# DISTRIBUTION OF GALLIUM IN HUMAN TISSUES AFTER INTRAVENOUS ADMINISTRATION

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Gallium-67 has recently been introduced for determining the location and extent of tumors in humans (*1–5*). Although the distribution of gallium after intravenous administration has been studied in animals (*6–8*), assays from humans are urgently needed to understand scans better and to assess the associated irradiation of normal tissues.

About 20 years ago radiogallium was investigated as a prospective agent for the diagnosis and treatment of neoplasms involving bone (*9,10*), as suggested by Dudley, Maddox, and La Rue, who discovered concentration of $^{72}Ga$ at sites of osteogenesis in animals (*11*). The $^{72}Ga$ was produced in a nuclear reactor by an n,$\gamma$ reaction on stable $^{71}Ga$, and the preparations necessarily contained considerable stable gallium. During the later stages of the clinical investigation of $^{72}Ga$, studies with $^{67}Ga$ essentially free of gallium "carrier" (cyclotron-produced by a p,2n interaction with $^{68}Zn$) revealed that the amount of stable gallium administered had a profound effect on the tissue distribution in rats (*12*). Thus the autopsy data published in 1953 on $^{72}Ga$ in humans (*13*) may not be applicable to the present use of $^{67}Ga$.

At this institution $^{67}Ga$ was first given to patients in 1951. Most of the doses administered from 1951 to 1953 were prepared with 0.2 mg gallium carrier per kilogram of body weight. Because experiments in rats have shown no important differences between carrier-free doses and carrier levels up to 0.25 mg/kg (*12,14,15*), the present report evaluates postmortem assays for $^{67}Ga$ given patients intravenously with and without added carrier.

## METHODS

Gallium-67 from the Oak Ridge National Laboratory was prepared in citrate solution for intravenous injection as previously described (*2*). The "carrier-free" preparations theoretically contained traces of stable gallium derived from impurities in the zinc target used in the cyclotron, but the amount of gallium was below the limit of spectrographic detectability (*12*).

The subjects of this study were patients who died in the years 1951 to 1953 and 1968 to 1970 despite treatment for malignant neoplasms. In the 1951–1953 series, samples were assayed by digesting in nitric acid and gamma counting in a Marinelli cup using a bismuth-walled G-M tube (*16*). With most samples adjacent tissue was taken for histologic examination. In the 1968–1970 series, specimens in histologic fixatives were assayed in sodium iodide well counters and subsequently examined histologically (*17*). In addition, some of the values were corroborated by assays of whole organs and by whole-body counts (*18–20*). Throughout the study, gross autoradiography was helpful in showing details of the distribution and in guiding the selection of assay samples.

Survey of our hospital records disclosed 26 autopsies with sufficient $^{67}Ga$ for assays. We reviewed the original assay data, morphologic descriptions, and histologic sections, and we recorded estimates of the percentage of tumor, inflammation, necrosis, fibrosis, and other components that could have altered $^{67}Ga$ localization. The analysis began with 1,616 assays from the 26 autopsies; three of these autopsies were considered separately because two of the patients had received doses with gallium carrier levels greater than 0.2 mg/kg, and the other had been given another radionuclide that interfered with radioassays. Paired organs and larger masses of tissue were usually represented by two or more samples from each autopsy. Samples of tumor were often selected to show the difference in activity between viable and necrotic portions. Except for tumor, the value rep-

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**TABLE 1. AUTOPSIES OF PATIENTS GIVEN $^{67}Ga$: DATA PERTINENT TO DISTRIBUTION**

