences in the age-range and race of the subjects in the different studies.

DISEASE ACTIVITY.

The role of disease activity in the genesis of the bone loss in RA is controversial. Some studies have shown no relationship between bone loss and disease activity (Virtama *et al* 1968, Reid *et al* 1982), while others (Steven *et al* 1982) have shown a significant relationship. Schorn (1983) showed that patients with RA receiving penicillamine increased their bone mass over a 3 year period of therapy. Although this improvement could have been largely due to improved hand function, it is possible that the anti-rheumatic effects of penicillamine on the inflammatory load had a role in this improvement in bone mass.

Table 43 summarises some of the clinical markers of disease activity in the subjects under study. The ARA criteria for remission (Alarcon *et al* 1987), as well as components of systemic indices (Lansbury and Haut 1958), were recorded in the subjects under study. The features of active disease were divided according to the history, physical examination and laboratory investigations. For the purpose of this discussion, functional assessment will be regarded as a separate evaluation. Various components are selected in developing a systemic index, which is based on a *weighted* evaluation of individual variables (Lansbury and Haut 1958; Mallya and Mace 1981; Bombardier and Tugwell 1982; Dixon and Wright 1986; Bull *et al* 1986).

Table 43. Features in the patient's history which indicate active disease.

Measure		%
Pain VAS (PVAS)	<5	69
	>5	31
Severity VAS (SVAS)	< 5	72
	> 5	28
Night Pain		57
Unable to Work Full Day		54
Fatigue	< 4 Hrs Awake	71
Morning Stiffness	> 45 min	55

The clinical usefulness of many of these subjective variables is limited by the lack of objectivity and poor reproducibility (Wright *et al* 1985; Hart and Huskisson 1972). Dixon *et al* (1988) provide useful guidelines in choosing the *best* measurements for monitoring activity in RA, in the short-term. The visual analogue scales (VAS) show that more than two-thirds of the subjects in this study had pain (PVAS) and severity (SVAS) scores of less than 5 / 10. Fifty-seven percent had night pain. More than 50% felt they were unable to work an 8-hour day. Fatigue was a prominent feature in 71%, while 55% had significant early morning stiffness (EMS).

Recent work has suggested that the patient's global evaluation be made a standard component of disease activity indices used in drug protocols (Meenan and Pincus 1987; Kazis *et al* 1988). Our findings suggest that the patients base their evaluation on different variables compared with standard medical practice. Table 44 shows a comparison of the above variables, in a correlation matrix. All the variables showed significant correlations with each other ($p < 0.01$).

Table 44. Correlation matrix of the comparison of features in the history, suggestive of active disease. (Spearman correlation showing r value in upper and p value in lower triangular matrix).

	SVAS	PVAS	Fatigue	MS
SVAS		0.57	-0.24	0.39
PVAS	0.0001		-0.29	0.41
Fatigue	0.02	0.003		-0.26
MS	0.0001	0.0001	0.01	

The table shows that the patients' overall impression of the severity of disease was closely related to the perception of pain ($r = 0.57$), EMS ($r = 0.39$) and time to onset of fatigue ($r = -0.24$). Patients with active disease developed fatigue within 4 hours of waking. It is interesting that the patients' evaluation of severity correlated significantly ($p < 0.03$) with all the other variables in this cluster, supporting our earlier suggestion that it was a useful index of disease activity.

The clinical measures of disease activity used in this study are summarised in table 45. These variables are also subject to significant observer differences (semi-objective). The findings in this study are based on the evaluation of a single observer, improving their objectivity (Kirwan *et al* 1983a & b; 1988).

Table 45 shows that the subjects under study represented a heterogeneous group with respect to disease activity and severity. The physician's overall assessment of activity is probably a reliable test of activity. It has been shown that therapeutic decisions are largely based on such an assessment (Kirwan *et al* 1983a & b). Forty-four

percent of the patients in this study were considered to have inactive disease, based on the physician's clinical evaluation.

Table 45. Features found on clinical examination which are indicative of active disease.

No. of Warm Joints	Mean	2.76
	Median	3
	Range	(0 - 12)
No. of Swollen Joints	Mean	4.44
	Median	3
	Range	(0 - 21)
Ritchie Articular Index	Mean	18.73
	Median	18
	Range	(0 - 50)
Physician Assessment of Activity	Nil	44
	Mild	30
	Moderate	19
	Severe	7
Modified Lansbury Systemic Index (LSI)	Mean	49.5
	Median	50
	Range	(12 - 107)

The clinical markers of disease activity are compared with each other in the table 46, which follows. The Ritchie articular index (RAI) correlated significantly with all the other variables ($p < 0.002$). The physician's assessment of disease activity correlated significantly with the number of swollen joints, the RAI, and the number of warm joints ($p < 0.004$). The comparison of the correlation with the Lansbury systemic index (LSI) confirms that the physician's assessment of the status of disease

was based on an objective evaluation of the features. Valid comparisons could, therefore, be made on an *active* and *inactive* group, based on the clinician's assessment.

Table 46. Correlation matrix of the comparison of the clinical features of disease activity in RA, with each other. (Spearman correlation showing r value in upper and p value in lower triangular matrix.

	Physician	Warm	Swollen	RAI	LSI
Physician		0.41	0.48	0.45	0.29
Warm	0.0001		0.84	0.25	0.3
Swollen	0.0001	0.0001		0.32	0.33
RAI	0.0001	0.01	0.001		0.61
LSI	0.004	0.003	0.001	0.0001	

Warmth and swelling of joints correlated very closely with each other. Warmth was evaluated subjectively, and the results with the use of thermography have been shown to be even more reproducible and accurate (Devereaux *et al* 1985). Table 46 shows that the physician's overall impression of activity may have been influenced by the number of warm and swollen joints as well as the RAI. The modified Lansbury systemic index (LSI) showed significant correlation with all the other measures of disease activity ($p < 0.01$). However, the RAI explained the greatest proportion of the variation in the Lansbury index ($r = 0.6$), confirming its value as a simple test of disease activity in RA.

The oblique principal component cluster analysis was used to establish the grouping of the clinical variables with respect to each other. The number of warm and swollen joints were separated as a cluster, while the RAI was included with PVAS

and SVAS as a separate cluster. These clinical variables are compared with each other in the correlation matrix depicted in table 47.

Table 47. Comparison of the correlation of features in the history and physical examination in the patient with active RA (Spearman).

		Physician	Warm	Swollen	RAI	LSI
SVAS	(*r*)	0.157	0.323	0.34	0.259	0.44
	(*p*)	NS	0.001	0.0006	0.01	0.0001
PVAS	(*r*)	0.192	0.27	0.207	0.402	0.468
	(*p*)	NS	0.008	0.04	0.0001	0.0001
Fatigue	(*r*)	0.11	-0.06	-0.04	-0.405	-0.59
	(*p*)	NS	NS	NS	0.0001	0.0001
MS	(*r*)	0.389	0.16	0.239	0.419	0.493
	(*p*)	0.0001	NS	0.02	0.0001	0.0001

It can be seen from table 47 that the RAI and the LSI correlated significantly with the more subjective measures of assessment of disease activity. The time to onset of fatigue, the duration of EMS and the PVAS were the most important subjective measures of disease activity in this group of patients, since they correlated more closely with the RAI and LSI.

changes are not significantly predicted by the clinical measures of disease activity in RA. It is clear from this that the clinical evaluation is a poor predictor of bone mass in RA.

The total group was then subdivided into 2 groups based on the physician's assessment of active disease. A discriminant analysis was performed using all the standard laboratory, radiological and dietary variables as well as SH groups, TBP, RBG and A1AT. The presence of night pain and hours to onset of fatigue were the best clinical predictors of disease activity, with a sensitivity of 78% and a specificity of 76%. However, the positive predictive value was only 58%, while the negative predictive value was much greater at 89%. This suggests that the absence of these 2 variables is predictive of inactive disease, while the presence does not necessarily imply active disease. None of the laboratory or radiological variables were significant predictors of disease activity.

It was not surprising to find that the ESR, PV and CRP were unable to predict the physician's evaluation of active disease, since this was usually based on the clinical evaluation only. In fact, none of the laboratory variables could significantly discriminate the 2 groups. Among the dietary constituents, zinc content was a significant discriminant. When all the above groups of variables were combined, only 21 subjects had all variables present for comparison. In this small number, the combination of dietary zinc content, night pain, fatigue and total width at the midshaft of the left 2nd metacarpal were able to discriminate the 15 active and 6 inactive subjects with 100% accuracy.

In the stepwise multiple regression analysis, where the physician's evaluation was the dependant variable, dietary constituents came through as remarkably significant predictors of active disease. When all the dietary variables were subjected to stepwise regression analysis, combination of calcium content, 20-CFA precursors of arachadonic acid and total phosphate content in the diet were able to predict up to 40% of the variation in disease activity. The femoral cortical width and white cell count increased the predictability to over 60%.

These findings are unusual and would be among the first to show this type of relationship, particularly with dietary components. Most other studies have concentrated on showing an improvement in laboratory variables of activity with fasting (Hafstrom *et al*, 1988). Our findings lend some credence to the age-old concept of dietary effects on RA. There is clearly a need for further evaluation of the relationship between dietary habits and activity of RA. A number of recent studies have looked at disease markers in response to fish-oil compounds (Kremer *et al* 1987; Panuch 1987; Belch *et al* 1988; Darlington 1988). They clearly seem to have a positive effect in relieving symptoms, but they are unlikely to have *disease-modifying* properties.

FUNCTIONAL STATUS.

The effects of immobilisation on bone mass are well known (Wright *et al* 1965; Kazarian *et al* 1969). Reference has been made to the difficulties in the measurement of physical activity. Functional tests, which are often used as a measure of disease activity in RA (Steinbrocker *et al* 1949), are the only reasonable indirect measure of the patient's ability to perform activities of daily living (ADL). They do not include recreational capabilities, activity in sport, or many of the other simple activities responsible for the close inter-relationships between bone production and muscle activity (Peacock and Francis 1983). Although it is known that physical activity is sometimes associated with increases in bone mass (Nilsson and Westlin 1971; Jones *et al* 1977; Dalsky *et al* 1988), while immobilisation reduces bone mass (Wright *et al* 1965), the quantity of physical activity / inactivity which causes the critical imbalance between formation and resorption is not known.

The earlier tests of function (Steinbrocker *et al* 1949), have remained in favour because of their simplicity. However, the simplicity limits their value in monitoring details of ADL, and reduces their usefulness in relating these with changes in bone mass. Grades 3 and 4 (ARA) are known to be associated with severe bone loss (Als *et al* 1985b). It is particularly in the less disabled group that a global functional test is required for evaluating patients with RA.

The Keitel function test (KFT) is a useful test of global disability in patients with RA. Convery *et al* (1977) and others (Helewa *et al* 1982), have also reported global functional tests for RA, but these have not been carefully evaluated with respect to observer differences and are often time-consuming. Liang *et al* (1981), reviewed the objectivity and reproducibility of the more recent tests in patients with RA, and suggested that the KFT fulfilled the requirements for a sensitive test of function. Badley *et al* (1984) have recommended 24 items of a Health Assessment Questionnaire (HAQ) as a measure of functional status in RA. The Stanford HAQ (Fries 1982) is also a marker of disease activity, as shown by Kirwan and Reeback (1986).

ARA & UK FUNCTIONAL CLASSES.

Table 48 shows the functional grades using the earliest classifications, the ARA (Steinbrocker *et al* 1949) and the UK (Joint Committee 1954). The difference in the 2 methods is that the latter method attempts to increase the scale of measurement.

Table 48. ARA and UK functional classification of activities of daily living in 98 subjects with RA.

		n
ARA Functional Class	1	22
	2	76
UK Functional Class	1	16
	2	34
	3	48

The above table shows that the ARA and UK functional classifications are very similar. However, the UK method succeeds in spreading the distribution. The UK FC delineates a slightly less disabled group, which is not seen with the ARA FC.

The inner diameter at the midshaft of all 6 metacarpals measured was significantly different in the 2 ARA functional classes ($p < 0.01$). The M6HS ($p < 0.01$) and the M6CA% ($p < 0.009$) were also significantly different in the 2 groups. The outer diameter was not affected, nor was the combined cortical width at the right 2nd metacarpal. The sum of the combined cortical widths, however, was significantly different in the groups.

The UK classification of function seemed to influence bone mass to a lesser extent, but the differences may be due to the smaller numbers in the respective groups. The combined cortical width at the right 2nd metacarpal was significantly different in the groups ($p < 0.03$). The sum of the cortical widths was also significantly different ($p < 0.04$). In addition, the CA/SA was the only measure of bone mass which was significantly different in the groups. The other measures of bone mass were not significantly different between the groups. These findings need to be interpreted with caution, since 33% (UK FC) to 50% (ARA FC) of the variation in bone mass in these groups could be explained purely by chance. However, it does indicate that even relatively minor disability could have a negative effect on bone mass.

KEITEL FUNCTION TEST.

The Keitel Function Test (KFT) (Keitel *et al* 1972) was shown by a group of workers (Eberl *et al* 1976) to be more reproducible than the RAI (Ritchie *et al* 1968). The strength of the RAI as a clinical test of activity lies in its simplicity. Ritchie *et al* (1968), showed that it could be performed in 2-3 minutes. The KFT is carried out in 12-15 minutes. For this reason, the KFT was arbitrarily divided according to groups of joints tested, in an effort to simplify the test. The test was analysed as a predictor of disease activity as well as bone mass.

The hands, wrists, shoulders and lower limbs broadly represent the components of the KFT. It can be seen that the component areas are disproportionately represented in the total score. A *standardised* Keitel score was therefore derived for comparison with other activity indices (Lansbury and Haut 1958; Ritchie *et al* 1968). The hand and wrist will be considered jointly as the hand functional index (HFI).

Table 49 shows that the patients with RA were considerably more disabled than those with SLE. The patient's with SLE had more extensive disease in the hands and wrists than in the shoulders or lower limbs. Both groups were significantly disabled compared with the normal controls. The articular disease in both these disorders was generalised (global). The patient's with SLE did not show significant disease of the shoulders ($p > 0.05$).

Table 49. Total Keitel score (KFT) and components in RA compared with SLE. The normal controls had a Keitel score of 4, which is the minimum score attainable. The higher the score, the greater the disability.

	Mean RA (SD)	Mean SLE (SD)	Range RA	Range SLE	*p* value of difference
HFI	27.21 (10.17)	12.89 (9.27)	4-42	4-36	0.0001
Shoulder	2.13 (2.97)	0.04 (0.2)	0-10	0-1	0.0001
Lower Limb	8.7 (7.43)	1.72 (3.49)	0-36	0-22	0.0001
KFT	38.04 (16.44)	14.65 (10.65)	4-86	4-39	0.0001

The KFT evaluates the right and left limbs separately. The complete test evaluates function in the interphalangeal, metacarpo-phalangeal, wrist, elbow, shoulder, hip, knee, ankle and metatarso-phalangeal joints. The comparison between the 2 sides confirmed that symmetry was the rule. However, the ability to bring the tip of the thumb to the hypothenar was affected on the left in 52% compared with 40% on the right. The ability to place the hand on the right shoulder was affected in 44% compared with 37% on the left. Patients found it easier to place the hand behind the neck; 25% experiencing some difficulty. The 2 sides were equally affected in this activity. In the group with SLE, patients found more difficulty bending the fingers of the left hand than the right. The left wrist was also more severely involved than the right. This asymmetry of involvement in the hands and wrists of patients with SLE has previously been reported in up to 25% of cases (Cronin 1988).

Thirty-eight percent (38%) of the RA patients had difficulty rising from bed, while 25% were unable to abduct the hips more than 50 cm apart. Less than 5% (4.17%) of the SLE group had difficulty with these activities. Twenty-three percent (23%) of the RA patients found difficulty rising from a chair, compared with 2.78% of the SLE patients. Thirty percent (30%) of the RA patients were unable to stand tip-toed for 15 seconds compared with 12.5% of the patients with SLE. Standing on the heels for 15 seconds was impossible for 26% of the RA group, but only 11.1% of the SLE subjects. Knee-bending exercises were impossible in 28% of the RA group and 4% of the SLE group.

The lower limb activities of individual joints showed symmetrical involvement of the hips in the RA group, while the left knee was more commonly involved. External rotation of the hip was symmetrically affected in 76% of the RA group. This is an unusual proportion, suggesting that the hip is commonly involved clinically in young patients with RA (mean < 40 years). This may also explain the significant femoral cortical thinning seen in the RA group. It is also interesting that 30% of the patients with SLE experienced some difficulty in externally rotating either hip. This may have been an early sign of avascular necrosis (AVN) of the femoral head, since we reported a prevalence of 7% of this disorder in patients with SLE (Kalla *et al* 1986). The right knee was difficult to bend in 4% compared with 12% in the left knee. None of the patients with SLE had difficulty bending the knees. Although rotation of the hip was severely limited in the RA group (76%), extension of the hip was limited in only 4% of the RA group and none of the SLE group.

The ability to walk 30 meters in 20 seconds was impaired in 54% of the patients with RA, compared with 6% of the patients with SLE. Forty-nine percent (49%) of RA subjects were unable to walk up 10 steps in 7 seconds, while 48% were unable to walk down 10 steps in that time. Only 6% of the SLE group had an impairment of these activities.

It can be seen that for most of the functional components tested, approximately two-thirds of the RA group showed no difficulty. The alarmingly large number of patients with difficulty in rotating the hips, suggests that very few of the subjects were capable of strenuous recreational activities. Although no attempt was made to accurately quantitate physical activity, it can be inferred that one-third (30%) of the patients with RA were severely disabled, compared with the normal controls. Patients with SLE were only slightly disabled.

The KFT cannot be performed in less than 10 minutes, limiting its value in a busy clinic. The correlation matrix which follows, is based on an attempt at compartmentalising the test to make it more practical. The tests concerned with function in the hand and wrist (HFI) can be carried out in less than a minute, compared with 2-3 minutes for the RAI.

Table 50 shows that the components correlated significantly with the total Keitel score. The degree of correlation is related to the relative contribution to the score by the individual components. In RA, the HFI explained 76% of the variation in the total Keitel score (the square of $r = 0.87$). This means that the hand score could ade-

quately replace the total score in the functional assessment of subjects with RA, as a global measure of disability.

Table 50. Comparison of the correlation between the Keitel components and the total Keitel score in patients with RA.

	HFI	SHOULDER	LOWER LIMB	KFT
HFI		0.533	0.376	0.873
SHOULDER	0.0001		0.428	0.675
LOWER LIMB	0.0001	0.0001		0.743
KFT	0.0001	0.0001	0.0001	

In patients with SLE, the hands and wrists explained over 90% of the variation in the total Keitel score. This means that these are the only areas which need to be evaluated to obtain a global measure of functional disability in SLE, as shown in table 51.

Table 51. Comparison of the correlation between the Keitel components and the total Keitel score in patients with SLE.

	HFI	SHOULDER	LOWER LIMB	KFT
HFI		0.152	0.348	0.95
SHOULDER	NS		-0.026	0.136
LOWER LIMB	0.003	NS		0.564
KFT	0.0001	NS	0.0001	

Functional impairment has potential as a marker of disease activity in RA, but has not previously been evaluated in this context. Bone mass is also closely related to functional impairment. Tables 52 and 53 aim to evaluate *i*) the role of functional impairment in the genesis of bone loss in the metacarpals of patients with RA, and *ii*) the KFT as a clinical marker of disease activity.

Table 52. Comparison of the correlation of the Keitel score and its components with measures of bone mass in 98 patients with RA.

		HFI	SHOULDER	LOWER LIMB	KFT
CA%	(*r*)	-0.204	-0.291	-0.326	-0.323
	(*p*)	0.04	0.004	0.001	0.001
CA/SA	(*r*)	-0.083	-0.141	-0.301	-0.124
	(*p*)	NS	NS	NS	NS
M6HS	(*r*)	-0.237	-0.322	-0.337	-0.358
	(*p*)	0.02	0.001	0.0007	0.0003
M6CA	(*r*)	-0.237	-0.324	-0.344	-0.359
	(*p*)	0.02	0.001	0.0005	0.0003
Carpal Length	(*r*)	-0.09	-0.32	-0.281	-0.213
	(*p*)	NS	0.001	0.005	0.04

The above table shows that disability contributed significantly to the fall in bone mass in the patients with RA. However, CA/SA was not dependant on the functional score, reaffirming its value as a measure of bone mass (Exton-Smith *et al* 1969a) in RA. It is interesting that the total Keitel score explained a greater proportion of the variation in the metacarpal scores than the HFI. In fact, the HFI explained the smal-

lest proportion of the variation in all the radiological assessments involving the metacarpals and wrists.

Table 53. Comparison of the correlation of KFT and components with clinical measures of disease activity in 100 subjects with RA.

