

METABOLISM AND DISTRIBUTION OF COLLOIDAL Au¹⁹⁸ INJECTED INTO SEROUS CAVITIES FOR TREATMENT OF EFFUSIONS ASSOCIATED WITH MALIGNANT NEOPLASMS

712405

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IN THE COURSE of a study of the use of colloidal Au¹⁹⁸ in the treatment of ascites and pleural effusions, data have been collected on the distribution and excretion of this isotope. This form of treatment, suggested by Müller, has proved of some value in symptomatic therapy of patients who have massive fluid collections resulting from metastatic neoplasms involving serous cavities. Clinical results of therapy in our series of cases have been previously reported.¹ The purpose of the present report is to present information upon the fate of the injected material and to record some of its general effects.

METHODS

The material used in these studies was a preparation of colloidal Au¹⁹⁸ containing a total amount of gold usually ranging from 3 to 20 mg. per ml. The radioactivity varied from 10 to 25 mc. per ml., except in a very few cases in which preparations of lower activity were used. Single doses varied from 10 to 235 mc. Details of dosage and method of administration have been reported.¹ The isotope was usually injected through a polyethylene tube inserted into the body cavity.

This report is based on the study of thirty patients who had pleural or peritoneal effusions associated with carcinomatosis. Tissue studies of radioactivity were made on thirteen cases examined at autopsy, laparotomy, or both. In several patients two polyethylene tubes, some distance apart, were inserted—one for administration of the gold and one for withdrawal of fluid for determination of radioactivity (Fig. 1). It was believed that fluid drawn through the tube of administration should not be used for assay, because it might have arti-

ficially high values as a result of poor mixing in the cavity and contamination at the time of withdrawal. Daily complete twenty-four-hour urine specimens and frequent blood samples were collected and assayed for radioactivity. Stool specimens were not assayed after extremely low levels of activity were found in those from the first two patients studied. Biopsy and autopsy specimens were obtained for histological study, radioassay, and autoradiographic exposures. All radioassays were performed by liquid techniques. Solid tissues were dissolved in concentrated nitric acid in preparation for assay, while urine and plasma were untreated or were simply diluted with water. In all cases, a 10-ml. specimen was placed in a standard small Petri dish and assayed under a calibrated end-window Geiger tube. All values were corrected for radioactive decay to the time of administration of the isotope. The autoradiograms shown in Figs. 4, 9, and 10 were prepared from gross tissue. The soft tissues were frozen solid in a deep freeze, sliced, and exposed on no-screen film for varying lengths of time. The exposure depended on the degree of radioactivity. The bone autoradiograms were prepared by the method of Lotz, Gallimore, and Boyd.

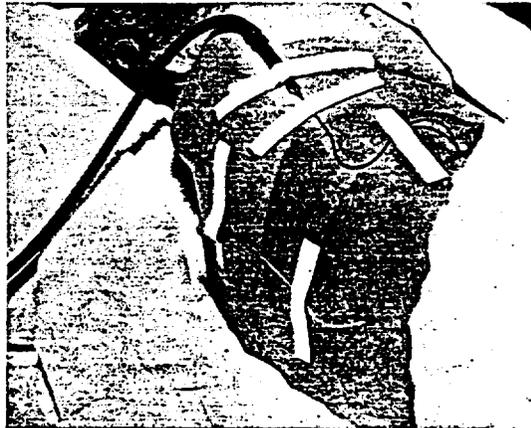


FIG. 1. Photograph of patient during injection of colloidal Au¹⁹⁸ into the pleural cavity. The additional polyethylene tube is for withdrawal of samples of pleural fluid after treatment.

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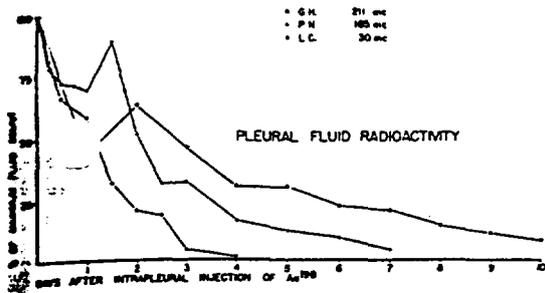


FIG. 2. Radioactivity of pleural fluid following intrapleural injection of colloidal Au¹⁹⁸. All values are corrected for radioactive decay.

