

THE DISTRIBUTION AND RADIATION EFFECTS OF
INTRAVENOUSLY ADMINISTERED COLLOIDAL
Au¹⁹⁸ IN MAN

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CLINICALLY, radioactive colloidal gold has been administered interstitially, into cavities, and intravenously. The distribution and effect are greatly influenced by the route of administration. The present report is entirely concerned with the intravenous injection of this material.

The tissue distribution after intravenous injection has been well established in dogs, rats,¹¹ and guinea pigs. In experimental animals, special studies have been done on the significance of particle size¹³ and upon the rate of removal from the blood stream.⁹ This radioactive colloid has been used to produce cirrhosis^{6, 7} and to study the effect of this form of irradiation upon the liver,⁷ hematopoietic tissue,¹² and blood-clotting mechanism.⁴ Its distribution in man has been recorded by Sheppard and co-workers, who reported information on two patients. It is apparent that this isotope offers a means of achieving a distinctive type of radiation distribution; the greatest part of the dose is delivered to the liver, with relatively smaller amounts reaching the spleen and bone marrow. Still smaller quantities are distributed in other tissues of the body. The chief therapeutic use reported for Au¹⁹⁸ administered intravenously is in the treatment of leukemia and lymphoma.⁵

The present study was undertaken to investigate a repeatedly suggested possibility of using Au¹⁹⁸ in the treatment of neoplasms located in the liver and to obtain additional general information on its distribution and effects in man.

Six patients, whose case histories and autopsy reports are presented in a brief form, received the isotope intravenously. In two of these, it was thought possible to attempt irra-

diation of neoplasms involving the liver. One other patient had carcinoma of the liver but was given rather small doses without much hope of therapeutic effect, since the two earlier cases had shown concentration of the isotope only in the normal liver. The other patients, two with extensive neoplasms and one with chronic granulocytic leukemia, were in terminal condition and were given the isotope shortly before death. A separate study of the use of intravenously administered colloidal Au¹⁹⁸ in leukemia will be reported at a later date,² as will also a study of the hematological effects of this isotope when it is given by various routes to patients who have a variety of neoplasms.

MATERIALS AND METHODS

The radiocolloidal gold was administered intravenously through a gravity-drip apparatus, which has been described for intracavitary infusion.¹

The colloidal Au¹⁹⁸ was prepared from Au¹⁹⁸Cl₃ by reducing Au (III) to Au (I) with ascorbic acid. The reduction occurred in alkaline solution in which Au (III) was dissolved with carbonate as a complex ion. The specific activity varied from 1.43 to 4.32 mc. per mg. In one patient (case 7) a collimated Geiger tube was placed over the liver and spleen, and serial counts were made for a period of several days in order to gain information on the concentration of the gold in these organs. Plasma levels of radioactivity were measured in two patients on blood obtained at intervals from a vein in the arm opposite the side of injection. The blood specimens were withdrawn in a heparinized syringe and the plasma radioactivity was determined by counting liquid samples with an end-window Geiger tube.¹ Tissues obtained at autopsy were digested with nitric acid and assayed in a similar manner. Gross autoradiograms were prepared from bone and various other organs.⁹

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CASE REPORTS AND AUTOPSY FINDINGS

Case 1. G. E. C., a 44-year-old man, had a diagnosis of follicular lymphoma established in 1949 through biopsy of a cervical lymph node. The patient was treated with roentgen-ray radiation from February, 1949, until admission to the ORINS Medical Division in November, 1950, at which time he was given intrapleural colloidal Au¹⁹⁸ because of intractable pleural effusion. Lymph-node biopsy in November, 1950, showed lymphosarcoma. He was given 2.3 mc. of Au¹⁹⁸ (approximately 0.6 mg. stable gold) intravenously twelve hours before death.

At autopsy, lymphosarcoma involving all lymph nodes, spleen, pleura, epicardium, pancreas, kidneys, and bone marrow was found. There was a hemothorax of 1400 cc. on the left side and a hydrothorax of 300 cc. on the right.

Microscopically, the hepatic architecture was preserved. Some pigment retention of bile was within the hepatic cells and cloudy swelling was present. Some of the Kupffer cells contained a fine dustlike black pigment. Sections of bone marrow showed complete replacement by lymphosarcoma. Sections of the spleen showed loss of splenic architecture with homogeneous, compactly arranged lymphoid tumor cells. Numerous petechiae were scattered over the skin. The findings relative to the intrapleural infusion of Au¹⁹⁸ included pigmentation on the pleural surfaces with some fibrous thickening.

Case 2. N. J. S. was a 53-year-old white woman who, since October, 1949, had had increasing symptoms secondary to widespread pelvic and abdominal metastases thought to be from a carcinoma of the cervix. She received two large tracer doses of gallium 72 intravenously and subsequent biopsies were done in order to determine its uptake in the neoplasm. Treatment with this isotope was not considered desirable, and she received deep roentgen-ray therapy. Soon after the onset of a hemorrhage from an abdominal vessel in the region of the neoplastic involvement, she received 10 mc. of colloidal Au¹⁹⁸ (approximately 5.5 mg. stable gold) intravenously. The patient died fourteen hours after the administration of the gold.

