INTRACAVITARY COLLOIDAL RADIOGOLD IN THE TREATMENT OF EFFUSIONS CAUSED BY MALIGNANT NEOPLASMS*

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PATIENTS WITH INOPERABLE NEOPLASMS involving the peritoneal or pleural surfaces often develop collections of fluid. In many instances, the fluid is of only incidental importance, but there is a large group of patients in whom rapid fluid collection, necessitating frequent paracenteses, constitutes the most annoying cause of symptoms during a considerable part of the survival period. For many years, roentgen ray therapy has been used in an effort to control these effusions, sometimes with good results. The radiation sickness which is often associated with conventional roentgen ray therapy directed to large areas of the body and the uncertainty of benefit have discouraged some radiation therapists from treating this group of patients.

The general suitability of Au^{198} as an isotope for the treatment of neoplasms has been emphasized by Hahn and his associates.[3, 4] Müller, a Swiss investigator, suggested in 1949 that the injection of colloidal radioactive gold directly into the body cavity might be an effective form of treatment for effusions caused by neoplasms and he is believed to be the first to use the isotope in this way.[8] Subsequently, several research groups have undertaken studies of this form of treatment.[5, 6] Late in 1950, our own studies were begun. At the present time we wish to report the method of administration, dosage and preliminary clinical results. In other publications[1, 7] information on the fate and distribution of the injected isotope and on the histologic effects of the treatment will be reported.

Gold 198 is a thermal neutron-produced isotope available in abundant quantities and in high specific activity. Its half-life is 2.7 days. On disintegration it produces a beta particle of 0.98 Mev and two gamma emissions of 0.12 and 0.41 Mev. Its effect in the body is believed to be largely that of the beta emission which penetrates only a few millimeters in tissue, and thus the radiation is localized to the immediate vicinity of the radioactive gold.

The gold 198 is in the form of a sterile colloidal solution† The preparation use usually contained at the time of injection from 10 to 25 millicuries per ml., but in a few instances solutions of lower activity were used. The amount of stable gold present was generally between 3 and 9 mg. per ml.

In this form the gold does not ionize appreciably and remains relatively inert biologically. When injected into a body cavity, most of the radioactive particles stay in or near the walls of the cavity.

Selection of Cases. The ultimate value of this treatment is unknown and it may be that further studies will indicate a wider

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† Purchased from Abbott Laboratories, Chicago, Illinois.

usefulness for it than is now apparent. Up to the present, we have limited its use to patients who have incurable neoplasms, in whom the collection of fluid in the pleural cavity or abdominal cavity is a cause for significant symptoms. Most of the patients selected for treatment have required multiple paracenteses for relief of symptoms. The most suitable patients are those who are in relatively good condition and who have no important symptoms except those related to the fluid. The presence of large masses of neoplastic tissue has appeared to be an unfavorable sign, but we have not refused to treat patients because of such masses. Patients who are becoming rapidly worse and who appear to be in nearly terminal condition do not appear to be helped significantly by this treatment.

We have not treated patients who have multiple peritoneal or pleural implants but who have no fluid collection. It may be that such individuals would benefit from intracavitary radiogold, and that later effusions could be prevented. Experimental treatment of such patients would be desirable. The prophylactic use of radiogold in patients who have no known metastases, but who have lesions which are considered likely to spread to the peritoneum, may also be worth consideration. In such cases, the potential harmful effects of the radiation in patients who may possibly have had all tumor resected should be given serious consideration.

In our series of patients, a considerable number were treated who were highly unsuitable for treatment. These included patients in practically terminal condition, and patients who had only small amounts of fluid and severe symptoms due to other manifestations of neoplasm. In these instances, the treatment was given primarily for the information which could be obtained and in the hope that some slight palliative effect might occur.