FATE OF THE ISOTOPE IN THE CAVITY

After injection of the colloidal Au¹⁹⁸, the patients were asked to move about at frequent intervals during the first few hours. Our experience suggests that complete mixing of the gold with the fluid in the cavity usually occurs within the first few hours. This was shown in surveys of radiation levels at the surface of the body made by means of a collimated Geiger tube. Additional evidence of this even distribution in the cavity is found in the radioactivity levels of fluid drawn from the cavity at sites distant from the point of injection. It is found that the fluid at these sites reaches a maximum radioactivity very rapidly.

In several patients, rather extensive records were made of the radioactivity levels of the fluid in the cavities for several days after the radii 1 injection, and Figs. 2 and 3 show these data. The fall in concentration of radioactivity, after correction for decay has been made, must be due to dilution of the gold by further fluid production or removal of the gold from the fluid or both. It is known that active effusion of fluid may continue for some time after the gold is given, even in patients who respond favorably to the treatment. However, it is not possible that there was sufficient dilution of the gold in the cavities to explain the

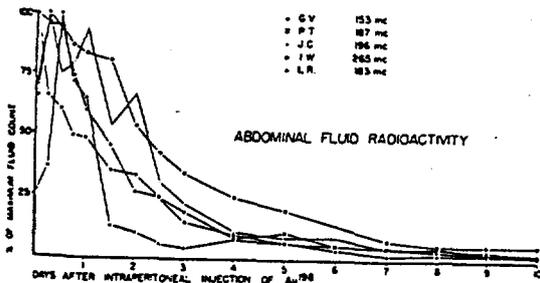


FIG. 3. Radioactivity of ascitic fluid following intraperitoneal injection of colloidal Au¹⁹⁸. All values are corrected for radioactive decay.

major part of the fall in concentration of radioactivity, since this would have required a much greater increase in volume than ever occurred. Studies of blood and urine levels of radioactivity in the period immediately following administration show that there is little absorption or excretion of the gold colloid, and external counting assays over the liver indicate that there is not a prominent localization in this organ. Furthermore, tissue assays indicate that a large portion of the radiogold becomes fixed in a superficial position on the serous surfaces. Autoradiograms confirm this distribution of the isotope (Fig. 4). The exact mechanism of this deposition is not known but it is believed to be a property of the colloid in relation to the surface. A similar tendency of the colloid to become attached to surfaces is seen in vitro. Another important event is phagocytosis of gold

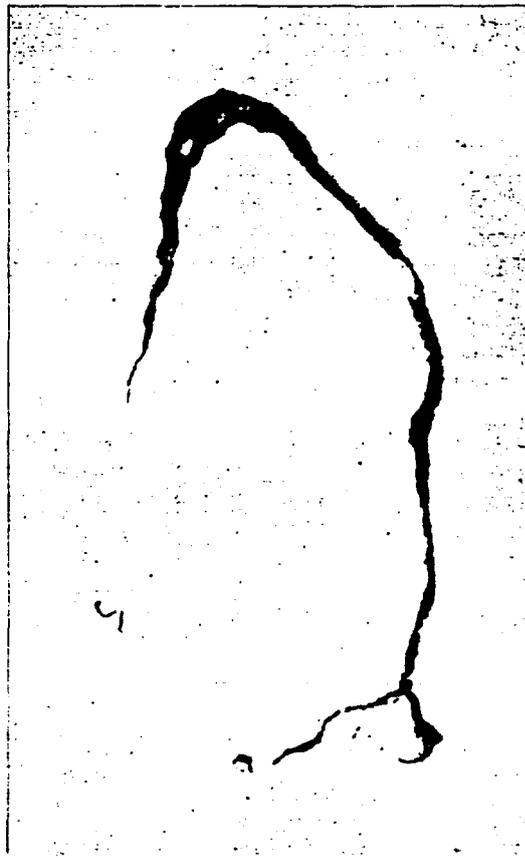


FIG. 4. Gross autoradiogram of lung of patient I. B. who received 78.4 mc. of colloidal Au¹⁹⁸ intrapleurally sixteen days before death. The width of the area of blackening is partly explained by the fact that the pleural surface was not perpendicular to the film but was folded and partially flattened against the film. The actual penetration in the tissue was thus less than it appears on the autoradiogram.

