

Treatment of pigmented villonodular synovitis of the knee with yttrium-90 silicate: prospective evaluations by arthroscopy, histology, and ^{99m}Tc pertechnetate uptake measurements

M J A M FRANSSEN,¹ A M Th BOERBOOMS,¹ R P KARTHAUS,² W C A M BUIJS,³ AND L B A VAN DE PUTTE¹

From the Departments of ¹Rheumatology, ²Orthopaedics, and ³Nuclear Medicine, University Hospital, Nijmegen, The Netherlands

SUMMARY The diffuse form of pigmented villonodular synovitis of eight knee joints of eight patients was treated by intra-articular injection of 185 MBq yttrium-90 silicate (^{90}Y). Six patients had a recurrence of disease after one or two surgical synovectomies. After treatment with ^{90}Y once or twice four knees showed clinical improvement with an accompanying decrease of the inflammatory activity as measured by the technetium-99m pertechnetate ($^{99m}\text{TcO}_4^-$) uptake ratio and the severity of the diseased synovial tissue. Arthroscopy was performed before and six months after each ^{90}Y treatment. The ratio of $^{99m}\text{TcO}_4^-$ uptake in the inflamed compared with the normal knee joint correlated well with the macroscopical grading of pigmented villonodular synovitis. In all cases areas of persistent synovitis were found after the ^{90}Y injection and this was confirmed both by histological examination and $^{99m}\text{TcO}_4^-$ uptake measurements. Biopsy specimens taken from the diseased synovial areas showed histologically mostly less prominent and less numerous villi. The cartilage damage was slightly increased in only two cases. No radiological deterioration was found during follow up (mean 24 months, range 12–41). No complications of the radiosynoviortheses were noted.

Pigmented villonodular synovitis is an uncommon proliferative synovial disease usually presenting as chronic monoarthritis of the knee joint.^{1–3} It occurs in either a diffuse or a localised form.⁴ The aetiology and pathogenesis are unknown. Localised or diffuse pigmented villonodular synovitis may be treated by surgical excision of the disease tissue. Recurrence after operation is common, however, especially in the diffuse form.⁵ In view of this high recurrence rate after surgical synovectomy, synovial irradiation by yttrium-90 silicate (^{90}Y) intra-articularly has been attempted and encouraging results reported.^{6–9} The effect of treatment with ^{90}Y has never been evaluated by arthroscopy with histological examination of biopsy specimens and objective measurement of the inflammation with technetium-99m pertechnetate

($^{99m}\text{TcO}_4^-$) uptake before injection and during follow up.

We report clinical and laboratory data, including $^{99m}\text{TcO}_4^-$ uptake measurements of the knee joint, radiology, arthroscopy with synovial biopsy, and follow up data, in a prospective study on radiosynoviorthesis with ^{90}Y intra-articularly in eight patients with pigmented villonodular synovitis of the knee joint.

Patients and methods

PATIENTS

Eight patients seen at the University Hospital, Nijmegen within a five year period (1983–1987) were included. All patients had monoarticular arthritis of the knee with histologically proved pigmented villonodular synovitis. A medial meniscectomy had been performed in three of the eight patients. In six patients one or two surgical synovectomies had previously been done (Table 1). All patients gave their informed consent.

Accepted for publication 5 April 1989.

Correspondence to Dr M J A M Franssen, Department of Rheumatology, Academic Hospital Nijmegen, PO Box 9101, 6500 HB Nijmegen, The Netherlands.

Table 1 Clinical characteristics of the patients

Patient No	Age at onset (years)	Sex	Interval between onset of symptoms and diagnosis (years)	Clinical presentation (P/S)*	Menisectomy (n)	Surgical synovectomy (n)
1	21	F	4	+/+†	1	2
2	15	M	2	-/+	0	1
3	34	M	1	+/+	1	1
4	18	M	4	+/+	0	0
5	18	M	10	+/+	0	2
6	18	M	4	+/+	0	2
7	53	M	0.5	+/+	1	0
8	18	M	0.2	-/+	0	1

*P=pain; S=swelling.

†+=present; -=absent.

