jnm/DIAGNOSTIC NUCLEAR MEDICINE

Gallium Imaging in Pediatrics

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Gallium-67 citrate imaging was carried out in 59 children from 3 mo to 20 yr of age. Indications for the study included the search for occult inflammatory disease and the detection and staging of malignant disease. The Ga-67 citrate scan had a 96% reliability in confirming or excluding the site of purulent material as a cause of sepsis, and 76% reliability in detecting malignant disease. Tissue distributions in children differ from those in adults primarily in that the epiphyseal plates, spleen, and thymus may show increased activity normally and in the presence of sepsis. These variations are illustrated as possible sources of incorrect interpretation. "Cold" defects may be seen in sterile collections and avascular masses. Experience in this age group seems sufficiently encouraging to continue the use of gallium-67 citrate for the purposes described.

J Nucl Med 18: 1057–1063, 1977

Early reports of the use of gallium-67 citrate for the imaging of bone, tumor, and purulent collections were sufficiently encouraging to merit several investigations and their resultant publication (*1–5*). The Ga-67 study has subsequently proven useful in evaluating a variety of disease entities and conditions. Reports of the use of Ga-67 citrate in pediatric diagnostic problems were, however, mostly anecdotal and were buried within the large series of adult patients being reported. The experience described here was initiated as a collaborative effort to determine the usefulness of Ga-67 citrate studies in pediatrics.

METHODS AND MATERIALS

Gallium-67 decays by electron capture with a 78-hr half-life, and has four principal gamma emissions—at 93, 185, 296, and 388 keV. Gallium-67 citrate used in all patients in this series was obtained from a single source. All patients were studied 24 to 96 hr after the injection of the material, using dual 12.5 cm rectilinear scanners. Images were made from head to upper thighs in anterior and posterior projections, using 1:5, 1:2, and 1:1 images depending upon the size of the child. Repeat and/or lateral and oblique views were obtained where deemed necessary. Bowel preparations were administered when clinically possible and were begun immediately after injection of the radiopharmaceutical. Dosage selections, up to a maximum of 3 mCi, were based on height and weight tables, adjusting adult doses for the surface area of the child (*6*). Sedation was given to children as indicated clinically, using the recommendations of Conway (*7*). Caution was exercised in preparation of the bowels of neonates and small children. Bowel preparation should be less vigorous in children, since there is generally less stool activity than in adults, but low-residue diets and gentle cathartics were usually prescribed.

TABLE 1. GALLIUM IMAGING IN 49 PEDIATRIC PATIENTS

	Patients	True +	True −	False +	False −	"Reliability"
Inflammatory diseases	32	17	14	0	1	96%
Malignant diseases	17	7	6	0	4	76%

Received Feb. 22, 1977; revision accepted June 7, 1977.

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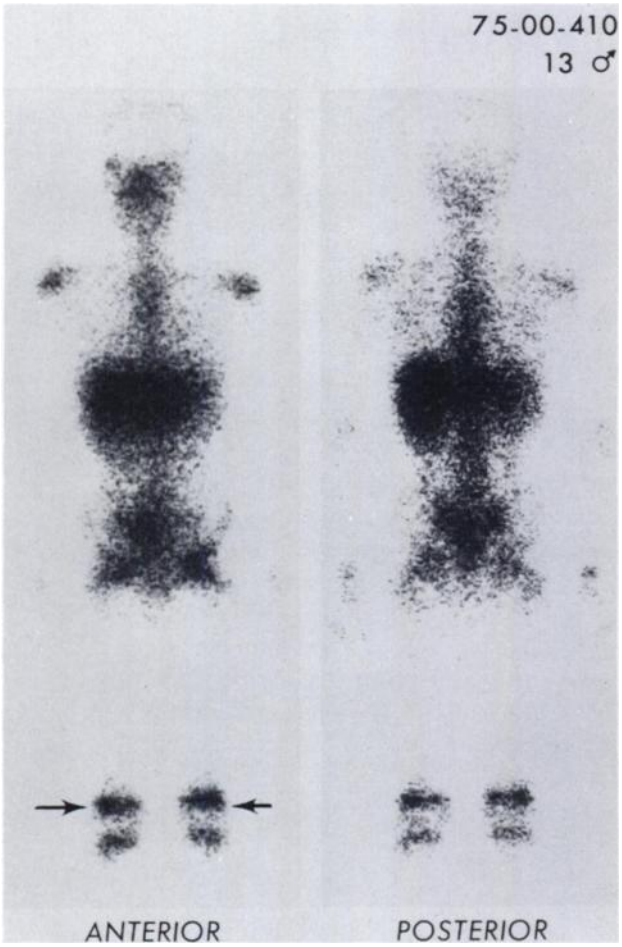