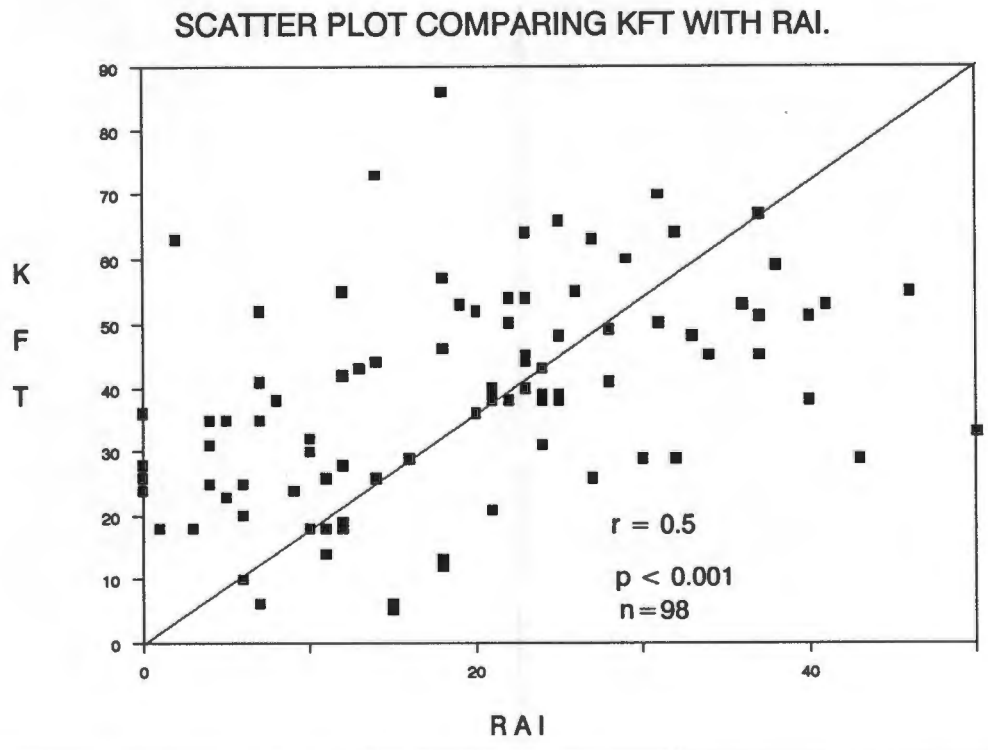
		HFI	SHOULDER	LOWER LIMB	KFT
SVAS	(*r*)	0.238	0.376	0.374	0.384
	(*p*)	0.02	0.0001	0.0001	0.0001
PVAS	(*r*)	0.05	0.154	0.346	0.223
	(*p*)	NS	NS	0.0005	0.03
Fatigue	(*r*)	-0.116	-0.066	-0.362	-0.248
	(*p*)	NS	NS	0.0003	0.01
MS	(*r*)	0.265	0.097	0.261	0.301
	(*p*)	0.008	NS	0.009	0.003
Physician	(*r*)	0.476	0.253	0.128	0.366
	(*p*)	0.0001	0.01	NS	0.0002
Warm	(*r*)	0.349	0.168	0.127	0.298
	(*p*)	0.0004	NS	NS	0.003
Swollen	(*r*)	0.454	0.241	0.139	0.392
	(*p*)	0.0001	0.02	NS	0.0001
RAI	(*r*)	0.41	0.232	0.444	0.502
	(*p*)	0.0001	0.02	0.0001	0.0001
LSI	(*r*)	0.393	0.296	0.564	0.54
	(*p*)	0.0001	0.003	0.0001	0.0001

Table 53 shows that the total KFT correlated significantly with all the currently used measures of disease activity. The RAI and the LSI are commonly used in drug trials evaluating changes in disease activity (Rhind *et al* 1980). The KFT has not been

used in such studies, although a recent evaluation of auranofin (oral gold) showed that the KFT is subject to changes by disease modifying drugs (Bombardier *et al* 1987). In the present group, the KFT explained over 25% of the variation in both the RAI and the modified LSI and correlated significantly ($p < 0.0001$) with these 2 validated tests of disease activity. Therefore, the KFT and its components would be a useful adjunct to the tests of disease activity in RA, but would not replace them ($r < 0.9$).

The scatter plot shown in figure 26 depicts the relationship between the KFT and the RAI. The KFT is probably a measure of disease activity, but the 2 tests are not mutually exclusive.

Figure 26. Scatter plot showing the relationship between the KFT and RAI in patients with Rheumatoid Arthritis.



The KFT and its components are more suitable tests of disease activity than the RAI and LSI, since they correlated significantly with the radiological changes as well. The carpal length (or carpo-metacarpal ratio) is considered a useful radiological test of activity in RA (Trentham and Masi 1976). The RAI and LSI did not correlate significantly with carpal length ($p > 0.05$), while the KFT did ($p < 0.05$). The components of the KFT also showed significant correlations with both radiological measures and disease activity measures, but explained only a small proportion of the variation in either group of variables.

These findings suggest that the KFT is a useful overall test of disease activity in RA. It needs to be evaluated in longitudinal studies and may prove to be a valuable measure of activity and outcome, as shown recently by Bombardier *et al* (1987).

DISABILITY QUESTIONNAIRE.

The Stanford Health Assessment Questionnaire (HAQ) (Fries 1982) is a useful and reproducible method of evaluating function (Kirwan and Reeback 1986). Badley *et al* (1984) have adapted the test so that 24 of the most important components were selected. This *disability questionnaire* (DQ) was recorded in the present group of patients with RA, in order to compare the method with the KFT, RAI and LSI when used by a single observer.

The 24 components were grouped for 5 major aspects of mobility, using the Guttman scale of severity, as recommended by the World Health Organisation (WHO) (Badley *et al* 1984).

Table 54 confirms that patients with RA were significantly less mobile than the patients with SLE. The normal subjects had a mobility score of zero. As with the KFT, the higher the score, the more disabled the subject. The differences between the groups remained significant even after correction for multiple comparisons, using Duncan's multiple range test.

Twenty-one percent (21%) of the patients with RA experienced some difficulty walking to the toilet, compared with 15.28% of the patients with SLE ($p > 0.05$). Climbing on/off the toilet was a problem for 26% of the RA group, compared with 5.5% of the SLE group ($p < 0.0005$).

Table 54. Pairwise comparisons of the 5 categories of the disability questionnaire (DQ) between subjects with RA and SLE. Normal subjects score "0" for this test. The higher the score, the greater the disability.

	Mean RA (SD)	Mean SLE (SD)	Range RA	SLE	p value
Mobility	6.87 (5.86)	3.76 (4.72)	0-24	0-23	0.0003
Bend Down	6.52 (7.77)	2.31 (4.16)	0-28	0-22	0.0001
Dexterity	13.74 (10.51)	6.58 (8.12)	0-35	0-31	0.0001
Bend Arm	3.09 (4.13)	0.63 (1.72)	0-17	0-10	0.0001
Reach Up	14.38 (13.7)	4.69 (7.68)	0-49	0-32	0.0001
Total DQ	44.6 (35.09)	17.97 (20.23)	0-135	0-98	0.0001

Table 55 reaffirms the global effects of RA on the subjects under study, since the total mobility score (DQ) is suitably represented in the component scores ($r = 0.82$; 0.83; 0.87; 0.69; 0.88). However, activities requiring the arm to be bent made the smallest contribution to the variation of the DQ.

Table 55. Correlation matrix of the components of the DQ in patients with RA. (Spearman correlation showing r value in upper and p value in lower triangular matrix.)

	MOBILITY	BENDING	DEXTERITY	BENDARM	REACH	TOTAL
MOBILITY		0.684	0.615	0.566	0.63	0.82
BENDING	0.0001		0.717	0.589	0.61	0.83
DEXTERITY	0.0001	0.0001		0.592	0.68	0.87
BEND ARM	0.0001	0.0001	0.0001		0.51	0.69
REACH	0.0001	0.0001	0.0001	0.0001		0.88
TOTAL	0.0001	0.0001	0.0001	0.0001	0.0001	

Table 56 shows that the DQ and its components correlated significantly with the KFT and its components. It can also be seen from table 57, that the DQ and components explained a greater proportion of the variation in RAI and LSI than did the KFT and components (Table 53). Therefore, the DQ could be regarded as a suitable test of disease activity in longitudinal studies of patients with RA, confirming the findings of Kirwan and Reeback (1986).

Table 56. Comparison of the DQ and its components with the KFT and components.

		MOBILITY	BENDING	DEXTERITY	BEND ARM	REACH	TOTAL
HFI	(r)	0.35	0.35	0.28	0.36	0.24	0.36
	(p)	0.0004	0.0004	0.006	0.0003	0.02	0.01
SHOULDER	(r)	0.322	0.403	0.31	0.36	0.34	0.41
	(p)	0.001	0.0001	0.002	0.0002	0.01	0.01
LOWER	(r)	0.64	0.56	0.44	0.304	0.55	0.62
LIMB	(p)	0.0001	0.0001	0.0001	0.002	0.01	0.01
KFT	(r)	0.56	0.54	0.41	0.41	0.46	0.57
	(p)	0.0001	0.0001	0.0001	0.0001	0.01	0.01

Table 57. Comparison of the DQ and its components with the Ritchie (RAI) and Lansbury (LSI) indices.

		MOBILITY	BENDING	DEXTERITY	BEND ARM	REACH	TOTAL
RAI	(r)	0.547	0.47	0.54	0.44	0.46	0.6
	(p)	0.0001	0.0001	0.0001	0.0001	0.01	0.01
LSI	(r)	0.549	0.53	0.46	0.37	0.55	0.61
	(p)	0.0001	0.0001	0.0001	0.0002	0.01	0.01

However, comparisons with laboratory and radiological measures showed that the DQ and components did not correlate significantly with ESR, CRP, PV, metacarpal bone mass or carpal length (not shown). For this reason, it would seem that the KFT is a superior test of overall disease activity assessment in RA. The DQ has not been evaluated in drug trials of disease modifying drugs, but it is likely to change with improvement or worsening of disease. Its similarities with the Stanford HAQ suggests that this is highly probable (Kirwan and Reeback 1986).

The above tables show that patients with RA are severely disabled and incapacitated by their disease. Lack of walking may have contributed to the differences in bone mass.

It can be seen from table 58 that a wide range of disability is present in so-called *mildly* disabled subjects, judging by the KFT and DQ assessments of functional disability. The range of 5-86 (KFT) and 0-135 (DQ) is the same for the ARA and UK FC, confirming the insensitivity of these older tests in evaluating patients with polyarticular diseases which affect predominantly smaller joints (Convery *et al* 1977). Our

findings suggest that objective measure of function may be a useful means of monitoring disease *activity* as well as *outcome* in RA.

Table 58. ARA and UK functional classification of activities of daily living in 98 subjects with RA, compared with corresponding KFT and DQ scores. Considerable disability is present even though independence of activity is maintained.

		n	Range of other Tests	
			KFT	HAQ
ARA Functional	1	22	5-40	0-51
Class	2	76	13-86	6-135
UK Functional	1	16	5-40	0-51
Class	2	34	6-64	0-99
	3	48	18-86	6-135

DIFFICULTIES WITH THE SEXUAL ACT.

The ease of sexual performance is a useful reflection of mobility (Cohen 1987). Although several factors control the sexual urge, performance is likely to be limited by severe disability. The patients with RA and SLE were questioned about sexual difficulties related to their arthritis. There are obvious problems in rating sexual difficulty according to a Guttman scale, as was used for the responses to questions regarding mobility. Twenty-two percent (22%) of the RA patients had sexual difficulties compared with 12.5% of the SLE patients ($p < 0.05$). Brown *et al* (1987) found

sexual problems in 71% of 254 patients with a variety of rheumatic diseases, but their study was not confined to young subjects or FC 1 and 2.

Comparison between the RAI, KFT, DQ, and difficulties in the sexual act are shown in table 59. It can be seen that the difficulty with sex was statistically significantly related to both the markers of disease activity and measures of functional impairment. However, if one considers that the question of sexual difficulties is a binary variable, at least 50% of the variation in the independent variable could be explained by chance. Since < 15% of the variation in the 3 variables was explained by the difficulties in the sexual act, it is unlikely that the correlations were clinically significant. It is likely that the sexual disability was not solely due to lack of mobility or active disease, but that other, unrelated factors obviously influenced performance. Perhaps body image may have played a role in determining this reduced libido in both partners. Although patients are generally reluctant to disclose personal matters of this nature, table 59 suggests that the responses of the patients were probably reliable.

Table 59. Correlation matrix showing difficulties with sexual activity as a marker of functional disability and disease activity in RA.

	SEX ACT	KFT	DQ	RAI
SEX ACT	0.312	0.362	0.288	
KFT	0.002		0.568	0.504
DQ	0.0002	0.0001		0.609
RAI	0.004	0.0001	0.0001	

A comparison between the sexually active group and the inactive group using multiple comparisons (BMDP - 7D), showed that total mobility ($p < 0.0001$) and KFT ($p < 0.0007$) were significantly different between the groups, but the RAI was not significantly different (not shown). This suggests that sexual inactivity was less significantly related to pain or disease activity than to disability.

The effect of sexual difficulties on bone mass measurements *(t-tests)*, are shown in table 60. The table shows that patients who expressed difficulty in performing sexual activities had a significantly lower bone mass (CA/SA; M6HS) than their sexually active counterparts. Since the hands are not specifically used in this activity, it is possible that the correlation is due to the generalised bone losing state in RA, which is most likely multi-factorial. The CMR was not significantly different in the 2 groups, perhaps suggesting that disability rather than disease activity was responsible for these differences.

Table 60. Comparison of bone mass in RA subjects who expressed difficulty with sexual activity compared with those who did not.

	Bone Mass Measurement.			
	CA	CA/SA	M6HS	CMR
Able	0.433	0.025	56.39	0.47
Unable	0.395	0.023	52.12	0.46
p value	NS	0.05	0.006	NS

In order to further evaluate the basis of the bone loss due to sexual inactivity, a discriminant analysis was used to predict sexual disability, using age, duration of disease, DQ, total KFT, RAI, LSI, number of warm and swollen joints, pain VAS, CA% and M6HS as the independent variables. Total mobility was found to be the most significant discriminant, with a sensitivity of 83% and specificity of 33%, further confirming that sexual inactivity was indirectly related to physical inactivity rather than disease activity. The positive predictive value was 71%, while the negative predictive value was no better than chance at 50%. This suggests that factors not related to the DQ may have played a significant additional role in the sexual difficulties described by these patients.

SIMPLE HAND FUNCTION.

Simple hand function was measured by an occupational therapist (OT), using tests recommended for evaluation following surgery (Clawson *et al* 1971). Four tests were used; testing the ability to use a knife and fork, doing up buttons, grip strength and power of pinch. These tests were performed in the patients with RA as well as the normal controls. The patients with SLE did not have these tests done, because the OT was stationed at one centre only. The results are summarised in the table which follows.

Table 61 shows that simple hand function was significantly reduced in the patients with RA. It can be seen that the range of time taken using a knife and fork and to do up buttons was much higher in the patients with RA. This confirms that the group comprised of a heterogeneous population of disabled patients with RA.

Table 61. Comparison of simple hand function between normal controls and patients with RA, measured by the occupational therapist (OT).

Test	Mean Control (SD)	Mean RA (SD)	*p* Value
Knife & Fork	39.23 (7.84)	104.78 sec (79.95)	0.0001
Buttonhole	117.83 (35.44)	185.17 sec (83.44)	0.0001
Grip Strength	91.99 (22.42)	28.69 mm Hg (20.27)	0.0001
Pinch	334.49 (96.97)	164.76 Kp (94.69)	0.0001

It can be seen from table 62 that bone loss in the hands of patients with RA was not related to the deterioration of the above-mentioned measures of hand function. The finding of a significant correlation with carpal length, however, is possibly a reflection of disease activity in the wrists, where function was probably inadequately assessed by these tests. The fingers and wrist function as a unit when the hand is used for even the most mundane activities.

Table 62. Comparison of the correlation between bone mass and simple hand function in patients with RA.

		CA%	CA/SA	M6HS	M6CA	Carpal Length
Knife & Fork	(*r*)	-0.06	-0.04	-0.21	-0.22	-0.23
	(*p*)	NS	NS	NS	0.04	0.03
Buttonhole	(*r*)	-0.14	-0.01	-0.25	-0.25	0.15
	(*p*)	NS	NS	0.02	0.02	NS
Grip	(*r*)	0.08	0.09	0.09	0.1	0.4
	(*p*)	NS	NS	NS	NS	0.0001
Pinch	(*r*)	0.07	0.04	0.09	0.09	0.29
	(*p*)	NS	NS	NS	NS	0.006

Simple hand function did not contribute significantly to bone mass in the normal hand, either (not shown). However, activities requiring strength (grip strength and pinch force), have a positive influence on bone mass, particularly the M6HS, even though they did not reach statistical significance ($p > 0.05$).

Table 63 is a comparison of the correlation between the above tests of hand function and the diameters at the metacarpal midshafts. The sum of the cortical widths of 6 metacarpals correlated significantly only with the grip strength ($r = 0.35$; $p < 0.005$) and pinch grip ($r = 0.26$; $p < 0.04$) in the normal controls. None of the other correlations were statistically significant.

Table 63. Comparison of the correlation between cortical thickness and simple hand function in normal controls.

		TW	MW	CCW	Σ (CCW)	CMR
Knife & Fork	(*r*)	0.12	-0.04	0.14	0.2	0.01
	(*p*)	NS	NS	NS	NS	NS
Buttonhole	(*r*)	0.26	0.2	0.15	0.14	0.02
	(*p*)	0.04	NS	NS	NS	NS
Grip Strength	(*r*)	0.23	-0.03	0.22	0.35	0.1
	(*p*)	NS	NS	NS	0.005	NS
Pinch	(*r*)	0.07	0.02	0.12	0.26	0.05
	(*p*)	NS	NS	NS	0.04	NS

In the RA group, the time taken to do up buttons correlated significantly with all the metacarpal diameters. The correlation for MW ($r = 0.35$; $p < 0.0006$) was better than for TW ($r = 0.30$; $p < 0.004$). Grip strength and pinch force correlated significantly with TW but not with MW (not shown).

HAND STRENGTH.

Although it has been shown that bone mass is related to strength (Dickson *et al* 1972; 1973), the relationship between functional impairment and strength in the hands is not known. One would expect that disabled hands would be weaker than normal. The five tests of strength measured with a dynamometer in the 3 groups of subjects are shown in table 64.

Table 64. Tests of strength in the right middle finger and right hand. Normal controls, patients with RA and patients with SLE.

MEASURE	Mean Control (SD)	Mean RA (SD)	Mean SLE (SD)
Flexion	20.23 (8.11)	9.5 (6.1)	13.57 (4.85)
Extension	3.33 (1.35)	1.85 (1.05)	2.25 (1.05)
Abduction	7.49 (2.73)	4.43 (2.72)	5.73 (1.97)
Adduction	6.09 (3.39)	2.9 (1.54)	3.5 (1.97)
Torque	55.35 (18.46)	26.55 (16.39)	36.28 (11.49)

It can be seen from table 64 that the 3 groups under study were significantly different from each other, with respect to strength in the right hand. The patients with SLE formed an intermediate group of subjects. Extension of the right middle finger was the weakest movement in all 3 groups. The weakness seen in the RA group was possibly related to deformities leading to weaker grip, rather than an intrinsic weakness of the muscle groups tested.

Table 65 shows the comparison between simple hand function and hand strength in normal people. They seem to require no strength in doing mundane activities with the hand. Power of pinch was the only test which depended on strength in the middle finger. Grip was not dependant on strength, using the Mannerfelt apparatus.

Table 65. Comparison of the correlation between hand strength and simple hand function in normal controls.

		FLEX	EXTEND	ABDUCT	ADDUCT	TORQUE
Knife & Fork	(*r*)	0.01	0.01	0.01	0.1	0.1
	(*p*)	NS	NS	NS	NS	NS
Buttonhole	(*r*)	0.21	0.06	0.15	0.02	0.27
	(*p*)	0.07	NS	NS	NS	0.02
Grip Strength	(*r*)	0.16	0.12	0.22	0.11	0.26
	(*p*)	NS	NS	0.06	NS	0.03
Pinch	(*r*)	0.28	0.29	0.22	0.25	0.18
	(*p*)	0.02	0.01	0.07	0.03	NS

Table 66 shows that the situation is different in RA, in that the only function not requiring strength was the ability to do up buttons.

Table 66. Comparison of the correlation between hand strength and simple hand function in patients with RA.

		FLEX	EXTEND	ABDUCT	ADDUCT	TORQUE
Knife & Fork	(*r*)	-0.45	-0.1	-0.39	-0.39	-0.52
	(*p*)	0.0001	NS	0.0002	0.0002	0.0001
Buttonhole	(*r*)	-0.19	-0.08	-0.1	-0.1	-0.17
	(*p*)	NS	NS	NS	NS	NS
Grip Strength	(*r*)	0.57	0.46	0.54	0.49	0.65
	(*p*)	0.0001	0.0001	0.0001	0.0001	0.0001
Pinch	(*r*)	0.72	0.39	0.65	0.59	0.76
	(*p*)	0.0001	0.0002	0.0001	0.0001	0.0001

Not surprisingly, extension of the middle finger seemed to make the least contribution to these tests of function. Grip strength and power of pinch were significantly correlated with hand strength in RA. It was surprising to find that weakness of extension explained over 20% of the variation in grip strength and pinch grip. It is clearly a sensitive index of overall strength in the hand.

Table 67 shows the correlation between hand strength and global function in RA. It is interesting that the HFI did not show any significant correlation with strength in the hand, apart from finger flexion ($p < 0.04$) and torque strength ($p < 0.03$). The KFT, on the other hand, correlated significantly with all the measures of hand and finger strength. Surprisingly, the DQ showed even more significant correlations with hand strength than the KFT (Table 67). The significant negative correlations with the

total KFT and total mobility tests, suggests that the patients with active disease had weaker hands. This is not surprising. The test of grip using the torquometer (Fig 10), was the most suitable test of hand function in patients with RA. This confirms the suggestion by De Choisy (1973) that this method be included in tests of therapeutic efficacy, since they found a significant correlation between torque strength and grip strength using a beaumanometer.

