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III. Clinical application and investigation

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Review of published and personal results

Criteria for selection of patients

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The first papers on the use of radiocolloids in the treatment of arthritis appeared in 1963 (Ansell, Crook, Mallard, and Bywaters, 1963; Makin, Robin, and Stein, 1963). One of these studies was partially controlled, in that the worse knee was treated and compared with the other, but it was not until 1973 that an adequately controlled study was published. In between, many papers describing the use of radiocolloids have appeared, and the first part of this paper outlines the published results of the use of radio-isotopes in arthritis. The analysis of the literature is difficult because the indications for treatment are often not stated, and there are variations in the dosage regimes, in the criteria of success, and in the duration of follow-up.

By far the most experienced group is that associated with Professor Delbarre at the *Hôpital Cochin* (Menkes, Aignan, Galmiche, and Le Go, 1972). Between 1966 and 1971, they performed 1,240 *synoviorthèses* in 460 patients, with an overall improvement rate of 77 per cent. at 6 months after the injection, 88 per cent. at 1 year, and 93 per cent. at 2 years. They qualify their 2-year figure, because many patients had been lost from the series by the end of 2 years, and they comment that there was a statistically significant correlation between a poor result at 6 months and a loss to follow-up at 2 years. Menkes and others (1972) pointed out that there was a highly significant statistical correlation ($P = 0{\cdot}0001$) between patients who had a good or very good result at 6 months and who were in the same grade after 2 years. This is a very important point to note; one can reasonably predict at 6 months whether the treatment is going to succeed or fail, and if the result is poor one can then plan either a further injection or a surgical synovectomy at that stage. At 3 months after injection, however, the eventual result may not be apparent. The patient should be told this, as some who do not seem to have had a good result at 3 months may still achieve a good result by 6 months. It appears to be rare for an initially good result to deteriorate.

In the series of Menkes and others (1972), in 1,240 injections, the overall complication rate was just less than 4 per cent.; some 2 per cent. of patients had an episode of fever or malaise after the injection, and 2 per cent. had more direct complications, such as skin eruptions, needle-track radiation burns, and later scars. Early in their experience, when they were using ^{90}Y in finger joints, there were cases of radionecrosis; Virkkunen, Krusius, and Heiskanen (1967) also noted pigmentation of the skin (*i.e.* a radiation burn) after the use of radio-gold in the smaller finger joints. Local painful reactions in the injected joints occurred in 42 per cent. of their series of injections, but one must remember that they were injecting many difficult joints, often under radioscopic control and were performing arthrograms to

check the position of their needle. The joints included the proximal interphalangeals, in which even a small acute effusion may give considerable pain. If their figures for the knee alone are considered, a painful reaction occurred in 25 per cent. of the knees treated with ^{198}Au and in 33 per cent. of those treated with ^{90}Y. As a routine, hydrocortisone and a local anaesthetic were used as a cocktail with the isotope.

The vast majority of the patients treated by Menkes and others (1972) had rheumatoid arthritis, and between 1 and 2 years after injection there was a statistically significant lower failure rate in the patients with seropositive rheumatoid arthritis (6.8 per cent.) than in those with seronegative rheumatoid arthritis (23.2 per cent.). Most of the rheumatoid patients had been previously treated with gold salts, and the group as a whole must be considered to have been either failures or incomplete responders to gold. The overall response 1 year after treatment for the various joints is shown in Table I. ^{90}Y was mainly used in the knee, while ^{198}Au was mainly used in the other joints shown. The criteria used for improvement are fairly standard, 'very good' meaning complete improvement and resolution of all manifestations, 'good' meaning improvement in almost but not quite all parameters. It should be noted that for the knee the good results total 65 per cent. and for the elbow 54 per cent., while for the wrist and shoulder there is quite a large proportion of non-responders. In the weight-bearing joints, the knee and the ankle, the results were significantly better where an *x*-ray examination showed Steinbrocker radiological Grades I and II only, *i.e.* no change or minimal osteoporosis or minimal joint space loss, compared with those showing Grades III and IV, in which there was obvious joint space narrowing and damage. In the shoulder and wrist, the severity of radiological change did not affect the results.