FIG. 1. Normal gallium-67 scan in 13-year-old youth. Note symmetrical increase in activity in epiphyseal plate areas reflecting increased blood flow to these regions. (Arrows on distal femoral epiphyseal plates.)

Fifty-nine patients were studied, the ages ranging from 3 mo to 20 yr. In 51 of these patients, sufficient followup was possible to permit evaluation for this report; two patients were subsequently excluded because of equivocal interpretations of the gallium study, prohibiting accurate correlation with the clinical diagnosis.

RESULTS

The results of our experience are shown in Table 1. Of the 49 patients reported here, 32 were studied for possible inflammatory disease, and 17 for the detection and/or staging of malignant disease.

Normal variations. Evaluation of the initial Ga-67 scans in children made it clear that the distribution of the radiopharmaceutical differs from that found in adults. The main differences found were:

1. Increased blood flow to the epiphyseal plate areas of the growing bones, with a symmetrical, relative increase of gallium-67 uptake in these regions. Uniform and symmetrical positioning of the joint areas therefore becomes critical in the pediatric population when Ga-67 scans are made (Fig. 1).

2. Thymic and splenic uptake of Ga-67 may be markedly increased in children, particularly in the presence of sepsis. Presence of increased activity in these areas should be cautiously interpreted and evaluated with full appreciation of the clinical findings, conventional roentgenograms, and symptoms (Figs. 2 and 3). Mechanism of this uptake is unclear, but may be related to death of thymic cells and increased macrophage infiltration into the thymic cortex, in patients under severe stress from infection,

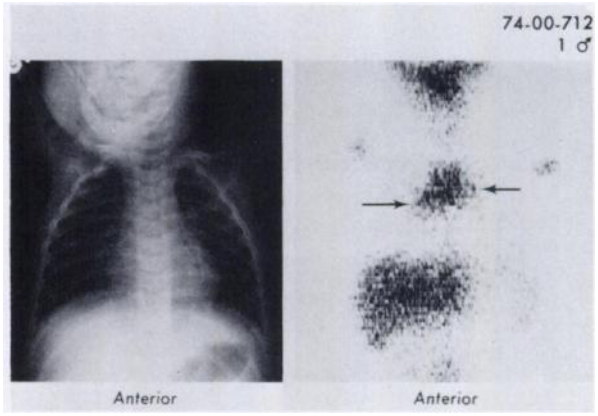

FIG. 2. One-year-old boy with meningitis, evaluated for possible cerebral or other abscess. Markedly increased accumulation of Ga-67 is seen in thymus, with typical "notches" at edges of right and left lobes (arrows). X-rays never showed thymic enlargement, and the child remained well 2 yr following recovery from meningitis (see text).

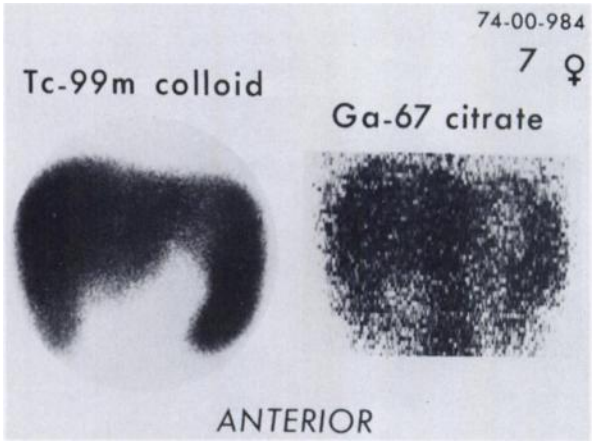

FIG. 3. Seven-year-old girl with splenomegaly and a febrile illness of obscure origin. Splenic enlargement and increased activity is seen on both Tc-99m sulfur colloid and Ga-67 scans. Child recovered from an apparent severe viremia and remains well 2 yr later without clinical splenomegaly.