METHODS

All patients were questioned and examined before the ^{90}Y injection by one of two authors (MF, AB). Variables used were tenderness, swelling, warmth, and effusion, which were graded in arbitrary categories of 0–2 (0=absent; 1=moderate; 2=severe). Results of treatment on the clinical variables were arbitrary classified in four grades: 0=no improvement; 1=only one of the four variables improved; 2=two of the four variables improved; 3=three of the four variables improved; 4=all four variables improved. Each radiosynoviorthesis was preceded by a $^{99\text{m}}\text{TcO}_4$ uptake measurement of the joint and arthroscopy with synovial biopsy. An x ray examination of the knee joint was made and scored according to Larsen.¹⁰ Haemoglobin and erythrocyte sedimentation rates were assessed before treatment and at follow up. Six months after the ^{90}Y injection clinical,

laboratory, $^{99\text{m}}\text{TcO}_4$ uptake measurement, radiological and arthroscopic evaluation were repeated. The patient's assessment of the response to treatment was recorded according to an arbitrary three point scale of effect (0=absent; 1=moderate; 2=good to excellent). If no remission had been obtained a second injection of 185 MBq ^{90}Y was given and evaluated in the same way. Thereafter, clinical and radiological evaluations were performed every six and 12 months respectively. After arthroscopy the ^{90}Y injection was delayed for six weeks to prevent possible leakage of ^{90}Y from the synovial lesions caused by arthroscopy and biopsy.

The arthroscopic findings of pigmented villonodular synovitis were classified in arbitrary categories of increasing disease areas from 0 to 4 (0=none; 1=only a few; 2=moderate number; 3=many; 4=diffuse). The cartilage was graded from 0 to 4

Table 2 Results of clinical evaluation and radiological assessment before (B) and after the first (Y_1) and second (Y_2) ^{90}Y injections

Patient No	Follow up after the last ^{90}Y injection (months)	Patient evaluation* of response		Response†		Radiological score‡		
		Y_1	Y_2	Y_1	Y_2	B	Y_1	Y_2
1	12	0	0	1	0	2	2	2
2	30	0	1	0	4	1	1	1
3	41	0		0		3	3	
4	12	2		4		0	0	
5	41	0		0		1	1	
6	32	1		2		0	0	
7	12	1	2	3	4	2	2	2
8	12	0	0	0	1	1	1	1

*Patients evaluation of response: 0=absent; 1=moderate; 2=good to excellent.

†Improvement of clinical variables (swelling, tenderness, warmth, and effusion): 0=none; 1=slight; 2=moderate; 3=good; 4=excellent.

‡Larsen score.¹⁰

(0=normal; 1=fibrillations; 2=some erosions; 3=moderate number of erosions; 4=many erosions).

^{99m}Tc PERTECHNETATE UPTAKE MEASUREMENTS

Joint inflammation was measured by ^{99m}TcO₄ uptake.¹¹ Briefly, patients were injected with 7.4 MBq ^{99m}TcO₄⁻. After 2¾ minutes the amount of radioactivity in the knee joints was assessed by measuring the γ radiation with the knee in a fixed position using a collimated NaI scintillation crystal.¹¹ The monoarthritic nature of the disease was shown by the ^{99m}TcO₄⁻ uptake ratio of the diseased compared with the non-diseased knee joint.¹²

RADIOSYNOVIORTHESIS

The radiosynoviorthesis was performed with 185 MBq ⁹⁰Y intra-articularly.¹³

LEAKAGE OF RADIOACTIVITY

To establish leakage of radioactivity from the knee joint 48 hours after ⁹⁰Y injection the count rates due to bremsstrahlung were measured above the knee joint, the inguinal nodes, the liver, and the heart and expressed as a percentage of the amount of radioactivity in the injected knee joint. This was done with a collimated, thallium activated sodium iodide crystal (2×2 inch) in the energy range from 100 to 200 keV.

Results

Table 1 summarises the main clinical characteristics of the eight patients. The mean interval between onset of complaints and diagnosis was 3.2 years (range 0.2–10). The time between the last surgical synovectomy and the intra-articular ⁹⁰Y injection in the knee joints of the six patients was 27 months (range 7–78). All these patients had subjectively a short term effect (at most three months) of the surgical synovectomy. Of the eight patients treated with 185 MBq ⁹⁰Y intra-articularly, four received a second injection after at least six months' follow up. Table 2 shows the patients' evaluations of the response and the clinical effect.