| Pt. No. | Time: dose-death | Age, Sex | Body wt. (kg) | Carrier gallium (mg/kg) | Diagnosis | Highest concentration* | | | Heart* (mean %/kg) | Whole-body retention at death (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Tumor (%/kg) | Other tissue (%/kg) | Other tissue Organ | | |
| | Hours | | | | | | | | | |
| 1 | 3 | 42 M | 42.3 | 0.0 | Glioblastoma multiforme | 0.2 | 7.1 | Kidney cortex | 1.0 | |
| 2 | 6 | 16 F | 40.9 | 0.0 | Ewing's sarcoma | 2.2 | 5.7 | Kidney cortex | 0.3 | |
| 3 | 9 | 47 F | 36.4 | 0.0 | Lymphosarcoma | 9.8 | 2.4 | Kidney cortex† | 1.1 | |
| 4 | 10 | 71 M | 67.0 | 0.0 | Reticulum-cell sarcoma | 9.4 | 4.6 | Kidney medulla | 0.7 | |
| 5 | 16 | 24 F | 54.3 | 0.2 | Hodgkin's granuloma | 2.7 | 7.4 | Bone | 0.4 | |
| 6 | 19 | 16 F | 40.5 | 0.0 | Osteosarcoma | 22.0 | 11.1 | Adrenal | 0.9 | 96 |
| 7 | 20 | 45 F | 51.3 | 0.0 | Adenocarcinoma, breast | 19.9 | 5.1 | Kidney | 0.7 | |
| | Days | | | | | | | | | |
| 8 | 1.2 | 15 M | 38.6 | 0.2 | Osteosarcoma | 14.9 | 9.2 | Bone | 0.2 | 69 |
| 9 | 1.9 | 14 F | 42.3 | 0.2 | Osteosarcoma | 11.0 | 6.6 | Bone | 0.4 | |
| 10 | 2.1 | 23 M | 40.0 | 0.2 | Osteosarcoma | 18.7 | 3.9 | Adrenal | 0.4 | <80 |
| 11 | 2.8 | 80 M | 51.9 | 0.2 | Adenocarcinoma, prostate | 8.8 | 6.3 | Spleen | 0.6 | <79 |
| 12 | 5.6 | 31 F | 47.3 | 0.0 | Hodgkin's granuloma | 7.2 | 11.5 | Adrenal | 0.6 | 67‡ |
| 13 | 5.8 | 46 F | 40.0 | 0.2 | Adenocarcinoma, breast | 1.9 | 1.3 | Lymph node | 0.3 | <85 |
| 14 | 6.8 | 60 M | 64.3 | 0.0 | Medullary carcinoma, thyroid | 5.4 | 8.6 | Spleen | 0.4 | |
| 15 | 7.1 | 41 F | 46.1 | 0.2 | Adenocarcinoma, breast | 41.0 | 6.3 | Spleen§ | 0.6 | <67 |
| 16 | 7.8 | 58 F | 42.3 | 0.0 | Adenocarcinoma, lung | 2.9 | 2.8 | Kidney cortex | 0.2 | <65 |
| 17 | 8.4 | 55 M | 37.8 | 0.2 | Adenocarcinoma, lung | 9.1 | 9.2 | Spleen | 0.4 | |
| 18 | 11.9 | 27 M | 42.7 | 0.2 | Fibrosarcoma | 4.6 | 4.3 | Liver | 0.1 | <73 |
| 19 | 12.2 | 53 F | 46.6 | 0.0 | Lymphoma, mixed lymphocytic and histiocytic | 16.2 | 8.4 | Spleen | 0.3 | |
| 20 | 15.2 | 45 F | 53.0 | 0.0 | Reticulum-cell sarcoma | 4.4 | 2.2 | Liver | 0.1 | 54‡ |
| 21 | 16.5 | 59 M | 88.6 | 0.0 | Small-cell carcinoma, lung | 13.7 | 10.2 | Spleen | 0.2 | 52‡ |
| 22 | 17.1 | 56 M | 46.0 | 0.0 | Squamous-cell carcinoma, lung | 3.5 | 3.0 | Spleen\|\| | — | |
| 23 | 22.7 | 58 M | 44.1 | 0.0 | Plasmacytoma, atypical (reticulum-cell sarcoma) | 16.8 | 5.3 | Spleen | 0.4 | 63‡ |

* All assay values are expressed as a percent of the administered dose corrected for physical decay to the time of the dose and normalized to a body weight of 70 kg; except for tumor, values are means of all available samples considered normal histologically.

† A lymph node had the same value, 2.4% dose/kg.

‡ Percent of dose measured by whole-body count, corrected for decay; other values in this column were determined by assay of urine and feces, with incomplete collections except for Patients No. 6 and 8.

§ Two other values are probably spurious: lymph node (13.0%/kg) and pituitary (7.8%/kg).

|| A lymph node with 6.6%/kg had pronounced histiocytic hyperplasia.

resenting each tissue was obtained by averaging the assays of all pertinent samples free of abnormalities known to affect $^{67}Ga$ concentration. The values were corrected for radioactive decay and expressed as a percent of the administered dose per kilogram of tissue, normalized to a body weight of 70 kg.

## RESULTS

Table 1 lists the 23 patients according to the interval from the dose to death and states for each the highest concentration of $^{67}Ga$ found at autopsy in tumor, the highest mean concentration in other tissue, and the mean concentration in a reference tissue (heart muscle). The highest tissue concentration, other than in tumor, shifts from the kidney to bone, adrenal, or lymph node in the first week, and later in the series to liver and spleen. This listing does not include fecal material in the rectum, which had greater activity than tumor or other tissue in two autopsies (No. 14, 37.6 %/kg; No. 16, 5.3 %/kg). Urinary excretion falls off rapidly in the first few days (Fig. 1), but a small renal calculus had 12.3 %/kg at 5.6 days (No. 12). The assay values of heart muscle are listed for comparison with tumor and other tissues because samples of myocardium free of tumor were taken from all but one patient, and they seemed to give an indication of the amount of $^{67}Ga$ retained by muscle and soft tissues generally.

In another group of patients at this institution with earlier stages of neoplastic disease, the whole-body retention after scanning doses of $^{67}Ga$ averaged 65% at 7 days, with 26% excreted in the urine and 9% in the feces. Although the whole-body retention data in the autopsy series are incomplete, we assumed that differences in renal function and circulatory status accounted in part for the variability

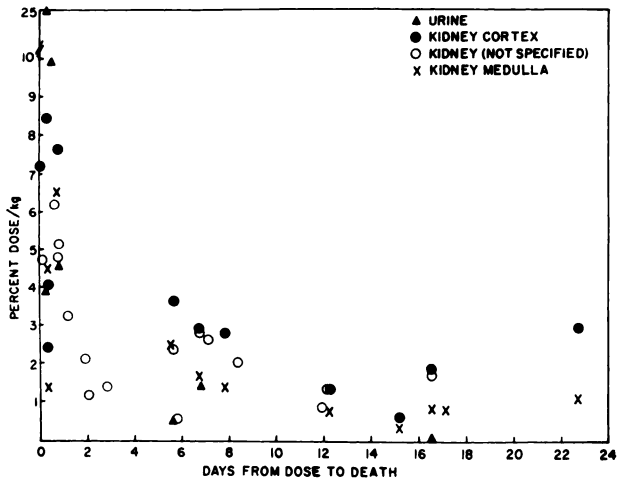


**FIG. 1.** Postmortem assays of renal tissue and urine corrected for decay and normalized to body weight of 70 kg. Each point in Figs. 1–6 represents sample or mean of replicate samples free of tumor or other abnormality known to affect $^{67}$Ga concentration. Note that cortex has more $^{67}$Ga than medulla. Wide range of values for urine and kidney samples is primarily related to decrease in concentrations with time.