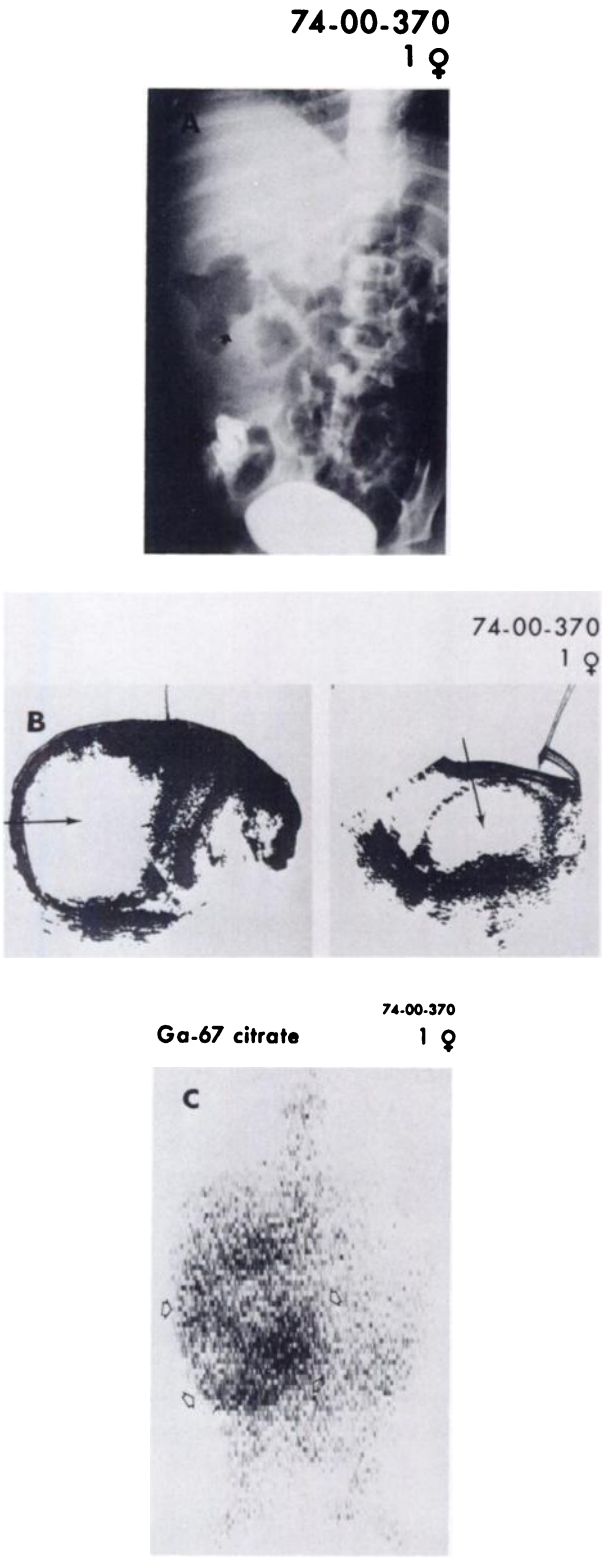

FIG. 4. One-year-old girl developed fever and right lower quadrant mass several months following surgery for perforated appendix. (A) IVP demonstrated elevation of the right kidney (arrows) with a right lower quadrant mass. (B) Sonogram demonstrated a large cystic mass in the right lower quadrant (arrows). Left panel = transverse section; right panel = longitudinal. (C) Gallium-67 scan demonstrated markedly increased activity in the right lower quadrant mass (arrows). A purulent abscess was drained surgically.

or similar processes. Evidence for this speculation has been presented by Gad and Clark; they produced acute thymic involution with increased macrophage activity in Swiss albino mice by the intraperitoneal injection of *S. typhosa* (*8*).

