

⁶⁷Ga-Accumulation in Malignant Tumors and in the Prelactating or Lactating Breast (36056)

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(Introduced by N. A. Thorn)

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The observation by Edwards and Hayes (1-4) that carrier free ⁶⁷Ga accumulates in a variety of malignant soft tissue tumors has recently been confirmed by others (5-8). The mechanism by which ⁶⁷Ga is taken up by malignant tumors is unknown. Therefore it seems justified to report an observation on the specific accumulation of ⁶⁷Ga in the pre-lactating or lactating mammary glands which may be important for further studies on the biological behaviour of gallium.

Material. Scintigrams with ⁶⁷Ga have been obtained in 92 patients with a variety of tumors. The material includes three patients examined in the puerperal period. Patient A was a 30-year-old woman who had delivered a stillborn child in the eighth month of gestation. X-Ray of the chest revealed a tumor in the superior mediastinum. The patient received ⁶⁷Ga 9 days after the delivery.

Patient B was 26 years old and had had an abortion in the sixth month of gestation. The patient suffered from genuine epilepsy and received regular treatment with diphenylhydantoin. Otherwise she was healthy. She was admitted to ⁶⁷Ga-scintigraphy on the day after abortion.

Patient C was a 39-year-old woman who had given birth to premature siblings in the eighth month of gestation. The babies were not nursed by the mother. The patient was febrile, and X-ray revealed an abscess in the right lung. ⁶⁷Ga was administered 14 days after the delivery.

Method. Carrier free ⁶⁷Ga (2.3 to 2.8 mCi) as a citrate (Philips Duphar) were given iv. The patients received daily laxatives prior to the examination to reduce "background counts" from the intestinal secretion of ⁶⁷Ga. Scintigrams were made 48-72 hr after the administration, at a time when the difference between the concentration of ⁶⁷Ga

in tumors and in blood was maximal.

A Picker Magna-scanner with a 5 in. crystal shielded with a 31 hole focusing collimator (no. 2112, focal distance: 3 in.) and connected to a Nukab Memonucleograph (*i.e.*, a magnetic tape recorder for scintigraphy) was used. The spectrometer was adjusted so that only photons in the 150-330 keV range were recorded. A count rate of 15,000 or more/min was found over most of the malignant tumors. Over the lactating mammae of patient A was found a count rate of 50,000/min.

Results. Figures 1 and 2 are ⁶⁷Ga-scintigrams from patient A who had a 5 × 5 × 4 cm tumor located in the left side of the superior mediastinum. A biopsy following scintigraphy gave the diagnosis Hodgkin's granuloma. Figure 1 is a front view scintigram of the chest showing two symmetrically located massive accumulations of radioactivity. Scintigrams taken from the right and left side of the chest showed that the symmetrical configurations shown in Fig. 1 were caused by a substantial uptake of ⁶⁷Ga in the mammary glands. The left lateral scintigram (Fig. 2) showed an accumulation in the mediastinal tumor. It was furthermore noticed that, in this patient, very little radioactivity had been taken up by the liver or sternum (Fig. 1). The ⁶⁷Ga-scintigraphy was repeated 6 weeks after the patient had completed a series of high voltage X-ray treatments. At this time, the mammary glands did not accumulate sufficient radioactivity to be visualized, and only sparse radioactivity was found at the location of the tumor. The liver and sternum, however, were visible on the scintigram in the second study.

A similarly intense uptake of ⁶⁷Ga in the mammary glands associated with a decreased uptake in the liver and sternum, was ob-

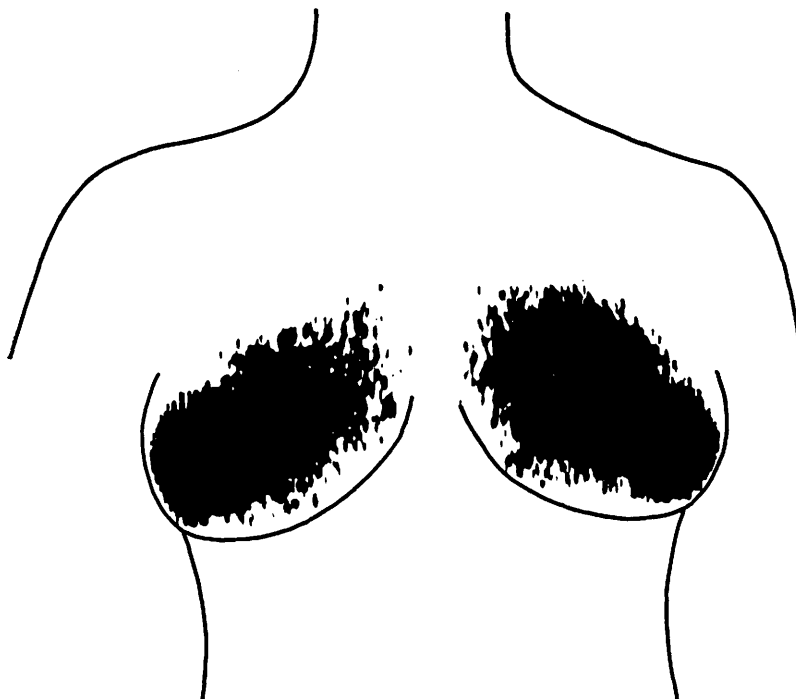


FIG. 1. ^{67}Ga -scintigram of patient A: accumulation of ^{67}Ga in mammary glands 9 days after delivery.

served in the other patients (B and C) scanned during the puerperal period.

