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ACCIDENTAL RADIOGOLD (^{198}Au) LIVER SCAN OVERDOSE
WITH FATAL OUTCOME

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1. INTRODUCTION

The use of radioisotopes for scanning has added significantly to the clinician's ability to detect and interpret disease manifestations. As with other useful materials administered intravenously to patients, radioisotopes must be most carefully monitored to prevent the type of accidental overdosage we will now describe.

2. CASE HISTORY

A 73-year-old white housewife was transferred to the Argonne Cancer Research Hospital in August, 1968. She had accidentally received 200 millicuries instead of the anticipated 200 microcurie dose of radioactive colloidal gold (^{198}Au) intravenously for a liver scan. She expired 69 days later of hemorrhagic complications related to thrombocytopenia. Before discussing our observations and management of this patient further let us briefly review the pertinent past history.

The patient had been in good general health, except for congenital deaf-mutism, until 1961. At that time she was first noted to have a hemoglobin of 9.0 grams %. The anemic condition was found to be refractory to multiple hematinics over the next seven years. She required blood transfusion on one occasion in 1963. In March, 1968 peripheral blood and bone marrow findings established the diagnosis of chronic erythremic myelosis [1-3] (Fig. 1). Figure 1 illustrates two fields from a bone marrow aspirate done at that time. The megaloblastoid maturation with bizarre

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nuclear configurations in the red cell line and atypical megakaryocytic forms are to be noted. A peripheral blood smear showed many nucleated red blood cells and early myeloid forms, including 5 % myelocytes. No therapy was instituted for her blood condition at that time.

Early in August, 1968 the patient was readmitted to her local hospital for evaluation of abdominal swelling and hepatomegaly. Repeat bone marrow aspirate confirmed the earlier findings. Evaluation of the hepatomegaly included the radioactive colloidal gold (^{198}Au) scanning procedure which is the subject of this report. As soon as the overdosage was realized the patient was placed in protective isolation and arrangements were made for her transfer to Argonne Cancer Research Hospital.

Upon arrival at the emergency room some 30 h after the radiogold injection, the patient was monitored externally to check the reported over-dose and to estimate her potential hazard to bedside personnel. The exposure dose rate at that time was 35 milliRoentgens/h at one meter distance, which was felt to be consistent with the reported dose of 200 millicuries. From the finding of 0.04 microcuries per milliliter of whole blood, it was calculated that less than 0.1 % of the injected dose remained in the total blood volume at 30 h after injection.

A whole body scan was performed without administering additional isotope (Fig. 2). The total body distribution of detected counts was felt to be typical for uptake of colloidal material by an abnormally extensive reticuloendothelial marrow. A similar result has been noted in patients who have polycythemia vera [4]. A scan of the upper abdomen done at the same time shows the liver and spleen contours (Fig. 3). The unusually large amount of radioactivity in these sites was corroborated by the sizeable count numbers accumulated very rapidly with a pinhole aperture on the detector.

Estimated dosages of radiation to be received by the several key target organs, namely, liver and spleen, bone marrow, and intestine were calculated by standard beta and gamma dose formulas [5]. Assumptions made for purposes of these calculations were: (1) that liver and spleen combined retained 95 % of the total administered isotope [4]; (2) that their weights were 1700 grams and 300 grams, respectively; (3) that the effective half-life in these organs of the radiogold-198 is equal to its physical half-life of 2.7 days; and (4) that the geometric factor for gamma dose is equal to that defined for a cylinder of radius 10 cm and length 5 cm. The resulting estimates are tabulated in Figure 4. The sizeable liver and bone marrow doses predicted clinical difficulties with these organs. No significant intestinal dysfunction was anticipated or observed [6].

On arrival at the Argonne Cancer Research Hospital the patient was alert, cooperative, and in no acute distress. Pertinent physical findings included a firm nontender liver edge palpable 5 cm below the right costal margin and spleen palpable 3 cm below the left costal margin. Several small

inguinal nodes were present bilaterally. Blood counts on admission were: hemoglobin - 9.7 grams %; white blood cell count - 5,450 per cubic millimeter; differential- 42 % polymorphonuclears, 19 % stab forms, 3 % metamyelocytes, 28 % lymphocytes, and 8 % monocytes. Five normoblasts were present for every 100 white blood cells. The reticulocyte count was 6.5 %. Other laboratory results included an elevated serum uric acid of 16.3 milligram %, a slightly increased serum alkaline phosphatase (68 International Units), blood urea nitrogen of 23 milligram %, and normal serum bilirubin and bleeding and clotting workup. The serum lactic dehydrogenase level was approximately 10 times the upper normal value, but this finding had been noted prior to administration of the radiogold.