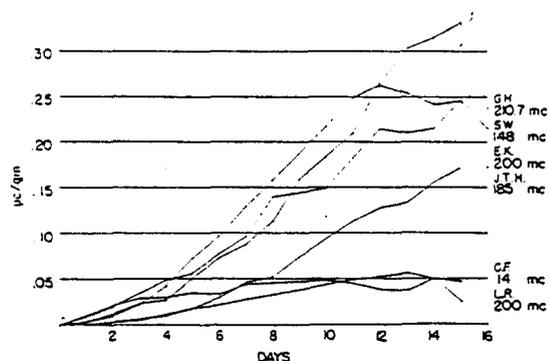


FIG. 5. Radioactivity of plasma following intrapleural injection of Au^{199} in six patients. (Corrected for decay.)

particles by macrophages on the walls of the cavity and free in the fluid.

BLOOD RADIOACTIVITY

Venous blood was obtained daily after treatment, heparinized, and, after centrifugation, red-cell and plasma fractions were assayed for radioactivity. The plasma showed levels of activity considerably greater than those of the red cells. Since the red-cell samples were not washed, the activity recorded for them may have been all or in part that of the included plasma.

Plasma radioactivity levels were low in relation to the total dose of the isotope. On the basis of estimated total plasma volumes for the patients, it is calculated that the amount present in the blood at one time is generally less than 1 per cent of the dose given.

A variable pattern of plasma levels of activity was seen after both intrapleural and intraperitoneal radiogold administration; but, for each individual patient, the changes in blood-activity levels from day to day were relatively slight (Figs. 5, 6). The patients given the isotope intrapleurally appeared to have a more gradual and

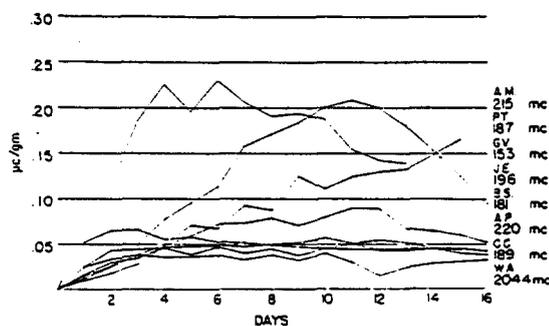


FIG. 6. Plasma radioactivity in eight patients after intraperitoneal injections of colloidal Au^{199} . (Corrected for decay.)

uniform rise in plasma radioactivity than those treated intraperitoneally.

The pattern of the rise in radioactivity in the blood does not appear to bear a direct time relationship to the fall in concentration in the fluid of the cavity, since the latter occurs much more rapidly. The activity in the blood is thought to be related to delayed mobilization of the colloidal material after it has been deposited on the walls of the cavity. It was not possible to correlate the plasma levels with the degree of fibrosis of the serous surfaces. One patient, C. F. (110084), had relatively high blood radioactivity levels after only 14 mc. of radiogold. This patient had a chylous effusion caused by the neoplasm invading the thoracic duct, and it is possible that much of the radiogold that reached the blood stream did so by entering this lymph channel directly from the pleural space.

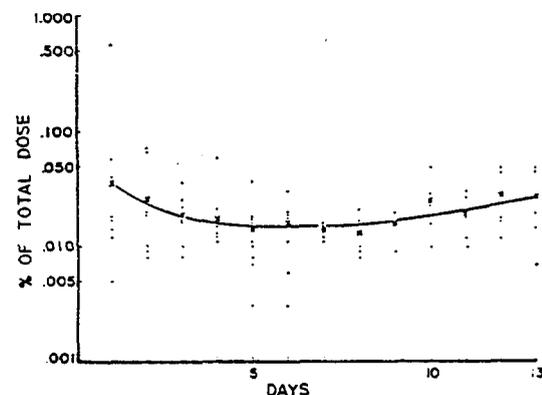


FIG. 7. Urinary excretion of Au^{198} after intrapleural injection. Each dot represents the total four-hour excretion for one patient, charted on a semilog scale. The line represents the approximate mean excretion. (Corrected for decay.)

No studies have been done to determine whether the relatively small quantity of radiogold that reaches the blood stream is in colloidal form or whether it may represent a small fraction of the gold that is ionized at the time of administration or that becomes ionized in the body. However, the distribution in liver, spleen, bone marrow, and other organs is similar to that seen after intravenous injection of a known colloidal preparation. This suggests that the gold that enters the blood stream is in colloidal form.