Menkes and others (1972) compared their results in the knee using 6 and 4 mCi. ^{198}Au and 6 and 4 mCi. ^{90}Y. There were fewer painful reactions using 4 mCi., especially with the ^{90}Y, and they found that their results using 4 mCi. ^{90}Y were no worse than with 6 mCi. and that 4 mCi. ^{90}Y was as good as 6 mCi. ^{198}Au. In addition, for the periods of 6 months to 1 year after treatment, the failure rate in the knee was 35 per cent. with ^{198}Au and 17·4 per cent. with ^{90}Y, whereas after 1 year it was 17·4 per cent. and 10·9 per cent. respectively. Menkes and his colleagues have now adopted a dose of 3 to 4 mCi. ^{90}Y as their standard treatment for the knee.

In the finger joints ^{169}Er was used for most of the injections, and the results for 6 months and for 1 year after treatment are shown in Table II.

Table II *Results obtained by Menkes and others (1972) in MCP and PIP joints after 6 mths and 1 yr*

Joints		*MCPs*		*PIPs*	
Duration		*6 mths*	*1 yr*	*6 mths*	*1 yr*
No. of cases		59	11	53	25
Results (per cent.)	Very good	28·8	1	24·5	36
	Good	27·1	3	34	32
	Some improvement	25·4	5	22·6	3
	No improvement	18·6	2	10	5

This is only a brief summary of their work and findings, but amongst the patients were eighteen with psoriatic arthropathy, of whom only 15·6 per cent. had a very good result and 44 per cent. had a poor result. I have not found very much information on the treatment of psoriatic arthritis with radiocolloids in the literature. One other group, that of Recordier, Roux, Alberti, Dehame, Paulin, and Bernard (1972), reported poor results at 3 months in cases of psoriatic arthritis, compared with cases of rheumatoid arthritis. The dosage regime used at the *Hôpital Cochin* was usually between 3 and 6 mCi. for the knee, 3 mCi. for the hip, 2 mCi. for the ankle, shoulder, and elbow, and 500 and 200 μCi. respectively for the metacarpophalangeal and proximal interphalangeal joints.

The question of dosage is an interesting one, and there a wide range is reported. The calculation of a suitable radiation dosage presents a great difficulty because we do not know the surface area of the synovium, either in health or in disease, nor do we know its thickness, nor can we predict the thickness of tissue that we wish to irradiate. Finally, we do not know how much of the injected dose will be taken up by the membrane and how much by fibrin deposits in the cavity, and how much will leak out of the joint. Ansell (personal communication) has some interesting

Table I *Results obtained by Menkes and others (1972) 1 year after injection*

Joint		*Knee*	*Shoulder*	*Elbow*	*Wrist*	*Hip*
No. of cases		139	30	37	83	7
Result (per cent.)	Very good	28·8	13·3	13·5	8·4	0
	Good	36·6	20	40·5	21·7	3
	Some improvement	22·3	43·3	43·2	39·8	2
	No improvement	12·9	23·3	2·7	30·5	2

unpublished data from her patients showing the variation in result assessed retrospectively in relation to the dosage (Table III). These are to some extent selected patients, for in her second series she excluded those with a bulky knee found in a trial aspiration, whether this bulkiness was due to a thickened synovium or to intra-articular fibrin. Most of the European workers have used between 4 and 8 mCi. and their results are similar to those described. Grahame, Ramsey, and Scott (1970) used larger doses, usually 12 mCi., in patients primarily with Baker's cysts, and they have had much the same proportion of successes and failures as have been obtained in other series.

Table III *Results obtained by Ansell (unpublished) with different amounts of* ^{198}Au

Dose ^{198}*Au (mCi.)*	*No. of cases*	*Result at 1 year*		
		Good	*Some*	*None*
1–1·9	19	9	5	5
2–2·9	10	7	2	1
3–5	16	13	3	0

In many series of patients there are a few with osteoarthrosis and presumably, but not stated, effusion troubles. Makin and Robin (1968) have an interesting series, the largest group of their patients, nineteen out of 41 having effusive osteoarthrosis with synovitis, or what might correctly be called osteoarthritis. Using a standard dose of 10 mCi. ^{198}Au they achieved a long-term result of 31 out of 41 being cured of chronic effusion; this is the only paper in the literature that reports such favourable results in osteoarthrosis. Another point of interest is that they list the reasons for the seven failures in these 41 patients—massive effusions in three, loculated effusions in two, and villonodular synovitis in two.

