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Intra-articular Treatment with Colloidal ^{198}Au for Persistent Synovial Effusion of the Knee

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Introduction

So-called persistent synovial effusion of the knee due to rheumatoid arthritis, chronic synovitis, etc. is generally treated by intra-articular injection of adrenal cortical hormone, synovectomy, etc. There are, however, occasional cases which do not respond to any ambitious course of treatment by such methods.

In 1963, Makin et al. [7]) successfully treated persistent synovial effusion of the knee by intra-articular injection of a colloidal suspension of ^{198}Au (particle size approximately 60μ).

The authors have been interested in this method of treatment for several years, but had discontinued studies temporarily due to the difficulty in obtaining large colloidal ^{198}Au particles of 60μ average size. Recently, through the efforts of Daiichi Radioisotope Co. Ltd., it was possible to import some of this material and to do studies on 15 knee joints of 14 Patients with persistent synovial effusion of the knee Several findings of interest were obtained and are reported.

Method

Selected for treatment were patients over 40 years of age with persistent synovial effusion of the knee in whom all previous treatment over a number of years had been unsuccessful (**Table 1**). Initially, 10 mCi of colloidal ^{198}Au was injected into the affected knee, and then the joint was mobilized for several minutes in order to facilitate spread of the injected colloid within the joint space. Later, the distribution of colloid was examined by scintigrams of the knee (**Figure 1**). In addition, the radioactivjty of the urine, blood and of the synovial fluid were measurd

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受付：昭和45年2月6日

別刷請求先：広島市千田町1-9-6
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鴛海良彦（〒 730）

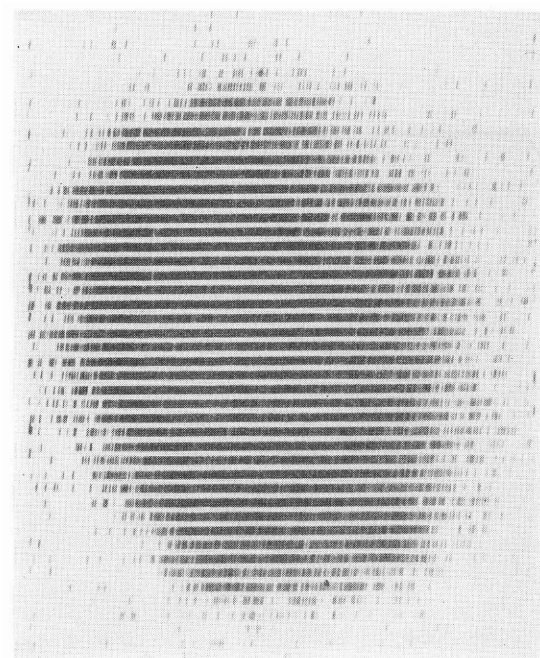

Fig. 1.
Scintigram of the knee (case No. 5)
Uniform distribution of the injected colloid is manifested.

Table 1. Clinical course of the cases treated with intra-articular injecton of clloidal ^{198}Au (15 knee joints of 14 cases)