in assays. With this in mind, we investigated the rather high retention of 63% at 23 days for Patient No. 23 and the corresponding high renal assays shown in Fig. 1. This patient was unusual in that scans before intensive treatment had shown much deposition of $^{67}$Ga in soft tissue tumors and in bone lesions, although patients with well-differentiated plasmacytoma had little localization in tumor. Histologically and clinically the tumor had features suggesting reticulum-cell sarcoma, with only occasional neoplastic plasma cells, consistent with the variant of plasmacytoma called "reticulomyeloma" (*21*). We could find no abnormal proteins in the serum or urine, or histologic abnormalities such as amyloidosis or "myeloma kidneys." Azotemia was absent, and the only explanation for the retention of $^{67}$Ga was the concentration in the extensive tumor.

Six patients were mildly azotemic and two had slight hydronephrosis, but we could not demonstrate that renal impairment caused high $^{67}$Ga values in any of the 23 autopsies. As might be expected from the excretion of $^{67}$Ga, patients dying at longer intervals after the dose had been administered tended to have lower concentrations in most tissues (Figs. 1–6). The trends varied in different tissues, and in many tissues the changes in concentration with time seemed less important than the individual differences among patients. Accordingly, Table 2 lists the tissues and fluids in the order of the average concentration for those represented in at least 11 of the 23 autopsies and provides the ranges of values.

A few high values are probably spurious; the value most suspect was the average of two assayed lymph nodes, one near the mean of all lymph nodes and the other ten times greater (Fig. 6). The node with the implausibly high assay value was free from tumor or inflammation, and no errors were found in calculations. Presumably, improper recording of the count or use of a contaminated test tube was at fault. A few similar errors of lesser magnitude might have been included in the analysis, but they could not influence the results importantly. After we discarded the highest value for each tissue, all the means in Table 2 were recalculated; those changed more than 20% are indicated. Discarding the lowest value did not raise the mean as much as 20% for any tissue.

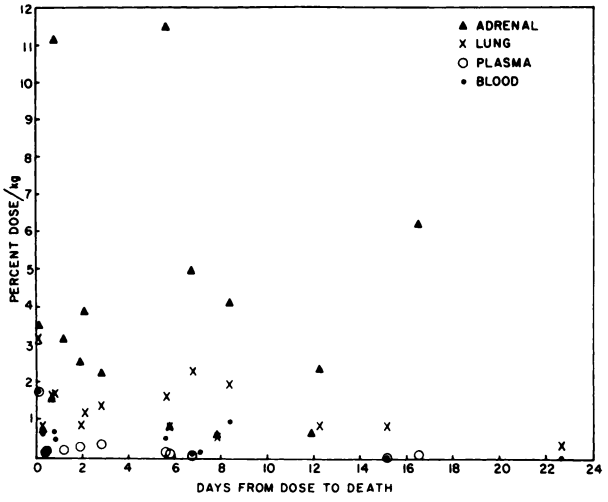


**FIG. 2.** Most values for lung and adrenal were means of samples from left and right, usually in close agreement. Again, each point represents mean of all appropriate samples from one autopsy. Wide range of adrenal values indicates considerable differences in patients.

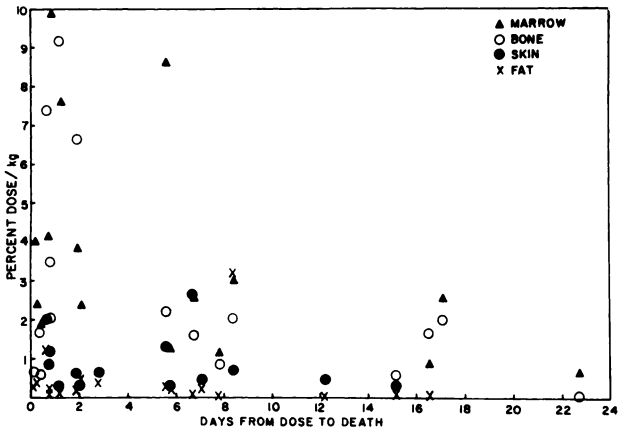


**FIG. 3.** Wide range in concentration of $^{67}$Ga in bone and marrow is evident. Multiple samples of bone and marrow from same patient also showed much variation as expected when sampling tissues with several constituents differing in concentration and distribution.

Table 3 gives other values of interest. The gonads were all atrophic (from treatment, inanition, or age), with little or no correlation between the assays and the degree of atrophy, from slight to severe. (In microscopic autoradiograms of mouse ovaries we have seen focal concentrations of $^{67}Ga$ in phagocytic cells of the corpus luteum, but we have not assayed a human corpus luteum.) Samples of spinal cord contained more $^{67}Ga$ than those of brain, but considerably less than choroid plexus and meninges. Spinal fluid was much less active (0.05 %/kg, mean of 7) although ascitic and pericardial fluid had activity similar to that given for pleural fluid in Table 2. Samples of diaphragm were consistently more active than other samples of skeletal muscle, and in several instances this was shown to be attributable to a considerable concentration of $^{67}Ga$ in the pleural and peritoneal serosa. Assays of the urinary bladder did not indicate any adsorption of the high concentrations of $^{67}Ga$ from the urine.

