The application of samarium-153 particulate hydroxyapatite, a new particulate radiopharmaceutical, for the treatment of chronic synovitis

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Abstract

This thesis reports the investigation of a new particulate radiopharmaceutical, samarium-153 particulate hydroxyapatite (Sm-153 PHYP). In the context of current radiation synovectomy practice, the potential use of this new radiopharmaceutical has been evaluated by determining in vitro labelling efficiency and binding stability, optimal intra-articular delivery methods, in vivo biodistribution, safety and short-term clinical efficacy.

In vitro Sm-153 labelling of PHYP is efficient. Binding stability is stable under varying physico-chemical conditions similar to those encountered at the time of injection. Activity injection efficiency may be maximised by careful injection technique and by either, reducing the size range of PHYP suspended in saline, or suspending PHYP in sodium hyaluronate.

Biodistribution and dosimetry data, derived from serial γ scan images of patients treated for chronic knee synovitis with intra-articular Sm-153 PHYP, indicate that treatment is associated with extremely low levels of extra-articular escape of activity and low extra-articular organ doses. Out-patient knee injection appears to be feasible and safe and associated with no observable side effects up to a year following treatment. The particulate radiopharmaceutical is engulfed by synovial tissue soon following injection. Histological examination of synovium, taken from the knee of a patient 3 months after Sm-153 PHYP injection, has shown no evidence of an inflammatory response invoked by PHYP. Sm-153 PHYP knee injection has a favourable impact on symptoms: there was a median response of 9 months in an open prospective study and a trend towards greater efficacy from Sm-153 PHYP compared to intra-articular glucocorticoid injection from an interim analysis of a double-blind randomised controlled study.

Radiation synovectomy with Sm-153 PHYP is safe in the short-term and is associated with low levels of extra-articular activity escape and organ doses. There is evidence of a clinical response in the short-term. Sm-153 PHYP is a potentially useful therapy for chronic synovitis.
Preface

The problem...and intent..

Removal of inflamed synovial tissue from joints has formed part of the management of chronic synovitis for over 30 years. Intra-articular injection of β-emitting radionuclides provides one way of removing chronically-inflamed synovial tissue which, if left untreated, may result in the acceleration of cartilage and bone degradation and joint deformity in RA and occasionally in other chronic inflammatory arthritides. Radiocolloids, such as Y-90 citrate or silicate, may be associated with substantial escape of activity from injected joints resulting in healthy tissue irradiation and raising concerns over long-term safety. One particulate radiopharmaceutical, dysprosium-165 ferric hydroxide macroaggregates (Dy-165 FHMA), has been shown to reduce extra-articular escape of activity compared to radiocolloids and therefore the risk of damage to healthy tissue. However, Dy-165 FHMA has a very short half-life (2.3 hours), limiting its availability to sites distant from the reactor. Dy-165 FHMA is the only available particulate radiopharmaceutical.

Sm-153 is a β-emitter with a half-life of 46.3 hours, making transport from a reactor to distant sites more feasible than is possible with Dy-165. Preliminary studies with Sm-153 have shown stable binding to diphosphonates and to synthetically-produced hydroxyapatite which, because of its similarity to endogenous hydroxyapatite, has been used safely in the fields of dental and joint prosthetics. Furthermore, small micron-sized particles of hydroxyapatite may be cheaply and simply produced and appear to be safe in vivo. The finding from animal studies that hydroxyapatite particle-bound Sm-153 is associated with low levels of activity escape from injected joints, suggests that further investigation of the effect of this radiopharmaceutical on synovitis in patients is warranted. In this thesis, biodistribution, in vivo dosimetry and efficacy of Sm-153 labelled hydroxyapatite particles are investigated for the first time.

The ideal characteristics of a β-emitting radionuclide and/or a radiopharmaceutical for radiation synovectomy have frequently been stated; however, statements have invariably been based on empiricism and assumption. Irradiation of inflamed synovium can be effective, but the relative
effects of radiation damage on the different cell types within inflamed synovium, is unknown. Similarly little is known about whether there are consistent conformational features of the synovial lining in any given joint or in any given type of chronic arthritis. The differences may be important in: predicting the most effective type of radionuclide or radiopharmaceutical; in choosing the best route of delivery; and in anticipating the dose delivered to the target cells. The lack of data impairs a robust evaluation of radiation synovectomy as a therapeutic tool. It is, therefore, perhaps wise to view the development of a new radiopharmaceutical as a prompt for exploring the complex relationship between the physico-chemical properties of the radiopharmaceutical and its intra-articular environment. As part of the evaluation of samarium-153-labelled hydroxyapatite particles, some studies reported in this thesis focus on the relationship between intra-articular distribution of this radiopharmaceutical, radionuclide β⁻ energy penetration, distribution of cellular targets in the synovial lining and tissue conformation. Only with a greater understanding of this relationship between energy distribution and therapeutic target, can one move from an empirically-based approach towards a more evidence-based approach for the use of radiopharmaceuticals.

Although radiation synovectomy appears to have been practised in many countries for many years, few large long-term randomised trials have been completed which compare radiopharmaceutical efficacy to other widely used modalities of treatment for chronic synovitis. Arguably, the most appropriate comparator is intra-articular injection of a long-acting glucocorticoid; however, there have only been a handful of small studies comparing efficacy of radiopharmaceuticals with glucocorticoid injection. Some of these studies have shown no difference in efficacy between the two treatments. The lack of data has almost certainly strengthened the perception of negative data, and has contributed to the scepticism, expressed by some rheumatologists, about the usefulness of radiation synovectomy. Therefore, should any radiopharmaceutical prove to be safe and show potential as a therapeutic agent, it is essential to have an understanding of its efficacy compared to intra-articular injection of long-acting glucocorticoid. The need for a long-term prospective study comparing Sm-153-labelled hydroxyapatite particles with...
intra-articular glucocorticoid is recognised as part of this thesis. The inception and interim analysis of such a study is reported.

Finally, radiation synovectomy is reputedly practised in many countries worldwide (with the major exception of the United States). No survey of radiation synovectomy practice has ever been undertaken before. In order to gain an insight into the perceived clinical use of radiation synovectomy and to identify practitioners interested in its application, a European-wide survey of radiation synovectomy practice has been included in this thesis. In future, it may only be possible to accomplish large meaningful clinical trials examining the role of radiation synovectomy, with the collaboration of interested physicians and co-operating centres, wherever they are.
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The entire parliament fell dead silent. For the first time since anyone could remember, one of the members voted “aye.”

Larson
Chapter 1

Introduction
1.1 The normal synovial lining

1.1.1 The synovial lining: structure

The tissue surrounding diarthrodial joints consists of loosely connected elements of fatty, fibrous and areolar connective tissue (Key 1932). Tissue lining the joint cavity is termed the synovial lining (Fig. 1.1) and may consist of any or a mixture of the connective tissue sub-types listed above. There is a rich plexus of venules and capillaries approximately 25-100μm below the synovial surface (Wilkinson and Edwards 1989).

Fig. 1.1 The structure of a synovial joint (human proximal interphalangeal joint, ×5). The synovial lining (s) is in close proximity to hyaline cartilage (hc) and is continuous with underlying connective tissue (ssct). The connective tissue is bounded by, but continuous with, a fibrous joint capsule (jc)
In addition to vascular endothelial cells, it is generally agreed that two main cell types exist within normal synovial lining: macrophages and specialised fibroblasts (Barland et al. 1962, Ghadially and Roy 1969). Macrophages are identified by histochemical detection of non-specific esterase activity and by tissue binding of monoclonal antibodies to epitopes of the lysosome-related molecule CD68 (Wilkinson et al. 1991). Fibroblasts may be discriminated from the macrophages by their electron microscopy appearance (Barland et al. 1962) and by their staining for uridine diphosphoglucose dehydrogenase (Pitsillides et al. 1993), an enzyme essential for the synthesis of the high molecular weight glycosaminoglycan hyaluronic acid.

The distribution of cells within the extra-cellular matrix may vary within a normal synovial lining, which is only a few tens of microns thick. Cells may appear as a single layer, which is occasionally incomplete, especially at points of pressure from tendons and other extra-articular structures, or as a layer consisting of cells up to 3 or 4 deep. The synovial lining surface layer is termed the intima, and deeper tissue, the subintima. The intima and subintima together may also be referred to as synovium.

1.1.2 The synovial lining: function

In normal joints, the synovium provides a deformable packing and a non-adherent surface with low surface friction. These are mechanical attributes which are likely to allow easy movement of articular structures (Henderson and Edwards 1987a). The production of hyaluronic acid by synovial cells is important for maintaining the viscosity of synovial fluid. The fluid viscosity contributes to certain aspects of the lubrication of intra-articular structures during joint movement (Wright and Dowson 1976).

The synovium is also responsible for the control of volume and composition of synovial fluid and the delivery of nutrients to chondrocytes. This occurs as a result of filtration of plasma from synovial blood vessels through fenestrated capillary endothelial cells into the extra-cellular space. Solutes and other small molecules diffuse through the tissue matrix, across the synovial surface layer (where there is an absence of both a basement membrane or inter-cellular ‘tight junctions’) and into synovial fluid (Simkin 1991).
Finally, synovial lining cells may phagocytose cellular and matrix ‘debris’ present at the synovial lining/fluid interface and lymphatics within the synovium can enhance removal of macromolecules from the joint (Noble et al. 1983).
1.2 Synovial inflammation (synovitis)

Synovitis may appear similar to the classical pattern of acute inflammation illustrated by a reaction to an exogenous stimulus, as noted since the time of Celsus in 38AD (Hurley 1983). Alternatively it may follow a chronic course, for which no obvious trigger is easily identified, with many, often largely unknown, factors contributing to the continuance of pathological changes.

1.2.1 Acute synovitis

In practice, acute synovitis occurs as a reaction to bacteria or crystals (e.g. monosodium urate). The joint will be painful and appear swollen and overlying skin will be erythematous and warm. The underlying processes, in common with acute inflammation in all tissues, comprises vasodilation, increased vascular permeability, exudation of plasma, raised lymph flow, cellular infiltration by (predominantly) polymorphonuclear leucocytes (polymorphs) and subsequently, phagacytosis (Whalley 1992). Fluid accumulates within the joint cavity and contains numerous polymorphs and fibrin. Although elements of these pathological features may be evident in chronic disease of synovium, generally both the clinical and histological appearances differ.

1.2.2 Chronic synovitis

1.2.2.1 Clinical features

The clinical features of chronic synovitis may include a variable degree of pain, stiffness, swelling and loss of joint mobility (Henderson and Edwards 1987b). Pain and stiffness are often related to joint inactivity and may indicate the presence of synovial tissue oedema. Swelling may be due to either an increase in accumulation of synovial fluid or to thickening of the synovial lining or to both. It is often difficult to discriminate clinically between the two at some affected joints; however, in others such as the knee, thickened synovial tissue may be felt around the superior and lateral borders of the patellar over the femoral condyles and joint effusion can be detected by either the 'patellar tap' test or Kellgren’s sign (Thould 1986). Loss of mobility is mainly attributable to soft-tissue thickening and fluid accumulation in early
disease but as the disease progresses, articular cartilage and subchondral bone degeneration can lead to an irreversible disruption of normal joint movement.

Chronic synovitis may be associated with a number of distinct patterns of connective tissue disease expression e.g. rheumatoid arthritis (RA), psoriatic arthritis. For example, the synovitis in RA classically affects peripheral small joints symmetrically whereas in psoriatic arthritis, which is one of a group of clinicopathologically-related diseases termed seronegative spondyloarthritides, it is often asymmetrical and oligoarticular and predominantly affects the lower limbs. However, there may be little difference in the appearance of synovitis in a single joint. Differences in underlying pathophysiology have been recognised and will be briefly mentioned (see 1.2.2.2).

1.2.2.2 Pathophysiology of chronic synovitis: emphasis on RA

In chronic synovitis the synovial lining becomes thickened. This is mainly attributable to increases in vascularity, cellularity and fibrosis (Henderson and Edwards 1987b). In rheumatoid synovitis the inflammatory tissue extends over and covers hyaline cartilage at its margins. Here it is referred to as pannus (derivation: ‘cloth’ in greek). Within the tissue, activated cells secrete proteases and other enzymes which result in collagen and proteoglycan degradation in adjacent hyaline cartilage and altered chondrocyte and subchondral bone metabolism. Unchecked inflammation can, therefore, lead to cartilage and bone erosion (Fig. 1.2).

The pattern of bone erosion and bone loss in the seronegative spondyloarthritides is recognised to be different to that in RA (Moll 1987). Psoriatic arthritis may be associated with significant and sometimes gross erosion (arthritis mutilans). Although this indicates that differences in pathophysiology between types of chronic synovitis are likely, these differences have not been fully characterised and are poorly understood. Most evidence for the cellular and soluble mediator (cytokine) interactions important in the immunopathophysiology of chronic synovitis has arisen from studies with animal models of RA and RA tissue in vitro. The following overview of cellular and cytokine pathophysiology in chronic synovitis (1.2.2.2.1-6) is based on what is known about rheumatoid arthritis.
1.2.2.1 Angiogenesis, vascular changes and joint effusions

Angiogenesis is a prominent feature of synovitis and may be initiated and sustained by both hypoxia and locally produced factors such as prostaglandins and interleukin-1 (IL-1) from lymphocytes and macrophages (Whalley 1992, Williams 1979). The pattern of distribution of blood vessels in the chronically inflamed rheumatoid synovial lining, though studied, has not been clearly resolved. Some investigators have noted increased capillary density in the soft-tissue surrounding inflamed RA joints compared to normal joints (Fitzgerald et al. 1991), but others suggest that vascularity is reduced in RA synovium (Stevens et al. 1991). Although there is some controversy over the precise methods used (Fitzgerald and Bresnihan 1992), there is evidence suggesting there may be some heterogeneity in vascular distribution dependent on the stage of the disease, individual joint or patient. There are, however, recognised changes in endothelial cell morphology at different stages of chronic synovitis which may reflect both underlying changes in pathogenetic mechanisms and modulating influences of anti-rheumatic drugs (Yanni et al. 1993).

There appear to be both structural (light and electron microscopic) and immunohistochemical differences between the vascular proliferation seen in RA and psoriatic arthritis (Espinoza et al. 1982, Veale et al. 1993) but the significance of this difference is not clear. Variations between the pattern of vascular changes in chronic synovitis in association with other diseases have not been widely studied and essential differences have not been identified.

Joint effusions may occur in synovitis associated with all diagnoses. The increased capillary permeability which occurs in the inflamed synovial lining (in response to soluble mediators such as prostaglandins. See 1.3.1.1) allows the escape of plasma proteins into the joint (Simkin 1991). Increasing concentrations of synovial interstitial protein will increase capillary filtration of fluid and result in the accumulation of a joint effusion (Levick and McDonald 1994); however, it is not known to what relative extent the accumulation of fluid in the joint relies on increased capillary permeability to water.
Fig. 1.2. The effects of chronic synovial inflammation. Inflamed synovium encroaches onto the hyaline cartilage especially at the articular margins to form pannus. Secretion of proteases and other enzymes lead to degradation of hyaline cartilage and erosion of subchondral bone (see 1.2.2.2.2)
1.2.2.2 Cellular infiltrate and cytokine interactions

In rheumatoid synovitis the cellular infiltrate mainly consists of macrophages, appearing both as an increased number of lining cells and as an increase in subintimal cells, and lymphocytes and plasma cells, appearing in perivascular aggregates below the surface layer (Ishikawa and Ziff 1976).

Based on their morphology, surface MHC class II expression and magnitude and variety of secreted cytokines, macrophages are highly activated in rheumatoid synovium. However, the expression of macrophage activation markers can occur in non-pathological synovium (Mapp and Revell 1988). The precise initial stimulus to activate macrophages in synovitis therefore remains essentially unknown. There is some evidence to suggest, however, that fewer macrophages infiltrate into the synovium in non-rheumatoid inflammatory arthritides (Veale et al. 1993, Barkley et al. 1989).

Macrophage cytokine production includes IL-1, tumour necrosis factor α (TNF-α), interleukin-6 (IL-6) and granulocyte-macrophage colony-stimulating factor (GM-CSF). These cytokines appear to act in the inflamed joint within a complex autocrine/paracrine schema, often synergistically (Firestein and Zvaifler 1990, Arend and Dayer 1990). For example, a schematic representation of cytokine and cellular interactions in rheumatoid synovitis is shown below (Fig. 1.3).

IL-1 and TNF-α stimulate synovial fibroblasts to proliferate in vitro, increasing secretion of IL-6, GM-CSF, collagenase, fibronectin and prostaglandins from these cells (Arend and Dayer 1990). Proliferation of fibroblasts may contribute to synovial lining thickening, fibrosis and scarring. IL-1 alone can directly induce the production of collagenase by fibroblasts (Postlethwaite et al. 1988). The effect is enhanced in the presence of TNF-α (Henderson and Pettipher 1989). Although produced by both T lymphocytes and macrophages, the major source of IL-6 in rheumatoid synovial lining appears to be fibroblasts. IL-6 is a potent inducer of immunoglobulin (Ig) by B lymphocytes and thus an important mediator in the production of rheumatoid factor (Arend and Dayer 1990).
Fig. 1.3 Postulated cellular and cytokine interactions in chronic rheumatoid synovitis. 

The degradation of collagen and proteoglycan in hyaline cartilage by collagenase and other synovial fibroblast-derived metalloproteinases are important and deleterious sequelae of rheumatoid synovitis and frequently occur if synovitis is persistent. Reflecting the clinical observation that bone erosion is seen infrequently in chronic seronegative arthritides, recent laboratory evidence has suggested that in reactive arthritis, extensive changes in articular cartilage metabolism only appear during the acute phase of the disease and do not seem to persist (Saxne et al. 1993).

IL-1, IL-6 and TNF-α are also mediators of the systemic acute phase response accompanying inflammatory arthritides. This includes the production of hepatic and haematological tissue-derived proteins such as C reactive protein (CRP), proteinase inhibitors, coagulation proteins and complement components (Emery and Luqmani 1993).
1.2.2.3 T lymphocytes

T lymphocytes (T cells) may be present in small numbers in normal synovium (Lindblad and Hedfors 1987) though are recruited to synovium from the circulating vascular pool in larger numbers in inflammatory arthritides. In chronic disease T cells may mediate a number of cellular and cytokine interactions (Arend and Dayer 1990).

Il-1 and TNF-α increase the ability of lymphocytes to bind to, and migrate through, vascular endothelium. These cytokines induce the expression of specific endothelial cell adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1), endothelial adhesion molecule 1 (ELAM-1) [which is now termed E-selectin] and lymphocyte function-associated antigen 3 (LFA-3) (Streeter et al. 1988). The expression of E-selectin (ELAM-1) may be less intense in the synovium of psoriatic arthritis compared to that in RA (Veale et al. 1993).

Although T cells migrate to, and accumulate in, inflamed synovium, their exact role in chronic synovitis has yet to be determined and is the focus of energetic debate. Although T cells are able to stimulate macrophages in vitro and have the potential for secreting a variety of cytokines such as interferon γ, Il-2, Il-6, TNF-α and GM-CSF, there is a lack of in vivo evidence to suggest that T cells remain highly activated in synovium in chronic synovitis. This has led to questioning of their central role in perpetuating chronic synovitis in RA (Firestein and Zvaifler 1990). Nevertheless, it appears that in chronic rheumatoid synovitis T cells are continually recruited to the synovial lining through specific cell adhesion mechanisms (Springer et al. 1987). This suggests that they do play some continuing role in modulating inflammatory changes in chronic synovitis.

1.2.2.4 B lymphocytes and immunoglobulin production

B lymphocytes (B cells) form part of the cellular infiltrate in synovitis though they are generally absent from normal synovium. Classically, B cells are thought to proliferate in lymphoid tissue in response to contact with antigen on the surface of both follicular dendritic cells (FDCs) and T cells. The FDCs and T cells can assist with expansion of B cell clones (McLennan 1994).
B cell immunoglobulin (Ig) production is reflected by rheumatoid factor and antibodies to collagen and nucleic acids (Stuart et al. 1983). Rheumatoid factors are Igs which bind the Fc domains of IgG. Defective glycosylation of IgG oligosaccharide side-chains, is likely to be important in immune-complex generation (Sharif et al. 1990). Ig complexes may form either in blood or tissue and can usually be detected in hyaline cartilage in RA joints (Cooke et al. 1975). Pannus macrophages probably phagacytose the cartilage-bound complexes and are activated by them (Shiozawa et al. 1980). Cells termed 'antigen presenting cells' (APCs), may bind immune complexes through their surface Fc receptors and in the presence of complement present this as antigen to B cells thus encouraging further B cell proliferation (McLennan 1994).

B cell activation and proliferation and plasma cell production of Ig occurs in both seropositive and seronegative arthritides. Immunochemical staining of inflamed synovium in the various arthritides suggests that it may be possible to distinguish seropositive RA from other arthritides on the basis of the pattern of deposition of Ig classes (Revell and Mayston 1986). There appear to be a greater number of plasma cells containing IgM in seropositive RA patients, but there appears to be no difference in the number of IgG-containing plasma cells when comparing seropositive and seronegative arthritides or when comparing the different subtypes of seronegative arthritis. It seems likely that whether the proliferation of B cells and production of Ig is central to, or a consequence of, initial immunological events, heightened B cell activation is a prominent feature of chronic inflammation in chronic synovitis.

1.2.2.2.5 Immunosuppressive regulatory mechanisms

There are characteristics associated with T cell (particularly CD8+ cells) function and cytokine behaviour to suggest that there are suppressive immunoregulatory as well as stimulatory interactions in chronic synovitis. These specific intercellular and cytokine interactions are likely to be of importance in dictating the pattern and severity of tissue destruction. Their role is not precisely known and to consider them here would introduce complex issues which are peripheral to this discussion. The reader is therefore referred to other reviews (Arend and Dayer 1990, Feldmann et al. 1992).
1.2.2.6 Summary of the pathophysiology of chronic synovitis

Left unchecked by endogenous immunomodulatory or dampening mechanisms or successful treatment, chronic synovitis results in persistent symptoms and may lead to gradual destruction of a joint. Persistent synovial inflammation results in the symptoms of pain and stiffness and clinical signs of swelling due to a thickened synovial lining, effusion or both. The immunopathology is characterised by persistent activation of macrophages, lymphocytes and synovial fibroblasts and in RA especially, by degradation of hyaline cartilage and subchondral bone.

Some clinical and histological differences between the different chronic arthritides have been recognised. There is some evidence that underlying pathogenetic mechanisms may differ between RA and seronegative spondyloarthritides and between (rheumatoid factor) seropositive and seronegative RA. Further studies will be needed to fully elucidate the cellular and cytokine interactions in arthritides where the clinical pattern of disease is recognised to be different.
1.3 Treatment of synovial inflammation

1.3.1 Systemic therapy

For patients with chronic synovitis, systemic drug therapy is the mainstay of treatment. It is especially useful for patients with a polyarticular pattern of disease expression.

1.3.1.1 Non-steroidal anti-inflammatory drugs

Symptomatic improvement is best effected by use of aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs). By inhibition of cycloxygenase, an enzyme essential for the breakdown of arachidonic acid, NSAIDs reduce the synthesis of prostaglandins. Through an inhibition of prostaglandin-mediated changes in vascularity, NSAIDs are able to reduce the accumulation of joint fluid (Pettipher et al. 1989). The major clinical effect of NSAID treatment is the reduction of pain and stiffness (Balint et al. 1977).

NSAIDs may be delivered orally or parenterally in either slow release or ‘pro-drug’ preparations. There are over 30 separate drugs from 7 chemically independent groups licensed for clinical use in the UK (source: British National Formulary, March 1995). There is no clinical or laboratory evidence however, that NSAIDs affect the progression of tissue damage in rheumatoid arthritis (Lipsky 1983).

NSAIDs are associated with a number of serious complications (Wright 1995). Prostaglandins are important in many tissues, particularly in the stomach where they regulate gastric mucosa acid secretion and stimulate production of the ‘mucosal protective’ gastric mucus. In blood vessels, especially in the kidney, they are important in mediating vasodilatation. The inhibition of prostaglandin synthesis by NSAID’s can result in upper gastrointestinal (GI) mucosal ulceration, deterioration in renal perfusion and function and aggravation of hypertension. These side-effects are not infrequent. A recent study among patients with osteoarthritis and RA using NSAIDs showed a prevalence of upper GI ulcers of 15-44% (Geis et al. 1991).

NSAIDs have become a cornerstone in the management of chronic synovitis. They are amongst the most frequently prescribed drugs in the world (CSM update 1986). Despite their proven efficacy in controlling synovitis
symptoms, NSAIDs carry with them the risk of serious GI and vascular toxic effects and, although strategies are devised to minimise these side-effects, reliance on NSAIDs for effective control of synovitis symptoms must be balanced by a careful appraisal of their risk in arthritis patients (Wright 1995).

1.3.1.2 Glucocorticoids

Dramatic symptomatic improvement of patients with RA after glucocorticoid treatment led investigators to hypothesise that RA develops as a consequence of adrenal insufficiency (Hench et al. 1948). Glucocorticoids given either enterally and parenterally have been used widely for controlling chronic synovitis for over 50 years.

Glucocorticoids modify immunopathophysiological processes in a number of ways (Clamen 1972, Fauci et al. 1976). They exert their effect by regulating gene expression by binding to a specific intra-cellular receptor important for regulating gene transcription (Russell and Krane 1993). As a result, glucocorticoids can have a suppressive effect on a number of cellular functions including cell proliferation, the production of cytokines and matrix-degrading enzymes such as collagenase and stromelysin and on cellular adhesion molecule expression. Glucocorticoids are therefore potent anti-rheumatic drugs.

Like NSAIDs, glucocorticoids can affect non-articular tissue metabolism and are therefore also associated with serious side-effects. Glucocorticoids regulate gene transcription of osteocyte-derived cytokines and growth factors, reduce bone protein and collagen synthesis and may also interfere with mechanisms in the gut and kidney essential for calcium and vitamin D homeostasis (Reid 1989). Consequently, bone turnover and bone mineral metabolism may be affected, resulting in osteoporosis and fractures in adults or retarded skeletal development in children and adolescents.

Regional and generalised skeletal osteoporosis are recognised features of early and persistent RA respectively (Peel et al. 1991). Further loss of bone as a result of glucocorticoid therapy therefore represents an additional risk of fracture in these patients. Not surprisingly, glucocorticoids are used sparingly in chronic synovitis and are often only reserved for severe exacerbations of polyarticular inflammation. Recently, however, there has been evidence that
glucocorticoid given early in RA in low doses (not associated with significant bone loss) may arrest the progression of articular erosions (Kirwan et al. 1995). Despite being in use for almost 50 years, the optimum role of glucocorticoids in the management of chronic synovitis has yet to be established.

1.3.1.3 Slow acting anti-rheumatic drugs

The major slow acting anti-rheumatic drugs (SAARDs) used in the management of chronic synovitis are shown in Table 1.1. All drugs in this group exert their effects over a prolonged period and when initially started may take up to 6 months to produce clinical improvement (Harris 1993). These drugs are occasionally referred to as disease modifying anti-rheumatic drugs (DMARDs); however, there is only weak evidence that some of the drugs can delay or halt the progression of tissue damage in chronic synovitis (Table 1.1).

Owing to the incidence of occasionally severe and life-threatening side effects, the use of most drugs requires regular monitoring of the patient’s renal, haematological and hepatic functions. Ophthalmological examination is necessary to monitor the retinal toxicity of hydroxychloroquine in patients who have received a high cumulative dose of the drug.

In managing synovitis, drugs such as gold and D-penicillamine are conventionally prescribed when symptoms become uncontrolled by a NSAID. On the basis that the most rapid joint destruction occurs within the first few years of RA (Fuchs et al 1989), there has been a recent trend towards earlier and more aggressive treatment of established RA (Wilke et al. 1993). Thus, patients may initially be given a NSAID and a SAARD together and SAARDs may be combined. However, it should be noted that, despite evidence to suggest that some drug combinations do not increase the incidence of side effects over single drug therapy (Boers and Ramsden 1991), there is, at the moment, only weak evidence that combination therapy is more efficacious.

Other pharmacological agents occasionally used to treat inflammatory arthritis include chlorambucil and cyclosporin-A. Cyclosporin-A reduces
Table 1.1 The major SAARDs used in the management of chronic synovitis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Mechanism of action</th>
<th>Evidence for prevention of tissue damage</th>
<th>Side effects (Refs: xv, xvi)</th>
</tr>
</thead>
</table>
| Gold (sodium aurothiomalate) | o/im  | Decrease in macrophage mediated T cell proliferation in vitro.  
Inhibition of IL-2 action. (Ref: i)                                                   | Delayed appearance of erosions in RA (im) (Ref: xi)                                                     | Mild/moderate: skin rash; alopecia; nausea; mucosal ulceration; colitis; proteinuria.  
Severe: hepatotoxicity; myelosuppression                                                                 |
| D-Penicillamine             | o     | Scavenger of reactive oxygen species. (Ref: ii)                                      | Delayed appearance of erosions (RA) (Ref: xii)                                                          | Mild/moderate: nausea; skin rash; taste loss; proteinuria; anemia.  
Severe: nephrotic syndrome; Stevens Johnson syndrome; myelosuppression (Ref: xvii) |
| Sulphasalazine              | o     | Inhibitor of folate dependent synthesis of purines.                                  | None                                                                                                   | Mild/moderate: nausea; peptic ulceration; skin rash; oligospermia.  
Severe: hepatitis; Stevens Johnson syndrome; nephrotic syndrome; myelosuppression (Ref: xvii) |
| Hydroxychloroquine          | o     | Inhibition of IL-1 effects on cartilage metabolism in vitro.  
Interference with macrophage antigen processing in vacuoles. (Refs: iii, iv) | None                                                                                                   | Mild/moderate: skin rash; nausea; retinopathy; myelosuppression; neuromyopathy and psychosis (rare) |
| Methotrexate                | o/im  | 11-1 activity inhibition.  
Arachidonic acid production inhibition.  
Inhibitor of folate dependent synthesis of purines. (Refs: v-vii) | Delayed appearance of erosions compared to oral gold and azathioprine. (Refs: xiii, xiv) | Mild/moderate: nausea; mucosal ulceration; nodulosis (RA).  
Severe: pneumonitis; pulmonary fibrosis; liver cirrhosis; myelosuppression |
| Azathioprine                | o     | Inhibition of purine synthesis/prostaglandin E2 production.  
Direct lymphotoxicity from imidazole derivatives (Ref: viii, ix) | None                                                                                                   | Mild/moderate: nausea; peptic ulceration; alopecia.  
Severe: hypersensitivity; arthrythmias; leukemia myelosuppression |
| Cyclophosphamide            | o/iv  | Decreases T cell proliferation (Ref: x)                                              | None                                                                                                   | Mild/moderate: nausea; cystitis.  
Severe: myelosuppression; leukemia |

ii Conaghan PG, Brooks P. *Curr Opin Rheumatol* 1993; 5(3): 276-81  
iii Rainford KD. *J Pharm Pharmacol* 1986; 38(11): 829-33  
v Fox RL. *Semin Arthritis Rheum* 1993; 23(2 Suppl 1): 82-91  
iv Fox RL. *Semin Arthritis Rheum* 1993; 23(2 Suppl 1): 82-91  
iv Fox RL. *Semin Arthritis Rheum* 1993; 23(2 Suppl 1): 82-91  
iii Rainford KD. *J Pharm Pharmacol* 1986; 38(11): 829-33  

radiographic progression of joint disease compared to placebo (Wells et al. 1993); however, its use has been limited by the risk of nephrotoxicity. Newer, but as yet unestablished, pharmacological agents which may be included in this group include tenidap and leflunomide (Smolen 1995).

1.3.1.4 Monoclonal antibody immunosuppressive therapy

The development and availability of monoclonal antibodies (mAbs) has allowed the identification of functionally important molecules expressed on the surface of, or produced by, cells involved in chronic synovial inflammation. Based on these developments and findings, new therapeutic strategies that selectively modulate the immune response in chronic synovial inflammation can be designed. Molecules chosen on the basis that they are critically involved in the immunopathology of chronic synovitis, can be specifically targeted. Targets include: CD4, expressed on the surface of T helper cells and monocytes; intercellular adhesion molecule ICAM-1, which, by binding to the leucocyte function-associated antigen (LFA-1), influences T cell transendothelial migration and activation; and TNF-α.