Table 67. Comparison of the correlation between hand strength and global dysfunction (KFT, DQ) in RA.

		FLEX	EXTEND	ABDUCT	ADDUCT	TORQUE
HFI	(*r*)	-0.41	-0.19	-0.13	-0.17	-0.23
	(*p*)	0.04	NS	NS	NS	0.03
KFT	(*r*)	-0.38	-0.26	-0.3	-0.32	-0.36
	(*p*)	0.0001	0.01	0.003	0.001	0.0003
DQ	(*r*)	-0.46	-0.16	-0.44	-0.39	-0.52
	(*p*)	0.0001	NS	0.0001	0.0001	0.0001

Dickson *et al* (1973), showed that function and bone mass, even in the normal hand, are related. They found that pinch force was significantly correlated with AI (area index), but flexion force was not.

Table 68 shows the variation of bone mass with strength in the hand, in the controls. All the tests of force correlated significantly with total width at the midshafts of 6 metacarpals, but not with bone mass. However, torque strength and extension showed significant correlations with metacarpal bone mass, while finger flexion, ab-

duction and adduction strength made no significant contribution to the variation in metacarpal bone mass. Less than 10% of the variation in bone mass could be predicted by the variation in torque strength, suggesting that its clinical usefulness in this regard was minimal. The significant relationship between hand strength and carpal length is interesting, but difficult to interpret. It probably indicates that hand strength is an important factor in the regulation of cartilage metabolism under normal circumstances.

Table 68. Comparison of the correlation between bone mass and strength in the hand, as measured with a dynamometer, in 96 normal controls.

		FLEX	EXTEND	ABDUCT	ADDUCT	TORQUE
TW	(*r*)	0.34	0.23	0.28	0.39	0.32
	(*p*)	0.002	0.03	0.008	0.0002	0.003
CA%	(*r*)	0.02	0.07	0.05	0.08	-0.24
	(*p*)	NS	NS	NS	NS	0.02
CA/SA	(*r*)	0.11	0.10	0.13	0.08	0.03
	(*p*)	NS	NS	NS	NS	NS
M6HS	(*r*)	0.04	-0.09	0.006	0.05	-0.28
	(*p*)	NS	NS	NS	NS	0.01
M6CA	(*r*)	0.05	0.23	0.02	-0.04	-0.29
	(*p*)	NS	0.02	NS	NS	0.006
Carpal	(*r*)	0.59	0.36	0.47	0.43	0.39
Length	(*p*)	0.0001	0.001	0.001	0.0001	0.001

Table 69 shows the variation of bone mass with strength in the hand, in patients with RA. Flexion force was not significantly correlated with bone mass in RA, confirming the findings Dickson *et al* (1973). However, they did not measure extension, abduction, adduction or torque strength. We measured all these variables in the normal control group as well as the patients with RA and SLE. These are summarised in the tables which follow. Differences in the patterns of correlation in the 3 groups could shed light on the pathogenesis of bone loss in RA.

Table 69. Comparison of the correlation between bone mass and strength in the hand, as measured with a dynamometer, in 98 patients with RA.

		FLEX	EXTEND	ABDUCT	ADDUCT	TORQUE
TW	(*r*)	0.36	0.20	0.44	0.39	0.33
	(*p*)	0.0003	0.04	0.0001	0.0001	0.0001
CA%	(*r*)	0.05	0.26	0.005	0.002	0.005
	(*p*)	NS	0.01	NS	NS	NS
CA/SA	(*r*)	0.11	0.41	0.13	0.08	0.03
	(*p*)	NS	0.0001	NS	NS	NS
M6HS	(*r*)	0.04	0.23	0.006	0.05	-0.01
	(*p*)	NS	0.03	NS	NS	NS
M6CA	(*r*)	0.05	0.23	0.02	-0.04	0.004
	(*p*)	NS	0.02	NS	NS	NS
Carpal	(*r*)	0.36	0.26	0.33	0.45	0.33
Length	(*p*)	0.0004	0.01	0.001	0.0001	0.001

Table 69 shows that strength of finger flexion, abduction, adduction or hand torque did not contribute significantly to the variation in bone mass in patients with RA. However, extension of the middle finger (the weakest action), made a significant contribution to variations in bone mass ($r=0.4$; $p<0.03$). Extension of the right middle finger seems to be a useful marker of hand strength, even in RA. Similar to normal subjects, TW correlated significantly with all the measures of strength in the finger and hand. The carpal length correlated significantly with hand torque as well as finger strength (all components). The variation in adduction of the middle finger explained up to 20% of the variation in carpal length ($r=0.45$; $p<0.0001$). This difference from the normal controls suggests that in RA, bone loss is related to changes in strength. However, other factors are more likely to be responsible for the metacarpal bone loss in RA, the likely culprits being the mediators of inflammation or some effect of the therapy of RA.

In SLE (not shown), flexion force and torque correlated significantly with TW and MW in all the metacarpals. However, torque strength was the only variable which correlated significantly with CA/SA ($r=-0.38$; $p<0.001$) and the six metacarpal bone mass ($r=-0.45$; $p<0.0002$). There was no significant correlation with CA or CA%. Carpal length correlated significantly only with torque strength ($r=0.38$; $p<0.002$). It is obvious that the bone resorptive effects in these 2 diseases are unlikely to be due purely to changes in hand or finger strength. The negative correlation between bone mass and finger strength in SLE is interesting. Since this is the first

study of these relationships in SLE, the significance is not clear. It does, however, suggest that the genesis of metacarpal bone loss in these 2 diseases is very different.

The findings in RA confirm the earlier suggestion (Dickson *et al* 1973) that flexion force does not correlate with bone mass. In addition, total hand strength, as represented in the torque, did not contribute significantly to bone mass in RA, which is surprising. This supports the concept that bone loss in RA is likely to be due to a *chemical* rather than a *mechanical* effect of the disease.

Stepwise discriminant analysis was used to establish the hand disability which was most useful in differentiating RA subjects from normals. This would be useful in aiding the diagnosis in doubtful cases or in patients with ill-defined symmetrical polyarthritis. The measures of simple hand function as well as strength were used as the independent variables which would predict the disease group, comparing RA with the normal controls. Grip strength and time to do up buttonholes predicted RA with remarkable accuracy. Used in conjunction, these had a sensitivity of 97% and a specificity of 98%. Further discriminant analysis of these 2 variables showed that grip strength was the more sensitive (93%) and specific (97%). The positive predictive value of 96% and negative predictive value of 95% is remarkable. This finding has not been previously reported in RA and bears further evaluation in a prospective study with other rheumatic diseases. The test may be a useful addition to the revised ARA criteria for classification of RA (Arnett *et al* 1988) and SLE (Tan *et al* 1982). Unfortunately, the tests of simple hand function were not performed on the subjects with SLE, so that the discriminant value in these 2 rheumatic diseases could not be evaluated.

Table 70 shows a comparison of the 3 groups using Duncan's method. They were found to be significantly different from each other, even after correction of the p value for multiple comparisons (Bonferroni). In the table, the same letter implies that the means are not significantly different ($p > 0.05$). It can be seen that the patients with SLE were a distinctly weaker group than the normal controls. However, patients with RA were significantly weaker than patients with SLE, except for adduction force in the middle finger of the right hand, which was equally weak in RA and SLE.

Table 70. Duncan's Multiple Range Test comparing hand strength in 3 groups of young subjects, measured with a dynamometer. The symbols (A, B, C) imply significantly different mean values ($p < 0.05$).

Measure	Control	RA	SLE
Abduction	A	B	C
Adduction	A	B	B
Flexion	A	B	C
Extension	A	B	C
Torque	A	B	C

Stepwise discriminant analysis using finger and hand force as the independent variables, was used to predict the underlying disease (SLE or RA : dependant variable). Finger flexion was the most useful discriminant, with a sensitivity of 61% and specificity of 71%. The positive predictive value was 61% while the negative predic-

tive value was 71%. It would seem from this analysis that the effects of arthritis in the hands has different sequelae with respect to hand strength in the 2 diseases. The predictive value of loss of finger flexion is statistically significant, but 30-40% of subjects would be at risk of being misclassified.

The dynamometer has been shown to be a reproducible method of measuring hand function in RA (Helliwell *et al* 1987). Our findings support such a claim.

NUTRITIONAL STATUS AND DIET.

NUTRITIONAL STATUS.

Nutritional status was calculated by 4 methods. The reason for selecting 4 different methods was to test whether skinfold thickness (SFT) is reduced in RA. This would result in a discrepancy between Sloan's (1967) measure and that of Willmore and Behnke (1970). The calculation of BMI does not require either SFT or body diameters.

Table 71 summarises the actual measurements. Pairwise comparisons using the T-test and the Bonferroni technique for multiple comparisons, showed that the patients with RA were not significantly different from the controls with respect to LBW. However, the patients with SLE were significantly leaner than the normal controls and patients with RA, particularly with respect to body diameters. None of the patients under study were malnourished, defining ideal LBM as the range encompassing 2 SD above and below the mean for the control group.

Table 71. Lean body weight (LBW) of 89 normal controls, 87 subjects with RA and 67 with SLE.

	Median Control	Median RA	Median SLE
n =	89	78	67
Sloan	1.097	1.098	1.098
W-B 1	69.59	70.0	68.78
W-B 2	5.98	5.92	5.42
BMI	22.99	22.49	17.14

Like bone mass, LBW is likely to be different due to the influence of race and gender. Duncan's multiple range test was used to compare the 3 groups with respect to the influence of race, gender and disease on the calculation of LBW. It was found that the LBW was comparable between the patients with RA and SLE and the normal controls. There was also no significant difference between Coloureds compared with the other race groups. However, males had a significantly higher LBW than females for all 4 calculations ($p < 0.05$). This was to be expected, so group comparisons were matched for gender.

In order to select the most useful measure of lean body mass, the 4 methods were compared against each other. Table 72 shows that in the normal subjects, the methods correlated significantly ($p < 0.001$) with each other. However, W-B 2 compared better with Sloan's method than W-B 1, and the BMI showed an inverse correlation with the other tests, suggesting that the correlation was mainly due to the subject's height. This is difficult to explain.

Table 72. Comparison of 4 calculations of bone mass using skinfold thickness and body diameters, in 89 normal controls. The correlation matrix shows the r value in the upper and p value in the lower triangular matrix.

	SLOAN	W - B 1	W - B 2	BMI
SLOAN		0.379	0.535	-0.780
W-B 1	0.0002		0.965	-0.410
W-B 2	0.0001	0.0001		-0.555
BMI	0.0001	0.0001	0.0001	

Table 73 shows that in patients with RA, on the other hand, the correlation between the anthropomorphic tests was more significant. In both groups, W-B 1 and W-B 2 were virtually replaceable ($r = 0.96$; 0.95). The table shows that W-B 2 is a more sensitive measurement than W-B 1 in RA subjects. The BMI showed very weak correlations with the body diameters, but a very significant inverse correlation with skinfold thicknesses. The BMI is, therefore, a suitable test of nutritional status in RA. The correlation matrix shows that in RA, the tests are not mutually exclusive.

Table 73. Comparison of 4 calculations of bone mass using skinfold thickness and body diameters, in 87 patients with RA. The correlation matrix shows the r value in the upper and p value in the lower triangular matrix.

	SLOAN	W - B 1	W - B 2	BMI
SLOAN		0.449	0.553	-0.616
W-B 1	0.0001		0.951	-0.174
W-B 2	0.0001	0.0001		-0.293
BMI	0.0001	NS	0.01	

It can be seen from table 74 that in patients with SLE the correlation between Sloan's method and W-B 1 was not statistically significant. Also, W-B 2 seems to be the more sensitive measure of LBM in SLE. The BMI appears to be a simple measure of nutritional status in SLE as well.

Table 74. Comparison of calculations of bone mass using skinfold thickness and body diameters, in 67 patients with SLE. The correlation matrix shows the r value in the upper and p value in the lower triangular matrix.

	SLOAN	W - B 1	W - B 2	BMI
SLOAN		0.19	0.23	-0.759
W-B 1	NS		0.94	-0.213
W-B 2	0.05	0.0001		-0.329
BMI	0.0001	NS	0.007	

When the above tables are analysed in conjunction, it is clear that W-B 2 is the most sensitive measure of LBW which is likely to help differentiate the 3 groups on the basis of nutritional status. However, Sloan's calculation is less complicated than the Willmore-Behnke formula, giving it a small practical advantage. The BMI is the simplest measure of nutritional status. It is probably the most suitable test since it shows significance in all the groups tested, and it correlates significantly with Sloan's method.

In the control group and patients with SLE, body diameters were found to correlate significantly with medullary and total width at the midshafts of all the metacarpals. Skinfold thicknesses did not show any significant correlations with metacarpal diameters. Furthermore, in the control group, BMI did not correlate with metacarpal diameters or metacarpal bone mass. Lean body mass calculated by the other 3 formulae, correlated significantly with metacarpal diameters, but only LBW1 and LBW2 correlated significantly with AI and CA. Carpal length correlated significantly with body diameters as well as skinfold thickness. The correlation with skinfold thick-

ness was negative, which is difficult to explain adequately. These findings suggest a significant relationship between nutritional status, bone formation and cartilage formation in health.

In RA, similar correlations were seen. However, LBM calculated from SFT (Sloan) did not correlate significantly with metacarpal diameters or bone mass. None of the skinfolds showed any significant negative correlations with bone parameters. The BMI did not correlate significantly with the metacarpal diameters or metacarpal bone mass. The carpal length correlated significantly with body diameters, skinfold thicknesses and lean body mass, but not with BMI. This probably means that the bone loss in RA is not related to factors which influence nutrition. Cartilage loss relates more significantly with disease activity than nutritional status in RA.

In the control subjects, height correlated significantly with metacarpal diameters, AI and CA, but not with the other calculations of bone mass. In the patients with RA, both height and weight correlated significantly with metacarpal diameters, AI and CA. Abdominal SFT did not correlate significantly with any of the radiological variables. All the above correlation coefficients were higher for comparisons in the RA group, suggesting that the same processes which influence bone mass in this disease may also influence lean body mass, but to a lesser degree.

McConkey *et al* (1965) found that older subjects receiving CS therapy had significant relationships between bone mass and SFT. They proposed that both defects were due to the same factor inhibiting collagen metabolism. Schorn and Mowat (1977) showed that penicillamine therapy had no influence on wound healing and

improved metacarpal bone mass. Their findings disputed the suggestion of McConkey *et al* (1965). The SFT measurements in our study were at different sites from those reported in the above studies, so our results cannot be compared. Measurements at the hands may be difficult due to soft-tissue swelling, while measurements at other sites may be influenced by loss of muscle bulk due to inactivity. Our findings suggest that thinning of the skinfolds is not a feature of RA in young subjects with metacarpal OP.

In a recent study by Pitt *et al* (1986), SFT was measured histologically and radiologically in RA subjects. The study was confined to postmenopausal subjects. They found, surprisingly, that although the RA subjects had reduced skin collagen, skin thickness was increased compared with normal controls matched for age and menopause. Our results cannot be compared with these results due to the differences in methodology.

DIETARY RECORD.

The 7-day dietary record allowed an analysis of the intake of various substances per 100G of food ingested. The calcium, phosphate, vitamin D, zinc, protein and total phosphate are likely to influence bone mass, so the analysis was restricted to these substances, and is shown in table 75. Recently, the 20-carbon fatty acids (20-CFA), such as arachadonic acid, have been implicated in diseases like RA and SLE.

For this reason, the 20-CFA were analysed in the 3 groups. The statistical techniques compensate for sample size (type I error).

Table 75. Chemical content per 100 Grams of food ingested by normal controls, patients with RA and SLE.

Chemical Compound Control	Mean SLE (SD) $n=44$	Mean RA (SD) $n=37$	Mean (SD) $n=76$
Protein	131.31 (162.6)	59.66 (18.96)	179.08 (185.85)
Calcium	915.15 (1111.8)	424.54 (193.87)	1390.7 (1844.13)
Phosphate	1749.07 (2055.6)	819.71 (294.35)	2596.91 (2911.66)
Zinc	18.71 (22.13)	8.51 (3.11)	24.52 (25.43)
Vit. D	2.38 (3.18)	1.22 (0.78)	4.66 (7.44)
Total Phos	1.51 (2.32)	0.95 (0.65)	2.80 (4.13)
20-CFA	0.30 (0.37)	0.12 (0.06)	0.37 (0.43)

The above dietary constituents were compared between the RA group and the controls, as well as groups matched for race and sex (not shown). There were significant racial differences ($p<0.05$) and males had a higher intake of all components ($p<0.1$) The protein content ($p<0.03$) and phosphate content ($p<0.02$) were signi-

ficantly higher in the RA group. Vitamin D intake was also significantly higher in the RA group. The other dietary components were not significantly different between the 2 groups. Since the bone mass in RA was significantly lower than that of the controls, it would seem unlikely that dietary habits significantly influenced metacarpal bone mass in these subjects. The other compounds were not significantly different in the 2 groups. No attempt was made to quantify dietary supplements. None of the subjects in this study was receiving vitamin D supplements at the time of the study.

The adequate intake of calcium and vitamin D, and the adequate sunlight in SA would suggest that OM was an unlikely cause of the osteopaenia in this group of subjects with RA. However, bone biopsy and vitamin D measurements in the serum were not carried out, so that OM was not conclusively excluded. OM is a recognised complication in some patients with RA (Ralston *et al* 1988). OM was also reported in 11% of elderly subjects thought to have OP (Schnitzler and Solomon 1983).

A comparison of the correlation between the various dietary compounds and the components of bone mass (TW, MW and CCW), confirmed the lack of any association. In the control group, protein, phosphate, zinc, folate and 20-CFA content showed a significant correlation with metacarpal lengths, but not with cortical widths. These correlations were absent in the RA group, suggesting that the effects of the disease override this potential dietary influence on bone metabolism. It would be interesting to evaluate the comparisons in patients with idiopathic post-menopausal OP, where dietary factors have been postulated in the pathogenesis (Richman *et al* 1979). We did not evaluate the relationships with vitamin C, which is a known factor in some patients with OP (Seftel *et al* 1966).

BIOCHEMISTRY.

Numerous biochemical variables were measured in the course of this study. These were directed towards an analysis of metabolic bone loss (serum and urine calcium and phosphorous,serum alkaline phosphatase, serum ionised calcium and PTH, urinary OH-Proline), nutritional status (serum albumen, cholesterol, retinol binding protein and thyroxine binding prealbumen), and disease activity (ESR, CRP, plasma viscosity, SH-groups, alpha-1-anti-trypsin). There is considerable overlap in these tests (Mbuyi *et al* 1982; Helliwell *et al* 1984b), but they will be separately grouped for the sake of convenience. SI units were used in the laboratory.

DISEASE ACTIVITY.

Several workers have compared radiological changes with laboratory changes in RA. With respect to the Larsen index, it has been shown that there is no correlation between improvement in laboratory variables and improvement in erosive change. Very few workers have related changes to bone mass, and the results are controversial (Reid *et al* 1982; Hancock *et al* 1978).

The erythrocyte sedimentation rate (ESR) (Westergren), C reactive protein (CRP) (mg/ml) and plasma viscosity (PV) (cP) are established laboratory markers of disease activity in RA. Other tests include the measurement of SH-groups (Lorber *et*

al 1964; Grimaldi 1980; Hall *et al* 1982), alpha-1-anti-trypsin, haemoglobin (Hb) and circulating immune complexes (CIC) (Forster and McConkey 1986). Retinol binding globulin (RBG) and thyroxine binding prealbumen (TBP) are markers of nutritional status in RA, but they may be elevated as an expression of the acute phase response (Helliwell 1984).

Some of these biochemical markers of disease activity are shown in table 76. The table shows that the RBG was not significantly different from that of the normal controls, but TBP and SH groups were both significantly higher in the RA group. This is surprising, since SH levels usually fall during active inflammation (Hall *et al* 1982).

Table 76. Laboratory markers of disease activity in patients with RA.

Test	*n*	Mean	Median	Range	
ESR	95	46.05	40	1-150	mm/Hr
CRP	80	2.68	1.9	0-11.5	mg/ml
PV	98	1.99	1.99	1.39-3.03	cP
A1AT	94	2.76	2.64	0.53-5.84	mg
SH	88	401.4	394	172-671	mg
TBPA	94	44.8	41	4-375	mg
RBG	70	43.57	46	8-88	mg

The ESR, CRP and PV, the standard tests of disease activity in RA, showed significant correlations with each other ($p < 0.0001$) [not shown]. However, the tests were not mutually exclusive, since the predictive value was less than 90% ($r < 0.9$) (not shown). Because there is some controversy about the value of the latter group of

tests (SH groups, RBG, TBP) in assessing disease activity in RA, we compared the correlation of these tests with the ESR, PV and CRP.

Table 77 demonstrates that the SH groups showed a significant negative correlation with ESR ($p < 0.002$; $r = -0.3$), confirming the findings of Hall *et al* (1982) but not with PV or CRP. TBP and RBG showed no correlations with these tests. A1AT, however, showed significant correlations with all 3 tests of activity. These findings show that A1AT may be a useful additional biochemical marker of disease activity in RA. Sulphydryl groups, RBG and TBP probably add little to the assessment of disease activity in RA. Despite recent criticisms (Chlud 1986), our findings confirm the value of the ESR as the standard against which newer tests should be evaluated. Bull *et al* (1986) also showed the importance of the ESR and PV in the laboratory evaluation of active RA.