The assays of contents of the alimentary tract only suggest certain sites of excretion. Obviously some of the $^{67}Ga$ is excreted in bile, but the samples of bile were from the gallbladder and may not represent the bile entering the duodenum before death. That is, bile from the hepatic ducts may be excreted directly into the duodenum, bypassing the gallbladder; or bile containing much $^{67}Ga$ may be stored in the gallbladder to be released later when $^{67}Ga$ levels in the rest of the body are lower. Although the assay values for intestinal contents were generally higher than for gastric contents, these values are also affected by circumstances extraneous to the excretion of $^{67}Ga$, such as the ingestion of food or drink. Occasional high values for fecal material in the rectum a week after the dose presumably resulted from retention and concentration of $^{67}Ga$ excreted in the bile and upper alimentary tract.

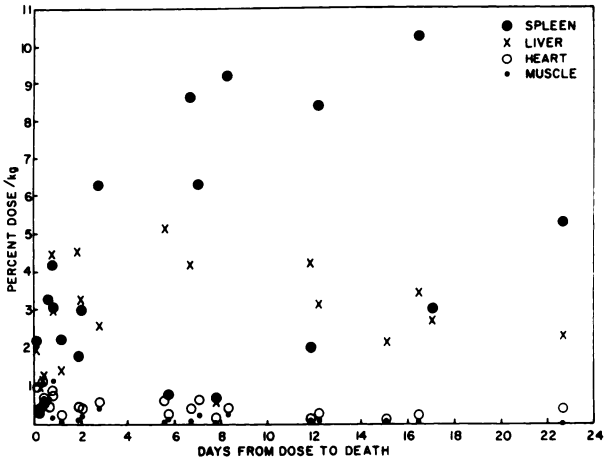


**FIG. 4.** Note considerable variation in $^{67}Ga$ concentration in spleens, despite close agreement of replicate samples. Samples of myocardium and diaphragm were almost always more active than other samples of striated muscle and were considered separately. Despite low concentration in skeletal muscle it retains appreciable part of administered $^{67}Ga$, because it constitutes much of body weight (30 kg in 70-kg "standard man").

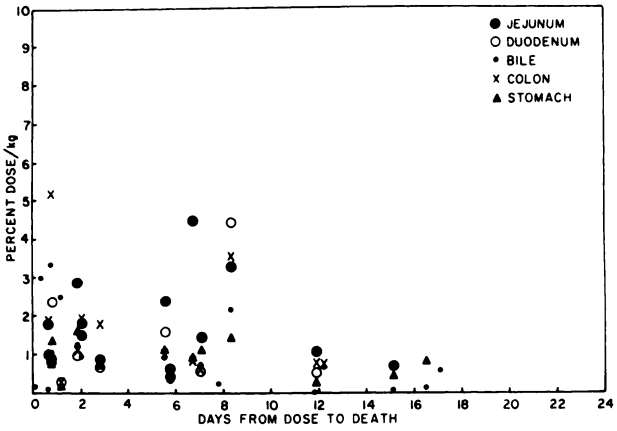


**FIG. 5.** Concentration of $^{67}Ga$ in samples of gastrointestinal tract (not including contents) and bile.

## DISCUSSION

**Reasons for wide ranges.** Variability in some tissues can readily be explained by problems of sampling related to differing concentrations of $^{67}Ga$ in various parts, especially in bone (Figs. 3, 7). Marrow samples similarly must reflect the proportions of cancellous bone, fat, and hemopoietic elements (*17*). However, problems of sampling do not explain the wide range in such organs as the adrenal and spleen (Figs. 2, 4), with many values well supported by duplicate assay samples. To investigate possible explanations for the considerable range of values, the data were grouped for analysis according to circumstances that have influenced gallium distribution in clinical or animal studies: time after dose, sex, nutritional state, age, tumor localization, amount of tumor, presence of inflammation, and stable gallium carrier. Differences between the early cases (1951–1953) and the current series were also considered.

The most important factor found was the interval between the dose and the time of death, so for further investigation of other variables the patients were separated into groups according to survival: (A) less than a day after the dose, (B) 1–3 days, (C) 5–9 days, and (D) more than 10 days. The means of values in these periods reflect the trends expected from Figs. 1–6. Because the assay data had a frequency distribution that is strongly skewed