Using a variety of IgG isotype murine-human chimaerised anti-CD4 mAbs the overall clinical effect from a number of open and short-term follow-up placebo-controlled studies has been modest (Kalden 1995). As a result, further studies with anti-CD4 mAbs have not been initiated. Early data from clinical studies using anti-ICAM-1 (Kavanaugh et al. 1994) and anti-TNFα mAbs (Elliot et al. 1994) show that these mAbs are associated with striking symptomatic improvement in the short-term. The results suggest that these monoclonal antibody techniques may represent a significant step forward in the development of potent anti-rheumatic therapy.

1.3.2 Local joint therapy

Intra-articular therapy directed at synovium for any particular joint is a useful adjunct to systemic therapy in patients with polyarticular synovitis but especially important for patients with chronic oligoarticular or monoarticular synovitis. Although polyarticular synovitis is often controlled by SAARD therapy, if one or two joints remain with persistent troublesome inflammation, they can be usefully treated with local therapy. This avoids the need to
increase the dose of, or change, the SAARD, thereby increasing the risk of side-effects. The potential gains from successful treatment are arguably greater in patients with only one or two symptomatic joints, as successful local therapy may remove the requirement for a SAARD completely.

1.3.2.1 Intra-articular glucocorticoid injection

The unwanted effects of systemically administered glucocorticoids can be minimised by intra-articular administration. Different preparations are available, some of which, by virtue of their crystalline nature, are thought to remain longer in the joint than soluble preparations e.g. triamcinolone hexacetonide.

Clinical results can be spectacular with remission of synovitis obtainable for many months. Results are improved for larger weight bearing joints if a period of immobility is observed following injection (Chakravarty et al. 1994). Joint injection is occasionally ineffective. The characteristics of synovitis which determine a poor response have not been determined.

The main risk from a single intra-articular glucocorticoid injection is joint infection although with careful technique the frequency is low (Owen 1993). Repeated injection may accelerate articular cartilage and bone destruction and therefore is practised judiciously in patients with chronic synovitis.

1.3.2.2 Synovectomy

The principle of removing pathological synovial tissue was originally aimed at either effecting a cure for arthritis or at least improving joint function in the short-term (Swett 1924). Synovectomy may be undertaken surgically or by intra-articular injection of chemical or radiation agents.

Regeneration of pathological synovium can occur following synovectomy (Patzakis et al. 1973). Any effect on articular symptoms or tissue destruction may therefore only be temporary as disease may recur in the regenerated tissue.

It is an accepted principle that both surgical and medical synovectomy is more effective in relieving symptoms if undertaken before the development of significant cartilage damage (Lloyd Jones 1984, Newman 1993), but it is
unknown whether early synovectomy ultimately delays the progression of articular cartilage and bone erosion.

1.3.2.2.1 Open surgical synovectomy

Surgical synovectomy was first reported in 1877 for a tuberculous knee joint (Volkmann 1877) and was first reported in rheumatoid arthritis patients in 1924 (Swett 1924). Open surgical synovectomy was subsequently developed and widely adopted as part of the management of infective and inflammatory arthritis.

Short-term results from open studies have suggested efficacy (London 1955, Aidem and Baker 1964), but as follow-up extends beyond 3 years there is a diminishing proportion of good results. These data are corroborated by the results from the only controlled trials comparing open synovectomy with conservative measures which suggest no difference in outcome at five years (ARC/BOA study 1975, McEwen 1988).

Recrudescence of symptoms may be partly due to regeneration of pathological synovium occasionally as early as one month following operation (Patzakis et al. 1973). It has been recognised that the degree of joint damage at the time of operation contributes to poor outcome (London 1955) and that better results can be obtained from operating early in the course of the disease of RA (Swett 1924). However, synovectomy carried out within a year of onset of synovitis has not been recommended because of the possibility of spontaneous remission (Lloyd-Jones 1984).

In the knee, difficulty in removing posterior compartment and parameniscal synovium is sometimes overcome by additional posterior approaches or by removal of the menisci respectively (Newman 1993). Not surprisingly, morbidity is high from open surgical synovectomy. Patients often require prolonged hospitalisation, rehabilitation and even occasional manipulation (Sim 1985). In some studies, the majority of patients ultimately suffer a loss of mobility (Paradies 1975).

Because of these drawbacks and the introduction of more conservative but equally efficacious techniques, the frequency of open surgical synovectomy is diminishing (Lloyd Jones 1984), however, it continues to remain a useful
therapeutic option particularly in the upper limb and in the earlier stages of polyarticular synovitides such as rheumatoid arthritis (Seyfer 1993).

1.3.2.2.2 Arthroscopic synovectomy

Over the last 30 years, the development of arthroscopic synovectomy for the larger joints has reduced patient morbidity compared to open techniques without compromising outcome. Manual punch forceps were initially used (Matsui et al. 1989) but the development of motorised suction instruments and introduction of video technology enabled the arthroscopist the opportunity to visualise and resect almost all of the synovial lining.

Uncontrolled studies suggest that symptom improvement can last for a number of years (Aritomi 1984, Ogilvie-Harris and Basinski 1991). All studies indicate that results are similar to those from open synovectomy (Newman 1993); however, there have been no controlled studies comparing arthroscopic synovectomy with conservative treatment and also the benefit of synovectomy over intra-articular glucocorticoid has not been shown.

There are some practical and theoretical disadvantages of arthroscopic synovectomy. Patients require 7-10 days rehabilitation following a knee joint procedure to regain the preoperative range of movement (Highgenboten 1982, Aritomi 1984). Although this is a vast improvement over open synovectomy, some patients may experience prolonged discomfort as a result of the procedure and some still require manipulation to improve movement. Additionally, arthroscopy is technically demanding and results are recognised to be highly dependent on the skill and experience of the operator (Highgenboten 1982). As for open synovectomy, surgical trauma to both hyaline and fibrocartilage is likely to occur. There are no data on the long-term effects of such damage.

1.3.2.2.3 Chemical synovectomy

The trend towards more conservative approaches in the management of synovitis led to the development and introduction of injected chemical (Von Reis and Swensson 1951) and radiation agents (Fellinger and Schmid 1952).

Osmic acid formulated as osmium tetroxide in a 1% or 2% aqueous solution, a protein denaturant (Von Reis and Swensson 1951), and thiotepa, an
alkylating agent (Fearnley 1963), were originally used. Varicocid, a mix of sodium salts of fish oil fatty acids which had shown promise as a tissue and intravascular sclerosant, was also studied (Kastner and Wessel 1977).

Clinical results from open (Delcambre et al. 1982) and placebo-controlled randomised studies (Sheppeard et al. 1981, Nissila et al. 1977a) suggest moderate efficacy from osmic acid injection but there appears to be no clinical benefit over either yttrium-90 radiation synovectomy or the injected glucocorticoid, triamcinolone hexacetonide (Antinnen and Oka 1975, Menkes and Delbarre 1977). Osmic acid injection is associated with radiological evidence of accelerated articular destruction (Menkes 1979a), severe effects on cartilage and epiphyseal growth (Menkes et al. 1972) and evidence of chondrocyte necrosis (Niculescu et al. 1976, Nissila et al. 1977b).

The results from open studies using varicocid for synovectomy appear to be modest (Kastner and Wessel 1977) and morphological changes in chondrocytes have been detected in hyaline cartilage of patients treated with varicocid (Niculescu et al. 1976). Clinical results with thiotepa and other alkylating agents have been poor and this approach has largely been abandoned (Menkes 1979a).

In summary, there is no strong evidence that chemical synovectomy agents are more efficacious than either radiation synovectomy or intra-articular glucocorticoid and a number of studies suggest a deleterious effect on cartilage. These findings may have reduced interest in using osmic acid. This is perhaps reflected by the low number of reports on the use of osmic acid in the literature recorded by the medical literature database, Medline (WinSPIRS™ 1.01 D6) [28 clinical studies in the last 30 years, but only 5 in the last 15 and one since 1987].
1.3.2.2.4 Radiation synovectomy

1.3.2.2.4.1 Rationale for radiation therapy

The first concerted use of internally delivered radiation to treat patients with chronic synovitis (Ansell et al. 1963) followed from the observation that, in patients with cancer, suspensions of radioactivity injected into a serosal cavity were effective in reducing malignant effusions (Menkes 1979b).

It was proposed that if the therapeutic effects of the injected radiation resulted in the destruction of the inflamed synovial lining, normal synovial lining regeneration would occur (Menkes 1979). A similar effect to surgical synovectomy could then be achieved though without the requirement of a general anaesthetic, the risk of peri-operative morbidity or the need for a period of post-procedure rehabilitation.

External beam X-Ray and internally delivered β radiation have been successfully employed for therapy and palliation of neoplastic disease for many years but there are few clues to indicate whether non-neoplastic inflamed tissue is sensitive to radiation. The major application of radiation in treating non-neoplastic disease has been in iodine-131 therapy of hyperthyroid disease (Klein et al. 1994). There is some clinical evidence (briefly reviewed below) that radiation can improve indices of inflammation in some rheumatological diseases.

Local external beam irradiation has been effective in relieving the spinal pain from ankylosing spondylitis (AS). However, radiation fields were necessarily wide, delivered doses to a number of organs were high (Lewis et al. 1988) and a 28% excess mortality from neoplastic disease in treated AS was identified compared to the general population (Darby et al. 1987). Although the risk of malignancy has been deemed too high to persist with radiation therapy for AS, an unquestionable and prolonged symptomatic response was achievable.

AS is one of the seronegative spondylarthritides (see 1.2.2.1) in which the presence of inflammatory arthritis shares an association with the multiple histocompatibility complex (MHC) class I molecule B27. Patients often develop oligoarticular synovitis and/or enthesitis (pain and inflammation at the site of tendon or fascia insertion into bone periosteum) in the lower limbs. Low dose (10Gy) local external beam radiotherapy has been found to improve
symptomatic inflammatory pedal lesions recalcitrant to NSAIDs in many patients (Mantell 1978, Grill et al. 1988).

It is unknown which cells or biological processes are critically affected by radiation in the HLA B27-associated spondylarthropathies. There are, however, many pathophysiological similarities between synovitis associated with these diseases and synovitis in RA (see 1.2.2.2) suggesting that cells or processes important in the generation of chronic synovitis per se might be sensitive to radiation therapy. The few published reports of the effect of radiation on chronic synovitis in psoriatic arthritis patients, however, suggest only a modest effect (Recordier et al. 1972, Gumpel 1973).

1.3.2.4.2 Historical perspective and overview

Radiation synovectomy was first reported in 1952 for the treatment of septic knee arthritis (Fellinger and Schmid 1952) though it was not until 1963 that large cohorts of patients with chronic synovitis were treated with gold-198 (Au-198) colloid (Ansell et al. 1963). The use of Au-198 colloid was replaced in many centres by rhenium-186 (Re-186) and yttrium-90 (Y-90). Because of its less energetic range of γ decay, Re-186 was considered an advantage as it would reduce unwanted radiation exposure (Ingrand 1973). Y-90 was introduced for its greater β⁺ penetration and less γ radiation compared to Au-198 (Table 1.2), aspects thought to improve the efficacy/risk ratio of the procedure (Ansell et al. 1963, Webb et al. 1969). Phosphorus-32 (P-32) [Johnson and Christian 1967] was subsequently introduced in colloidal form. The radionuclide erbium-169 (Er-169) was later introduced (Delbarre et al. 1977) on the basis that the weaker β⁺ penetration would make it more suitable than Y-90 for the treatment of smaller joints.

Each of these radionuclides has been administered in colloidal form. Escape of up to 48% of administered Au-198 activity (Virkkunen et al. 1967) and 45% of administered Y-90 activity (Gumpel et al. 1975) from an injected joint has been demonstrated using a colloidal vehicle. This was despite using colloids with an optimal size (0.1μm) to reduce extra-articular escape of the radiopharmaceutical (Ingrand 1973). Concomitant intra-articular glucocorticoid injection (Goode and Howie 1973) and post-injection joint
immobilisation (Williams et al. 1981) help to reduce extra-articular spread of activity following radiocolloid injection.

Later studies, that assessed the escape of radionuclide-labelled particles from an injected rabbit joint, suggested that larger particles (5-15μm) might be retained for longer in the joint, thus reducing the escape of activity (Sledge et al. 1977, Noble et al. 1983). Consequently, a number of different radiopharmaceuticals utilising larger particles have been studied (Sledge et al. 1984, Mumper et al. 1992, Chinol et al. 1993). However, physicochemical attributes have meant that the conventionally used radionuclides have not always been the most successful in binding to larger particles (Davis and Chinol 1989). Thus, over the last decade, other radionuclides such as dysprosium-165 (Dy-165), holmium-166 (Ho-166) and samarium-153 (Sm-153) have been introduced.

The prevalence of radiation synovectomy practice is currently unknown (see Chapter 7). Use of radiopharmaceuticals may reflect legislative differences in licensing. For example, no radiation synovectomy radiopharmaceutical is licensed for routine clinical use in the United States. In contrast, reports regularly appear in the literature from Australian and European centres suggesting that the technique is widely employed in these continents.

1.4 Radiation synovectomy radiopharmaceuticals

All radionuclides used for radiation synovectomy exert their therapeutic effect by releasing energy from emitted $\beta^-$ particles in the synovial lining. $\beta^-$ decay is the expulsion of an electron from an unstable nucleus where there is a higher ratio of neutrons to protons compared to the ratio in the stable daughter nuclide(s). The physical characteristics of radionuclides, either in use or studied for use in radiation synovectomy, are listed in Table 1.2.

The characteristics important in determining suitability of a radionuclide for synovectomy relate both to its physical characteristics and to a knowledge of the nature and distribution of the biological target. These have frequently been discussed in the literature (Ingrand 1973, Menkes 1979b, Harbert 1987, Johnson and Yanch 1991, Deutsch et al. 1993). Also, the choice of radionuclide cannot be considered independently from the radionuclide
vehicle, as the chemical form of the final radiopharmaceutical will play a vital part in the distribution and fate of the radionuclide within the joint and synovial tissue. The following sections (1.4.1 - 1.4.6.2) summarise factors important in choosing a radionuclide and designing its vehicle. The discussion is illustrated by reference to the characteristics of radiopharmaceuticals in clinical use.

Table 1.2 Physical characteristics of radionuclides either in use clinically, or which have been investigated for radiation synovectomy. Source: Raddecay 2.02 IBM PC-compatible software. © Grove Engineering Inc

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Half-life (days)</th>
<th>Range of mean β^- energy /decay (MeV)</th>
<th>Most abundant mean β^- energies [MeV (%)]</th>
<th>*Range in soft-tissue (mm)</th>
<th>Most abundant γ energy [keV (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-32</td>
<td>14.3</td>
<td>0.695</td>
<td>0.695 (100%)</td>
<td>7.9</td>
<td>2.2</td>
</tr>
<tr>
<td>Au-198</td>
<td>2.7</td>
<td>0.079 - 0.467</td>
<td>0.315 (99%)</td>
<td>3.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Y-90</td>
<td>2.8</td>
<td>0.935</td>
<td>0.935 (100%)</td>
<td>10.8</td>
<td>2.8</td>
</tr>
<tr>
<td>Re-186</td>
<td>3.8</td>
<td>0.087 - 0.362</td>
<td>0.309 (22%)</td>
<td>4.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Er-169</td>
<td>9.4</td>
<td>0.074 - 0.101</td>
<td>0.098 (45%)</td>
<td>1.0</td>
<td>-</td>
</tr>
<tr>
<td>Dy-165</td>
<td>0.1</td>
<td>0.056 - 0.453</td>
<td>0.453 (84%)</td>
<td>5.6</td>
<td>1.3</td>
</tr>
<tr>
<td>§Re-188</td>
<td>0.7</td>
<td>0.048 - 0.795</td>
<td>0.729 (25%)</td>
<td>10.1</td>
<td>2.1</td>
</tr>
<tr>
<td>§Ho-166</td>
<td>1.1</td>
<td>0.052 - 0.693</td>
<td>0.651 (48%)</td>
<td>8.7</td>
<td>2.1</td>
</tr>
<tr>
<td>§Sm-153</td>
<td>1.9</td>
<td>0.081 - 0.263</td>
<td>0.199 (34%)</td>
<td>3.1</td>
<td>0.7</td>
</tr>
</tbody>
</table>

*Defined as the depth in the synovial lining at which the % dose = 10% of the maximum dose deposited at the synovial lining surface (Johnson and Yanch 1991 and see also Fig. 1.4)

*No clinical data has been published for these radionuclides

*Data from Johnson et al. 1995 except that for Er-169 which is from Deutsch et al. 1993

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1.4.1. Radionuclide \( \beta^- \) energy

1.4.1.1 Therapeutic effects

The therapeutic effect of any radiation treatment on any given cell depends on absorption of radiation energy sufficient to kill it or favourably alter its function. For cellular tissue adjacent to, or surrounding a \( \beta^- \) emitting radionuclide, the absorbed energy is directly related to the total \( \beta^- \) energy emitted by the radionuclide. However, absorbed energy will also be influenced by tissue-specific factors such as mass and shape and on the scatter of particles within the tissue and from surrounding structures.

For radiation synovectomy it has been frequently stated that the ideal radionuclide \( \beta^- \) energy should be sufficient to penetrate the thickness of the synovial lining but sufficiently weak so as to avoid cartilage and bone marrow irradiation or irradiation of overlying skin (Ingrand 1973, Menkes 1979b). From this maxim and on the basis that size of joint determines thickness of synovial tissue, radionuclides with different energies have been recommended for different sized joints (Harbert 1987). Thus Y-90 (maximum \( \beta^- \) penetration 10.8mm) has been recommended for large joints such as knees, Er-169 (maximum \( \beta^- \) penetration 1.0mm) for small joints such as finger joints and Re-186 (maximum \( \beta^- \) penetration 4.5mm) for joints of intermediate size (Newman 1993).

This, however, may be too simple an argument and fails to consider: firstly, the relationship between \( \beta^- \) penetration and absorbed dose; secondly, the identity of the cellular biological target; thirdly, its distribution within the synovial lining; and finally, the distribution of the radionuclide in relation to the target. These issues are critical to the application of therapeutic radiation in treating synovitis. It is important to note, however, that the difference in range over which energy is deposited from the various \( \beta^- \) emitters, is less than that suggested by a brief comparison of their maximum penetration in soft-tissue (Fig. 1.4). Also, the nature and distribution of the cellular biological target is essentially unknown and consistent differences in synovial lining shape and dimensions between different joints have not been described. Furthermore, in most joints, a radiopharmaceutical in the synovial fluid is likely to be as close to cartilage as it is to synovium (see Figs. 1.1 and 1.2),
implying that the survival of cartilage may depend more on factors such as its radioresistance than on $\beta^-$ penetration and, thus, choice of radionuclide.

These issues suggest that the rationale underpinning the joint-specific application of $\beta^-$ emitters may be flawed and are the focus of debate throughout this thesis. A detailed discussion is included in Chapters 3.4 and 8.3.2.3.

![Diagram of therapeutic $\beta^-$ penetration and maximum $\beta^-$ penetration in soft-tissue for various radionuclides used for radiation synovectomy. For numerical values see Table 1.2. Adapted from Johnson and Yanch 1991. For explanation of $x_{90}$, see legend to Table 1.2](image)

As a result of a lack of data, the amount of activity of any radionuclide needed to achieve a therapeutic response is unknown. There have only been a few attempts to derive theoretical estimates of intra-articular $\beta^-$ dosimetry in radiation synovectomy (Ingrand 1973, Husak et al. 1973, Topp and Cross 1970, Johnson and Yanch 1991, Johnson et al. 1995). In practice, reliable measurements of dose are difficult to make in vivo. Realistic models of articular dosimetry based on the Monte Carlo principle have been constructed (Johnson and Yanch 1991) and verified by recording activity within injected cadaveric joints with radiachromic film dosimeters (Johnson et al. 1995).
These advances, however, are recent, and the convention that recommendations of administered activity remain empirically based on the activity observed to provide a clinical response (Gumpel et al. 1975, Sledge et al. 1984) has remained for over 30 years (Deutsch et al. 1993).

1.4.1.2 Unwanted effects

There is a risk of irradiation of extra-articular healthy tissue from the $\beta^-$ activity within an injected joint and from activity which may escape from the joint.

1.4.1.2.1 Articular and peri-articular tissue irradiation

The main structures at risk are soft-tissue underlying the synovial subintima and within the joint cavity e.g. cruciate ligaments in the knee, cartilage and bone. The amount of irradiation will depend on the distribution of activity within the joint and the penetration of $\beta^-$ particles.

Both colloidal (Isomaki et al. 1972, Webb et al. 1969) and particulate radiopharmaceuticals (Shortkroff et al. 1992) are engulfed by synovial tissue, including that part of the synovial lining which lies adjacent to hyaline cartilage at its margins (Bonneton 1972). It is therefore inevitable that there will be some irradiation of cartilage and subchondral bone with all but the least penetrative $\beta^-$ emitting radiopharmaceuticals. On the basis that chondrocytes in adult articular cartilage have little, if any, mitotic activity, hyaline cartilage might be expected to be relatively radioresistant. In support of this, only minimal histological change has been seen in cartilage following irradiation (Rubin et al. 1972). However, ultrastructural changes (Kerschbaumer et al. 1979) and metabolic effects (Hugenberg et al. 1989) have been identified in human and canine hyaline cartilage respectively, following intra-articular injection of strongly penetrating ($Y$-90) $\beta^-$ irradiation. The long-term effects of radiation on the progression of cartilage degeneration are not known.

Peri-articular soft-tissue may be irradiated as a result of energy deposition from penetrative intra-articular $\beta^-$ particles or from local extravasation of the radiopharmaceutical into subintimal tissue. Damage may be evident by erythema or, if severe, by overlying skin necrosis (Menkes 1972, Peters and
Lee 1994). It has been customary to avoid injecting penetrative $\beta^-$ emitters (such as Au-198 or Y-90) into smaller joints such as the interphalangeal or metacarpophalangeal joints as this practice appears to be associated with peri-articular soft-tissue and skin lesions (Menkes 1972, Virkkunen et al. 1967). Only very infrequently are skin lesions noted when using less penetrative radionuclides such as Er-169 for small joint injection.

1.4.1.2.2 Extra-articular tissue

Irradiation of extra-articular tissue from $\beta^-$ particles will mainly depend on the fraction of activity which escapes from the joint. There may be an additional (small) component from bremsstrahlung (photons produced from the interaction of decelerating electrons and the electric field of a nucleus or atomic electrons) arising primarily from intra-articular $\beta^-$ particle/tissue interaction. The amount of activity escape from a joint may depend critically on the radiation carrier (see 1.4.4.1). If escaped activity remains bound to its carrier then the biodistribution characteristics of the carrier will strongly influence the pattern of extra-articular tissue irradiation.

The liver and lymph nodes appear to be the primary sites of extra-articular activity accumulation following joint injection with radiocolloids (Virkkunen et al. 1967, Gumpel et al. 1972). The absorbed dose of regional lymph node tissue may occasionally be quite large. Following knee injection with Y-90 colloid for example, regional lymph node absorbed dose has been calculated to be up to 100Gy (Oka et al. 1971). Consequently, studies of the effects of extra-articular $\beta^-$ irradiation have focused mainly on lymphocytes.

In patients treated with radiocolloids, lymphocyte chromosome damage is induced in vivo, occurs as a result of focal accumulation of activity in lymphoid tissue and correlates to the amount of activity which escapes from the joint (Stevenson 1973). The clinical effects and predictive risks of lymphocyte chromosome aberrations, however, are unknown. Although haematological malignancy has been reported in patients following radiation synovectomy with Au-198 colloid (Lipton and Messner 1991), the risk of malignancy following radiation synovectomy, estimated from atomic bomb survivors and patients receiving external beam radiotherapy, is relatively small.
in comparison to the risk of naturally occurring cancer (Stevenson 1973, Dolphin 1973).

1.4.2 Radionuclide γ (photon) emission

Conventionally, it has been considered disadvantageous to use radionuclides which have had γ decay on the basis that the radiation is of no benefit and would increase both extra-articular healthy tissue irradiation in the patient and the exposure to those administering the radiopharmaceutical (Ingrand 1973). However, a tiny amount of low energy γ emission within an energy range that is easily detected by conventional γ camera systems (70-550keV) may be an advantage in that it allows both intra-articular and extra-articular distribution of the injected activity to be documented, thus defining its biodistribution characteristics and allowing its dosimetry to be estimated. Furthermore, energy derived from the photons emitted by intra-articular radionuclides does not contribute much to the extra-articular tissue absorbed dose (particularly lymphocytes) compared to the dose from β⁻ particles which have escaped from the joint (Stevenson 1973).

1.4.3 Radionuclide physical half-life

The physical half-life is an important consideration when developing a radiopharmaceutical for a number of practical reasons (see 1.4.1.5). There are also sound biological reasons for carefully considering the influence of half-life on potential therapeutic and toxic effects of any given radiopharmaceutical.

The half-life of a radionuclide is inversely proportional to its dose rate. The dose rate of a pure β⁻ emitting radionuclide can be regarded as the rate of delivery of β⁻ energy. For any irradiated tissue therefore there is also a rate at which the energy is absorbed. This rate may be important in determining whether cells can survive radiation damage through natural repair mechanisms and may vary for different tissues depending on the ability of the cell population in the tissue to perform this function. If the rate of energy absorption is low, then molecular, particularly DNA, damage may be repaired by enzymatic repair mechanisms. If the rate of energy absorption is high, repair mechanisms may be ineffective. The paucity of data and published
discussion addressing this aspect of radiation biology in relation to half-life reflects this neglected area of research.

1.4.4 Radionuclide carrier

The need to administer radionuclides as preparations which would distribute evenly around the joint, but be retained within the joint, led initially to the use of a radiocolloid (Ansell et al. 1963). Many different radiocolloids have been produced and include Y-90 citrate, silicate, ferric hydroxide and resin colloids, P-32 chromic phosphate colloid, Er-169 citrate colloid and Re-186 sulphide colloid.

1.4.4.1 Influence on intra-articular distribution of activity

Colloidal particles of around 10nm in size were thought optimal to be evenly distributed over the synovial lining (Ingrand 1973). Particles of several hundred nm were thought to be too large for even intra-articular distribution of activity; however, no reliable data have been made available to support or refute this.

Obtaining a homogeneous size of colloid particle may be difficult owing to the complex chemical methods needed for particle growth. Often particle size varies by factors of 10-100 (Ingrand 1973). Homogeneity of particle size was most successfully achieved with synthetic resin colloid. However, the only resin colloid used extensively (Y-90 resin colloid) is no longer produced owing to manufacturing problems (Gumpel et al. 1975).

Most imaging studies suggest that despite the heterogeneity of particle size, colloids may be evenly distributed throughout injected joints (Ingrand 1973). However, autoradiography of synovium removed following radiation synovectomy with Y-90 colloid, has shown patchy distribution (Dunscombe and Ramsey 1980), suggesting that imaging studies, at least for Y-90, may be an insensitive indicator of distribution of synovial uptake of colloid. It is possible that some colloids may preferentially accumulate in areas of synovium which, by corresponding to areas accumulating pertechnetate, may be more inflamed (Kyle et al. 1983).
The intra-articular distribution characteristics of larger particulate radiopharmaceuticals, designed to reduce the amount of extra-articular spread of activity compared to radiocolloids (see 1.4.4.2), have not been studied.

1.4.4.2 Influence on extra-articular escape of activity

Prior to 1960, investigators had suggested that size was critical in limiting the egress of particles from a synovial joint (Adkins and Davies 1940, Bauer et al. 1933, Rodnan and Maclachlan 1960) although there was little evidence that activity escape from an injected joint could be predicted from the colloidal particle size, at least in the range 1-1000nm (Ingrand 1973).

The consistent problem with all colloids has always been the escape of activity from an injected joint into blood and lymphatics. Up to 48% of injected activity Au-198 colloid (Virkkunen et al. 1967) and 45% of Y-90 colloid (Prichard et al. 1970) may be lost from an injected knee joint. The synthetic Y-90 resin was found to be retained slightly better within the joint than other Y-90 colloids (Gumpel et al. 1975) but was withdrawn because of production difficulties. Manoeuvres important in reducing extra-articular spread of activity included post-procedure joint splinting, bed rest or joint immobilisation (Roberts and Gillespie 1973, Gumpel et al. 1975, Williams et al. 1981).

Around 20 years after the initial radiocolloid reports, the results of studies using various radiolabelled particles of varying sizes injected into rabbit knee joints (Sledge et al. 1977, Noble et al. 1983) supported the notion that larger particulate radionuclide carriers (5-10μm) might be associated with lower rates of activity egress from injected joints. From that time on, a number of particulate carriers for radionuclides have been investigated (Table 1.3). The most widely used has been Dy-165 ferric hydroxide macroaggregates (FHMA) [Sledge et al. 1986].

The type of radionuclide carrier may contribute to invoking synovitis 'flares' occurring immediately after radiopharmaceutical joint injection (see 1.4.7.1). This was a particular problem with resin colloid (Gumpel 1973) used briefly in the 1970s, but it is no longer produced.
Table 1.3 Particulate radiopharmaceuticals. Escape of activity from injected joints: animal and patient data

<table>
<thead>
<tr>
<th>Reference</th>
<th>Radio-pharmaceutical</th>
<th>Particle size (μm)</th>
<th>Disease or animal model studied</th>
<th>Extra-articular organ in which activity accumulated</th>
<th>Mean injected activity accumulation in organ (hrs post injection)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sledge et al. 1977</td>
<td>Dy-165 FHMA</td>
<td>3-10</td>
<td>AIA NZ, white rabbit</td>
<td>Whole body</td>
<td>&lt;1.2% (24)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Liver</td>
<td>0.34% (24)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Regional lymph nodes</td>
<td>0.001% (24)</td>
</tr>
<tr>
<td>Hnatowich et al. 1978</td>
<td>Dy-165 FHMA</td>
<td>3-10</td>
<td>AIA NZ, white rabbit</td>
<td>Liver</td>
<td>0.1%</td>
</tr>
<tr>
<td>Sledge et al. 1984</td>
<td>Dy-165 FHMA</td>
<td>3-10</td>
<td>Knee in RA patients</td>
<td>Liver</td>
<td>0-1.5% (24)*</td>
</tr>
<tr>
<td>Zalutskiy et al. 1986</td>
<td>Dy-165 FHMA</td>
<td>3-10</td>
<td>Knee in RA patients</td>
<td>Regional lymph nodes</td>
<td>0.12% (19)*</td>
</tr>
<tr>
<td>Sledge et al. 1986</td>
<td>Dy-165 FHMA</td>
<td>3-10</td>
<td>Knee in RA patients</td>
<td>Liver</td>
<td>0.6% (24)^*</td>
</tr>
<tr>
<td>Zuckerman et al. 1986</td>
<td>Dy-165 FHMA</td>
<td>3-10</td>
<td>Knee in RA patients</td>
<td>Regional lymph nodes</td>
<td>0.2% (24)</td>
</tr>
<tr>
<td>Davis and Chinol 1989</td>
<td>Y-90 FHMA</td>
<td>95% &gt;10</td>
<td>AIA NZ, white rabbit</td>
<td>Whole body</td>
<td>3.3% (120)</td>
</tr>
<tr>
<td></td>
<td>Y-90 calcium oxalate</td>
<td>90% &lt;10</td>
<td>AIA NZ, white rabbit</td>
<td>Regional lymph nodes</td>
<td>&lt;0.01% (120)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Whole body</td>
<td>&lt;5% (120)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Regional lymph nodes</td>
<td>&lt;0.01% (120)</td>
</tr>
<tr>
<td>Mumper et al. 1991</td>
<td>Ho-166 poly-L-lactate microspheres</td>
<td>2-13</td>
<td>Normal NZ, white rabbit</td>
<td>Whole body</td>
<td>&lt;2% (120)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Regional lymph nodes</td>
<td>Nil</td>
</tr>
</tbody>
</table>

*Mean activity corresponds to dose of 25mGy
^Corresponds to a dose of 166mGy
^Corresponds to a dose of 32mGy
1.4.5 Practical aspects of radiopharmaceutical production and preparation

There are a number of aspects of production which are important in determining the potential clinical utility of a radiopharmaceutical.

Ideally, the stable nuclides from which radionuclides are produced should be easily and cheaply available. The radionuclide should be easily and efficiently produced in either a cyclotron or a reactor and its half-life should be sufficient to allow transport and handling between the point of production to the site of administration before excessive decay has occurred. Finally, the preparation required at the site of administration (if any) should be quick and easy to undertake.