It seemed clear that the first major management problem would be support of the patient's hematopoietic system [6]. Bone marrow transplantation was considered, but not attempted because of the lack of a closely compatible donor and the uncertain value of such a procedure in the 400-500 R bone marrow dose range in humans [7]. The patient was initially placed in protective isolation with strict limitation of exposure time for personnel at the bedside. By the end of the first week, when her absolute granulocyte count had fallen below 500 cells per cubic millimeter, she was in a special two-room isolation suite designed to provide surgical asepsis in the patient's half of the area. Clothing, food, water, utensils, and all other items entering the patient's room were pre-sterilized. The air in the patient's room was kept as dust-free as possible by filtration through laminar flow air hoods (Abbott Clean Air Centers manufactured by Air Control, Inc., Norristown, Pennsylvania, and kindly loaned to us by Abbott Laboratories, North Chicago, Illinois). Oral Neomycin sulfate and Nystatin were started on admission in an effort to reduce the possibility of bacteremia from endogenous intestinal flora. Vitamin K_1, pyridoxine, and folic acid were other oral medications given throughout the hospital course to replace substances normally made by intestinal flora and/or destroyed by food sterilization. Allopurinol was started soon after admission, and the serum uric acid had returned to normal by the tenth day.

The patient was given intermittent transfusions of fresh whole blood, but the number of compatible units available was limited by her A negative blood type. During the first three to four weeks daily infusions of buffy coat concentrates containing granulocytes and platelets [8] were given, but later platelet concentrates were substituted because of febrile reactions noted after administration of buffy coat preparations.

Daily peripheral blood counts were performed and are illustrated in Figure 5. As expected, the absolute lymphocyte count fell most rapidly and eventually showed some recovery. The granulocyte level dropped somewhat later than the lymphocyte count and showed sufficient improvement by the 9th week to permit discontinuation of the isolation procedures. There was never any significant difficulty with infection. The platelet count reached lowest levels by the third week, but never could be raised above 8,000 per cubic millimeter thereafter despite the infusions of platelet concentrates.

Intermittent injections of androgen were given in hopes of stimulating marrow function [9], and, later, corticosteroids were started in an effort to reduce capillary fragility and possibly prolong platelet lifespan.

Despite these measures aimed at increasing platelet levels the patient had persistent marked thrombocytopenia and petechiae, intermittent hematuria, and subconjunctival hemorrhage. As the hospital course progressed, the liver and spleen were noted to decrease in size. There was no significant deterioration of the liver function tests. The patient remained alert and ambulatory within her room until the terminal event. On the 68th hospital day she complained of sudden dizziness and fell to the floor. She complained of severe headache, and became progressively obtunded. Consciousness was not regained, and she expired the following day.

3. POST MORTEM FINDINGS

Post mortem findings of special interest were in the bone marrow, liver, lymph nodes, and brain (Fig. 6). Femoral marrow was generally hypo-cellular, but there were readily identifiable islands of erythroid and granulocyte precursors. Megakaryocytes were notably scarce. Rib, sternal and vertebral marrow specimens were similar. The liver weighed 2090 grams. The spleen weighed 490 grams. Microscopic changes in the liver were non-specific--a number of hepatocytes were seen to have hyperchromatic and/or double nuclei. Special stains failed to reveal more than a very slight increase in the amount of collagen in the liver. Lymph nodes were somewhat atrophic with prominent extramedullary hematopoiesis both within the medullary regions of the nodes and in the pericapsular fat. Intracerebral, subdural, and subarachnoid hemorrhage were identified.

