Radioactive colloidal gold

In chronic knee effusions with Baker's cyst formation

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In recent years radioactive colloidal gold, ^{198}Au , has been used by a number of workers in the treatment of chronic synovial effusion by partial synovial ablation. Ansell, Crook, Mallard, and Bywaters (1963) gave thirty injections to a group of patients suffering from a variety of conditions, but at the end of one year a good result, as evidenced by complete disappearance of effusion and pain, was observed in only sixteen cases. The estimated dose, however, was low, lying in the range 480 to 1,000 r. The particle size was not recorded. Significant radioactivity was not encountered at 24 hours after the injection in the regional lymph nodes, blood, or synovial fluid.

In a larger series of patients—predominantly sufferers from rheumatoid arthritis—Virkkunen, Krusius, and Heiskanen (1967) injected ^{198}Au into a variety of joints including metacarpophalangeal joints. Effusion and pain in knee joints were diminished in 39 of 85 cases and disappeared completely in 28. There was, however, considerable leakage of radioactivity to the regional lymph nodes, amounting to more than 10 per cent. of the injected dose in 36 per cent. of cases. In one case the estimated dose to the lymph nodes was 15,000 r. In this study the average particle size was $0.02\ \mu$.

Using a dose of 10 millicuries (mCi) in 41 patients, mostly with osteoarthritis or 'idiopathic hydrops' of the knee, Makin and Robin (1968) reported permanent remission of effusion in 31 cases and temporary relief in three. Of the 31 cases treated with 6 mCi intra-articular ^{198}Au to the knee joint by Delbarre, Cayla, Aignan, Roucayrol, Menkes, and Ingrand (1968), nineteen (60 per cent.) improved after 5 months compared with nineteen of 25 similar cases treated with the same dose of colloidal yttrium 90 (75 per cent.).

In recent years there has been renewed interest in the pathogenesis and treatment of synovial cysts which occur in the popliteal region (Baker's cysts) in the presence of a chronic knee effusion under tension. There is evidence of a valvular

mechanism by which fluid is pumped from the knee joint into the cyst but is unable to return (Jayson, 1968). The cyst consequently enlarges and is liable to spread into the calf and rupture into the tissues (Hall and Scott, 1966). Though many such cysts disappear spontaneously or in response to a local corticosteroid injection, others require surgical management by synovectomy of the knee joint with or without removal of the cyst itself.

In the present study radioactive colloidal gold was used in chronic synovial effusions with special reference to any possible beneficial effect on such cysts.

Method

The gold was administered as a colloidal suspension, stabilized with gelatin, and containing glucose and sodium chloride (Radiochemical Centre preparation GCSIP). The total gold concentration, including non-radioactive gold, was 10 mg./ml. and the activity was approximately 2 mCi./ml. The particle sizes ranged up to $0.02\ \mu$, those of 0.01 to $0.0125\ \mu$ accounting for the greatest proportion of radioactivity.

^{198}Au decays with a half-life of 2.70 days, emitting beta and gamma radiation. 99 per cent. of the beta emission has an energy of $0.06\ \text{MeV}$, the maximum range in soft tissue being 3.8 mm., but most of the energy is absorbed in the first 1 mm. 95.6 per cent. of the gamma emission is at $0.412\ \text{MeV}$. This highly-penetrating radiation gives a calculated gonad dose allowing for attenuation in the tissues of the thigh of about 400 mrad in the male. Gonad dosage in the female will be of the same order.

After insertion of a wide-bore aspirating needle, a few ml. of joint fluid was removed but the joint was not aspirated to dryness.

The gold was injected, the usual dose being 12 mCi, in a volume of 6 ml. One patient received 15 mCi, one 10 mCi, and one received 12 mCi initially and a second dose in the same knee of 7.5 mCi, 8 months later. The usual precautions were taken to minimize radiation to the operator's hands and to prevent spread of contamination from any small leakage of radioactive gold during or after the injection.

It is known that after intracavitary instillation of colloidal radioactive gold, the activity becomes almost

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entirely confined to the membrane lining the cavity (Makin and Robin, 1968). Assuming that the ^{198}Au is deposited uniformly and that the dose is 12 mCi, and taking an arbitrary estimate for the area of this membrane of say 50 cm.² for the knee joint and 50 cm.² for a cyst, then the calculated dose from the beta radiation falls off very rapidly below the surface as shown in Table I. The figures are derived from calculations by Cross (1967). 99 per cent. of the total beta dose is delivered within 18 days. The calculated contribution from gamma radiation is shown in the third column of Table I. (These figures give the calculated dose from an 8 cm. diameter disc of uniformly distributed activity, carrying half the injected dose. A hypothetical distribution of the injected material half in the knee joint space and half in the cyst is assumed, and the dose to the knee joint membrane from ^{198}Au in the cyst is ignored.)