Almost all radionuclides used for radiation synovectomy have a half-life of around 2 days or more (Table 1.2) often making shipping from the reactor (for example) to the site of administration quite feasible. Dy-165, for example, has a half-life of under 2.5 hours thus making the planning of treatment a particular problem if the reactor and site of administration are not close (Edmonds et al. 1994, see also Chapter 8.2.1).

All radiocolloids in clinical use are prepared at the site of radionuclide production leaving little preparation needed at the site of administration. Larger particulate radiopharmaceuticals are more likely to be prepared at the site of administration (Deutsch et al. 1993). Complicated preparation steps are ideally avoided. For example, the preparation methods of Re-188 heptasulphide (Venkatesan et al. 1990) are laborious and may preclude its acceptance in a clinical setting (Deutsch et al. 1993) irrespective of its in vivo effects. The preparation and labelling of Dy-165 FHMA, although requiring only 20 minutes, is complicated (Hnatowich et al. 1978) and requires the expertise of a radiochemist at the site of administration.

1.4.6 Radiochemical purity

Radionuclide production and labelling procedures may result in the coincidental production of impurities. A knowledge of the nature and amount of impurities may be important in predicting the potential for in vivo activity distribution and risks to health.
1.4.6.1 Radionuclidic impurities

Radionuclidic impurities do not occur as a result of Y-90 production from Y-89. However, Re-188 (<0.04%) may be present as a result of the production of Re-186 from Re-185, likewise Au-199 (<5%) as a consequence of Au-198 production from Au-197 (Ingrand 1973). The only radionuclidic impurity produced with Dy-165 from the neutron irradiation of Dy$_2$O$_3$ is Na-24 (10$^{10}$ % Dy-165 activity) [Hnatowich et al, 1978]. The amounts of these impurities are small, differ little in their physical and chemical characteristics from the primary produced radionuclide and are likely to be clinically insignificant if present in the radiopharmaceutical preparation.

1.4.6.2 Radiochemical impurities

Soluble components may be produced as a result of the production of the radiocolloids Y-90, Re-186, Au-198 and Er-169 (Ingrand 1973). With the rare earth elements (yttrium, erbium) and rhenium the amount of soluble component present based on production of a given specific activity is unlikely to result in a pharmacological effect (Ingrand 1973) and none has been reported. However, typical reactions observed following treatment with intra-articular Au-198 colloid (Menkes et al. 1972) suggest that soluble gold forms occur as a result of Au-198 colloid production and pharmacologically significant amounts may be injected with the colloid.

1.4.7 Efficacy of radiopharmaceuticals

Evidence for efficacy of radiation synovectomy is based on data from histopathological analysis of animal or patient synovium, imaging or clinical studies.

1.4.7.1 Evidence for efficacy: I. Histopathology and autoradiography

The administration of Y-90 into normal rabbit knees initially causes thickening of the synovial membrane and an increase in the cellular infiltrate (Pavelka et al. 1975). Thrombotic occlusion of capillaries in the superficial synovial lining is striking. Within a few weeks, a substantial amount of interstitial fibrous tissue is evident and areas of normal synovium seem to reappear. A similar inflammatory reaction occurs to Y-90 in normal canine.
joints (Myers et al. 1978). Larger administered activities are associated with a persistence of mononuclear cell infiltrate.

Animal data therefore suggest that Y-90 colloid may be pro-inflammatory before the beneficial effects of irradiation are likely to be seen. Whether this is a direct effect of irradiation of tissue or a reaction to the radiopharmaceutical is not entirely clear. Synovial tissue from patients treated with intra-articular radiation has generally been obtained 4 weeks or more after treatment (Yates 1973, Onetti et al. 1982) making it likely that any ‘reactive’ inflammatory changes may have been missed. Summarised below are observations of changes in synovial pathophysiology following radiation synovectomy in RA patients.

Four weeks after Y-90 colloid radiation synovectomy, a reduction in the number and vascularity of synovial surface projections can be seen arthroscopically (Yates 1973). At this early stage the synovial lining may appear thickened with increased fibrin deposition in the surface layers compared to pre-treatment tissue. There may be little change in the extent of cellular infiltrate.

Weeks to months after treatment with Au-198 colloid there may be a decrease in thickness of the synovial membrane, reduction in cellular infiltrate and increased fibrosis which may affect the blood vessels (Ansell 1973). Obliteration of blood vessels and peri-vascular fibrosis are evident up to a year following treatment (Ingrand 1973), but are not necessarily associated with a prolonged clinical response (Coombe et al. 1989).

As no study has prospectively compared changes in synovial tissue in patients receiving radiation synovectomy and controls, it is not clear whether specific patterns of tissue changes are associated with clinical improvement or relapse. However, there are clues that some changes seen in synovial tissue may relate to changes observed clinically. For example, in addition to interfering with a number of pro-inflammatory functions of vascular endothelial cells, vascular occlusion and fibrosis might be expected to decrease the accumulation of fluid in inflamed joints. A reduction in effusion was one of the first reported benefits of radiation synovectomy (Ansell et al. 1963).
1.4.7.2 Evidence for efficacy: II. Imaging studies

There are no established, specific, non-invasive techniques for imaging the synovial lining. Arthrography performed 6-12 months after P-32 colloidal radiation synovectomy of the knee has demonstrated a reduction in size, or disappearance, of peri-articular bursae when compared to pre-treatment arthrography studies (Onetti et al. 1982). Although this suggests efficacy, the study was uncontrolled.

Table 1.4 Clinical outcome from radiation synovectomy: data from a selection of open studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients (no. of injected joints)</th>
<th>Disease/Joints</th>
<th>Radio-pharmaceutical</th>
<th>Activity (MBq)</th>
<th>Frequency of symptom response (follow-up)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virkkunen et al. 1967</td>
<td>85(91) RA, OA/knees</td>
<td>Au-198 colloid</td>
<td>185-370</td>
<td>86% 'benefit' (4-24 months)</td>
<td></td>
</tr>
<tr>
<td>Boerbooms et al. 1985</td>
<td>57(66) RA/knees</td>
<td>Au-198 colloid</td>
<td>185</td>
<td>51% 'excellent/good' (12 months)</td>
<td></td>
</tr>
<tr>
<td>Onetti et al. 1982</td>
<td>111 (217) RA/knees, ankles, hips, elbows, wrists, MCPs, PIPs</td>
<td>P-32 colloidal chromic phosphate 11-MCPs and PIPs 227-others</td>
<td>84% 'satisfactory' (1-10 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oka et al. 1971</td>
<td>20(22) RA/knees</td>
<td>Y-90 resin colloid</td>
<td>111-227</td>
<td>91% 'good/excellent' (12 months)</td>
<td></td>
</tr>
<tr>
<td>Spooren et al. 1985</td>
<td>48(33) RA, OA/knees</td>
<td>Y-90 silicate colloid</td>
<td>185</td>
<td>42% 'improvement' (22 months)</td>
<td></td>
</tr>
<tr>
<td>Will et al. 1992</td>
<td>32(45) RA/knees, hips, elbows, shoulders</td>
<td>Y-90 silicate colloid</td>
<td>81-163</td>
<td>74% 'good' (12 months)</td>
<td></td>
</tr>
<tr>
<td>Sledge et al. 1986</td>
<td>93(108) RA/knees</td>
<td>Dy-165 FHMA</td>
<td>9990</td>
<td>61% 'good' (12 months)</td>
<td></td>
</tr>
<tr>
<td>Gregoir &amp; Menkes 1991</td>
<td>69(103) RA/elbows</td>
<td>Re-186 sulphate colloid</td>
<td>74</td>
<td>83% 'good/very good' (12 months)</td>
<td></td>
</tr>
</tbody>
</table>
1.4.7.3 Evidence for efficacy: III. Clinical outcome studies

A recent review identified over 70 studies assessing clinical outcome following radiation synovectomy (Deutsch et al. 1993) although this is almost certainly an underestimate. The vast majority are uncontrolled studies (Table 1.4). A few studies have compared the effects of a radiopharmaceutical with placebo or no treatment in patients with RA (Bridgman et al. 1973, Delbarre et al. 1974, Szanto 1978, Yates et al. 1979, Boussina et al. 1979). However, utilising data from the reviews of Deutsch (Deutsch et al. 1993) and Jones (Jones 1993) and information from a search of the medical literature database Medline from 1962-1995 (WinSPIRS™ 1.01 D6), it appears that there are only 9 studies in the English and French literature which randomly compare a radiopharmaceutical with another radiopharmaceutical or another local therapy for synovitis. Eight of these were conducted using RA patient cohorts, and one was undertaken in patients with synovial thickening associated with chondrocalcinosis (Doherty and Dieppe 1981). These studies are briefly reviewed in the following sections which focus on individual radiopharmaceuticals.

Clinical outcome from radiation synovectomy is discussed briefly in Chapter 4.4.2 and Chapter 6.4 and in more detail in Chapter 8.3.2.

1.4.7.3.1 Gold-198 colloid

Uncontrolled studies using between 18.5-370MBq (0.5-10mCi) Au-198 colloid to treat mainly knee joints in RA have shown that symptomatic benefit can be obtained in 50-90% of patients one year following injection (Table 1.4). Similar benefits are seen in patients treated for haemophilic arthritis (Deutsch et al. 1993). There have been no randomised controlled studies comparing the efficacy of Au-198 with either placebo, surgical synovectomy or intra-articular glucocorticoid. One German study has concluded that there is no difference in clinical outcome between patients treated with Au-198 or Y-90 colloid (Reichel et al. 1979).

1.4.7.3.2 Phosphorus-32 chromic phosphate colloid

Symptomatic improvement from a number of joint injections can be achieved in RA patients with overall results similar to those from Au-198 and
Y-90 colloids (Onetti et al. 1982). Additionally, up to 37MBq (1mCi) of intra-articular P-32 colloid has been used to treat haemophilic arthropathy with some success (Rivard 1990). However, these data, like that from studies in RA, are derived from uncontrolled studies.

1.4.7.3.3 Yttrium-90 colloids

Most uncontrolled studies indicate that symptomatic benefit from a single Y-90 colloid joint injection may occur in up to 80% of RA patients after one year (Newman 1993). There are 3 studies comparing Y-90 colloid to either placebo or no treatment (Bridgman et al. 1973, Delbarre et al. 1974, Yates et al. 1979). Bridgman randomised patients with chronic knee synovitis to receive either 111MBq (3mCi) Y-90 resin colloid or saline. After one year there was a significant improvement in knee flexion range and circumference compared to the placebo group. Delbarre confirmed an effect of Y-90 over both saline and non-radioactive ('cold') yttrium. In contrast, Yates identified no symptomatic benefit of 185MBq (5mCi) Y-90 compared to cold yttrium in a double-blind randomised trial in patients with chronic knee synovitis followed over 2 years. The study of Szanto (Szanto 1978) compared clinical outcome following Y-90 resin colloid with that of methylprednisolone acetate injected simultaneously into patients with bilateral knee synovitis. Outcome was significantly better in the Y-90 group. However, glucocorticoid non-responders had been specifically recruited to the study and injections were not randomised, suggesting that there may have been some bias.

There have been 6 randomised studies comparing Y-90 colloid to other local therapies for chronic rheumatoid synovitis. Five of these studies are reviewed in a meta-analysis of Y-90 synovectomy (Jones 1993) and are broadly comparable because similar groups of patients were enrolled and in 3 of the studies a similar activity (185MBq) of Y-90 was administered. In only one study (Menkes et al. 1972) was the odds ratio of a beneficial response from Y-90 greater than 1 when compared to an alternative treatment. This study, which appeared in abstract form only, found a significant advantage of Y-90 colloid over both triamcinolone hexacetonide and osmic acid in reducing chronic synovitis symptoms. Notably, the only other study to compare Y-90 colloid with triamcinolone hexacetonide in a randomised study (ARC study
1984), did not identify any difference between the two treatments, though the study was stopped before enough patients were recruited to obtain sufficient power for a valid analysis of statistical significance. The sixth study found no significant difference in outcome between Y-90 silicate and Dy-165 FHMA synovectomy in patients with either RA or osteoarthritis (Edmonds et al. 1994).

In addition to studying patients with RA, a number of series have included patients with osteoarthritis (Delbarre et al. 1973, Gumpel 1973, Stucki et al. 1993). These studies often suggest efficacy although there have been no randomised placebo or glucocorticoid-controlled studies. However, the combination of Y-90 colloid and 20mg triamcinolone hexacetonide was found to be more efficacious than glucocorticoid alone in improving swelling and range of movement when randomly compared for the treatment of synovial thickening associated with bilateral knee chondrocalcinosis (Doherty and Dieppe 1981).

It should be noted that Y-90 synovectomy produces similar results to those from surgical synovectomy (Gumpel and Roles 1975, Nissila et al. 1978) and as a therapeutic option has been favoured on the basis of a lower risk of morbidity, side effects and post-procedure rehabilitation duration.

1.4.7.3.4 Rhenium-186 sulphur colloid

There are few published data of the efficacy of Re-186 colloid but a 50-60% ‘good or excellent’ benefit was reported in RA patients one year after injection (Menkes 1979b). There are no randomised placebo or treatment controlled studies assessing its benefit.

1.4.7.3.5 Erbium-169 citrate colloid

According to published data, Er-169 colloid (citrate) has almost exclusively been employed in small joint synovectomy (see Chapter 7.4.6). There are 4 studies which have compared the efficacy of Er-169 citrate colloid with intra-articular glucocorticoid for chronic synovitis symptoms (Delbarre et al. 1977, Gumpel et al. 1979, Boussina et al. 1979, Ruotsi et al. 1979).

In a double-blind study Boussina showed a significant improvement of symptoms in seropositive rheumatoid digital joints (70) following Er-169
citrate colloid compared to saline injection after 12 months. Delbarre
compared Er-169 citrate and prednisolone acetate injection of 201 rheumatoid
digital joints with saline and prednisolone acetate injection in a double-blind
study. There was a significantly prolonged response to Er-169/glucocorticoid
up to a year after treatment. Taken together, these studies would suggest a
useful clinical role for Er-169 citrate colloid in providing prolonged
symptomatic response in rheumatoid digital joints. However, when the long-
acting glucocorticoid triamcinolone hexacetonide was used as the comparator
to Er-169 in a similar study of 127 rheumatoid digital joints (Ruotsi et al.
1979), the number of remissions was higher in the glucocorticoid group at 1, 3
and 6 months. These findings were more in agreement with those of Gumpel
(Gumpel et al. 1979) who compared methylprednisolone acetate, another
long-acting preparation, to Er-169 citrate. No difference in outcome between
joints treated with the radiopharmaceutical or glucocorticoid was observed in
the year following injection.

1.4.7.3.6 Dysprosium-165 ferric hydroxide macroaggregates

Most experience using this particulate radiopharmaceutical has been
obtained by one group which has demonstrated 61-66% 'good' improvement
in the symptoms of chronic rheumatoid knee synovitis one year after injection
(Sledge et al. 1984, Sledge et al. 1986, Sledge et al. 1987). Dy-165 hydroxy
macroaggregates (HMA) appears as efficacious as Y-90 colloid in treating the
symptoms of chronic rheumatoid knee synovitis and the arthropathy of
osteoarthritis (Edmonds et al. 1994). However, there has been no randomised
trial of Dy-165 FHMA or Dy-165 HMA and intra-articular glucocorticoid.

1.4.7.4 Important factors influencing efficacy

There are a few underlying factors which may be important in determining
outcome of radiation synovectomy regardless of which radiopharmaceutical is
used. These are reviewed below (1.4.7.4.1-3).

1.4.7.4.1 Administered activity

The empirical basis by which the amount of activity of any
radiopharmaceutical is administered has been discussed (see 1.4.1.1). A lower
limit of activity needed for a response has been suggested (Ingrand 1973) and, although it is not possible to prove that lack of activity alone is responsible for a poor response in any one patient, there are some data to support this suggestion (Fellinger and Schmid 1952, Gumpel et al. 1973). Despite some evidence to suggest that small differences in activity have no effect on Y-90 efficacy (Menkes et al. 1972), formal ‘dose ranging’ studies for any radiopharmaceutical have not been undertaken.

1.4.7.4.2 Joint destruction

In studies which undertake to assess their patients radiologically it is a ubiquitous finding that the duration of response in the knee from radiation synovectomy is inversely related to the amount of cartilage and bone destruction (Deutsch et al. 1993). There is some evidence that this may not necessarily apply for upper limb joints (Menkes et al. 1972). These findings emphasise the importance of screening appropriate patients for radiological evidence of cartilage and bone destruction prior to considering radiation synovectomy. These findings also stress the importance of discriminating pain arising from inflamed synovium and pain originating from cartilage or bone destruction, so that patients with pain from the latter, which is likely to be unaffected by radiation synovectomy, are prevented from having unnecessary treatment.

1.4.7.4.3 General disease activity

It has become clear from a number of studies that patients with higher indices of active inflammation at the time of treatment appear to have a worse clinical outcome (Winfield and Gumpel 1979, Schütte and Rau 1983). It is not clear whether this is an effect associated with polyarticular synovitis nor whether the same indices in patients with oligoarticular or monoarticular disease predict outcome from injection of that joint.

1.4.7.5 Other efficacy studies

There are contradictory data on whether repeat radiation synovectomy in poor responders to a first injection, has any benefit (Winfield and Gumpel 1979, Vella et al. 1988, Stucki et al. 1993). Although arthroscopic
synovectomy can be successfully undertaken in patients unresponsive to Y-90 synovectomy (Combe et al. 1989), combined medical and surgical procedures have not been compared to medical synovectomy alone.

1.4.7.6 Summary of efficacy data

An overview of the results from some of the Y-90 and Er-169 studies emphasises that although a radiopharmaceutical may be efficacious compared to placebo, it may compare poorly to some therapeutic alternatives. This is especially relevant with respect to the long-acting injectable glucocorticoids such as triamcinolone. To fully determine the clinical utility of any radiopharmaceutical, its effect on clinical outcome should be compared with the effect achieved with triamcinolone in large randomised studies.

By extrapolation of this argument and using available evidence, radiation synovectomy cannot be cited as useful merely because its efficacy compares favourably to the efficacy of surgical synovectomy. Surgical procedures have not been satisfactorily compared to the most long-acting intra-articular glucocorticoid preparations.
1.5 Samarium-153 particulate hydroxyapatite

1.5.1 Production of samarium-153 (Sm-153)

At the time of writing, all Sm-153 for biological and medical research in Europe or North America is produced in the Research Reactor of the University of Missouri, Columbia MO., USA. The production techniques are briefly described below (L. Ayers, personal communication). A summary of Sm-153 production details is included in Appendix A.

The target submitted for neutron irradiation is samarium-152 nitrate. This is prepared from enriched (99%) samarium-152 oxide by dissolving the oxide in 1N nitric acid and leaving the sample to evaporate to dryness in a high purity quartz vial. A pellet of samarium-152 nitrate is left in the base of the vial. The vial is flame-sealed under vacuum and encapsulated in an aluminium container for irradiation. The irradiation takes place in the graphite reflector that surrounds the reactor core. The thermal neutron flux at this reflector position is approximately $8.0 \times 10^{15}$ n/cm$^2$sec. The reactor run time depends on activity to be produced, but for practical purposes 24-48 hours is sufficient.

The vial is removed from the reactor, measured for samarium-153 activity and broken open in a glove box. The pellet is dissolved in 0.1N hydrochloric acid and transferred to a glass vial for shipment. Quality control includes measurement of the hydrochloric acid solution pH and verification of Sm-153 identity and radioisotopic purity by $\gamma$ spectroscopy. A number of radionuclide impurities may be produced (Appendix A), most of which are radionuclides with long half-lives. However, for the amounts of Sm-153 produced, the levels of activity from these impurities will be tiny.

1.5.2 Physical characteristics of Sm-153

Sm-153 is a lanthanide (rare earth) radionuclide with a half-life of 46.3 hours. It decays to the stable nuclide europium-153. Sm-153 has both $\beta^-$ and $\gamma$ decay. There are 5 possible $\beta^-$ decay energies. The mean energies range from 0.081-0.263MeV and maximum energies from 0.262-0.632MeV. The most abundant $\beta^-$ emission (44.1%) has a mean energy of 0.224MeV and a maximum of 0.702MeV. The $\gamma$ emission energies range from 5.8-422.7keV though the most abundant (31.2% and 28.3%) have energies of 41.5keV and 103.2keV respectively. This latter $\gamma$ energy allows detection of Sm-153 by
conventional γ camera equipment. Complete physical characteristics of Sm-153 and emission energy data are included in Appendix Aiii.

The mean soft-tissue ‘therapeutic’ penetration of Sm-153 is 0.7mm and the maximum is 3.1mm (Johnson and Yanch 1995). Therapeutic penetration is defined as the distance in tissue in which 90% of the absorbed dose is deposited (Johnson and Yanch 1991).

1.5.3 Hydroxyapatite

Hydroxyapatite is the insoluble mineralised crystalline component of bone. The inorganic crystal is recognised for its mechanical strength and as an optimal means of facilitating the absorption and precipitation of calcium and phosphate during bone turnover. Industrially-produced hydroxyapatite is proving to be useful in reconstructive surgery where a biocompatible ‘support’ material is required.

1.5.3.1 Industrial production of hydroxyapatite

Hydroxyapatite may be industrially-produced in two ways. The conversion of the calcium carbonate exoskeleton of coral by a hydrothermal chemical exchange reaction (White et al. 1972) produces a porous form of inorganic calcium phosphate hydroxyapatite with a mineral content and microarchitecture identical to human bone. Coralline hydroxyapatite bone grafts have been evaluated for use in oral surgery and periodontics (Finn et al. 1980), orthopaedic surgery (Oonishi 1991) and as ‘fixation’ orbital implants for artificial eyes (Dutton 1991). A particulate form of hydroxyapatite can also be synthesised. Particles with a diameter in the μm range are prepared by forming a precipitate from the reaction of Ca(NO₃)₂ and (NH₄)₃PO₄ at high pH (Hayek 1963). The precipitate is suspended in aqueous solution and subjected to a ‘spray-drying’ process to produce particles of controlled size and range. Particulate hydroxyapatite has been particularly useful as implant material in orthodontic surgery (Quayle and McCord 1992).

Particles recently produced for the intra-articular delivery of radiation differ from those used for dental implants in that they are not subjected to a sintering process (designed to ‘toughen’ the material) and are consequently recognised to be more biodegradable (Chinol et al. 1993. See Fig. 2.1).
1.5.3.2 Biological fate of hydroxyapatite in non-osseous tissue

There is substantial evidence to suggest that industrially-produced coralline hydroxyapatite implants placed in soft-tissue do not provoke an inflammatory response (Shields et al. 1992). However, the deposition of endogenously-derived hydroxyapatite crystals in articular soft-tissue has been associated with a vigorous inflammatory response (Halverson et al. 1981).

The potential of 'ectopic' extra-osseous hydroxyapatite (either endogenously or exogenously derived) for provoking inflammation may vary depending on the physical nature of the crystals (R. Schumacher, personal communication) thus intimating that some forms of hydroxyapatite are inert in soft-tissue. For example, when injected into normal rabbit knees, unsintered hydroxyapatite particles (5-45μm) are totally degraded within the synovial lining within 6 weeks of injection (Shortkroff et al. 1992). The effects of hydroxyapatite deposition in soft-tissue and the synovial lining are discussed briefly in Chapter 5.4.3 and further in Chapter 8.2.3.4.

1.5.4 In vitro and animal studies

Only a few data on Sm-153-labelled hydroxyapatite particles (Sm-153 PHYP) are available. The methods of labelling hydroxyapatite particles with Sm-153 and aspects of the radiochemistry of Sm-153 PHYP have previously been published (Chinol et al. 1993). Biodistribution data from intra-articular injection of Sm-153 PHYP in rabbit joints has also been reported (Shortkroff et al. 1992, Chinol et al. 1993). The results of these studies taken together with the findings of in vitro stability of binding (see 1.5.4.1-2), suggest that hydroxyapatite particles are an attractive carrier for intra-articular Sm-153 radiation synovectomy.

1.5.4.1 Particle labelling

Briefly, Sm-153 is supplied from the reactor site as samarium chloride. Citric acid is added in excess and the Sm-153 citrate solution added to a vial containing hydroxyapatite particles which is then agitated gently at room temperature. The labelled particles are then rinsed and spun. Any free Sm-153 or unbound impurities can therefore be removed with the solution. Labelled
particles are then resuspended in saline and, if intended for in vivo use, are autoclaved. Labelling efficiency by this method is >95% (Chinol et al. 1993). Detailed labelling methods are included in Chapter 2.2.1.

1.5.4.2 Stability of binding

As a basic oxide Sm-153 is likely to bind strongly to the OH\(^-\) and PO\(_4\)^{3-}\ moieties present in hydroxyapatite. The evidence that Sm-153 binding to hydroxyapatite is stable is provided by data which show less than 1% Sm-153 dissociates from particles over a period of 3 half-lives (approximately 6 days) in a combination of saline and synovial fluid (Chinol et al. 1993).

1.5.4.3 Animal studies

Sm-153 PHYP injected into normal and antigen-induced arthritic rabbit knee joints appear to disperse throughout the synovial lining (Chinol et al. 1993). The cumulative amount of activity escaping from the joint is <0.2% of the injected activity at 3 days and <0.3% at 6 days.
Chapter 2

Supportive laboratory data I. Labelling efficiency and binding stability of samarium-153 particulate hydroxyapatite (Sm-153 PHYP) in vitro, and analysis of particulate hydroxyapatite (PHYP) size range
2.1 Introduction

Following the injection of a radiopharmaceutical into a joint, escape of activity from the joint will result in both increasing the radiation risk to healthy tissue and reducing the activity available for synovial irradiation (see Chapter 1.4.1.2.2 and 1.4.4.2). Radiopharmaceuticals associated with significant extra-articular losses of activity are perceived to involve unacceptable risks (Sledge et al. 1984, Deutsch et al. 1993). The successful development of a new radiopharmaceutical for radiation synovectomy may depend on how much, or how little, activity escapes from the injected joint. Two important characteristics of a particulate radiopharmaceutical which may influence egress of radioactivity from an injected joint are stability of binding of radionuclide to the particulate carrier (see Chapter 1.5.4) and particle carrier size (see Chapter 1.4.4).

2.1.1 Stability of Sm-153 PHYP binding

In theory, dissociation of the radiopharmaceutical occurring prior to injection or in vivo following injection, may result in the appearance of unbound Sm-153 in the joint cavity. As a basic oxide, 'free' Sm-153 is likely to form insoluble hydroxides within the soft-tissue and thus be retained in the joint; however, some may escape and could accumulate in bone (Chinol et al. 1993).

Binding of Sm-153 to hydroxyapatite particles appears stable in saline and synovial fluid (see Chapter 1.5.4.2). It is noted that under extreme acid conditions (pH 1-2), hydroxyapatite itself would not be stable (J. Brodack, personal communication) and then Sm-153 hydroxyapatite binding would be affected. In the first of these two in vitro experiments, the stability of binding of Sm-153 to particulate hydroxyapatite (PHYP) is evaluated under physicochemical conditions likely to be encountered at the time of joint injection. Stability of binding is evaluated in synovial fluid and in triamcinolone hexacetonide, a 'long-acting' glucocorticoid used for intra-articular treatment of chronic synovitis (see Chapter 1.3.2.1). Sm-153 PHYP may be combined with triamcinolone hexacetonide in the injection apparatus to simplify co-injection technique.
2.1.2 PHYP size range determination

Size may be critical in limiting the removal of particles from a synovial joint (Bauer et al. 1933, Adkins et al. 1940, Noble et al. 1983) [also see Chapter 1.4.4.2]. Results obtained with radiolabelled particles indicate that reducing the biodegradability of the particle or increasing its size, or both, reduces radioactivity losses from an injected joint (Noble et al. 1983). Samples of hydroxyapatite particles commercially available for clinical studies consist of a range of particle sizes. The particles are effectively porous crystals and thus, being fragile, may be easily damaged. Tiny fragments may occur (Fig. 2.1), and, in theory, when labelled with a radionuclide and injected into a joint, may be more liable to escape from the joint than larger particles. Particle escape will increase the chance of extra-articular activity accumulation.

In the second in vitro experiment, the aim is to establish whether simple aspiration of a suspension of PHYP during particle sedimentation can alter particle size range in the sedimenting sample. The particle size frequency and range in both unaltered and suspension-aspirated samples may be quantified with a view to evaluating the influence of particle size on radiation escape from an injected joint in subsequent in vivo experiments conducted using both samples.
Fig. 2.1 Particulate hydroxyapatite (PHYP) [oil immersion]. Particle fragments (f) are frequently seen in slide preparations.
2.2 Materials and Methods

2.2.1 Labelling efficiency and binding stability

Sm-153 was supplied by the University of Missouri-Columbia Research Reactor (MURR) as 1ml Sm-153 chloride in 0.1N HCL (specific activity 5.55-10.36GBq [150-280mCi] Sm-153/mg Sm2O3). The production details are outlined in Appendix A. The delay caused by shipping between the end of Sm-153 production and arrival (approximately 3-4 days/≈2 half-lives) meant that more activity than was ultimately needed was produced.

Unsintered PHYP was supplied by CeraMed Corp., Lakewood, CO. The precise particle size range was unknown; however, it was requested that particles of a similar size to those previously studied (Shortkroff et al. 1992, Chinol et al. 1993) be produced.

Sm-153 citrate solution was produced by adding 18mM citric acid in excess to the Sm-153 chloride. Equal aliquots of 1.5mls of Sm-153 citrate solution, containing approximately 550MBq Sm-153, were injected into 4 vials, each containing 40mg of PHYP. No air was aspirated resulting in a slight positive pressure being maintained in each vial. The vials were gently swirled for approximately 5 minutes at room temperature. A 2ml volume of air was removed from each vial to normalise the pressure. The activity in each of the vials was measured using a Capintec CRC-120 radioisotope calibrator using a calibration factor of 230. Samples were spun at 1500rpm for 8 minutes, the supernatant was carefully removed from each vial using a 21 gauge needle and samples were re-suspended in 1.5mls saline. The vials were gently agitated for 5 minutes and the activity in each was measured again. The labelling efficiency in each vial was calculated from the difference between the two activity values.

After one hour in an upright position at room temperature, the supernatant was removed from each vial and, in consecutive vials, the labelled particles were re-suspended in: a) 2ml of normal saline; b) 2ml of fresh synovial fluid obtained from a patient with rheumatoid arthritis; c) 2ml of 20mg/ml triamcinolone hexacetonide (Lederspan, Lederle) and d) 1ml of synovial fluid combined with 1ml of 20mg/ml triamcinolone hexacetonide. The samples were spun at 1500rpm for 8 minutes (Centaur 2 centrifuge). The activity in
each vial was then measured and recorded as total baseline labelling activity. Vials were gently swirled and then left to stand in at room temperature.

At various times up to 6 days (≈3 half-lives) thereafter the %activity remaining bound to the particles was calculated. Firstly, each vial was spun (1500rpm for 8 minutes) and the activity measured in the vial. Using a 21 gauge needle, the supernatant was then removed and kept. The activity in the pellet was measured and from the difference in the two measurements, the %activity remaining in the hydroxyapatite pellet was calculated. This was taken as the %bound activity. At each sampling time, the pH of each aspirated supernatant was tested (Wharton pH indicator strips) before re-injecting the supernatant back into the appropriate vial and gently swirling the mixture.

2.2.2.2 PHYP size range analysis

2.2.2.1 PHYP sedimentation and timing of suspension aspiration

The rate at which the PHYP settled in normal saline was studied using video-linked computer software. A cuvette with a base raised by gelatin and containing 40mg of PHYP in 2mls filtered normal saline (Acrodisc 32, Gelman Sciences) was agitated and placed immediately between a tungsten light source and video camera (Panasonic WV- BL600). The camera was fitted with a macro lens and connected to an Apple-Macintosh SE computer. Images were digitised and displayed using Microsoft Image NIH 1.6969. An index of light absorbance of the suspension was measured from a region of interest (ROI) placed centrally on the 2D image of the cuvette at 10 second intervals for 3 minutes. Mean values were determined from repeated sampling measurements.

An optimal time for aspiration of the PHYP suspension was then based on the results (see 2.3.3.1) such that the slower falling, smaller particles would be removed.

2.2.2.2 Light microscopy analysis of PHYP size range

Two samples of PHYP were prepared. Each was suspended in 2mls of filtered normal saline in a vial. At the optimal time following agitation (see 2.3.3.1), the suspension in one vial was aspirated and discarded. The pellet was re-suspended in 2mls saline. The subsequent slide preparation was then
identical for both samples. As each vial was being swirled, 1ml of suspension was drawn into a syringe; an aliquot was placed immediately onto a dry alcohol-cleaned slide and secured with aquamount (BDH) and a coverslip.