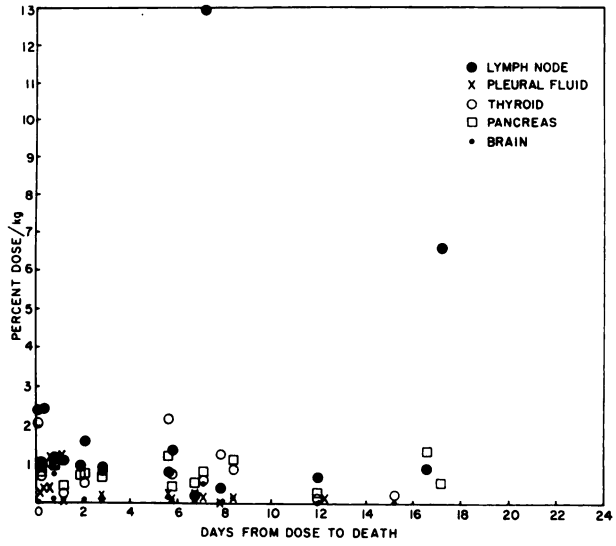


**FIG. 6.** Concentration of $^{67}Ga$ in pleural fluid and miscellaneous tissues listed in Table 2. High lymph-node value on Day 7 (Patient No. 15) is considered spurious; high value on Day 17 (Patient No. 22) may be attributable to histiocytic hyperplasia in benign node near carcinoma.

rather than Gaussian, we chose a nonparametric method for statistical analysis, the Wilcoxon (Mann-Whitney) rank test (*22*).

**Effect of sex.** Although female rats of certain strains have lower concentrations in muscle, spleen, and marrow (Hayes, unpublished data) and clinical studies have shown a pelvic localization in women (*4*), we detected no remarkable sexual differences in assay values for the series as a whole or within the various groups.

**Effect of nutritional state.** Normalization of the assays to the "standard man" weight of 70 kg would be expected to introduce errors because the variation in size of organs was not always proportionate to the body weight. However, comparison by body weight or nutritional status disclosed no statistically significant effect on $^{67}Ga$ concentration, even in the emaciated patients or those with mid-thigh amputations.

**Effect of age.** The mean values from the four adolescents tended to be greater than the means of the 19 adults and were more than twice as high in bone, marrow, and bile although adults had higher assay values in a few tissues, notably spleen (Table 4). These differences, although statistically significant for bone (at the 0.01 level) and bile (at the 0.05 level), were less impressive after we took into account the fact that all adolescents had died within 2 days after the dose when most tissues except spleen have higher concentrations. Differences between the values for adolescents and those for the seven adults

**TABLE 2. CONCENTRATION OF $^{67}Ga$ IN TISSUES AND FLUIDS***

| | No. of patients | Assays (% admin. dose/kg)† Mean | Range |
|---|---|---|---|
| Spleen | 20 | 4.1 | 0.4 –10.2 |
| Kidney cortex | 12 | 3.8 | 0.7 – 8.4 |
| Adrenal | 16 (8) | 3.8 (5.1) | 0.6 –11.5 |
| Marrow | 16 | 3.6 | 0.7 – 9.9 |
| Liver | 19 | 2.8 | 0.6 – 5.2 |
| Kidney | 16 (7) | 2.7 (3.3) | 0.6 – 6.2 |
| Bone | 16 (12) | 2.6 (1.4) | 0.04– 9.2 (3.5) |
| Lymph nodes | 16 | 2.2 [1.5] | 0.2 –13.0 [6.6] |
| Kidney medulla | 11 | 2.0 [1.6] | 0.4 – 6.5 [4.6] |
| Jejunum | 12 (4) | 1.9 (2.0) | 0.6 – 4.5 |
| Colon | 13 (4) | 1.6 (2.0) | 0.3 – 5.2 |
| Lung | 15 | 1.3 | 0.3 – 3.0 |
| Duodenum | 12 | 1.3 [1.0] | 0.3 – 4.4 [2.4] |
| Bile | 19 | 1.0 | 0.04– 3.4 |
| Stomach | 15 | 0.9 | 0.2 – 1.7 |
| Thyroid | 14 (6) | 0.9 (1.2) | 0.1 – 2.2 |
| Skin | 14 (6) | 0.9 (1.1) | 0.3 – 2.6 |
| Pancreas | 15 | 0.8 | 0.3 – 1.3 |
| Heart | 22 | 0.5 | 0.1 – 1.1 |
| Blood | 12 | 0.5 [0.4] | 0.01– 1.8 [1.0] |
| Pleural fluid | 15 | 0.4 | 0.03– 1.2 |
| Fat | 18 | 0.4 [0.3] | 0.04– 3.2 [1.2] |
| Plasma | 11 | 0.3 | 0.02– 1.8 |
| Muscle | 21 | 0.2 | 0.03– 1.1 |
| Brain | 14 | 0.1 | 0.00– 0.7 [0.5] |

* Numbers in parentheses indicate values after omission of patients with gallium carrier; numbers in brackets indicate values after omission of possibly spurious high value. (Values not revised unless mean differs more than 20% from mean of whole series.)

† Corrected for radioactive decay and normalized to a body weight of 70 kg.