Table 77. Correlation table comparing different biochemical tests of disease activity in RA.

		ESR	PV	CRP
SH	(*r*)	-0.31	-0.004	0.107
	(*p*)	0.002	NS	NS
TBPA	(*r*)	0.081	0.061	0.138
	(*p*)	NS	NS	NS
RBG	(*r*)	-0.139	-0.024	-0.033
	(*p*)	NS	NS	NS
A1AT	(*r*)	0.324	0.289	0.361
	(*p*)	0.001	0.004	0.0003

Earlier, we showed that the physician's evaluation of disease activity was an acceptable representation of clinical variables generally in use. In order to examine the relationship between laboratory variables and the physicians' impression, pairwise comparisons were performed between the 2 groups (*active vs inactive*) for ESR, CRP, PV, SH-groups, TBP, RBG and A1AT. Each group was simultaneously compared with the normal controls for the latter 4 variables. The only variables which were significantly different between the active and inactive groups were the A1AT and TBP (not shown). However, the SH-groups, TBP and A1AT were significantly different in the active group compared with the normal control values, but not in the inactive group.

Discriminant analysis showed that none of the laboratory variables were able to adequately differentiate the 2 groups due to the wide overlap of positive tests in patients with clinically inactive disease.

METABOLIC BONE DISEASE.

A wide range of tests in the urine and serum were used to study the biochemical effects of bone loss in RA. These are summarised in table 78.

Table 78. Biochemical tests of bone metabolism in patients with RA.

Test	Number	Mean RA	RA Range	Normal Range	
Total Calcium	97	2.36	2.13-2.77	2.1-2.6	(mmoles)
Inorganic Phosphate	96	1.08	0.7 -1.57	0.8-1.4	(mmoles)
Ionised Calcium	72	1.19	1.1 -1.7	1.1-1.2	(mmoles)
Urinary Calcium	90	1.76	0.1-10.8	1-5	(mmoles/l)
Urinary Phosphate	89	15.85	3.4-55.0	<35	(mmoles/l)
Urinary OH-Proline	93	204	41-999	(110-330)	(mg/l)
Plasma PTH	100	2.17	0-22.0	(0-10)	(*p*mol/l)
Alkaline PO4	96	95.8	2-253	(30-115)	(IU)

Table 78 shows that the range of biochemical readings in the patients with RA was higher than expected. The change must be due to abnormalities resulting from disease or related factors. Caution needs to be exercised in the interpretation of these changes. Although they may reflect metabolic bone events, they may also be related to disease activity (Mbuyi *et al* 1982). Table 79 shows the proportion of results which were abnormal in the patients with RA.

Table 79. Proportion of patients with RA whose biochemical tests were outside the upper limit of normal.

Test	% Abnormal
Total Calcium	3
Inorganic Phosphate	3
Ionised Calcium	**49**
Urinary Calcium	1
Urinary Phosphate	2
Urinary OH-Proline	10
Plasma PTH	1
Alkaline PO4	25

It can be seen from table 79 that less than 5% of subjects with RA developed significant abnormalities in total calcium, inorganic phosphate, urinary calcium and phosphorous, and plasma PTH. Elevated urinary OH-Proline levels are often regarded as a sign of bone resorption (Sambrook *et al* 1985a). However, it is possible that the elevation is due to active RA rather than an indication of bone resorption (Mbuyi *et al* 1982), particularly in view of the normal PTH, serum and urinary calcium and phosphorous seen in the subjects under study. The finding of an elevated ionised calcium in 49% is difficult to explain. It could have resulted in a suppression of PTH secretion. These findings confirm those of Kennedy *et al* (1979), but differ from those of Scott *et al* (1981) and Verstraeten and Dequeker (1986), who found low and normal levels respectively.

The fact that a greater proportion of subjects had elevations of AP than OH-P suggests that subjects with RA have excessive bone formation, probably as a reparative response to the chemically mediated resorption. However, AP may also be elevated in the acute phase response, making the interpretation difficult. The fact that GGT

levels were not simultaneously elevated suggests that the AP originated in bone rather than liver. Osteocalcin levels were not measured in this study, but have been found to be elevated by some workers, who have proposed that the OP in RA is certainly not due to a defect in bone formation (Gevers *et al* 1986).

Kennedy *et al* (1976) proposed that bone resorptive activity in RA is increased due to a resorption stimulating factor, which causes an elevation in Ca^{2+}. Our finding of increased ionised calcium with normal PTH lends support to this concept. Table 80 compares the correlation of ionised calcium and PTH, with bone mass measurements.

Table 80. Comparison of the correlation of ionised calcium, urinary OH-Proline and serum PTH with metacarpal bone mass in RA.

		Ionised Calcium	OH Proline	Serum PTH
CA%	(*r*)	0.17	0.10	-0.25
	(*p*)	NS	NS	0.01
CA/SA	(*r*)	0.1	0.10	-0.2
	(*p*)	NS	NS	0.05
M6HS	(*r*)	0.24	0.06	-0.23
	(*p*)	0.02	NS	0.02
M6CA	(*r*)	0.24	0.06	-0.24
	(*p*)	0.02	NS	0.01
Carpal Length	(*r*)	-0.1	0.01	-0.18
	(*p*)	NS	NS	NS

It can be seen from the table that ionised calcium was positively correlated with the 6 metacarpal bone mass but not the right 2nd metacarpal bone mass. These positive correlations would imply that bone is not the source of the ionised calcium. This effect was associated with a significant negative correlation with medullary width, probably suggesting that at least *some* of the Ca^{2+} was from resorbing bone. PTH, on the other hand, had a negative effect on 2nd metacarpal and 6 metacarpal bone mass. The mechanism of the resorption is not clear, since there was no significant correlation with total width or medullary width at the midpoint of the metacarpals. Urinary OH-proline, phosphate and calcium excretion did not correlate significantly with bone mass or the determinants of cortical thickness. These findings need to be interpreted against the background that bone mass changes reflect the result of disease over time while the blood results are a single measure at the time of study. Perhaps the elevated levels of ionised Ca^{2+} reflect some defect in transcellular transport of calcium in RA osteoblasts. Reith (1983) has demonstrated the complexity of this process under normal circumstances. Wouters *et al* (1985) proposed a possible relationship with rapidly destructive polyarthritis in a patient with adult onset Still's disease who became hypercalcaemic.

Stepwise multiple discriminant analysis was used to evaluate the predictive value of the above biochemical markers with respect to bone mass. CA% was the dependant variable for this analysis. Ionised calcium was the only significant predictor, but the predictive value was only marginally better than chance at 6%. The other biochemical markers were unable to significantly differentiate the osteopaenic group, as defined by a bone mass below the 10 percentile value of the normal control group.

It has been suggested that the ionised calcium may be a marker of disease activity in RA (Kennedy *et al* 1979). The levels showed no significant correlations with ESR, CRP or PV in our group of RA patients. We confirmed an earlier finding (Scott *et al* 1981) of a significant correlation between ionised calcium and total calcium levels ($r = 0.4; p < 0.0001$). However, while total calcium was elevated in only 3%, Ca^{2+} was elevated in 49%. This suggests that in our subjects with RA, Ca^{2+} was a more sensitive marker of metabolic events. Scott *et al* (1981) reported that RA is associated with hypocalcaemia, which is difficult to explain.

Urinary OH-proline correlated significantly with urinary calcium and phosphate, but not with serum PTH levels. This could imply that urinary OH-P was elevated as an acute phase response. Alkaline phosphatase levels correlated significantly ($p < 0.01$) with the ESR ($r = 0.32$), CRP ($r = 0.25$) and the PV ($r = 0.35$), confirming our earlier suggestion that the serum AP in RA may be an expression of the acute phase response. There was also a significant correlation between AP, total calcium and inorganic phosphate ($p < 0.01$). These findings are difficult to interpret adequately, but probably reflect that the biochemical changes are related to disease activity rather than bone kinetics. Our findings confirm the suggestion by Mbuyi *et al* (1982) that caution is needed in interpreting the changes in markers of metabolic bone disease in RA.

NUTRITIONAL STATUS.

Serum albumen is regarded as the most useful lab test of nutritional status (Anderson and Wochos 1982). Levels may also be reduced as a result of the negative acute phase response. The RBG has been used in nutritional evaluation of RA, but there has been some suggestion that it may actually be a marker of disease activity. The TBP has similar problems (Helliwell *et al* 1984). Table 77 showed that both (the RBG and TBP) showed no significant correlation with clinical variables such as the number of swollen joints and Ritchie index, or laboratory markers such as ESR, PV or CRP (table 77). It is likely that they were a measure of nutritional status instead. Albumin, on the other hand, showed a significant negative correlation with ESR and PV, but not CRP. It therefore, tends to behave as a negative acute phase reactant in RA, and is therefore an unsuitable measure of nutritional status in this disease.

Table 81 shows the biochemical measures of nutritional status in SLE. Comparison with the results in RA (Table 76) shows that there are differences in the 2 groups, but only the TBP levels were significantly higher in the RA group ($p < 0.0001$).

Table 81. Biochemical tests of nutritional status in patients with SLE.

Test $n=71$	Mean	Median	Range
RBG	55.79	55	18 - 108
TBPA	37.38	37	7 - 75
Serum Albumen	38.9	34.2	21-47
S-H Groups	391.03	378	205 - 691

A comparison of the correlation between these 2 lab tests (TBPA and RBG) and nutritional status using the 4 anthropomorphic methods in this study showed a significant correlation between the method of Sloan and TBP ($p<0.03$; $r=-0.24$) (not shown). The negative correlation is difficult to explain, implying that well nourished subjects have lower TBP levels. Further work is needed to clarify the significance of this finding. Our results do not compare favorably with those of Helliwell *et al* (1984a & b), who suggested that RA patients were significantly malnourished.

TREATMENT OF THE UNDERLYING DISEASE.

Almost all (96%) of the subjects in this study received regular NSAI drugs. Table 82 provides a breakdown of the type of therapy being used by the patients at the time of study. 39% of the RA group had received a disease modifying agent (DMA) at some stage of the disease. The patients with SLE required NSAI drugs less often (41%) and 18% of this group required Chloroquine Phosphate. Corticosteroid therapy was used at some stage of the disease in up to 28% of the patients with RA, compared with 69% of the SLE subjects. 13% of the RA subjects and 38% of the SLE subjects were receiving CS therapy at the time of study.

Table 82. Drug therapy in RA and SLE. A number of different non-steroidal anti-inflammatory drugs (NSAID) and disease modifying agents (DMA) were used. In the SLE subjects, Chloroquine was the only DMA in use.

Medication		RA	SLE
n		100	72
NSAID		94%	41%
SAARD		39%	18%
Prednisone	Past	28%	69%
	Present	13%	38%

NON STEROIDAL ANTI INFLAMMATORIES (NSAID).

Table 83 summarises the different NSAI drugs used in the treatment of the patients with RA. The mean and range are dependant on the dose and duration of therapy. These were not analysed any further, since changes were frequent and equivalent doses varied tremendously.

Table 83. Non-Steroidal Anti-inflammatory drug (NSAID) therapy in RA.

Drug	Number	Mean Dose	Dose Range
Indocid	65	27,009 mg.	(2100-67200)
Voltaren	68	33,446 mg.	(2100-50400)
Naprosyn	25	165,760 mg.	(14000-336000)
Feldene	27	3,090 mg.	(560-6720)
Other	20	75,250 mg.	(11200-268800)

Table 83 shows that diclofenac (Voltaren) was the commonest agent, often used in combination with indomethacin (Indocid). The preference for Diclofenac (Voltaren) reflects the bias of the clinician. The physicians at this clinic seemed to favour the use of oral diclofenac combined with rectal indomethacin.

The effects of NSAID on bone mass were not evaluated. However, recent evidence has shown that indocid and aspirin can inhibit osteoblast activity (Khokher and Dandona 1988). The osteopaenia of RA could be due to a reduced rate of formation, although studies of osteocalcin (Gevers *et al* 1986) mitigate against this possibility. It

is conceivable that the hypercalcaemia in RA is related to reduced incorporation of calcium into bone, due to an inhibitory effect of NSAID. However, the prevalence of hypercalcaemia was 49%, while 94% of the RA subjects were using NSAID regularly.

DISEASE MODIFYING AGENTS (DMA).

The disease modifying agents (DMA) listed in table 84 were those most widely used in the RA subjects under study. As with the NSAID, equivalent doses of these drugs vary, so a comparative study using total dose at time of study was not possible for these agents. Penicillamine and myocrisin are the oldest DMA's in use, so it is not surprising that these drugs were used more commonly. The frequency of use of a particular agent reflects the bias at this clinic for Gold and Penicillamine.

Table 84. Disease modifying agents (DMA) used in subjects with Rheumatoid Arthritis.

Drug	Number	Mean	Range
Penicillamine	25	163,968 mg.	(12600-1008000)
Myocrisin	24	1,334 mg.	(200-4800)
Ridaura	13	3,980 mg.	(336-10080)
Chloroquine	13	400,077 mg.	(14000-2555000)
Salazopyrine	14	402,000 mg.	(56000-1344000)

The mean duration of therapy with DMA's is shown in table 85. The period varied between 7 months and 5 years (mean 57 months). The tolerance was greatest with chloroquine, which was used longest. Reasons for stopping therapy with myocrisin or penicillamine ranged from skin rashes through blood dyscrasias, proteinuria and lack of efficacy. Skin rashes were the commonest side effect.

Table 85. Comparison of the duration of disease modifying agent (DMA) usage in patients with RA.

Drug	Mean	Range
Penicillamine	16 mths.	(3 - 60)
Myocrisin	20 mths	(1 - 96)
Ridaura	23 mths	(2 - 60)
Chloroquine	57 mths	(2 - 365)
Salazopyrine	7 mths	(1 - 24)

The effects of DMA's on bone mass were also evaluated (not shown). A comparison of the correlation between type of therapy and bone mass was performed for all 5 agents. This showed that there was no correlation between 2nd metacarpal bone mass and total dose of drug used, except for penicillamine. In addition, the total dose ($p < 0.0001$; $r = -0.4$) and duration of penicillamine therapy ($p < 0.0001$; $r = -0.36$) correlated significantly with femoral cortical width. The negative correlation was unexpected and may indicate that penicillamine has a negative effect on femoral cortical collagen metabolism. Another possible explanation for this may be that the peni-

cillamine group had greater impairment of lower limb function. Penicillamine was also negatively correlated with carpal length, supporting the suggestion that these patients had severe disease. When the bone mass of treated subjects was compared with those of untreated subjects, there were no significant differences. The possibility of a type I error cannot be excluded with the small numbers of treated subjects. The positive correlation with metacarpal bone mass supports the findings of Schorn (1983).

The total dose of ridaura correlated significantly with the 6 metacarpal bone mass ($p < 0.05$; $r = -0.2$) and medullary width of the right 2nd metacarpal, but not with 2nd metacarpal bone mass. The negative correlation probably implies more severe disease in the ridaura group. Chloroquine therapy showed a significant correlation with carpal length ($p < 0.0003$) and CMR ($p < 0.0007$), but not with bone mass. Total width in the metacarpals correlated significantly with chloroquine usage. Salazopyrine therapy did not correlate with bone mass or carpal length. However, there was a significant correlation with the length of all the metacarpals. Since these results are based on use of these drugs at any stage of the disease, one is unable to comment further on their effects on skeletal dynamics.

Significant correlations were also observed with the raw measurements of cortical thickness. Penicillamine therapy was significantly inversely correlated with inner diameter at the midshaft ($r = -0.23$). The possible reasons for this apparent paradox have been alluded to above, with respect to femoral cortical width. The work of Schorn and Mowat (1977) showed that this relationship with penicillamine therapy is unlikely to be due to the interference with collagen metabolism associated with the use of this drug. However, the effects of penicillamine on bone are not known.

Stepwise multiple regression analysis was applied to the evaluation of the clinical, laboratory, radiological and nutritional variables which might help in predicting the use of DMA therapy. In the analysis of penicillamine, the femoral cortical width was the best discriminant overall ($r^2 = 0.16$), while the CMR was the next best radiological discriminant ($r^2 = 0.04$). This supports the concept that penicillamine use is influenced by radiological severity. Duration of disease was the only significant discriminant of myocrisin therapy ($r^2 = 0.10$). This suggests either a trend to later use of myocrisin therapy or that patients tolerated it better. With respect to ridaura, the ESR was the most useful laboratory discriminant ($r^2 = 0.11$), while the CMR combined with CA% was the best radiological discriminant ($r^2 = 0.10$). The treated patients had more severe radiological changes. The use of chloroquine could be predicted by a number of laboratory tests. However, age at onset of disease was the most significant predictor ($r^2 = 0.08$), while the addition of ESR and RBG increased the predictive value to 20% ($r^2 = 0.20$). Carpal length was a significant predictor ($r^2 = 0.16$) and when combined with the femoral cortical width, X-Rays could predict over 20% of the variation in chloroquine usage. These findings suggest that DMA were generally reserved for the more severe cases. Similar studies are not available for comparison. Varying sample size may have had a role in some of the differences observed.

Dietary constituents were not generally useful predictors of the drug used, except in the case of chloroquine. Arachidonic acid fatty acid precursors (C-20 FA) in the diet had a significant predictive value of 16%. In fact, the combination with zinc, fibre and polyunsaturated fats gave a predictive value of 30%. These interesting findings

need to be explored further and may provide some important clues about the relationship between diet and disease activity in RA.

While none of the laboratory and radiological variables were of any predictive value in discriminating patients using salazopyrine, the dietary analysis proved very interesting. Folate content was able to predict 30% of the variation in the use of this drug. Together with polyunsaturated fats and calcium in the diet, over 40% of the variation in the use of salazopyrine could be predicted on a dietary analysis alone. This is the first such report and the implications are not clear. It is likely that the doctors using this drug were careful in warning their patients about increasing their intake of folate. The clinical variables were unable to significantly predict any of the treatment groups. These findings suggest that the use of DMA's at the clinic was probably based on a rational evaluation of clinical, laboratory and X-Ray features of the disease.

CORTICOSTEROID THERAPY.

The effect of corticosteroid therapy on bone is controversial (Guyatt *et al* 1984). Most studies are flawed by the overlap with menopausal subjects, making it difficult to remove the confounding effect of this important variable (Guyatt *et al* 1984). Some reports suggest that the effect is confined to trabecular bone, sparing the cortical bone of the metacarpals and femoral neck (Dykman *et al* 1985). It is not at all clear why this selective attack on trabecular bone should occur, since osteoblasts and osteoclasts from these areas have similar *in vitro* responses to biochemical stimuli. One possible explanation for these apparent differences could be the relative insensitivity of the Vernier caliper technique of radiogrammetry. Studies with SPA

measurement of bone mass have shown differences between treated and untreated subjects (Dykman *et al* 1985), offering the DM/MM ratio as a measure of this effect of CS therapy. Studies have also shown that a fluorinated form of prednisone (Deflazacort), causes less bone loss than prednisone (Gennari *et al* 1984; Balsan *et al* 1987).

Our data on CS therapy was analysed within each disease group (treated vs untreated) as well as across the groups (RA *vs* SLE). Table 6 showed that the patients with SLE required CS therapy for longer periods than those with RA. This is not surprising if one considers the nature of the respective diseases. Patients in the treated group received CS at some stage of their disease. They were not necessarily receiving CS at the time of study, and no record was kept of the period that steroids were discontinued prior to study.

Table 86 shows the amount of CS required by the 2 groups of patients. It is clear that CS requirements in SLE were considerably greater than in RA. The groups under study serve as a useful basis for comparing the effects of high-dose CS therapy (SLE) with low-dose therapy (RA), on metacarpal bone mass.

Table 86. Comparison of the total dose of corticosteroids used by patients with RA and SLE.

		RA	SLE
	Number	27(27%)	50(69%)
Daily Dose	Total	341 mg.	1327 mg.
	Mean	12.63 mg.	26.55mg.
	Range	1 - 35 mg.	5 - 60 mg.
Cumulative Dose	Total	277,116 mg.	1,092,840 mg.
	Mean	10,263 mg.	21,856 mg.
	Range	336 - 90,720	2520 - 75600

The comparison of metacarpal bone mass in the 2 groups showed that patients with SLE had a higher metacarpal bone mass than patients with RA, despite the greater requirements for CS therapy. The differences found between treated and untreated subjects in either group, are shown in Table 87. The SLE subjects who were untreated formed too small a sample so the results need to be viewed with caution.

Table 87. Bone mass in patients with RA and SLE based on prior use of CS therapy.Comparison of the total dose of corticosteroids used by patients with RA and SLE.

	SLE		*p*	RA		*p*
	CS(44)	No CS(15)		CS(27)	No CS(71)	
TW	0.81	0.81	NS	0.86	0.85	NS
MW	0.31	0.29	NS	0.41	0.37	0.03
CCW	0.51	0.52	NS	0.45	0.49	0.06
CA%	82.98	82.77	NS	74.07	77.56	NS
M6HS	61.47	62.36	NS	52.31	56.69	0.02

A correlation matrix showed that the 6 metacarpal index just reached significance when compared with the total dose of CS therapy ($p < 0.05; r = -0.2$). No correlation was found with daily dose or duration of therapy. The Larsen index at the right wrist also correlated significantly with the total dose of CS ($p < 0.02; r = 0.25$), suggesting that in RA, it was the patients with more severe disease who required such therapy. These effects on bone and cartilage are more likely to be due to disease activity than CS therapy.