URINARY EXCRETION

A small, but highly variable, portion of the total dose given is excreted in the urine. Figures

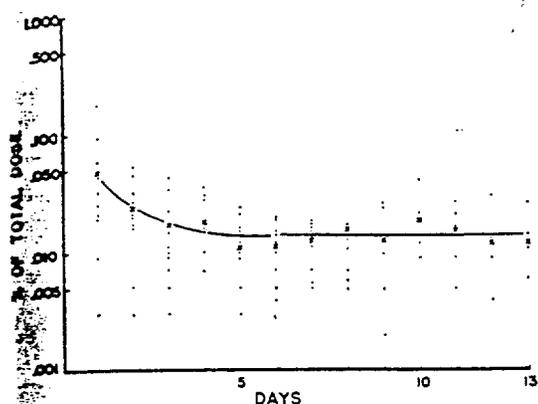


FIG. 8. A chart similar to Fig. 7, showing the excretion following intraperitoneal injection. (Corrected for decay.)

7 and 8 indicate the daily excretion levels for the two groups—intraleural and intraperitoneal. The excretion curves differ decidedly from those of the blood levels in that the highest excretion occurs in the first twenty-four hours while the blood activity is low. After this initial period, there is a tendency for the amount excreted in the urine to be proportional to the blood levels in individual patients. It is suggested that the early, relatively high urinary concentration may be explained by the presence of a small amount of ionized gold in the preparation given, this fraction being readily absorbed and readily excreted, whereas the later values may represent the colloidal material, which is both slowly absorbed and poorly excreted.

TISSUE ASSAYS

In studying the tissue distribution of the isotopes injected into body cavities, we have encountered one particular difficulty: the presence of the isotope in the free fluid of the body cavity is likely to lead to smearing and contamination of tissues removed at operation or autopsy so that assay of these tissues for radioactivity may be misleading. In an effort to avoid this error at the time of autopsy, the cavity that contains the isotope is not entered until all other available tissues have been obtained for radioassay. When, in selecting specimens from the treated cavity for radioassay, an area not including the serous surface is to be assayed, the free fluid is first wiped off and the contaminated exterior is then carefully cut off with the use of successive clean knives. It has been found that once the gold is deposited on the lining of the cavity it is not easily dislodged, so that the

main source of contamination is the relatively small amount of the isotope free in the fluid of the cavity.

In assaying the serous surfaces of the treated cavities for radioactivity, we have generally cut a thin layer of tissue for assay and determined the radioactivity per unit weight. It now appears that this is a rather unsatisfactory procedure, since most of the colloidal gold is in an extremely superficial layer and specimens usually include some deeper tissues that contain very little of the isotope. Thus, the thickness of the specimens may influence the apparent concentration of gold if calculations are made on the basis of weight. It appears that a much more significant value under these circumstances is the activity per unit of surface area, and we are now attempting to obtain this information.

SURGICAL DATA

On several occasions following the administration of intracavitary radiogold, surgical procedures were done that yielded tissue specimens for study. These cases and the radioactivity levels of the tissues are summarized here.

C. B. R. 010034. The patient was a 37-year-old woman who had extensive intra-abdominal metastases of a papillary adenocarcinoma, probably of ovarian origin. She had a localized collection of fluid in the lesser omental cavity, which had been temporarily relieved by previous surgery. On October 15, 1950, 100 mc. of colloidal Au¹⁹⁸ was injected by means of a long needle inserted into what was believed to be the lesser omental cavity. One week after the injection of the gold, another laparotomy was done. Radioassay values are found in Table 1.

TABLE 1
RADIOASSAY VALUES ON C. B. R.

Specimen	μc./gm.
Peritoneum from lesser omental cavity	115.16
Peritoneum from greater omental cavity	0.05
Tumor from mesocolon	1.71
Fluid from lesser omental cavity	0.34
Fluid from greater omental cavity	0.05
Fluid from cystic spaces in neoplasm (sample a)	0.19
(sample b)	0.11

B. S. 110123. The patient was a 46-year-old man who had been subjected to a thoracotomy after the discovery of a pleural effusion and an abdominal mass. Tissue obtained at this operation had revealed an unusual malignant lesion, probably a mesothelioma. When the patient was in almost terminal condition, a laparotomy was done nine days after 181 mc. Au¹⁹⁸ had been given intraperitoneally. This

TABLE 2
RADIOASSAY VALUES ON B. S.

Specimen	$\mu\text{c./gm.}$
Tumor from two different areas (sample a)	0.23
(sample b)	0.50
Parietal peritoneum	1.18
Abdominal fluid	0.24
Skin	0.04
Plasma	0.04

second operation was performed in an attempt to relieve distention believed to be caused by loculated fluid. Several biopsies were obtained; the radioactivity levels are shown in Table 2.