**TABLE 3. CONCENTRATION OF $^{67}Ga$ IN CERTAIN TISSUES AND FLUIDS REPRESENTED BY FEWER THAN 11 OF THE 23 AUTOPSIES***

| | No. of patients | Assays (% admin. dose/kg)† Mean | Range |
|---|---|---|---|
| Ovary | 5 (2) | 1.0 | 0.5– 1.3 (0.8–1.1) |
| Testis | 5 (2) | 0.7 (1.0) | 0.4– 1.1 (0.9–1.1) |
| Prostate | 8 (4) | 1.1 (1.6) | 0.3– 3.2 (0.5–3.2) |
| Uterus | 6 (2) | 0.7 (0.5) | 0.3– 1.3 (0.3–0.8) |
| Pituitary | 9 (2) | 2.0 (1.4) | 0.6– 7.8 (1.3–1.6) |
| Spinal cord | 10 (3) | 0.4 (0.5) | 0.0– 1.9 (0.1–1.3) |
| Diaphragm | 9 (5) | 0.6 | 0.2– 1.3 (0.2–1.3) |
| Bladder | 10 (7) | 0.7 | 0.2– 2.6 (0.2–2.6) |
| Urine | 7 (7) | 6.6 | 0.1–25.5 |
| Esophagus | 9 (2) | 0.8 (1.4) | 0.4– 1.8 (1.0–1.8) |
| Ileum | 10 (1) | 1.3 (2.4) | 0.4– 2.8 |
| Contents of stomach | 6 (6) | 0.2 | 0.1– 0.4 |
| Contents of small intestines | 6 (6) | 2.3 | 0.0– 5.3 |
| Contents of colon | 7 (7) | 8.0 | 1.3–37.7 |

* Numbers in parentheses indicate values after omission of patients with gallium carrier; mean not given unless differing more than 20% from mean of whole series.

† Corrected to the time of dose and normalized to a body weight of 70 kg.

dying in the first 3 days were not significant at the 0.05 level. However, skeletal concentrations of $^{67}$Ga are higher in growing rats than in adults (Hayes, unpublished data), and autoradiograms from adolescent patients (e.g., Patient No. 9, cited in the legend for Fig. 7) show intense epiphyseal and periosteal localization (*17*).

**Effect of tumor.** The concentration of $^{67}$Ga often differed considerably in various samples from the same neoplasm, depending on such factors as necrosis or fibrosis. In only 14 of the 23 patients was the concentration of $^{67}$Ga in at least one sample of tumor greater than any of the mean values for histologically normal tissue. Better localization occurs in most untreated malignancies of these types (*2,5*), and several of the tumors with low concentrations at autopsy had shown considerable localization in scans before treatment. Otherwise, the assay values in the tumors listed in Table 1 are consistent with clinical information from scans and surgical specimens. The evaluation of factors affecting $^{67}$Ga distribution is complicated by the variety of neoplasms and the fact that patients with certain types of tumors were not evenly distributed in the series. All four patients with osteosarcoma were youthful and were in the early series (1951–1953); most of the patients with malignant lymphoma were in the recent series.

In addition to the malignant neoplasms, several patients had incidental tumors. A small rectal carcinoid had a low assay value, 1.8 %/kg (Patient No. 21); rectal polyps in two other patients had slightly higher concentrations of $^{67}$Ga; and a uterine leiomyoma had a lower concentration. The largest benign tumor, a 40-gm meningioma (Patient No. 20) had only 0.6 %/kg.

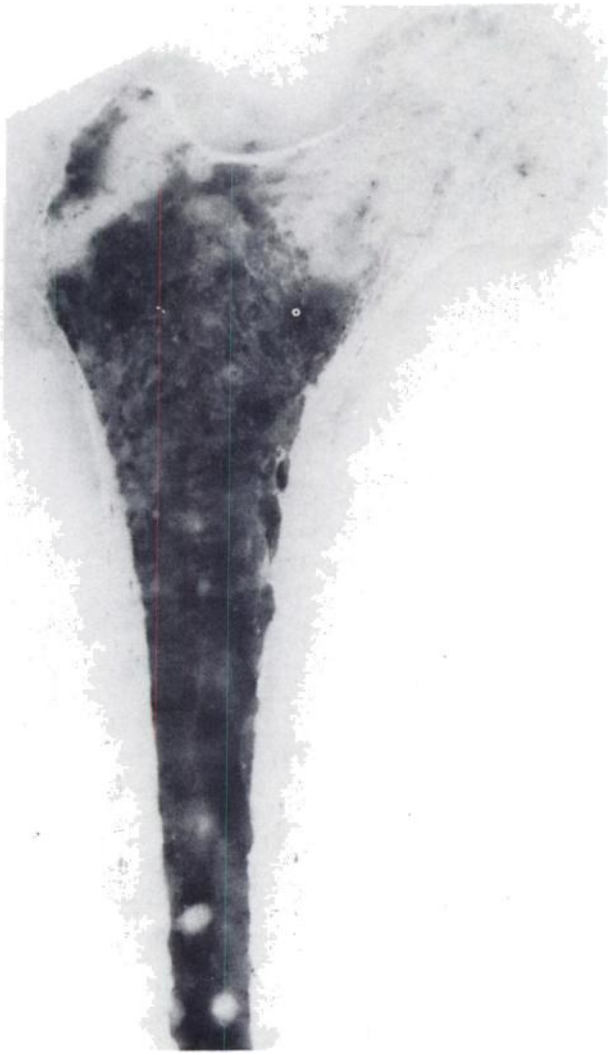

**FIG. 7.** Autoradiogram of femur (Patient No. 12, Table 1) showing much $^{67}$Ga in marrow (stimulated to unusual hemopoietic activity) and in minute foci in cortical bone. Concentration is low in fibrotic nodules of Hodgkin's granuloma in marrow of shaft and in heavily irradiated marrow of head and greater trochanter. This pattern differs greatly from that in femur of adolescent (Patient No. 9) previously used to illustrate problem of sampling tissues with mixture of components (17).

