MALIGNANT EFFUSIONS TREATED BY COLLOIDAL RADIOACTIVE YTTRIUM SILICATE*

BY

J. WALTER, M.A., B.M., F.F.R., M.R.C.P.
D.M.R.E.

Clinical Teacher in Radiotherapy, University of Sheffield;
Deputy Medical Director, Sheffield National Centre
for Radiotherapy; Consultant Radiotherapist,
United Sheffield Hospitals.

Intracavitary isotope therapy of malignant effusions in peritoneal and pleural cavities is now commonly practised in many departments. The most frequently used isotope is colloidal radioactive gold (^{198}Au), and details may be found in standard texts of isotope therapy—for example, Hahn (1956) and Beierwaltes *et al.* (1957). Our own experience has also been described (Walter, 1953). It is a form of internal "bath" therapy, in which the serous linings are subjected to irradiation by beta-particles of low penetration (Table I). The mode of action, as well as the mechanism of production of the effusions, is only imperfectly understood. Some of the possible factors include a direct damaging effect on superficial cancer cells, obliteration of capillary blood-vessels and lymph vessels, formation of fibrous layers on the surfaces, and irradiation of local lymph nodes by transported material. The method, however, is clinically effective, and has been found to give useful palliation in about one-third to one-half of the cases treated. The most favourable subjects are those in reasonably good condition, where the repeated effusion is the chief cause of symptoms and there are no large masses of growth. Since the technique is simple and involves only slight inconvenience to the patient, this treatment marks a definite advance in the handling of malignant exudates, as they are usually uncontrollable by present-day conventional external radiation.

In addition to the betas, however, ^{198}Au gives off a fraction of penetrating gamma-radiation†. This has the advantage of making it easy to detect and plot the distribution of active material by a Geiger-counter outside the body. Otherwise it is generally regarded as undesirable, as it gives an unwanted total-body fraction of radiation to the patient, increases the radiation background in the ward (exposure of nurses, etc.), and materially complicates the problem of handling and dispensing, with hazards to physicists, doctors, and others. Search was therefore made for pure beta-emitting isotopes with appropriate characteristics, and interest has centred mainly on two such: (1) phosphorus-32 in the form of colloidal chromic phosphate, and (2) yttrium-90 in various preparations, including the ionic chloride, colloidal phosphate, fluoride, hydroxide, and now the silicate ($^{90}\text{Y}_2(\text{SiO}_3)_3$).

Chromic phosphate has been tried (Root *et al.*, 1954), but does not seem to have established itself, possibly owing to the relative difficulty of preparing it.

Physical Properties of Yttrium-90.—There are two methods of preparation—(1) from decay of strontium-90, which is a fission product of the breakdown of uranium in the nuclear reactor; and the ^{90}Y thus obtained by

separation is *carrier-free*—that is, unmixed with atoms of stable non-radioactive yttrium (^{89}Y); (2) from irradiation of stable ^{89}Y in the nuclear reactor; variable amounts of carrier yttrium will be present, depending on the specific activity obtainable (which in turn depends on the neutron flux available in the reactor). ^{90}Y is prepared at present at Harwell by the second method, and this was used to produce the silicate colloid (Cook *et al.*, 1958). Table I lists the chief physical properties

TABLE I.—Physical Properties of ^{198}Au , ^{32}P , and ^{90}Y

Isotope	Half-life (Days)	Maximum Beta Energy (MeV)	Mean Beta Energy (MeV)	Maximum Range in Tissue (mm.)	Half-value Thickness* (mm.)
^{198}Au	2.7	0.960	0.32	3.8	0.245
^{32}P	14.3	1.707	0.70	7.6	0.65
^{90}Y	2.7	2.260	0.90	10.5	0.98

* Depth in tissue at which dose has fallen to half that at surface.

of interest to the therapist. The beta is much more energetic than that of ^{32}P or ^{198}Au and consequently penetrates to a greater effective distance below the surface. The old argument against the use of pure beta-emitters—that is, that they could not be detected by counters external to the body—is no longer valid, since modern *scintillation counters* can use the "bremsstrahlung"‡ from ^{90}Y betas to give isodose plots quite comparable to those from ^{198}Au (see Fig.).