H. I. 110051. This 48-year-old white woman had extensive intra-abdominal metastases from a pseudomucin-forming carcinoma of the ovary. A laparotomy was done three days after intraperitoneal administration of 48.2 mc. of colloidal Au^{198} . Table 3 shows the results of radioassay.

TABLE 3
RADIOASSAY VALUES ON H. I.

Specimen	$\mu\text{c./g m}$
Thin layer of normal peritoneum	8.72
Fat from just beneath peritoneum	0.02
Peritoneum with tumor	0.48
Tumor	
Superficial gelatinous nodules	115.12
Cystic superficial nodules	3.83
Solid, more than 1 cm. from surface	0.001
Other tumor samples	0.07
	0.42
	0.73
	5.63
Abdominal fluid	2.08
Liver without capsule	0.82
Muscle from abdominal wall	0.07

J. B. McG. 110078. This 53-year-old white woman had a carcinoma of the uterus with multiple intra-abdominal metastases. On May 24, 1951, she was given 232 mc. of colloidal Au^{198} intraperitoneally. On June 19, 1951, twenty-six days later, a laparotomy was necessary because of obstruction of the colon. The peritoneum, wherever it was not involved with

TABLE 4
RADIOASSAY VALUES ON J. B. McG.

Specimen	$\mu\text{c./gm.}$
Normal peritoneum	22.29
Pigmented peritoneum	3271.42
Tumor	
Nodule free in abdominal cavity	764.29
Mass in omentum	144.29
Mass between two loops of small bowel	7.93
Ascitic fluid	0.09
Fluid from cyst in pelvis	0.05
Skin, fascia, and tumor from abdominal wall	No detectable activity

tumor, showed pronounced variation in color. The surface in the upper abdomen looked normal, while that in the pelvis and around the bladder had a distinct bluish-purple pigmentation, presumably owing to the gold. Assay of radioactivity is shown in Table 4.

G. F. 110121. This patient was a 49-year-old woman who had a papillary and solid adenocarcinoma of ovarian origin, with widespread intra-abdominal metastases and prominent ascites. She was given 153 mc. of colloidal Au^{198} intraperitoneally. An operation was performed fifteen days later in an effort to correct intestinal obstruction that had developed following treatment. The results of radioassay are shown in Table 5.

TABLE 5
RADIOASSAY VALUES ON G. V.

Specimen	$\mu\text{c./gm.}$
Adhesion from small bowel with tumor	39.43
Other samples of tumor from large masses adherent to intestine	0.34
	5.91
	40.14
Parietal peritoneum with microscopic area of tumor	6.51
Plasma	0.13

A. M. 010032. This patient was a 69-year-old white woman who had a pseudomucin-forming carcinoma of the ovary with extensive intra-abdominal metastases. During the three months preceding operation, the patient had received seven intraperitoneal injections of colloidal Au^{198} , varying from 10 to 100 mc. The last dose, three days before operation, was 52 mc. The operation was done to evaluate effects of treatment. Radioassays of various samples are shown in Table 6.

TABLE 6
RADIOASSAY VALUES ON A. M.

Specimen	$\mu\text{c./gm.}$
Tumor	
Cystic areas in omentum	1.71
Nodule in omentum	6.13
Nodule on surface of bowel	24.22
Deep cystic area	0.01
Deep solid area	0.05
Peritoneum with pseudomyxomatous tissue	
(sample a)	0.28
(sample b)	31.63
Omentum	0.21
Adhesions around tumor	0.56
Gelatinous fluid	3.24
Fluid from within cysts	0.00
Skin	0.00

The radioactivity values of the surgical specimens show wide variations in concentration of the isotope, that cannot be explained by the nature of the tissue assayed. Most of these

TABLE 7
RADIOACTIVITY PER GRAM OF TISSUES OBTAINED AT AUTOPSY AFTER INTRACAVITARY AU¹⁹⁸ TREATMENT
 All Counts Are Corrected to Time of Last Dose