The concentration of ^{67}Ga in the milk was measured in one of the patients, and was found to be equal to that of the blood. Hence, the presence of ^{67}Ga in the milk is not likely to be the explanation of the intense accumulation of the radionuclide in lactating mammae. Out of the total number of patients scanned, several were women within the fertile age. None of these showed any significant uptake of ^{67}Ga in the mammary glands. The scintigram of a 40-year-old woman illustrated in Fig. 3, for example, shows a distinct accumulation of ^{67}Ga in a carcinoma in the right breast, but virtually no radioactivity in the remaining part of the mammary glands. The accumulation of ^{67}Ga in the mammary glands of patients A, B, and C, therefore, must be due to physiological changes in the mammary glands during pregnancy or puerperium. The uniquely high affinity of ^{67}Ga for malignant tumors is indicated by the results of ^{67}Ga -scintigraphy in 92 patients (Table I). Of 66 patients with histolo-

gically malignant tumors, 59 showed one or more pathological accumulations of ^{67}Ga on the scintigrams. The malignant tumors included 13 different types, some of which are quite rare, *e.g.*, malignant thymoma, hepatoblastoma, and malignant cystic mesodermal breast tumor. In four patients, ^{67}Ga -scintigraphy revealed tumors or metastases which had not been otherwise discovered. Rescintigraphy in some patients following treatment with X-rays or cytostatics showed that the tumors lose the ability to accumulate ^{67}Ga as a result of the therapy. Determination of the concentration of ^{67}Ga per gram of malignant tissue removed at surgery shortly after the scintigraphy, generally showed a 10- to 20-fold increase over that of the normal surrounding tissue or blood. A reticulosarcoma showed a tumor concentration 300 times the concentration in the blood. Seven of the malignant tumors were not visualized by scintigraphy. They were all squamous cell carcinomas. Two pulmonary tumors were rather small, measuring $2 \times 2 \times 2$ cm or less. The concentration of ^{67}Ga was measured in

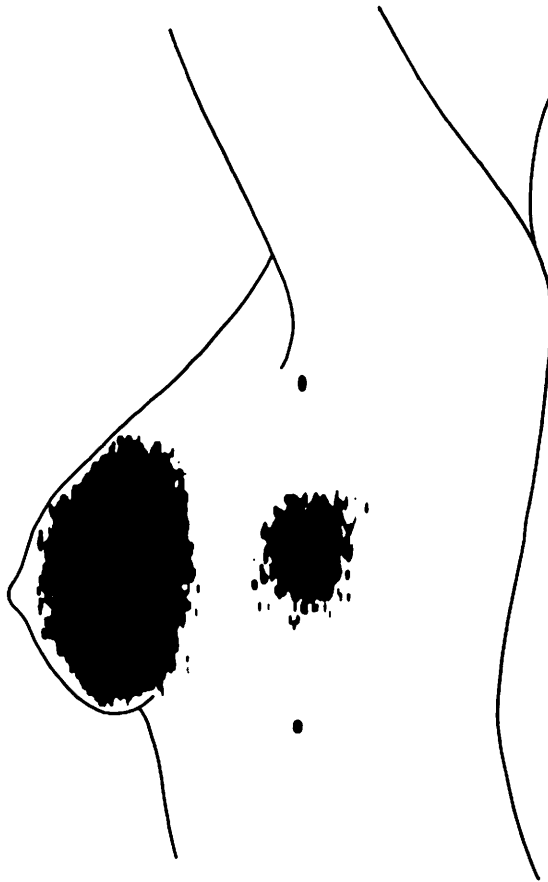


FIG. 2. ^{67}Ga -scintigram of patient A: uptake of ^{67}Ga in mediastinal tumor (Hodgkin's granuloma).

one of these, and was found to be only 1.5 times above that of the surrounding normal tissue. One mammary tumor was diffuse, and infiltrated a greater part of the breast. The other mammary tumor, which could not be seen on the scintigram, was located in the lower half of the right breast, and may have been obscured by the radioactivity in the liver. The two oesophagus tumors may have been missed because of the location close to the spine.

The benign lesions and tumor-like conditions were abscesses, granulomas, hematomas, fibroadenomas, a hamartoma, an ependymoma, and a Boeck's sarcoid. Only 1 of 22 histologically benign lesions accumulated sufficient ^{67}Ga to be visualized by scintigraphy. This was a granuloma of Boeck's sarcoid located in the mediastinum. A specimen of

the lesion, removed shortly after scintigraphy, contained 15 times more ^{67}Ga per gram of tissue than the unaffected lung tissue.