Biological Properties of Yttrium-90.—The rare-earth elements, of which yttrium is a member, have been subjected to recent intensive study—biochemical, pharmacological, and metabolic (Kyker and Anderson, 1956). There is very little absorption of ionic yttrium after oral, subcutaneous, or intramuscular administration; any fraction reaching the blood-stream is deposited mainly in the skeleton, as yttrium is a *bone-seeker*; much smaller amounts are excreted or taken up by liver and spleen. After intravenous injection the highest uptake is in liver, spleen, and bone-marrow; in fact, ionic yttrium behaves like a colloid, and forms complexes with body proteins. After intracavitary injection, the amount retained in the cavity depends largely on the amount of carrier; with high carrier content, over 90% may be retained and deposited more or less on the serous surfaces (Lewin *et al.*, 1954; Andrews *et al.*, 1956).

Isodose contours obtained from the "bremsstrahlung" after intraperitoneal injection of radioyttrium silicate.

†From the German "Bremse"=brake, and "Strahlung"=radiation. The impact of the betas on the atoms in tissue gives rise to x rays, some of which are sufficiently penetrating to emerge from the body and affect an external counter. These rays are exactly analogous to ordinary x rays produced by the impact of electrons (beta-particles or rays) in an x-ray tube when they are suddenly halted by the target.

*Based on a paper presented at the International Congress of Radiology, Munich, 1959.

†For the relative dose due to gamma-radiation a figure of 10% is sometimes given; however, the ratio will vary considerably with the physical conditions and the point of interest.

Ionic yttrium has been found to be toxic—for example, to mice (Cook *et al.*, 1958), but if we can extrapolate their findings on a weight basis to man there seems to be no real danger; the chloride has been used with apparent success at high carrier levels in patients (Siegel *et al.*, 1956).

Present Investigation

Our work was preceded by an investigation at Harwell using mice (Cook *et al.*, 1958), where a comparison between yttrium chloride, colloidal yttrium silicate, and colloidal gold showed a preferable overall distribution in favour of the silicate.

Preliminary investigation on patients was begun with tracer quantities of the silicate (about 200 μ c.) injected into malignant effusions. The levels of activity in blood in the first few days were found to be low—for example, 0.002–0.02% of administered dose per litre—with correspondingly low urinary output—for example, less than 1% integrated over five days. One post-mortem tissue assay became available six days after 240 μ c. intraperitoneally; this showed low values—for example, the centre of the liver contained 0.00128% per g., which corresponded to 178 rads for a therapeutic injection. A comparable figure (for liver dosage) obtained after 200 mc. of ^{198}Au was 380 rads (Walter, 1953).

Since the tracer investigation pointed to the safety of the new compound, a therapeutic series was begun of patients with intractable effusions. Some of them were in poor condition, with a very bad prognosis because of the extent of growth. It is not very surprising, therefore, that out of 15 patients treated 6 died within one month. These have been neglected in the following assessment, as giving no useful indication of the value of the method.

The quantities injected ranged from 21 to 75 mc., according to the amounts available from Harwell, which were limited. The specific activity obtainable was low, so that the fluid volumes to be instilled ranged from about 100 to 400 ml.; this was of no great moment in abdominal cases, but sometimes involved larger volumes in the chest than we would have wished. The technique was simple, and identical with that used for gold (Walter, 1953). After previous tapping of most of the exudate, a simple funnel with tubing was used to instil the first 50 ml. of saline, then the colloid, then a final 50–100 ml. of saline to flush the tubing, all by gravity feed. The patient was rotated in the theatre and later in the ward, and intermittent raising of the foot of the bed for several hours all helped to ensure good mixing and as uniform a distribution of the isotope as conditions allowed. Samples of blood and cavity fluid were withdrawn at intervals, so far as the patient's condition permitted; urine was estimated in daily batches; and a body scan was made after 24 hours. Distribution was almost always satisfactory; one case of loculation was found. General reactions were minimal, and there was no obvious effect on the blood count.

TABLE II.—*Results of Treatment with Intracavitary Radio-yttrium Silicate. (Total Cases, 15. Died Within One Month, 6)*

Pleural	Peritoneal
Satisfactory at 5 months	Satisfactory at 5 months
" " 9 "	" " 10 "
" " 19 "	No effect at 6 months (died)
No effect at 8 months (died)	" " 14 "

In all pleural cases the primary was in the breast. In all peritoneal cases the primary was in an ovary.