Patient Hospital no.	J.B. 210201	S.W. 110077	C.F. 110081	O.S. 210148	P.T. 110132	A.B. 110082	U.S. 110123	M.R. 110052	R.H. 110070
Amount of last dose	78.4 mc.	19 mc.	23 mc.	3 mc.	187 mc.	153.5 mc.	34 mc.	11 mc.	10 mc.
Residual in body from prev. doses at time of last dose	0	1.18 mc.	0	0	0	0	0	2.13 mc.	1.39 mc.
Route of administration	L., pleural	L., pleural	R., pleural	R., pleural	Pelitoneal	Pelitoneal	Pelitoneal	Pelitoneal	Pelitoneal
Time from last dose to death	16 days	3 days	11 days	5 days	14 days	1 day	12 days	5 days	6 days
Fluid from cavity	0.25 µc./gm.	9.79 µc./gm.	0.01 µc./gm.	0.32 µc./gm.	1.01 µc./gm.	20.0 µc./gm.	17.93 µc./gm.	0.11 µc./gm.	19.21 µc./gm.
Serosal lining of treated cavity	463.21 µc./gm.	2.79 µc./gm.	0.13 µc./gm.	9.29 µc./gm.	10.07 µc./gm.	49.14 µc./gm.	18.0 µc./gm.	18.92 µc./gm.	145.71 µc./gm.
Liver	0.95 µc./gm.	0.02 µc./gm.	2.21 µc./gm.	BKGG†	17.0 µc./gm.	4.1 µc./gm.†	13.37 µc./gm.‡	3.72 µc./gm.	0.10 µc./gm.
Spleen	0.52 µc./gm.	0.01 µc./gm.	1.07 µc./gm.	0.16 µc./gm.	59.57 µc./gm.‡	0.01 µc./gm.	0.01 µc./gm.	1.01 µc./gm.	0.01 µc./gm.
Bone marrow	BKGG	0.01 µc./gm.	BKGG	BKGG	6.6 µc./gm.	0.01 µc./gm.	0.01 µc./gm.	0.01 µc./gm.	0.14 µc./gm.
Thyroid	BKGG	BKGG	0.03 µc./gm.	0.01 µc./gm.	1.49 µc./gm.	0.01 µc./gm.	0.01 µc./gm.	0.01 µc./gm.	0.01 µc./gm.
Adrenal	BKGG	BKGG	BKGG	BKGG	0.15 µc./gm.	0.01 µc./gm.	0.01 µc./gm.	0.01 µc./gm.	0.01 µc./gm.
Lung	BKGG	BKGG	BKGG	BKGG	0.05 µc./gm.	0.05 µc./gm.	0.01 µc./gm.	0.01 µc./gm.	0.01 µc./gm.
Plasma	BKGG	BKGG	BKGG	BKGG	0.71 µc./gm.	0.01 µc./gm.	0.01 µc./gm.	0.01 µc./gm.	0.01 µc./gm.
Bladder	BKGG	BKGG	BKGG	BKGG	0.01 µc./gm.	0.02 µc./gm.	0.01 µc./gm.	0.02 µc./gm.	0.01 µc./gm.
Lymph node near treated cavity	BKGG	BKGG	BKGG	BKGG	0.01 µc./gm.	0.01 µc./gm.	0.01 µc./gm.	0.01 µc./gm.	0.01 µc./gm.
Lymph node—distant	BKGG	BKGG	0.17 µc./gm.	0.05 µc./gm.	0.01 µc./gm.	0.01 µc./gm.	0.01 µc./gm.	0.01 µc./gm.	0.01 µc./gm.
Kidney	BKGG	BKGG	0.01 µc./gm.	0.01 µc./gm.	0.01 µc./gm.	0.01 µc./gm.	0.01 µc./gm.	0.01 µc./gm.	0.01 µc./gm.
Pancreas	BKGG	BKGG	BKGG	BKGG	0.01 µc./gm.	0.01 µc./gm.	0.01 µc./gm.	0.01 µc./gm.	0.01 µc./gm.
Bile	BKGG	BKGG	BKGG	BKGG	0.01 µc./gm.	0.01 µc./gm.	0.01 µc./gm.	0.01 µc./gm.	0.01 µc./gm.

†Extensive tumor may have prevented free spread in cavity.
 ‡These are not believed to be representative of the average liver and spleen values, because, when multiplied by the weights of the organs, the calculated recovery is greater than the administered dose.

variations are due to the fact that the isotope is deposited on the surface of the specimens, and the amount of surface varies greatly in relation to the weight of the sample. In one patient, J. B. McG. (110078), there was an extreme difference in the radioactivity of two specimens of peritoneum without tumor. The specimen that had a high activity was pigmented; the one that had a low activity was not. There was obviously a very uneven deposition of the isotope on the surface in this case.