Table I *Radiation dose*

Depth below surface of membrane (mm.)	Radiation dose (r)	
	Due to beta rays	Due to gamma rays
0.1	73,592	1,150
0.2	49,705	900
0.4	29,071	690
0.6	18,277	640
0.8	11,714	590
1.0	7,529	560
2.0	561	450
2.8	22	395
3.0	0	380

Selection of patients

Fifteen patients (10 women and 5 men) aged 44 to 72 years and attending the Rheumatology Clinic at the West London Hospital were included in the trial. All patients were suffering from a chronic synovial effusion of the knee joint resistant to other measures, including repeated aspiration and intra-articular injection of prednisolone.

Table II *Intra-articular ^{198}Au knee injection*

Case No.	Sex	Age (yrs)	Disease	Cyst			Dose (mCi)	Follow-up (mths)	Result		
				Popliteal	Calf	Side			Pain relief	Reduction in size of effusion	Cyst disappeared
1	F	66	RA	+	0	L	12	11	+	+	+
2	F	51	RA	+	0	R(x2)	7/7.5	11	+	—	—
3	M	67	RA	0	0	L	12	11	+	+	N/A
4	F	60	RA	+	+	L	12	11	+	+	—
5	F	54	RA	+	0	L+R	12+12	11	+/+	-/-	-/-
6	F	44	RA	+	0	R	6.6	10	+	+	+
7	F	47	Monarthritis	0	0	R	10	10	+	++	N/A
8	F	57	RA	+	0	L	12	9	+	+	—
9	M	54	Ankylosing spondylitis	+	0	L	12	8	—	—	—
10	M	50	RA	+	0	R	12	8	—	+	—
11	F	62	RA	+	0	R	12	7	—	+	+
12	M	66	RA	+	+	R	12	6	+	+	+
13	F	72	RA	+	0	R	12	5	+	+	—
14	M	57	RA	+	0	R	12	8	—	+	—
15	F	56	RA	+	0	L	12	2	+	—	—

RA = rheumatoid arthritis. N/A = not applicable

In the majority of cases the underlying disease was rheumatoid arthritis. All except two patients showed a popliteal cyst, confirmed by contrast arthrography, and in two cases this had extended into the calf. Further details of the patients are given in Table II.

Distribution of ^{198}Au

After injection of radioactive suspension into the knee joint, a gamma-scan was made of the distribution of activity in the joint and in the cyst. In all cases the gold had become distributed throughout the available space. Examples of anterior and medial scans are shown in Fig. 1(a) and (b) and a corresponding arthrogram in Fig. 2 (opposite).

At 1 to 2 hours after injection, and daily for 2 to 4 days, the trunk was scanned to determine the site of localization of any ^{198}Au leaving the joint space. Wide variations were found in the quantity of activity and the sites located. Activity was most commonly found in the external iliac region, with smaller amounts in the femoral region, and occasionally in the para-aortic region. One patient showed more activity in the inguinal than in the external iliac region. Another showed a relatively high uptake in the aortic glands and liver, but generally the uptake in the liver was negligible. Attempts were made to assess quantitatively the activity in the glands, and to correlate this with measurements taken over the knee with either a collimated Geiger counter or a scintillation counter. Considerable discrepancies were found, owing to the difficulty of making accurate quantitative estimates of gland content from a dot scan, but it appears that as much as 2.5 mCi of activity could leave the joint. The average loss was about 0.5 mCi, but in some cases was so small as to be barely detectable.

Urine collections were made for 24 hours after injection. Losses of ^{198}Au in the urine ranged from 0.2 to 7 μCi , the usual figure being about 1 μCi , which is some 1/10,000th part of the activity in the knee.

(a) Anterior scan

(b) Medial scan.

FIG. 1 Gamma scan of distribution of activity in knee joint and popliteal cyst

FIG. 2 Corresponding arthrogram to Fig. 1(b), with hypaque injected into joint cavity.

Clinical results

In three patients there was a brisk local reaction occurring within 3 weeks of the injection, with increased pain and effusion requiring aspiration

of the knee and instillation of prednisolone. The tendency in most cases was towards a gradual amelioration in the size of the effusion and pain over the next 3 months. After this time there was little further improvement. One patient (Case 5), who derived benefit from one injection, had the other knee similarly treated. Another patient (Case 2), who failed to respond to the first injection, derived benefit from a second given to the same knee 6 months later.

About two-thirds of patients experienced relief of pain after the radioactive gold injection (Table II). This pain relief was not necessarily associated with reduction in the size of the effusion or of the cyst. A similar proportion experienced a reduction in the size of the effusion but in only four cases was this complete.

In one-third of cases with a synovial cyst, the cyst disappeared after treatment.