Slides were analysed with light microscopy (Nikon *optiphoto*) using an eye-piece graticule (x25). A graticule field was analysed once every 3 graticule-widths over the whole slide by moving the slide from side to side. The diameter of all particles within the field was recorded (µm). A diameter greater than 5µm was recorded to the nearest 5µm. Particles less than 5µm in diameter were recorded as 'fragments'. Three unaspirated and 2 suspension-aspirated samples were analysed to assess the reproducibility of the technique.

As fragments were occasionally indistinguishable from debris on the slide, 2 identically-prepared control slides were analysed. An aliquot of filtered saline was placed on an alcohol-cleaned slide and secured with aquamount and a coverslip. The 'particulate debris' per graticule-field (x25) was recorded following the same method as above at the same power. Total fragment counts in original samples were then adjusted for background particulate debris.
2.3 Results

2.3.1 Labelling efficiency

In all 4 samples the labelling efficiency was >95% (Table 2.1).

2.3.2 Binding stability

Binding stability results are shown in Tables 2.2-2.5. The pH of saline, synovial fluid and of triamcinolone hexacetonide tested independently was 7.0, 7.0 and 4.0 respectively.

Table 2.1 Labelling efficiency of Sm-153PHYP

<table>
<thead>
<tr>
<th>Prepared activity (MBq)</th>
<th>Pellet activity* (MBq)</th>
<th>Labelling efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>125</td>
<td>120</td>
<td>96%</td>
</tr>
<tr>
<td>128</td>
<td>125</td>
<td>98%</td>
</tr>
<tr>
<td>159</td>
<td>151</td>
<td>95%</td>
</tr>
<tr>
<td>154</td>
<td>152</td>
<td>99%</td>
</tr>
</tbody>
</table>

*Activity remaining after sample spun and supernatant removed

Table 2.2 Binding stability of Sm-153 PHYP in normal saline

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Activity in vial (MBq)</th>
<th>Activity in vial with supernatant removed (MBq)</th>
<th>% bound activity</th>
<th>pH of supernatant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>119</td>
<td>119</td>
<td>100%</td>
<td>6.5</td>
</tr>
<tr>
<td>23</td>
<td>84</td>
<td>85</td>
<td>100%</td>
<td>7.0</td>
</tr>
<tr>
<td>42</td>
<td>64</td>
<td>62</td>
<td>97%</td>
<td>7.0</td>
</tr>
<tr>
<td>140</td>
<td>15</td>
<td>14</td>
<td>93%</td>
<td>7.1</td>
</tr>
</tbody>
</table>
Table 2.3  Binding stability of Sm-153 PHYP in synovial fluid

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Activity in vial (MBq)</th>
<th>Activity in vial with supernatant removed (MBq)</th>
<th>% bound activity</th>
<th>pH of supernatant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>125</td>
<td>125</td>
<td>100%</td>
<td>7.0</td>
</tr>
<tr>
<td>23</td>
<td>89</td>
<td>90</td>
<td>100%</td>
<td>7.0</td>
</tr>
<tr>
<td>42</td>
<td>46</td>
<td>46</td>
<td>100%</td>
<td>7.0</td>
</tr>
<tr>
<td>140</td>
<td>15</td>
<td>15</td>
<td>100%</td>
<td>7.0</td>
</tr>
</tbody>
</table>

Table 2.4  Binding stability of Sm-153 PHYP in 20mg/ml of triamcinolone hexacetonide

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Activity in vial (MBq)</th>
<th>Activity in vial with supernatant removed (MBq)</th>
<th>% bound activity</th>
<th>pH of supernatant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>150</td>
<td>150</td>
<td>100%</td>
<td>4.0</td>
</tr>
<tr>
<td>23</td>
<td>105</td>
<td>104</td>
<td>99%</td>
<td>3.5</td>
</tr>
<tr>
<td>42</td>
<td>56</td>
<td>54</td>
<td>96%</td>
<td>3.5</td>
</tr>
<tr>
<td>140</td>
<td>18</td>
<td>17</td>
<td>94%</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Table 2.5  Binding stability of Sm-153 PHYP in synovial fluid and 20mg/ml triamcinolone hexacetonide

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Activity in vial (MBq)</th>
<th>Activity in vial with supernatant removed (MBq)</th>
<th>% bound activity</th>
<th>pH of supernatant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>152</td>
<td>152</td>
<td>100%</td>
<td>7.0</td>
</tr>
<tr>
<td>23</td>
<td>106</td>
<td>105</td>
<td>99%</td>
<td>7.0</td>
</tr>
<tr>
<td>42</td>
<td>56</td>
<td>56</td>
<td>100%</td>
<td>7.0</td>
</tr>
<tr>
<td>140</td>
<td>18</td>
<td>18</td>
<td>100%</td>
<td>7.0</td>
</tr>
</tbody>
</table>
2.3.3 PHYP size range

2.3.3.1 Alteration of PHYP size range by suspension aspiration

Optical absorbance recorded within the ROI in the centre of the cuvette started to decrease immediately after the agitated particles were placed at rest. The absorbance initially decreased linearly (Fig. 2.2a). There appeared to be no further change in optical absorbance in the suspension after 150 seconds.

![Graph](image)

*Fig. 2.2 Mean (±2 s.d.) optical absorbance of light of (a) an unaltered preparation (n=8) and (b) a suspension aspirated preparation (n=8) of PHYP up to 3 minutes after agitation of the suspension*

The interpretation of these findings, assuming the rate of sedimentation of the particles was size-dependent, was that the early and rapid decrease in optical absorbance was due to the rapid fall and earlier sedimentation of large particles and the subsequent slower decrease due to the slower fall of smaller particles remaining in suspension. The implication was that smaller particles and fragments could be removed by aspirating the suspension at some time before all the particles had settled. This would result in a sediment containing particles with a greater mean size than in the original preparation.

To prepare a sample of larger mean PHYP size, removal of the suspension 30 seconds after agitation was considered optimal because the 30 second delay would allow many of the larger particles to sediment before suspension.
removal but was not too long such that small particles and fragments had fallen into the sediment during the aspiration procedure (approximately 30-40 seconds). A sample was prepared by aspirating the suspension 30 seconds after agitation of 40mg PHYP in 2mls saline in a cuvette. Particles were then re-suspended in 2mls saline. The change in optical absorbance of this particle suspension after agitation was then studied and compared with that of the original sample (Fig. 2.2). Methods reported in section 2.2.2.2 relied on this technique of suspension aspiration.

2.3.3.2 Quantification of PHYP size and size range

The mean diameter of particles taken from 3 normal samples (105 fields) was $15.9 \pm 0.3\mu m$ (range 5-45\mu m diameter). With aspiration of the suspension commencing 30 seconds after agitation, the mean diameter of particles remaining in the sediment was $21.9 \pm 0.9\mu m$ (range 5-45\mu m). The difference between the means was 6.0 with a 95% confidence interval (CI) from 5.2 to 7.8; the t-test statistic was 9.6 with an associated p value of p<0.0001. Data from each sample analysis is shown in Table 2.6. A comparison of independently analysed samples is shown in Fig. 2.3.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Number of fields*</th>
<th>Particles /field*</th>
<th>Fragments /field*</th>
<th>Mean particle size (\mu m)</th>
<th>Particle size range (\mu m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>40</td>
<td>3.35</td>
<td>2.45</td>
<td>15.8</td>
<td>5-40</td>
</tr>
<tr>
<td>Normal</td>
<td>15</td>
<td>5.47</td>
<td>5.60</td>
<td>16.3</td>
<td>5-45</td>
</tr>
<tr>
<td>Normal</td>
<td>50</td>
<td>5.70</td>
<td>5.16</td>
<td>15.6</td>
<td>5-40</td>
</tr>
<tr>
<td>Aspirated*</td>
<td>50</td>
<td>5.44</td>
<td>1.12</td>
<td>22.8</td>
<td>5-45</td>
</tr>
<tr>
<td>Aspirated*</td>
<td>50</td>
<td>2.78</td>
<td>0.64</td>
<td>21.0</td>
<td>5-40</td>
</tr>
</tbody>
</table>

*Field (equivalent to 1 graticule-field) = x25.

*Aspirated = suspension aspirated 30 seconds after vial agitation. Pellet sediment analysed
2.3.3.3 PHYP fragment analysis

Mean number of fragments/graticule-field in the unaltered sample of PHYP was 4.40 (pooled sample data). The number of fragments/graticule-field in the pellet after removal of particles remaining in suspension 30 seconds after agitation, was 0.88. To correct for non-hydroxyapatite particulate debris on the slides, data were acquired from the analysis of 100 graticule-fields in 2 (50+50 field analyses) control slides. PHYP fragments/graticule-field were respectively 0.3 and 0.5 with a mean of 0.4 fragments/field. Corrected counts of fragments/graticule-field were, therefore, 4.00 fragments/field for a normal PHYP sample and 0.48 fragments/field for a suspension-aspirated sample.
2.4 Discussion

2.4.1 Labelling efficiency

The data show that this preparation of PHYP is extremely efficiently labelled by these methods. The values may even have been higher than 95% but for the difficulty in removing the supernatant without any labelled particles after the sample had been spun.

2.4.2 Binding stability

Binding stability data suggest that, in vitro, Sm-153 PHYP binding is stable in saline, synovial fluid, and triamcinolone hexacetonide combined with synovial fluid. Binding is slightly less efficient in the short-term in moderate acidic conditions associated with triamcinolone hexacetonide alone.

It is likely that a small amount of citrate remaining in each vial may contribute to the lowering of pH recorded at baseline (Table 2.2). Mild acidity as a result of citrate contamination may be buffered by the hydroxyapatite or synovial fluid, or both, where present. In contrast, the low pH of the sample in triamcinolone hexacetonide may reflect citrate contamination and the relatively weak buffering capacity of hydroxyapatite alone. The pH of Lederspan (pH 7. Source: Q&A, Lederle) was confirmed for all samples used, and all were within the expiry date. In practice, it is unlikely that labelled PHYP will be in contact with triamcinolone hexacetonide alone for a substantial duration of time during the preparation stage of Sm-153 PHYP.

These results are in accordance with those reporting Sm-153 binding to a different preparation of PHYP (Chinol et al. 1993). The results also suggest that Sm-153 PHYP is likely to be stable in vivo. Mild acidic conditions may exist within pathological synovial fluid and this correlates to the degree of leucocytosis (Ward 1978). Changes in synovial fluid oxygen tension may also occur in relation to synovial fluid volume and may affect fluid pH (Richman et al. 1981); however, owing to its protein content, synovial fluid has significant buffering capacity. The effect of synovial fluid as a buffer is illustrated in this experiment by its significant effect on the pH of a solution of triamcinolone hexacetonide. This buffering capacity should be more than adequate to prevent the large changes in pH which, according to these data, would be required to significantly affect Sm-153 PHYP binding in vivo.
2.4.3 PHYP size

There is a wide variation in particle size in the commercially-supplied hydroxyapatite preparation. Moreover, there are also particle fragments, some of which appear to be less than 1µm in diameter. As the particles are porous, it is possible that they may become fragmented secondary to trauma sustained either during transport or labelling.

As particle size appears to be inversely related to escape of particle-bound activity from a joint (Noble et al. 1983), is it possible that the tiny particles may increase the likelihood of extra-articular activity escape after joint injection of Sm-153 PHYP? Perhaps not necessarily. Firstly, there is no evidence to suggest a reduction in labelling efficiency in samples which clearly contain small particles and particle fragments. There is no plausible chemical reason to explain why smaller particles or particle fragments will bind less efficiently to Sm-153 or remain less tightly bound than the larger particles. Secondly, if ‘free’ Sm-153 is released into synovium as a result of particle degradation, it is likely to form insoluble hydroxides in the tissue (Chinol et al. 1993) or may bind endogenously-derived apatite deposited in the tissue thus ‘trapping’ the released Sm-153 within the tissue. Finally, phagocytosis may influence the dissociation of Sm-153 from PHYP in vivo. Although it appears that PHYP may be phagacytosed in arthritic synovial tissue (Shortkroff et al. 1992), it is unknown whether the smaller particles are degraded more readily than the larger particles. Evidence from animal studies suggest that even the smallest particles remain in the synovial lining beyond the time of complete Sm-153 decay (S. Shortkroff, personal communication).

These results show that simple aspiration of an agitated PHYP suspension substantially changes the rate of sedimentation and mean particle size of the sediment compared to the original sample. This implies that manipulation of mean particle size in a PHYP preparation in vitro is possible and may be used to study the effect of PHYP size on the escape of activity from injected joints. These studies are reported in Chapter 4.
Chapter 3

Supportive laboratory data II. Targeting the inflamed tissue: the relationship of cell distribution in the synovial lining and distribution of Sm-153 activity
3.1 Introduction

One of the recommendations often made about radiation synovectomy (Ingrand 1973, Menkes 1979b) is that the whole thickness of the synovial lining needs to be irradiated for an effective response. There is no supporting evidence for this assertion but nevertheless, the assumption has guided the design and application of radiopharmaceuticals for radiation synovectomy for many years (Deutsch et al. 1993, Johnson et al. 1995).

Irradiation of the synovial lining will depend on a number of factors influencing distribution of \( \beta^- \) energy, including the extent of radiopharmaceutical distribution over the synovial surface, uptake of the radiopharmaceutical into the tissue, and its rate of distribution within the tissue in relation to its half-life. However, it is unknown to where in the synovial lining energy must be delivered because the target cells and their distribution within the tissue have not been identified.

Cells which may be important candidates for targeting include infiltrating lymphocytes and macrophages, vascular endothelial cells, which proliferate to form new blood vessels in chronic synovitis (Folkman et al. 1985), and synovial fibroblasts. An investigation of the radiosensitivity of all cells likely to be present in the inflamed synovium is beyond the scope of this thesis; however, knowledge of the distribution of all cells in the synovial lining represents the first step in focusing on the likely distribution of the radiation target and may help to improve the accuracy of assumptions made about \( \beta^- \) penetration and dosimetry.

The studies reported in this chapter and elsewhere (Chapter 4 and Chapter 5) focus on determining the distribution of cells in inflamed synovium and evaluating whether Sm-153 PHYP is suitable as a therapeutic radiopharmaceutical, given the \( \beta^- \) penetration of Sm-153 and distribution of PHYP in the joint and synovial lining.

In this study, the aim is to numerically evaluate the distribution of cells at depths in the synovial lining in tissue obtained from patients with chronic rheumatoid synovitis. The aim is then to determine areas of greatest cell density in the rheumatoid synovial subintima and thus to identify the most important target areas for radiation within the tissue.
In addition, distances between intimal surfaces are evaluated to estimate the potential of β particles to penetrate into the deeper parts of the subintima. The measurements include distances between the clefts in the surface layer and also the spaces within the subintima, which are known to communicate with the joint cavity (Edwards et al. 1983).
3.2 Materials and methods

Sections of synovial lining tissue obtained from open or arthroscopic biopsy of the joints of patients with RA and filed in a slide library were examined by light microscopy (Nikon ophtiphot). All sections had been originally stained with haematoxylin and eosin.

3.2.1 Cell density analysis

All complete sections with an identifiable and intact intimal layer and a subintima extending for 3mm or more beneath the intimal layer, were chosen for cell density analysis using light microscopy (x25). An eye-piece graticule was used to measure distance along the intimal surface and to depths in the subintima (100 grid squares, each 40μm²). Cellular distribution in a profile perpendicular to the intima was analysed at 80μm intervals along the intima. This pattern of analysis was continued for the length of the intima in the whole section. Profile analysis consisted of recording the number of all cells lying within each grid square at 40μm depths through the full thickness of the section. The number of cells per grid square was arbitrarily taken to represent cell number at a depth equal to the distance from the intima to the nearest point of the grid square within the profile. Profiles through synovial clefts or gaps were discarded although profiles through lymphoid follicles and blood vessels were included.

3.2.2 Synovial space and cleft analysis and inter-space distances

The largest sections were analysed using light microscopy (x5) for the presence of synovial spaces and clefts. For each section >90mm², inter-space distances in the tissue were measured in 10 different (straight line) profiles determined by a grid (Fig. 3.1). Distances were measured between consecutive synovial surfaces (either a space or cleft) along the profile using an eye-piece graticule. The number of measurements made for each section, adjusted for section size, was taken as the extent of synovial space and cleft formation in the tissue (Table 3.1).
Fig. 3.1 The analysis of large synovial sections to determine the extent of synovial spaces and clefts in each section. Distances between consecutive intimal surfaces was measured along 10 straight-line profiles. Profiles were based on a grid marked on a piece of cellophane placed over the slide.
3.3 Results

3.3.1 Tissue sections

In total, 28/53 (53%) of the library sections, each from a different patient, were analysed. All analysed sections were knee joint synovia. Most of the 25 remaining sections, which did not satisfy criteria for either analysis (47%), consisted mainly of small fragments of tissue, all <3mm thick.

![Graph showing cell count at depths from intima](image)

Fig. 3.2 Mean number cells/40\(\mu\)m\(^2\) at depths in the synovial lining. Cell counts recorded along profiles (n=169) perpendicular to the synovial intima from 19 sections prepared from 19 patients with RA

3.3.2 Cell density

There were 169 separate profiles analysed from 19/53 (36%) sections which satisfied criteria for analysis. There was a mean 16.4 ± 6.0 cells per 40\(\mu\)m\(^2\) at the synovial intima which decreased to a mean of 1.3 ± 1.6 cells per 40\(\mu\)m\(^2\) at a depth of 2.8mm in the subintima (Fig. 3.2). Overall, 49.5% of all cells identified were within 0.6mm of the synovial intima and 90% were within 2.0mm (Fig. 3.3). At this depth in the tissue there were few, if any, mononuclear cells; blood vessels were scanty and those present showed no evidence of a perivascular mononuclear cell infiltrate (Fig. 3.4). Cell density at depths greater than 2.8mm in tissue sections was not analysed.
Fig. 3.3 Cumulative % cells (mean values) at increasing depths in the synovial lining measured perpendicular to the synovial intima. Over 90% of the cells were found within 2 mm of the intima. Data from 169 profiles in 19 tissue sections from 19 RA patients.
Fig. 3.4 The synovial lining in RA (haematoxylin and eosin, ×12.5). At a depth of 2.4mm or more below the synovial surface (ss) [hatched line] there are few, only scattered, cells. Blood vessels are scanty.
3.3.3 Synovial spaces, clefts and inter-space distances

There were 80 profiles analysed from 8 tissue sections. Mean size of tissue section analysed was 137mm$^2$. The number of measurements/mm$^2$ of tissue between spaces and clefts in the tissue varied from 15 to 64 for different sections (Table 3.1). Clefts were present in all sections, and spaces, deep within the synovial lining, were evident in many sections (Fig. 3.5). The mean (± s.d.) inter-space or inter-cleft distance overall was small (2.62 ± 1.29mm), though it varied for different sections. Mean (± s.d.), median and range of inter-space distances for each section are shown in Table 3.1.

Table 3.1 Analysis of inter-space distances in the synovial lining. Only large (>90mm$^2$) sections of RA synovial lining tissue were analysed

<table>
<thead>
<tr>
<th>*Section area (mm$^2$)</th>
<th>Number of measurements</th>
<th>Number of measurements /mm$^2$</th>
<th>Mean ± (s.d.) inter-space distance (mm)</th>
<th>Median (range) inter-space distance (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>138</td>
<td>15</td>
<td>0.11</td>
<td>3.53 (2.09)</td>
<td>3.00 (1.00-7.20)</td>
</tr>
<tr>
<td>90</td>
<td>42</td>
<td>0.47</td>
<td>3.01 (1.05)</td>
<td>1.97 (0.29-6.76)</td>
</tr>
<tr>
<td>247</td>
<td>24</td>
<td>0.10</td>
<td>2.95 (2.52)</td>
<td>1.70 (0.30-8.60)</td>
</tr>
<tr>
<td>95</td>
<td>16</td>
<td>0.17</td>
<td>0.35 (0.22)</td>
<td>0.33 (0.08-0.70)</td>
</tr>
<tr>
<td>153</td>
<td>27</td>
<td>0.18</td>
<td>3.94 (1.81)</td>
<td>2.96 (0.04-7.11)</td>
</tr>
<tr>
<td>91</td>
<td>20</td>
<td>0.22</td>
<td>4.24 (0.93)</td>
<td>4.06 (1.43-7.48)</td>
</tr>
<tr>
<td>104</td>
<td>35</td>
<td>0.34</td>
<td>1.70 (1.26)</td>
<td>1.40 (0.20-3.00)</td>
</tr>
<tr>
<td>180</td>
<td>64</td>
<td>0.36</td>
<td>1.24 (1.16)</td>
<td>0.80 (0.20-5.80)</td>
</tr>
</tbody>
</table>

* Approximate section area measured with a ruler (no magnification)
Fig. 3.5 Synovial lining section from a patient with RA (haematoxylin and eosin, ×5). Clefts (c) and spaces (sp) are seen deep in the tissue. Subsynovial connective tissue can be seen (ssct). These appearances are consistent with the suggestion that clefts and spaces are formed as a result of folding of the synovial lining (Edwards et al. 1983). The spaces have been shown to communicate with the joint cavity.
3.4 Discussion

3.4.1 Proximity of activity to the biological target

The results of this study suggest that cell density in the synovial lining of the knee joint in chronic rheumatoid synovitis is greatest in the surface layers. At depths of 2.5 to 3mm in the tissue there are relatively few cells which, histopathologically, show any evidence of a cellular infiltrate. A majority of cells are within 0.6mm of the intima, and are, therefore, within the therapeutic range (0.7mm) of any Sm-153 β particles present at the synovial surface. Could this imply that cells deeper in the subintima will not receive a therapeutic dose from Sm-153 PHYP? Probably not, for two reasons. Firstly, when injected into arthritic rabbit joints, PHYP appears to distribute throughout synovial tissue (Shortkroff et al. 1992). Because Sm-153 remains tightly bound to the PHYP in vivo (Chinol et al. 1993) and migration of the PHYP into the tissue is likely to occur before Sm-153 has decayed (S. Shortkroff, personal communication), the biological fate of PHYP in the joint is likely to enhance the delivery of Sm-153 to deeper areas in the synovial lining. Intra-articular distribution of PHYP in patients is studied further (see Chapter 4.2.9, 4.3.7, 4.4.1.5 and Chapter 5). Secondly, the results from the analysis of spaces and surface clefts within synovial lining sections suggest that most areas of subintima are in close proximity to the surface at some point. As these clefts and spaces communicate with the joint cavity (Edwards et al. 1983) and taking the mean synovial inter-space distance of 2.6mm determined from this study, it would appear that most tissue between the spaces would be within the therapeutic range of Sm-153 β particles evenly distributed along the surfaces. More extensive irradiation of subintimal areas of tissue would then occur as the PHYP particles are engulfed by the tissue.

3.4.2 Comments on data collection

There are a number of points arising from the methods used in data collection which should be noted.

Firstly, clinical and intra-operative data were not available and reasons for arthroscopic or open biopsy could not be determined. It was therefore assumed that all tissue sections were derived from patients with chronic persistent rheumatoid synovitis.
Secondly, as there is no accepted description of cell density in normal synovial subintima, the depth in the tissue to which the cellular infiltrate extended could not be accurately defined i.e. the point where cell density would putatively decline to ‘normal’ levels. This made a relative analysis of cell density unavoidable. It remains an open question whether the cell density in the deepest part of the tissue (2.8mm) was similar to the cell density in normal synovial subintima. However, at this depth in the tissue, cell density was low (Fig. 3.2), mononuclear cells were scarce and there was no evidence of peri-vascular inflammation.

Thirdly, all sections were taken from the knee. Synovial tissue from other (smaller) joints was not available. There are no available data to suggest whether the distribution of cells in a chronically-inflamed synovial lining varies in different joints. It is also not known whether there is a significant influence of mechanical constraints on the extent and distribution of inflammatory synovial tissue in different joints. Such physical effects might account for joint-specific differences in the development of clefts and spaces in the synovial lining. Access of Sm-153 PHYP or any other radiopharmaceutical to deeper areas of the synovial lining may therefore vary for different joints depending on these characteristics.
Chapter 4

Patient studies: biodistribution studies and open Sm-153 PHYP treatment for chronic knee synovitis
4.1 Introduction

To be acceptable and potentially safe for clinical use, radiation synovectomy radiopharmaceuticals should ideally be associated with low levels of extra-articular activity escape (see Chapter 1.4.1.2 and 1.4.4.2). Animal studies have shown that low levels of extra-articular leakage of activity may occur following joint injection with Sm-153 PHYP (Chinol et al. 1993) [see also Chapter 1.5.4.3]. However, no human studies have been undertaken.

The following studies focus on the biodistribution of Sm-153 in patients treated with intra-articular Sm-153 PHYP for chronic knee synovitis. In addition to quantifying extra-articular activity accumulation and evaluating factors which may be important in determining activity escape, intra-articular distribution of Sm-153 PHYP is analysed. The methodology used to quantify activity distribution is examined by two short experiments and a sub-analysis of whole-body scintigrams (see 4.2.7.2).

A further aim of this study is to document the clinical outcome in patients up to a year after treatment and retrospectively evaluate clinical, technical and procedural factors which may have influenced relapse.

The knee has been chosen as the study joint for both clinical and practical reasons. The knee is one of the most frequently affected joints in rheumatoid arthritis and is often inflamed in the seronegative arthritides. It is also, arguably, the simplest joint to inject.
4.2 Patients, materials and methods

4.2.1 Patients

Patients with chronic (>2 years) inflammatory synovitis were accepted for consideration of synovectomy if judged to require an intra-articular glucocorticoid injection by their rheumatologist. All patients required a symptom score of '2' (see 4.2.2) for study entry. Patients with significant cartilage loss indicated by <2 mm joint space (measured with a ruler at the site of minimum distance between femoral condyle and tibia) in either medial or lateral compartments on weight-bearing antero-posterior knee radiographs were excluded. Radiographs of patients with RA were graded (Steinbrocher et al. 1949). Pregnant or breast feeding women and patients under 18 were excluded. Written informed consent was obtained from patients, and ethical approval was granted by the University College London Medical School, Clinical Investigations Panel. Patient studies with Sm-153 PHYP were approved under the Administration of Radioactive Substances (ARSAC) certificate reference number RPC 141-2 (40), November 12th 1992. Patient details are shown in Table 4.1.

4.2.2 Clinical assessment

Clinical assessments were made before and at 3 month intervals following treatment. The primary measure of outcome was based on an index of symptoms designed also to reflect function. A symptom score (0, 1 or 2) based on each patient's response to questioning was recorded at each visit. Scores were: 2 = pain and/or stiffness in the knee interfering with mobility; 1 = pain and/or stiffness in the knee; 0 = no pain or stiffness in the knee. A patient responding to any question with, 'sometimes' was included in the highest scoring category for which they gave that response. A return to a symptom score of 2 following an initial improvement in score was considered a full relapse. A partial relapse was defined by a symptom score of 1. At the initial consultation patients were asked to describe the duration of symptomatic benefit they had experienced from their (immediately) previous intra-articular glucocorticoid injection.

Examination of the knee included measurement of joint circumference 1cm above the superior border of the patellar (Kirwan et al. 1979) and flexion
range with a goniometer. These baseline measurements were taken immediately after radiopharmaceutical injection. A Ritchie Articular Index (RAI) [Ritchie et al. 1968] was recorded to illustrate the extent of synovitis in patients with polyarticular disease. Haematological indices of inflammation including an erythrocyte sedimentation rate (ESR) were assayed prior to treatment and at 3 monthly intervals.

4.2.3 Preparation of Sm-153 PHYP

Hydroxyapatite particles (Ceramed Corp., Lakewood, CO) were labelled with 555MBq (15mCi) of Sm-153 (University of Missouri Research Reactor, Columbia, MO). Methods for labelling were identical to those outlined in detail in Chapter 2.2.1. Alternately for the first 15 treatments, a different size range of particulate hydroxyapatite was prepared (see Chapter 2.3.2.1). The two size ranges of particle prepared had a mean size of 16µm and 24µm (Fig. 2.3). Patient number 16, and those numbered subsequently, received the smaller mean particle size range.

4.2.4 Injection procedure

Either a medial or lateral injection approach was used. The skin and subcutaneous tissues were anaesthetised with 1% lignocaine. Any synovial fluid was aspirated through a 21 gauge needle. In the first 4 patients, the following procedure was then followed: after disconnecting the syringe, Sm-153 PHYP in 2 mls normal saline was injected through the needle and flushed through with 40 mg of triamcinolone hexacetonide (Lederspan, Lederle). A total volume of 4 ml was injected. In the remaining patients, however, a 3-way tap was used. The 3-way tap was attached to the needle in situ and Sm-153 PHYP suspended in 2mls triamcinolone hexacetonide was injected. The apparatus was then flushed 3 times using 1.5ml aliquots of 1% lignocaine from a syringe attached to the side-port and drawn into the original syringe. Lignocaine was co-injected to reduce any pain that might be caused by a reaction to the radiopharmaceutical in the short-term. This change in technique was undertaken because the former procedure was thought to be associated with a higher risk of contamination and an increased likelihood of a greater number
of particles remaining in the injection apparatus and reducing total injected activity.

Immediately after injection, the knee was passively flexed twice to augment intra-articular distribution (S. Shortkroff, personal communication) and the range of flexion recorded. A Robert-Jones orthopaedic bandage was applied to serve as a semi-rigid splint. The patient remained non weight-bearing for 4 hours with the leg supported. This was chosen as the maximum reasonable period of time over which to keep an arthritic patient immobile in a chair. Patients were allowed home 4 hours after injection, advised to rest but allowed to resume their normal activities the following day.

4.2.5 Injection apparatus activity analysis

Both the activity prepared and the activity remaining in the injection apparatus were measured using a Capintec CRC-120 radioisotope calibrator using a calibration factor of 230. The counts were corrected for decay, where necessary, from the time of injection. Both injected activity and the efficiency of activity injection (defined as the % of prepared activity which was injected) was recorded.

4.2.6 Urine and blood activity analysis

In 13 patients, urine was collected over the 4 hours following injection and blood drawn hourly for activity analysis. A further 24 hour urine collection was analysed in 6 patients. A 20ml sample of urine from each sample was analysed by single channel pulse height analysis using a sodium iodide crystal scintillation counter. The photopeak was set at 103keV with a ±10% window. Counts were corrected for background and decay from the time of injection. Total urine activity was then calculated by comparing the counts to those obtained from a Sm-153 standard of known activity. Blood (5 ml) was collected in EDTA vacutainers and an aliquot of 2 ml analysed as above. Total Sm-153 blood-pool activity was estimated by assuming blood volume to be 7% total body weight.
4.2.7 Extra-articular activity detection and quantification

Extra-articular activity distribution data were derived from serial whole-body scintigrams.

4.2.7.1 Whole-body scans

Anterior and posterior whole-body scans were acquired immediately following injection, 4, 24, 72 and 168 hours (7 days) later on an IGE single headed \( \gamma \) camera (XCT or Starcam) with a low energy, high resolution (LEHR) collimator. Images were obtained using a detector photopeak centered at 103keV with a \( \pm 10\% \) window offset +3% and with a 128 x 512 matrix over a field of view of 0.4 x 2 meters. All scans on each patient were performed with the same camera. Background counts were obtained from 'dummy' (anterior and posterior) whole-body acquisitions (without patients) just prior to treatment. A geometric mean of the counts detected in anterior and posterior views from the whole-body, knee region of interest (ROI) and any focal activity (minus background) was calculated from each pair of scans.

From the whole-body count data, a quantitative estimate of relative activity distribution was made (see 4.2.7.3). Then, from the record of total injected activity, the activity in the whole body, any remaining in the knee and in various organs was calculated. These results formed the basis for dosimetry estimates.

4.2.7.2 Validity of scintigraphic techniques for quantifying activity distribution

The principle of calculating extra-articular activity from any whole-body scan relies on accurate count detection from the knee, whole-body and from organs to which the activity may have been distributed. Factors which may have influenced the accuracy of count detection and calculation of activity distribution have been studied.

4.2.7.2.1 Detector parameters

In theory, the injected activity may accumulate into foci within the knee. These small sources of high photon emission may result in high count rates. Non-optimal detector characteristics such as inadequate collimation or too
wide an energy window may lead to detector saturation at high count rates which may result in an underestimate of activity present. The effect of using either a LEHR or low energy all purpose (LEAP) collimator on count rates from a Sm-153 source of up to 1200MBq was investigated.