The radioassays from surgical material confirm the fact that the radioactivity of the fluid becomes less than that of the serosal surfaces. They also serve to emphasize the almost complete failure of the isotope to penetrate significantly beneath the surface.

AUTOPSY STUDIES

Data are available on radioactivity of tissues obtained at autopsy from nine patients who died at intervals of from one to sixteen days following injection of gold.

Table 7 indicates the radioactivity levels per gram of a representative group of tissues. The values for the walls of the treated cavities show great fluctuations, which may be explained partly on the basis of the variations in the thickness of the samples taken for assay. In most instances the cavity walls had an activity per gram considerably higher than that of the fluid within the cavity. One patient, C. F. (110084), had relatively low activity in the specimen from the cavity wall as compared with the liver and the spleen. These findings are believed to be explained by the unusual degree of absorption into the blood stream of the colloidal material in this case, possibly injected inadvertently into a vein.

Table 8 shows the total per cent of the injected radioactivity that could be recovered in the livers and spleens of patients autopsied at varying intervals after treatment. These values were obtained by multiplying the activity per gram of samples of these organs by the total organ weights.

In a few instances in which more than one treatment had been given, the calculated residual activity in the body from earlier injections was added to the amount of the latest dose as a basis for percentage calculations. In no case was this residual activity large in relation to the last dose. One patient, B. S. (110123), was excluded from the chart because of unsatisfactory assays of liver and spleen activity. In this case

TABLE 8
AUTOPSY DISTRIBUTION OF COLLOIDAL Au¹⁹⁸
AFTER INTRACAVITARY INJECTION

Pat.	Time after last dose, days	Cavity of injection	% in liver	% in spleen
A.B.	1	Peritoneal	3.88*	BKG
S.W.	3	Pleural	0.10	0.01
B.F.	4	Pleural	BKG	BKG
O.S.	5	Pleural	1.12	0.38
M.R.	5	Peritoneal	5.26	4.21
B.B.	6	Peritoneal	3.02	0.09
C.F.	11	Pleural	15.39	0.83
P.T.	14	Peritoneal	11.27	3.19
I.B.	16	Pleural	2.39	0.15

*Probably false high value because of smearing.

the calculated recovery is greater than the initial dose given. In other cases in which multiple samples of liver were assayed, there was close agreement in isotope concentrations.

On the basis of limited data, it appears that lymph nodes adjacent to the cavity of injection have relatively high concentrations of radioactivity, whereas those distant from this site have much lower values. A more complete study of this aspect of the distribution would be of value.

EFFECTS OF RADIATION FROM COLLOIDAL Au¹⁹⁸

The locally effective radiation is almost entirely the result of the β emission of the isotope. This radiation is largely dissipated in the first millimeter of the surface of the cavity lining. Assuming that the isotope is concentrated in a thin film at the surface, Chamberlain has calculated that the β dosage at the surface is approximately 900 equivalent roentgens for each 1 mc. spread over 1000 sq. cm. If 100 mc. were injected intraperitoneally in an average adult with a peritoneal surface of 30,000 sq. cm., the average surface dose would be about 3000 equivalent roentgens, assuming, of course, that all of it deposited on the surface.

The γ emissions are of such energy that a significant part of their ionization occurs outside the body; within the body, their effect is quite diffuse. The γ emission from the gold probably has little to do with the effect upon fluid formation but contributes significantly to the total-body-radiation effect.

Since a large portion of the radiogold that reaches the blood stream is removed by the liver, it was of interest to study liver-function tests in relation to the gold injections. In eight patients thymol-turbidity and cephalin-choles-

terol-flocculation tests were performed upon the serum before and at varying intervals after treatment. Half of this group had abnormalities by these tests before the radiogold was given. Following treatment, there were some fluctuations but no distinct effect that appeared related to the radioisotope treatment.

Hematological studies showed a variable, early, mild leukocytosis and distinct eosinopenia, particularly in those patients who had evidence of local inflammatory reaction after injection. Individuals who received large doses of the radiogold showed in addition a more uniform sequence of changes characteristic of mild radiation damage to the bone marrow. These effects included a prompt lymphopenia with a later mild depression of granulocytes and thrombocytes. A delayed monocytosis was prominent in some cases. Patients given multiple intracavitary injections of the isotope, with a large total dose, developed a moderately severe leukopenia that persisted for months. Effects upon red-cell values were difficult to interpret because of multiple factors contributing to anemia.