Autopsy showed the pelvis to be studded with nodular tumor and the intestines matted in a mass that could be separated only with great difficulty. There was large firm tumor in the pelvis with fistulous communications to the cecum, vagina, and sigmoid. The tumor grossly was then thought to be of ovarian origin, since the cervix was not involved.

Microscopically, a section of the liver showed some atrophy of cords with pigment retention in the hepatic cells. This pigmen-

tion was more pronounced in the central portions of the lobule and may represent passive congestion. Patchy areas of fatty degeneration were also observed, such as would be expected in carcinomatosis with emaciation. Gold particles were not seen. Sections of bone marrow showed fairly active hematopoiesis. These sections did not show marrow markedly depressed from radiation. The tumor was composed of rather bizarre-appearing cells with numerous multinucleated giant tumor forms. The neoplasm failed to form any pattern and there were zones of necrosis.

A section of the spleen showed a rather small and sometimes indistinct white pulp. The red pulp was increased in amount with more nuclei and what appeared to be lymphocytes. Plasma cells were also found. No lymph nodes were seen in the material.

Case 3. In March, 1953, M. C. D., a 51-year-old woman, had a left radical mastectomy performed because of a scirrhous adenocarcinoma of the breast, which was metastatic to one axillary lymph node. Following surgery she received deep roentgen-ray therapy over the left chest. In September, 1953, she had right upper abdominal discomfort and anorexia, followed about a month later by jaundice, which became progressively more intense. With the onset of jaundice her appetite improved. She noted increasing drowsiness, lethargy, and weakness but maintained her weight fairly well. Her liver was nodular and palpable 14 cm. below the right costal margin. She was given small amounts of colloidal Au¹⁹⁸ intravenously in order to obtain scintiscan records over the liver. The dosages were as follows: November 24, 1953, 3.83 mc.; December 10, 3.76 mc.; December 17, 1953, 3.35 mc.; January 3, 1954, 9.4 mc. This last dose was given twenty hours before death.

At autopsy the body was deeply jaundiced. There was massive metastatic carcinoma involving the liver, which weighed 3600 gm. The gallbladder was (surgically) absent; there was no obstruction of the common bile duct. The liver was extensively replaced by tumor with cystic and hemorrhagic necrosis throughout the larger zones of tumor. There were viable peripheral margins. There were metastases to the left adrenal, bone, and para-aortic lymph nodes. Microscopic examination showed no evidence of radiation effect on the normal liver tissue or on the tumor. Scattered dustlike particles of pigment could be found in the Kupffer cells. The bone marrow, lymph nodes, and spleen did not show any radiation effect.

Case 4. J. M. M., a 27-year-old white man, had been treated with roentgen-ray radiation for chronic granulocytic leukemia from May,

1949, until admission to the ORINS Medical Division, at which time he had ceased to respond to therapy. He had also received 38 mc. of colloidal Au¹⁹⁸ intravenously, as treatment for his disease, eight months prior to admission. From March 5, 1951, through April 12, 1951, he was given a trial of gallium 72 intravenously, because of widespread persistent joint and bone pains, thought to be due to leukemic periosteal infiltrations. He received 33 mc. of colloidal Au¹⁹⁸ (approximately 14.6 mg. stable gold) intravenously fifty-five hours before death.

Autopsy showed marked splenomegaly (4040 gm.) and hepatomegaly (5340 gm.) with generalized slight enlargement of lymph nodes, leukemic infiltrations of kidney, and replacement of normal marrow by leukemic cells. There were leukemic infiltrates in the liver, adrenals, brain, spleen, lymph nodes, and testes.

The hepatic cells did not show any changes that could be attributed to radiation. No pigmented Kupffer cells were observed. Because of the diffuse replacement of the bone marrow by leukemic cells, no radiation effect on the marrow could be determined.

Case 5. In 1948 this patient, J. M., a 50-year-old white woman, was treated with radium and deep roentgen-ray therapy for carcinoma of the cervix. She did well until about March, 1952, when she began to lose weight. In December, 1952, an exploratory laparotomy revealed metastatic nodules in the liver. Later she developed edema of the lower extremities, increase in anorexia, and loss of weight. She was given small doses of intravenous gold as follows: April 9, 1953, 2.9 mc.; April 17, 21.2 mc.; April 28, 11.8 mc.; May 5, 1953, 23.3 mc. (This last dose, administered five days before the patient died, contained approximately 8.1 mg. of stable gold.) Plasma assay levels, expressed as per cent of the maximal plasma concentration two minutes after injection, determined on specimens obtained at intervals of two, five, ten, twenty, and forty minutes and four hours following administration, were 100, 41, 10, 1, 0.2, and 0.09 per cent respectively. There was thus a rapid disappearance of the gold from the plasma; at the end of forty minutes more than 99 per cent of the colloid had been cleared from it.

At autopsy, spread of the carcinoma to local pelvic structures with obstruction of the right ureter and compression of the iliac arteries was found. There were metastases to abdominal lymph nodes and massive areas of metastases in the liver. The liver weighed 3250 gm. Thrombophlebitis of iliac veins was present.

Sections of the liver did not show any changes that could be attributed to radiation.