In general, the ^{90}Y preparation used in continental Europe is the citrate, while in Great Britain and in Finland the resin colloid was usually used until its withdrawal last year. There is one very good controlled study (Bridgman, Bruckner, Eisen, Tucker, and Bleehen, 1973), comparing 3 mCi. ^{90}Y resin with saline in the opposite knee, in pairs of knees; after 1 year they found a statistically significant difference in terms of perimeter of the knee and of movement. Perhaps, if pain on walking had not been included amongst their questions, the results for pain would have been better. Oka (1973), who has also used the yttrium resin, had the following results: 60 per cent. of his 48 knees were excellent or good at one year, at 18 months this proportion was reduced to 49 per cent., and at 2 years to only 36 per cent.

The second half of this paper concerns the 91 injections of ^{90}Y into knees which have been given here at Harrow or at Taplow up to the middle of June, 1973. In all there have been sixty patients; 21 had both knees injected and ten have had second injections. All were personally selected by me, and all had marked synovitis as shown by palpably thickened synovium or by recurrent effusion or by Baker's cysts. These manifestations had not improved or had recurred after steroid injection, and persisted after 6 weeks intensive static quadriceps contractions. At least five additional patients improved spontaneously during the 6-week period or while awaiting hospital admission. In all patients the knee or knees were judged to be the major source of synovitis, and where several joints were involved the patients were treated with gold salts systemically rather than locally with ^{90}Y. This latter criteria is similar to that used for surgical synovectomy. However, while the surgeons have a marked preference for knees with radiological changes, most of these patients had radiological changes, many of them severe, and often evidence of instability as well. Only three knees would be classed as showing no *x*-ray changes. No patient with definite synovitis of the knee was excluded because of severe *x*-ray change or instability, but where the inflammatory element was minimal, or where the symptoms were principally those of severely damaged or grossly unstable knees, they were excluded.

As the series has grown, much more care has been taken to assess before treatment the various components of knee pain of which the patient complained. In favour of inflammatory disease and therefore likely response, were morning stiffness in the knees, improving with exercise, and stiffening on resting, and swelling. Where there is pain on exercise, crepitus, or instability, the patient is told that, while the inflammatory component may be improved, there may be much less chance of improving the pain on exercise. Occasionally I have been surprised by the marked improvement in knees in which the main symptoms had been apparently of secondary degenerative pain, and I have sometimes used the response to a steroid injection to aid evaluation in difficult cases.

All the patients have been treated as inpatients, and after the first few patients had been treated and Oka, Isomäki, Rekonen, Ruotsi, and Seppälä (1972) had demonstrated at the Paris meeting in 1971 the marked improvement in retention of radio-isotope in the knee with rest in bed and with splinting, all have been kept at rest in bed for 3 days after injection, and a few have worn unstiffened Plastazote splints.

Marked febrile episodes occurred on the evening or day after injection in two patients. The resin undoubtedly produced more reaction in the knees than the citrate, and this was fairly obvious when

the two isotopes were compared in a pair of knees (Gumpel, Farran, and Williams, 1974). We can confirm the observation of Menkes and others (1972) that there is marked painful effusion after 6 mCi. and much less after 5 or 4 mCi. Four mild needle-track discolourations have been noted, and this small number is perhaps due to technical care, always leaving a certain amount of air in the syringe to flush out the needle at the end, and immediately applying firm pressure after withdrawing the needle.

Our current results are shown in Table IV, in which each patient appears only once. As in so many studies in rheumatoid arthritis, the long-term results are complicated by subsequent treatment, and several of these patients have subsequently been given gold or penicillamine. This was usually because disease activity started again in joints other than that treated with ^{90}Y, but in three patients, in retrospect, failure of *synoviorthèse* was associated with a generalized low activity rheumatoid arthritis that responded well to chrysotherapy, as well as the previously treated knee. One patient failure was a success as far as the doctor was concerned, in that the synovitis disappeared, but the patient's persistent complaint was of pain resulting from instability.

Table IV *Results obtained by Gumpel with* ^{90}Y *(Non-cumulative)*

Duration (yrs)	*2*	*1½*	*1*
Excellent	6	8 (2)	9 (1)
Good	2	9 (2)	5
Some improvement	0	1	2
Poor	3 (2)	0	1

No. of knees. ( )=osteoarthr*itis*

One other failure occurred in a patient with osteoarthritis and effusion, although in general the results in the other patients with osteoarthritis have been very satisfactory. In assessing these patients, pain on exercise has been largely disregarded, as I feel that this is usually a symptom of secondary degenerative arthritis rather than of inflammatory disease.