Discussion. The present results confirm the findings of others that carrier free ^{67}Ga accumulates in a variety of malignant tumors, and show that ^{67}Ga -scintigraphy is of significance for the diagnosis of malignant tumors. No other chemical is known to accumulate in malignant neoplasms with such a specificity and contrast as does ^{67}Ga , and the uniquely high affinity of ^{67}Ga for malignant cells may provide investigators with a new approach to the cancer problems.

At present, virtually nothing is known about the mechanism by which ^{67}Ga is taken up by cells, nor is it known whether gallium plays any part in the biological system. According to our experience, ^{67}Ga is not specifi-

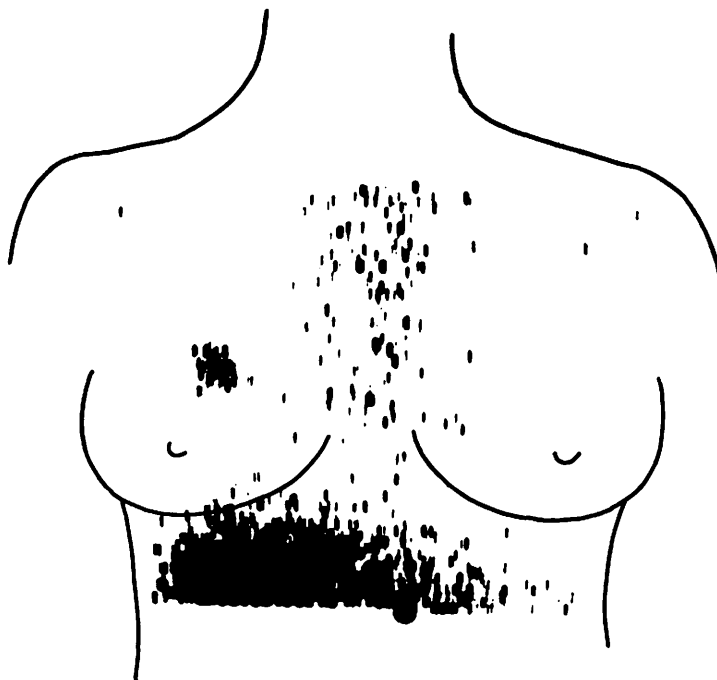


FIG. 3. ^{67}Ga -accumulation in a carcinoma of the right breast in a 40-year-old woman: The accumulation of ^{67}Ga in liver and sternum are normal findings.

cally accumulated in reticuloendothelial or necrotic cells, *e.g.*, no significant accumulation of ^{67}Ga is observed in normal lymph nodes or in the spleen; and necrotic areas within a tumor are often presented as "cold" areas on the scintigrams. ^{67}Ga -Accumulation in cells does not seem to be correlated to the rate of cell proliferation. Hence no significant accumulation of ^{67}Ga is observed in the testes. In addition to malignant cells, ^{67}Ga is taken up by some normal cells in the liver and bones (*e.g.*, see Fig. 3). We have observed that the count rates over liver, sternum, and spine are significantly decreased in patients with certain tumors, *e.g.*, lymphosarcomas and reticulosarcomas, which have a particularly high affinity for ^{67}Ga . This indicates that these organs and the tumor compete for ^{67}Ga . It may well be that the mechanism by which ^{67}Ga is taken up by malignant cells and by some benign is identical, and one approach to study the mechanism of intracellular accumulation of ^{67}Ga would be to look for biological similarities between the different ^{67}Ga -accumulating organs, lesions, and tumors. The present obser-

vation that the physiological changes in the mammary glands during pregnancy enable these to accumulate ^{67}Ga may be a key to further studies on this problem.

Summary. It has been confirmed that carrier free ^{67}Ga has a uniquely high affinity for malignant tumors. The mechanism by which ^{67}Ga is taken up by the tumor cells is unknown. It was observed that physiological changes in the mammary glands during pregnancy enable this organ to accumulate ^{67}Ga . This observation may be of importance for further studies on the biological behavior of gallium and for studies on malignant tissues.

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TABLE I. ^{67}Ga -Accumulation in Tumors and Tumor-Like Lesions.

Results of ^{67}Ga -scintigraphy of 92 patients with histologically identified tumors or tumor-like lesions: Pos, clearly visible tumor on scintigram; Neg, tumor or tumor-like lesion not revealed by scintigraphy.

	Malignant		Benign	
	Pos	Neg	Pos	Neg
Chest	34	2	1 ^a	10
Breast	5	2	0	8
Brain	3	0	0	2
Bones	4	0	0	0
Liver	3	0	0	0
Thyroid gl.	0	0	0	2
Esophagus	0	2	0	1
Eyes	1	0	0	2
Kidneys	3	0	0	0
Parotis gl.	1	0	0	0
Pancreas	(1)	0	0	0
Spleen	1	0	0	0
Peripheral lymph nodes	3	1	0	0
	59	7	1	25
Total	92			

^a A granuloma of Boeck's sarcoid (after the conclusion of the present work, a significant accumulation of ^{67}Ga in Boeck's sarcoid has been observed in 5 more patients).

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