

UPTAKE OF COLLOIDAL RADIOACTIVE YTTRIUM BY SYNOVIAL MEMBRANE

BY

F. W. S. WEBB, J. LOWE, AND R. BLUESTONE

Department of Medicine and Medical Physics, Royal Postgraduate Medical School, London

Surgical synovectomy is sometimes useful in the management of patients with rheumatoid arthritis. Ansell, Crook, Mallard, and Bywaters (1963) reported some encouraging results using radioactive colloidal gold, ^{198}Au , given into the knee joints of patients with persistent effusions in rheumatoid arthritis and allied conditions, with the aim of producing a radiation synovectomy or ablation.

Any small particle present in synovial fluid within a joint is taken up by the synovial membrane, because amongst the secretory cells making up the membrane there is a population of phagocytic cells. These cells were shown to take up the colloidal particles of radioactive gold and to retain them for at least 24 hours.

^{198}Au has a maximum beta-particle energy of 0.96 MeV and a range of 4 mm., although the average penetration is only about 1 mm. The inflamed synovial membrane of the knee joint in rheumatoid arthritis varies greatly in thickness, but often exceeds 1 cm. Although it was realized that ^{198}Au was not able to deliver an effective radiation dose to the full thickness of the inflamed membrane, it was hoped to achieve some useful effect by irradiating to an average depth of 1 mm. Ansell and others (1963) suggested that ^{90}Y might be preferable to ^{198}Au because of its more energetic beta emission.

^{90}Y has a maximum beta-particle energy of 2.25 MeV, and a maximum range of 11 mm. The average penetration is about 4 mm. It has a half-life of 2.67 days, similar to that of ^{198}Au , 2.70 days. The short half-life is an advantage in radio-therapeutic applications where there is any danger of the isotope diffusing from the site of administration over a long period.

The surface density of ^{198}Au needed to give a dose of 10,000 rads at a depth of 1 mm. is 145 μc . per sq. cm. The corresponding density for ^{90}Y is 37 μc . per sq. cm. The doses at 2 mm. depth for these

densities of the two isotopes are 100 rads and 3,000 rads respectively.

A further advantage of the pure beta-emitter, ^{90}Y , over ^{198}Au , which has a 0.41 MeV gamma-ray, is the absence of any appreciable gamma dose to distant organs, such as the gonads.

In view of these indications of ^{90}Y as a more suitable therapeutic agent than ^{198}Au , we undertook a study of the behaviour of the resin colloid of ^{90}Y injected into the knee joint of the rabbit.

Methods

Rabbits with normal and arthritic knee joints were used. A chronic inflammatory arthritis was induced by the method of Dumonde and Glynn (1962). The resin colloid of ^{90}Y was obtained from the Radiochemical Centre, Amersham. ^{90}Y is added to Zeocarb 225 ion exchange resin so as to make a colloid with a particle size range of 20-50 $\text{m}\mu$, which is stable at pH 7-8.

Between 100 μc . and 1 mc. of the colloid was injected into the knee joints. The animals were killed 24 hours later. In all, eight rabbits were investigated. Two were scanned using a collimated scintillation counter and were also surveyed with a thin window Geiger counter. The secondary radiation from the ^{90}Y (bremsstrahlung) allowed easy localization of the ^{90}Y by external scanning as described by Simon, Feitelberg, Warner, Greenspan, Edelman, and Baron (1966).

In two experiments, urine and faeces were collected after ^{90}Y injection until death, and in all cases a blood sample was taken immediately after death. These samples were analysed for activity, using the bremsstrahlung in an automatic gamma counter.

The knee joint previously injected with ^{90}Y was then dissected and autoradiographs of microscopic sections of the synovial membrane were prepared, using a stripping film method.

Results

External scanning of the animal showed that 24 hours after injection the ^{90}Y remained localized to the injected joint. By external scanning, no evidence

of radioactivity could be found elsewhere in the rabbit. In particular, there was no evidence of activity over the groin lymph nodes or over the liver.