Inflammatory diseases. In 17 of the 32 patients with inflammatory disease the site of infection was correctly identified (53% true +) (Figs. 4 and 5). In 14 of 32 patients the study was normal, with no subsequent source of bacterial infection identified and normal course confirmed retrospectively (44% true −). The overall "reliability" of this study, then, was 97% (31 of 32 patients) in suspected inflammatory diseases. There were no false-positive studies in the group. The single false-negative study was in a child with an infected neuroenteric fistula with an approximately 2 cm (diameter) purulent sac.

The images obtained from the subject of Fig. 6 were of exceptional interest. It has been our experience that "cold spot" appearances can be found with large avascular masses and should not be overlooked. In the child demonstrated in Fig. 6, palpation of the "cold" area revealed a mass that was found at surgery to be a sterile hydrops of the gallbladder secondary to duct obstruction by lymph-node hyperplasia resultant from Echo 19 virus infection.

Malignant diseases. Seventeen children were studied for the staging of malignant disease. Seven of the 17 (41%) were found to have lesions subsequently confirmed as malignant (Figs. 7 and 8). Six of 17 patients (35%) were found to be normal by gallium scan and confirmed by other studies and clinical course to have no malignancy. No children were found to have positive scans in the absence of tumor, but four of 17 children (24%) with proven malignancies had normal scans. The overall detection rate or "reliability" of the Ga-67 scan in children with malignancies, then, was 76%. Tumors missed in this series included: fibrosarcoma (neck), retroperitoneal neuroblastoma, Hodgkin's lymphoma (pelvis), and rhabdomyosarcoma (Table 2).

DISCUSSION

Gallium-67 citrate was first investigated as a bone-scanning agent and found to localize in a variety of soft-tissue tumors (*1,2*). Numerous subsequent studies indicated that malignant tumors with lysosomally active cellular kinetics (such as lymphomas and bronchogenic cancers) would be "gallium positive." Gastrointestinal adenocarcinomas, myelomas, and thyroid carcinomas are among those malignant tumors most notably "gallium negative" (*9–11,15*). The appearance of gallium uptake in sites of purulent collections likewise suggested that the gallium-67, after initial transport in the blood stream bound to