No.	Name	Sex Age	Diagnosis	Knee Joints	Injected Dose(mCi)	Period until disppearance of fluid(week)	Arthralgia	Period of observaton (month)	Fluid
1.	M. Y.	♀ 80	synovitis	lett	5mCi	7 W(transient)	±	31M	disappearance
				right	5	7 W(transient)	±	31M	disappearance →recurrence
2.	S. F.	♀ 64	rheumatoid arthritis	right	10	5 W	−	31M	disappearance
3.	S. T.	♀ 72	synovitis	right	10				
rejected 3 months later				sight	10	13 W(transient)	−	12M	disappearance →recurrence
4.	T. N.	♂ 46	osteoarthritis	left	10	12 W(decrease)	−	6M	decrease
5.	Y. U.	♀ 61	osteoarthritis	right	10	5 W	−	13M	disappearance
6.	H. O.	♂ 73	osteoarthritis	left	10	3 W	−	2M	disappearance
7.	S. M.	♂ 49	osteoarthritis	left	10		+	12M	unchange
8.	A. K.	♀ 58	osteoarthritis	right	10	3 W(transient)	+	10M	disappearance →recurrence
Colloidal ^{198}Au of 60 in size was used in the following cases.									
9.	D. K.	♂ 75	osteoarthritis	left	10	0.5W	−		disappearance This patient died on the 17th day after injection due to cerebral hemorrhage
10.	T. U.	♂ 54	rheumatoid arthritis	right	10	1.5W (transient)	−	7M	disappearance →recurrence
11.	T. W.	♂ 72	osteoarthritis	right	10		+	4M	unchange
12.	H. Y.	♀ 55	synovitis	right	10	1.5W	+	8M	disappearance
13.	K. Y.	♀ 43	rheumatoid arthritis	right	10		+	3M	unchange
14.	H. U.	♂ 74	osteoarthritts	right	10		+	3M	unchange

at 24 hours afer injection, and linear scanning with determinaton of the liver-knee joint ratio was performed at 1, 3, 8 and 15 days after injection. Cases 1 to 8 were given conventional ^{198}Au (average particle siz 25 mμ), while cases 9 to 14 were given large particles of 60μ.

Results

1) Comparison of conventional (average size 25 mμ) and large particle (60μ) colloidal ^{198}Au.

Colloidal ^{198}Au commercially availabel heretofore in Japan consisted of small particles of 25mμ average size, and particles larger than this size could not be obtained. Recently, with the cooperation of Daiichi Radioisotope Ltd., colloidal ^{198}Au with particle size of 60μ was obtained from France. This material, prepared using a carbon nucleus, contains Au in the proportion 1 mg Au/mg carbon, and dextran solution is provided separately as solvent to be thoroughly mixed with the carbon immediately before use.

The comparison of this material with conventionally available material is shown in Table 2. It is noted that although material 60μ is more expensive than that of 25mμ. ^{198}Au of 60μ has a lower rate of escape from the joint space so that the therapeutic efficacy is greater even whem the same dose is administered.

2) Radioactivity of the urine, blood and some of the synovial fluid from all patients as 24 hours after injection showed results close to the background level.

3) Linear Scanning

Linear scanning was performed four times, at 1, 3, 8 and 15 days after injection. These scannings

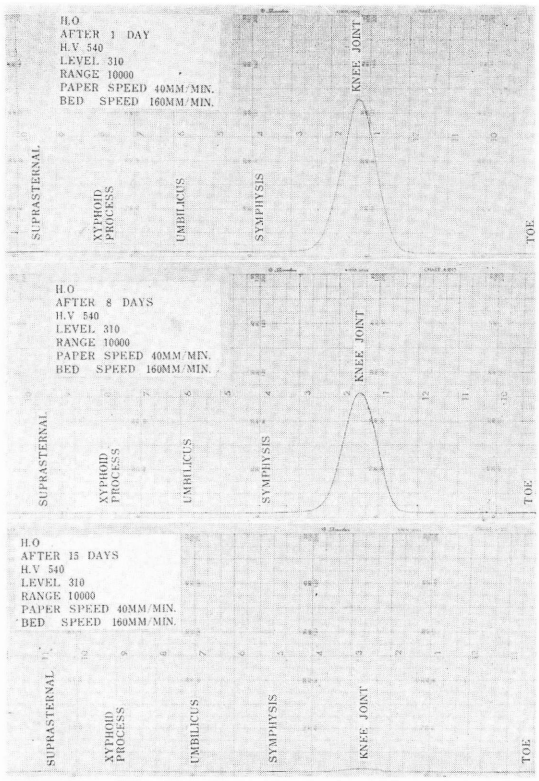

Fig. 2.
Whole body scanning at 1, 8, 15 days after injection (case No. 6)

were made under identical conditions each time. Under these conditions, a large peak of activity was noted in the area of the joint, but not other regions. Moreover, this peak showed a gradual decline with time. (**Fig. 2**)

4) Transient reaction following injection

The transient reaction after injection was examined by whether there had been any increase in the amount of fluid or pain as compared to before injection as well as by the period until the fluid increased to the maximum amount. (**Table 3**) of the 15 joints, an increase in amount of fluid was noted in 11 joints, while no increse occurred in 4 joints. The period until the fluid increased to the maximum amount was four weeks at the longest, and ranged from one to four weeks. Patients who developed an increase in the amount of fluid, of course, had pain.