No Kupffer cells with pigment were to be found. Sections studied at the borders of the growing edge of metastasis and hepatic tissue did not show any evidence of radiation destruction of the tumor. Section of the spleen showed decrease in width of the white pulp. The red pulp showed an apparent increase in the stromal tissues. Sections of the bone marrow indicated some decrease in hematopoiesis; however, hematopoiesis was present even in sections of the ilium where perhaps larger amounts of radiation had been given. Numerous precursors of granulocytic series were present.

Case 6. F. L. S. was a 7-year-old boy in whom the diagnosis of hepatoma was established at exploratory laparotomy in August, 1950. Following this procedure, the patient became progressively worse with increasing swelling of the abdomen, development of a right hydrothorax, and engorgement of the veins over the abdominal wall and lower chest. He received two doses of colloidal Au¹⁹⁸ intravenously. The first dose of 21 mc. was given ten days before death; the second dose of 42 mc. (approximately 13.8 mg. stable gold) was given 5.3 days before death.

Autopsy showed the liver to have a massive bright-yellow neoplasm, 12 cm. in diameter, involving the right lobe. It was sharply demarcated from the remainder of the hepatic tissue; the tumor extended into the hepatic vein, vena cava, and upward into the right auricle. There was also caudal extension of the tumor and thrombus to the femoral vein. Several small metastatic nodules were found in the right lung.

Microscopic sections showed a rather anaplastic hepatoma without ducts being formed. The spleen showed a relative increase in stromal tissues of the red pulp with prominence of the cells lining the sinusoids. The relative amount of white pulp was sparse, particularly so for a young person. No phagocytic cells containing gold pigment could be seen. Sections of non-neoplastic liver showed central passive congestion and necrosis owing to the obstruction of the vena cava. On rare occasions fine dustlike material could be seen in some Kupffer cells. No bone marrow was available for study.

Case 7. In January, 1950, R. T., a 47-year-old white man, had a resection of the sigmoid colon, which histologically showed adenocarcinoma. In May, 1951, a second laparotomy was performed, at which time he was seen to have liver metastases. The site of the resected sigmoid colon was apparently free of tumor. In October, 1951, he developed cervical pain, as well as some difficulty in speech, which was at-

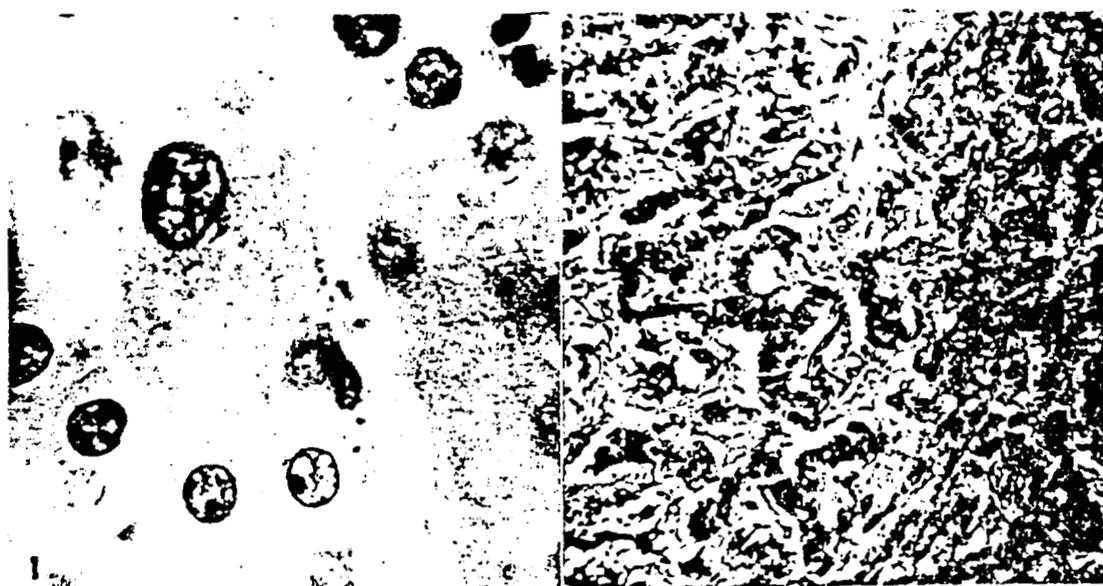


FIG. 1. The Kupffer cell contains black particles of pigment. These particles are aggregates of gold. ($\times 1080$.)

FIG. 2. The growing zone of metastatic adenocarcinoma shows no radiation effect from the Au¹⁹⁸ that was deposited in the liver. Normal liver parenchyma also shows no radiation effect. ($\times 100$.)

tributed to cranial metastases. After admission to ORINS Medical Division, he received deep roentgen-ray therapy over the right side of the neck with considerable relief of pain and some decrease in neurological findings. Examination in January, 1952, showed the liver to have increased in size and to be nodular and non-tender. A biopsy of the liver, which showed only normal liver tissue, was performed. On January 17, 1952, he was given 105 mc. of radiocolloidal gold (approximately 82.5 mg. of stable gold) intravenously. External counts with a collimated Geiger tube were made over the liver and spleen, and plasma assays for radioactivity were made on specimens taken at intervals. There was no immediate reaction to the intravenous gold, but, three days following its administration, tenderness developed over the liver, which gradually subsided during the following week. The patient was anorexic for about the first week, but his appetite gradually returned to its previous level. On February 5, 1952, the patient passed grossly bloody stools. He was given multiple blood transfusions but died in peripheral vascular shock twenty-three days after he received the gold. Radiation effect on the blood was manifested chiefly by depression of platelets, which fell to low levels shortly before death. Although there was no evidence of generalized bleeding and a localized bleeding site was found at autopsy, it was felt that the thrombocytopenia contributed somewhat to his final hemorrhage.