DISCUSSION

Since relatively little is known about the factors causing fluid accumulation in patients with neoplasms, it is difficult to explain the therapeutic action of colloidal Au¹⁹⁸ in these situations. Whatever the mode of operation, it is obvious that the balance between fluid formation and fluid removal must be altered. Most patients with carcinoma do not have effusions in the absence of lesions involving the serous surfaces of body cavities. Hodgkin's disease, on the other hand, sometimes produces pleural-fluid collections that appear to result from lymphatic blockage without direct invasion of the pleura.

Several possible mechanisms for the action of the radioisotope in controlling fluid collection have been suggested:

1. The radiogold may produce superficial radiation damage and resultant fibrosis of the tumor surface projecting into the cavity. The formation of fibrous tissue in some of our cases seems compatible with this theory. However, there is no evidence of selective deposition of the isotope on the surfaces of the neoplasms, and morphological evidences of radiation effects upon the tumors have been rather slight.
2. The radiogold carried to the lymph nodes in



FIG. 9. Gross autoradiogram of spleen of patient P. T., who died fourteen days after 187 mc. of colloidal Au¹⁹⁸ was given intraperitoneally. This shows the superficially deposited isotope on the surface of the organ, as well as the diffusely spread blood-borne radiogold throughout the parenchyma.

The region of the cavities may control neoplasm there and relieve lymphatic obstruction. This seems unlikely in view of the relatively small amount of gold that reaches the lymph nodes and the absence of radiation effect upon neoplasm in these nodes. It seems probable that if this mechanism has any importance, it is chiefly in the patients with Hodgkin's disease and lymphoma.

An inflammatory response resulting in obliteration of the serous cavity might account for the cessation of fluid collection. Our experience indicates that a mild inflammatory response does sometimes occur, but autopsy studies fail to show extensive fibrous adhesions obliterating the serous cavities.

Some unknown mechanism of action, possibly upon surfaces not involved with tumor, may be important.

Animal work by Goldie et al. has indicated

that intraperitoneal injections of colloidal Au¹⁹⁸ have a profound effect upon tumor cells inoculated into the body cavity and that treatment will greatly prolong the life of the animals. This seems to substantiate a true radiotherapeutic effect upon malignant tissue. However, in this situation the free malignant cells are dispersed in a manner that makes them highly vulnerable to the short-range β particles. The disappearance of free tumor cells from fluids, which we have noted after treatment of certain human patients, appears to be a comparable effect. Fixed masses of tumor in the walls of the cavity are usually too thick to be affected—except on their most superficial areas—but this may be sufficient to decrease fluid exudation.

SUMMARY

1. Information has been presented that shows the fate and distribution of colloidal Au¹⁹⁸ injected into serous cavities. This data was obtained from a group of thirty patients treated with this isotope for effusions caused by malignant neoplasm.



FIG. 10. Gross autoradiogram of upper end of femur from patient C. F., who died eleven days after 33 mc. of colloidal Au¹⁹⁸ was given intrapleurally. The isotope is seen to be deposited in the areas of active marrow.

2. The greater part of the colloidal Au¹⁹⁸ injected into the body cavities is rather rapidly removed from the free fluid and is fixed on or near the surface of the lining of the cavity, partly within phagocytes and partly adsorbed on surfaces. Although the colloidal material generally mixes well with the fluid in the body cavity, its deposition on the walls is uneven. No special affinity for local tumor implants has been demonstrated.

3. The Au¹⁹⁸ does not penetrate significantly into the neoplastic or normal tissues adjoining the cavity. The superficial location of most of the colloid on the walls of the cavity and the short range of its β emission prohibit effective radiation beyond a depth of 2 or 3 mm.

4. A small but appreciable quantity of the isotope slowly finds its way, probably through

lymphatic channels into the blood stream, from which it is largely removed by the liver, spleen, and bone marrow.

A small amount is excreted chiefly in the urine and measurable quantities are found in many organs.

5. The penetrating γ emission from the treated cavity combined with the local radiation in distant organs from the blood-borne and lymph-borne fractions result in significant total-body radiation. Indications of this are seen chiefly in the blood and bone-marrow changes during a period of a few weeks following injection of the isotope.

6. Although the metabolism and distribution of this isotope have been studied in some detail, its exact mechanism of action is not as yet known.

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