After the first injection three patients improved subjectively or clinically, or both (Nos 4, 6, and 7). One of them (No 4) had an excellent response. After the second ⁹⁰Y injection, two patients (Nos 2 and 7) improved and clinically both showed an excellent response (Table 2). Two of the three patients with a good to excellent response subjectively and clinically (Nos 4 and 7) had refused a surgical synovectomy (Table 1). Of the four patients

who did not receive a second ⁹⁰Y injection, two (Nos 4 and 6) had an excellent or moderate clinical response and the other two (Nos 3 and 5) refused a second injection. In all patients erythrocyte sedimentation rate and haemoglobin were normal before and after injection of ⁹⁰Y. Table 3 shows the macroscopic evaluations of the synovium and cartilage condition. Initial arthroscopy showed a moderate number or many areas of pigmented villonodular synovitis. Amazingly only minimal scar tissues and adhesions or none at all were present in the cases with previous surgical synovectomy. After the first ⁹⁰Y treatment the arthroscopy fibrotic scar tissue and adhesions were found in a few or a moderate number of areas. Some of these were covered with villonodular synovium as evidence of relapse of the synovitis. The medial and lateral gutter and intercondylar notch were always involved. In contrast, the suprapatellar bursa was more fibrotic with local signs of some pigmented villonodular synovitis. The synovitis was decreased in patients Nos 2, 4, and 6 after the first ⁹⁰Y injection.

The cartilage was, except for some fibrillation in patient No 4 and some erosions in No 8, essentially unchanged during the follow up period, and the menisci were also unchanged. In patients Nos 1, 2, and 8 a second ⁹⁰Y injection was performed. The arthroscopic findings after this injection did not differ from those mentioned above. Unfortunately, arthroscopic findings in patient No 7 are missing as the procedure was not allowed because of a recent heart attack. Before ⁹⁰Y injection the synovium showed histologically prominent villi covered with several layers of proliferating synovial lining cells. In the hypervascular stroma an extensive mononuclear cell infiltrate was seen with intracellular and extracellular haemosiderin pigment and multinucleated giant cells and foam cells, and cells with pale nuclei. After ⁹⁰Y injection the most important changes in the diseased synovium were that the villi were mostly less prominent and covered with only one or two layers of synovial lining cells. In the stroma of macroscopically inactive areas extensive fibrosis was found with occasionally a giant and foam cell and haemosiderin pigment (Fig. 1).

Table 3 shows also the ^{99m}TcO₄⁻ uptake ratios before and after the first and second ⁹⁰Y injection in the knee joint. These ratios correlated well with the macroscopical grading of the synovium (p<0.01). In four patients (Nos 2, 4, 6, and 7) the ^{99m}TcO₄⁻ uptake ratio declined after the first ⁹⁰Y injection. In the four patients who received a second ⁹⁰Y injection (Nos 1, 2, 7, and 8) a ^{99m}TcO₄⁻ uptake measurement was made six months after this injection. In two of them (Nos 2 and 8) the ^{99m}TcO₄⁻ uptake ratio six months after the second ⁹⁰Y injection decreased