Autopsy showed carcinoma metastatic to the retrosternal area near the site of the surgical anastomosis, with metastases to periaortic abdominal lymph nodes, liver, right adrenal, lungs, and jejunum. Involvement of the liver consisted of massive partially necrotic tumor nodules. The primary site of gastrointestinal hemorrhage was found at an area in which the jejunum was eroded by metastatic carcinoma. Petechial hemorrhages of the skin of the antecubital fossae and shoulders were seen. They were also present on the serosa of the bowel and gastric mucosa.

Microscopic examination showed the non-neoplastic portions of the liver to be free of any change that could be attributed to radiation. Kupffer cells contained fine black particulate matter (Fig. 1). There was no evidence of any zone of inhibition at the border between the growing edge of metastatic neoplasm and gold-containing normal hepatic tissue (Fig. 2). The spleen showed some decrease in the size of the white-pulp zones, although tufts of lymphoid cells around the central arterioles did persist. Sections of the bone marrow showed erythropoiesis, but there was some decrease in activity with relative increase in the amounts of fatty tissue within the marrow. Megakaryocytes were scarce.

RESULTS

Although the concentration of activity was measured with a high degree of accuracy in

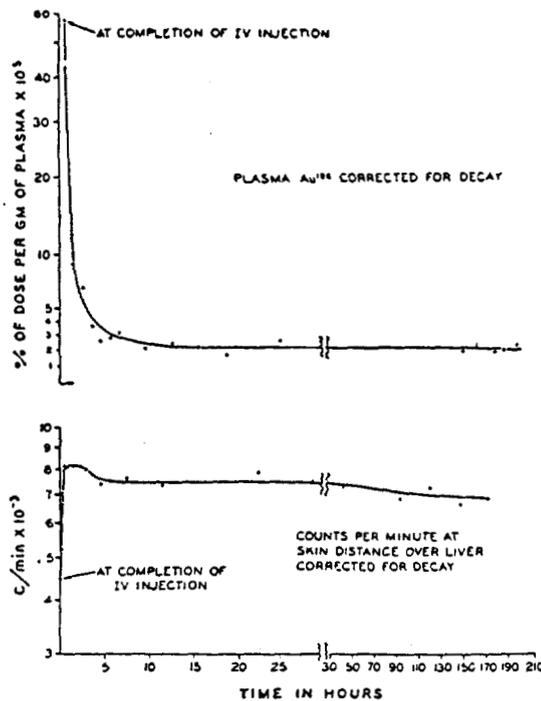


FIG. 3. Plasma and liver radioactivity after injection of 105 mc. Au^{198} intravenously. Patient R. T.

small samples of tissue, direct measurements were not made on whole organs to determine the per cent of the total administered dose that was deposited in each one. When the concentration per gram is multiplied by the known or estimated weight of the organ, various obvious errors prevent the resulting figure from representing the true amount of isotope contained. The weight of the bone marrow in these patients could only be estimated, with a wide range of error. The concentration of radioactivity varied widely from area to area. When extensive neoplastic nodules are present in the liver, the determination of their weight is difficult and therefore it was only estimated. Thus, the weight of normal liver tissue is not accurately known. In spite of

these limitations, it may be worth while to present our rough estimates of the distribution of the total dose. The normal liver tissue probably contained from 60 to 94 per cent of the administered dose of Au^{198} . The spleen was calculated to contain from 5 to 16 per cent, except for one instance in which the figure of only 1.2 per cent was obtained. There is a large error in estimating the total bone-marrow content, but it appears that this organ may contain total amounts of the isotope in the same range as the quantities in the spleen. The kidneys were calculated to contain from 0.05 to 0.24 per cent, and the lungs from 0.8 to 3.2 per cent, of the administered dose. The adrenals had less than 0.1 per cent and the total plasma was estimated to contain, at the time of death, from 0.1 to 0.7 per cent.

Plasma Levels and Excretion. In these patients the Au^{198} was administered over a period of ten to thirty minutes and most of it had left the plasma before the injection was completed. Therefore critical studies of the initial removal from plasma could not be done. In case 7, external counting studies of the activity in liver and studies of plasma activity were begun at the completion of the injection (Fig. 3). This shows the rapid fall in plasma radioactivity, the early localization of the isotope in the liver, and its continued concentration there over a period of several days. After the initial decline caused by deposition in reticulo-endothelial organs, the plasma radioactivity remained at a low but rather constant level for many days. Information is not available to show whether the Au^{198} in the plasma is colloidal or ionic. A similar early rapid fall was seen in the plasma activity of case 5 (see case report).