**TABLE 4. COMPARISON OF CONCENTRATIONS OF $^{67}$Ga IN ADULTS AND ADOLESCENTS***

| | Assays (% dose/kg)† | | | | | |
|---|---|---|---|---|---|---|
| | Adults (age 23–80) | | | Adolescents (age 14–16) | | |
| | No. of patients | Mean | Range | No. of patients | Mean | Range |
| Spleen | 16 | 4.5 | 0.5–10.2 | 4 | 2.1 | 0.4–4.2 |
| Marrow | 12 | 2.8 | 0.7– 8.6 | 4 | 5.9 | 2.4–9.9 |
| Kidney | 13 | 2.5 | 0.6– 6.2 | 3 | 3.4 | 2.1–4.8 |
| Bone | 13 | 1.8 | 0.0– 7.4 | 3 | 6.4 | 3.5–9.2 |
| Bile | 16 | 0.8 | 0.0– 3.0 | 3 | 2.4 | 1.3–3.4 |
| Duodenum | 9 | 1.5 | 0.4– 4.4 | 3 | 0.8 | 0.3–1.0 |

* Listing of apparent differences; no significant differences were detected in liver, pancreas, colon, skin, heart, muscle, thyroid, adrenals, or gonads.

† Corrected for radioactive decay and normalized to a body weight of 70 kg.

Because clinical scans and assay data showed that some tumors retain a large part of administered $^{67}$Ga, we expected that diversion of activity to tumor could cause low values in normal tissues. To investigate this possibility the amount of $^{67}$Ga in tumor at death was estimated from the autopsy descriptions and assays. The patient (No. 8) ranked third in the amount of $^{67}$Ga in tumor—26% of the dose—had assay values lower than the means given for 16 of the tissues in Table 2, with higher values in only four tissues (bone, marrow, bile, and kidney). However, the patient (No. 10) with by far the most $^{67}$Ga in tumor—more than half the dose—had values lower

than the means for only 12 tissues, and six were higher (stomach, duodenum, colon, liver, adrenal, and fat). The evidence for diversion of $^{67}$Ga from normal tissues was not enhanced when values for these two patients were compared with values from other patients dying in the same interval after the dose (1–3 days). We found no remarkably low values in assays of normal tissues of the two other patients estimated to have more than 20% of the dose in tumor (No. 23 and 15), or the seven patients considered to have 10–20% of the dose in tumor.

For our listing of "normal" tissue values the diversion of $^{67}$Ga to tumor was apparently less important than other variables because none of the means in Table 2 would have been altered by deletion of the two patients (No. 8 and 10) with the observed differences. Both of these patients had osteosarcoma, but we cannot relate the alterations in the distribution of $^{67}$Ga in normal tissues to the histologic type of neoplasm.

**Concentration of $^{67}$Ga in inflammatory lesions.** Animal experiments had shown moderate $^{67}$Ga concentration in abscesses and granulomas, so we reviewed all samples consisting of at least 50% inflammatory tissue. A kidney with acute pyelonephritis resulting from bacillemia had an assay value of 11.4 %/kg. Relatively normal renal cortex comprised about half the sample, but the unremarkable cortex of the opposite kidney had only 5.9 %/kg; the samples of tumor in this patient (No. 2) had 2.2 %/kg or less. Two patients (No. 22 and 23) had no unusual localization in suppurative pulmonary lesions arising many days after the $^{67}$Ga was given. The high value (6.6/kg) in a lymph node at 17 days was associated with pronounced sinus histiocytosis induced by adjacent neoplasm. No other inflammatory lesions were suitable for analysis, and we failed to recognize remote effects of infection on $^{67}$Ga distribution.

**Carrier effect.** Compared with rats given carrier-free $^{67}$Ga, those dosed with 2.5 mg gallium/kg body weight excrete more radionuclide in the urine, retain less in soft tissues, and have the same skeletal concentration (*12*). When the values for tissues from the nine patients given $^{67}$Ga with 0.2 mg gallium/kg were compared with those from the 14 with carrier, only bone showed a difference statistically significant at 0.01 level. However, the difference can be related to the fact that samples of bone free of tumor were available from only four of the patients given carrier. Three of these happened to be youthful and died in the first 2 days after the dose; their assay values for bone were more than twice the highest bone-value for carrier-free patients (also from an adolescent, dying 19 hr after the dose). The means for soft tissues tended to be lower with carrier, especially in the kidney, adrenal, and thyroid, but were not significant at the 0.05 level. No effects attributable to carrier and significant at the 0.05 level were detected in groupings arranged by dose-to-death intervals.

A comparison of the 1951–1953 series with the 1968–1970 series gave results similar to the analyses for carrier effects. Bone had higher concentrations in the early series ($p < 0.01$); other tissue differences were not significant. The similarity could be anticipated because the old series included all nine patients given doses with carrier and only two without carrier (No. 6 and 7, Table 1). Further analysis supports our interpretation that the periods of survival after the dose and the youthful patients with bone tumors in the 1951–1953 series account for the differences.

An argument against a significant carrier effect in humans at low levels (0.2 mg/kg) is the fact that no such effect was evident in extensive assays from a patient not included in the tabulations because the $^{67}$Ga had been given with 1.0 mg gallium/kg; death occurred 4.5 days after the dose. A patient dying 24 hr after $^{67}$Ga with 0.2 mg/kg carrier, excluded from the tabulations because a dose with 2.0 mg/kg gallium carrier was given 9 days previously, also showed no carrier effect.