A comparison of the correlation between bone mass and CS use showed that in SLE, the daily dose of CS was significantly correlated with 2nd metacarpal CCT ($p < 0.06$). In the patients with RA, these drugs had a significant negative effect on metacarpal length ($p < 0.05$). However, the correlation with TW, MW, CCT or M6HS was not statistically significant. MW was the only variable which reached a significant correlation with daily dose, duration and total CS dose ($0.05 > p < 0.1$). These findings support the earlier suggestion that these effects on bone metabolism are more likely to be a reflection of disease than a direct effect of CS therapy.

It is clear, therefore, that metacarpal osteopaenia in RA is a reflection of the disease process rather than the effect of therapy. This would support the suggestion by Byron and Kirwan (1986) that it is essential to evaluate the disease modifying effects of low-dose CS therapy. It is also possible that the use of this agent together with DMA may be better than either agent alone. There are likely to be reports of such combination therapy in the future.

Bijlsma *et al* (1986; 1988), have shown that the effects of methyl prednisolone pulse therapy are significantly different from those of regular CS therapy. These relationships need to be more carefully evaluated in young subjects with RA, particularly with respect to trabecular bone mass. None of the RA patients under study had received high-dose methyl prednisolone pulse therapy in the course of their disease. The relationship between bone mass and CS therapy could be the subject of a separate thesis.

SMOKING AND ALCOHOL CONSUMPTION.

Table 88 shows the number of smokers in the 3 groups of subjects studied. The numbers of smokers was too small for statistical analysis. The same was found for alcohol consumption. No statistically significant differences were demonstrated between the groups, controlling for the Type I error. The numbers of smokers and drinkers are surprisingly low in all the groups studied. The reasons for this are not clear, but *may* be related to the fact that many of the subjects were female. The relationship with caffeine intake was not evaluated in this study.

Table 88. Number of patients who smoked cigarettes or consumed alcohol among the 3 groups of subjects under study.

Study Group	Smokers	Non - Smokers
Controls	8	92
Lupus	13	59
Rheumatoid	12	88
	Drinkers	Non - Drinkers
Controls	6	94
Lupus	2	70
Rheumatoid	7	93

GENETICS.

The genetics of RA are not clearly understood. Studies in families suggest a hereditary tendency of auto-immune diseases in relatives of patients with the disease. However, twin studies have failed to show a simple Mendelian form of inheritance. Recent work has shown an association with the HLA (human leucocyte antigen) locus of the short arm of chromosome 6. HLA-DR4 is the antigen most strongly implicated. There is some suggestion that DR4 codes for seropositivity. Other evidence suggests that the gene codes for severity of disease (Gran *et al* 1984).

The analysis of our HLA data was confined to the Coloured group, since these were the largest in number. 16 A loci, 24 B loci, 7 C loci and 10 DR loci were tested. The Fisher exact t-tests were applied to the analysis. HLA A1 showed a significant association with RA in the Coloured group ($p < 0.03$; corrected $p = 0.06$) with a relative risk (rr) of 2.3. None of the B or C loci showed a significant association with RA. None of the patients in this series possessed HLA-B27, in contrast with recent overseas reports (Khan *et al* 1987; Dahlqvist 1986). HLA DR4, on the other hand, showed a very significant association with RA (corrected $p < 0.0002$). The relative risk of RA in DR4 positive Coloureds was 3.3. This corresponds with a Canadian report in Caucasians (Gladman and Anhorn 1986).

Stepwise discriminant analysis was applied to the prediction of CA%, using the HLA data. The only significant predictor of OP was HLA-A2. The sensitivity was 69.4%

and the specificity 54.8%. The DR antigens were not predictive at all. Although HLA-A2 has been implicated in RA (Tiwari and Terasaki 1985), it is conceivable that the presence of HLA-A2 may be an independent risk factor in the development of OP. Studies in postmenopausal OP do not support any HLA association with bone loss (Dequeker, personal communication), but our findings suggest that further studies are needed. It is conceivable that the uncoupling of resorption and formation may be related to a gene-specific defect in bone cells coding for collagen synthesis (Prockop 1988; Shapiro and Rowe 1984).

The relationships between HLA antigens and RA has also been studied with respect to disease severity and toxic reactions to therapy (Moens *et al* 1987). When the total group was divided according to DR4 status, we found that Whites who had DR4 had more active disease than those who did not, based on the clinical and laboratory evaluation. These differences were not seen in the Coloureds.

SEROLOGICAL STATUS.

Some workers have suggested that seronegative RA may be a different disease with a more favorable outcome. Numerous problems relate to the definition of seropositivity, as outlined by Gran and Husby (1987). Many of the patients included in the present study had been attending the arthritis clinic for some time before this research was undertaken. Since changes in sero-reactivity may be associated with DMA therapy, there was no point in dividing the total group according to seropositivity. In fact, our laboratory has a positive titre of 40 using the Latex test for RF, so that there is a further reason for not engaging in this artificial exercise. The 1987 revised ARA criteria (Arnett *et al* 1988) do not specify a titre for seropositivity. Although studies of prognosis suggest that seropositivity and subcutaneous nodules signal a worse prognosis, there is no evidence that disease activity is related to the degree of seropositivity at a particular moment in time, even though titre of RF may feature in multivariate analysis.

PREVALENCE OF OP IN RA.

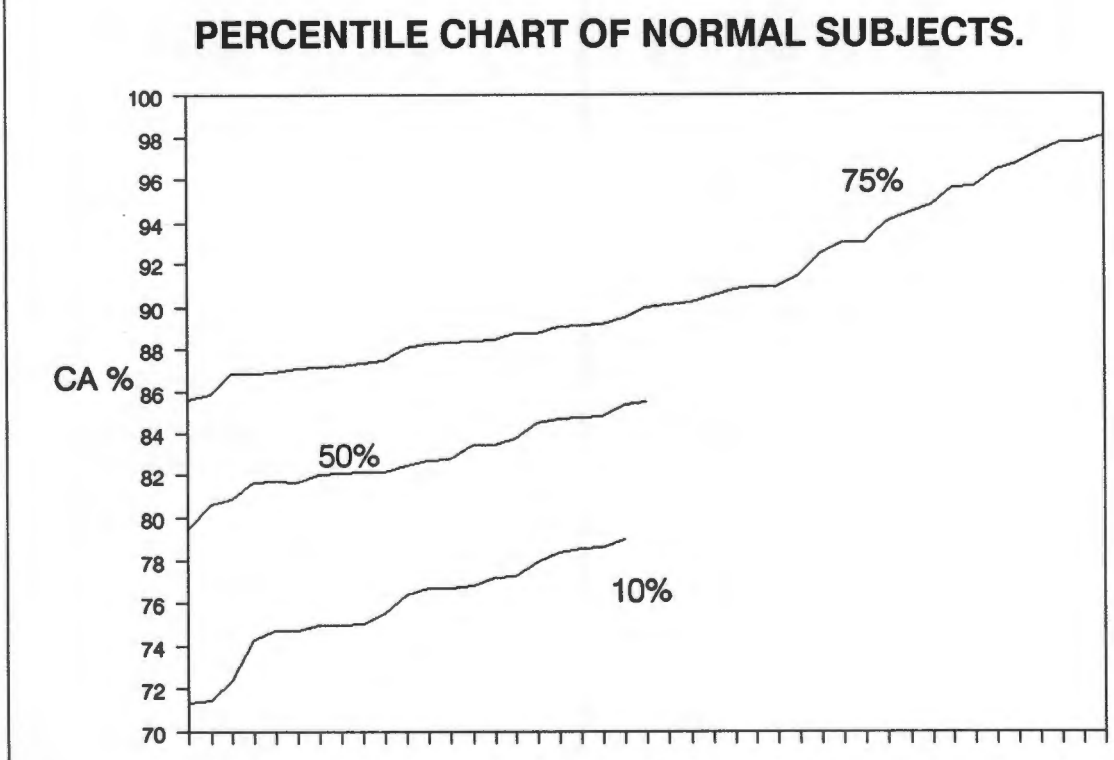
There is no consensus regarding the definition of osteoporosis. Confining the definition to subjects who have evidence of vertebral fracture runs the risk of late diagnosis and poor response to therapy. The numerical definition of osteopaenia is arbitrary, and varies with the method of bone mass calculation. This is confirmed in table 89. We divided the group according to Nordin's suggestion that subjects whose bone mass is below 2SD from the normal mean are more susceptible to the complications of OP (*fracture threshold*).

Table 89. Prevalence of osteopaenia using the 10 percentile of the control subjects as the cut-off point. CA/SA appears to be the most sensitive marker of OP in RA.

Measurement	Prevalence of Osteopaenia < 10 percentile Value
CA	33.7%
CA%	39 %
CA/SA	58.2%
M6HS	32.7%
M6CA	33.7%

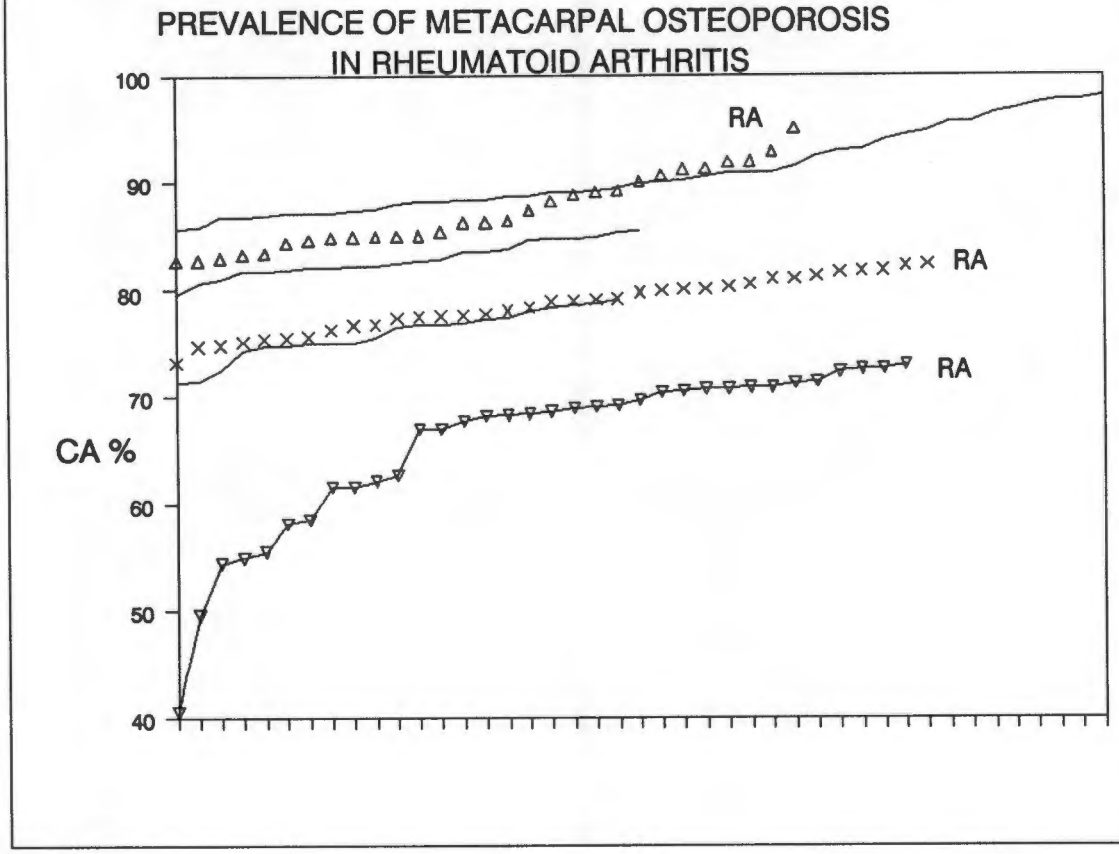
It is possible to construct a normogram for metacarpal bone mass, using the results obtained in the normal controls, as shown in Figure 27. The graph has been constructed to represent the ascending order of bone mass according to percentiles. The 25 th percentile has been used as the lower limit for this relationship.

Figure 27. Normogram for metacarpal bone mass derived from measurements in healthy young subjects aged between 18 and 50 years.



Patients at risk of fracture usually have bone mass below the 25 th percentile. Figure 28 shows the values for the RA subjects superimposed on the normogram in ascending order. There is a distinct group of RA subjects with osteopaenia.

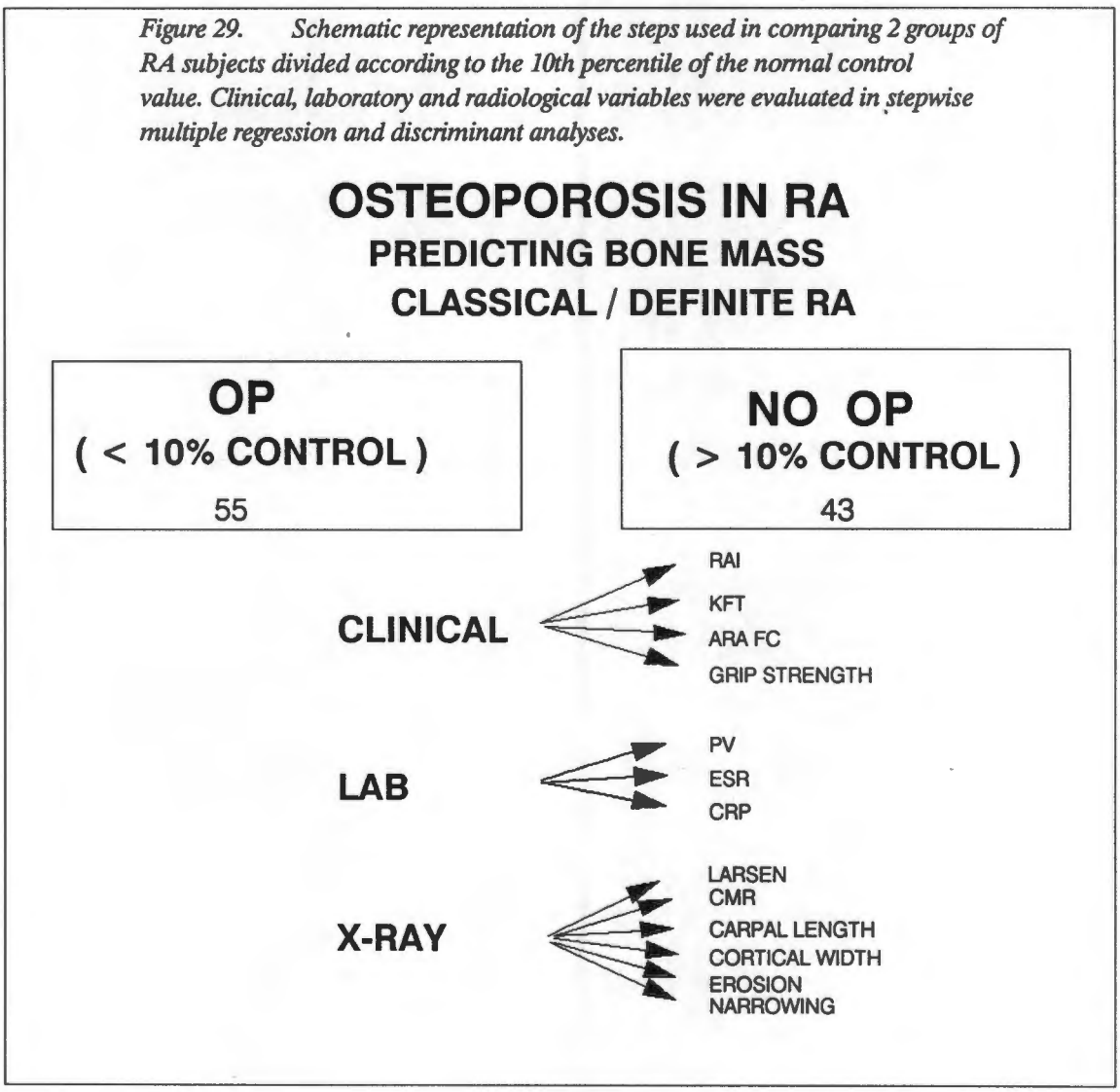
Figure 28. Metacarpal bone mass in rheumatoid subjects, superimposed on the normogram. There is a distinct group of RA subjects who are relatively osteopaenic. Subjects whose bone mass is below 25% of the normal control value are at high risk for fractures.



Using this information, 2 groups were defined each for CA% and M6HS according to the 25 th percentile of the normal controls.

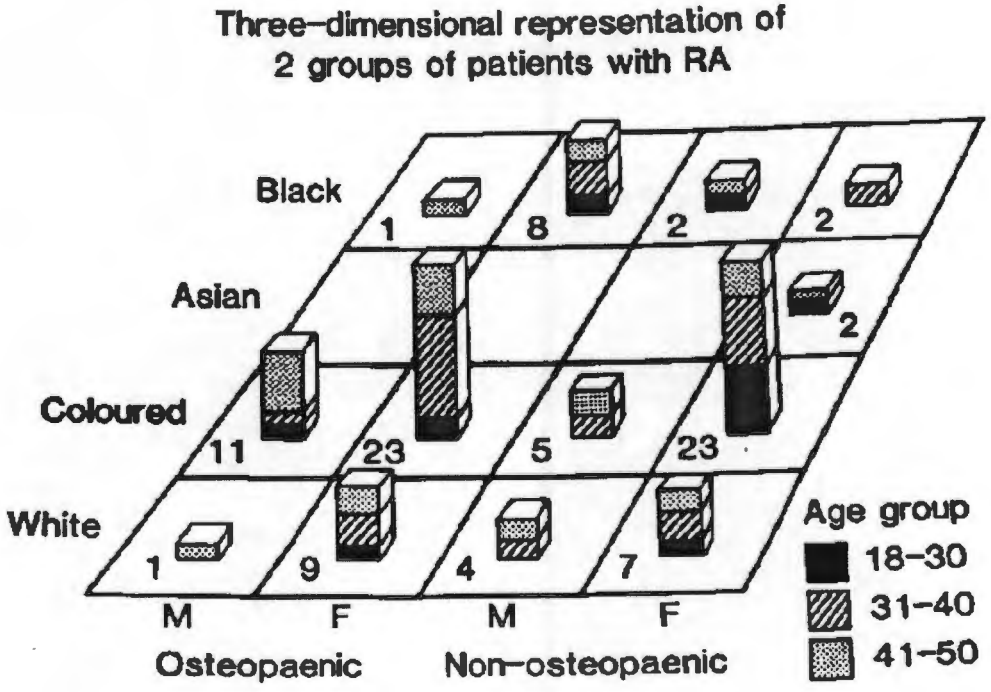
These were then compared with respect to clinical markers of disease activity, as well as age and disease duration (DOD), as outlined in figure 29.

Figure 29. Schematic representation of the steps used in comparing 2 groups of RA subjects divided according to the 10th percentile of the normal control value. Clinical, laboratory and radiological variables were evaluated in stepwise multiple regression and discriminant analyses.



The demographic features for the 2 groups are shown in figure 30. Osteopaenic subjects were comparable to non-osteopaenic subjects with respect to age, race and sex.

Figure 30. Histogram showing some of the demographic features in the group of patients with RA, comparing osteopaenic and non-osteopaenic subgroups, using a 3-dimensional model (M = Male; F = Female).



Patients who were osteopaenic had their disease for a significantly longer period of time, and were clinically distinguishable from their normopaenic counterparts by a significantly higher Keitel score. The results are shown in table 90. Comparison of the cortical thicknesses showed that the medullary diameter (endosteal resorption) explained the greatest degree of the variation in bone mass (CA%) in the groups.

Table 90. Clinical, laboratory and radiological variables which help to predict combined cortical width (CCW) in Rheumatoid Arthritis, using stepwise multiple regression analysis.

Predictor	Partial %	Total %
CLINICAL		
1. Biacromial Diameter	21.69	
2. Duration of Disease	7.92	29.61
3. Extension	3.71	33.32
LABORATORY		
1. DOD	11.64	
2. TBG	7	18.64
RADIOLOGICAL		
1. Carpal Length	13.02	
2. CMR	11.62	24.64

These findings confirmed those of the discriminant analysis, which showed low sensitivity and specificity for the clinical and laboratory variables (Table 91). When all the variables were included in the discriminant analysis, the sum of medullary widths was the most powerful predictor of OP in RA.

Table 91. Discriminant analysis for classifying subjects with RA into 2 groups based on the 10 percentile of normal control subjects, using CA% as the dependant variable.

Variable	CLINICAL Duration of Disease	LAB PV Σ TW	XRAY Σ MW Σ CCW	ALL Σ MW
SENSITIVITY	75%	70%	90%	90%
SPECIFICITY	60%	60%	85%	85%

The sensitivity of digitised radiogrammetry in the diagnosis of OP in RA was tested by stepwise discriminant comparison between the RA group and normal controls. The metacarpal diameters of the right 2nd as well as the sum of 6 metacarpals were the independent variables, while the underlying diagnosis was the dependant variable. The sum of CCW of 6 metacarpals was the best discriminator, with a sensitivity of 61% and a specificity of 68%. The positive predictive value was 66% and the negative predictive value was 63%. This means that the technique is confidently able to detect up to two-thirds of osteopaenic patients. This is far superior to the *eyeballing* technique, which has an unacceptable false positive and false negative rate (Pogrund *et al* 1981). These results, when incorporated in Bayes' theorem (Ott *et al* 1983; Fletcher *et al* 1982; Lequesne 1988), show a prevalence of osteopaenia in RA of 55%, not too dissimilar from our prevalence of 58% using CA/SA.