The total urinary excretion was very low, but there was a much larger amount during the first day with extremely low, rather uniform amounts excreted on succeeding days (Fig. 4). An effort was made to estimate

TABLE I
LIVER-FUNCTION STUDIES OBTAINED ON CASE 7 BEFORE AND AFTER INTRAVENOUS INJECTION OF 105 MC. Au^{198} , JANUARY 17, 1952

	9/16/51	1/8/52	1/17/52	1/22/52	1/25/52	2/2/52
Cephalin flocculation, 48 hr.	0	0	0	0	0	0
Thymol turbidity, units	4.9	5.4	8.1	6	2.7	2.5
Total protein, gm./100 cc.	6.4	5.4	6.7	5.8	5.6	5.4
albumin, gm./100 cc.	4.1	4.2	3.4	3.3	3.6	4.0
globulin, gm./100 cc.	2.3	1.2	3.3	2.5	2.0	1.4
Total serum cholesterol, mg./100 cc.	350	163	310	280	320	225
Per cent esters	64	67	63	78	53	22
Per cent bromsulfalein (5 mg./kg.) retention in 45 min.	7	2.8			12.6	

roughly the quantitative relationship between the radioactivities of plasma and urine. After the initial fall in plasma radioactivity, twenty-four-hour urine samples contained approximately 26.6 to 10.6 per cent of the estimated total-body plasma content.

Clinical Effects. The intravenous injection of the radioactive colloid produced no immediate clinical reactions. Transient localized tenderness of the liver was noted in the patient who received the largest dose of the isotope. The course of the disease process did not appear to be influenced in any way, although in the one patient who was given the largest dose, the hematological studies suggested that a serious bone-marrow depression was developing. Manifestations of this marrow depression might have appeared if the patient had not died from a localized hemorrhage.

A series of liver-function tests were per-

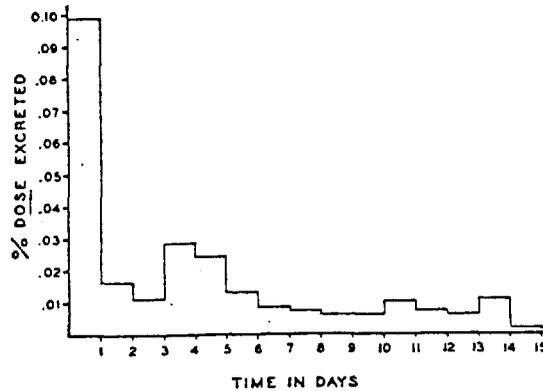


FIG. 4. Excretion of Au¹⁹⁸ in the urine after intravenous administration of 105 mc. Patient R. T.

formed on case 7 and these are shown in Table 1. Most of these studies were normal throughout the course. The bromsulfalein retention was slightly increased above normal but not

TABLE 2
RELATIVE DISTRIBUTION OF COLLOIDAL Au¹⁹⁸ IN SEVEN PATIENTS AT AUTOPSY FOLLOWING INTRAVENOUS INJECTION

Case no.	1		2		3		4		5		6		7	
Dose, mc.	2.3		10		9.4		33		25.2		42		105	
Durat. hr.*	12		14		17		55		120		128		552	
Organ	μc./gm.	DAR†	Cts./gm.‡	DAR§	μc./gm.	DAR†								
Liver	0.98	23.95	11.40	55.06	7.58	14.29	9.86	20.75	40.11	87.77	330,400	249.52	61.36	38.28
			8.15	39.35	9.36	17.67	1.76	3.70	25.10	54.93	198,800	150.15	56.00	34.93
Spleen	0.31	7.44	0.66	3.20	4.13	7.80	0.61	1.28	49.65	108.64	826,600	624.32	53.57	33.42
			0.44	2.13			0.21	0.45	35.47	77.62			52.14	32.52
Sternal marrow					0.76	1.44	0.05	0.11	9.03	19.76	191,800	144.90	1.86	1.16
Vertebral marrow	0.02	0.41	1.90	9.16	0.24	0.45	0.05	0.10	10.78	23.59	296,400	223.57	5.31	3.31
							0.02¶	0.03			54,900	41.51	2.90¶	1.81
Rib marrow			0.63	3.06			0.00¶	0.01			91,600	69.18	2.12¶	1.32
Lymph nodes	B.G.**	0.02	B.G.**	0.02	0.03	0.06	0.01	0.02	0.11¶	0.24				B.G.†
	B.G.**	0.02	B.G.**	0.01	0.04	0.07	0.00¶	0.01						
Lung	0.02	0.43	0.30	1.46	0.61	1.16	0.09	0.19	0.50	1.10	12,200	9.36	0.91	0.57
	B.G.**	0.03	0.22	1.07	0.53	1.01	0.09	0.19	0.18	0.40	5,800	4.41	0.45	0.28
Kidney	0.01	0.14	0.07	0.34	0.01	0.02	0.08	0.16	0.25	0.55	5,800	4.36	0.47	0.30
	B.G.**	0.10	0.07	0.32			0.02	0.03	0.18	0.40			0.45¶	0.28
Adrenal	0.04	1.02	0.37	1.81	0.08	0.15	0.06	0.13	1.42	3.10	28,200	21.33	0.52¶	0.32
					0.09	0.18	0.04	0.09	0.89	1.95	24,600	18.61	0.51¶	0.32
Pituitary							B.G.**	0.02	0.06¶	0.12	3,030	2.29	B.G.††	
Thyroid	B.G.**	0.01	0.04	0.21	0.01	0.02			0.03	0.06	615	0.46	B.G.††	
Stomach	B.G.**	0.01	0.01	0.06	0.01	0.01	0.01	0.01	0.03	0.06	516¶	0.39	B.G.††	
Small bowel	B.G.**	0.01	0.03	0.15	0.02	0.04	B.G.**	0.02			1,183	0.89	0.18¶	0.11
Colon	B.G.**	0.02	0.03	0.13	0.01	0.02					581	0.44	0.19	0.12
Diaphragm			0.02	0.08	0.02	0.03			0.02	0.04	2,064	1.56		
Skin	B.G.**	0.03	0.03	0.16	0.00¶	0.01	B.G.**	0.00			529	0.40	B.G.††	
Muscle	B.G.**	0.01	0.09	0.42	0.00¶	0.01	B.G.**	0.00	0.01¶	0.01	783	0.59	B.G.††	
Cerebral cortex			B.G.**	0.02	B.G.††		B.G.**	0.00			71¶	0.05	B.G.††	
Plasma	B.G.**	0.05	0.02	0.11	0.00	0.01	B.G.**	0.02	0.02	0.04	183	0.14	0.03¶	0.02
Urine							B.G.**	0.00			162	0.12		
Bile			0.01	0.07							31¶	0.02		
Tumor	B.G.**	0.02	0.36	1.74	0.02	0.03			0.03¶	0.12	4,529	3.42	B.G.††	
			0.03	0.14	0.01	0.02			0.02¶	0.04	2,176	1.64	B.G.††	