5) Course of patients following treatment

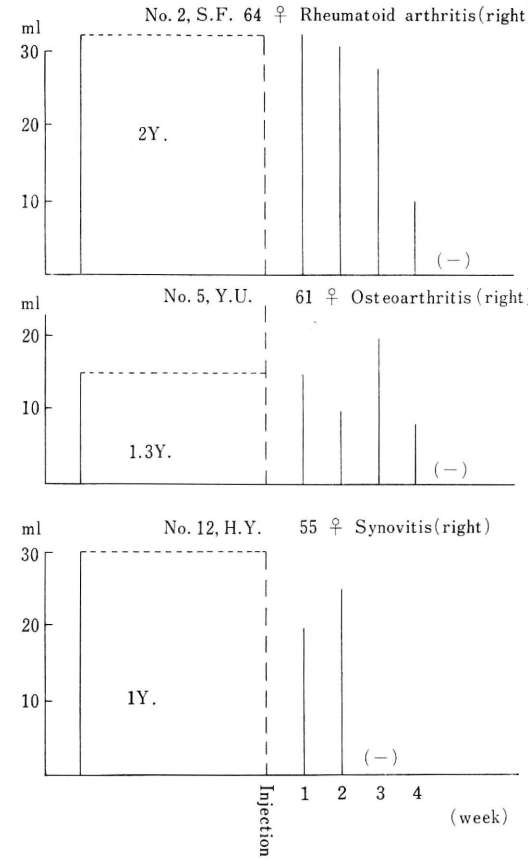

Fig. 3.
Intra-articular fluid befor and after change of intra-articular fluid volume following injection of colloidal ^{198}Au in the cases of No. 2, 5, and 12

The course of each patient after treatment is shown in table 1. In case 9, disappearance of fluid occurred in half a week after treatment, but this patient died on the 17th day due to cerebral hemorrhage. Case 6 also showed disappearance of fluid in three weeks, but moved out of the city two months after treatment so that the subsequent course is unknown.

It has been possible to do follow-up studies on 12 patients, until August 1969. The period of observation ranged from three months to two years seven months. Among the 13 joints of these 12 patients, disappearance of fluid occurred in 8 joints; disappearance occurred in half a week to seven weeks after injection in seven cases and in 13 weeks after repeated injection in the

Table 2. Comparison of 25mμ with 60μ of Colloidal ^{198}Au

Colloid	Specific Activity	Colloidal Size	Cost	Liver/Joint Ratio%		
				1st day	2nd day	3rd day
^{198}Au	4mCi/mg	25mμ	4,400 yen	1.76	0.12	0.59
^{198}Au on carbon	1.66m Ci/mg	60mμ	43,000 yen	0.15	0.44	0.12

Table 3. Transient Reaction Following Injection

No.	Fluid increas	Period until fluid increase to the maximum (week)	Arthralgia
1.	+	2 W	+
	+	2 W	+
2.	+	1 W	+
3.	+	4 W	+
	+	3 W	+
4.	+	4 W	+
5.	+	3 W	+
6.	−	0	−
7.	+	2 W	+
8.	+	2 W	+
9.	−	0	−
10.	−	0	−
11.	+	3 W	+
12.	−	-	−
13.	+	2 W	+
14.	+	4 W	+

other one case. Observation of the subsequent course, however, revealed fluid again in five cases, but was milder than cefore treatment. Two of the five joints, which developed recurrence, had been administered only 5mCi.