The thin-window Geiger tube also showed no activity other than at the injection site. The minimum detectable activity for this counter was about $0.1 \mu\text{c.}$, assuming an intervening tissue thickness of 5 mm., but it must be remembered that activity at a depth greater than 11 mm. would not be detected at all.

Very small amounts of activity were detected in the animals' blood, urine, and faeces. Taking an estimated total blood volume for the rabbit, the total activity in the blood amounted to less than 0.2 per cent. of the injected dose, and the 24-hour collections of urine and faeces were found to contain less than 0.4 and 0.13 per cent. respectively.

The autoradiographs of the synovial membrane showed a reasonably even distribution of radioactivity in the cells of the synovial membrane itself. Fig. 1 shows a representative field, where the black grains in the microphotograph show the presence of beta-activity, corresponding to the synovial cells. This we interpret as showing that 24 hours after injection of the radiocolloid into the knee joint, the colloidal particles have been taken up by phagocytosis into the synovial cells, just as has been previously shown with other small particles, as for example in the work of Cochrane, Davies, and Palfrey (1965) using thorium dioxide particles of 50-100Å in size.

At a higher magnification (Fig. 2, overleaf), it can

be seen that the black grains are densely placed over the cytoplasm of the synovial cells, whereas the nuclei stand out as areas relatively free of activity, as would be anticipated if phagocytosis by the synovial cells is responsible for the uptake of the ^{90}Y colloid.

A search among the deeper supporting parts of the synovial membrane showed an absence of any diffuse distribution of black grains, apart from occasional cells. We have assumed that these cells represent wandering macrophages which have taken up ^{90}Y and then left the synovial surface during the 24 hours after injection.

Exactly comparable results were found whether the resin was injected into normal rabbit knee joints or into those in which we had induced the immune arthritis of Dumonde and Glynn (1962), which histologically bears a very close resemblance to rheumatoid arthritis in man.

Summary

A resin colloid of the powerful beta emitter ^{90}Y has been shown to be taken up more or less evenly by normal and inflamed rabbit synovium. Only small amounts of radioactivity were found to escape from the injected joint. This colloid resin of ^{90}Y may therefore be considered for intra-articular injection, where a radiation ablation of synovial membrane is thought desirable.

We thank Mr K. V. Swettenham of the Department of Experimental Pathology, The London Hospital, E.1., who prepared the autoradiographs, and Mr W. M. Brackenbury of the Royal Postgraduate Medical School, who prepared the photomicrographs.

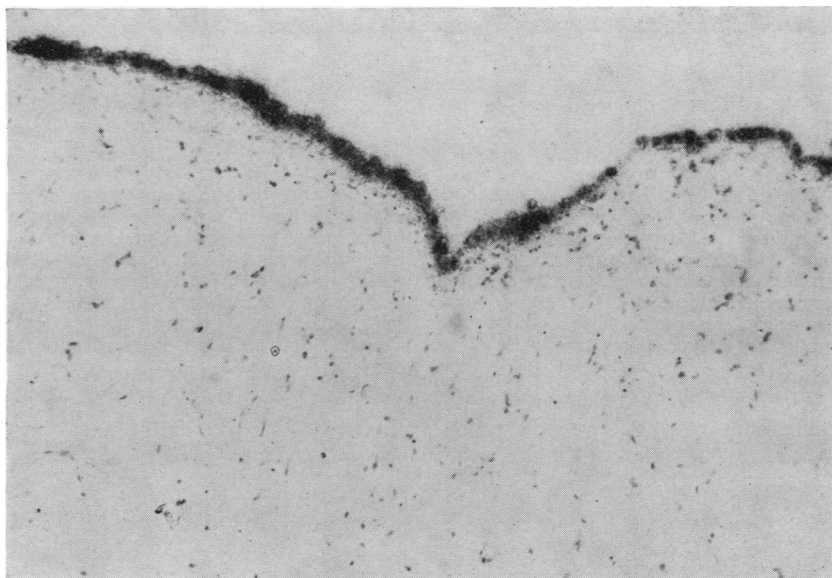


Fig. 1.—Autoradiograph of synovial membrane. $\times 100$.