Table II summarizes the clinical results. "Satisfactory" connotes reasonable freedom from symptoms and the need for tapping. Out of the nine cases listed, therefore, useful palliation was achieved in six, for periods of time ranging from 5 to 19 months. The number is, of course, small, but these results compare very favourably with those reported for ^{198}Au by ourselves and others, in the region of 50% receiving useful palliation.

Blood and urine levels never gave cause for anxiety—for example, 0.001% /litre in blood at four hours and 0.003% at 29 hours; and 0.04% in urine integrated over 48 hours. Three post-mortem assays were made at 11, 3, and 1.5 days after injection; the liver doses corresponded to 244, 4.7, and 12 rads respectively.

Serial assays of cavity fluid showed that in most cases (9 out of 12) precipitation was quite marked and quite rapid, as judged by the concentration of activity in the fluid—for example, 7.4% /litre at four hours and 3.3% at 48 hours. After the first day the fall of activity in the fluid was only gradual.

Discussion

From the physical standpoint the most striking feature of ^{90}Y in the present context is its energetic beta-radiation (Table I) and consequent superior depth-dose as compared with gold or phosphorus. In order to compare depth-doses, we must make some assumptions about the geometrical conditions in the body cavities, concerning the possible thicknesses of fluid layers, etc. It can then be shown that the ratio of depth-dosage $^{90}\text{Y}/^{198}\text{Au}$ rises to a maximum of about 3.1–3.6 at a depth of 1.5 mm. The effective ratio for $^{90}\text{Y}/^{198}\text{Au}$ will, of course, vary with the physical conditions obtaining, but a tentative figure might be between 2 and 3.

Yttrium compounds have not yet received extensive clinical investigation as intracavitary agents. Most of the work published so far concerns preliminary animal, or human tracer, investigations. Of this work, most has been done with yttrium chloride, and it gradually became clear that large carrier quantities of yttrium were necessary to ensure adequate localization in the cavity. One therapeutic series has been reported from New York (Siegel *et al.*, 1956); 10–30 mc. of ^{90}Y as chloride was used, with 100–200 mg. of yttrium carrier, and 8 out of 16 patients derived useful benefit. The levels in blood, urine, liver, etc., reported by them appear to be roughly comparable with ours.

Theoretically, early precipitation on to the serous surfaces would seem desirable in order to achieve the maximal radiation effect. High-carrier chloride seems to deposit more slowly than the silicate, if we compare our findings above with published reports (Laszlo, 1956; Andrews *et al.*, 1956). This is a possible advantage of the silicate, if our findings are typical. The actual distribution on the serous surfaces is very irregular indeed, as our post-mortem assays showed, but this is not likely to be due to inadequate mixing, which would be expected to show up in the body scan (see Fig.) Similar wide variations are also found with ^{198}Au (Walter, 1953).

From the standpoint of protection and diminution of radiation hazard to personnel, there is no question that ^{90}Y would be a boon as compared with ^{198}Au . If experience confirms its safety, it could well replace ^{198}Au for intracavitary work. Nowadays, of course, intracavitary isotope therapy has to compete with chemotherapy

(intracavitary nitrogen mustard, thiotepe, etc.), but it still has a place where alternative methods fail, as they often do.

The comparative merits and demerits of the various preparations of yttrium have still to be determined and checked against clinical experience. In the colloidal silicate we appear to have a substance of promise, worthy of further investigation.

It is proposed to publish elsewhere full technical details of the above investigation, including physical data on dosage, post-mortem assays, activity in blood, urine, and cavitary fluid, etc.

Summary

As an alternative to radioactive gold for control of malignant pleural and peritoneal effusions, the use is described of a new compound, colloidal radioactive yttrium silicate ($^{90}\text{Y}_2(\text{SiO}_3)_3$). A preliminary report is made of its therapeutic use in 15 cases. Out of nine cases surviving over one month, six received good palliation for 5 to 19 months. The advantages of yttrium over gold are discussed, especially the superior surface penetration of the beta-particles and the lesser radiation hazards owing to absence of penetrating gamma-radiation.

Thanks are due to my physicist colleagues, on whom this work depended, in particular Mr. J. C. Jones (now at the Royal Marsden Hospital, London), and Mrs. Monica Fisher; to my colleague, Dr. Frank Neal, for helpful liaison; to Mrs. Ruth Martin for secretarial assistance; and to Miss D. Wemm for the Figure.