Mode of Administration. The radioactive gold is injected directly into the affected cavity. The method of administration is essentially the same for pleural and peritoneal cavities. Because of the energetic gamma emission of the gold, the personnel protection problem is important. Our plan of administration has been as follows: after preliminary studies are completed, a paracentesis is done on the day of treatment or the day preceding treatment. Most of the fluid is removed from the cavity so that there will not be excessive dilution of the gold. However, we avoid removing so much fluid that the space will be difficult to locate. A 15 gauge needle is usually used for the thoracentesis, and after most of the fluid is removed, a 25 cm. segment of polyethylene tubing is inserted through the needle so that several centimeters of it are within the body cavity. The tubing* used has an outer diameter of 1.52 mm. and an inner diameter of 0.86 mm. The outer needle is then withdrawn from around the tubing and a purse-string suture placed in the skin and subcutaneous tissue and tied so that the polyethylene tube is held tightly in place. It is felt that the polyethylene tubing is of great advantage in this administration because once it is in place, it remains fixed in position in the cavity. In contrast, a needle held in position by hand would result in considerable radiation exposure to the physician, and there is always the possibility that as a result of change in position of the patient, a viscus may be penetrated or the needle may be pulled out so that the gold would be discharged into the tissues of the body wall.

After the polyethylene tubing is in place, a 20 gauge needle is inserted into its outer end and this, in turn, is attached to the rubber tubing of a special apparatus† which

* This tubing is supplied by Clay-Adams Company, catalog number P 100.

† Commercially available from A. S. Aloe Company, St. Louis, Mo.

resembles an intravenous infusion set. This apparatus is arranged so that by means of a Y-tube and three separate screw clamps, it is possible to administer physiological saline or the radioisotope, in mixture or alternately, and it is possible to rinse with saline the isotope container. All this can be done while the operator is at a safe distance from the isotope, since the clamps can be adjusted by a metal rod about three feet long. The gold is allowed to drip in at a moderate rate and the tubing and isotope container are rinsed at least three times so that the total administration requires approximately half an hour. Usually, about 200 or 300 ml. of physiological saline solution are used for the rinsing procedure. After the administration is complete, the polyethylene tubing is withdrawn, either immediately or within the next day or two. The opening is inspected and if there is any leakage of fluid, additional sutures are rapidly placed, with a minimum of time spent near the patient. The patient is then moved about to facilitate spread of gold within the fluid of the body cavity. When the gold is injected into the pleural cavity, the patient is asked to assume a head down position over the side of the bed as in postural drainage, in order to let the fluid reach the apex of the lung. No elaborate method of mixing the fluid has been undertaken. It is desirable that the patient change position every five minutes for the first hour and at frequent intervals during the next 12 hours.

TABLE I.—*Results of Intracavitary Colloidal Au^{198} for Fluid Accumulations in Malignancy.*

Good control of fluid	9
Slight or questionable decrease	4
Death from primary disease too early for evaluation	7
Failure	1
Indeterminate	3
Total	24

After the gold has been administered, the hazard to personnel is still significant. Unless there is leakage of the isotope out of the opening through which it was injected, this hazard is almost entirely that of the gamma radiation coming from within the patient. Since relatively little of the isotope is excreted, the handling of feces and urine presents no serious problem. General technics used in dealing with the radiation hazard at this hospital have been reported elsewhere.[2]

Immediate Effects of Treatment. The patients notice no particular discomfort during the administration of the radiogold. About 12 to 24 hours following treatment, some of them have nausea and vomiting. This may last for two or three days, and is quite variable in severity. It is more prominent with intraperitoneal administration than with intrapleural administration. A moderately severe diarrhea has occurred also in a few patients given intraperitoneal radiogold. A few patients have required intravenous fluids in the immediate post-treatment period, but there have been no serious or prolonged unfavorable reactions even when rather large doses have been given. Along with the nausea and vomiting, patients have had considerable weakness and malaise which usually disappears promptly. Patients given intrapleural radiogold sometimes have a distinct pleuritis with the presence of a pleural friction rub and some pleural and diaphragmatic pain.

Bone marrow depression of slight degree has been produced in many of the patients as a result of the radiogold treatment. One patient, E. B. R., who was given very large amounts of the isotope, a total of 501.4 mc. in divided doses, had a rather pronounced but not alarming bone marrow depression from which recovery promptly occurred.