Sm-153 citrate in a glass vial was placed 6cm below the centre of the detector of an IGE XCT camera at various times over 1 week. Count rates were recorded (average over 60 seconds) each time using a LEHR and a LEAP collimator on a 256x256 matrix over a field of view of 0.4m in diameter. With each detector, data were acquired using two photopeaks. These were 103keV ± 10% and 103keV ± 10% offset +3%.

4.2.7.2.2 Evaluation of photon scatter from areas of high activity

It was assumed that as most activity would remain in the knee, areas of low activity accumulation in other body regions may be difficult to detect on a whole-body image owing to scatter of photons originating from the activity source in the knee. Repeat whole-body scanning with knee shielding was one option considered. However, the scanning procedure (which included tomography) is time-consuming, and patients with painful polyarticular disease are prone to discomfort during prolonged immobility. To avoid prolonged scanning protocols, therefore, only one anterior and one posterior scan was acquired, and all data used to calculate extra-articular activity accumulation were derived from these scans. It was then necessary to examine photon scatter from the knee and to determine whether the photons would interfere with quantification of counts from other body regions.

Each series of anterior and posterior whole-body scans from the first 2 scanned patients were analysed. Using a ‘strip’ ROI (pixels: 77x/2y), mean counts/pixel/ROI were recorded at distances from the centre of the knee in a cranial direction. The results were compared to background counts/pixel recorded from the background scan. Furthermore, after 10 patients had been treated and scanned, the analysis was undertaken for the patients who had received the greatest amount of injected activity. From these analyses, the distance from the knee at which count rates fell to a level similar to background became apparent. Data were utilised to guide whether corrections
to count rates recorded in ROIs in proximity to the knee would have to be made.

4.2.7.2.3 Organ attenuation of resident Sm-153 γ activity

ROIs were adjusted by 'attenuation correction factors' to account for the variable attenuation by different organs. These factors were derived from the relative attenuation of 103keV Sm-153 photons by different body regions of a 75kg healthy male volunteer.

An aliquot (3mls) of Sm-153 (48MBq) citrate was injected into a small square perspex void filled with saline. The relative attenuation of photons by liver, lungs, knee and soft-tissue of the thigh, was compared by measuring the diminution in counts when the flood was covered by the appropriate body area from both anterior and posterior aspects (Fig. 4.1). An IGE single headed γ camera (XCT) with a LEHR collimator was used. Each image was obtained for 60 seconds using a detector photopeak of 103keV with a ±10% energy window offset +3% and with a 128 x 128 matrix over a field of view of 0.4m diameter. In each case, counts were measured in ROIs placed over the organ/body region which was identified from images.

The fraction of counts \( C_{fo} \) detected as a result of photons attenuated in an organ \( o \) was determined from:

\[
C_{fo} = \frac{C_{gmo}}{C_{gms}} = \sqrt{\left(\frac{aC_o \times pC_o}{aC_s \times pC_s}\right)} \quad \text{4.21}
\]

where: \( C_{gmo} \) is the geometric mean of counts detected when photons were attenuated by the organ; \( C_{gms} \) is the geometric mean of counts from the unattenuated photon source; \( aC_o \) is the number of counts detected from an anterior whole-body scan with the source placed behind the organ; \( pC_o \) is the number of counts detected from a posterior whole-body scan with the source placed anterior to the organ, and \( aC_s \) and \( pC_s \) are counts detected from an unattenuated source from anterior and posterior aspects respectively.

\( C_{fo} \) for each organ was then normalised to total counts through the knee (taken as 1), to derive organ attenuation correction factors.
Fig. 4.1 Relative Sm-153 γ attenuation by different body regions. The geometric mean count rate from the photon source (phantom) was measured from anterior and posterior camera positions (A). The geometric mean of counts detected from anterior and posterior whole-body scans (camera positions a-a', b-b' etc.) were taken to represent relative attenuation of source photons by the lung (1), the liver (2), soft-tissue (3) and the knee (4), respectively. Camera positions relative to the body of a volunteer and the photon source are shown in B and C. Detector distances from source (x and y) were consistent.
4.2.7.3 Extra-articular activity quantification

All injected activity was assumed to be retained in the body (see 4.3.5). Activity was decay-corrected to the time of the scan. After each ROI was adjusted for background and differential organ attenuation, a geometric mean of the counts detected in anterior and posterior views from a) the whole-body, b) the knee region of interest (ROI) and c) any focal activity, was calculated from each pair of scans (Fig. 4.2). From the quantitative estimate of relative activity distribution and the record of injected activity, the activity a) in the whole body, b) remaining in the knee and c) in various organs, was calculated for various times following injection. These results formed the basis for dosimetry estimates.

4.2.8 Dosimetry estimates

Time-activity curves were constructed for each extra-articular organ ROI for each patient. In calculating an organ-absorbed dose, the following assumptions were made:

• that there was no activity clearance from the organ;
• that all β energy emitted in the organ was evenly absorbed within the organ;
• that the γ energy from the resident activity did not contribute to the organ-absorbed dose;
• that all energy from knee activity γ emissions would contribute to organ-absorbed energy if incident on the organ.

In this latter case, incident γ energy on a cross-sectional area of the organ ($E_{Y_o}$) was assumed to be:

$$E_{Y_o} = a \times \frac{E_{Y_t}}{4\pi r^2} \quad \text{(4.22)}$$

where: 'a' is the estimated cross-sectional organ area ($m^2$) on which photons originating from activity in the knee are incident; 'r' is the distance (m) from the centre of the knee to the organ's surface and 'E_{Y_t}' is the total γ energy from activity in the knee.
Assumptions made for 'a' and 'r' for each organ, 'Ey', and the \( \gamma \) integral dose for whole-body dosimetry estimates (\( E_{Y_{\text{twb}}} \)) are included in Appendix Bi. All assumptions were made so as to slightly overestimate absorbed energy within an organ.

Fig. 4.2 Extra-articular activity quantification. At various times following injection, the geometric mean of the counts in the anterior (A) and posterior (not shown) knee ROIs was calculated for each pair of scans and subtracted from the geometric mean of the counts in the whole body ROI. The % activity remaining in the knee at intervals following knee injection was then calculated. The scan on the left was acquired 72 hours post-injection and the scan on the right 168 hours post-injection. Similar calculations were made for other organ ROIs e.g. regional lymph node ROIs illustrated by (C) on the 168 hour post-injection scan.
Estimates were made of the absorbed energy by synovial lining tissue from activity remaining in the knee. Assumptions made in these calculations, mathematical modelling and an appraisal of the limitations of the calculation are included in Appendix Biii.

4.2.9 Intra-articular distribution of Sm-153 PHYP

Distribution of Sm-153 within the knee after injection was studied with serial planar and tomographic scintigraphy.

4.2.9.1 Planar knee scintigraphy

Anterior and lateral planar knee scans were performed at intervals during the week following treatment using an IGE XCT or Starcam camera fitted with a LEHR collimator. Data were acquired for 3 minutes/view on a 256 x 256 matrix using a detector photopeak of 103keV with a ±10% energy window offset +3%.

4.2.9.2 Tomographic knee scintigraphy

In the week following injection, single photon emission tomography (SPET) knee images were acquired using an IGE Optima twin-headed camera fitted with a LEHR collimator on a 128 x 128 matrix. The radius of rotation ranged from 0.15-0.18m. Most patients were scanned 7 days following treatment. Each image was acquired for 10 seconds a view and 128 views over 360° were obtained. Patients' legs were immobilised by strapping. Saline bags, serving as soft-tissue equivalent, were packed between their knees. Images were reconstructed using a Butterworth filter with a cut-off frequency of 0.55cm⁻¹ and a power factor of 10. Activity distribution in the suprapatellar pouch, anterolateral and anteromedial compartments and four areas of the posterior knee compartment was subjectively scored (good=2, patchy=1, poor=0).

'Activity distribution indices' were calculated for each joint compartment by dividing the sum of distribution scores (for $n$ patients) by the maximum possible sum of distribution scores ($2n$).
4.3 Results

4.3.1 Patient details at baseline

In total, intra-articular treatment with Sm-153 PHYP together with glucocorticoid was undertaken in 19 patients. Patient characteristics and clinical data at the time of treatment are shown in Table 4.1. Biodistribution data was not acquired from the first 2 patients treated (nos. 14 and 15) and patients 16-19. This latter group comprised patients within the randomised study protocol (see Chapter 5) who, when unblinded owing to a symptomatic relapse, were found to have had glucocorticoid alone. Biodistribution data from 13 patients (nos. 1-13) have been published (Clunie et al. 1995a). Follow-up data from the first 9 RA patients treated have been included in a recently presented report (Clunie et al. 1994).

Table 4.1 Patient characteristics and treatment details at the time of Sm-153 PHYP knee injection in 19 patients with chronic synovitis

<table>
<thead>
<tr>
<th>Patient number/age/sex</th>
<th>Diagnosis &amp; duration (years)</th>
<th>Previous local joint treatment</th>
<th>Duration symptom relief from last GC injection (weeks)</th>
<th>Knee flexion range (°)</th>
<th>RA Index</th>
<th>ESR (mm/hr)</th>
<th>Joint fluid aspirated (mls)</th>
<th>Mean size PHYP (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/48/F</td>
<td>RA/16</td>
<td>+ GC 6</td>
<td>2</td>
<td>120°</td>
<td>27</td>
<td>68</td>
<td>-</td>
<td>16</td>
</tr>
<tr>
<td>2/63/F</td>
<td>RA/7</td>
<td>+ GC 3</td>
<td>4</td>
<td>105°</td>
<td>3</td>
<td>40</td>
<td>-</td>
<td>25</td>
</tr>
<tr>
<td>3/55/M</td>
<td>PsA/12</td>
<td>+ GC 8</td>
<td>-</td>
<td>90°/S</td>
<td>3</td>
<td>40</td>
<td>80</td>
<td>25</td>
</tr>
<tr>
<td>4/54/F</td>
<td>RA/5</td>
<td>+ GC 10+</td>
<td>-</td>
<td>90°/S</td>
<td>12</td>
<td>28</td>
<td>30</td>
<td>16</td>
</tr>
<tr>
<td>5/62/M</td>
<td>RA/35</td>
<td>- GC 8/SI 1</td>
<td>26</td>
<td>105°</td>
<td>3</td>
<td>13</td>
<td>30</td>
<td>16</td>
</tr>
<tr>
<td>6/25/F</td>
<td>RA/20</td>
<td>+ GC 8</td>
<td>-</td>
<td>120°</td>
<td>5</td>
<td>14</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>7/60/F</td>
<td>RA/28</td>
<td>+ GC 1</td>
<td>&lt;1</td>
<td>110°</td>
<td>4</td>
<td>17</td>
<td>-</td>
<td>16</td>
</tr>
<tr>
<td>8/26/M</td>
<td>PsA/8</td>
<td>+ GC 1</td>
<td>&lt;1</td>
<td>140°</td>
<td>4</td>
<td>67</td>
<td>-</td>
<td>16</td>
</tr>
<tr>
<td>9/76/F</td>
<td>RA/7</td>
<td>- GC 10+</td>
<td>2</td>
<td>85°/S</td>
<td>36</td>
<td>82</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>10/27/M</td>
<td>PsA/10</td>
<td>+ GC 3/SI 1</td>
<td>1</td>
<td>130°</td>
<td>17</td>
<td>27</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>11/29/M</td>
<td>SARA/5</td>
<td>- GC 3</td>
<td>2</td>
<td>135°</td>
<td>3</td>
<td>60</td>
<td>-</td>
<td>16</td>
</tr>
<tr>
<td>12/39/M</td>
<td>RA/25</td>
<td>+ GC 10+</td>
<td>3</td>
<td>140°</td>
<td>5</td>
<td>66</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>13/24/F</td>
<td>RA/12</td>
<td>+ GC 3</td>
<td>&lt;1</td>
<td>135°</td>
<td>5</td>
<td>14</td>
<td>-</td>
<td>16</td>
</tr>
<tr>
<td>14/69/F</td>
<td>RA/33</td>
<td>+ GC 7</td>
<td>&lt;1</td>
<td>70°/S</td>
<td>32</td>
<td>20</td>
<td>-</td>
<td>16</td>
</tr>
<tr>
<td>15/65/F</td>
<td>RA/17</td>
<td>+ GC 10+</td>
<td>2</td>
<td>120°/S</td>
<td>45</td>
<td>84</td>
<td>-</td>
<td>25</td>
</tr>
<tr>
<td>16/77/F</td>
<td>RA/8</td>
<td>+ GC 10+</td>
<td>2</td>
<td>95°</td>
<td>17</td>
<td>69</td>
<td>-</td>
<td>16</td>
</tr>
<tr>
<td>17/40/M</td>
<td>RA/26</td>
<td>+ GC 10+</td>
<td>3</td>
<td>140°</td>
<td>5</td>
<td>77</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td>18/33/M</td>
<td>PAN/2</td>
<td>+ GC 6</td>
<td>&lt;1</td>
<td>100°</td>
<td>4</td>
<td>8</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>19/64/M</td>
<td>RA/7</td>
<td>+ GC 3</td>
<td>2</td>
<td>130°</td>
<td>2</td>
<td>5</td>
<td>16</td>
<td>16</td>
</tr>
</tbody>
</table>

* RA= rheumatoid arthritis; PsA= psoriatic arthritis; SARA= sexually acquired reactive arthritis; PAN= polyarteritis nodosa
1SAARD= slow-acting anti-rheumatic drug: gold; penicillamine; sulphasalazine; methotrexate; hydroxychloroquine; azathioprine; combination therapy
2GC= glucocorticoid; SI= saline irrigation
3FCC= fixed flexion contracture
4RAI= Ritchie Articular Index
5ESR= Erythrocyte Sedimentation Rate
4.3.2 Symptomatic response

The injection procedure appeared to cause no substantial discomfort. When asked over the telephone one week after treatment, all patients reported a significant improvement in symptoms from the treated knee in response to the injection. Response from Sm-153 PHYP alone cannot be ascertained from this study owing to co-injection of glucocorticoid.

4.3.3 Symptomatic relapse

Minimum follow-up was 4 months, though in 15/19 (79%) patients, data were available for a year following injection. One patient was lost to follow-up (no. 11) because of a move abroad. Individual relapse data are shown in Table 4.2.

Table 4.2 Injected activity, intra-articular activity distribution scores and clinical relapse following Sm-153 PHYP knee injection

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Injected activity (MBq)</th>
<th>Intra-articular distribution score</th>
<th>Follow-up (weeks)</th>
<th>Relapse to symptom score 1 (weeks)</th>
<th>Relapse to symptom score 2 (weeks)</th>
</tr>
</thead>
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<td>12</td>
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</table>

* 'no' denotes non-relapse at these times

*Patient lost to follow-up
Within 12 months, 9/14 (64%) patients had had a full symptomatic relapse. Symptom score frequency at 3 monthly intervals is shown in Fig. 4.3. Two patients had had no recurrent knee symptoms within the year and 36% patients overall had lower symptom scores at the 12 month follow-up than at baseline.

Symptomatic relapse compared to relapse from previous treatment and in association with indices of severity of synovitis are reported below (4.3.3.1-2). Relapse in association with injected activity and intra-articular distribution are reported in sections 4.3.4 and 4.3.8.2.1 respectively.

![Symptom Score Frequency](image)

**Fig. 4.3** Frequency of symptomatic relapse at 3 month intervals following intra-articular injection with Sm-153 PHYP for chronic knee synovitis. All patients had a pre-treatment symptom score of 2

4.3.3.1 Time to relapse: comparison to previous glucocorticoid

There were 13 patients for whom data regarding the duration of symptomatic benefit from the previous intra-articular glucocorticoid injection were reliably obtained. Overall there was a significant improvement in duration of symptom relief from combined Sm-153 PHYP/glucocorticoid treatment over the previous intra-articular glucocorticoid injection (p<0.0015,
Wilcoxon signed-rank). In the 8/13 patients who had a full symptomatic relapse following Sm-153 PHYP/glucocorticoid within a year, the duration of symptomatic relief had been a mean 15 times (3-50 weeks) longer than symptom relief following the previous glucocorticoid injection. In the 5 patients who had not fully relapsed within a year, the duration of symptomatic relief was at least a mean 25 times (13-51 weeks) longer than following the previous glucocorticoid treatment.

4.3.3.2 Time to relapse: indices of synovitis severity at baseline

The baseline RAI was significantly higher in patients who then had a partial or full relapse within 3 months of treatment, compared to symptom-free patients at 3 months (p<0.001, Mann Whitney U). The baseline RAI was not significantly different in relapsers and non-relapsers when outcome was compared after 9 months (too few data at 12 months follow-up were available for a valid comparison). Conversely, although baseline ESR was not significantly different in those relapsing and those asymptomatic at 3 months, it was significantly higher in patients who were found to have relapsed compared to asymptomatic patients at 9 months (p<0.025 Mann Whitney U).

4.3.4 Injected activity and activity injection efficiency

Mean injected activity overall was 404 MBq (range 134-682 MBq, n=19). For procedures using a 3-way tap, the mean injected activity was 457 MBq (range 301-682 MBq, n=15). The injection efficiency varied from 27-92%. There was no difference in mean activity retained in the injection apparatus between groups injected with different size ranges of particulate hydroxyapatite. Injected activity had been significantly higher in those who then remained asymptomatic for 3 months following injection (p<0.05, Mann Whitney U), though there was no difference in injected activity when patient groups were compared at 9 months.

4.3.5 Urine and blood activity analysis

Low levels of activity were present in urine over the initial 24 hours following injection and traces of activity were detected in blood at all sampling times (Table 4.3).
4.3.6 Whole-body extra-articular activity analysis

4.3.6.1 Extra-articular activity detection

In 7/13 (54%) patients no discrete extra-articular activity accumulation was detected by serial whole-body scans. Specific organ activity was detected in 6/13 (46%) patients in the lung, liver and regional lymph nodes in the groin. The pattern of appearance of this activity over time is shown in Table 4.4.

---

**Table 4.4 Post-injection urine and blood activity analysis**

<table>
<thead>
<tr>
<th>Sample (no. patients)</th>
<th>Mean % injected activity</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine 0-4 hours (n=13)</td>
<td>0.003</td>
<td>&lt;0.001- 0.01</td>
</tr>
<tr>
<td>Urine 4-24 hours (n=6)</td>
<td>0.007</td>
<td>&lt;0.001 - 0.02</td>
</tr>
<tr>
<td>Blood +1 hour (n=6)</td>
<td>0.001</td>
<td>&lt;0.001 - 0.004</td>
</tr>
<tr>
<td>Blood +2 hours (n=6)</td>
<td>0.003</td>
<td>&lt;0.001 - 0.12</td>
</tr>
<tr>
<td>Blood +3 hours (n=6)</td>
<td>0.002</td>
<td>&lt;0.001 - 0.12</td>
</tr>
<tr>
<td>Blood +4 hours (n=5)</td>
<td>0.004</td>
<td>&lt;0.001 - 0.14</td>
</tr>
</tbody>
</table>
**Table 4.4 Patterns of extra-articular activity accumulation**

<table>
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<th>Patient</th>
<th>Organ</th>
<th>Time following injection (hrs)</th>
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<td></td>
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</tr>
<tr>
<td>1</td>
<td>Lung</td>
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</tr>
<tr>
<td></td>
<td>Liver</td>
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</tr>
<tr>
<td></td>
<td>Lymph nodes</td>
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<tr>
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<td>Liver</td>
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<tr>
<td></td>
<td>Lymph nodes</td>
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<td></td>
<td>Lymph nodes</td>
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<td></td>
<td>Lymph nodes</td>
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<td>Liver</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Lymph nodes</td>
<td>-</td>
</tr>
</tbody>
</table>

*ns = not scanned
4.3.6.2 Validity of scintigraphic techniques

4.3.6.2.1 Detector parameters

There was no observable saturation of either detector using either energy window from a small source of Sm-153 for activities up to 1230MBq (Fig. 4.4).

![Graph showing count rates from a Sm-153 source using either a LEHR or LEAP collimator. The 20% energy window was centred on either 103keV or 103+3% keV.]

Fig. 4.4 Count rates from a Sm-153 source using either a LEHR or LEAP collimator. The 20% energy window was centred on either 103keV or 103+3% keV.

4.3.6.2.2 Regional count detection

Scans from patients 1, 2 and 8 were analysed. Injected activity in these patients was 198, 486 and 517MBq respectively. From the comparison of data in these patients, the distance from the knee at which counts/pixel fell to background levels was proportional to injected activity (Fig. 4.5a) and to time from injection (Fig. 4.5b). Even in early post-injection whole-body scans, count rates fell to background levels within 0.5-0.6m of the knee, indicating that photon penetration beyond this distance was not significant. Although knee ROIs extending to this level were necessary in the early scans, photon penetration from the knee did not reach the level of the lung (Fig. 4.5a).
Fig. 4.5 (a) Variation in counts/pixel in an anterior whole-body scan at distances from an unshielded knee 4 hours after knee injection. Data for 3 patients (A, B and C). Injected activity was $A = 517\text{ MBq}$, $B = 486\text{ MBq}$, $C = 198\text{ MBq}$ Sm-153 PHYP. A small amount of lung activity has accumulated in one patient (c).

(b) Variation in counts/pixel in an anterior whole-body scan at distances from an unshielded knee $A = 0.5$, $B = 4$, $C = 24$, $D = 72$ hours after knee injection with $517\text{ MBq}$ Sm-153 PHYP.

Background counts/pixel are represented by the dotted line (-----).
As a consequence, for quantification of extra-articular activity, knee ROIs were extended to 0.6 m from the knee in all except 24, 72 and 168 hours post-injection scans when a ROI extending 0.4m was used (see C and D in Fig. 4.5b). Regional lymph node ROIs were corrected for additional counts detected as a result of proximity to the knee (Fig. 4.6).

**4.3.6.2.3 Organ attenuation of resident Sm-153 γ activity**

Results from the external Sm-153 source attenuation study are shown in Table 4.5. Relative attenuation ratios were calculated and attenuation correction factors derived. These were subsequently applied to all relevant ROI count data prior to calculation of activity.

**4.3.6.3 Extra-articular activity quantification**

From quantitative ROI analysis, extra-articular activity was detected in 7/13 (54%) patients. The mean (maximum) extra-articular activity accumulation was 1.3% (range 0.2-3.1%) for those in whom it was detected but was 0.7% for the whole patient series. Data from quantitative ROI analysis are shown in Table 4.6.
Extra-articular organ uptake of activity was detected in 6 patients. The mean (maximum) extra-articular activity detected in the lung, liver and regional lymph nodes was estimated to represent 1.56%, 0.17% and 0.33% respectively in those patients in whom it was detected (Fig. 4.7).

Table 4.5  Differential organ attenuation of Sm-153 photons

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<th>Attenuating organ (o)</th>
<th>Counts</th>
<th>C_{gmo}/C_{gms} (relative ratio)*</th>
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<td>geometric mean (*C_{gmo})</td>
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<td>Soft-tissue</td>
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<tr>
<td>Knee</td>
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\textsuperscript{*}C_{gmo} = geometric mean counts for an organ (o)
\textsuperscript{\textdagger}Based on C_{gmo}/C_{gms} for knee (0.69) = 1
\textsuperscript{\textdagger}C_{gms} = geometric mean counts for source (s)
### Table 4.6 Extra-articular activity accumulation: counts, activity and % injected activity

<table>
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<tr>
<th>Patient/injected activity (MBq)</th>
<th>Time post-injection (hours)</th>
<th>Whole-body geometric mean counts* - knee ROI geometric mean counts*</th>
<th>Decay corrected extra-articular activity (MBq)</th>
<th>Total extra-articular activity: % Injected activity</th>
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117
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<th>Background Count</th>
<th>Count</th>
<th>Percent</th>
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</tr>
</tbody>
</table>

*The whole-body geometric mean activity count is calculated from √(Cawb-Cawb(bg))−(Cpwb-Cpwb(bg)) where: Cawb is the total count in the anterior whole-body scan; Cawb(bg) is the number of background counts for the whole-body ROI; Cpwb represents the counts in the posterior whole-body scan and Cpwb(bg), the background counts for the posterior whole-body ROI.

*The knee ROI geometric mean counts is calculated from √(Cak-Cak(bg))−(Cpk-Cpk(bg)) where: Cak represents the counts detected in the anterior knee ROI; Cak(bg) is the background counts for the anterior knee ROI; Cpk represents the counts detected in the posterior knee ROI and Cpk(bg) represents the background counts for the posterior knee ROI.
4.3.7 Dosimetry

Absorbed dose estimates for the whole body and extra-articular organs are shown in Table 4.7. Individual organ cumulative activity, integral $\beta$ and $\gamma$ absorbed doses are included in Appendix Bi and ii. Results of knee synovium absorbed dose estimates are included in Appendix Biii.

Table 4.7 Extra-articular organ mean absorbed dose (unwanted radiation dose) from extra-articular $\beta$ and intra-articular $\gamma$ activity

<table>
<thead>
<tr>
<th>Organ/region</th>
<th>Mean absorbed dose (mGy)</th>
<th>All patients (range)</th>
<th>Patients with detected organ activity (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>6.3 (0.2-23.6)</td>
<td>18.9 (15.2-23.6)*</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>1.4 (0.1-8.6)</td>
<td>3.6 (1.4-8.6)*</td>
<td></td>
</tr>
<tr>
<td>Regional lymph nodes</td>
<td>9.6 (0.1-35.1)</td>
<td>20.7 (8.8-35.1)*</td>
<td></td>
</tr>
<tr>
<td>Whole body</td>
<td>0.2 (0.1-0.3)</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

* $n=4$ patients
* $n=4$ patients
* $n=6$ patients

Fig. 4.7 Mean extra-articular activity accumulation in lung (A), regional lymph nodes (B) and liver (C) following Sm-153 PHYP knee injection ($n=7$)
4.3.8 Intra-articular distribution of radiation

4.3.8.1 Planar scintigraphy

Images provided early post-injection evidence of whether radiation was distributed to anterior, posterior, medial, lateral compartments of the joint. Count profile analysis of serial scans suggested that there was little redistribution after 4 hours (Fig. 4.8) in the majority of patients and no gross change in activity distribution a maximum 24 hours following injection in the remainder of patients.

Fig. 4.8 Count profiles through anterior planar left knee images acquired 24 (A) and 72 (B) hours after intra-articular injection of Sm-153 PHYP. The ratio of counts/pixel in medial and lateral joint compartments is similar in the two studies (1:2), indicating no gross change in activity distribution in the compartments after 24 hours following injection.
4.3.8.2 Tomographic scintigraphy

4.3.8.2.1 Intra-articular distribution scores

Tomographically-derived intra-articular distribution scores for 14 scanned patients are included in Table 4.2. There was a weakly significant association between scores and knee flexion range at baseline (R=0.7, p<0.01 ANOVA, Fig. 4.9). Scores were not significantly different between patients with and without an effusion or between patients receiving the different size ranges of particulate hydroxyapatite (Mann Whitney U). Scores were significantly better in those patients who remained asymptomatic at 3 months compared to those who had a partial or full relapse (p=0.05, Mann Whitney U). However, distribution scores were no different in patients remaining asymptomatic at 9 months compared to those who had relapsed.

![Intra-articular distribution scores and knee flexion range at the time of joint injection](image)

*Fig. 4.9 Intra-articular distribution scores and knee flexion range at the time of joint injection (R=0.7, p<0.01 ANOVA, n=14)*
4.3.8.2.2 Knee compartment activity distribution indices

Joint compartment distribution indices are shown in Table 4.8. Indices of activity distribution to the various compartments were maximal for the suprapatellar pouch. Indices were independent of injection approach or size range of hydroxyapatite particles. In each compartment, a lower activity distribution index was seen in patients unable to flex the knee more than 110° immediately post-injection compared to those with a good range of flexion.

Distance-graded, surface-shaded 3D images were reconstructed from transaxial datasets in a number of scans (Fig. 4.10). Scans were not used for data analysis but were interpreted to illustrate the approximate distribution of intra-articular Sm-153 PHYP.

Table 4.8 Joint compartment distribution indices

<table>
<thead>
<tr>
<th>Patient groups</th>
<th>Knee compartment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anterior or Inferior</td>
</tr>
<tr>
<td></td>
<td>*SPP</td>
</tr>
<tr>
<td>All (n=13)</td>
<td>1</td>
</tr>
<tr>
<td>Injection approach:</td>
<td></td>
</tr>
<tr>
<td>medial</td>
<td>1</td>
</tr>
<tr>
<td>lateral</td>
<td>1</td>
</tr>
<tr>
<td>PHYP size range:</td>
<td></td>
</tr>
<tr>
<td>Full (n=7)</td>
<td>1</td>
</tr>
<tr>
<td>Adjusted (n=6)</td>
<td>1</td>
</tr>
<tr>
<td>Effusion:</td>
<td></td>
</tr>
<tr>
<td>+ (n=8)</td>
<td>1</td>
</tr>
<tr>
<td>- (n=5)</td>
<td>1</td>
</tr>
<tr>
<td>Knee flexion:</td>
<td></td>
</tr>
<tr>
<td>&lt;110 (n=4)</td>
<td>1</td>
</tr>
<tr>
<td>&gt;110 (n=9)</td>
<td>1</td>
</tr>
</tbody>
</table>

*SPP = suprapatellar pouch
Fig. 4.10 Surface-shaded 3D scintigraphic Sm-153 knee images constructed from transaxial tomographic datasets. Data obtained from tomographic images of 2 patients, each acquired 3 days following intra-articular Sm-153 PHYP injection. Four projections of the 3D image are shown. Top image: LAO= left anterior oblique; RAO= right anterior oblique; P= posterior; L= lateral. Images illustrate the distribution of Sm-153 in the injected knees.
4.4 Discussion
4.4.1 Methodology
4.4.1.1 Detectors and energy detection windows

For the amounts of Sm-153 activity injected into a knee, it appears that detector saturation is not likely to occur using either a LEHR or LEAP collimator. For subsequent whole-body scintigraphy, it was therefore decided to use a LEHR collimator to afford greater resolution of small extra-articular foci of activity. An offset of +3% from the 103keV photopeak was subsequently employed to reduce the effects of scattered photons.

4.4.1.2 Regional count detection

Photons emitted from activity in the knee did not appear to interfere with count detection from either liver or lung; however, count rates detected from activity accumulating in the regional lymph nodes within 24 hours of knee injection were affected by the scatter of photons from the knee, but were adjusted by subtracting counts from an adjacent ROI equidistant from the photon source in the knee.

ROIs employed for knee activity photon detection were necessarily large to include scattered photons. ROIs extended as far as the abdomen in some early post-treatment scans. In theory, extra-articular activity may have been underestimated if it had either accumulated in the tissues included in the knee ROI or remained undetected by the scans. This was unlikely, however, based on the pattern of activity escape from the joint, as early escape of activity from the joint appeared to accumulate in the lung (see Table 4.4).

4.4.1.3 Organ photon attenuation

Attenuation of photons incident on a material depends on the density, composition and size of that material. These characteristics will vary for different body organs. Counts recorded from activity resident in different organs will vary according to the attenuation and scatter of photons within the organ and in surrounding structures. To adjust for differential organ attenuation, a relative rather than absolute scale of correction was adopted. Had an absolute scale been adopted, count detection from different organs would have had to be normalised to 'true count' detection (i.e. equivalent to
counts from an unattenuated photon source). As a result, there would then have been a small correction on the counts detected from all photon sources where some attenuation existed, including the knee. Because of the large amount of activity in the knee, the amount of surrounding bony structures and the difficulty in reproducibly positioning the detector, this correction would potentially have led to a large error. Therefore, normalising the photon attenuation of the different extra-articular organs to the attenuation of photons by the knee (taken as unity) was adopted to give an indication of relative organ attenuation.

4.4.1.4 Dosimetry calculations

Approximations of the energy absorbed by extra-articular organs as a result of escape of activity from the joint and intra-articular photon emission were obtained. Additionally, the range of synovial lining dose was estimated for the range of activities injected. The methods of calculation are briefly discussed here but the implications of extra-articular organ dosimetry are discussed in 4.4.3.1 below and in Chapter 8.2.3.1.

4.4.1.4.1 Extra-articular organs

Assumptions made in the calculation of extra-articular organ-absorbed doses were designed to slightly overestimate, rather than underestimate, values (see 4.2.8). For example, firstly, it was assumed that there was no clearance of activity from an organ once it had accumulated even though imaging of patients nos. 10 and 13 suggested that activity may have been cleared from regional lymph nodes and liver respectively (see Table 4.4). Secondly, all photons incident on an organ (see equation 4.22) were assumed to deposit their energy within the organ. In reality, however, high energy photons would pass through the tissue without depositing all their energy. These assumptions may have resulted in small over-estimates of individual organ absorbed doses.