4. DISCUSSION

The pattern of radiation injury expected from overdosage of intra-venous radiogold colloid is predictable from our knowledge of the fate of injected colloidal particles and the radioactive decay parameters of the specific isotope. The metallic gold particles in colloidal form are 25 to 50 millimicra in size and are avidly phagocytosed by the reticuloendothelial system [10]. These particles are almost completely cleared from the blood in 10 to 30 minutes. The gold particles are metabolically inert and chemically nontoxic in the human body. They are irreversibly trapped in the macrophages until the cells degenerate and die. As a result of this effective sequestration the colloidal material is not excreted to any significant extent in feces or urine. Our patient, for example, excreted only 2.2 microcuries of radiogold or .001 % of the injected dose in the stools over the first 4 days of hospitalization. Urinary radioactivity during this period was also minimal. Attempts at mobilization of the particles with two,three dimercapto-propanol (British anti-Lewisite, BAL) and other chelating agents have been unsuccessful [11]. Thus, once cleared by the reticuloendothelial system, the particles are strategically fixed adjacent to proliferating radiosensitive cells in bone marrow, liver, and spleen.

The time course and type of radiation injury sustained by these sensitive cells is dependent on certain physical properties of the gold isotope, which are indicated in Figure 7. The major damage from radioactive decay is due to the beta emission. The gamma emission is useful for external monitoring and thus for scanning and dosage estimates. It is also responsible for the exposure hazard to bedside personnel in circumstances of overdosage. We realized that the physical half-life of 2.7 days permitted some time to attempt removal or neutralization of the particles before the vast majority of the radiation dose would be delivered, but no effective method of preventing the inevitable radioactive decay at the sites of particle localization is known at present.

It was clear from the initial dosage estimates, from the considerations just mentioned, from numerous studies in animals, and from the subsequent clinical course that serious hematopoietic insufficiency is the major early problem. We also suspected that even if that phase could be weathered with supportive care later hepatic damage was likely. Our expectations in this regard were confirmed by the as yet unreported experience of Brodsky [11] with a similar overdose accident in which the patient survived a prolonged period of hematopoietic insufficiency with thrombocytopenia as a major feature only to expire of hepatic insufficiency months later. It must be pointed out, however, that the exact nature of the hepatic pathology was not clear in Brodsky's case, and that hepatitis secondary to extensive blood product replacement during the hematopoietic failure phase may have been an important contributing factor.

In contrast to the paucity of information about the toxicity of intravenous radiogold in humans [12], considerable data are available from animal studies. Blood dyscrasias [13] and several types of delayed hepatic pathology including hepatoma formation [14], cystic changes, fibrosis, necrosis, and cirrhosis have been noted [15].

A very interesting aspect of our patient's story, which complicates interpretation of her clinical course and pathologic findings, is her preexisting hematologic disorder. We were uncertain how the presence of this condition might modify several aspects of the body's ability to handle the radiation injury and recover. It was clear at the outset from the scan of the whole body (Fig. 2) and the whole blood count rate at 30 hours, that there was no significant impairment of trapping of the radioactive particles. In fact, the more extensive reticuloendothelial system may have accelerated clearance from the blood. It is known that considerably smaller dosages of intravenous radiogold (approximately 40 millicuries) may be beneficial in the therapy of patients with related myeloproliferative disorders [16]. It occurred to us that the overdose might have inadvertently represented "curative" treatment for the patient's condition if she could be supported long enough and if her marrow had the ability to repopulate with normal cell lines. We speculated further that the liver and spleen which presumably were enlarged as a feature of the erythremic

myelosis might have intensified the depression of peripheral blood counts by acting as irradiators of the blood elements circulating through them.

Our patient's post mortem findings, viewed in light of the blood count changes after the overdose, seem consistent with attempted regeneration in the hematopoietic tissues with additional foci of blood formation in certain extramedullary sites such as lymph nodes. It is not clear whether the extramedullary hematopoiesis represents a residue of the pre-existing blood condition or an attempt at compensation for the suppressive effect of the approximately LD_{50} dose to the marrow. In either case it is interesting that in the autopsy material the process is seen in lymph nodes, but not in more likely sites such as liver and spleen [2]. This suggested to us that the lymph nodes, despite their significant reticular cell content, may have had access to fewer gold particles than had the liver and spleen because of the very effective irreversible trapping of the particles in these enlarged organs. As a result, the beta radiation dose to the nodes might have been considerably less than to liver and spleen and extramedullary blood formation might have either continued throughout the course of the over- dosage, if it was present before, or have been permitted to begin anew during recovery more readily than in liver or spleen. Consistent with this interpretation is the clinical observation of the necessity for giving intralymphatic rather than intravenous injections of radiogold to effect significant changes in pathologic lymph nodes [8,16].