A repeat injection, varying from 2·5 to 5 mCi., was given in three patients with a suboptimal response, one of whom also had a major leakage of isotope at the first, but not the second injection, and in five knees in which the knee had been, and remained, very bulky, either because of a greatly thickened synovium, or because of large quantities of intra-articular fibrin. In general, the second injections have been successful.

Finally, I include some preliminary results of a current trial at Taplow, where, with my medical and surgical colleagues, a randomly selected comparison of ^{90}Y and surgical synovectomy has been started. There are two who had virtually simultaneous synovial ablation, surgical on one side and yttrium on the other, nearly 2 years ago; another pair was treated similarly 1 year ago, and there are several randomly selected single knees at similar stages. In no case has there been a recurrence of inflammatory pain or synovitis. If anything the balance swings a little to the ^{90}Y, as several of the surgical patients have needed additional outpatient physiotherapy and one, for instance, had a post-operative deep vein thrombosis. As for the patients who have had both treatments, they tend to have a slight preference for the knee treated with ^{90}Y, not for a good medical reason, but because of the ease of flexing the knee, for instance in getting in and out of a car, or sitting in a confined space.

In summary, this is clearly a useful technique, which may be of considerable benefit to the patient, and may improve the economics of health care. The preliminary results are satisfactory, and there is now a need for controlled trials to establish its value and the duration of effect and to contrast these with established techniques such as surgical synovectomy.

Discussion

DR. GLYN Did you tell us the minimum age of the patients you would treat and did you tell us whether you put in a cocktail?

DR. GUMPEL I do not use a cocktail, but isotope diluted in saline. I have never found it necessary with 4 or 5 mCi. to use a cocktail, as the patients do not have that much pain, and since we have stopped using the resin, the pain is less. All the patients were selected according to the MRC criteria, apart from one who had an aortic homograft and was perhaps not going to live the full statistical time.

DR. CLARK Can you repeat the injection more than once or is one repeat injection the maximum?

DR. GUMPEL I think this is going to be a subject for discussion. Those treating thyroid went through several swings of opinion—first one shot and then several shots—and then finally went back to one or two shots and this was because they were concerned about eventual hypothyroidism. We are guessing with our doses, perhaps 3 mCi. as a repeat is right, perhaps 4. I have given only one second dose so far, so the maximum has been 8 or 10 mCi. in one knee.

DR. CLARK Do you think it may be important to rest the joints before injection? Dr. Andrews mentioned this earlier on. Dr. Ansell mentioned synovial fibrosis. I wonder if she felt this was progressive fibrosis and whether in the long term it has any clinical repercussions?

DR. ANSELL I do not think fibrosis goes on to produce marked stiffening of the knee. We are

finding recurrences in the knees treated with ^{198}Au at Taplow after about 3 years. Some have come to surgical synovectomy, and we find no problems then.

DR. LAL What is the average time between the first and the second injections?

DR. GUMPEL Between 6 months and 1 year. It ought to be about 6 or 8 months, but because of the variable availability of isotope in the last few months the gap has sometimes been longer.

DR. SCOTT I should like to ask a question about the comparative trial of synovectomy and yttrium. One can understand the inclusion of patients with large recurrent effusions and relatively thin synovia, but there is a group of patients in whom one suggests synovectomy: those without very large effusions, but with very thick synovium and relatively advanced erosive damage, where one just feels that yttrium would be less satisfactory than surgical synovectomy. Are such patients included in your trial?

DR. GUMPEL Yes, there are some. We have included any patient recommended for surgical synovectomy (depending on age and consent).

MR. FEARN What size of needle do you use for your injections of yttrium?

DR. GUMPEL We did use the serum II needles, but we now use the serum I. Initially we thought the larger needle might be concerned with leakage, but in talking about needle size, it has been suggested that you should not carry out a synovial biopsy or a large-needle aspiration in the days just before injection of a radiocolloid, because there is a definite increase in risk of leakage from the puncture site. I think the practice in France and some other places is to do an arthroclysis to clear the fibrin from the knee beforehand, and I think this is very praiseworthy, but it should be done at least a week beforehand so that the scar has healed satisfactorily. I do not think, for instance, that an injection of radiocolloid should be combined with a simultaneous synovial biopsy.