4.4.1.4.2 Synovial lining

There are no established methods for calculating absorbed doses of the synovial lining after intra-articular injection of a radionuclide. A range of
doses have been calculated based on assumptions of intra-articular activity
distribution and estimates of synovial mass and are included in Appendix Biii.

Potentially the largest error in the calculation may arise as a result of an
inability to monitor accurately the pattern of intra-articular distribution of the
activity. The range of values obtained is wide. Evidence from scanning studies
suggests that there may be an uneven distribution of Sm-153 PHYP
throughout the joint (see 4.3.8.2.1-2). This raises the possibility of uneven
delivery of $\beta^-$ energy to the synovial lining. Uneven distribution may have
implications on the ability of Sm-153 PHYP to provide a clinical response
(see 4.4.2).

4.4.1.5 Tomographic knee scintigraphy

Although tomographic (SPET) Tc-99m MDP knee scintigraphy has been
described (Murray et al. 1990), SPET scans of the knee utilising the $\gamma$ decay of
a radiopharmaceutical injected into a joint, has not been described before.
Unique acquisition and reconstruction parameters were therefore employed
and could not be compared with established reconstruction parameters.

The tomographic datasets were useful for confirming distribution
throughout the joint. Assuming particle uptake into the synovial lining was
complete after 7 days, the images were interpreted to represent synovial
distribution of the radiopharmaceutical. Because of repositioning difficulties
and patient movement during the acquisition, the tomographic images added
little to the information derived from planar images about the changes in intra-
articular activity distribution in the few days following injection. The
distance-graded, surface-shaded 3D images constructed from transaxial
tomographic datasets were obtained from a number of scans. Although
interpreted to indicate approximate distribution of Sm-153 PHYP in the
synovial lining, they were not used for data analysis.

4.4.2 Symptomatic relapse

A number of factors may influence clinical outcome following radiation
synovectomy (see Chapter 1.4.7.4). Some attempt to identify factors important
in influencing outcome in this patient cohort was made, despite the small
number in the series.
All patients improved after injection, though symptoms were not abolished in all patients and 73% of patients still had symptoms 6 months after the treatment. This suggests a modest clinical effect in this patient cohort compared to data from studies with other radiopharmaceuticals (see Table 1.4).

Prior to the study, many patients had had numerous previous intra-articular glucocorticoid injections, often with poor outcome. Although this may indicate that symptoms may have been unresponsive to glucocorticoid in the past, it may also indicate that symptoms may not have been a consequence of synovial pathology but a consequence of bone and cartilage destruction. Although patients with gross articular destruction were excluded from the study, many patients had radiological evidence of some articular bone and cartilage destruction. This may have been a consequence of the patient referral pattern, as physicians, who were unused to referring their patients for radiation synovectomy, referred patients late in their disease. The importance of avoiding patients with bone and cartilage destruction to ensure a good response to radiation synovectomy has often been emphasised (see Chapter 1.4.7.4.2). Conceivably, many of these patients would have otherwise been considered for surgical synovectomy rather than intra-articular glucocorticoid injection on the basis of the chronicity of disease duration and poor response to previous intra-articular glucocorticoid.

Because patients were injected with long-acting glucocorticoid as well as Sm-153 PHYP, efficacy may be attributable to either agent or a combination of both. Glucocorticoid was co-injected following the rationale that it may not only reduce the extent of any transient PHYP-induced synovial inflammation but may also help to reduce the thickness of the synovial lining thus increasing the efficiency of Sm-153 β⁺ penetration.

There was a distinct advantage in duration of symptom relief following co-injection of Sm-153 PHYP and glucocorticoid injection over glucocorticoid alone when outcome from patients’ previous knee injection was compared. These results, which may have been influenced by recall bias, and a variation in conditions of treatment, must be interpreted with caution. Patients invariably receive intra-articular glucocorticoid injections in an out-patient clinic and then ambulate immediately. This had been the case for all
patients referred to us for treatment. A period of non-ambulation and rest following glucocorticoid knee injection improves outcome (Chakravarty et al. 1994). Our patients were all immobilised for 4 hours following the procedure then strongly advised to rest at home for the remainder of the day. It is possible therefore that post-injection immobility in this study contributed to the efficacy of glucocorticoid.

Relapse of symptoms appeared to be associated with higher indices of inflammatory activity at the time of treatment. This is similar to results with other radiopharmaceuticals (Winfield and Gumpel 1979, Schütte and Rau 1983). The discussion is expanded in Chapter 8.3.

The finding that lower levels of injected activity within the range 134-517MBq may be associated with short-term relapse may have been attributable to delivery of sub-therapeutic levels of activity. Particles labelled with up to 80% of the prepared activity may be retained in the injection apparatus (see 4.4.5).

Finally, distribution of the particulate radiopharmaceutical uniformly to the synovial surface may be of crucial importance in providing a therapeutic dose to the synovial lining (see Chapter 1.4.4.1). There is evidence to suggest that intra-articular Sm-153 PHYP distribution may depend on the degree of knee flexion obtainable at the time of treatment. This point is discussed further in 8.3.2.1.

4.4.3 Extra-articular activity accumulation of Sm-153 PHYP

Immediate post-injection accumulation of activity in the lung was observed in two patients and implies the passage of Sm-153 PHYP into the blood (presumably as a result of traumatisation of synovial vessels during the procedure) with trapping in the pulmonary capillaries. The fate of Sm-153 PHYP in the lung is unknown. There were, however, no short-term symptomatic sequelae as a result of this small amount of lung exposure.

Perhaps not surprisingly, a small amount of liver activity accumulated in patients who had had prior or concomitant extra-articular organ activity uptake. As the amounts were small it was difficult to interpret from time-activity curves from which site the activity principally originated. It would, however, seem reasonable to assume that this activity was largely particle
bound, as 'free' Sm-153 is likely to be either excreted by the kidney or bound to bone (Chinol et al. 1993).

The low levels of activity detected in urine collected immediately after injection may either originate from 'unbound' injected Sm-153 citrate or in vivo 'particle dissociated' Sm-153. The pattern of activity 'residency' (allowing for accumulation and decay) in lung and lymph tissue suggests there was little removal of activity from each tissue, which might be expected if extensive dissociation of Sm-153 from PHYP was occurring. Also Sm-153 PHYP has been shown to remain tightly bound in vivo (Chinol et al. 1993). It would therefore seem more likely that the urine activity is the result of excretion of a small amount of free Sm-153. This hypothesis has not been fully tested by activity analysis of delayed urine collections, which putatively would not contain significant activity, but if correct it would further enhance the reputation of PHYP as a particulate carrier capable of extremely stable Sm-153 binding in vivo.

Regional lymph node activity invariably accumulates following radiation synovectomy irrespective of whether a colloid or particulate radiation vehicle is used (Edmonds et al. 1994). Larger particulate carriers, however, are invariably associated with substantially less escape of activity to the regional lymphatics than colloids (Deutsch et al. 1993. See Table 1.3). Consequently, lymph tissue dose is invariably greater with colloidal than with particulate preparations (see 4.4.3.1 below and Chapter 1.4.4.1).

4.4.3.1 Extra-articular organ absorbed doses

Absorbed doses calculated for extra-articular organs as a result of knee injection with 400MBq (11mCi) of Sm-153 PHYP appear to be similar to those calculated for 9990MBq (270mCi) Dy-165 FHMA. Doses from these two radiopharmaceuticals are substantially smaller than doses calculated for Y-90 or Au-198 colloids (see Chapter 8). These data suggest that Sm-153 PHYP may represent a positive step in helping to minimise the risk to healthy tissue associated with intra-articular administration of radiopharmaceuticals. Moreover, these data were obtained in patients who were allowed to ambulate from 4 hours after injection suggesting that prolonged immobilisation is not
necessary to restrict extra-articular escape of activity and that out-patient treatment may be feasible.

4.4.4 Particulate hydroxyapatite size range

There was no evidence of improved intra-articular radiopharmaceutical distribution, retention of intra-articular activity or efficacy in patients receiving one or other PHYP size range. Particle size may be an important determinant of egress of initially bound radioactivity from an injected joint (Noble et al. 1983). However, hydroxyapatite samples containing tiny (submicron) fragments appear to be associated with virtually complete retention of activity within the joint. This suggests firstly, that the biological half-life of PHYP within the joint is sufficiently long so that bound Sm-153 is not released and secondly, that the chemical nature of hydroxyapatite itself, irrespective of size, is an important influence on escape of particle-bound Sm-153 from the joint.

4.4.5 Injection efficiency

Injection efficiency (% of prepared activity injected) varied and clearly depended on the amount of PHYP retained in the injection apparatus but did not appear dependent on PHYP size range. The problem may be partially overcome by careful technique, including flushing the injection apparatus. Technique was improved by using a 3-way tap with side-port (see 4.2.4).

Although the activity required to deliver a therapeutic dose is not exactly known, it is possible that poor injection efficiency may result in sub-therapeutic levels of activity administration. There is some suggestion that low activities within the range 134-682MBq may have been associated with poor outcome (see 4.4.2). As a result of this analysis all future injection procedures were carefully undertaken using 3 separate flush injections of a total of 5mls of 1% lignocaine through the side-port of the 3-way tap. Possible techniques designed to optimise delivery of Sm-153 PHYP have been studied and are reported in Chapter 5.
Chapter 5

Supportive laboratory data III. Labelling efficiency and binding stability of pHYP, a modified preparation of particulate hydroxyapatite and effect of fluid vehicle on activity injection efficiency and synovial distribution of PHYP
5.1 Introduction

The work reported in this chapter focuses on two aspects of Sm-153 PHYP radiation synovectomy arising from the studies reported in Chapter 4. The first is the difficulty in ensuring a predictable amount of activity is injected into the joint (injection efficiency). The second is an analysis of the fate of Sm-153 PHYP in synovial tissue.

5.1.1 Inconsistencies in administered activity

It was soon evident from the first few procedures that a range of Sm-153 activity may be injected as a result of the Sm-153 PHYP injection procedure (see Chapter 4.3.3). Although the minimum administered activity required for a therapeutic dose to the synovial lining is not known, it is conceivable that differences in outcome may, in part, be attributable to variations in administered activity (see Chapter 4.3.4).

Inconsistencies in administered activity occur because particles may be retained in the injection apparatus. One option for maximising and improving Sm-153 PHYP injection efficiency might be to extend the duration of particle suspension so that particle sedimentation does not occur in the syringe or needle hub before injection. In theory this may be done either by reducing the size of the particles or by increasing the viscosity of the fluid. Both options are explored.

5.1.1.1 Influence of PHYP size

The PHYP which was supplied for initial studies and was the focus of experiments in Chapter 2 and clinical studies reported in Chapters 4 and 6, had a mean diameter of 16μm and a range of <5μm to 45μm (see Chapter 2.3.2.2). Discussions with the Research and Development department of Mallinckrodt Medical Inc. (MMI) during the course of these studies led to the hypothesis that smaller, and thus lighter, particles may be more efficiently injected because they remain in suspension for longer. In support of this was the finding that a decrease in mean PHYP size was associated with a decrease in its sedimentation rate in saline (see Chapter 2.2.2.1 and 2.3.2.1). A modified preparation of PHYP with a smaller mean size (pHYP) was subsequently produced, though was only available after the start of the
randomised study (see Chapter 6). In this chapter, the radiochemical properties (labelling efficiency and binding stability) and injection efficiency of Sm-153 pHYP are investigated.

5.1.1.2 Viscosity of fluid vehicle

Hyaluronan is a high molecular weight glycosaminoglycan and the major constituent of synovial fluid contributing to its viscosity (see Chapter 1.1.2). It is also present in the synovial lining, vitreous humour in the eye and as ‘Wharton’s jelly’ in the umbilical cord. Human hyaluronan isolated from the umbilical cord is available commercially. In a concentrated solution it is useful in a number of ophthalmic and otologic conditions, used as vitreous replacement in ophthalmic surgery and may improve the symptoms of osteoarthritis when injected intra-articularly (Laurent and Fraser 1992). As a viscous fluid in which to suspend particles and to inject safely into a joint, it may be ideal. The injection efficiency of Sm-153-labelled PHYP (24μm mean diameter particles) suspended in hyaluronan, is assessed below.

5.1.2 Fate of PHYP in vivo

In the antigen-induced arthritis rabbit, intra-articular injected Sm-153 PHYP was found to be distributed throughout the synovium after 6 days (Chinol et al. 1993). In rabbit synovium, the PHYP may provoke a transient inflammatory reaction characterised by influx of polymorphonuclear leucocytes and appears to be degraded within approximately 6 weeks of injection (Shortkroff et al. 1992). By obtaining synovial tissue from the knee of a patient 3 months after treatment with Sm-153 PHYP, the fate of PHYP in vivo was evaluated histologically.
5.2 Materials and Methods

5.2.1 Labelling efficiency of Sm-153 pHYP

Sm-153 was supplied by University of Missouri Research Reactor (see Chapter 2.2.1). The pHYP was supplied by MMI, St. Louis, MO. The mean particle size range, determined by Coulter\textsuperscript{R} particle size analysis, was 4.7 ± 2.5\(\mu\)m (J. Brodack, personal communication). This size range analysis undertaken by MMI is included in Appendix C.

Two aliquots of Sm-153 citrate (1ml), prepared as reported in Chapter 2.2.1, were added to 2 samples of 40mg pHYP contained in sealed vials. The vials were gently swirled for approximately 5 minutes at room temperature. A 2ml volume of air was removed from each vial to normalise the pressure. The activity in each of the vials was measured using a Capintec CRC-120 radioisotope calibrator using a calibration factor of 230. Samples were spun at 1500rpm for 8 minutes (Centaur 2 centrifuge), the supernatant carefully removed from each vial using a 21 gauge needle and samples re-suspended in 1ml saline. The vials were gently agitated for 5 minutes and the activity in each measured again. The labelling efficiency in each vial was calculated from the serial differences in activity.

5.2.2 Binding stability of Sm-153 pHYP

Binding stability was evaluated in synovial fluid and triamcinolone hexacetonide (Lederspan, Lederle) over 6 days. Labelled samples were spun at 1500rpm for 8 minutes and the supernatant removed. Synovial fluid (2mls) obtained from a patient with RA was then added to one sample and 2mls of 20mg/ml triamcinolone hexacetonide to the other. Vials were agitated gently for 5 minutes and the activity recorded in each. Vials were left at room temperature. At 24, 48, 72 and 144 hours later, samples were re-analysed. First, the activity in each vial was measured. Samples were spun (1500rpm for 8 minutes) and the supernatant removed carefully with a 21-gauge needle and retained. The activity in the pellet was measured and the %activity remaining bound to the pHYP calculated from the difference in the two measurements. The pH of the supernatant was measured (Wharton pH indicator strips) at each sampling time before it was replaced in the appropriate vial. Vials were gently swirled before storing.
5.2.3 Injection efficiency of Sm-153 pHYP in saline

The pHYP (40mg) was labelled according to methods written above (see 5.2.1). Particles were suspended in a 5ml syringe in 2mls saline which was then fitted with a 3-way tap. The activity in the apparatus was measured (Capintec CRC-120). A syringe containing 5mls saline was attached to the side port. To simulate a joint injection procedure, the pHYP suspension was injected into an empty vial maintained under slight positive pressure through a 21 gauge needle. After the injection, the 3-way tap was flushed by drawing 1.5mls saline from the syringe attached to the side port into the syringe containing the Sm-153 pHYP, and then injecting the bolus through the 3-way tap into the vial. The apparatus was flushed twice more each time with a 1.5ml saline bolus. After the initial injection and each flush, the activity remaining in the injection apparatus was measured. The injection efficiency after each flush was taken as the %activity expelled from the injection apparatus. The complete procedure was repeated with a separately prepared pHYP suspension to test the reproducibility of the procedure.

5.2.4 Injection efficiency of Sm-153 PHYP in hyaluronan

Sodium hyaluronate isolated from human umbilical cord (Sigma Chemical Co., St. Louis, MO) was dissolved in saline to form a solution of concentration 1mg/ml. Two ml's of the solution were added to 40mg PHYP (original particles) which were labelled with Sm-153 according to methods reported in Chapter 2.2.1. The solution was drawn into a 5ml syringe which was fitted with a 3-way tap attached to a 21 gauge needle. The procedure to measure injection efficiency through the apparatus into a vial maintained under positive pressure, and the effect of 1, 2 and 3 subsequent flushes with 1.5mls saline, was followed as above (see 5.2.3). Two separately prepared pHYP/hyaluronate suspensions were assessed to test the reproducibility of the procedure.

5.2.5 Post-treatment synovial lining analysis

All tissue was obtained from the knee of a patient with seropositive RA, 3 months following radiation synovectomy. The patient, who was the first patient treated with Sm-153 PHYP, had symptomatically relapsed and
synovial biopsy was considered ethical to exclude synovitis secondary to injected PHYP. Synovial sections were prepared and analysed under light microscopy (Nikon *ophtiphot*).

5.2.5.1 Synovial biopsy and tissue preparation

Multiple synovial lining samples were obtained from arthroscopic biopsy under general anaesthetic. Samples were taken from both medial and lateral spaces as part of a joint lavage procedure. All samples were trimmed and chilled by precipitate immersion in *n*-hexane at -70°C. The tissue was stored in dry tubes at -70°C until used. Sections were cut at a thickness of 10mm in a Bright's cryostat with a cabinet temperature of -35°C, flash-dried onto glass slides and stored.

5.2.5.2 Staining methods

5.2.5.2.1 Haematoxylin and eosin

Unfixed sections were washed gently in distilled water and stained with Mayer's haematoxylin, as reported by Stevens (Stevens 1990a), for 1-2 minutes. Sections were washed thoroughly in running tap water for 3-4 minutes then briefly washed with 1% acid alcohol solution (1% hydrochloric acid in 70% alcohol). Sections were washed in tap water until 'blue' and stained in 1% eosin Y for 10 minutes. Finally the sections were washed in running tap water, dehydrated in graded concentrations of alcohol to xylene and mounted using aquamount (BDH) and a coverslip.

5.2.5.2.2 Perls' Prussian Blue reaction for ferric iron

The method of Perls was followed as reported by Stevens (Stevens 1990b). Briefly, unfixed sections were transferred to a freshly prepared incubating solution containing 2% potassium ferrocyanide and 2% hydrochloric acid for 10 minutes. Sections were washed in running tap water and counterstained with neutral red. Sections were washed again and dehydrated through graded concentrations of alcohol solution and finally xylene. Fixed slides were mounted using aquamount and a coverslip.
5.2.5.2.3 Alizarin Red S stain for calcium

The method of McGee-Russell (McGee-Russell 1958) was followed as reported by Stevens (Stevens 1990b). Briefly, unfixed sections were rinsed in distilled water and transferred to 2% aqueous alizarin red S solution (pH 4) for 4 minutes. Sections were blotted, washed in acetone and treated with acetone-xylene (1:1) for 15 seconds. Sections were rinsed again in xylene and mounted using aquamount and a coverslip.
5.3 Results

5.3.1 Labelling efficiency of Sm-153 pHYP

Labelling efficiency of the two pHYP samples (Table 5.1) was over 99%.

5.3.2 Binding stability of Sm-153 pHYP

Over a 6 day period, binding stability of Sm-153 pHYP was over 99% in both synovial fluid (Table 5.2) and triamcinolone hexacetonide at an acid pH (Table 5.3).

\textit{Table 5.1  Labelling efficiency of Sm-153 pHYP}

<table>
<thead>
<tr>
<th>Prepared activity (MBq)</th>
<th>Pellet activity* (MBq)</th>
<th>Labelling efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>415</td>
<td>410</td>
<td>99%</td>
</tr>
<tr>
<td>382</td>
<td>382</td>
<td>100%</td>
</tr>
</tbody>
</table>

*Activity remaining after sample spun and supernatant removed

\textit{Table 5.2  Binding stability of Sm-153 pHYP in synovial fluid}

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Activity in vial (MBq)</th>
<th>Activity in vial with supernatant removed (MBq)</th>
<th>% bound activity</th>
<th>pH of supernatant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>365</td>
<td>365</td>
<td>100%</td>
<td>7.5</td>
</tr>
<tr>
<td>24</td>
<td>255</td>
<td>255</td>
<td>100%</td>
<td>7.5</td>
</tr>
<tr>
<td>48</td>
<td>177</td>
<td>176</td>
<td>99%</td>
<td>7.5</td>
</tr>
<tr>
<td>72</td>
<td>122</td>
<td>121</td>
<td>99%</td>
<td>7.5</td>
</tr>
<tr>
<td>144</td>
<td>40</td>
<td>40</td>
<td>100%</td>
<td>7.5</td>
</tr>
</tbody>
</table>
Table 5.3 Binding stability of Sm-153 pHYP in triamcinolone hexacetonide 20mg/ml

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Activity in vial (MBq)</th>
<th>Activity in vial with supernatant removed (MBq)</th>
<th>% bound activity</th>
<th>pH of supernatant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>394</td>
<td>394</td>
<td>100%</td>
<td>3.5</td>
</tr>
<tr>
<td>24</td>
<td>275</td>
<td>275</td>
<td>100%</td>
<td>3.5</td>
</tr>
<tr>
<td>48</td>
<td>202</td>
<td>200</td>
<td>99%</td>
<td>3.5</td>
</tr>
<tr>
<td>72</td>
<td>132</td>
<td>131</td>
<td>99%</td>
<td>3.5</td>
</tr>
<tr>
<td>144</td>
<td>44</td>
<td>44</td>
<td>100%</td>
<td>3.5</td>
</tr>
</tbody>
</table>

5.3.3 Activity injection efficiency of Sm-153 pHYP in saline

A high percentage of activity was expelled from the injection apparatus using a single injection. All activity was expelled from the injection apparatus using 2 or 3 flushes of saline (Table 5.4).

5.3.4 Activity injection efficiency of Sm-153 pHYP in hyaluronan

Over 50% of activity was injected through the apparatus using a single injection and virtually all activity expelled after 2 or 3 flushes (Table 5.4).

Table 5.4 Injection efficiency of Sm-153-labelled particulate hydroxyapatite through a 3-way tap using different particulate preparations and fluid vehicles

<table>
<thead>
<tr>
<th>Particle type</th>
<th>Fluid vehicle</th>
<th>Sample</th>
<th>Injection efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Injection only</td>
</tr>
<tr>
<td>pHYP</td>
<td>Saline</td>
<td>1</td>
<td>77%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>81%</td>
</tr>
<tr>
<td>PHYP</td>
<td>Hyaluronan (1 mg/ml)</td>
<td>1</td>
<td>56%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>72%</td>
</tr>
</tbody>
</table>

*Each flush was 1.5ml saline
5.3.5 Post-treatment synovial lining analysis

Inflammation consistent with changes seen in chronic rheumatoid synovitis was confirmed in all samples. Small amounts of refractile material was observed scattered through the synovial lining (Fig. 5.1). There appeared to be no local increase in cellularity around the refractile material in any of the samples suggesting that it was not the focus of a specific inflammatory reaction. The material did not contain iron (3+) [Fig. 5.2] or calcium (Fig. 5.3) although these minerals were readily identifiable elsewhere in the tissue as haemosiderin or native hydroxyapatite fragments respectively.

The material was thought to be consistent with the remnants of PHYP which had been degraded and from which the calcium had been released. The material was termed ‘PHYP ghosts’. Similar non-calcium containing ghosts have been found in animal joints following injection of PHYP (S. Shortkroff, personal communication).

Fig. 5.1 Synovial lining from patient with RA treated with Sm-153 PHYP 3 months previously (haematoxylin and eosin, oil immersion). Refractile material, termed ‘PHYP ghosts’, is seen within the synovial lining
Fig. 5.2 Synovial lining from patient with RA treated with Sm-153 PHYYP 3 months previously (Perls' Prussian Blue, x50). Although Fe$^{3+}$ is readily identifiable in the synovial lining (fe), the material (arrowed) does not accumulate the stain.
Fig. 5.3 Synovial lining from patient with RA treated with Sm-153 PHYP 3 months previously (Alizarin red S, x50). The material (arrowed) does not stain for calcium, indicating that calcium has been released from the hydroxyapatite crystal. Calcium elsewhere in the synovium is readily identified (ca)
5.4 Discussion

5.4.1 Radiochemical characteristics of Sm-153 pHYP

The modified preparation of particles, pHYP, was efficiently labelled with Sm-153. The binding appeared to be stable in vitro under different conditions. Thus pHYP shares similar characteristics with PHYP (see Chapter 2). The small difference in labelling efficiency between PHYP (95-99%) and pHYP (99-100%) may have been attributable to the relative ease with which the supernatant can be removed from the spun samples. Smaller particles were observed to remain compact in the pellet after spinning whereas larger particles in the PHYP tended to dislodge from the pellet and thus were more likely to be aspirated in the supernatant (see Chapter 2.4.1). Although the differences are small, use of the smaller size range of particles will result in more efficient labelling of Sm-153.

The labelled pHYP appears to be stable in vitro both in synovial fluid and under moderately acidic conditions. As it seems no different to PHYP in this respect, it is also likely to be stable in vivo. The influence of size on the rate of degradation of particulate hydroxyapatite and thus release of ‘free’ Sm-153 remains to be determined from biodistribution studies in patients. However, using a rabbit model, pHYP does not appear to be associated with an increased incidence of extra-articular activity escape (S. Shortkroff, personal communication).

5.4.2 Effect of fluid vehicle on activity injection efficiency

5.4.2.1 Injection efficiency of Sm-153 pHYP in saline

The injection efficiency of Sm-153 PHYP in a non-viscous fluid vehicle (triamcinolone hexacetonide or lignocaine) was found to vary between 27-92% (see Chapter 4.3.4 and 4.4.5). It appears that although it has not been tested under identical (clinical) conditions, labelled pHYP is substantially more efficiently injected through a 3-way tap than labelled PHYP. One flush, at least, with a small volume of fluid, is essential to clear the particles from the injection apparatus. The use of pHYP is likely to represent an improvement over that of PHYP in that a predictable amount of activity may be injected in a non-viscous fluid vehicle.
5.4.2.2 Injection efficiency of Sm-153 PHYP in hyaluronan

Suspending PHYP in hyaluronan appears to be an effective alternative to reducing the particle size in overcoming the problems of poor Sm-153 PHYP injection efficiency. Concentrated hyaluronan solution injected intra-articularly has been used safely for many years in treating traumatic equine arthritis (Balazs and Denlinger 1989) and patients with osteoarthritis (Pelletier et al. 1993, Aviad and Houpt 1994, Ghosh 1994). Thus, to use it as a fluid vehicle for a substance injected into a joint, although unusual, is not new.

There may be other, theoretical, advantages to using a viscous solution as the vehicle for PHYP or pHYP injection. For example, some heterogeneity in intra-articular distribution has been noted with PHYP (see Chapter 4.3.8.2.2). Although it is unknown whether this represents intra-cavity distribution or the variation of uptake into the synovial lining (discussed in Chapter 8.3.2.2), it is likely that factors which influence intra-cavity distribution are important. Further investigation of the influences of intra-articular particle distribution may be warranted if particle injection in a non-viscous fluid vehicle is adopted.

5.4.3 Fate of PHYP in the synovial lining

It was assumed that the refractile material represented PHYP remnants. The novel appearance and lack of staining characteristics were consistent with this identity. Only limited conclusions can be drawn about the distribution of Sm-153-labelled PHYP owing to the delay following treatment in obtaining tissue. Characteristics of early distribution in the synovial lining are unknown though both animal data (Shortkroff et al. 1992) and scanning data (see Chapter 4.3.8) suggest that PHYP is taken up readily into the synovial lining after injection. The subsequent pattern of distribution within the tissue is unknown and may differ in patients who experience a reduction in synovial thickening and in those where the cellular infiltrate and tissue thickening continues unabated.

While there was evidence that phagocytosis of the material had occurred there was no suggestion of focal inflammatory activity. Although synovial hydroxyapatite deposition is itself associated with destructive arthropathy in certain patients (McCarty et al. 1981), factors important in modulating
synovitis associated with hydroxyapatite deposition are poorly understood. The consequence of unwanted effects from PHYP in vivo are discussed further in Chapter 8.2.3.4.
Chapter 6

A randomised double-blind glucocorticoid-controlled trial of intra-articular Sm-153 PHYP for chronic knee synovitis: an interim analysis
6.1 Introduction

One important examination of the role of a new treatment is to compare its therapeutic effect with the most widely used efficacious therapies in clinical practice. Ideally, therefore, the effect of a radiopharmaceutical in treating the symptoms of chronic synovitis should be compared to that of either intra-articular triamcinolone hexacetonide or arthroscopic synovectomy (see Chapter 1.4.7).

In this study, the effect of Sm-153 PHYP on the symptoms of chronic knee synovitis is compared to that of intra-articular triamcinolone hexacetonide in a randomised double-blind fashion. As recruitment is continuing, only an interim analysis of outcome after 1 year in 20 patients is included.

Although it is an important outcome in the short-term, it should be noted that symptomatic benefit is only one criterion by which the therapeutic effect of a treatment for chronic synovitis may be judged. For example, articular cartilage and sub-chondral bone destruction are also important consequences of chronic synovial inflammation, and, as predictive of future disability and functional incapacity (Young et al. 1987), may also be appropriate outcome measures by which to judge the relative efficacy of different therapies. The difficulty in making these measurements reliably and the long follow-up period required may have influenced investigative practice in the past and may account for the infrequency of use of these outcome measures in studies of radiation synovectomy. As part of the protocol, therefore, a radiological evaluation of articular cartilage thickness has been made in patients receiving both Sm-153 PHYP and glucocorticoid to evaluate the effect of Sm-153 PHYP on the loss of articular cartilage in chronic synovitis. Additionally, measurements of the change in volume of synovial lining have been made using contrast-enhanced magnetic resonance (MR) imaging (Clunie et al. 1995b). Although the technique still remains to be validated, the results may provide quantitative data of the thickness of the synovial lining. This parameter has been discussed as a useful index of chronic synovitis (see Chapter 1.2.2.2). The results of the research undertaken in developing this technique are not reported here.
Much of the information derived from the results of the ‘open’ treatment study (see Chapter 4) was used to help construct a protocol for treatment based on an out-patient procedure. Data collection has focused on clinical outcome and no activity biodistribution or scintigraphic data have been collected.
6.2 Patients, materials and methods

6.2.1 Patients

The consideration for acceptance, and clinical and radiological entry criteria were identical to those for the open study (see Chapter 4.2.1). An additional requirement was that, if patients were receiving a SAARD, their general disease had remained controlled, according to clinical criteria, on the same dose of a SAARD for 4 months prior to treatment.

The study was conducted under ARSAC certificate reference number RPC 141-2 (40), November 12th 1992. Ethical approval for the study was given by the UCL Hospitals Clinical Investigations panel.

6.2.2 Study design

6.2.2.1 Randomisation

Patients were randomised (1:1) to receive either 555MBq (15mCi) Sm-153 PHYP together with 40mg triamcinolone hexacetonide (Lederspan, Lederle) or 40mg triamcinolone hexacetonide alone. The randomisation codes were contained in sealed envelopes and were held by the principal radiopharmacist. On patient entry, the radiopharmacist was notified and a date set for treatment between 2 and 3 weeks following randomisation. This was to allow, if necessary, the delivery of Sm-153 from St. Louis.

6.2.2.2 Outcome measures

Primary outcome was judged from a symptom score (2 = pain and/or stiffness in the knee interfering with mobility; 1= pain and/or stiffness in the knee; 0 = no pain or stiffness in the knee) registered at a consultation before injection and at 3 monthly intervals after treatment. The ‘end-point’ of the study for ‘interim’ assessment of symptom score is 12 months post-injection though follow-up is planned for 2 years.

Two secondary outcome measures have been included as part of the study. Firstly, a measure of medial and lateral compartment tibiofemoral joint space was taken from weight-bearing anteroposterior knee radiographs with a ruler and taken as an indication of articular cartilage thickness. A repeat evaluation of cartilage thickness from further radiographs is planned 3-5 years following radiation synovectomy. Joint space measurement data are not included in this
report. Secondly, synovial lining volume, taken as an index of synovial lining thickness (Clunie et al. 1995b), has been calculated using contrast-enhanced MR techniques. Studies have been undertaken in some patients both before, and 3 months after, treatment and will continue as part of the randomised protocol. Data are not included here because of small patient numbers.