*Interval between administration and death.
 †Differential absorption ratio as compared with calculated average retained activity/gm. body weight.
 ‡Expressed as counts per gram because absolute calibration was not available.
 §Differential absorption ratio as compared with activity/gm. heart.
 ¶High and low values of seven aliquots.
 ††Probable counting errors greater than 5 per cent.
 **B.G. Slightly greater than background with probable counting errors greater than 5 per cent.
 ††B.G. Background.

TABLE 3
RANGE OF ACTIVITY IN MULTIPLE SAMPLES OF LIVER AND TUMOR FOLLOWING
INTRAVENOUS Au^{198} IN CASE 5

	$\mu\text{c./gm.}$	Mean & standard deviation						
Liver	40.11	36.151	35.33	32.88	29.47	27.69	25.10	32.04 = 4.74
Tumor	0.005	0.047	0.048	0.044	0.027	0.023	0.019	0.038 = 0.014

distinctly related to the Au^{198} injection. After the isotope was given, an apparent decrease in the per cent of cholesterol esters developed.

Distribution Data. The patients died at intervals of twelve hours to twenty-three days after injection of the colloidal Au^{198} . Table 2 shows the concentration per gram weight of tissue of the Au^{198} as determined at autopsy. When more than one dose was given, the residual activity was chiefly that of the final dose and corrections for decay were on the

basis of that dose. In calculating total distribution of the isotope, residual activity from previous doses was considered as if the activity remaining from earlier doses had been given with the last dose. The liver, spleen, and marrow, in that order, retain the largest share of the Au^{198} . The extremely low retention in the non-reticulo-endothelial tissues is illustrated, as is the minimal concentration in tumor tissue. Table 3 shows the range in concentration of Au^{198} per gram of wet weight in



FIG. 5. A, Photograph and, B, gross autoradiogram of liver from case 7 with liver metastases from carcinoma of the colon. The patient received 105 mc. Au^{198} intravenously 552 hours before death. The autoradiogram shows the absence of Au^{198} in the areas of metastatic tumor.

multiple samples of liver and of tumor as determined at autopsy of case 5.

DISCUSSION

Most of the gold given becomes firmly lodged in normal liver tissue. The firmness of this attachment is perhaps indicated by the low levels of activity in the bile. It was clear that discrete areas of neoplasm in the liver, regardless of size or adequacy of blood supply, completely failed to share in the liver's ability to concentrate the isotope (Fig. 5, A, B). The distribution in reasonably normal liver parenchyma was grossly quite uniform, with a fine pattern of increased concentration related to lobular architecture. As compared with isotope distributions in general, this is one of the most homogeneous we have seen. When more than one sample of liver was assayed, concentrations of activity were found to be quite uniform except where there was an obvious explanation for a more patchy distribution (Table 3). In the young boy with hepatic-cell carcinoma (case 6) there was extensive interference with the blood supply of the liver, which probably accounts for the unequal activity of the two samples assayed, as well as for the fact that the spleen showed more of the isotope per gram than did the liver. In the patient with granulocytic leukemia (case 4), dense leukemic infiltrates were associated with decreased concentration of Au^{198} . This was verified by autoradiogram. In the patients in whom there were discrete metastases surrounded by apparently normal liver tissue, it appeared that there was a greater unevenness of distribution in the hepatic tissue immediately adjacent to the tumor nodules.