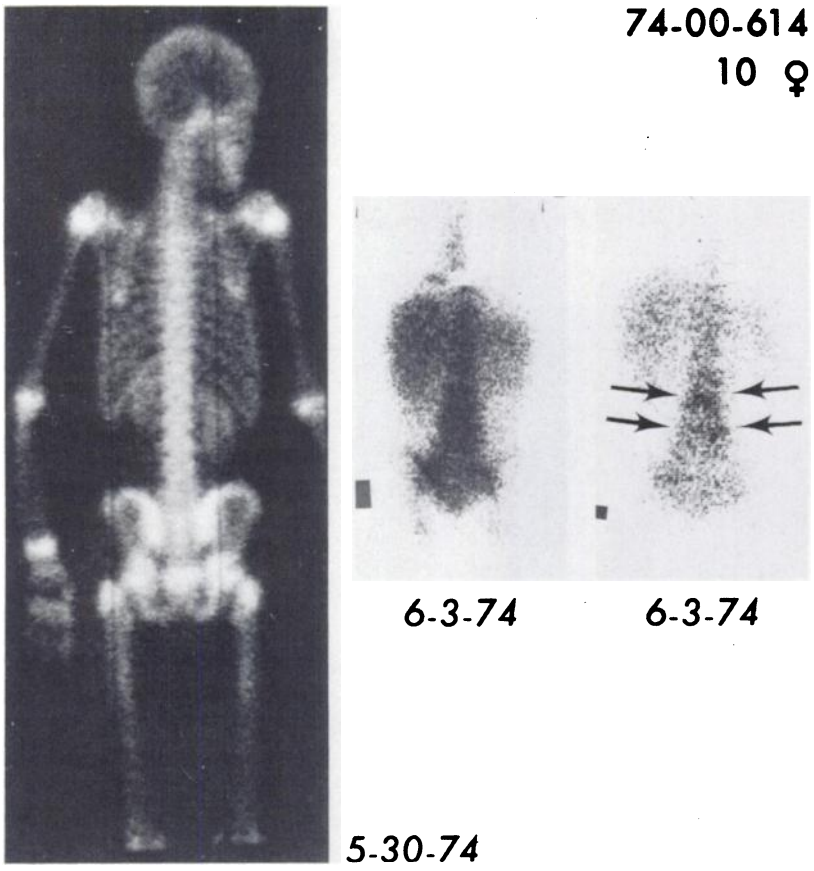

FIG. 5. A 10-year-old girl developed fever and severe back pain. X-rays of the spine were normal. Tc-99m HEDP bone scan was normal (5–30–74). Gallium-67 citrate scans at different intensities on 6–3–74, demonstrated bilaterally increased activity in the paraspinal areas corresponding to the para-aortic nodal chains (arrows; see "normal" Fig. 1 for comparison). Blood cultures and surgical biopsy of nodes both produced *Staph. aureus* as cause of bacteremia and sepsis.

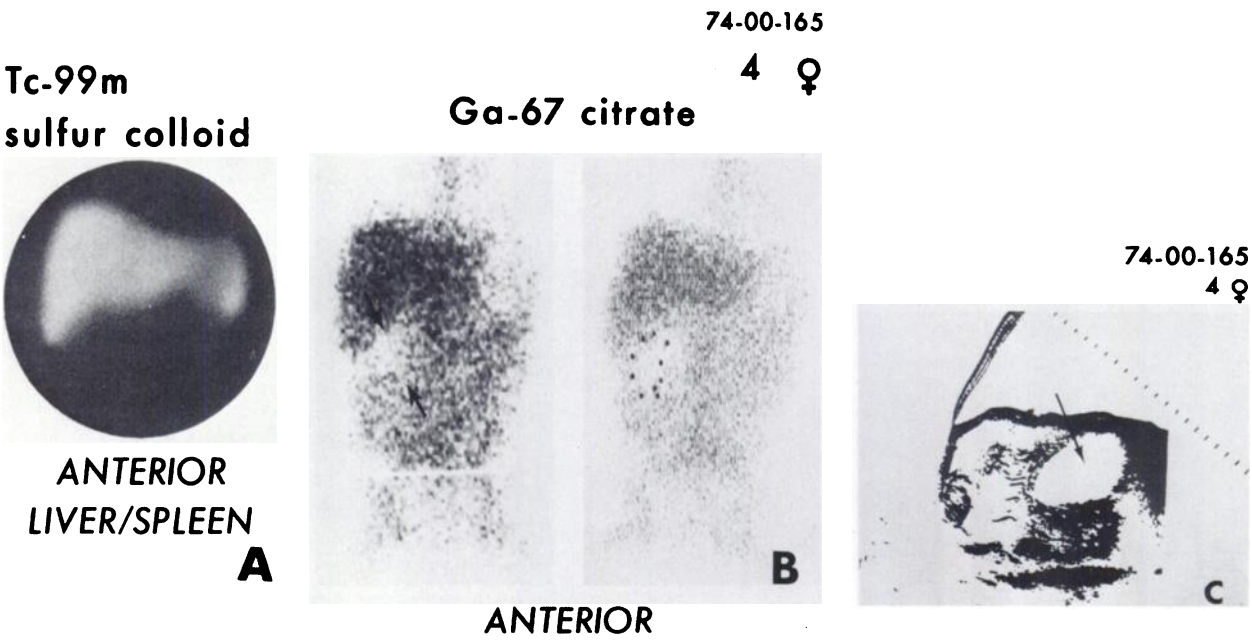

FIG. 6. Four-year-old girl with fever, leukocytosis (predominantly lymphocytic). She developed an ill-defined right upper quadrant mass on day of Ga-67 scan. (A) Normal Tc-99m sulfur colloid liver scan. (B) Gallium-67 scan demonstrated "cold" defect in area of gallbladder. Before repeat scan, markers were placed in area of palpable mass and correspond to "cold" or photopenic area. (C) Sonogram demonstrates echo-free mass in area of gallbladder (arrow). Surgical diagnosis was sterile hydrops of gallbladder due to obstruction by enlarged periportal nodes.