Dosage. At the present state of experience, very little is known about the optimal dosage. Our early patients were treated with multiple, rather small doses,

TABLE II.

Initials Age Sex	Diagnosis and Physical Findings	Intrapleural Treatment with Au^{198}	Effect On Fluid and Outcome
J. T. H. 63 ♂	Bronchogenic carcinoma.	184.6 mc. intrapleurally in one injection.	Fluid collection definitely decreased after treatment. Patient died eight weeks after treatment, from further growth of the tumor.
E. K. 48 ♀	Ovarian adenocarcinoma with abdominal and pleural metastases. No palpable abdominal mass; no parenchymal pulmonary lesions by roentgenogram.	200 mc. single injection into right pleural cavity. (Technical difficulties with administration made actual amount given about 10 per cent less than this.)	Distinct decrease in pleural fluid reaccumulation and change from grossly bloody to slightly blood tinged. Died 90 days following Au^{198}.
S. W. 61 ♀	Squamous carcinoma probable primary in lung with pleural metastases. No large pulmonary masses.	360.9 mc. intrapleurally in 5 injections over five month period.	Distinct decrease in fluid reaccumulation with change from grossly bloody to blood tinged, and disappearance of malignant cells. Died 144 days after first Au^{198} Autopsy.
L. R. 18 ♂	Hodgkin's Disease.	Single injection 200 mc. left pleural cavity.	Fluid reaccumulation decreased, but evaluation complicated by treatment with roentgen ray and nitrogen mustard. Died five months after treatment with Au^{198}.
G. E. C. 44 ♂	Lymphosarcoma with left hydrothorax.	228.5 mc. total intrapleurally in five weekly injections.	Fluid originally loaded with primitive lymphosarcoma cells. After treatment there were fewer malignant cells, more neutrophils. No clinical empyema. Fuid gradually became thinner and collected slightly less rapidly. Little if any benefit from treatment. Patient died 11 weeks after intrapleural injection. Autopsy.
J. C. 72 ♀	Adenocarcinoma of ovary with abdominal and pelvic metastases. No large abdominal masses palpable.	Single injection 196 mc. into intraperitoneal cavity.	Distinct decrease in reaccumulation of ascitic fluid. Patient living 4 months after treatment.
I. W. 58 ♀	Adenocarcinoma of ovary or uterus with pelvic, abdominal, and pleural metastases. Large abdominal mass.	Single injection 205 mc. into peritoneal cavity.	Died 9 days following injection of Au^{198}. No evaluation possible.
A. B. 45 ♀	Adenocarinomatosis of abdomen, primary site not known. (? ovary). Large abdominal masses.	Single injection 153.5 mc. into peritoneal cavity.	Died 24 hours after Au^{198} injection. No evaluation possible. Autopsy.
J. B. M. 54 ♀	Carcinoma of the uterus with abdominal metastases. Large abdominal mass.	Single injection 232 mc. into peritoneal cavity.	Died 49 days after Au^{198}. Colostomy required for intestinal obstruction due to tumor. Evaluation of Au^{198} effect unsatisfactory.
P. T. 43 ♀	Carcinoma undifferentiated of stomach with abdominal metastases.	Single injection 187 mc. intraperitoneally.	Died too soon for evaluation; 2 weeks after Au^{198} given. Autopsy.
C. F. 42 ♂	Adenocarcinoma of pancreas with chylous ascites and pleural effusion.	Single injection 122 mc. intraperitoneally, 309 mc. intrapleurally in 5 injections, over 3½ month period.	No significant decrease in fluid reaccumulation. Died 4 months post Au^{198}. Autopsy.
M. B. R. 76 ♀	Mucinous adenocarcinoma of stomach resected; peritoneal metastases. No large abdominal masses.	97 mc. total intraperitoneally in 2 injections two weeks apart.	No recurrence of fluid in brief period of observation. Patient died 19 days after first treatment from pneumonia and lung abscess, believed unrelated to gold therapy. No opportunity to evaluate treatment. Autopsy.
B. B. 47 ♀	Adenocarcinoma of ovary with peritoneal metastases. Large abdominal masses.	46.2 mc. total intraperitoneally in 7 small doses, over period of two months.	Amount of ascitic fluid decreased after laparotomy and small doses of gold. Patient died of intestinal obstruction about 2 months after gold given. Autopsy.