In conclusion, it is important to point out that overdosage with intravenous radiogold colloid is a model type of radiation exposure. The pattern of retention and the chemical inertness of the colloidal particles are most similar to those seen with thorotrast [17]. Several important points of difference are to be noted, however. Radiogold is a beta and gamma emitter rather than an alpha emitter. In addition, the very much shorter physical half-life of radiogold permits the more rapid radiation dose delivery which makes possible the acute as well as chronic sequelae of overdosage. Until it is possible to devise a means of mobilizing retained particles or a method of internal shielding, possibly by giving followup doses of non- radioactive gold colloid, our strongest protection against radiogold intoxication is prevention of overdose through scrupulous monitoring tech- nique before intravenous administration.

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Figure Captions for SM-119/39

Fig. 1--Bone marrow smear made prior to accidental Radiogold (^{198}Au) Colloid overdosage. Note red cell and megakaryocyte changes of erythremic myelosis. (Wright's stain x180)

Fig. 2--Whole body scan made with a gamma scintillation camera (Anger) using a pin-hole collimator at thirty hours after intravenous dose of 200 millicuries of Radiogold (^{198}Au) Colloid. This figure is a composite of three images made with equal exposure time. Note the abnormally extensive distribution of reticuloendothelial marrow.

Fig. 3--Anterior liver scan made in same manner as Fig. 2 with a one minute exposure time (728,000 counts). Midpoint of liver was 31 cm from the pin-hole aperture. Liver and spleen appear adjacent with no marked difference between activity in the spleen and the left lobe of the liver.

Fig. 4--Estimated absorbed doses after 200 millicuries Radiogold (^{198}Au) Colloid intravenously. Figures are based on standard beta and gamma dose formulae (Johns, H.E., The Physics of Radiology, pp. 562, 565, Second Edition, C.C. Thomas Publisher).

Fig. 5--Peripheral blood leukocyte and platelet counts following intravenous Radiogold (^{198}Au) Colloid (200 millicuries) given on day zero (arrow). Note early fall of absolute lymphocyte and granulocyte counts with later partial recovery. Platelet levels fall later without evidence for recovery by day 70 (patient's demise).

Fig. 6--Postmortem microscopic changes in femoral bone marrow (a,b), liver (c), and lymph node (d). Note moderate hypocellularity with islands of erythroid activity and absence of megakaryocytes in marrow areas. (a-Azure-eosin x45; b-Azure-eosin x72), focal nuclear atypia and congestion in liver (c-Hematoxylin and eosin x45), and lymphoid depletion and hematopoiesis in pericapsular fat of lymph node (d-Hematoxylin and eosin x72).

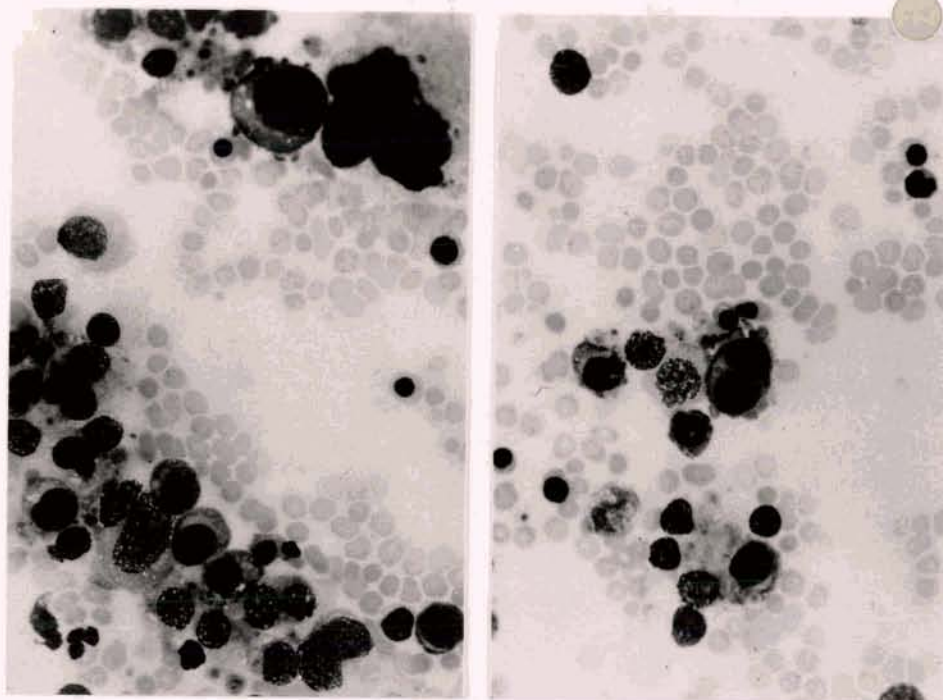Fig. 7--Physical characteristics of radiogold (^{198}Au).