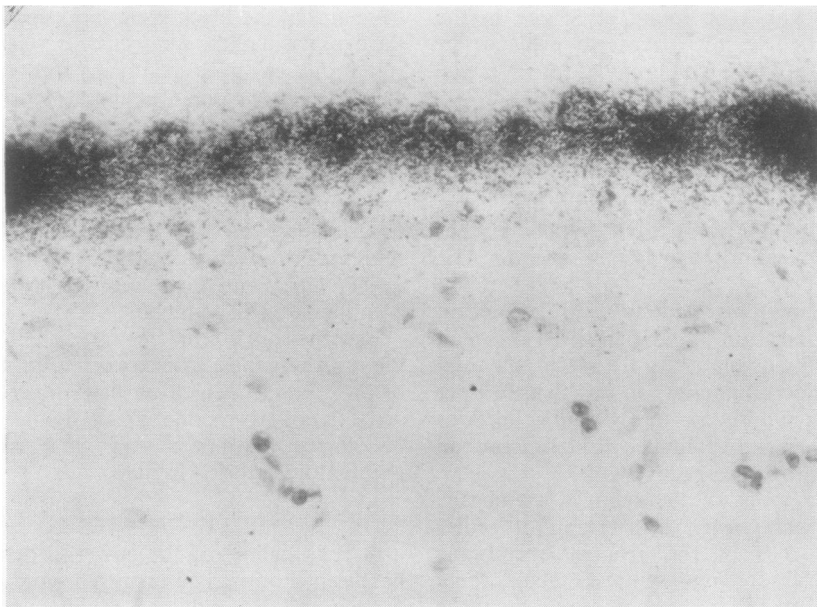


Fig. 2.—Autoradiograph of synovial membrane. $\times 400$.

REFERENCES

- Ansell, B. M., Crook, A., Mallard, J. R., and Bywaters, E. G. L. (1963). *Ann. rheum. Dis.*, **22**, 435 (Evaluation of intra-articular colloidal gold ^{198}Au in the treatment of persistent knee effusions).
- Cochrane, W., Davies, D. V., and Palfrey, A. J. (1965). *Ibid.*, **24**, 2 (Absorptive functions of the synovial membrane).
- Dumonde, D. C., and Glynn, L. E. (1962). *Brit. J. exp. Path.*, **43**, 373 (The production of arthritis in rabbits by an immunological reaction to fibrin).
- Simon, N., Feitelberg, S., Warner, R. R. P., Greenspan, E. M., Edelman, S., and Baron, M. G. (1966). *J. Mt Sinai Hosp.*, **33**, 365 (External scanning of internal beta-emitters).

L'absorption de l'Yttrium radioactif par la membrane synoviale

RÉSUMÉ

Une résine colloïdale de la puissante émettrice beta ^{90}Y a été démontrée comme étant absorbée plus ou moins régulièrement par la synoviale normale ou enflammée du lapin. De petites quantités seulement de radioactivité ont été vues échappant de l'articulation injectée. Cette résine colloïdale de ^{90}Y peut donc se prêter à une injection intra-articulaire, quand une ablation de la membrane synoviale par radiation est pensée désirable.

Absorción de Itrio radiactivo por la membrana sinovial

SUMARIO

Se ha observado que una resina coloidal del poderoso emisor de beta ^{90}Y es absorbida más o menos parejamente por el sinovio de conejo normal e inflamado. Se notó que solamente escapaban pequeñas cantidades de radiactividad de la articulación inyectada. Así pues, esta resina coloidal del ^{90}Y podría ser tenida en cuenta para inyecciones intraarticulares, donde se considera deseable una ablación, por radiación, de la membrana sinovial.