TABLE II.—(*Cont'd*)

Initials Age Sex	Diagnosis and Physical Findings	Intrapleural Treatment with Au^{198}	Effect On Fluid and Outcome
H. I. 48 ♀	Pseudomucinous carcinoma of ovary. Large abdominal metastases.	474.3 mc. total given intraperitoneally in 10 injections over a 3 month period.	Large amount of gelatinous material in the abdomen at laparotomy, but no fluid was ever aspirated and the effect of treatment difficult to ascertain. No distinct effect of the treatment upon the growth of the masses in the abdomen. The patient had a moderate temporary hematologic depression following the treatment. Her general condition remains fairly good 11 months after last Au^{198} injection. No ascites, but continued slow growth of abdominal mass.
J. F. 70 ♂	Adenocarcinoma sigmoid colon.	49.7 mc. in one injection intraperitoneally.	No effect noted in brief time patient lived (10 days) following the injection. Colostomy done because of intestinal obstruction prior to injection of Au^{198}.
W. H. A. 69 ♂	Sclerosing small cell carcinoma involving peritoneal surfaces and umbilicus-primary site undetermined.	204 mc. in one injection intraperitoneally.	Fluid collection stopped after treatment. Patient has not had recurrance of ascites as of 8 months after treatment.
A. P. 56 ♀	Papillary adenocarcinoma of ovary. No large abdominal masses.	220 mc. intraperitoneally in one injection.	Definite decrease in reaccumulation of fluid. Died 5 months after treatment. Autopsy.
G. V. 49 ♀	Papillary adenocarcinoma of ovary. Large abdominal mass.	153 mc. intraperitoneally in one injection.	Definite decrease in reaccumulation of fluid. Enteroenterostomy done because of intestinal obstruction due to tumor 15 days following treatment with Au^{198}.
A. M. 69 ♀	Pseudomucinous cystadenoma of ovary (Pseudomyxoma peritonei). No abdominal masses.	659 mc. intraperitoneally over 10 month period in 9 injections.	Some decrease in fluid reaccumulation but difficult to evaluate therapy because of difficulty in aspirating gelatinous fluid. Died 13 months after first injection of Au^{198}. Autopsy.
L. C. 35 ♀	Adenocarcinoma breast with metastases to pleura. No parenchymal pulmonary metastases.	142 mc. total in 4 weekly injections right pleural space.	Definite decrease in reaccumulation of fluid. No fluid for 14 months after last treatment. Died 14 months after Au^{198}.
G. H. 57 ♀	Adenocarcinoma of breast with pleural metastases.	210.7 mc. intrapleurally in single injection.	Rate of fluid formation decreased slightly. Death 2½ months after treatment. Possible slight benefit from treatment. Autopsy.
J. W. K. 54 ♂	Lymphosarcoma. No large masses.	185.8 mc. intrapleurally in one injection.	Slight decrease in rate of fluid formation. Death 3 months after gold therapy. Disease became rapidly generalized a few weeks before death.
E. B. R. 37 ♀	Papillary adenocarcinoma of ovary.	501.4 mc. in 6 doses over 6 weeks period. Injected chiefly into lesser omental cavity at operation.	Distinct decrease in fluid formation. Symptoms of intestinal obstruction lessened following treatment. Good palliative result.
B. S. 47 ♂	Malignant mesothelioma involving pleura and peritoneum. Large abdominal tumor.	240 mc. intraperitoneally in two injections (170 and 34 mc.), one month apart.	Slight decrease in rate of fluid formation. Patient died 40 days after treatment. Autopsy.