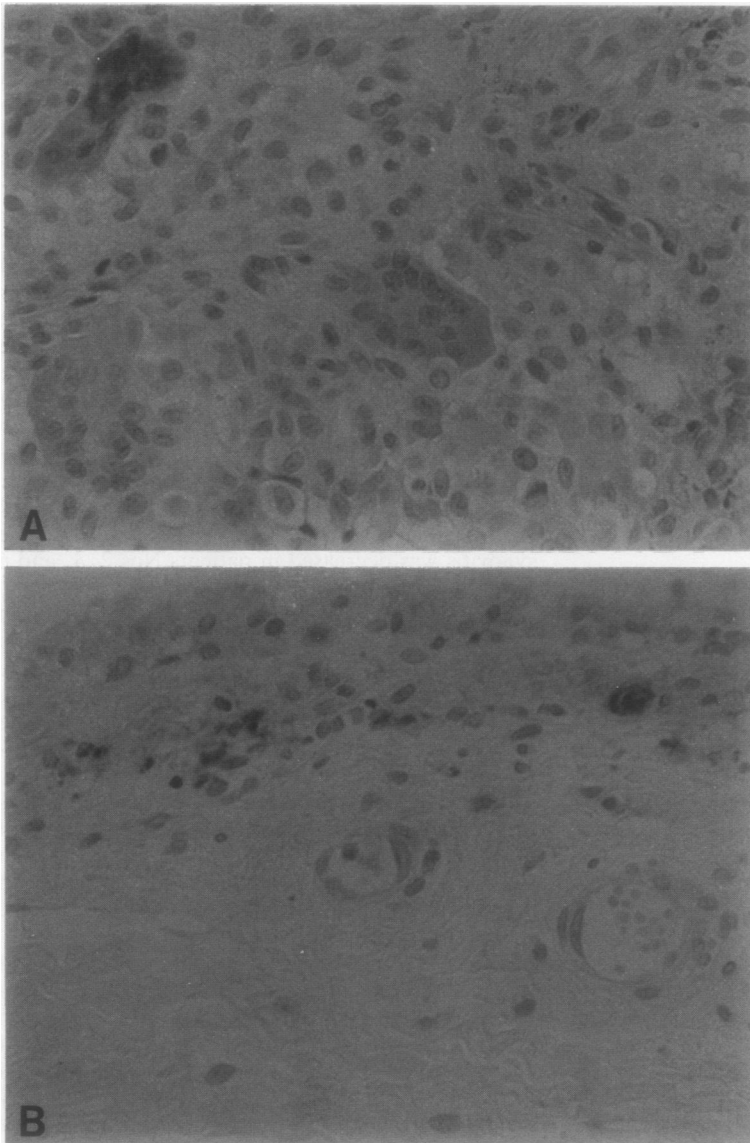


Fig. 1 *Histological picture before (A) and after (B) yttrium-90 silicate (^{90}Y) injection showing a change from a hypervascular and hypercellular stroma to a stroma with extensive fibrosis with an occasional giant and foam cell and haemosiderin pigment. (Haematoxylin and eosin.)*

in comparison with the ratio taken at six months after the first ^{90}Y injection. One patient (No 6) had nearly normal $^{99\text{m}}\text{TcO}_4^-$ uptake ratio before injection and a minimal decline after the injection. None of the other patients in whom $^{99\text{m}}\text{TcO}_4^-$ uptake ratios declined reached the normal value. The fluctuations in quantitative assessments by $^{99\text{m}}\text{TcO}_4^-$ uptake corresponded well with clinical evaluations and the macroscopic evaluation of the synovium (Tables 2 and 3).

Six patients showed radiological changes accord-

ing to Larsen¹⁰ before the ^{90}Y injection (Table 2). One patient showed erosions, cysts, and joint space narrowing (grade 3), two patients scored grade 2 according to Larsen, and three patients had slight abnormalities (grade 1). No further radiological deterioration was found during follow up (mean 24 months, range 12–41).

The count rate of activity measured above the inguinal lymph nodes, liver, and heart varied from 0.2 to 1.2% of the count rate measured above the knee joint.

Table 3 Technetium-99m pertechnetate (^{99m}TcO₄⁻) uptake measurements (inflamed/normal knee joint ratios) and the macroscopical grading of the synovium and of the cartilage in the knee joints with pigmented villonodular synovitis before (B) and after the first (Y₁) and second (Y₂) ⁹⁰Y injection

Patient No	^{99m} TcO ₄ ⁻ uptake of the inflamed/non-inflamed knee joint*			Synovium macroscopically† (0-4)			Cartilage‡ (0-4)		
	B	Y ₁	Y ₂	B	Y ₁	Y ₂	B	Y ₁	Y ₂
1	3.1	3.1	3.9	3	3	4	2	2	2
2	2.2	1.9	1.6	2	1	1	1	1	1
3	3.9	4.6		3	4		4	4	
4	2.7	1.7		3	1		0	1	
5	3.2	3.7		3	3		1	1	
6	1.2	1.0		2	1		1	1	
7	2.6	1.9	2.0	3	ND‡	ND§	2	ND§	ND§
8	2.1	2.5	2.2	3	3	3	1	1	2

*Correlation between ^{99m}TcO₄⁻ uptake and the synovium macroscopical grading in the knee joints with pigmented villonodular synovitis; p<0.01 (Spearman rank correlation, corrected for ties).

†Synovium grading of disease areas: 0=none, 1=only a few, 2=moderate number, 3=many, 4=diffuse; cartilage grading: 0=normal, 1=fibrillations, 2=some erosions, 3=moderate number of erosions, 4=many erosions.

‡Heart attack.

§Refused.

Discussion

Several authors have suggested in case reports the possibility of radiation synovectomy with ⁹⁰Y in the treatment of pigmented villonodular synovitis⁶⁻⁹ as an alternative treatment for surgical synovectomy.

The main reason for use of ⁹⁰Y in our study was the common recurrence of pigmented villonodular synovitis after surgical synovectomy.

Thirty two months (mean) after treatment with ⁹⁰Y 50% of treated knees showed a clinical improvement of the synovitis. Suppression of the synovitis was also seen from the ^{99m}TcO₄⁻ uptake ratio and by arthroscopy. In the cases with a good clinical response the ^{99m}TcO₄⁻ uptake ratios did not reach normal values and arthroscopy showed that some areas of persistent synovitis were always present. Biopsy specimens from these areas showed histological evidence of pigmented villonodular synovitis; the aspect varied, but mostly there were less prominent villi covered with less layers of the synovial lining cells than before ⁹⁰Y injection. Otherwise the histology of these villi was not clearly changed.