Fig. 1 Bone marrow smear made prior to accidental
Radiogold (^{198}Au) Colloid overdosage. Note red cell
and megakaryocyte changes of erythremic myelosis.
(Wright's stain x180)

FIG. 2. Whole body scan made with a
gamma scintillation camera (Anger) using
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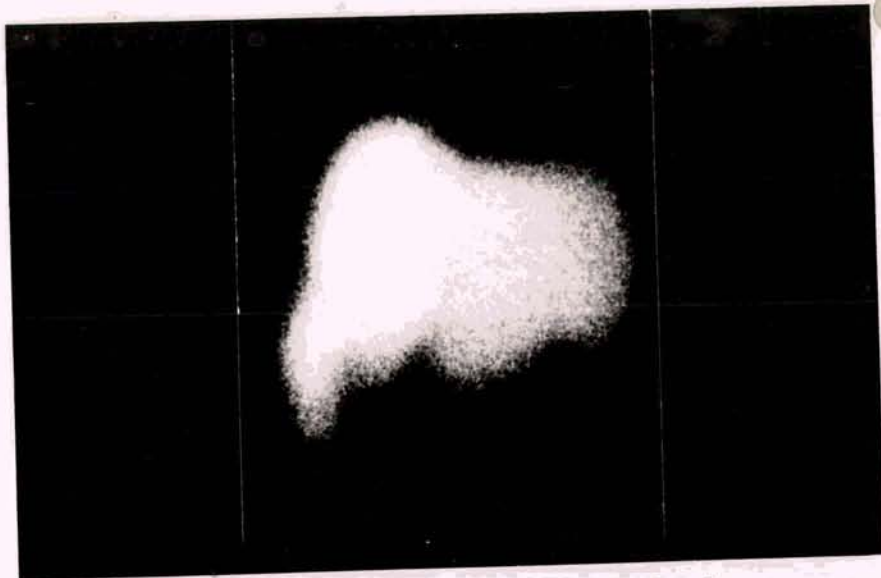extensive distribution of reticulo-endothelial
marrow.

FIG. 3. Anterior liver scan made in same manner as Fig. 2 with a one minute exposure time (728,000 counts). Midpoint of liver was 31cm. from the pin-hole aperture. Liver and spleen appear adjacent with no marked difference between activity in the spleen and the left lobe of the liver.

ORGAN	ESTIMATED ABSORBED DOSE
LIVER	7,300 rads
SPLEEN	7,300 rads
INTESTINE ADJACENT TO LIVER AND SPLEEN	600 rads
RED BONE MARROW	440 rads
INTESTINE OF MID ABDOMEN	60 rads