6.2.2.3 Sample size

Assuming that the difference in response between the 2 groups is small (5-10%), then to detect a significant difference in symptom scores (at the 5% level) between the two groups with 80% power, over 200 patients would be required in each randomisation arm. However, it is likely that many patients will be referred because of a failure to respond to previous intra-articular glucocorticoids. This implies that the chance of a large difference in response between the two groups is maximised at the recruitment stage. Although previous failure to glucocorticoids is not a requirement of study entry, there is some evidence that this referral pattern occurs (see Chapter 4.4.2).

Furthermore, there is some evidence of a difference between response to previous glucocorticoid injection and subsequent Sm-153 PHYP treatment (see Chapter 4.3.3.1). Therefore, it may be hypothesised, that the number of patients required to allow a significant difference in outcome to be observed, without losing power, may not be large.

Accurate predictions of outcome, in order to guide precise estimates of sample size, cannot be made, owing to a lack of Sm-153 PHYP and a paucity of intra-articular glucocorticoid outcome data. It was proposed therefore that 30-50 patients should be recruited to each treatment arm.

6.2.2.4 Unblinding from double-blind protocol

Patients were unblinded if scoring a symptom score of 2 at any of the follow-up appointments. This was taken as indication of a relapse and of termination of follow-up within the double-blind protocol. A score of 1 or 0 at any of the 3 month follow-up visits was considered a response. An unchanged score of 2 at the first follow-up visit (3 months) was taken as an indication of no substantial effect from the treatment and was judged a treatment failure. This was considered equivalent to a relapse and patients were consequently
unblinded. All unblinded patients who originally received glucocorticoid only, were offered Sm-153 PHYP. Some early data from these (open) treatments are included in the analysis of relapse in Chapter 4.

6.2.2.5 Statistical analysis

A response, indicated by a symptom score of either 0 or 1, or relapse, indicated by a symptom score of 2 was noted at 3 monthly intervals. The significance of the difference in response of the 2 treatment groups at each 3 month follow-up was tested using a $\chi^2$ analysis with Yates' correction.

To establish whether factors present at the time of treatment may have had an influence on outcome in the 2 groups, the significance of the difference between the 2 groups in disease duration, minimum tibiofemoral joint space, baseline RAI and ESR (see 6.2.3) and knee flexion range were tested using the Mann Whitney U test (Statworks™ v1.2 on an Apple-Macintosh computer). Multivariate analysis was not undertaken owing to the small number of cases.

6.2.3 Additional clinical assessment

In addition to measures of outcome (see 6.2.2.1), measures of general disease activity were made at baseline and 3 monthly intervals. These included a Ritchie Articular Index (RAI) [Ritchie et al. 1968] and ESR. Together with alteration of type or increase or decrease in dosage of systemic therapy, changes in RAI and ESR were taken to reflect the variation in articular inflammatory activity.

6.2.4 Treatment procedure

Sm-153 was supplied by University of Missouri Research Reactor, Columbia, MO. Particulate hydroxyapatite was supplied by CeraMed Corp., Lakewood, CO. For Sm-153 PHYP treatments, particles were labelled according to methods previously reported (see Chapter 1.5.4.1). The study pharmaceutical (see 6.2.2.1) was prepared in a total 2mls volume in a 5ml syringe attached to a 3-way tap. The syringe, transparent parts of the 3-way tap and delivery port were obscured by coloured tape to maintain blinding.

Knee injection procedure was identical throughout. Patients' skin and subcutaneous tissues were anaesthetised with 1% lignocaine around the
anterolateral aspect of the knee. Any effusion was aspirated through a 21-gauge needle. The injection apparatus was agitated to ensure particles remained in suspension before attaching the 3-way tap injection port to the needle in situ. After injecting the study pharmaceutical, the injection apparatus was flushed, with a total of 4.5mls 1% saline drawn from a reservoir syringe attached to the side port, in 3 separate injections before the needle was withdrawn. The knee was passively flexed twice. Saline flush was substituted for lignocaine, used in the open study, as there had been no indication of procedure-related pain or synovitis flare immediately following Sm-153 PHYP injection.

The prepared activity and activity remaining in the injection apparatus was measured using a Capintec CRC-120 radioisotope calibrator using a calibration factor of 230. Where necessary, the activity was corrected for decay from the time of injection.

Patients’ knees were immobilised in a semi-rigid splint and elevated for a period of 4 hours after injection. Patients were then allowed home by private vehicle, advised to ‘rest as much as possible off their feet for the remainder of the day’ but to resume their normal activities on the following day.
6.3 Results

6.3.1 Baseline characteristics

Clinical details of the 20 patients are shown in Table 6.1. Disease prevalence and systemic therapy in patients treated with Sm-153 PHYP and glucocorticoid and glucocorticoid alone, are shown in Table 6.2. There was no significant difference in disease duration, RAI, knee flexion range, ESR or minimum tibiofemoral joint space between the 2 groups.

Table 6.1 Clinical details at baseline of the first 20 patients entered in the randomised study of intra-articular Sm-153 PHYP and triamcinolone hexacetonide vs. triamcinolone hexacetonide alone, for chronic knee synovitis

<table>
<thead>
<tr>
<th>Patient number/age/sex</th>
<th>Diagnosis* /duration (years)</th>
<th>*NSAID therapy</th>
<th>*SAARD therapy</th>
<th>Minimum joint space (mm)</th>
<th>Knee flexion/FFC</th>
<th>^RAI</th>
<th>^ESR (mm/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/41/m PsA/16</td>
<td>y y</td>
<td>-</td>
<td>115°</td>
<td>11</td>
<td>58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/75/f RA/8</td>
<td>y y</td>
<td>3</td>
<td>100°</td>
<td>19</td>
<td>51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/30/m PsA/6</td>
<td>y y</td>
<td>N/A</td>
<td>115°</td>
<td>18</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4/72/m UC/8</td>
<td>n y</td>
<td>-</td>
<td>120°</td>
<td>5</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5/34/f RA/3</td>
<td>y y</td>
<td>4</td>
<td>120°</td>
<td>9</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6/51/f RA/13</td>
<td>y y</td>
<td>-</td>
<td>95°</td>
<td>16</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7/64/m RA/13</td>
<td>y y</td>
<td>2.5</td>
<td>130°</td>
<td>3</td>
<td>86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8/51/f UC/6</td>
<td>n y</td>
<td>2</td>
<td>105°</td>
<td>2</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9/33/m PAN/2</td>
<td>n y</td>
<td>-</td>
<td>90°</td>
<td>4</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10/38/m PsA/12</td>
<td>y y</td>
<td>-</td>
<td>110°</td>
<td>17</td>
<td>54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11/39/m RA/25</td>
<td>y n</td>
<td>3</td>
<td>115°</td>
<td>4</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12/33/f RA/22</td>
<td>y y</td>
<td>3</td>
<td>120°</td>
<td>10</td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13/30/f RA/6</td>
<td>n n</td>
<td>3</td>
<td>130°</td>
<td>1</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14/54/f RA/5</td>
<td>y y</td>
<td>-</td>
<td>145°</td>
<td>4</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15/41/f RA/8</td>
<td>y y</td>
<td>2</td>
<td>125°</td>
<td>28</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16/43/m EARA/4</td>
<td>y n</td>
<td>3</td>
<td>145°</td>
<td>3</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17/54/f AS/32</td>
<td>n y</td>
<td>4</td>
<td>130°</td>
<td>5</td>
<td>90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18/64/m RA/5</td>
<td>y y</td>
<td>2</td>
<td>125°</td>
<td>5</td>
<td>81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19/51/f RA/12</td>
<td>y n</td>
<td>2</td>
<td>95°/5</td>
<td>8</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20/62/m RA/6</td>
<td>y y</td>
<td>3</td>
<td>120°</td>
<td>32</td>
<td>64</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*RA = rheumatoid arthritis; PsA = psoriatic arthritis; UC = ulcerative colitis (associated with seronegative chronic synovitis); EARA = enteral acquired reactive arthritis; AS = ankylosing spondylitis

*NSAID = non-steroidal anti-inflammatory drug

*SAARD = slow-acting anti-rheumatic drug

^Taken from either medial or lateral tibiofemoral compartment; N/A=not available

^Fixed flexion contracture

^RAI = Ritchie Articular Index

^ESR = Erythrocyte Sedimentation Rate; N/A=not available
Table 6.2 Baseline characteristics compared for patients in the 2 treatment groups

<table>
<thead>
<tr>
<th>Characteristic at baseline</th>
<th>Clinical details of patients treated with:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sm-153 PHYP + triamcinolone hexacetonide</td>
<td>Triamcinolone hexacetonide alone</td>
</tr>
<tr>
<td>Diagnosis (no. patients):</td>
<td>RA 5 7</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Seronegative spondyloarthropathy 5 3</td>
<td>3</td>
</tr>
<tr>
<td>No. receiving SAARD</td>
<td>8 7</td>
<td></td>
</tr>
<tr>
<td>No. receiving NSAID</td>
<td>7 8</td>
<td></td>
</tr>
<tr>
<td>Mean (± s.d.) disease duration (years)</td>
<td>11.4 ± 9.0 9.0 ± 7.0</td>
<td>*p=0.48</td>
</tr>
<tr>
<td>Mean (± s.d.) RAI</td>
<td>11 ± 10 9 ± 8</td>
<td>*p=0.49</td>
</tr>
<tr>
<td>Mean (± s.d.) knee flexion range (degrees)</td>
<td>123 ± 15 112 ± 15</td>
<td>*p=0.45</td>
</tr>
<tr>
<td>Mean (± s.d.) ESR</td>
<td>43 ± 28 50 ± 28</td>
<td>*p=0.47</td>
</tr>
<tr>
<td>Mean (± s.d.) minimum tibiofemoral joint space (mm)</td>
<td>3.2 ± 0.4 2.6 ± 0.7</td>
<td>*p=0.21</td>
</tr>
</tbody>
</table>

*Mann Whitney U

6.3.2 Primary outcome: change in symptom score

There was no obvious difference in the pattern of change in symptom scores in the year following injection in the 2 treatment groups, although at each of the 3 month assessments the number of patients with a symptom score of 2 was consistently higher in patients who had received glucocorticoid only (Fig. 6.1). There was no significant difference between those with and without symptoms or indeed further, between those maintaining a response and those relapsing at any of the 3 month follow-up assessments using a $\chi^2$ analysis (Table 6.3).
6.3.3 Changes in systemic therapy post-treatment

During the blinded follow-up period changes in systemic therapy were made on 11 occasions in 9 patients (Table 6.4). Changes were made by the patient's rheumatologist. There were 4 changes in 3 patients who received Sm-153 PHYP and glucocorticoid and 7 changes in 6 patients who received glucocorticoid only. In those who received glucocorticoid only, a decrease or cessation of systemic therapy accounted for 3 therapy changes and an increase in dose or commencement of a drug accounted for 4 therapy changes. Of the changes in therapy made in patients receiving Sm-153 PHYP and glucocorticoid, only 1 was influenced by a change in indices of disease activity (patient no. 20). In this case, an increase in disease activity. Two changes (both in patient no. 6) were made as a consequence of the patient deciding to change their own medication and one change (patient no. 12) was made owing to the development of unacceptable side effects. All patients remained on the same NSAID dose throughout the follow-up period.

A statistical comparison of the number of changes of therapy in the 2 groups was not made owing to the wide variation in types and dosages of administered drug therapy and the relatively small number of cases.
A statistical comparison of the number of changes of therapy in the 2 groups was not made owing to the wide variation in types and dosages of administered drug therapy and the relatively small number of cases.

**Table 6.3** Comparison of outcome (symptom score) at 3 monthly intervals following treatment

<table>
<thead>
<tr>
<th>Months following injection</th>
<th>$\chi^2$ No symptoms (symptom score 0 vs. 1 or 2)</th>
<th>$\chi^2$ Response (symptom score 0 or 1 vs. 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>0.07</td>
<td>0.24</td>
</tr>
<tr>
<td>*ns</td>
<td></td>
<td>p&gt;0.2</td>
</tr>
<tr>
<td>6</td>
<td>0.00</td>
<td>1.88</td>
</tr>
<tr>
<td>*ns</td>
<td></td>
<td>p&lt;0.2</td>
</tr>
<tr>
<td>9</td>
<td>0.00</td>
<td>1.88</td>
</tr>
<tr>
<td>*ns</td>
<td></td>
<td>p&lt;0.2</td>
</tr>
<tr>
<td>12</td>
<td>0.00</td>
<td>1.88</td>
</tr>
<tr>
<td>*ns</td>
<td></td>
<td>p&lt;0.2</td>
</tr>
</tbody>
</table>

*ns = not significant
<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Treatment group</th>
<th>Time of change in therapy</th>
<th>Change in therapy</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Glucocorticoid</td>
<td>0-3 months</td>
<td>Methotrexate 7.5-10mg weekly</td>
<td>Poor disease control suggested by indices of joint and systemic inflammation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3-6 months</td>
<td>Methotrexate 10-15mg weekly</td>
<td>Inadequate disease control indicated by indices of joint and systemic inflammation</td>
</tr>
<tr>
<td>6</td>
<td>Sm-153 PHYP+ glucocorticoid</td>
<td>0-3 months</td>
<td>Hydroxychloroquine 250-125mg daily</td>
<td>Patient initiated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3-6 months</td>
<td>Hydroxychloroquine 125-250mg daily</td>
<td>Dose correction</td>
</tr>
<tr>
<td>7</td>
<td>Glucocorticoid</td>
<td>3-6 months</td>
<td>Sulphasalazine 3-2g daily</td>
<td>Disease controlled indicated by indices of joint and systemic inflammation</td>
</tr>
<tr>
<td>8</td>
<td>Glucocorticoid</td>
<td>0-3 months</td>
<td>Sulphasalazine stopped</td>
<td>Patient initiated (&quot;felt well&quot;)</td>
</tr>
<tr>
<td>9</td>
<td>Glucocorticoid</td>
<td>0-3 months</td>
<td>Cyclophosphamide 150-100mg daily. Prednisolone 15-12.5mg daily</td>
<td>Disease controlled. Overall decrease in drug therapy desired</td>
</tr>
<tr>
<td>11</td>
<td>Glucocorticoid</td>
<td>0-3 months</td>
<td>Methylprednisolone 125mg im stat. Gold 50mg weekly started</td>
<td>General disease flare indicated by indices of joint and systemic inflammation</td>
</tr>
<tr>
<td>12</td>
<td>Sm-153 PHYP+ glucocorticoid</td>
<td>3-6 months</td>
<td>Gold stopped and hydroxychloroquine started</td>
<td>No change in indices of disease activity. Gold rash occurred</td>
</tr>
<tr>
<td>19</td>
<td>Glucocorticoid</td>
<td>0-3 months</td>
<td>Sulphasalazine started</td>
<td>General disease flare indicated by indices of joint and systemic inflammation</td>
</tr>
<tr>
<td>20</td>
<td>Sm-153 PHYP+ glucocorticoid</td>
<td>6-9 months</td>
<td>Methotrexate 17.5-20mg weekly. Hydroxychloroquine stopped. Methylprednisolone 125mg im stat.</td>
<td>Inadequate disease control indicated by indices of joint and systemic inflammation</td>
</tr>
</tbody>
</table>
6.4 Discussion

The decision to perform an interim analysis was mainly guided by the results obtained with pHYP (see Chapter 5). With the improved physical characteristics of pHYP (see Chapter 5.4.1-2), it is likely that this particle preparation, rather than the larger size range - PHYP, will be developed commercially. Therefore, there would have been an argument for terminating the study and moving on to study pHYP, had there been a highly significant difference in outcome either way in an interim analysis.

Limited conclusions may be drawn from the results in view of the small number of cases analysed, however, there appears to be a positive although non-significant effect on symptoms of Sm-153 PHYP and glucocorticoid over glucocorticoid alone suggested by the $\chi^2$ analysis. Importantly, there is no obvious deleterious effect of Sm-153 PHYP injection compared to glucocorticoid either from symptom score analysis or from an appraisal of changes in systemic therapy.

The decision to continue study recruitment and to continue using PHYP was made on the basis of this interim analysis and was influenced by the likelihood that pHYP would be unavailable for a number of months. With 60+ patients, the chances of detecting a significant result either way are far greater than with 20 (see 6.2.2.3). It may be worth speculating briefly, that if the proportions of patients experiencing a response after 12 months remain the same in the 2 treatment groups after 60 patients have been recruited, then the $\chi^2$ value would be 8.4 and $p<0.01$. This would suggest a significant desirable effect of Sm-153 PHYP over triamcinolone hexacetonide.

Furthermore, no large randomised controlled study comparing any radiopharmaceutical to triamcinolone hexacetonide has been completed. Data from large prospective studies are needed to enable a clarification of the role of Sm-153 PHYP and other types of radiopharmaceuticals in managing chronic synovitis. As a result patient recruitment efforts have doubled and further personnel have been employed to continue the study.
Chapter 7

The variation and extent of radiation synovectomy practice in Europe
7.1 Introduction

Radiation synovectomy has been practised for over 30 years. It is generally understood, however, that there is a geographical variation in the prevalence of the technique. It is practised mainly in Europe, Australia and Canada but not in the United States, as no radiopharmaceuticals are licensed for routine clinical radiation synovectomy by the Food and Drug Administration (FDA). There are, however, no published data on the extent and frequency of this technique.

Since the introduction of the particulate radiopharmaceutical Dy-165 FHMA (Sledge et al. 1984), consistently lower levels of extra-articular activity accumulation have been demonstrated both with it and with other particulate radiopharmaceuticals compared to radiocolloids (see Chapter 1.4.1.2.2 and 1.4.4.2). The risks from activity escape from an injected joint have been one of the major concerns of the Food and Drug Administration (FDA) [C. Sledge, personal communication]. The particulate radiopharmaceuticals provide a theoretically safer treatment than radiocolloids and a good reason why there has been renewed interest in radiation synovectomy (Deutsch et al. 1993).

With the emergence of ‘new’ particulate agents and questioning of the ‘old’ colloidal ones, it is an appropriate time to appraise the practice of radiation synovectomy. An appropriate initial step is to document prevalence and variation in radiation synovectomy practice and the use of radiation synovectomy agents. This has been undertaken by means of a postal questionnaire in Europe. Historically, the extent of practice of radiation synovectomy in Europe is thought to exceed the extent of practice elsewhere in the world.
7.2 Materials and Methods

7.2.1 Target population

Members of the European Association of Nuclear Medicine (EANM) were sent a postal questionnaire together with an explanatory letter written in English. Addresses registered with the EANM and available on a database were used. Recipients were asked to liaise with colleagues in the department/clinic where they worked and return 1 questionnaire from each department/clinic.

7.2.2 The questionnaire

Members were asked about radiation synovectomy practice from 1991 to 1993 inclusive. The questionnaire was written on 1 A4 sheet and consisted of 3 main sections: (1) the frequency of radiation synovectomy; (2) patients and joints treated; (3) radiopharmaceuticals used. If the member or their department did not undertake radiation synovectomy in any of the 3 years, they were asked to return a blank questionnaire.

The questions in section 1 were: ‘How many injections have you/your department given in 1991-3? How many patients was this? Do you give more than one injection to the same joint? If yes, what is the maximum given? Which joint(s) was this?’ In section 2 the questions were: ‘Which joints do you/have you injected (answer yes/no), knee, ankle, wrist, elbow, fingers, others? What % of total joint injected are ..knee, ..ankle, ..wrist, ..elbow, ..fingers, ..other? Do you/your department treat patients with (yes/no and % of total injections) ..rheumatoid arthritis, ..psoriatic arthritis, ..reactive arthritis, ..osteoarthritis, ..gout/CPPD, ..haemophilic arthritis, ..other?’ In section 3 the questions were: ‘Do you/your department use (yes/no) ..Y-90 silicate colloid, ..Y-90 citrate colloid, ..Y-90 resin colloid, .. Y-90 Fe hydrate colloid, ..Er-169, ..Dy-165 FHMA, ..P-32, ..Au-198?, ..Re-186, ..other? Do you use one agent specifically for, ..one joint (yes/no), .. diagnosis?’

7.2.3 Glucocorticoid co-administration enquiry

All positive respondents from European centres were asked in a second letter about glucocorticoid co-injection. The questions were: ‘Do you routinely
co-inject glucocorticoid (yes/no)? If yes, which glucocorticoid do you inject?
Also, if questions had been left unanswered, positive respondents were specifically asked about the relevant practice.

7.2.4 Repeat sampling of non-responder population

To assess whether the respondents (positive and negative) were representative of the whole sample, non-respondents from 6 different European countries were contacted by letter in their native language. The letters were sent 6 months after the original questionnaire. Fifteen members from each of 6 countries were chosen at random from the EANM members’ database. Four of the countries were chosen because they had the lowest response rate of all European countries and 2 because they had the greatest number of recorded members.
7.3 Results

7.3.1 Questionnaire response

Questionnaires were sent to 2306 European members of the EANM (including members in Israel and Turkey). There were initially replies from 458 different centres/institutions in 29 European countries. From the estimate of centres using radiopharmaceuticals in Europe (according to EANM records), this represented an initial response rate of 458/1004 (46%). Of the responding centres, 112/458 (24%) in 23 different countries practised radiation synovectomy over the period 1991-1993.

7.3.2 Non-responders

The replies from original non-responders was 32/90 (36%) and included replies from all 6 countries sampled (Belgium 5, France 9, Germany 6, Spain 4, Turkey 2, Italy 6). Of these responders, 11/28 (39%) did not receive the original questionnaire, 4/28 (14%) worked in centres from which a colleague had already returned the questionnaire. Of the responding centres, 7/32 (22%) in 4 countries (Belgium, France, Germany, Spain) practised radiation synovectomy. Data from repeat sampling were pooled with that from the original questionnaire. All subsequent results refer to the pooled data.

7.3.3 Distribution of centres

In total there were 119 centres in 23 countries where radiation synovectomy was practised during 1991-3 (Fig. 7.1). Using the membership database as an indication of the number of centres in each country administering radiopharmaceuticals, the percentage of centres in each country where radiation synovectomy was undertaken, was estimated (Fig. 7.2).

7.3.4 Patients and diseases

In the 3 years, 8578 patients were treated with one or more radiation synovectomy injection (Fig. 7.3). RA was the most prevalent disease in treated patients (71%) and was the only disease in patients treated in 22/119 (19%) centres (Fig. 7.4). There were 4 centres where treatment was exclusively given to haemophilic arthritis patients, though this only represented 18% of all haemophilic arthritis patients treated.
Fig. 7.1 Distribution of centres practising radiation synovectomy in Europe (1991-3)
7.3.5 Injections and joints

There were 13450 separate joint injections in the 8578 patients (Fig. 7.3). Repeat joint injections or multiple joint injections in the same patient were not uncommon. There were 65/119 (55%) centres where joint injections had been repeated and in 21/65 (32%) centres this had been done 3 or more times in at least one patient. The most frequently re-treated joint was the knee (65% centres), although finger, wrist, elbow, shoulder and ankle joints were also reported to have been re-treated. Multiple joint injections had been given in the same patient in 60/119 (50%) centres. Patients had received from 2-6 joint injections, though in one centre up to 13 different joints had been injected in a single patient. The most frequently treated joints were knee (46%) and finger joints (20%). The frequency of treatment of all joints is shown in Fig. 7.5.
Fig. 7.3  Number of radiation synovectomy injections and patients treated in Europe (1991-3)
Fig. 7.4 Prevalence of disease in patients treated by radiation synovectomy in Europe (1991-3). *Abbreviations: AS=ankylosing spondylitis; JCA=juvenile chronic arthritis; PVNS=pigmented villonodular synovitis
Fig. 7.5 The frequency of joint treatment by radiation synovectomy in Europe (1991-3)
7.3.6 Radiopharmaceutical use

Over the 3 years, 8 different radiation synovectomy radiopharmaceuticals were in clinical use (Fig. 7.6). The most widely used were the Y-90 colloids in 112/119 (94%) centres with Y-90 citrate colloid in 73/119 centres. Y-90 resin colloid was not in use.

![Fig. 7.6 The use of various radiopharmaceuticals in the European centres practising radiation synovectomy (n=119)]

In centres where more than one type of joint was treated, different radiopharmaceuticals were often used. The joint specificity of use of a radiopharmaceutical was greatest for Y-90 colloids and Er-169. These were employed for the treatment of knees (64% joints treated) and finger joints (76%) respectively (Table 7.1).

7.3.7 Glucocorticoid co-administration

From the 119 positive respondents, 60 (50%) were subsequently asked about glucocorticoid co-injection. 36/60 (60%) centres who reported routinely co-injecting glucocorticoid. Triamcinolone hexacetonide was most widely used (46% of centres), though a number of different glucocorticoids were
employed (Fig. 7.7). Physicians in 11 (18%) centres reported undertaking glucocorticoid co-injection for the large joints only (shoulder, hip and knee).

Table 7.1 The application of the most frequently used radiopharmaceuticals in appendicular joint injection (Europe 1991-3)

<table>
<thead>
<tr>
<th>Joint</th>
<th>Number of centres using radiopharmaceutical for joint injection (Total number = 119)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Y-90 colloids</td>
</tr>
<tr>
<td>Shoulder</td>
<td>12</td>
</tr>
<tr>
<td>Elbow</td>
<td>19</td>
</tr>
<tr>
<td>Wrist</td>
<td>5</td>
</tr>
<tr>
<td>Finger joints</td>
<td>2</td>
</tr>
<tr>
<td>Hip</td>
<td>6</td>
</tr>
<tr>
<td>Knee</td>
<td>100</td>
</tr>
<tr>
<td>Ankle</td>
<td>12</td>
</tr>
</tbody>
</table>

Fig. 7.7  The most widely used intra-articular glucocorticoid preparations for co-injection with radiation synovectomy radiopharmaceuticals
7.4 Discussion

7.4.1 Sampling methods

Choice of target population was based on maximising the chance of contacting workers responsible for handling radiopharmaceuticals. Access to the member database of a European organisation such as the EANM made this choice of method practicable. Although it is likely in some countries that rheumatologists or orthopaedic surgeons administer the joint injections, contacting sufficient numbers may have proved prohibitively difficult. This latter route of investigation would have succeeded only through contacting members of a rheumatological society in each country. Based on 1994 figures from the European League Against Rheumatism (EULAR), this would have implied the need to contact 10618 people in 35 countries (F. Wyss, executive secretary EULAR, personal communication). It was reasoned that if EANM members did not have the required data, they would be in a position to pass-on the questionnaire to those who had. This occurred in a number of instances.

7.4.2 Response rate and validity of survey

The percentage of positive replies from the secondary questionnaire was comparable to the positive reply rate from the original (22% vs 24% respectively) indicating that it was unlikely that response to the original questionnaire was significantly biased in favour of either users or non-users of radiation synovectomy. Whether all centres practising radiation synovectomy replied to the questionnaires will have depended on a number of factors including poor quality of postal services. This problem may have been reflected by the number of members who did not receive the original questionnaire but subsequently responded (39%) and the low response to repeat sampling.

It is possible that this survey will have underestimated the number of centres employing radiation synovectomy and thus the number of injections administered and patients treated. How large is the underestimate? This is difficult to answer without confirming firstly, the number of centres practising radiation synovectomy though not in any way connected to the EANM, and secondly, whether the questionnaire was received by all those to whom it was sent. Because of the logistical difficulties involved, this was not undertaken.
7.4.3 Extent of radiation synovectomy practice

Radiation synovectomy is widely practised throughout Europe. As all EANM members received the questionnaire, we also received replies from around the world. Other countries where radiation synovectomy is practised are: Australia, Canada, South Africa and Mexico. Taken together, 71% of the European centres in our survey practising radiation synovectomy were concentrated in 6 countries (Belgium, France, Germany, Holland, Spain and UK). This is likely to reflect a number of factors including differences in population density and resource distribution. We did not survey variations in the expense of the technique nor in logistical factors influencing acquisition of a radiopharmaceutical, however, it is likely that these too are important factors in determining radiation synovectomy practice in some European countries.

7.4.4 Prevalence of treated disease

Over 71% of patients treated had rheumatoid arthritis. The management of rheumatoid synovitis will vary according to the availability of drugs, drug monitoring and surgery. Where these resources are scarce, radiation synovectomy may be perceived as a useful treatment.

Approximately 13% of patients treated had seronegative inflammatory arthritides (ankylosing spondylitis, psoriatic and reactive arthritis). Classically, these patients more frequently exhibit an oligoarticular pattern of arthritis (Wright and Moll 1976) compared to patients with rheumatoid arthritis, whose arthropathy is commonly polyarticular. Thus the impact of local joint therapy such as glucocorticoid injection or radiation synovectomy, may be greater in this group of patients than in patients with polyarticular rheumatoid arthritis. Although seronegative arthritis is less common than rheumatoid arthritis, the survey raises the question that radiation synovectomy may be an under used resource in the management of seronegative arthritis patients.

7.4.5 Joint injections

The survey has shown that almost all appendicular synovial joints may be treated with radiopharmaceuticals, though the variation in technique e.g. the use of an image intensifier for hip injection, is not known. There are few, if any, studies which document the success of intra-articular radiopharmaceutical
injection of the smaller joints. In theory, there is no reason why radiation synovectomy cannot be considered for any synovial joint.

Almost exclusively finger joints were injected with Er-169 colloid. Er-169 was also occasionally used for injecting other joints. The results from Er-169 colloid finger joint injection have been compared to those from intra-articular glucocorticoid in 3 studies (Delbarre et al. 1977, Gumpel et al. 1979, Ruotsi et al. 1979). Two of the 3 studies (Gumpel et al. 1979, Ruotsi et al. 1979) showed no benefit of Er-169 over glucocorticoid, therefore, leaving reasonable doubt as to whether Er-169 is more efficacious than intra-articular glucocorticoid injection for small finger joints. Despite these findings and the absence of subsequent published data suggesting efficacy over glucocorticoid, it appears Er-169 is still widely employed for finger joint treatment.

7.4.6 Radiopharmaceutical use

A relatively large number of radiopharmaceuticals are used throughout Europe. Use may partially be reflected by ease of supply and expense. There has, however, been a recent recognition of the need to rationalise radiopharmaceutical use by comparison of clinical outcome in randomised studies (Edmonds et al. 1994).

Knowledge of the $\beta^-$ penetration of various radionuclides has led to the rationale that average $\beta^-$ penetration is tailored to joint size, thus Y-90 preparations are used for larger joints, Er-169 for small joints and Re-186 for joints of intermediate size (Harbert 1977). There seems to be broad agreement with this approach in the European practice of radiation synovectomy. It has been intimated that these recommendations may be based on imprecise assumptions about the distribution of inflammatory tissue within the joints (Deutsch et al. 1993). This discussion is developed further in Chapter 8.3.
Chapter 8

General discussion
8.1 Discussion outline

Firstly, by drawing on data obtained from both in vitro and in vivo studies reported in Chapters 2, 4, 5 and 6, the suitability of Sm-153 PHYP for clinical use is discussed in the light of practical details relating to its production and handling, its physical and radiochemical characteristics, and its biodistribution and safety characteristics (see 8.2). Secondly, the evidence for efficacy is reviewed, and factors which may critically influence outcome are discussed (see 8.3). Lastly, the broader issue of the potential role of Sm-153 PHYP and other radiopharmaceuticals in the management of inflammatory arthritis is discussed (see 8.4).

8.2 Suitability of Sm-153 PHYP as a therapeutic tool

The factors important for the development of a suitable radiopharmaceutical for radiation synovectomy have been reviewed (see Chapter 1.4).

8.2.1 Production and supply of Sm-153 PHYP

The production process of Sm-153 and radiochemical properties of the radionuclide (see Chapter 1.5 and Appendix A) appear to satisfy the major criteria which are important in determining the clinical utility of a radiopharmaceutical (see Chapter 1.4.5-6).

Samarium is readily available and Sm-153 easily and efficiently produced in the reactor with virtually no radionuclidic impurities (see Appendix A). It is an important practical point that minimal decay of a potential therapeutic radionuclide occurs before it has been shipped from its point of production to the treatment centre. With long half-life radionuclides such as Y-90, this is not a problem. Y-90 produced in England is regularly shipped to Australia for radiation synovectomy (F. Lovegrove, personal communication). On the other hand, the half-life of Dy-165 (2.4 hours) requires either, that a much greater activity than is needed for injection is shipped to allow for decay, or, that patients to be treated with Dy-165 FHMA travel to a centre near to the production site (Deutsch et al. 1993). Neither option is desirable. The first constitutes a hazard, the second may entail long periods of travel for arthritic,
and therefore relatively poorly ambulant patients (S. Shortkroff, personal communication).