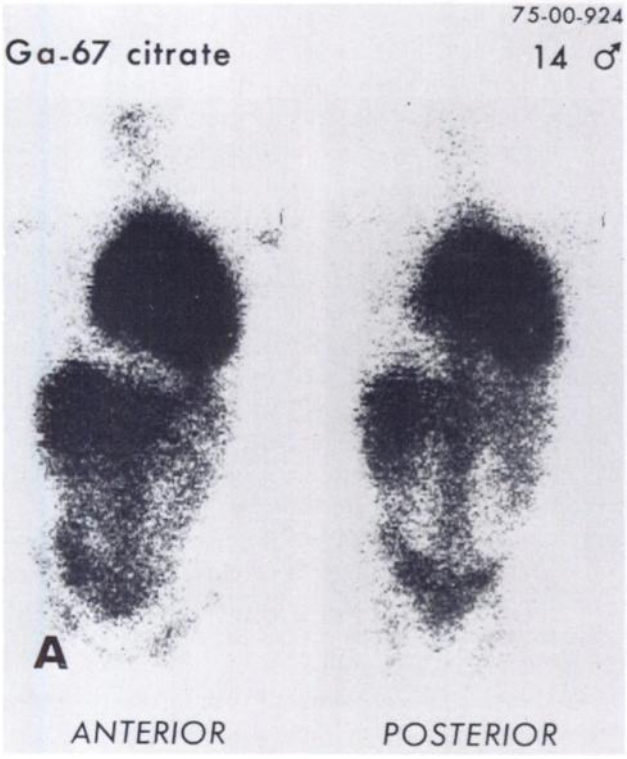

FIG. 7. Fourteen-year-old youth presented with shortness of breath and enlarged cardiac silhouette. Echocardiogram suggested pericardial effusion, but chest film was typical for mediastinal mass. (A) Gallium-67 scan demonstrated avid uptake in mass closely corresponding with x-ray silhouette. (B) Chest film, gallium scan, and combined overlay demonstrate the corresponding uptake of the material in the mass. Surgical resection confirmed the presence of reticulum-cell sarcoma.

protein such as transferrin (16), became localized in the region of lysosomal structures in leukocytes, thereby making the purulent areas "gallium positive" (*17*). Additional reports appeared confirming the clinical usefulness of Ga-67 imaging in the detection of occult inflammatory diseases (*4,18–24*). Since pediatricians are commonly faced with the dilemma of children with "fever of undetermined origin" (*25*) and/or unexplained masses, it seemed worthwhile to apply the gallium scan to pediatric patients. Mussa (*26*) had previously reported encouraging results from Ga-67 studies in 21 children.

The reliability of our early results with Ga-67 imaging in patients with inflammatory disease led to wider applications of the Ga-67 scan in pediatric patients at our institutions. In several instances of acute hematogenous osteomyelitis and septic arthritis, initial Tc-99m phosphate bone scans were equivocal or normal, whereas the gallium scans were markedly abnormal. These findings have been presented elsewhere (*27*), and were predictable. Tc-99m phosphate bone scans will become positive when hyperemia, osteolysis, or repair processes occur in the osseous structure, but acute hematogenous osteomyelitis generally has its origin within the *marrow*, with purulent collections there, and involves the osseous structures only later. In fact, there may be *decreased* flow to the bone matrix adjacent to the infected marrow space, due to purulent thrombosis of nutrient vessels (*28*). One of us has described a femoral head that was "cold" by Tc-99m phosphate scan in a child with acute hematogenous osteomyelitis due to *Staphylococcus aureus*; this