Reports of 11 patients with pigmented villonodular synovitis treated intra-articularly with ⁹⁰Y have been published (Table 4). Nine had a good to excellent clinical response and two a moderate clinical result. The follow up was 3-72 months (mean 31). Arthroscopic evaluation with synovial biopsy was performed in only one case.⁶ Two of the 11 cases had undergone a previous surgical synovectomy. This contrasts with our study in which six of the eight patients had undergone one or two previous surgical synovectomies. These surgical synovectomies had only a short term favourable effect or none

at all. Only two of these six patients (Nos 2 and 6) showed improvement after ⁹⁰Y injection. These two patients, before the ⁹⁰Y treatment, had a low ^{99m}TcO₄⁻ uptake ratio and macroscopically their synovitis (category 2) was less severe than in the other cases (Table 3). The remaining two patients (no surgical synovectomy) had an excellent response, but the follow up period was quite short (Table 2). These knee joints had a relatively high ^{99m}TcO₄⁻ uptake ratio and macroscopically their synovitis was category 3 before the ⁹⁰Y injection. Previous failed surgical synovectomy may be seen as a more serious condition, resulting in a lower success rate. Patients in whom ⁹⁰Y intra-articular (knee) injection had a good effect showed, apart from one patient, only minimal cartilage destruction or none at all. Previous studies reported that in rheumatoid knee joint synovitis ⁹⁰Y and ¹⁹⁸Au radiocolloids had the best results in knees with minimal radiographic evidence of bone and cartilage destruction.^{13 14}

The ^{99m}TcO₄⁻ uptake ratios correspond well with clinical and patients' evaluations in assessing the activity and response to treatment and the macroscopic synovium findings. The knee joints with most radiological damage had all undergone a meniscectomy. To what extent the meniscectomy had caused joint damage is not known. During the follow up no further radiological damage was found. As pigmented villonodular synovitis is primarily a benign disease of young people one should be aware of the potential risks of radiation exposure. To reduce leakage of radioactive material from the joint we immobilised the joint after the injection, thereby reducing the risks of potential damage.^{15 16} The

Table 4 *Review of 19 patients with pigmented villonodular synovitis treated intra-articularly with ⁹⁰Y*

Patient No	Age/sex	⁹⁰ Y injection (n)	Follow up (months)	Effect*	Synovectomy	References
1	21/F	2	12	0	+	This study
2	15/M	2	30	1	+	
3	34/M	1	48	0	+	
4	18/M	1	6	2	-	
5	18/M	1	42	0	+	
6	18/M	1	25	1	+	
7	53/M	2	6	2	-	
8	18/M	2	6	0	+	
9	29/F	1	12	2	-	8
10	48/F	2	36	2	-	
11	62/F	1	21	2	-	
12	55/M	1	3	2	-	
13	69/F	1	15	1	-	
14	26/M	1	72	2	-	7
15	45/F	1	42	2	+	6
16	19/F	2	48	2	-	9
17	21/F	1	48	2	-	
18	36/F	2	48	2	-	
19	45/F	1	48	1	+	

*0=no response; 1=moderate; 2=good/excellent.

leakage of radioactive material from the joint we immobilised the joint after the injection, thereby reducing the risks of potential damage.^{15 16} The leakage of radioactivity in our patients did not appear to be different from that in published reports.^{13 17 18} The total body radiation load due to leakage of ⁹⁰Y was calculated to be 0.8 cGy (the inguinal lymph nodes and knee joint excluded). This can be compared with the effective dose equivalent due to urography (1.8 cGy).¹⁹ Moreover, no malignancies have so far been reported after radiosynoviorthesis with ⁹⁰Y. The follow up of patients with pigmented villonodular synovitis treated intra-articularly with ⁹⁰Y, including those in other published reports, is quite short, with a mean of 31 months (ranging from three to 72 months; Table 4); therefore no conclusions can be made about the long term recurrence rate after ⁹⁰Y injections.