No systemic side-effects were encountered and the blood count was not depressed in any case. A few patients, however, experienced erythema of the skin (like sun-burn) at the site of the injection, presumably due to reflux of ^{198}Au back along the needle track. This area was never more than a few cm. in diameter and after 2 weeks or so gave place to an area of pigmentation which lasted several months but caused no other inconvenience.

Discussion

The factors likely to be of major importance in determining the efficacy of this treatment are:

- (i) The radiosensitivity and thickness of the synovial membrane;
- (ii) The site of disposition of the isotope;
- (iii) The penetrating power of the radiation.

There is little information on the relative radiosensitivity of different types of diseased synovia. The limited success of our own series of patients, who were almost all suffering from rheumatoid arthritis, compared for example with the better result obtained by Makin and Robin (1968) in patients with osteoarthritis or idiopathic effusion of the knee, could reflect diminished radiosensitivity in rheumatoid arthritis. It is more likely, however, that the disparity in clinical results is a factor of the thickness of the synovial membrane, since in rheumatoid arthritis the membrane may be several cm. thick.

Table I shows that the destructive effects of the radiation extend to approximately 1 mm. from the source, presumed to be in a continuous plane, if any dose greater than 7,500 r be taken as lethal. Doubling the dose would increase this layer to 1.3 mm., and halving it would effectively treat 0.07 mm. If a substantially greater thickness is to be treated effectively, it is apparent that an isotope emitting beta rays of greater energy, such as yttrium⁹⁰, would offer advantages.

In the same way as ¹⁹⁸Au injected experimentally into rabbit's knees is taken up by the synovial cells (Makin and Robin, 1968), ⁹⁰Y has also been shown to be taken up by the synovial cells both in healthy rabbits knees and also into those affected with an experimental immune arthritis (Webb, Lowe, and Bluestone, 1969).

The favourable response to ⁹⁰Y in rheumatoid knees as compared with Delbarre and others (1968) is encouraging and further study of the therapeutic potentialities of ⁹⁰Y is clearly indicated.

In further clinical trials it will probably be necessary to use suitably controlled methods. The results of the present study, and of others, indicate the likelihood of therapeutic effect, but in the absence of untreated control subjects it is impossible to be certain about this. Knee effusion and popliteal cysts can remit spontaneously or following simple aspiration.

One disquieting aspect of the present study is the relatively large amount of radioactivity sometimes found in the regional lymph glands. This was not observed by Ansell and others (1963) or by Makin and Robin (1968), but has been strongly confirmed by Virkkunen and others (1967). Estimation of dosage is hampered by a lack of precise knowledge of the quantity of radioactive material in any gland, and the amount of tissue that it effectively irradiates. Assuming values for these two quantities of 100 μ Ci and 0.5 g., the dose from beta radiation would be 12,700 r, and from gamma radiation approximately 8 r. The former figure is unacceptably high, and means of reducing it should be sought. One method might be to use larger colloid particles, so as to reduce escape from the knee joint space.

Summary

The results of treating a series of fifteen rheumatoid patients suffering from chronic synovial knee effusions, mostly with Baker's cysts, with an intra-articular injection of radioactive colloidal gold are presented. There was relief of pain and reduction in the size of the effusion in approximately two-thirds of patients. In one-third the Baker's cyst disappeared after the injection.

Significant leakage of radioactivity from the knee joint was found in some cases. The suitability of ¹⁹⁸Au for this application is discussed.

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RÉSUMÉ

L'or colloïdal radioactif dans les effusions chroniques du genou avec la formation des kystes de Baker

Les résultats du traitement d'un groupe de quinze malades rhumatoïdes atteints d'effusion synoviale chronique du genou, la plupart montrant des kystes de Baker, par une injection d'or colloïdal radioactif par voie intra-articulaire sont présentés. Une diminution de la douleur et une réduction dans le volume de l'effusion chez approximativement deux tiers des malades ont eu lieu. Chez un tiers le kyste de Baker a disparu après l'injection.

Une fuite marquée de radioactivité de l'articulation du genou a été remarquée chez quelques cas. Le choix de ^{198}Au pour ce traitement est discuté.

SUMARIO

Oro coloidal radiactivo en derrames crónicos de la rodilla, con formación de quiste de Baker

Se exponen los resultados del tratamiento de una serie de quince pacientes reumatoïdes que sufren de derrames crónicos sinoviales de la rodilla, en su mayoría con quiste de Baker, con una inyección intraarticular de oro coloidal radiactivo. Hubo alivio del dolor y reducción del tamaño del derrame en aproximadamente dos tercios de los pacientes. En un tercio, el quiste de Baker desapareció después de la inyección.

En algunos casos se descubrió una fuga significativa de radiactividad de la articulación de la rodilla. Se discute la conveniencia del Au^{198} aplicado de este modo.