In SLE, TW was the most significant discriminant, with a sensitivity of 64% and specificity of 48%. The positive predictive value was 58%, while the negative predic-

tive value was 57%. This is not surprising, since the genesis of the bone loss in the 2 diseases is obviously different.

If one confined the discriminant analysis to the comparison between the RA OP group (as defined earlier) and the normal controls, the combined effect of the sum of TW and the sum of CCW of the 6 metacarpals showed a sensitivity of 75% and a specificity of 91%. The positive and negative predictive value was 81%, so that only 20% of such patients might be misclassified. Clearly, the digitised technique appears to be ideal for quantitating bone mass in patients who have radiologically obvious cortical thinning, as well as those patients with RA who do not have evidence of erosive disease at presentation. This latter group is particularly important, since studies with the use of MRI have shown erosions when JAOP is the only radiological feature present (Gilkeson *et al* 1988). Similar discrepancies with regard to erosions have been shown with the use of microfocal radiography (Buckland-Wright 1983a & b).

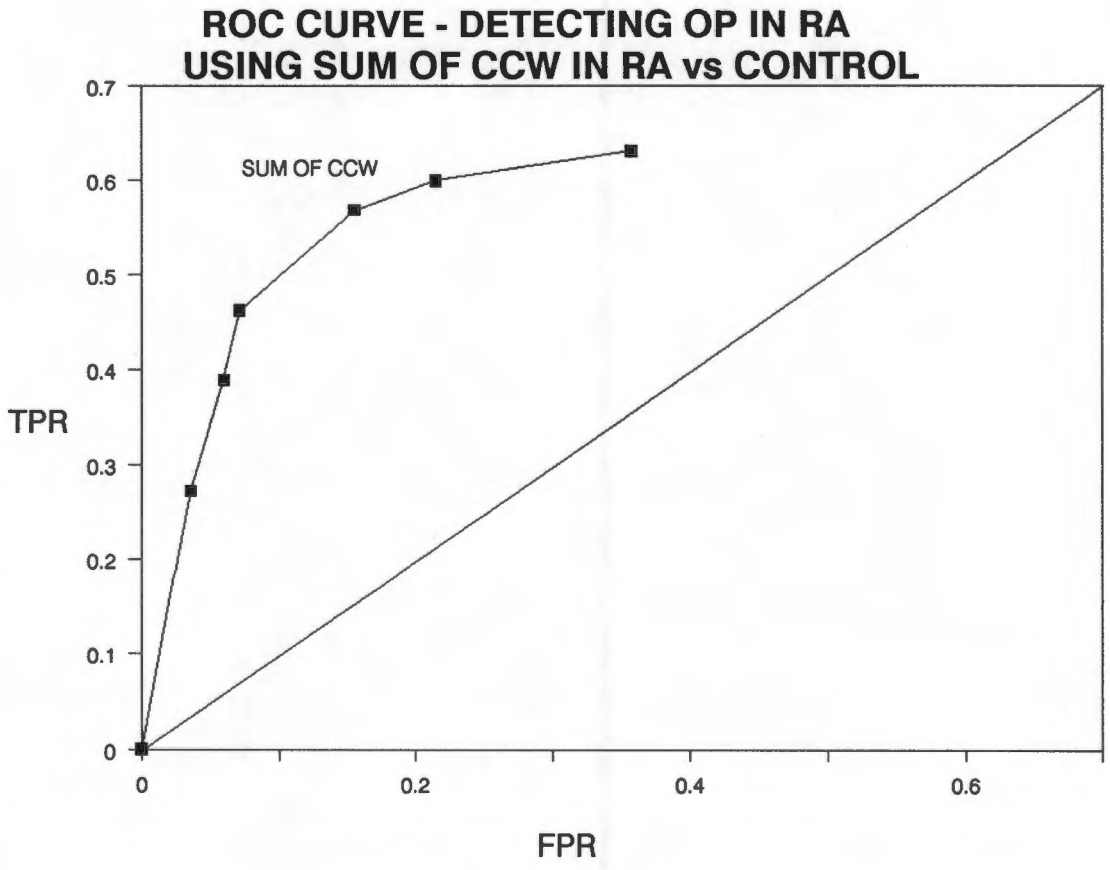
Its value in the serial evaluation of patients with RA receiving DMA's needs to be studied in a prospective, randomised, controlled fashion. The method shows potential for application in RA, meeting several of the requirements proposed by Pullar and Capell (1985; 1986).

DETECTABILITY OF OP - ROC ANALYSIS.

Although stepwise multiple regression analysis and stepwise discriminant analysis are useful in evaluating relationships between independent variables, they offer little information regarding the likelihood of detecting an abnormality (*detectability*). Receiving operator characteristic (ROC) curves have proved to be a useful adjunct to clinical radiology (Centor 1985a & b). The development of a Visicalc programme (Centor 1985a) for use on the personal computer (PC) makes this a *user friendly* device in statistics. The meaning of the area under the ROC curve is explained by Hanley and Mc Neil (1982). The technique has not previously been applied to the evaluation of OP in RA. In the first instance, ROC curves were used to determine the most useful radiogrammetry measurement for detecting RA.

Figure 31 shows that the Σ CCW was very effective in detecting OP in RA. Although the true positive ratio (TPR) and false positive ratio (FPR) do not reach 1.0, the area under the ROC curve is statistically very significant. The lower FPR suggests that wrong diagnoses would be made less frequently using this radiological technique. It also confirms that the Σ CCW was an important measure of metacarpal OP.

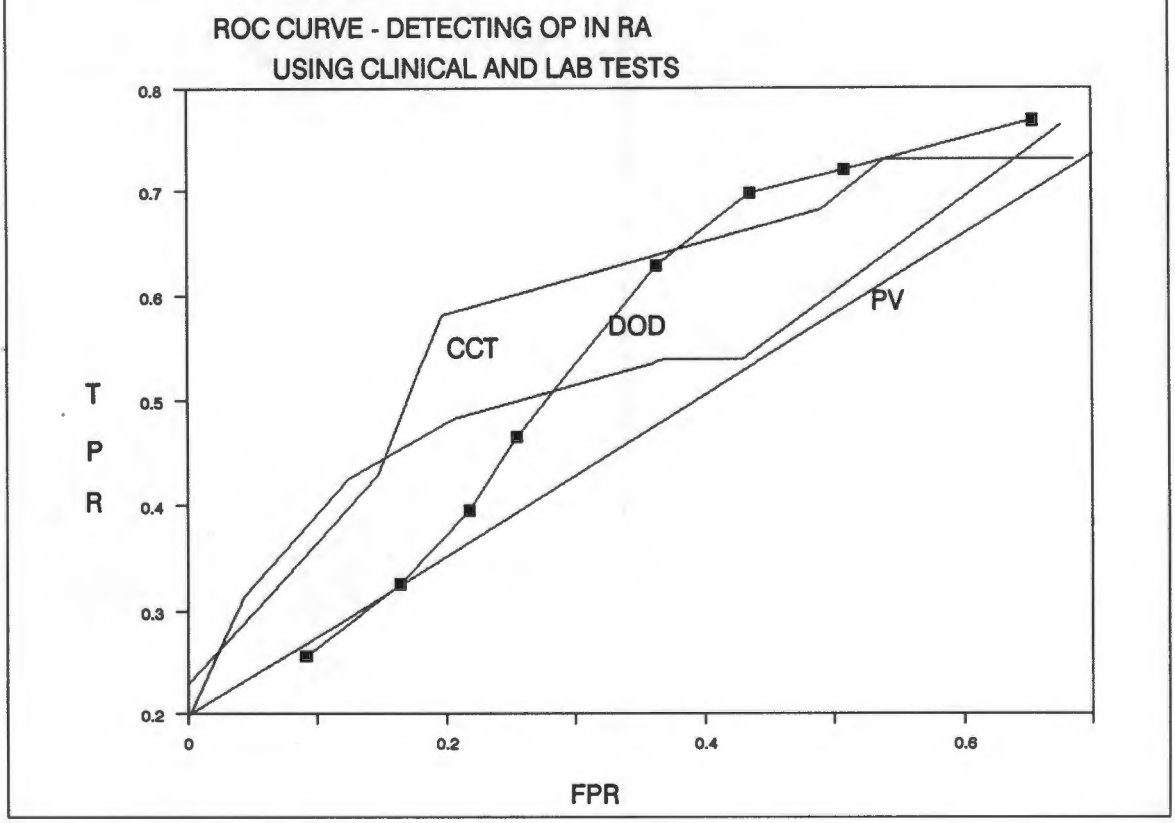
Figure 31. Receiving operator characteristic (ROC) analysis of factors which may be useful in detecting osteoporosis. The Σ CCW was the most useful variable in detecting OP at the metacarpals. The TPR and FPR are less than 1.0, but the area under the ROC curve is statistically significant ($p < 0.05$).



In the 2nd part of the analysis, the markers of disease activity based on the discriminant and regression analyses were tested for their ability to detect OP in patients with RA. A complete evaluation of all the variables is beyond the scope of this thesis.

Figure 32 shows the ROC curve derived from a comparison between OP and non-OP subjects with RA. The area under the ROC curve is far less than in the earlier curve. The reason for this is probably due to the wide overlap in metacarpal bone mass in the 2 groups of patients with RA. Although duration of disease and PV showed a significant ability in detecting osteopaenia, measurement of the combined cortical widths of 6 metacarpals was clearly the superior test in a dichotomised decision making process. This lends further support to the earlier suggestion that bone mass cannot be adequately predicted from clinical and laboratory variables alone.

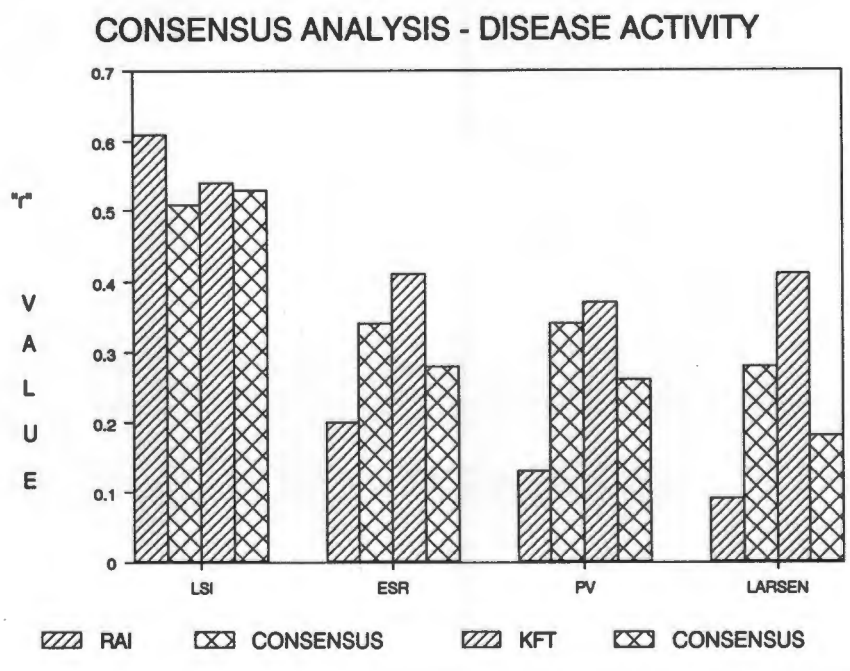
Figure 32. Receiving operator characteristic (ROC) analysis of factors which may be useful in detecting osteoporosis in RA. The duration of disease and the plasma viscosity were the most important determinants of the osteopaenia in RA subjects whose bone mass was less than the 10 percentile for matched normal subjects. The TPR and FPR are less than 1.0, but the area under the ROC curve is statistically significant ($p < 0.05$).



DETECTABILITY OF DISEASE ACTIVITY IN RA.

Consensus analysis (Bull *et al* 1986) was used in the evaluation of the various clinical, laboratory and radiological variables which help to assess inflammatory activity of RA. The RAI and KFT were the basis for comparison. However, the DQ and HFI were also used in determining a consensus correlation coefficient (Bull *et al*, 1986). These 4 clinical variables were correlated with the other clinical variables, the ESR, CRP, PV and radiological variables (CA%, Larsen index and CMR at the right wrist). The consensus analysis for the more important variables is depicted in the histogram shown in figure 33.

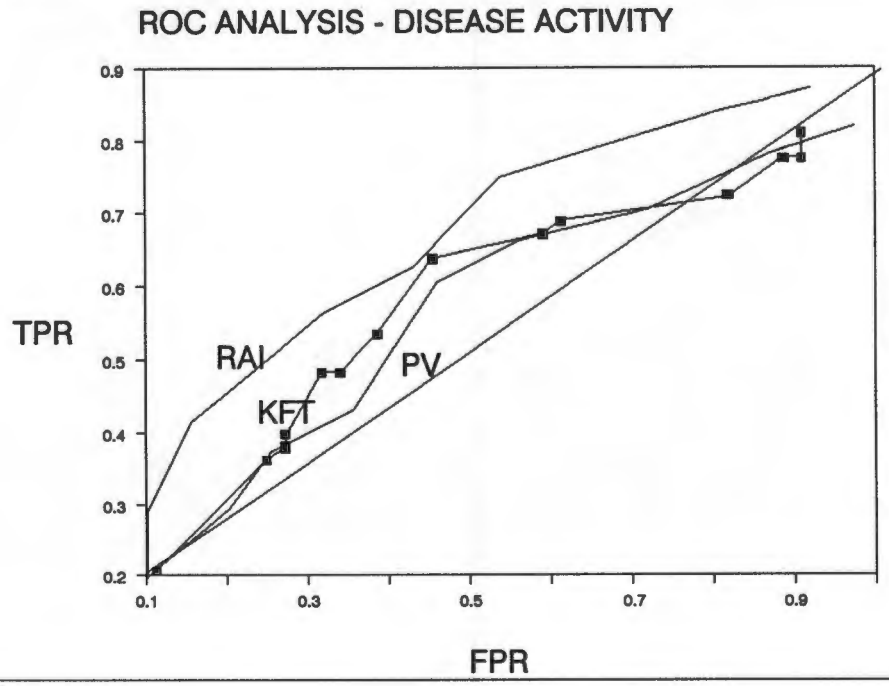
Figure 33. Histogram showing the effects of consensus analysis on the comparison between the RAI and the KFT as measures of disease activity. The consensus was derived from the RAI, KFT, HFI and DQ. Comparisons were made with the LSI, ESR, PV and Larsen index at the right wrist. The KFT is superior to the RAI as a measure of disease activity in this group of young subjects.



With respect to the LSI, the RAI and KFT compared similarly. In the case of the ESR and PV, the correlation with KFT was considerably better than the consensus, while the correlation with RAI was less than the consensus. The most significant finding was the marked difference in the correlation with the Larsen index at the right wrist. The KFT was superior to the RAI in these relationships.

In addition, the concept of the ROC curve was applied to the detectability of disease activity using clinical and laboratory variables. This has not been previously reported in RA. Figure 34 shows that the RAI had the greatest area under the curve, followed by the KFT and finally the PV. It is interesting that ESR, CRP, CA%, M6HS and carpal length had no significant area under the ROC curve.

Figure 34. Receiving operator characteristic (ROC) analysis of factors which may be useful in detecting disease activity in RA. Other clinical, laboratory and radiological variables did not have a significant area under the ROC curve. The KFT performed better than the RAI in this test of detectability.



It is clear from these findings that the clinical evaluation is a good reflection of laboratory and radiological features in the majority of patients, particularly if this is based on the KFT.

PATHOGENESIS OF BONE LOSS IN RA.

The pathogenesis of bone loss in RA is not known. Several different statistical techniques were used to determine the possible causes of bone loss in this group of subjects with RA

STEPWISE MULTIPLE REGRESSION ANALYSIS.

The stepwise multiple regression analysis for CA% provided a number of predictors of bone mass. The independent variables tested included all the clinical, laboratory and radiological investigations outlined in the protocol. These were used to predict CA% and combined cortical width (CCW) as separate dependant variables for analysis. The predictive values of the tests for CCW are shown in table 90. The stepwise multiple regression analysis for CA% showed that measurement of cortical width at the right 2nd metacarpal could predict up to 45% of the variation in bone mass.

DISCRIMINANT ANALYSIS.

These same variables were then applied in a discriminant analysis to obtain the sensitivity and specificity of the individual tests, as shown in table 91.

The analysis showed that radiology is absolutely essential in the evaluation of OP in RA. Furthermore, it can be seen that an accurate assessment of OP can be achieved only by careful measurement of the total width and medullary width at the midshaft of 6 metacarpals. We did not analyse the calculation of bone mass using 3 (Reid; personal communication) or 4 metacarpals (Virtama *et al* 1968). Table 91 shows that digitised measurements were very effective in discriminating the osteopaenic RA subjects.

Not surprisingly, radiogrammetry was the most sensitive and specific method of detecting OP in RA. The sum of TW and MW of 6 metacarpals had a specificity of 90% and a sensitivity of 85%. When one analysed the clinical, laboratory and radiological variables as a group, the sum of the MW and CCW of 6 metacarpals proved to be the most sensitive and specific predictors of OP in RA. These findings suggest that radiology is absolutely essential in the diagnosis of OP in RA. Little inference can be drawn regarding the presence of OP based on clinical, anthropomorphic or laboratory measures in these patients.

Table 92 shows the differences between the osteopaenic and non-osteopaenic groups with respect to the important variables identified by the stepwise regression analysis.

Table 92. Comparison of osteopaenic and non-osteopaenic subjects with RA, showing the differences between some of the clinical markers of disease activity in RA.

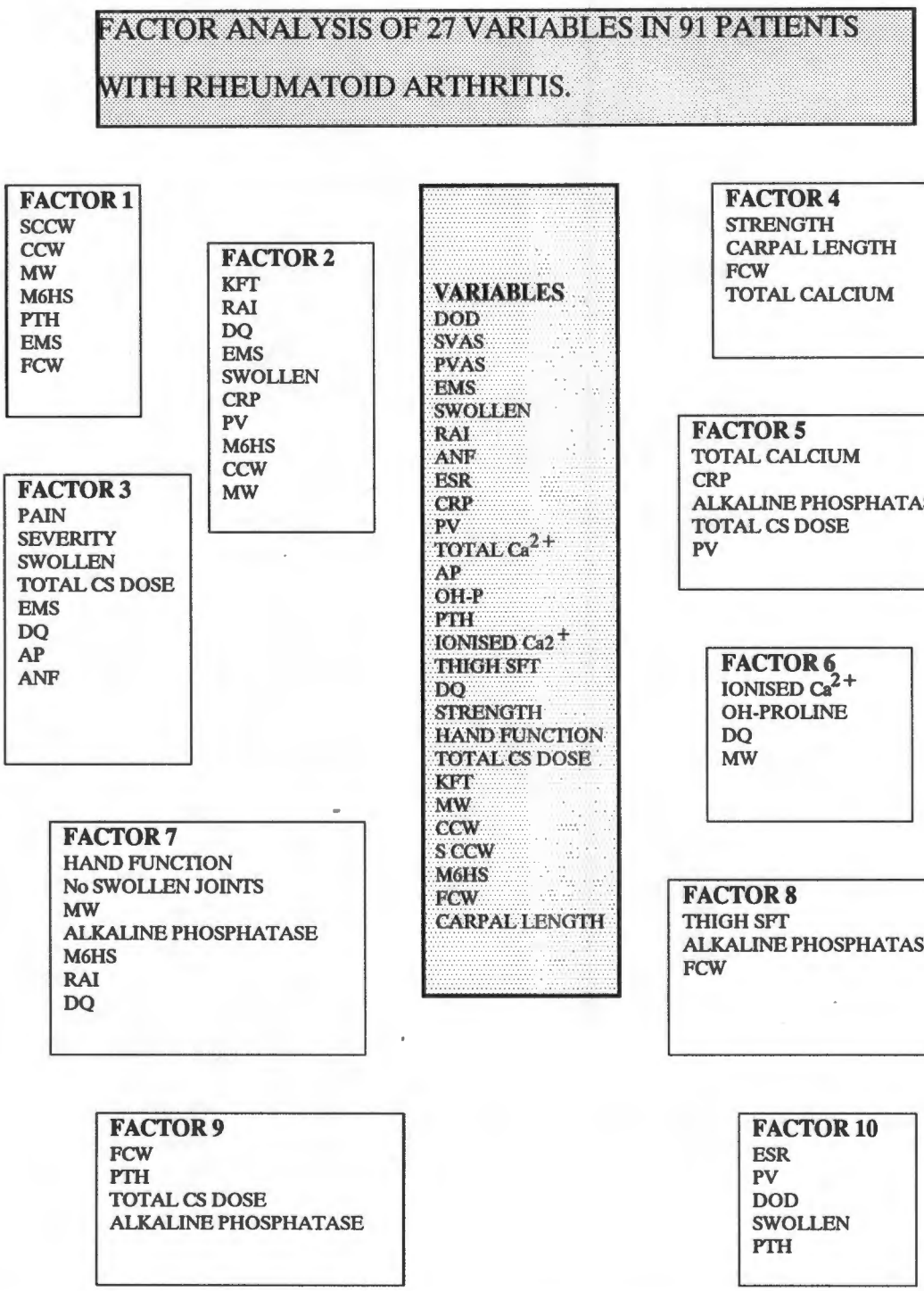
	OP	Non-OP	*p* value
Age	39.46	36.27	NS
DOD	124.8	72.48	0.0001
RAI	19.32	17.71	NS
KFT	40.88	33.62	0.05
LSI	48.72	48.44	NS
DQ	46.09	40.64	0.05
Swollen	5	4	NS

It is clear that the stepwise multiple regression and discriminant analyses did not provide conclusive information regarding pathogenesis of the reduced bone mass seen in RA.