Fig. 4. Estimated absorbed doses after 200 milli-curies Radiogold (^{198}Au) Colloid intravenously. Figures are based on standard beta and gamma dose formulae (Johns, H.E., The Physics of Radiology, pp. 562, 565, Second Edition, C.C. Thomas Publisher).
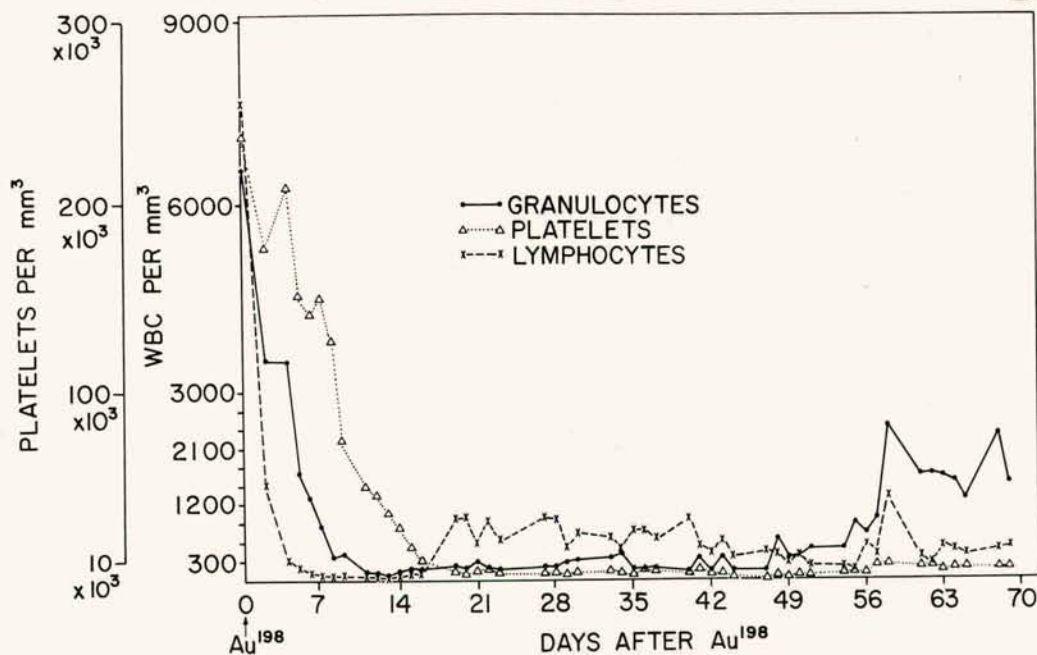

FIG. 5 Peripheral blood leukocyte and platelet counts following intravenous Radiogold (^{198}Au) Colloid (200 millicuries) given on day zero (arrow). Note early fall of absolute lymphocyte and granulocyte counts with later partial recovery. Platelet levels fall later without evidence for recovery by day 70 (patient's demise).
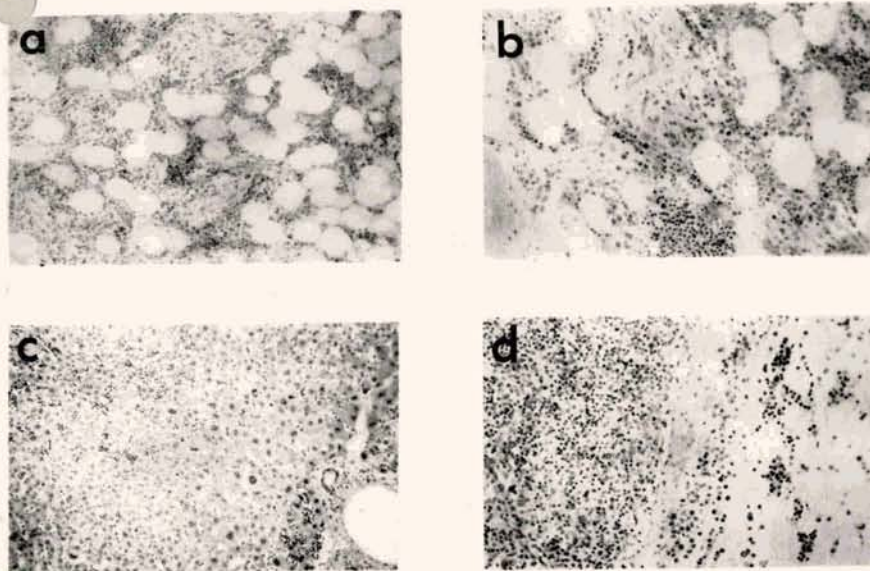
FIG. 6 Postmortem microscopic changes in femoral bone marrow (a, b), liver (c), and lymph node (d). Note moderate hypocellularity with islands of erythroid activity and and absence of megakaryocytes in marrow areas (a-Azure-eosin x45; b-Azure-eosin x72), focal nuclear atypia and congestion in liver (c-Hematoxylin and eosin x45), and lymphoid depletion and hematopoiesis in pericapsular fat of lymph node (d-Hematoxylin and eosin x72).

PHYSICAL HALF LIFE	2.7 days
AVERAGE BETA ENERGY	0.328 meV
PRIMARY GAMMA ENERGY	0.411 meV
DOSE RATE CONSTANT (Roentgens per hour one cm. from a one millicurie point source)	2.7 R per hr.

Fig 7. Physical Characteristics of Radiogold (^{198}Au)