and subsequently we have tended to give single, rather large doses. In the early period, we did not realize that even in the favorable cases there was sometimes a considerable lag between the administration of the isotope and the cessation of fluid formation, and some of the initial small doses which seemed inadequate may not have been so. It is our impression that the dosage required for the peritoneal cavity is larger

than that required for the pleural cavity. It appears that a more profound systemic effect occurs from a given dose if it is injected into a relatively normal cavity with only a few nodules of tumor, than occurs from the same dose injected into a cavity completely surrounded by thick fibrotic tumor. We believe that the dose should be adjusted to the individual patient and that in many instances, it is justifiable to give a relatively small dose and to follow it by a larger one, if after several weeks there is no effect from the initial treatment. We would suggest that doses of 75 mc. in the chest and 150 mc. in the abdomen not be exceeded as initial doses. Many of our patients were treated with larger doses than this, but it is our present feeling that similar results might have been obtained with somewhat smaller amounts. The disadvantage of excessive doses seems to be chiefly that of excessive local fibrotic reaction, rather than systemic radiation damage.

Results of Treatment. Table I gives a brief summary of the immediate clinical effects of treatment in 23 cases. Table II gives more detailed information about the same group of patients.

Patients who have favorable results often continue to collect fluid for a few weeks after treatment. In some of these patients the fluid became clearer and contained less blood after treatment. Another evidence of improvement was seen in the disappearance of malignant cells from the fluid aspirated from these cavities. Of the eight patients who had good clinical results from treatment, four had had previous roentgen ray therapy without control of the fluid. Two of these, however, had discontinued therapy before completion of the planned course because of severe radiation sickness. Of the eight patients who had good control of fluids, four had a distinct improvement in their general well being, as well as control of the fluid.

The patients who died soon after treatment were individuals who were in late stages of disease and were not particularly suitable for the radiogold treatment because of cachexia and massive neoplasm. Intestinal obstruction was a prominent problem in these patients. The patients who had slight or questionable decrease in the fluid included two patients with lymphosarcoma, G. C. and J. W. K. Two patients who had pseudomucin forming carcinoma of the ovary, with extensive peritoneal involvement, are listed as having indeterminate results. Neither of these patients had fluid which could be easily aspirated and it was very difficult to establish any definite effect from the treatment. One of them, H. I., is doing well at the present time. The other, A. M., having received a total of 659 mc. of radiogold over a period of ten months, died in a state of cachexia after a prolonged period of vomiting. At autopsy, the peritoneal cavity showed a profound fibrotic reaction with adherence of loops of small bowel to each other. There was also extensive neoplasm compressing the intestinal tract in several areas, but there was no definite obstruction from either the neoplasm or the fibrosis.

One patient, E. B. R., had an unusual fluid collection localized in the omental bursa. She was treated by repeated laparatomies and injection of the gold directly into this space instead of into the greater peritoneal cavity. Following treatment, the collection of fluid decreased and symptoms of obstruction were relieved at the same time that the patient's general condition improved.

DISCUSSION

The results appear to us to indicate that intracavitary colloidal radiogold injection is of distinct palliative value in selected cases. It appears to produce less radiation sickness than a course of conventional roentgen ray therapy. It is relatively simple to administer and the unfavorable reactions appear to be minimal.

The mode of action of the treatment is not clearly understood. Presumably the effect of radiation on the superficial surfaces of neoplastic tissues lining the body cavities is important in controlling the fluid. It is not certain, however, that the effect of radiogold on normal tissues is not important in producing the effect seen. Further studies on fate and distribution of the gold and the histologic effects produced may contribute to the understanding of the mode of action.

There is little evidence as yet to suggest any benefit from this treatment except the control of fluid and resulting symptomatic improvement. However, it is not certain that the therapy will not have a more fundamental effect in certain patients whose neoplasm is localized to very superficial plaques immediately on the surface of the body cavity.

SUMMARY

1. Intracavitary injection of colloidal radiogold appears to be a worthwhile palliative measure in selected patients with pleural effusions or ascites caused by malignant neoplasms.

2. The results of such treatment in a group of 24 patients are reported.

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