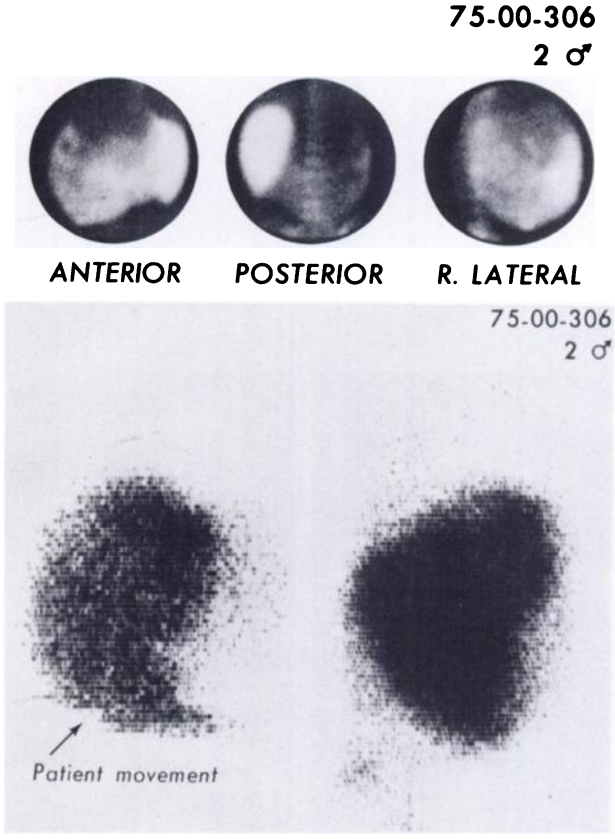

FIG. 8. Two-year-old boy with abdominal distention and hepatomegaly. (A) Tc-99m sulfur colloid liver scan demonstrated large right-lobe mass replacing hepatic parenchyma, particularly superiorly, with splenic and marrow "shunting." (B) Gallium-67 scan demonstrated "filling in" of defects seen on colloid scan. Anterior view (left panel) and right lateral (right panel). Marked liver uptake makes it difficult to see remainder of body activity in marrow, etc. Surgery confirmed presence of inoperable hepatoma.

TABLE 2. GALLIUM IMAGING IN SURGICALLY CONFIRMED MALIGNANCIES

True positives	False negatives
Reticulum cell sarcoma (abdomen)	Neuroblastoma (retroperitoneum)
Hepatoblastosarcoma	Rhabdomyosarcoma (orbit)
Hepatocellular carcinoma	Hodgkin's disease (pelvis)
Rhabdomyosarcoma (hip)	Fibrosarcoma (neck)
Wilms tumor (renal)	
Mixed teratocarcinoma/embryonal (mediastinum)	
Poorly differentiated lymphoma (mediastinum)	

seems to confirm the suggested sequence of events (*29*). Since the Ga-67 is a bone-marrow seeker and appears to label the leukocytes, it is logical that the infected marrow space will be "gallium positive" before a bone scan that reflects hyperemia and osseous cellular changes (Fig. 9). Caution is necessary in patients with leukopenia, however, since this has been shown to alter the mechanisms of gallium uptake in purulent collections (*17*).

The variability and nonspecificity of Ga-67 uptake in malignant tumors requires even more cautious interpretation. While Wilms tumors, neuroblastomas, rhabdomyosarcomas, lymphomas of several types, testicular tumors, ovarian carcinomas, and osseous sarcomas have all been shown to be "gallium positive," perfect node-by-node reproducibility has not been found. False-negative studies have also been found in most of these tumor types. Necrotic and fibrotic tumors, as well as those treated with radiotherapy, will take up less gallium (*2*). It seems prudent then to use the "gallium-positive" study with some degree of confidence in tumor imaging but to be wary of the normal gallium scan in children under high suspicion of malignancy. While one of us has reported somewhat better results with In-111 bleomycin in imaging pediatric tumors (*30*), the results have not been significantly better to warrant abandonment of Ga-67 for this purpose. Bowel activity seen with Ga-67 citrate produces problems in interpretation not experienced with In-111 bleomycin, and this gives the latter agent a clear advantage. Widespread commercial availability, NDA status, and cost factors, however, seem to favor Ga-67 citrate at the present time.

As with all roentgenographic or nuclear imaging procedures in children, judicious use cannot be overemphasized, and good clinical information must be obtained from the referring pediatrician before performing the study. This will, moreover, increase the diagnostic reliability of the procedure.