Distribution of radioactivity in the parenchyma of the spleen also tended to be fairly uniform as indicated by radioassay and autoradiograms (Fig. 6, A, B). In the two patients (cases 5 and 7) who had multiple discrete metastatic lesions in the liver and who were probably nearest to normal in reticulo-endothelial function, the concentration of radioactivity per gram was very nearly the same in the liver and in the spleen. The total amount in the liver, however, was obviously many times greater owing to the greater weight of this organ. The patient with granulocytic leukemia (case 4) had a very large spleen that was filled with leukemic cells and possibly had a very inadequate blood supply. Presumably the re-

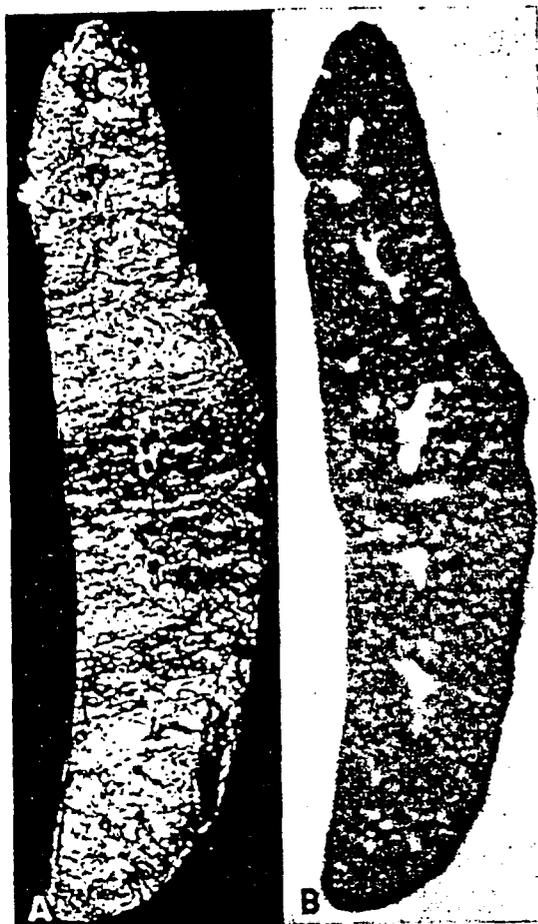


FIG. 6. A, Photograph and, B, gross autoradiogram of spleen from case 5 with metastatic carcinoma of the cervix. The patient received 23.3 mc. Au^{198} 120 hours before death. The relatively uniform distribution of Au^{198} is shown.

sulting impairment of reticulo-endothelial function accounts for the uneven and generally low concentration of the isotope. Less severe but similar factors may have accounted for the rather low concentration of the isotope in the spleen of the patient (case 1) with lymphosarcoma. The remaining patient (case 2) was one who was in shock from massive gastrointestinal bleeding at the time the isotope was given, which was only a few hours before death. In this instance there was a strikingly low concentration in the spleen.

The bone marrow has fairly high concentrations of the colloidal isotope. The samples in Table 2 listed as vertebrae and sternum were chiefly cancellous bone with cellular marrow and contained relatively little bone cortex or fatty marrow. Autoradiograms indicate a patchy, uneven distribution of the isotope with most of the activity in the areas of active