The course of fluld disappearance in the three patients, whohad demonstrated marked effect, is shown in figure 3. Decrease of fluid was noted in one joint, while no efect was noted in four joints.

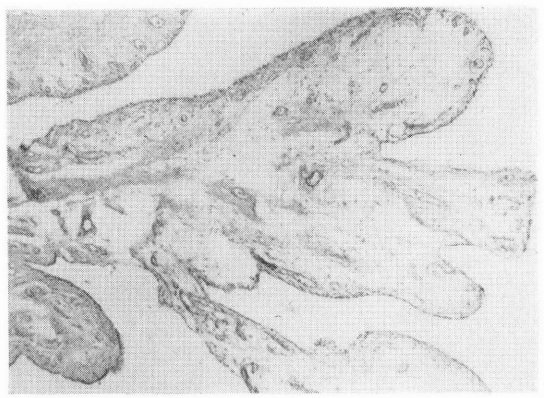

Fig. 4.

The histological picture of the synovial memdrane at the time of autopsy (case No, 9)
Marked irreglarity and focal thickning of the villi are noted, Mild edema and round cell infiltration are also seen.

Further, case 3 had been administered 10 mCi twice, whereas all the other cases had been given only one injection.

Discussion

So-called persistent synovial effusion of the knee has heretofore been treated by intra-articular injection of adrenal cortical hormone, synovectomy, etc., but there frequuently are cases in which vigorous treatment by such methods prove to be unsuccessful.

The effect of ^{198}Au on the synovial membrane of the knee had been described by Low-Beer[6] as early as in 1950. He stated that experimentel studies by Bertram et al. indicated a high uptake of gold by reticulo-endothelial cells of synovial membrane, and showed that the bulk of of colloidal ^{198}Au injected into the knee joints is concentrated in the synovium.

In 1963, Makin et al.[7] performed radiation therapy for suuch persistent synovial effusion of the knee by the intra-articular injection of colloidal ^{198}Au into the knee. Although non-radioactive gold therapy has been used for a long time in the treatment of joint effusion due to rheumatoid arthritis, the purpose of treatment by colloidal ^{198}Au is to suppress the production of effusion by inducing mild fibrosis with bete rate rays.

The size of colloidal particles is an important factor in obtaining the maximum effect of colloidal ^{198}Au radiation therapy. In animal experiments using normal rabbits by Adkins and Davies,[1] it has been found that colloidal particles as large as 10mμ escape from the joint space into the subsynovial tissue and enter thely mphatic circulation. The limiting size of colloidal particles for escape from the joint space to the lymph node is said to be 100mμ.[1] Those larger than this do not escape.

The conventional colloidal ^{198}Au consists of particles of 25mμ average size so that a considerable amount will perhaps escape from the joint. Therefore, the liver joint ratio was compared between the conventional material (25mμ) and colloidal ^{198}Au with large particles (60μ). The ratio at one, three and five days after injection was 1.76, 0.59 and 0.44, respectively, with particles of 25 mμ, while the ratio was 0.12, 0.15 and 0.12 with those of 60μ. Thus, the liver joint ratio of large particle ^{198}Au at one, three and fivedays is only 6.7%, 25% and 25% respectively of the liver joint ratio of small particle ^{198}Au. Further, the radioactivity of blood and urine over a 24-hour period following administration was close to the background level.

With respect to large prticle, Jacox,[4] Fine,[2] Makin,[8] etc. have also mentioned that escape from the joint spaceis very low.

The excretion into the stool and urine following injection has been reported to show that 28 to 55% of the total excretion into the stool occurs within the first week and that less than 50% of fecal gold is excreted in the bile.[5] Futher, the circulating gold is saidto be protein bound.

In any case, larger particles escape less readily from the joint space so that the radiation exposure of tissues and organs other than the joint can be minimum and a more effective dose can be deliverd to the synovial membrane.