FACTOR ANALYSIS.

The application of factor analysis (Gorsuch 1974; Green 1978) is useful in further elucidating possible mechanisms of disease. For the sake of convenience, only 27 variables were evaluated with the use of factor analysis. These represented disease activity, disability, laboratory and radiological markers of bone metabolism. The technique isolated 10 factors consisting of a number of variables, shown in Figure 35.

Figure 35. Results of factor analysis, using 27 variables selected to represent features of disease activity, functional disability, nutritional status, measures of bone mass and metabolic bone disease.



Careful examination of the individual factors provides useful information for speculating about the cause of OP in RA. Each factor shows the variables relative to the *load* within that factor (*factor loading*).

Factor 1 shows that serum PTH and duration of EMS were significantly associated with metacarpal cortical thinning. It shows also that femoral cortical width (FCW) is reduced similarly to the metacarpal cortical width. It would seem from this that PTH plays a significant role in the genesis of OP in RA. The fact that duration of EMS is included in this factor probably reflects the effect of disease activity on PTH metabolism (bone mass). It is interesting that the laboratory measurements of PTH revealed values within the normal range for most subjects. Perhaps the effect is due to a PTH-like substance, as suggested by Kennedy *et al* (1976).

Factor 2 shows that the KFT and DQ behave as disease activity markers rather than *pure* measures of disability. In addition, it would seem that measurement of metacarpal bone mass is a useful radiological measure of disease activity in RA. The variables in this factor show that OP is an effect of the inflammatory process, supporting the suggestions that circulating or locally produced substances are responsible for the relative bone deficiency in RA.

Factor 3 shows that the PVAS and SVAS are useful markers of disease activity. In addition, alkaline phosphatase elevation is likely to be a manifestation of the acute phase response. The ANF titre *may* reflect active disease. This factor shows that the use of CS therapy was generally confined to patients with active disease at the time of study. The potential effects of CS on bone metabolism are likely to be indirectly re-

lated to the osteopaenic effects of active disease rather than a direct effect of CS on bone.

Factor 4 is difficult to interpret with confidence. It would appear that changes in strength of the fingers and hand are associated with loss of cartilage (at the wrist) as well as loss of cortical bone (at the femur). This osteopaenic effect *may* be reflected to some extent in the level of serum calcium.

Factor 5 consists of variables generally associated with active disease. The fact that total calcium is included in this factor supports the view that bone deficiency in RA is a systemic feature of the underlying disease.

Factor 6 shows that ionised calcium and OH-proline (markers of bone resorption) probably reflect endosteal resorption at the metacarpals in RA. The inclusion of DQ in this factor is likely to be due to its value in assessing active disease. This finding is in support of the recent report (Wolfe *et al* 1988) that the Stanford HAQ could be used to grade disease activity in RA.

The variables included in *factor 7* add further support to the role of inflammation in mediating the osteopaenia of RA. It is interesting to see that the test of simple hand function are also useful in evaluating disease activity.

Factor 8 shows that thigh SFT is significantly associated with femoral cortical thinning. This could imply that the systemic mediator of the bone deficiency state in RA has a comparable effect on skin collagen, as postulated by Mc Conkey *et al* (1965). The significance of alkaline phosphatase in this factor is not clear. It seems to

behave as an acute phase reactant in RA, so that one might interpret this as further evidence for the role of inflammation as a cause of the OP in RA. Osteocalcin levels are probably better than alkaline phosphatase (Tanaka *et al* 1988).

Factor 9 shows that CS usage is generally associated with femoral cortical thinning, which is most likely mediated by a PTH-like substance. The presence of alkaline phosphatase in this factor is probably reflecting the earlier suggestion (*factor 3*) that CS therapy is generally confined to patients with active disease. It is interesting to speculate that this factor supports a bone-depleting effect of CS therapy (inhibiting formation and stimulating resorption), but it is more likely that disease activity is the dominant factor unifying these variables.

Analysis of *factor 10* shows that the disease was more active in patients who had long-standing disease. The effect of duration is likely to be cumulative. Bone loss in RA is likely to be due to prolonged exposure to a PTH-like substance. Evidence from the literature (Gowen *et al* 1988) suggests that this substance is likely to be related to either IL-1, tumour necrosis factor (TNF) or other, yet unknown, stimulant of bone loss in RA.

The above analysis shows convincingly that metacarpal osteopaenia in RA is due to disease activity rather than the disability associated with the disease or the drugs used in controlling inflammation.

CONCLUSION.

REMARKS.

1. Rheumatoid Arthritis causes osteoporosis and the effect is worst at the metacarpals. DPA measurements of vertebral BMD are needed in young RA subjects to determine the extent of the generalised OP.

2. The metacarpal bone mass can be objectively measured by digitised radiogrammetry. The correlations with erosion scores and CMR suggests that it may be useful in the progressive evaluation of radiological change in RA.

3. The lack of a universal definition of osteoporosis results in conflicting data on prevalence. The prevalence of 55% in this study is higher than other reported series. This difference may be due to the improved precision of the digitiser technique.

4. Osteoporosis at the metacarpals cannot be detected early without careful measurements of the diameters at the midshafts of 6 metacarpals.

5. CA% is the most suitable single measure of metacarpal bone mass in RA.

6. The prevalence of hypercalcaemia is close to 50% in young adults with RA. Total calcium is not a good enough measure of this increase, which is not associated with increased levels of PTH. The mechanism of the hypercalcaemia was not clarified by this study. The source of the ionised calcium was likely to be from resorbed bone, but other explanations need to be con-

sidered. It is possible that the inflammatory process interferes with the deposition of calcium into bone from the effects of the disease either on cellular membrane transport or incorporation into proteins. Another possible source may have been the inadvertent ingestion of milk or other dairy products prior to drawing blood for analysis. Further research using *in-vitro* studies of serum and bone from young patients with RA are needed to clarify these osteopaenic effects of the disease.

7. *Simple* hand function is significantly impaired in RA, but this does not seem to have any significant role in the genesis of metacarpal osteopaenia. The effect on bone mass is mediated through inflammation, which is suitably represented in the loss of hand function.

8. In contrast, loss of hand strength as a result of arthritis contributed significantly to the loss of metacarpal bone in RA. It was also associated with loss of bone in the femur as well as loss of cartilage at the wrist. These findings confirm the important relationship between muscular activities and bone and cartilage metabolism. The lack of an association between the HFI and metacarpal bone mass suggests that systemic factors are more likely to be responsible for the osteopaenia.

9. Young patients with RA are generally well nourished. Generalised thinning of the skin did not accompany the generalised OP seen in our young subjects with the disease. Malnutrition was an unlikely cause of the OP seen in these subjects. Thigh SFT was associated with active disease in the factor

analysis, suggesting that the mediators of inflammation may have a common effect on bone and skin collagen synthesis.

10. Dietary factors did not appear to play a role in the development of OP in RA. In fact, RA patients had better dietary habits than the normal controls and patients with SLE in this study. However, dietary factors seemed to be important in the inflammatory process and need to be more carefully studied from that point of view. Some interesting relationships were observed between dietary habits and DMA usage. These need to be looked at more critically in future research.

11. Biochemical markers of bone turnover were generally unhelpful in the evaluation of OP in RA subjects who were osteopaenic. Contradictory changes were found in the markers of bone formation and resorption. The acute phase proteins were able to explain a significant proportion of the variation in alkaline phosphatase and ionised Ca^{2+} but not OH-proline. This suggests that the pathogenesis was probably related to a combination of increased resorption and decreased formation. Ionised calcium was a more sensitive index of osteopaenia than total serum calcium.

12. Corticosteroid therapy was associated with metacarpal osteopaenia. However, patients with active disease were more likely to receive CS therapy. Therefore, it is not certain whether the CS or the disease activity was the overriding factor in this bone loss. Patients with SLE used bigger doses for longer periods than patients with RA, but their metacarpal bone mass was

higher than that of the RA subjects. The findings showed that the systemic factor in RA was not significantly modified by the administration of CS.

13. NSAID's and DMA's did not contribute significantly to metacarpal osteopaenia. The lower bone mass in patients receiving DMA's was more likely to be a manifestation of more severe disease than a direct effect of these drugs on bone metabolism. Prospective studies are needed to evaluate the effects of DMA's in retarding bone loss. In the light of the recent evidence suggesting an inhibitory effect of NSAID's on bone formation, future studies should evaluate a group of RA subjects not receiving NSAID.

14. The finding of an increased prevalence of HLA A2 in this group of subjects *could* be the potential genetic link with OP. This is an interesting area for future research.

15. Disability and disease activity seemed to have a synergistic effect on bone loss in RA. However, disease activity is much more important than disability in the genesis of the OP in RA. Although longer disease duration contributed significantly to bone loss in RA, the mechanism was not due to progressive disability as suggested in previous studies (Als *et al* 1985), but more likely due to the prolonged effects of inflammatory mediators on bone metabolism.

16. The clinical measures of disease activity correlated more significantly with radiological changes of RA, than did the laboratory investigations. These findings support those of other studies and confirm the importance of careful clinical examination in the assessment of disease activity in RA.

17. Objective functional evaluation by detailed techniques such as the Keitel function test and modified HAQ (DQ) may be a more useful and reproducible measure of active disease than the conventional measures such as the Ritchie index or Lansbury systemic index.

18. Bone mass can be significantly predicted by anthropomorphic and clinical measurements. However, the predictive value is far less than that of careful measurement of metacarpal cortical width using a digitiser.

19. Generalised OP is a feature of SLE. The bone loss at the femur may predispose to the development of avascular necrosis of the femoral head in the small proportion of subjects in whom this is not associated with CS usage. This is an exciting area for research in the future.

20. There are several differences in the mechanism of metacarpal osteopaenia in RA and SLE. This study confirmed that the metacarpal bone loss in RA is predominantly endosteal, similar to idiopathic OP. In SLE, however, resorption is primarily periosteal. This similarity with hyperparathyroidism needs to be explored, since elevations in PTH levels have not been reported in SLE. It seems that the metabolic effects of SLE on bone are under-estimated, but may be important in the light of improved survival.

SHORTCOMINGS.

1. Cross-sectional studies of this nature do not allow one to extrapolate longitudinally regarding the effects of bone loss in RA. However, the lack of previous evidence of OP in young subjects with RA required a careful cross-sectional analysis in order to establish this finding.

2. A prospective evaluation is required to clarify the relationship with commonly used drugs such as DMA's and CS. Such an analysis would be more valuable if it incorporated the findings of bone biopsy in patients requiring surgical therapy.

3. It is impossible to remove the effects of NSAID in this evaluation, since 90% of the subjects had been using the agents for at least 6 months prior to the investigation. Future research on bone metabolism will have to evaluate a group of RA subjects not receiving these agents. Perhaps such patients may be obtained from the private sector, but it seems unlikely that patients attending specialist Rheumatology units would fulfill this criterion.

4. Bone biopsies were not performed in any of the subjects. This is a vital component of the evaluation of bone metabolism and should be a pre-requisite for future studies in RA.

5. *In-vitro* effects of the serum of hypercalcaemic subjects was not evaluated. Future researchers should be advised about providing for this possibility if the facilities are available.

6. Measurement of osteocalcin levels was not included in the protocol due to technical reasons. However, it seems that this substance is a better reflection of bone metabolism than alkaline phosphatase in RA, so that future research should endeavour to include this measurement in the overall evaluation.

7. The effects of sex-steroids in these pre-menopausal subjects was not studied. There is a paucity of information regarding the effects in young subjects with RA and there is clearly a need for a careful analysis of their possible effects on bone metabolism in premenopausal patients with RA.

8. Patients with resorptive arthropathy due to RA reflect the severe end of the spectrum of metabolic bone disease in RA. They need to be carefully studied as a group, particularly with respect the imbalance between formation and resorption.

9. This study did not evaluate the bone loss of systemic lupus erythematosus in any great detail. There is a dire need for detailed assessment of the pathogenesis of osteopaenia in SLE, particularly in view of the improved survival and use of corticosteroids in postmenopausal females.

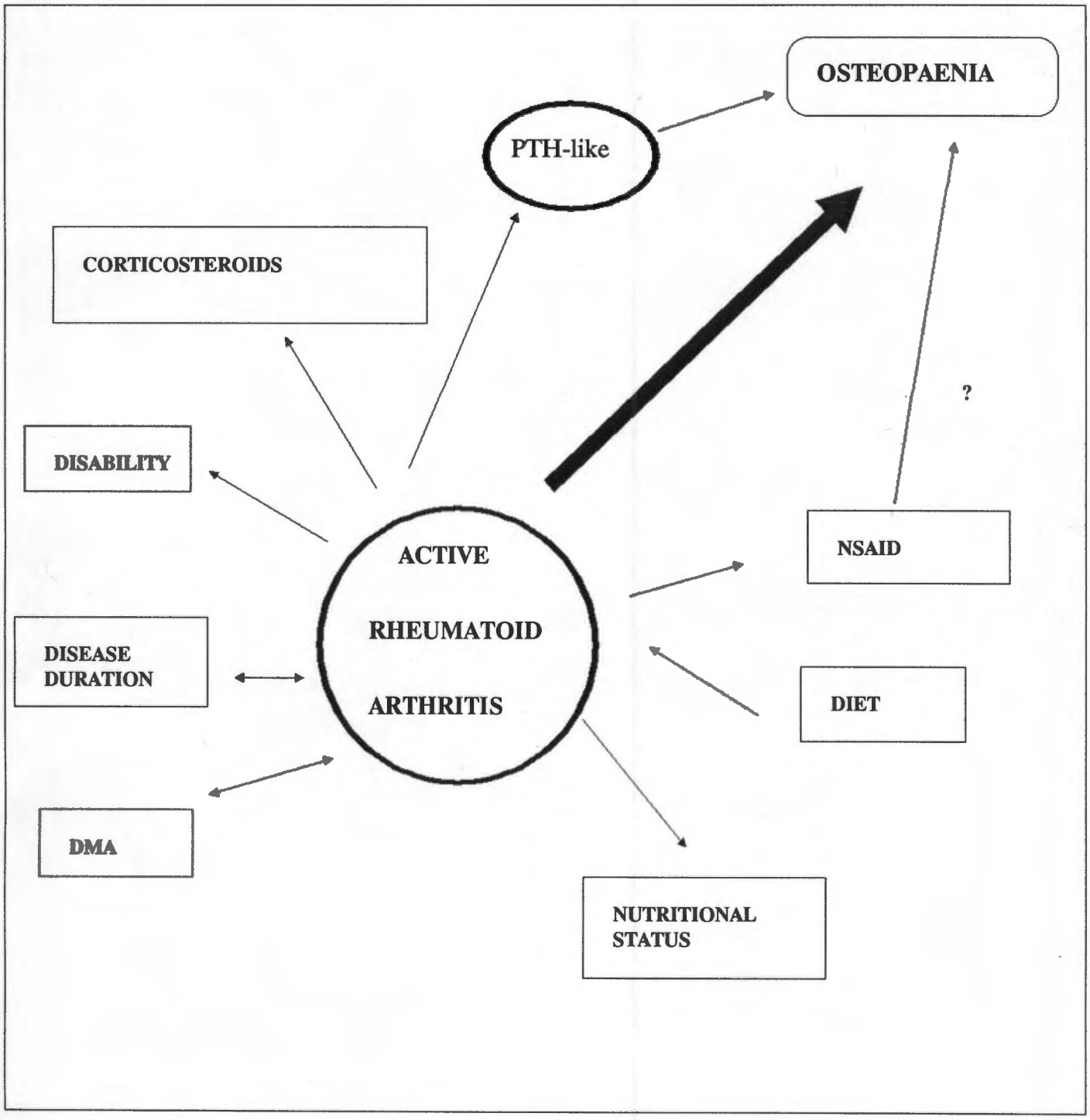
This study has shown that RA causes generalised osteopaenia. The systemic nature of the process is significantly represented at the metacarpal midshaft. The metacarpal bone mass can be objectively and reproducibly measured with the use

of a computer-assisted digitising technique. Cortical thinning is due to endosteal bone loss. Local, mechanical factors seem less important than systemic, inflammatory mediators. Diet and nutritional status do not contribute to the osteopaenic process. Drug therapy has no influence on the process and corticosteroids do not worsen this effect. The objective measurement of metacarpal bone mass could potentially be a useful radiological measure of the effects of RA on bone and joints, as shown by the significant correlations with the Larsen index and carpometacarpal ratio. Biochemical markers of bone metabolism are poor predictors of the changes observed. Further research should be directed at illucidating the effects of the disease on osteoblast and osteoclast activity, using *in-vitro* studies as well as bone biopsy.

Figure 36 summarises the hypothesis which emanates from the analysis of the data. **Disease activity is central to the development of osteopaenia in RA.** All the other factors seem much less important, and probably mediate their effect on bone during active disease.

Patients with active disease are more disabled, but not to the extent where local immobilisation affects bone metabolism. The effect of prolonged disease is one of cumulative interference with bone metabolism. Disease modifying agents are important in modifying disease activity and are usually given to patients with unremitting disease. Their effects on disease activity may have a modifying effect on bone metabolism. Nutritional status is influenced by the presence of active disease, but does not have a direct influence on bone mass. Dietary factors may aggravate disease activity and could influence bone mass indirectly. NSAID are used routinely in the management of patients with RA. Although no significant relationship was shown from the analysis, recent evidence regarding their inhibitory effect on bone formation in vitro suggests that they may have a direct effect on bone cells. Corticosteroid therapy is generally reserved for patients with active disease and the effects on bone seem to be predominantly due to the systemic effects of the disease rather than the drug. Their effect on bone is probably mediated through a combination of PTH-stimulated bone resorption as well as inhibition of osteoblast activity. Total calcium and ionised Ca^{2+} reflect these metabolic bone events. This group of patients did not have any significant increase in PTH levels.

Figure 36. Diagramatic representation of HYPOTHESIS relating to the genesis of OP in RA.



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APPENDIX A.

RHEUMATIC DISEASES UNIT.

EVALUATION OF OP IN RA

Dr. A. A. Kalla

Card No.		M 1.	
Study No.		M 2.	
PATIENT DATA			
PAOH No.		*M 3.*	
GSH No.		*M 4.*	
Age		*M 5.*	
D.O.B.		*M 6.*	*dd/mm/yy*
Marital Status	*1=S; 2=M; 3=D*	*M 7.*	
Tel. No.		*M 8.*	
Name		*M 9.*	
Address.		*M 10.*	
Race . Sex ..	*1 - 8*	*M 11.*	
Do you work ?	*1=FT; 2=PT; 3= Nil.*	*M 12.*	
Does anyone in your family have arthritis?			
1=Y; 2=N; 3=D (Don't know)		*M 13.*	
How much time do you spend in the sun?			
1=1 Hr; 2=2 Hrs; 3=4 Hrs; 4=6 Hrs; 5=8 Hr;		*M 14.*	
HLA		*U 222.*	
Associated Diseases.		*M 19.*	
0=Nil; 1=H/T; 2=D/M; 3=Epilepsy; 4=Other.			

DATE : --/--/--.

Card No.	M 1.
Study No.	M 2.

DISEASE DATA

Age at onset of RA.	*M 15.*
Duration of RA.	*M 16.*
Dominant Side. 1=R; 2=L; 3=B	*N 17.*
MS. 1=Y; 2=N	*N 18.*
Joint Swelling.	*N 19.*
Joint Pain.	*N 20.*
Other joint swelling.	*N 21.*
Positive Serology.	*N 22.*
Symmetrical , Simultaneous.	*N 23.*
Nodules.	*N 24.*
Poor Mucin Clot.	*N 25.*
Synovial Histology.	*N 26.*
Nodule Histology.	*N 27.*
X-RAY Changes of RA.	*N 30.*
ARA Classification. 1=C; 2=D; 3=P	*N 28.*
NY Classification. 1=1; 2=2; 3=3; 4=4	*N 29.*

Card No. M 1.

Study No. M 2.

DISEASE ACTIVITY DATA

How do you grade the severity of your disease ?

0----------5----------10 *N 31.*

How much pain do you have at present ?

0----------5----------10 *N 32.*

Functional Class (ARA) *N 33.*

Functional Class (U.K) *N 34.*

Do you have pain at night ? *N 35.*

Do you manage a full working day ? *N 36.*

No. of warm joints. *N 37.*

Duration of MS. 1=2; 2=3; 3=4; 4=5 Hr. *N 38.*

0 = <45 min.

How soon after waking do you feel tired ?

1=Hrs; 1=2Hrs; 2=4Hrs; 3=6Hrs; 4=8Hrs. *N 39.*

No. of swollen joints. *N 40.*

Articular Index (Ritchie). *N 41.*

Keitel Functional Score. *V 261.*

Clinical Disease Activity Grade.