The execution of the clinical studies reported above demonstrates that Sm-153 can be shipped easily and safely, without substantial decay, to treatment centres distant from its production site. Commonly, 11,100MBq (300mCi) Sm-153 were produced from 0.5mg Sm-152 in St Louis, Missouri and shipped for treatment planned 5 days later in London. By then, decay to 1850MBq (50mCi) had occurred. This was enough activity for 3 patient treatments based on 555MBq (15mCi) per treatment. There were no reported events which may have constituted a health risk to people handling the radionuclide.

8.2.2 Radiochemical properties of Sm-153 PHYP
8.2.2.1 In vitro stability

The binding of Sm-153 to PHYP in vitro is easily and efficiently achieved in the radiopharmacy and appears to be stable in vitro under conditions likely to be encountered at the time of injection (see Chapter 2.4.1-2).

The only other particulate radiopharmaceuticals in current use with which to compare Sm-153 PHYP are Dy-165 FHMA (Sledge et al. 1977, Sledge et al. 1984) and Dy-165 hydroxymacroaggregates (Edmonds et al. 1994). The production methods required to obtain a predictable size of FHMA are complicated and labelling methods laborious (Hnatowich et al. 1978). Moreover, Dy-165 FHMA binding may be unstable under acidic conditions and even at physiological pH (McLaren et al. 1990).

The stability of binding has important implications for the potential utility of Sm-153 PHYP. It is likely to be possible to complete the preparation of the radiopharmaceutical at the site of radionuclide production and supply labelled-PHYP to the treatment centre with little, if any, Sm-153 dissociation from PHYP. In this way, the hazards from handling activity are minimised and preparation steps are simplified, saving time for the radiopharmacist.

8.2.2.2 In vivo stability

There is evidence to suggest from biodistribution studies that Sm-153 remains bound to PHYP both in joints and extra-articular tissues (see Chapter 4.4.3). Unbound (‘free’) Sm-153 escapes from injected joints (Chinol et al. 1976).
1993), therefore stable Sm-153 PHYP binding until total activity decay is highly desirable. The absence of extra-articular activity accumulation in many patients illustrates that this often occurs. Stable binding is less desirable for Sm-153 PHYP which may accumulate and remain in the pulmonary vascular bed (see Chapter 4.4.3) because prolonged irradiation of the lung may occur. However, doses are small and there are no obvious deleterious clinical consequences in the short-term. Because an important characteristic of Sm-153 PHYP is that little activity escapes from the injected joint (see Chapter 4.3.6.3), stable binding in vivo is an advantageous characteristic.

8.2.3 Biodistribution of Sm-153 PHYP

The extent and pattern of both intra-articular and extra-articular biodistribution of a radiopharmaceutical has critical implications for its potential safety and efficacy as a radiation synovectomy tool.

8.2.3.1 Radionuclide $\beta^-$ energy: unwanted effects

There was no evidence from these studies to suggest either peri-articular or extra-articular tissue radiation damage from Sm-153. It has been observed that peri-articular radiation burns appear to occur almost exclusively with the more penetrative $\beta^-$-emitters such as Y-90 and Au-198 (Peters and Lee 1994). In the Sm-153 PHYP studies, there was some extra-articular escape of activity in a minority of patients (see Chapter 4.4.4) which obviously increases the risk to damage of healthy tissue. Lower levels of activity escape are recognised following immobilisation after knee injection with radiocolloid (Reksen et al. 1976, Williams et al. 1981); however, these measures involve either rigid knee splinting or hospital admission. The ability of patients to return home only a few hours after knee injection with Sm-153 PHYP injection with no subsequent extra-articular escape of activity suggests that precautionary, uncomfortable and logistically complicated measures to immobilise the knee after injection may not be necessary with Sm-153 PHYP treatment.

In terms of % injected activity, escape of activity from an injected joint is lower with Sm-153 PHYP than with any other studied radiopharmaceutical. The most critical tissues which do receive unwanted irradiation are
lymphocytes and other cells in the regional lymph tissue, and hyaline cartilage in the injected joint.

8.2.3.1.1 Lymphocyte irradiation

Following Sm-153 PHYP knee injection, regional lymph node dose is similar to the dose from Dy-165 after Dy-165 FHMA knee injection (Zalutsky et al. 1986) but appears to be much smaller than the dose observed for either Y-90 (Oka et al. 1971) or Au-198 (Virkkunen et al. 1967) radiocolloids.

A detailed discussion of the structural and functional cytogenetic abnormalities detected in lymphocytes, presumably irradiated either within synovium or regional lymph tissue, is beyond the scope of this thesis. The reader is referred to other reviews (Stevenson 1973, Tawn and Holdsworth 1992). However, as discussed in Chapter 1.4.1.2.2, the consequence of cytogenetic lymphocyte abnormalities following radiation synovectomy have not generally been recognised through an excess incidence of lymphoproliferative disorders although leukaemia has been reported anecdotally (Lipton and Messner 1991). Nevertheless, lymphocyte cytogenetic analysis following Sm-153 PHYP knee synovectomy will be undertaken as part of the further investigation of this radiopharmaceutical.

8.2.3.1.2 Articular cartilage irradiation

The preservation of articular cartilage integrity is important in preventing and arresting the decline in structure and function in a joint which is chronically inflamed (see Fig. 1.2 and Chapter 1.2.2.2.2). The effects of Sm-153 on hyaline cartilage have not been studied here. There is, however, evidence for an effect of Y-90 on the hyaline cartilage of injected joints (reviewed in Chapter 1.4.1.2.1). By virtue of its shorter $\beta^-$ range and half-life, intra-articular Sm-153 will result in less cartilage irradiation than Y-90. Moreover, once engulfed by the synovial lining, there is likely to be even less cartilage irradiation from Sm-153 because in chronic synovitis the synovial lining and articular cartilage will be separated further from one another by any effusion (see comparison of Fig. 1.1 and Fig. 1.2). Ultimately, long-term follow-up of patients within the randomised study may provide data on
whether the rate of cartilage degradation is arrested or increased relative to glucocorticoid in these patients with chronic synovitis.

8.2.3.2  Radionuclide $\gamma$ energy

Therapeutic radionuclides with a $\gamma$ decay component have conventionally been thought undesirable as they confer no therapeutic benefit but add to the risk (see Chapter 1.4.2). In these experiments the 103keV $\gamma$ decay of Sm-153 has proved extremely useful in determining in vivo distribution of Sm-153 PHYP and estimating doses from extra-articular activity (see Chapter 4.3.7 and 4.4.1.4) with little dose contribution from its own tissue deposition. In patients where organ uptake was detected, the $\gamma$ integral dose was estimated to contribute only 2.3-4.5%, 6.4-15.2% and 0.3-1.1% of total organ-absorbed dose for lung, liver and lymph nodes respectively.

8.2.3.3  Malignancy risk

There are recommendations for employing Y-90 radiocolloids for radiation synovectomy only in those over 50 (Dolphin 1973), where the risk of malignancy, calculated from radiation dose estimates from radiocolloid data, is not significantly greater than that of the age-matched population. Radiation escape from knees injected with Sm-153 PHYP, however, appears to be far less than with radiocolloids.

A crude estimate of malignancy risk as a result of knee synovectomy with Sm-153 PHYP can be made using data derived from these studies. A notational whole body dose can be calculated on the assumption of uniform radiation distribution of the radionuclide throughout the body tissues. This is a useful concept but a most unlikely event. Thus, for a patient with RA, assuming the mean dose delivered to synovium to be 50Gy (see Appendix Biii), and the average mass of synovial tissue to be 0.13kg (Clunie et al. 1995b), whole-body dose may be calculated as $50 \times 0.13/70 = 93$mgGy (9.3rad) for a 70kg adult. The dose from extra-articular radiation (see Table 4.7) when calculated to be uniformly distributed throughout the body is virtually negligible compared to the dose absorbed by the synovium. Even assuming maximum possible extra-articular escape of activity from the knee (calculated from data in the third column of Table 4.7), this dose may
contribute at most 1mGy (0.1rad). Risk coefficients for cancer incidence as a result of exposure to low energy linear energy transfer (LET) radiation have been compiled from studies of irradiated ankylosing spondylitis patients and Japanese survivors from the bombing of Nagasaki (reviewed in Dolphin 1973). For low dose LET radiation, the coefficient is 30 cancers per million man-rads. Therefore, the risk in the patients treated with Sm-153 PHYP may be calculated as $30 \times 9.4 = 282$ cancers per million of population. This risk can be compared to the age-specific risk of developing cancer over a 20 year period (Table 8.1).

Table 8.1  Cancer registration in England and Wales for men and women. (Data compiled by Cancer Research Campaign, 1988. Personal communication)

<table>
<thead>
<tr>
<th>Age</th>
<th>Age-specific cancer registration per million of population over the subsequent 20 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>men</td>
</tr>
<tr>
<td>20</td>
<td>900</td>
</tr>
<tr>
<td>40</td>
<td>11500</td>
</tr>
<tr>
<td>60</td>
<td>25900</td>
</tr>
</tbody>
</table>

A comparison of data shows that the risk of malignancy from Sm-153 PHYP knee synovectomy is small compared to the naturally-occurring risk of malignancy with perhaps the exception of young males (262 per million vs. 900 per million respectively). According to these data, Sm-153 PHYP treatment in a man aged 20 might therefore increase the risk of cancer from 0.09% to 0.12% over the subsequent 20 years. Malignancy risks from radiation will be higher in children owing to the smaller incidence of naturally-occurring cancer; therefore it would be wise to avoid radiation synovectomy in paediatric patients with a good disease prognosis.

How are these data summarised? Despite over 30 years of use, a significant excess incidence of malignancy in patients treated with intra-articular radiopharmaceuticals has not been reported. Importantly, there has been no report of peri-articular connective tissue, bone or cartilage neoplasia.
Additionally, treatment with Sm-153 PHYP is associated with less risk of malignancy than has been calculated for either Au-198 or Y-90 radiocolloids (Dolphin 1973).

An appraisal of risk would not be complete without emphasising the context in which many patients with chronic arthritis are treated. Chronic arthritis is associated with reduced mortality compared to the general population, considerable morbidity and the risk of severe life-threatening side-effects from SAARD treatment. The risks from radiation treatment must be considered in the light of these factors for any individual patient.

8.2.3.4 Effects of PHYP in vivo
8.2.3.4.1 Intra-articular effects

Owing to factors which affect the distribution of a particle within a chronically-inflamed joint, intra-articular distribution of particulate hydroxyapatite is likely to be an important influence on the efficacy of Sm-153 PHYP (see 8.3.2.2). It is unknown whether there are significant deleterious effects of PHYP in vivo but is important to consider any possible effects both within the joint and in extra-articular tissue.

In inflamed rabbit synovium, PHYP may cause a transient increase in synovial lining cell infiltrate but is degraded by 6-8 weeks after injection (Shortkroff et al. 1992). The suggestion of invoking or aggravating inflammation in the short-term led us to adopt a protocol whereby a long-acting glucocorticoid accompanied Sm-153 PHYP injection in all cases. Invoking an inflammatory response in the short-term does not necessarily preclude the use of the radiopharmaceutical if a therapeutic response is anticipated in the long-term. This is analogous to a transient synovitis flare invoked by some intra-articular glucocorticoid preparations in patients who subsequently respond to the injection. Synovial tissue recovered from a patient treated with Sm-153 PHYP showed no evidence of local aggregation of monocytes or of granulomata formation (see Chapter 5). Although the patient had clinically relapsed there was no convincing evidence that the relapse was related to the Sm-153 PHYP treatment.

The effect of hydroxyapatite on cells in chronically-inflamed synovium and on hyaline cartilage in inflamed joints in vivo is unknown. There is some
evidence that hydroxyapatite crystals are mitogenic for fibroblasts in vitro (Cheung et al. 1984, Cheung and McCarty 1985). This effect is dependent on endocytosis of the crystals rather than on extracellular solubilisation of the crystals with release of calcium. The mitogenic effect is accompanied by stromelysin and collagenase induction and secretion in vitro (McCarthy et al. 1992). Synovial fluid hydroxyapatite-containing microparticles have been associated with a severe destructive form of shoulder arthropathy (Halverson et al. 1981). Often the appearance of hydroxyapatite crystals in the joint is associated with extensive soft-tissue osteochondromatosis within the joint (Garancis et al. 1981). Whether this is a single condition is unclear; however, the clinical picture of synovitis, hydroxyapatite crystals in the fluid, periarticular calcification and bone and cartilage destruction is known as 'Milwaukee shoulder'. Whether it is caused by the primary abnormality of synovium or other intra-articular tissue or whether the hydroxyapatite crystals, either released from bone or formed owing to unknown factors, themselves invoke and sustain a chronic inflammatory arthropathy is essentially unknown.

In support of the notion that hydroxyapatite crystals are arthritogenic, hydroxyapatite-coated joint prostheses have been linked to persistent synovial inflammation with multinucleated giant cells (Nilsson et al. 1994). However, the exposure to the crystals may need to be persistent to be pro-inflammatory, because hydroxyapatite formation in the soft-tissues of a normal joint induced by a calcergen is accompanied by aggregation of macrophages and granulation tissue formation, which ultimately resolves completely with no cartilage degeneration (McClure 1984). Only when repeated exposure to the calcergen occurs is there persistent inflammation with fibroblast proliferation and synovial adherence to articular cartilage.

Thus, there may be conditions under which repeated or persistent exposure to hydroxyapatite crystals may result in aggravation of chronic inflammation and cartilage degradation. Careful follow-up studies of patients treated with Sm-153 PHYP will be needed to determine whether a significant deleterious effect on articular cartilage occurs in the long-term from a single intra-articular injection. Follow-up of patients treated within both the open and randomised protocols suggests that there is a beneficial effect in terms of reducing indices of chronic synovial inflammation. The possible deleterious
effects of PHYP on cartilage must be weighed against those which may occur as a result of an alternative procedure such as surgical synovectomy or long-acting glucocorticoid injection. Ultimately the risk of cartilage damage from Sm-153 PHYP injection, or indeed any local therapy, must be considered in comparison to the risk involved with leaving synovial inflammation unchecked with continuing production of cartilage and bone matrix degrading proteases and cytokines.

8.2.3.4.2 Extra-articular effects

No local clinical sequelae were identified as a result of extra-articular PHYP accumulation. It is likely that PHYP accumulating in lymph tissue will be phagacytosed by mononuclear cells. The fate of PHYP in the intra-vascular compartment is unclear, though from imaging studies it appears to remain bound to activity for some days before it is degraded. Theoretical concerns over triggering pneumonitis or thrombosis as a result of particles lodging in the pulmonary vasculature have been unsubstantiated by clinical observations. It is important to remain aware of this possible serious consequence of PHYP escape into blood vessels at the site of injection.

In summary, stable binding of PHYP to Sm-153 and slow rates of PHYP degradation in the joint or removal from it, appear important in reducing extra-articular activity escape.

8.3 Sm-153 PHYP efficacy
8.3.1 Evidence for efficacy

The median response from a single injection of Sm-153 PHYP combined with glucocorticoid was 9 months (see Chapter 4.3.3). The effect of the radiopharmaceutical cannot be considered independently of the effect of the glucocorticoid; however, all patients had had a particularly poor response to glucocorticoid previously. Even allowing for differences in injection technique and procedure, the data suggest that there may be a positive effect of Sm-153 PHYP.

There is also some evidence to suggest that a long-term clinical response may be achievable for up to a year compared to intra-articular triamcinolone.
hexacetonide injection (see Chapter 4.3.3 and Chapter 6.3.2). The completion of the study is important to confirm these interim data.

8.3.2 Factors affecting efficacy

8.3.2.1 Clinical features at baseline

The open study results suggest that patients with active polyarticular synovitis evaluated by an RAI at the time of treatment, may have a poor outcome (ESR in these patients was invariably high and not associated with relapse at 3 months but was associated with relapse by 9 months). These observations are in accordance with results of Y-90 colloid synovectomy, where response duration is recognised to be reduced in patients with high compared with low general disease activity at the time of treatment (Winfield and Gumpel 1979, Schütte and Rau 1983). These data may be explained if the treatment is more effective for patients with oligoarticular rather than polyarticular synovitis. This is reasoned from the observation that all relapers at 3 months had multiple joint disease and therefore were more likely to have a high RAI. The non-relapers at 3 months mainly consisted of patients with seronegative spondylarthropathy and oligoarticular RA. Because fewer joints were affected by disease these patients naturally had a low RAI at baseline, though many did have a high ESR. The significance of high ESR may not have become apparent until 9-12 months following treatment when many of the oligoarticular arthritis patients began to relapse. It has frequently been suggested that radiation synovectomy may be of more potential benefit in patients with oligoarthritis than in those with polyarthritis (Ansell et al. 1963, Delbarre et al. 1973, Gumpel and Roles 1975) although studies comparing efficacy in the 2 groups have not been undertaken. Our interpretation of these data may have implications for the relative efficacy of Sm-153 PHYP in patients with multiple and single joint disease.

8.3.2.2 Intra-articular Sm-153 PHYP distribution

Distribution of the particulate radiopharmaceutical uniformly to the synovial surface may be of crucial importance in view of the $\beta^-$ range of Sm-153 (see above). In this study there is evidence to suggest that poor intra-articular distribution of PHYP is associated with relapse in the short-term.
This does not seem highly dependent on PHYP size as a relationship between mean particle size and intra-articular activity distribution was not detected. The degree of knee flexion obtainable at the time of treatment is clearly associated with activity distribution and thus particle distribution within the joint. It is unclear whether poor knee flexion directly influences particle distribution or whether there are common factors which affect both the range of joint mobility and access of particles to all the various knee compartments. As patients with a poor range of knee flexion at baseline might be expected to benefit less from treatment, careful assessment of knee mobility is recommended when considering Sm-153 PHYP radiation synovectomy. These data may have implications for the application of all particulate radiopharmaceuticals.

8.3.2.3 Radionuclide β⁺ energy

Because the nature and distribution of the biological target within the synovial lining is essentially unknown, there is no easy way of predicting the minimum effective penetration required of a β⁺ emitting radionuclide. For example, although it is implicit in the arguments of those who advocate tailoring β⁺ penetration to joint size (reviewed by Harbert 1987 and Newman 1993), there is no evidence to suggest that the whole synovial subintima requires irradiation to obtain a clinical response.

The maximum β⁺ penetration of Sm-153 in soft-tissue is 2.5mm. This is less than the maximum penetration for either Y-90 (10.8mm) or Dy-165 (5.6mm), the radionuclides most commonly used (see Chapter 7). Is this penetration sufficient to result in an effective therapeutic response when injected into the inflamed knee? There are grounds to consider that it might be.

Firstly, one must consider that there is no simple, linear relationship between maximum particle penetration and the energy absorbed by tissue (Wessels and Griffith 1986, Johnson and Yanch 1991). Those few particles emitted with the maximum energy and thus potential to penetrate to the maximum depth, progressively lose their energy through successive interactions within the tissue. These particles are relatively few and some do not scatter away from the source. Often the ones that do have little energy at
the end of their penetration range and the absorbed dose is very small. Thus the range of particles which are likely to provide a useful therapeutic response (therapeutic range) will be less than the maximum range.

A useful measure of the therapeutic range of a radionuclide in a tissue, is given by its $x_{90}$ value. This is defined as the distance from the source in which 90% of the absorbed dose is imparted to the tissues (Husak et al. 1973, Simpkin and Mackie 1990, Johnson and Yanch 1991). The calculated therapeutic ranges of various radionuclides are shown in Table 1.3. It can be seen that for each radionuclide, the $x_{90}$ is far less than the maximum range, and overall, that the relationship between maximum and therapeutic penetration is not linear. It should be noted that the therapeutic ranges of Dy-165 and Sm-153 are in fact quite similar.

Secondly, in order effectively kill cells in the chronically-inflamed synovial lining, most of the dose will need to be delivered to surface synovial areas, within 1-2mm of the synovial intima (see Chapter 3). However, a radiopharmaceutical distributed evenly over the synovial lining including the surface which lines its folds and clefts, will irradiate (the apparently) deeper subintimal tissue. Strong $\beta^+$ penetration, such as that from Y-90, may, therefore, be unnecessary.

Thirdly, Sm-153 PHYP is engulfed by the synovial lining (Chinol et al. 1993, Shortkroff et al. 1992 and see Chapter 5.4.3). By virtue of its relatively long half-life (46.3 hours), this suggests that the radiopharmaceutical will continue to irradiate cells from within the synovium after the PHYP has been engulfed. It should be noted that because of the short Dy-165 half-life (2.3 hours), the use of Dy-165 FHMA almost certainly requires that the delivery of the majority of absorbed dose to the synovial lining must occur from activity at the synovial surface i.e. before the FHMA is engulfed by the synovium.

In summary, when compared to other radionuclides (see Table 1.3) or their radiopharmaceutical preparations, there are reasons for expecting that the relatively weakly $\beta^+$ penetrating radionuclide Sm-153, when combined with PHYP/pHYP, will result in sufficient irradiation of the synovial lining.
8.4 The role of radiation synovectomy

Ideally, for any joint or disease treated by radiopharmaceutical injection, the physician should know the likelihood and duration of symptomatic response and long-term effect on articular cartilage associated with injection of the radiopharmaceutical compared to both intra-articular long-acting glucocorticoid injection and surgical (arthroscopic and open) synovectomy. On the positive side, despite conclusions from a meta-analysis of Y-90 colloid studies (Jones 1993), there are no convincing data that categorically dismiss the notion of radiation synovectomy as an effective therapy. From the results of the European survey (see Chapter 7), there is clearly a perceived need for intra-articular medical therapy of chronic synovitis; however, as discussed in Chapter 1, there are few large carefully-controlled trials providing efficacy data on which to confidently base practice. It is likely that this has led to uncertainty as to how best to apply the technique of radiation synovectomy. This uncertainty may be reflected by the wide variation of practice identified throughout Europe (Clunie and Ell 1995. Also, see Chapter 7). By publishing the survey it was hoped that some discussion might ensue amongst physicians practising radiation synovectomy in Europe. It was hoped that, as a consequence, a core of interest might develop, thus providing the opportunity for further, large-scale research efforts within Europe. Only when physicians launch a concerted and collaborative scientific approach to establishing large long-term comparative studies will the most appropriate role of radiation synovectomy be identified with certainty.

8.5 Future studies

The most important unanswered question is whether radiopharmaceuticals are more efficacious, safer and less deleterious in the long-term than intra-articular glucocorticoid injection? If so, which? The interim analysis from a study comparing triamcinolone to Sm-153 PHYP and triamcinolone are presented in Chapter 6. A protocol has been developed, and funding established, for a large multicentre European study comparing the efficacy of Sm-153 pHYP and intra-articular glucocorticoid with osmic acid injection and arthroscopic synovectomy. New open-label studies using Sm-153 pHYP have
begun in Holland. Ultimately this radiopharmaceutical will be compared to long-acting intra-articular glucocorticoid.

It should be noted that there may be reasons in addition to safety and efficacy for considering both different radiopharmaceuticals for radiation synovectomy and alternative synovectomy techniques for management of chronic synovitis (see Chapter 7.4.3-6). For example, expense, resource allocation, referral patterns and the logistics of monitoring chronic disease are all important considerations. However, a balanced view of practice should include these considerations, not be dictated by them. Ultimately, the safest, most effective treatment, is the best one for the patient. From this standpoint, the argument for prioritising the identification of relative efficacy of Sm-153 PHYP compared to other therapies, is persuasive.

This work has sought to establish the practicability and safety of a new radiopharmaceutical, Sm-153 PHYP, for use in patients with chronic synovitis. Studies have focused on identifying factors which may, in future, guide the most appropriate application of this and other radiopharmaceuticals in treating chronic synovitis.
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Appendices
Appendix A

(i) Production details for Sm-153

Research Material:
Target: ~0.5mg of 99% enriched Sm-152 (as nitrate)
Irradiation time: ~30 hours
Neutron flux: ~8E13 (thermal) and ~2E12 (epithermal)
Theoretical specific activity: ~850mCi/mg (31.45GBq/mg) Sm
Sm-153 production: ~70% of theoretical
Specific activity: ~600mCi/mg (22.2GBq/mg) Sm
Actual activity: ~300mCi (11.1GBq) for each 0.5mg run (at calibration)

Radionuclide impurities

<table>
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<th>Isotope</th>
<th>Half-life</th>
<th>At end of irradiation (mCi Sm-153)*</th>
</tr>
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<tbody>
<tr>
<td>Sm-145</td>
<td>340 days</td>
<td>Not detectable</td>
</tr>
<tr>
<td>Sm-151</td>
<td>93 years</td>
<td>&lt;4μCi</td>
</tr>
<tr>
<td>Eu-155</td>
<td>4.8 years</td>
<td>&lt;2μCi</td>
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<tr>
<td>Eu-154</td>
<td>8.2 years</td>
<td>&lt;10μCi</td>
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<tr>
<td>Eu-152</td>
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<td>&lt;0.06μCi</td>
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<tr>
<td>Eu-156</td>
<td>15.2 years</td>
<td>&lt;50μCi</td>
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</tbody>
</table>

*1Ci = 3.7 × 10^4 MBq
(ii) Cross-sectional diagram of reactor used for production of Sm-153

Samarium-152 nitrate for irradiation is placed within the graphite reflector which surrounds the reactor core. This position is very accessible and samples can be inserted or withdrawn at any time.
(iii) Physical and decay characteristics of Sm-153

Half-life: 46.29 hours
Experimental mass defect: -72.569MeV
Nuclear spin; parity: 5/2; +
(n$_{th}$, γ) cross section: 334.5E-24cm$^2$

### $\beta^-$ energies

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<th>$\beta^-$ decay</th>
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<th>Mean energy (keV)</th>
<th>Probability of decay</th>
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### $\gamma$ energies

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Appendix B

(i) Extra-articular organ absorbed dose in 6 patients in whom extra-articular activity was identified

<table>
<thead>
<tr>
<th>Patient/ injected activity</th>
<th>Organ/region</th>
<th>Cumulative activity (MBq hours)*</th>
<th>$\beta^*$ integral dose (mJ)</th>
<th>$\gamma$ integral dose (mJ)*</th>
<th>Total organ dose (mGy)$^*$</th>
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<tr>
<td>1/198</td>
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<td>37.072</td>
<td>5.686</td>
<td>5.888</td>
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<td>106</td>
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<td>8.726</td>
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<td>28135</td>
<td>4315</td>
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<td>10/422</td>
<td>whole body</td>
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<td>3.992</td>
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</table>

*Data calculated up to 168 hours (3.6 Sm-153 half-lives) after injection

*From equation 4.22 (see Chapter 4.2.8). Assumptions: $a=0.2^*, 0.15^*$ and $0.02^*$ (m$^2$) for lung, liver and regional lymph nodes respectively; $r=1, 1$ and 0.5 (m) for lung, liver and regional lymph nodes respectively; whole-body $\gamma$ integral dose is based on total absorption of incident $\gamma$ energy ($E_{\gamma}^*$) where $E_{\gamma}^*$ is $1/18E_{\gamma}$ (i.e. all $\gamma$ energy from emissions 20° or less from a cranio-caudal axis through the knee in a cranial direction)

^For synovial absorbed dose estimates, refer to Appendix B(ii)

^Patient scanned only up to 72 hours post-injection
Extra-articular organ absorbed dose in 7 patients where no extra-articular activity uptake was identified. For all assumptions made, see footnote to Table in Appendix Bi.

<table>
<thead>
<tr>
<th>Patient/injected activity</th>
<th>Organ/region</th>
<th>Cumulative activity (MBq hours)</th>
<th>$\beta$ integral dose (mJ)</th>
<th>$\gamma$ integral dose (mJ)</th>
<th>Total organ dose (mGy)</th>
</tr>
</thead>
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<tr>
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</table>
(iii) Synovial tissue absorbed dose estimation

Assumptions made in calculation:
- All injected activity is evenly distributed and immediately engulfed by surface of synovium. Absorbed energy will realistically lie between minimum (β− energy absorption = 0.5 x total β− energy i.e. activity retained at or on synovial surface) and maximum (total β− energy is absorbed i.e. activity immediately engulfed by synovial lining to a depth equivalent to the maximum β− penetration).
- No photon energy is absorbed by the synovium.
- Density of pathological synovial tissue equivalent to 1mg/cm³. No excretion of activity.
- Mass of pathological synovial tissue range 50-300g. The estimate is based on unpublished observations (J. Edwards, personal communication) and magnetic resonance synovial volume quantification data (Clunie et al. 1995b).

(a) Assuming half β− energy absorbed

1MeV = 1.6 × 10⁻¹³ J

Mean life = \(1.44 \times t_{0.5} = 1.44 \times 46.3\) hours (for Sm-153)

For 1Bq the time-activity integral \((A_h) = 1Bq \times 1.44 \times 46.3 \times 60 \times 60\) seconds

\[A_h = 2.40 \times 10^5\text{Bq}\]

Energy released (and fully absorbed) = \(n_iE_i = 0.5 \times 0.26629\text{MeV}\)

\[n_iE_i = 2.13 \times 10^{-14}\text{J/Bq}\]

Absorbed dose = \(A_h \times n_iE_i \times 1/m\) (where \(m\) is the mass of the synovium)

Substituting for \(m\) (0.05 to 0.3kg)

*Minimum absorbed dose ranges from \(1.02 \times 10^{-7}\) to \(1.7 \times 10^{-8}\) Gy/Bq*
(b) Assuming total $\beta^-$ energy absorbed

Energy released (and fully absorbed) = $n_iE_i = 0.26629\text{MeV}$

$$n_iE_i = 4.26 \times 10^{-14} \text{J/Bq}$$

Substituting for $m$ (0.05 to 0.3kg)

*Minimum absorbed dose ranges from $2.05 \times 10^{-7}$ to $3.4 \times 10^{-8} \text{Gy/Bq}$*

**Estimated patient synovial lining absorbed dose ranges**

The ranges of estimated absorbed doses for patients studied are tabulated below. Dose estimates are included for extremes of synovial mass estimation and maximum and minimum injected activity recorded (see Table 4.2).

<table>
<thead>
<tr>
<th>Estimated synovial mass (kg)</th>
<th>Injected activity (MBq)</th>
<th>Estimated absorbed synovial dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Minimum</td>
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<tr>
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<td>682</td>
<td>12</td>
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</tbody>
</table>
Errata

2. Section 1.1.2. Para 3. Line 1. Page 24: '..phagacytose..' should read '..phagocytose..'
3. Section 1.3.2.2.4.1. Para 2. Line 3. Page 43: '..(Menkes 1979)...' should read '...(Menkes 1979a)..' 
4. Section 1.3.2.2.4.1. Para 5. Line 2. Page 43: '..multiple..' should read '..major..'
5. Section 1.4.4.1. Para 1. Line 4. Page 52: '..data hase..' should read '.. data have..'
7. Section 1.4.7.4.3. Para 1. Line 5. Page 63: '..(Menkes et al. 1972)...' should read '...(Delbarre et al. 1977)..'
8. Legend to Table 4.6. Page 118: '..v(Cawb-Cawb(bg))-(Cpwb-Cpwb(bg))..' should read '..v(Cawb-Cawb(bg))x(Cpwb-Cpwb(bg))..'
9. Legend to Table 4.6. Page 118: '..v(Cak-Cak(bg))-(Cpk-Cpk(bg))..' should read '..v(Cak-Cak(bg))x(Cpk-Cpk(bg))..'
10. Section 6.2.2.1. Para 1. Line 4. Page 149: '..principle..' should read '..principal..'
11. Section 6.3.3. Page 156: Paragraph 2 is erroneously repeated.
12. Section 7.4.3. Para 1. Line 2. Page 172: '..members received..' should read '..members sent..' 
13. Section 8.2.3.3. Para 2. Line 3. Page 179: '..notational..' should read '..notional..' 
14. Section 8.2.3.3. Para 3. Line 1. Page 180: '..262..' should read '..282..' 
15. Section 8.2.3.3. Para 5. Line 3. Page 181: '..reduced mortality..' should read '..increased mortality..' 
17. Reference section. Page 193. Line 32: '..autologenous..' should read '..autologous..' 

Corrigenda

1. The entry in the fourth cell of the last row of Table 1.1, Page 37, is incorrect. Evidence for prevention of cartilage and bone damage in patients treated with cyclophosphamide is provided in, Cooperating clinics committee of the American Rheumatism Association. N Engl J Med 1970; 283(17): 883-9

2. The term '..fixed flexion contracture..' written in the legend of Table 4.1, Page 107, and abbreviated to FFC in the table, is inaccurate. The clinical feature is more accurately referred to as '..fixed loss of extension..'