Conclusions

Our data suggest 1. Yttrium-90 silicate injections in the knee joints may be an alternative treatment for pigmented villonodular synovitis, especially in patients without previous surgical synovectomy. 2. It seems that intra-articular ⁹⁰Y, in cases in which a previous surgical synovectomy has failed, has the best results in knee joints with pigmented villo-

nodular synovitis disease activity. 3. There is a good correlation between the clinical improvement, ^{99m}TcO₄⁻ uptake ratios, and the severity of the diseased synovium tissue of pigmented villonodular synovitis in the knee joint. 4. Even when a clinically good result was obtained in the knee joint six months after ⁹⁰Y treatment areas of pigmented villonodular synovitis still remained.

We wish to thank Dr Kubat of the department of pathology for carrying out the microscopic examination and Marianne Verhoeven for typing the manuscript.

References

- 1 Docken W P. Pigmented villonodular synovitis: review with illustrative case reports. *Semin Arthritis Rheum* 1979; **9**: 1-22.
- 2 Myers B W, Masi A T, Feigenbaum S L. Pigmented villonodular synovitis and tenosynovitis: a clinical epidemiologic study of 166 cases and literature review. *Medicine (Baltimore)* 1980; **59**: 223-38.
- 3 Granowitz S P, D'Antonio J, Mankin H L. The pathogenesis and long-term end results of pigmented villonodular synovitis. *Clin Orthop* 1976; **114**: 335-51.
- 4 Schumacher H R, Lotke P, Athreya B, Rothfuss S. Pigmented villonodular synovitis: light and electron microscopic studies. *Semin Arthritis Rheum* 1982; **12**: 32-43.
- 5 Byers P D, Cotton R E, Deacon O W, et al. The diagnosis and treatment of pigmented villonodular synovitis. *J Bone Joint Surg [Br]* 1968; **50**: 290-305.
- 6 Wiss D A. Recurrent villonodular synovitis of the knee: successful treatment with yttrium-90. *Clin Orthop* 1982; **169**: 139-44.
- 7 Züllig R, Gross D, Frank Th, Rättimann A. Results of intra-

- articular treatment with yttrium-90 of persistent knee effusions. *Schweiz Rundsch Med Prax* 1979; **68**: 1150-5.
- 8 D'Eschoungnes J R, Delcambre B, Delbart Ph. Synovite villonodulaire hémopigmentée et synoviorthèse radio-isotopique. *Lille Medicine* 1975; **20**: 438-46.
- 9 O'Sullivan M M O, Yates D B, Pritchard M H. Yttrium 90 synovectomy—a new treatment for pigmented villonodular synovitis. *Br J Rheumatol* 1987; **26**: 71-2.
- 10 Larsen A. A radiological method for grading the severity of RA. Helsinki University, 1974. (M D thesis.)
- 11 Boerbooms A M Th, Buijs W C A M. Rapid assessment of ^{99m}Tc-pertechnetate uptake in the knee joint as a parameter of inflammatory activity. *Arthritis Rheum* 1978; **21**: 348-52.
- 12 Lens J W, Van den Berg W B, Van de Putte L B A. Quantitation of arthritis by ^{99m}Tc-uptake measurements in the mouse knee joint: correlation with histological joint in inflammation scores. *Agents Actions* 1984; **14**: 723-8.
- 13 Boerbooms A M Th, Buijs W C A M, Danen M, van de Putte L B A, Vandenbroucke J P. Radiosynovectomy in chronic synovitis of the knee-joint in patients with rheumatoid arthritis. *Eur J Nucl Med* 1985; **10**: 441-5.
- 14 Spooen P F M J, Rasker J J, Arens R P J H. Synovectomy of the knee with ⁹⁰Y. *Eur J Nucl Med* 1985; **10**: 446-9.
- 15 De la Chapelle A, Oka M, Rekonen A, Raotsi A. Chromosome damage after intra-articular injections of radioactive yttrium. *Ann Rheum Dis* 1972; **31**: 508-12.
- 16 Roberts S D, Gillespie P J. Effects of immobilisation on retention of ⁹⁰Y. *Ann Rheum Dis* 1973; **32** (suppl): 46-7.
- 17 Kyle V, Hazleman B L, Wright E P. Yttrium-90 therapy and ^{99m}Tc-pertechnetate knee uptake measurements in the management of rheumatoid arthritis. *Ann Rheum Dis* 1983; **42**: 132-7.
- 18 Gumpel J M, Williams E D, Glass H I. Use of yttrium-90 in persistent synovitis of the knee. Retention in the knee and spread in the body after injection. *Ann Rheum Dis* 1973; **32**: 223-7.
- 19 Jankowski J. Organ doses in diagnostic X-ray procedures. *Health Physics* 1984; **46**: 228-34.