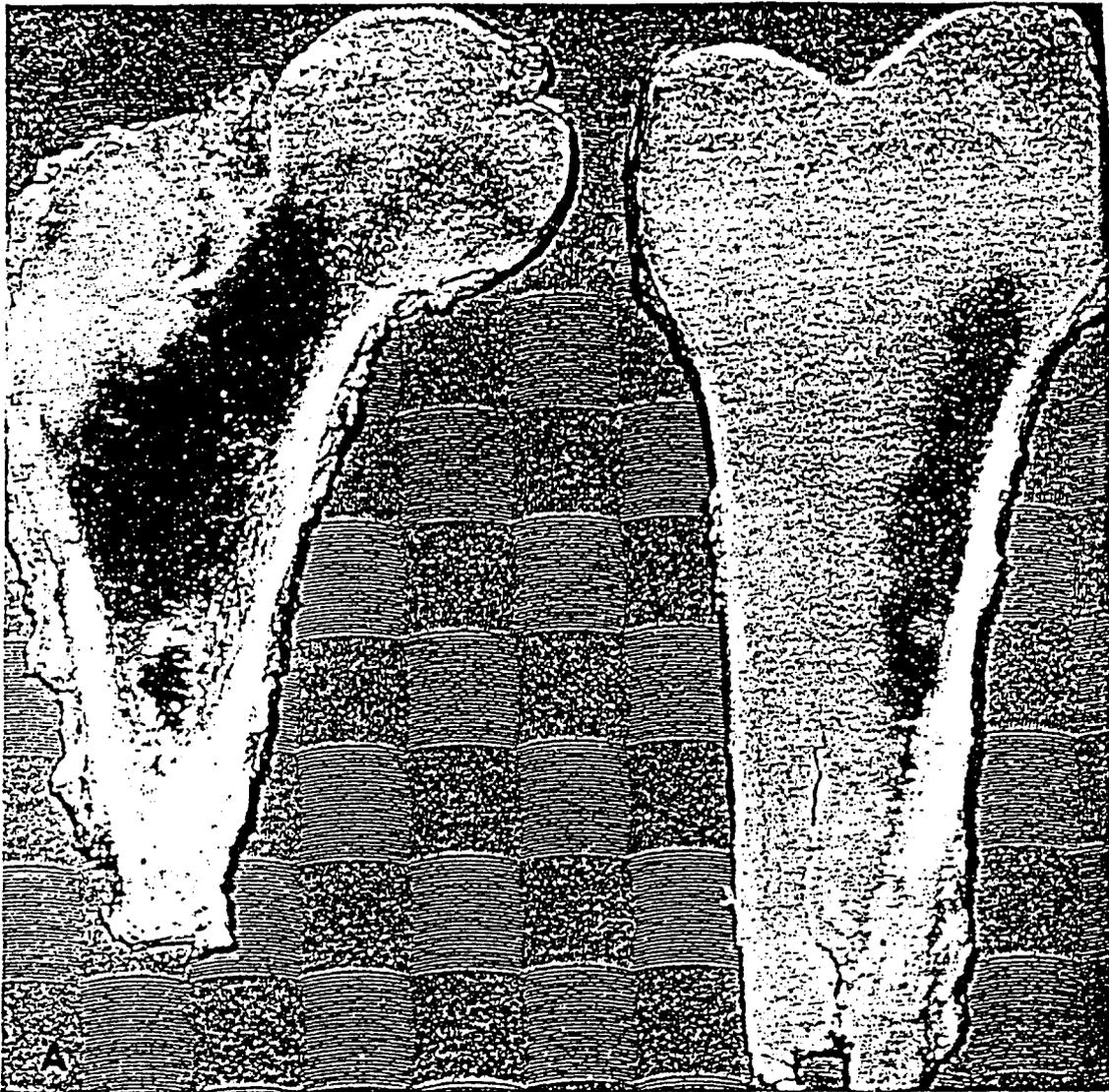


FIG. 7. A. Photograph and, B. autoradiogram (see opposite page) of femur from case 5. One hundred and twenty hours before death, 23.5 mc. of Au^{198} was given intravenously. The areas of radioactivity are those of active, cellular marrow.

cellular marrow (Fig. 7,A, B). Diffuse abnormalities of the marrow associated with chronic granulocytic leukemia and lymphosarcoma were associated with relatively low concentrations of the isotope.

The concentration of the colloidal material in normal lymph nodes is perhaps lower than one might be led to expect in view of their importance in the reticulo-endothelial system. It is well known that adjacent lymph nodes contain relatively large amounts of this colloidal isotope when it is injected interstitially. They represent an efficient filtering device for the material in the lymphatic channels. When the gold is given intravenously, how-

ever, the blood supply of the lymph nodes, or their ability to clear the blood, is such that relatively low levels of Au^{198} concentration are developed as related to liver and spleen.

The lungs show a rather high, if somewhat uneven concentration of the Au^{198} . In the kidney the localization is chiefly in the cortex. Endocrine organs show concentrations considerably higher than those of mesodermal derivatives and this may be due to a small amount of reticulo-endothelial tissue in these organs.

The administration of Au^{198} intravenously caused little untoward effects in the patients. In a few instances there was anorexia for a few days, and, in one patient who received



(For caption see opposite page.)

105 mc., there was transient liver tenderness. At autopsy none of the livers examined showed evidence of radiation damage. Liver-function tests showed no significant changes following the Au^{198} . Although two of the patients received Au^{198} at too short an interval before death to expect any evidence of radiation effect, the others received fairly large doses at intervals long enough to permit radiation changes to develop. On the basis of the evidence of bone-marrow depression in case 7 and of animal experiments,^{4, 12} early death from a single dose of Au^{198} would be expected to result from bone-marrow damage rather than from radiation effect on the liver. Radiation damage to the bone marrow would prob-

ably be the factor limiting the dosages of Au^{198} . The present study has not ruled out the possibility that diffuse, minute neoplastic tissue in the liver might be more effectively irradiated by colloidal Au^{198} than by other means. In some cases of lymphosarcoma with extensive, diffuse liver involvement better results might be obtained from the use of colloidal Au^{198} than by other means of therapy. Patients in whom the disease is localized mostly in lymph nodes would not be expected to respond so well in view of the low concentration of the isotope in even relatively normal lymph nodes.

Although the therapeutic possibilities of intravenously administered colloidal radiogold

appear exceedingly limited, the unique behavior of colloidal materials and their concentration in reticulo-endothelial tissues are the basis of worth-while experiments going on at the present time in several institutions. The production of experimental cirrhosis has already been alluded to. The rate of removal of the isotope from the blood may eventually give information on blood flow in the liver or reticulo-endothelial function. Studies of this type with another colloid, chromic phosphate (P^{32}), have been reported.³ The absence of concentration of colloidal Au^{198} in tumors in the liver with the resulting area of low activity in a field of high activity suggests the obvious possibility that external counting studies might reveal unknown areas of neoplasm in the liver.

Such studies, based upon the information in the present report, are in progress.

SUMMARY

1. Radioactive gold in colloidal form can be injected intravenously into the human being without immediate untoward reactions.

2. The isotope rapidly leaves the blood stream and deposits largely in reticulo-endothelial organs.

3. Neoplasms that replace reticulo-endothelial tissue in liver do not concentrate the isotope and these lesions contrast strikingly with surrounding tissue having high levels of activity.

4. This information on a small number of cases suggests that intravenous colloidal radiogold has no promise in the treatment of discrete primary or metastatic lesions of the liver but does not rule out the possibility that very fine, diffuse lesions could be treated advantageously.

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