Some are of the opinion that a dose of 5 mCi is adequate and that additional doses can be given as necessary.[3] However, Makin[8] feelsthat a dose of 10 mCi is appropriate, and in general administration in doses of 10 mCi is given Among the patients of the authors, case 1 had been given 5 mCi to each knee and, through there was temporary disappearance of fluid, recurrence developed later. This case indicates that a dose of 5 mCi is inadequate and requires additional treatment.

The radiation dose with the administration of 10 mCi is estimated to be approxjmately 5,000 R, [8] but the surface area of the synovium varies among individuals and cannot de measured so that we were not able to make calculations for this determination.

As to possible side effects following injection, no systemic symptoms such as vomiting, headache or general malaise were noted. However, a considerable amount of local symptoms was noted in the effected region. This has also been pointed out by Makin [8] and Fine,[2] and in 11 of 15 joints studied by the authors, there was increase of fluid and pain which perhaps are transien reactions. was increase of fluid and pain which perhaps are transient reactions. The fluid decreased and symptoms improved in all cases within four weeks.

Of the patients studied by the authors, one died due to cerebral hemorrhage on the 17th day after injection. Shown in figre 4 is a representative photomicrograph of the synovial membrane at time of autopsy. There is marked irregularity of the villi and focal thickning of the epithelia of the villi is noted. Immadiately beneath the epithelia is seen mild edema and round cell infiltration with may dilated ccpillary blood vesseis. but no fibrosis or saar formation of the villi is seen yet at this stage.

Conciderable therapeutic effects are described in the reports of Makin[8] and others.

In the 15 joints of the 14 patients of the authors, disappearance of fluid, even though only temporary in some case, was noted in 10 joints mostly in half a week to seven weeks. However, when the course was followed for a longer period, recurrence of effusion was noted in 5 joints, though to a milder degree than before treatment. This indicates that the ealua tion of the therapeutic effects requires a follow-up study over a considerable long time. Further, there was a greater rate of recurrence among cases with a

longer time period required until disappearance of fluid, and recurrence seems to be unlikely among those in whom disappearance of fluid occurred within at least five weeks (**Table 4**).

Table 4. Results of Treatment by Injection of the Knee Joints with Colloidal ^{198}Au (15 Knee joints 14 cases)

Disppearance of Fluid	10	(67%)
No. 2, No. 5, No.12 : complete disappearance No. 6 : not followed up after 2 months No. 9 : died on the 17th day after injectiondue to cerebral hemorrage No. 1 (bilateral) No.3, No. 8, No. 10 : recurrence		
Persistent slight effusion	1	No. 4, (7%)
No effect	4	(27%)
Total	15	

In view of the foregoing results, it appears that this method of treatment should be attempted once.

Conclusion

Irtra-articular injection of colloidal ^{198}Au was made into 15 knee joints of 14 patinets over 40 years of age with pesistent synovial effusion of the knee. Seeveral findings of interest were obtained and are reported.

1) To prevent escape of colloidal ^{198}Au from the joint cavity and to achieve an effective radiation dose, the colloidal particles shoud be as large as possible.

2) Administration of 10 mCi is appropriate.

3) Of the 15 joints of 14 patients, disappearance of fluid occured in 10 joints, but one case died of cerebral hemorrage and another case moved out of the city after two months so that the subsequent couse is unknown. Recurrence was noted later in five cases. This treatment did not have effect in four joints.

4) Follow-up should be continued for as long as possible in view of possible recurrence. If disappearance of fluid occurs at least within five weeks, the likelihood of recurrence seems to be low.

5) This method of treatment should be sttempted when other methods have proved to be ineffective.

(ACKNOWLEDGEMENT : The authors are indebted to Prof. Dr. Hideo Irie for guidance during this study and for his review and criticism of the manuscript. Our appreciation also goes to Assist. Prof. Dr. Katsuji Watanabe for his assistance during this work.)

(The outline of the study was presented at the 9th general meeting of the Japanese Society of Nuclear Medicine.)

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