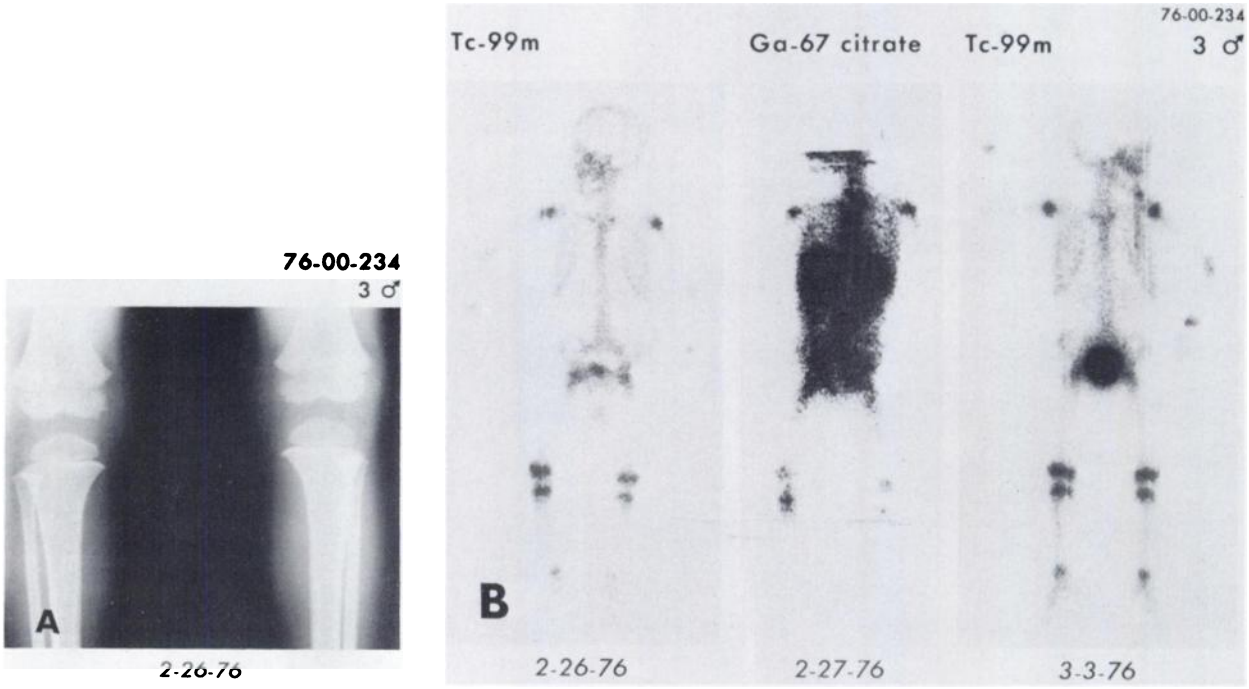

FIG. 9. Three-year-old boy with fever and painful, hot right knee. (A) Radiographic examination of knees was normal. (B) Initial Tc-99m HEDP bone scan (2–26–76) demonstrated minimally increased activity in epiphyseal plate areas of right distal femur and proximal and distal tibia. Gallium-67 scan showed disparately increased activity in right proximal tibia. Blood cultures and clinical course confirmed acute hematogenous osteomyelitis. Repeat bone scan (3–3–76) after 4 days of intravenous antibiotics was completely normal.

CONCLUSION

Gallium-67 imaging has been found useful in detecting and characterizing sites of inflammatory disease and malignant tumor in children, with sufficiently high accuracy to merit its continued use for these purposes. The most reliable study in our series was the search for occult inflammatory diseases, which resulted in 97% accuracy. While it is suspected that this rate may decrease in larger series and in less closely selected populations, the method is currently the most reliable for locating soft-tissue abscesses, early osteomyelitis, and septic arthritis. Tumor imaging with Ga-67 citrate is less reliable than in the search for infections, but competitive enough with other techniques to merit a useful place in the workup of patients with suspected malignant disease, particularly of certain cell types. This is especially true when pre- and postoperative staging is difficult by other conventional techniques and when post-therapy followup is desirable. Normal variations, not seen in adults, exist in children, particularly increased uptake in epiphyseal plates, thymus, and spleen. "Cold" areas on the gallium scan may provide additional information as to the nature of palpable and nonpalpable soft-tissue masses.

ACKNOWLEDGMENTS

The authors wish to thank their technologists, pediatric staff, and nursing services for their patience, assistance, and encouragement. Special thanks to Louis Bartolucci for the correlative sonographic information and illustrations contained in this publication.

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