0=Nil; 1=Mild; 2=Moderate; 3=Severe *N 58.*

Card No.	M 1.
Study No.	M 2.
BIOCHEMISTRY	
SCAT.	*N 42.*
Latex.	*N 43.*
ANF.	*N 44.*
ESR.	*N 45.*
CRP.	*N 46.*
Plasma Viscosity.	*N 47.*
Albumen.	*N 48.*
Serum Calcium.	*N 49.*
Serum Phosphorous.	*N 50.*
Alkaline Phosphatase.	*N 51.*
Gamma G-T.	*N 52.*
Haemoglobin.	*N 53.*
Alpha - 1 A-T	*N 54.*
SH - Groups.	*N 55.*
Retinol-Binding Globulin.	*N 56.*
Thyroxine-Binding Globulin.	*N 57.*
Reserve	*N 59.*
Reserve	*N 60.*

Card No.	M 1.
Study No.	M 2.

NUTRITIONAL STATUS

Height	*O 71.*
Weight	*O 72.*
Bi-Acromial Diameter --.-- --.-- --.--	*P 73.*
Bi-Iliac Diameter --.-- --.-- --.--	*P 74.*
Bi-Trochanteric Diameter -.-- --.-- --.--	*P 75.*
Bi-Ankle Diameter --.-- --.-- --.--	*P 76.*
Bi-Wrist Diameter --.-- --.-- --.--	*P 77.*
Chest Width --.-- --.-- --.--	*P 78.*
Chest Depth --.-- --.-- --.--	*P 79.*
Chest Expansion --.-- --.-- --.--	*S 159.*
Spinal Stretch --.-- --.-- --.--	*S 160.*
Subscap. Skin Fold Thickness	*P 80.*
Thigh S.F.T. --.-- --.--	*P 81.*
Upper Arm S.F.T. --.-- --.-- --.--	*P 82.*
Upper Arm Diameter --.-- --.-- --.--	*P 83.*

(See Special Dietary History) (D)

Card No.	M 1.
Study No.	M 2.

SPECIAL CHEMISTRY

Urine Calcium	*Q 84.*
Urine OH-Proline	*Q 85.*
Urine Phosphorous	*Q 86.*
Serum PTH	*Q 87.*
Serum Vit D (Reserve)	*Q 88.*
Thyroxine Binding Globulin	*Q 89.*
Retinol Binding Globulin	*Q 90.*
Reserve	*Q 95.*
HLA Status	*U 222*

Card No.	M 1.	
Study No.	M 2.	

MOBILITY ASSESSMENT (DQ)

A: Mobility.

Can you walk to toilet 1=Y; 2=N	*R 111.*
Can you climb on/off the toilet	*R 112.*
Can you climb in/out of bed	*R 113.*
Can you walk up/down stairs	*R 114.*
Can you climb in/out of a bath	*R 115.*
Can you turn in bed	*R 116.*

B: Bending Down.

Can you put on shoes/tie laces	*R 117.*
Can you pull on socks/tights	*R 118.*
Can you wash below the waist	*R 119.*
Can you cut your toe/finger nails	*R 120.*
Are you able to have sex	*R 121.*

C: Dexterity.

Can you unscrew jar lids	*R 122.*
Can you prepare vegetables	*R 123.*
Can you carve meat	*R 124.*
Can you slice bread	*R 125.*
Can you cut your toe/finger nails	*R 126.*

Card No. M 1.

Study No. M 2.

MOBILITY ASSESSMENT II.

D: Bending Arm.

Can you drink from a full cup *R 127.*

Can you shave/apply cosmetics *R 128.*

Can you wash face/neck towel dry *R 129.*

Can you wash trunk/arms towel dry *R 130.*

E: Reaching Up.

Can you wear clothes over your head *R 131.*

Can you brush/comb your hair *R 132.*

Can you wash your hair *R 133.*

Can you put a plug in at shoulder ht. *R 134.*

Can you peg out washing *R 135.*

Can you use shelves above shoulder ht. *R 136.*

Can you open/clean high windows *R 137.*

TOTAL = R 306.

0 = No difficulties encountered.

1 = Difficulties encountered.

2 = Abnormal performance.

3 = Aids were required

4 = Aids with a helping hand.

5 = Personal assistance.

6 = Personal help + aid.

7 = Activity impossible.

Card No.	M 1.
Study No.	M 2.

KEITEL FUNCTION TEST. (K)

1.Tip of thumb touches hypothenar.	*V 222.*
0 = Fully,no delay; 1 = fully,delay + effort;	*V 223.*
2 = Tip of thumb PIP 3/4; 3 = unable. R + L	
2.Bending of 2nd finger.	*V 224.*
0 = normal clutch;1 = abnormal,tip reaches palm;	*V 225.*
2 = tip does not reach palm. R + L	
3.Bending of 3rd finger.	*V 226.*
(0-2) As Above.	*V 227.*
4.Bending of 4th finger.	*V 228.*
(0-2) As Above.	*V 229.*
5.Bending of 5th finger.	*V 230.*
(0-2) As Above.	*V 231.*
6.Forearms horizontal,palms together,	
tips upward.	*V 232.*
1 = Fully,no delay; 2 = fully,delay + effort;	*V 233.*
3 = volar + dorsal flexion = 45o R + L	
7.Forearms horizontal,back of hands together.	*V 234.*
(1-3) As Above.	*V 235.*
8.Both dorsum on table,ulnar end lifted.	*V 236.*
0 = Fully ; 1 = back of hands lie fully,margin	*V 237.*
cannot lift; 2 = backs of hands not fully on table.	

Card No.	M 1.
Study No.	M 2.

KEITEL II (K)

9.Radial margin of hands	
simultaneously on table.	*V 238.*
0 = Fully; 1 = planes of hands perpendicular,cannot	*V 239.*
be inclined inwards; 2 = planes of hands not vertical.	
10.Both hands simult on ipsilateral shoulder.	*V 240.*
0 = Normal; 1 = fingertips up to 5cm	
from shoulder;	*V 241.*
2 = greater distance.	
11.Both hands simult behind neck.	
(below ear level).	*V 242.*
0 = Fully,no delay; 1 = fully,effort + delay;	*V 243.*
2 = fingertips touch neck; 3 = no tips reach neck.	
12.Rising from lying position.(Examination bed.)	*V 244.*
0 = Quickly hands extended; 1 = Effort hands extended;	
2 = Reinforcements; 4 = Extraneous assistance;6 = Impossible.	
13.Active spreading of legs in bed.	*V 245.*
0 = 50 cm condylar distance; 1 = 20cm condylar distance;	
2 = 20-50 cm condylar distance.	
14.Rising from chair.	*V 246.*
As in 12 Above.	

Card No.	M 1.
Study No	M 2.

KEITEL III

15.Standing tip-toed for 15 secs.	*V 247.*
0 = 15 secs; 1 = secs; 2 = Impossible.	
16.Standing on heels for 15 secs.	
(Straight ? support.)	*V 248.*
As Above.	
17.Knee-bending exercise;	
heel to gluteal region.	*V 249.*
0 = Normal; 1 = Partial; 2 = Impossible.	
18.Standing on one leg for 15 secs.	
(support permitted.)	*V 250.*
0 = 15 secs; 1 = secs; 2 = Impossible.	*V 251.*
19.External rotation hip;	
heel on supporting leg.	*V 252.*
0 = Fully; 1 = L of foot axes = 90°;	
2 = L of foot axes < 90°.	*V 253.*
20.Plantar surface on chair;knee bent.	*V 254.*
0 = Fully ?delayed;1 = Leg lifted from floor;	
2 = Impossible	*V 255.*

Card No.	M 1.
Study No	M 2.

KEITEL IV

21.Heel on chair : 1m : knee extended.	*V 256.*
As Above.	*V 257.*
22.Walk 30m in standard time of 20 secs.	
0 = No difficulty; 1 = Visible difficulty;	
2 = 25 secs; 3 = 30 secs; 4 = 40 secs;	*V 258.*
5 = Few steps; 6 = Impossible.	
23.Walk 10 steps upstairs; standard time 7 secs.	
0 = No railing std. time;	
1 = Up to 14 secs + rails;	*V 259.*
2 = 14 secs + some effort; 3 = No steps.	
24.Walk 10 steps down; standard time 7 secs.	*V 260.*
As Above.	
TOTAL	*V 261*
	/ 100.

Card No. M 1.

Study No. M 2.

FUNCTIONAL ASSESSMENT

Knee Pain

	(0-3) = Severe-Nil	*S 138.*	*L 138*
Function	*(0-3)*	*S 139.*	*L 139*
Motion	*(0-4) = Nil-Full*	*S 140.*	*L 140*
Total Score		*S 141*	*L 141*

Hip Pain

	(0-6)	*S 142.*	*L 142*
Function	*(0-6)* "	*S 158.*	*L 158*
Total Score	/ 12	*S 143.*	*L 143*

Finger

Abduction Strength	--.-- --.-- --.--	*S 144.*
Adduction Strength	--.-- --.-- --.--	*S 145.*
Flexion Strength	--.-- --.-- --.--	*S 150.*
Extension Strength	--.-- --.-- --.--	*S 151.*
Torque Strength	--.-- --.-- --.--	*S 161.*

Hand:

Knife & Fork Test	--.-- --.-- --.--	*S 146.*
Button - Hole Test	--.-- --.-- --.--	*S 147.*
Grip Strength	--.-- --.-- --.--	*S 148.*
3 - Point Pinch	--.-- --.-- --.--	*S 149.*

Card No.		M 1.
Study No.		M 2.
DRUG HISTORY (Past Year)		
NSAID		
Indocid	*1=Y; 0=N*	*T 161.*
	Dose	*T 162.*
	Duration	*T 163.*
	Total Dose	*T 164.*
Voltaren	*1=Y; 0=N*	*T 165.*
	Dose	*T 166.*
	Duration	*T 167.*
	Total Dose	*T 168.*
Naprosyn	*1=Y; 0=N*	*T 169.*
	Dose	*T 170.*
	Duration	*T 171.*
	Total Dose	*T 172.*
Feldene	*1=Y; 0=N*	*T 173.*
	Dose	*T 174.*
	Duration	*T 175.*
	Total Dose	*T 176.*
Other NSAID	*1=Y; 0=N*	*T 177.*
	Dose	*T 178.*
	Duration	*T 179.*
	Total Dose	*T 180.*

Card No.		M 1.
Study No.		M 2.

DRUG HISTORY (Past Year)

DISEASE MODIFYING AGENT

Penicillamine	*1=Y; 0=N*	*T 181.*
	Dose	*T 182.*
	Duration	*T 183.*
	Total Dose	*T 184.*
Myocrisin	*1=Y; 0=N*	*T 185.*
	Dose	*T 186.*
	Duration	*T 187.*
	Total Dose	*T 188.*
Ridaura	*1=Y; 0=N*	*T 189.*
	Dose	*T 190.*
	Duration	*T 191.*
	Total Dose	*T 192.*
Chloroquine	*1=Y; 0=N*	*T 193.*
	Dose	*T 194.*
	Duration	*T 195.*
	Total Dose	*T 196.*
Salazopyrine	*1=Y; 0=N*	*T 197.*
	Dose	*T 198.*
	Duration	*T 199.*
	Total Dose	*T 200.*

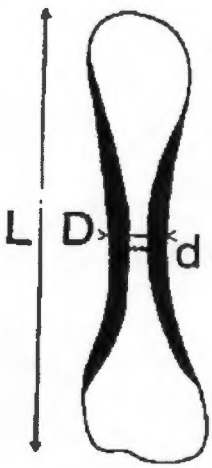
OESTROGEN REPLACEMENT

	1=Y; 0=N	*T 201.*
	Dose	*T 202.*
	Duration	*T 203.*
	Total Dose	*T 204.*

Card No.		M 1.
Study No.		M 2.
ORAL CONTRACEPTIVE		
1=Y 0=N		*T 205.*
Type of OCP		*T 206.*
Duration		*T 207.*
When was your last menstrual period?		*T 250.*
STEROIDS		
Oral	*1=Y; 0=N*	*U 208.*
Dose		*U 209.*
Duration		*U 210.*
Total Dose		*U 211.*
Articular	*1=Y; 0=N*	*U 212.*
Number		*U 213.*
Period		*U 214.*
Effect	*G/B/N*	*U 215.*
Pulse Medrol	*1=Y 0=N*	*U 216.*
Dose		*U 217.*
Number		*U 218.*
Total Dose		*U 219.*
Protocol		*U 220.*
Effect		*U 221.*

APPENDIX B.

TECHNIQUE OF DIGITISED RADIOGRAMMETRY.



SCREENING FOR OSTEOPOROSIS

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DIGITISED RADIOGRAMMETRY.

INTRODUCTION.

The program has been designed for measurements of **metacarpal bone mass.** It has been customised for the systemic recording of inner and outer diameters at the midshaft of six digits of the left and right hand respectively. Additional options exist for measurement of the carpo-metacarpal ratio as well as femoral cortical width and femoral index at the left hip. A separate program is included for testing **reproducibility.**

HARDWARE REQUIREMENTS.

1. IBM PC / XT / AT.
2. 256 KB Memory.
3. Serial Adapter addressed to COM 1.
4. Monochrome ar Color Adapter.
5. Houston Instruments HIPAD or similar Digitiser.
6. DOS Version 2.0 or greater.

Figure 37 shows the digitiser interfaced with the IBM PC. The apparatus is connected via a RS 232 serial port.

Figure 37. Houston Hipad digitiser interfaced with the IBM PC, connected via a serial port. The digitiser rests on a portable X-Ray viewing box as a light source.

OPERATION.

The method of operation is demonstrated in Figure 38. The following set of instructions provides a detailed outline of the steps involved in digitised radiogrammetry.

Figure 38. Demonstration of operation of digitiser. The length is plotted followed by sequential measurement of outer and inner diameters of metacarpal cortical bone.

1. Ensure that the machine is set up with the digitiser connected to the serial port (COM 1).

2. Boot the computer.

3. At the DOS prompt, enter **RGRAM.**

4. Key in the patient's name, folder number, study code, age, race and sex (defined by a numeric code combining both variables). The date is also entered.

5. Indicate if you wish to measure the right 2nd metacarpal alone, or the sum of six metacarpals.

6. If the six metacarpal hand score is to be measured, load the X-Ray of left hand first, with the thumb on the left of the digitiser grid.

7. Plot the base, then the tip of the 2nd metacarpal of the left hand, as directed on the computer screen, using the landmarks shown in the picture.

8. A continuous bleep will sound at this point, with a message to move the cursor to the midpoint (pre-defined). As soon as the midpoint is reached, the bleeper stops. Plot the left and right margins for the outer diameter, followed by the margins of the inner diameter, at the midpoint.

ENSURE THAT THE X-RAY DOES NOT MOVE AFTER THE BASE AND TIP HAVE BEEN DIGITISED.

9. Indicate if you are satisfied with the measurement. If the response is affirmative, a message will appear to indicate that the next metacarpal should be digitised.

10. Follow these steps until the 2nd, 3rd and 4th metacarpals of the left hand have been measured.

11. You will then be directed to load the X-Ray of the right hand.

ENSURE THAT THE THUMB IS ON THE LEFT OF THE DIGITISER GRID.

12. Repeat steps 7 to 10 for the right hand.

13. You will then be directed to plot the carpal length of the right hand.

14. The next step is to load the X-Ray of the left hip.

15. Plot the margins of the femoral cortical width, just proximal to the lesser trochanter.

16. Plot the margins of the trabecular width, 1 cm proximal to the lesser trochanter. This measurement needs to be repeated three times, the largest of the values being used in calculating the femoral index.

17. Insert a comment, e.g. Larsen index at the right wrist. One byte is allowed, so you should establish a numeric code which describes the comment.

18. Space is allocated for 2 further comments, e.g. the serial X-Rays for that individual may be numbered in chronological order. The 3rd comment may be reserved for any further special comments, e.g. type of therapy (again coded numerically).

19. You will then be requested to indicate if the procedure should be continued or terminated. If you decide to continue, you will be asked to indicate if the X-Rays which are to follow belong to the same patient or not. If not, the name, folder number, etc. would need to be typed in, as above. If the X-Rays belong to the same patient, only the new date of the X-Ray would need to be entered (dd/mm/yy).

20. Repeat steps 7-18 as above.

21. At the DOS prompt, rename the default file (**XXXX.DGT**) to a name of your choice. If the name is not changed, subsequent records would be added to the original file, in the order in which they have been entered. The records exist as an **ASCII** (SDF Format) file, which can be read into a database management system such as **CONDOR 3, DBASE III or DBASE III +**, provided the fields have been defined for length of metacarpal, the diameters (TW, MW), combined cortical width (TW - MW), the squares of the diameters (TW^2, MW^2) as well as the difference of the squares of the diameters ($TW^2 - MW^2$) (i.e. 7 values per metacarpal). Additional fields should be provided for recording the bone mass at the right 2nd metacarpal as well as six metacarpals, using the formulae provided in the Appendix.

These calculations are done automatically. A total of 75 fields need to be defined per record, with 2 decimal places for all measured and calculated values (see example form for CONDOR 3).

REPRODUCIBILITY.

A separate program has been included for testing reproducibility of measurements. It differs from the main program only in the nature of the output file which records the length, outer and inner diameter of the metacarpal. The program is designed to record a set of six measurements (either a reference metacarpal or cadaver digit included in the X-Ray picture can be used for testing reproducibility).

TEST OF REPRODUCIBILITY.

1. Ensure that the machine is set up with the digitiser connected to the serial port (COM 1).

2. Boot the computer.

3. At the DOS prompt, enter .

4. Key in the patient's name, folder number, study code, age, race and sex. The date is also entered.

5 Plot the base, then the tip of the metacarpal.

ENSURE THAT THE X-RAY DOES NOT MOVE AFTER THE BASE AND TIP HAVE BEEN DIGITISED.

6. A continuous bleep is then sounded, with a message to move the cursor to the midpoint (pre-defined). As soon as the midpoint is reached, the bleeper stops. Plot the left and right margins for the outer diameter, followed by the margins of the inner diameter, at the midpoint.

7. Repeat steps 4 - 6 for six measurements.

8. You will then be requested to indicate if the procedure should be continued or terminated. If you decide to continue, you will be asked to indicate if the X-Rays which are to follow belong to the same patient or not. If not, the name, folder number, etc. would need to be typed in, as above. If the X-Rays belong to the same patient, only the new date of the X-Ray would need to be entered (dd/mm/yy).

9. At the DOS prompt, rename the default file **(XXXX.TST)** to a name of your choice. If the name is not changed, subsequent records would be added to the original file, in the order in which they had been entered. The records exist as an ASCII (SDF format) file, which can be read into a database management system such as CONDOR 3, DBASE III or DBASE III +, provided the fields have been defined for length and the diameters (TW, MW). A total of 24 fields per record.

HOUSTON INSTRUMENTS HIPAD DIGITISER MUST BE SETUP AS FOLLOWS:

1. SERIAL ASCII MODE.

2. 4800 BAUD.

3. FIXED ORIGIN.

NB!DIGITISER MUST BE SET TO STREAM MODE !

EVALUATION OF OP IN RA.

Hospital No. [M3] _____ Study No. [A3] ___ R.S [M11] _ Age [M5] __ [Hosp.No.] _____ [DATE] _____

DETAILED RADIOGRAMMETRY (X)

[XA] ____ *Length Digit A [X262]____ [X263]____ TWa & MWa [X264]____ [X265]____ TWa - MWa & TWa * TWa [X266]____ [X267]____ MWa * MWa & 265 - 266*

[XB] ____ *Length Digit B [X268]____ [X269]____ TWb & MWb [X270]____ [X271]____ TWb - MWb & TWb * TWb [X272]____ [X273]____ MWb * MWb & 271 - 272*

[XC] ____ *Length Digit C. [X274]____ [X275]____ TWc & MWc [X276]____ [X277]____ TWc - MWc & TWc * TWc [X278]____ [X279]____ MWc * MWc & 277 - 278*

[XD] ____ *Length Digit D. [X280]____ [X281]____ TWd & MWd [X282]____ [X283]____ TWd - MWd & TWd * TWd [X284]____ [X285]____ MWd * MWd & 283 - 284*

[XE] ____ *Length Digit E. [X286]____ [X287]____ TWe & MWe [X288]____ [X289]____ TWe - MWe & TWe * TWe [X290]____ [X291]____ MWe * TWe & 289 - 290*

[XF] ____ *Length Digit F. [X292]____ [X293]____ TWf & MWf [X294]____ [X295]____ TWf - MWf & TWf * TWf [X296]____ [X297]____ MWf * MWf & 295 - 296*

[X298]____ 264+70+76+82+88+94 [X299]____ 262+68+74+80+86+92 [X300]____ 298 / 299 = **M6HS** *[X301]____ 267+73+79+85+91+97*

[X302]____ 265+71+77+83+89+95 [X303]____ 301 / 302 = **M6CA%**

*[X10] ____ 288/286 [X11] ____ X10*100 [X12]____ 291*100*

*[X13] ____ 291/XE*286 [X14] ____ 291/XE*4*286*

*[WBD] ____ X12*2 [WBA]____ X12*1150 [WBCa]____ X12*450*

[X5]____ **Carpal Length** *[X6] ____* **Carpo/Metacarpal Ratio**

[X0] ____ **Fem.Cortical Width** *[X1] ____* **Femoral Neck Index.**

[X2] _ **Singh Index** *[X3] _* **Spinal Index** *[X7] _* **Larsen Index.** *[X8] _ Record No. [X9]_ [Z1]_* **Trabecular Width** *[FI1]____ [FI2]____ [FI3]____*