REFERENCES

- Andrews, G. A., Kniseley, R. M., Palmer, E. L., and Kretchmar, A. L. (1956). *Proceedings of International Conference on Peaceful Uses of Atomic Energy*, 10, 122. United Nations, New York.
- Beierwaltes, W. H., Johnson, P. C., and Solari, A. J. (1957). *Clinical Use of Radioisotopes*. Saunders, Philadelphia.
- Cook, G. B., Miles, B. J., Neal, F. E., and Thomson, A. R. (1958). *Strahlentherapie*, 38, Sonderbände, p. 348.
- Hahn, P. F. (Editor) (1956). *Therapeutic Use of Artificial Radioisotopes*. Wiley New York.
- Kyker, G. C., and Anderson, E. B. (Editors) (1956). *Rare Earths in Biochemical and Medical Research*. Oak Ridge Institute of Nuclear Studies, 12.
- Laszlo, D. (1956). *Ibid.*, p. 193.
- Lewin, R., Hart, H. E., Greenberg, J., Spencer, H., Stern, K. G., and Laszlo, D. (1954). *J. nat. Cancer Inst.*, 15, 131.
- Root, S. W., Tyor, M. P., Andrews, G. A., and Kniseley, R. M. (1954). *Radiology*, 63, 251.
- Siegel, E. P., Hart, H. E., Brothers, M., Spencer, H., and Laszlo, D. (1956). *J. Amer. med. Ass.*, 161, 499.
- Walter, J. (1953). *Proc. roy. Soc. Med.*, 46, 466.

"The aims of the Association of Social Workers and also present-day thought in social work show that there are elements common to all social work practice whatever its setting. To discern these common elements, recast them as a discipline and find effective ways of teaching them is a major challenge which merits special study and research. Evaluation studies of techniques in casework are needed and the criteria of success and failure in casework practice require to be explored. So far only small sporadic studies of this kind have been made in Britain. The probation field with its preponderance of unwilling clients would seem to offer a unique opportunity for comparative studies into the histories of such clients and for analysing the ways in which they can be enabled to draw help from the relationship with the worker and from the resources of the community. Such studies might well have a bearing on future social planning and could usefully have a wider reference to include analyses of existing training, work studies, and job evaluations in each of the social work specialties." (*Evidence Submitted to the Departmental Committee on the Probation Service*, Association of Social Workers; price 1s. 6d.)

DYSTROPHIA MYOTONICA IN CHILDHOOD

BY

T. M. VANIER, M.B., M.R.C.P.

Assistant Medical Registrar, Hospital for Sick Children,
Great Ormond Street, London

The clinical development of dystrophia myotonica in adults is commonly the following: a family history of senile cataracts in an early generation, of presenile cataracts in the next, and finally the full picture of the disease in the third. The early development and evolution of the disease in infants and children, of whose parents one may show only certain features of dystrophia myotonica, is less familiar. Six such cases have been seen at the Hospital for Sick Children in the past five years. Only three cases of myotonia congenita are recorded over the same period, and yet this disease, while it, too, is rare, is reputedly of earlier onset than dystrophia myotonica. Though the two diseases present differently and have a widely different prognosis, there is no doubt that they are interrelated. There are records of patients with myotonia congenita diagnosed in childhood who many years later developed stigmata of dystrophia myotonica; also of families in which the two diseases have occurred in different individuals (Maas and Paterson, 1950; Walton and Nattrass, 1954).

Because dystrophia myotonica is not widely recognized as a cause either of flaccid paresis in infancy (amyotonia congenita syndrome of Oppenheim) or of congenital facial diplegia the following cases are reported.

Case Histories

The diagnosis was made while the child was under the care of the physician whose name appears in parentheses, and at the first age mentioned. When a second figure for age is given this indicates the length of follow-up. In no family is there parental consanguinity.

FIG. 1.—Case 1. Dystrophia myotonica in girl aged 13.

Case 1.—Girl (Dr. P. H. Sandifer) 13 years (Fig. 1). Breech delivery after normal pregnancy. Bilateral talipes noted shortly after birth. Difficulty with sucking. Floppy infant. Delayed motor and speech development. Assessed as ineducable. No history of deterioration in performance. On examination: mentally retarded. Complete bilateral facial paralysis, ptosis, wasted temporal muscles but strong