## CONCLUSIONS

The assay values presented here should be useful for appraising the radiation doses received by patients given $^{67}$Ga intravenously and for providing information relevant to the interpretation of tumor scans. In this study many organs, especially the kidneys, showed a rapid fall from early high values and a later slow decrease; changes similar to those seen in our clinical whole-body counts and attributed to excretion. Other tissues had no consistent trend. Sex and age affect the distribution in animals but factors other than the time after the dose are not clearly manifest in these patients dying from neoplasm, except in growing bones of adolescents as demonstrated by autoradiography.

The demonstration of considerable variation in tissue concentrations from patient to patient is important. The widest ranges in absolute numbers were in tissues with generally high values, notably spleen and adrenal, but most tissues had at least a tenfold range in values. Although we were unable to demonstrate differences caused by abnormal circulation, nutrition, or renal function, the derangements of physiology in these dying patients are expected to result in wider ranges of values than those of healthy

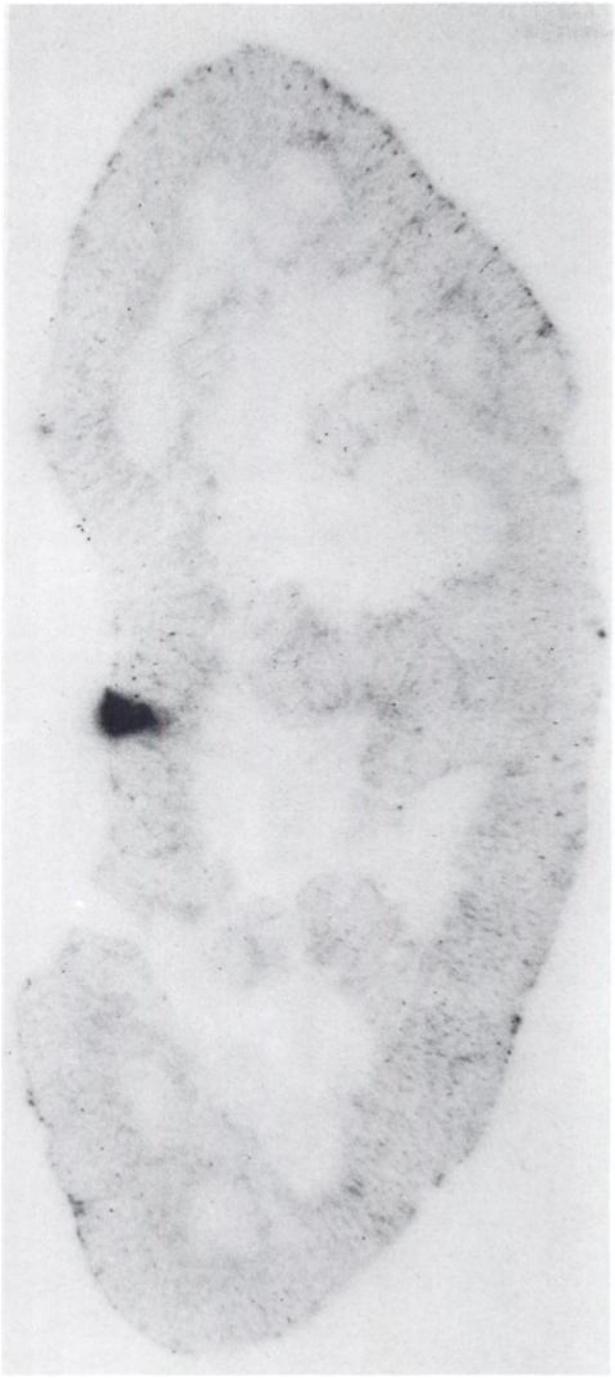

**FIG. 8.** Autoradiogram from slice of kidney (Patient No. 14, Table 1) showing higher concentration of $^{67}$Ga in cortex, with complex, delicate pattern of distribution. "Hot spot" over hilar aspect of cortex was also seen with adjacent slice, but histologic examination failed to provide explanation (lesion lost in processing?). Such spot on autoradiogram from Patient No. 3 led to discovery of 2-mm renal metastasis (17).

persons or laboratory animals. Whatever the causes, the variations encountered with disease should be considered when appraising the irradiation from radiopharmaceuticals.

The different concentrations in various parts of the same organ should also be considered. For example, not only does the renal cortex have a higher $^{67}$Ga concentration than the medulla (Table 2 and Fig. 8), but much of the activity in the cortex is in a relatively small volume of convoluted tubules (*23,24*). Because the irradiation from internal conversion electrons and Auger electrons (*25*) is high focally, dosimetric calculations will be needed for anatomic details on a comparable scale. Rats and mice have concentrations in lysosome-like bodies (*23,24*), especially in macrophages, accounting for concentration in some tumors and normal tissues. The intracellular distribution of $^{67}$Ga in humans has not been reported, but provisional estimations of local irradiation doses can be made pending the results of studies in progress.

## SUMMARY

To provide data for radiation dosimetry of $^{67}$Ga, recently introduced for scanning tumors, we have tabulated the tissue distribution of 23 autopsies after intravenous administration. Relatively high concentrations were usual in the spleen, renal cortex, adrenal, and marrow but assays showed a wide range of values in all tissues. We have also illustrated with autoradiograms an uneven distribution in certain tissues. The radiation dose to those tissues is influenced by cellular localization because much of the energy from $^{67}$Ga decay is expended by electrons with a very short range.

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