16. Shin MS, Ho JK. Diffuse thymic hyperplasia following chemotherapy for nodular sclerosing Hodgkin's disease. *Cancer* 1983;51:30–33.
17. Front D, Ben-Haim S, Israel O, et al. Lymphoma: predictive value of Ga-67 scintigraphy after treatment. *Radiology* 1992;182:359–363.
18. Weiner M, Leventhal B, Cantor A, et al. Gallium-67 scans as an adjunct to computed tomography scans for the assessment of a residual mediastinal mass in pediatric patients with Hodgkin's disease. *Cancer* 1991;68:2478–2480.
19. Israel O, Front D, Epelbaum R. Residual mass and negative gallium scintigraphy in treated lymphoma. *J Nucl Med* 1990;31:365–368.
20. Front D, Israel O, Epelbaum R, et al. Gallium-67 SPECT before and after treatment of lymphoma. *Radiology* 1990;175:515–519.

EDITORIAL

Benign Mediastinal and Parahilar Uptake of Gallium-67 in Treated Lymphoma: Do We Have All the Answers?

Gallium-67 scintigraphy is now a clinically useful technique for the assessment of treated lymphoma due to newer cameras, SPECT techniques and the understanding that ^{67}Ga is a viability agent. Although the sensitivity and specificity of ^{67}Ga scintigraphy are reasonable, computed tomography (CT) and magnetic resonance imaging (MRI) are the usual techniques used for imaging patients with newly diagnosed lymphoma. On the other hand, ^{67}Ga has been found to be a useful test in assessing response to treatment and predicting survival. Since there is effective treatment for lymphomas, ^{67}Ga plays an important role in patient management, especially in patients who have residual mass after treatment (*1,2*).

Time and experience, however, have taught us that not every mass remaining after treatment of lymphoma is malignant nor that ^{67}Ga uptake after treatment indicates viable tumor. The interpretation of ^{67}Ga scintigraphy after treatment is not without problems. Nontumor ^{67}Ga uptake in the mediastinum in children and in adults is a problem for which a solution still has to be found. The use of SPECT enhances this mediastinal and parahilar uptake. Knowledge of normal and abnormal distribution of ^{67}Ga does not always help in determining the nature of benign uptake.

In this issue of the *Journal*, Harris et al. (*3*) present a case of a 5-yr-old boy with Hodgkin's disease, nodular sclerosis type, who demonstrated ^{67}Ga uptake in what was apparently a benign thymic hyperplasia after treatment. The mass, which was demonstrated by CT, took up ^{67}Ga but was not considered to have taken up ^{201}Tl. The patient did not receive further treatment, and follow-up showed that he was indeed in complete remission. Peylan-Ramu et al. (*4*) found that ^{67}Ga uptake after treatment in patients with non-Hodgkin's lymphoma had a frequency of 43% in children under 15 yr of age. The problem of rebound thymic hyperplasia (*5–12*), which takes up ^{67}Ga, is apparently common and if the use of ^{201}Tl will indeed differentiate between benign and malignant lesions after treatment, it will provide significant aid in determining treatment effectiveness.

Presently, thallium's value in differentiating the nature of a mediastinal mass which takes up ^{67}Ga after treatment is yet to be established. It is not clear that the statement "no mediastinal uptake of ^{201}Tl following chemotherapy in a patient with Hodgkin's disease is supportive evidence against the presence of viable tumor" (*3*) has a sound base. In fact, we believe that there is some uptake of ^{201}Tl in the hyperplastic thymus of the patient described by Harris et al. (see Harris et al. Fig. 3), even if it is of definitely lower intensity than that of the ^{67}Ga (*3*). A study which shows that ^{201}Tl scintigraphy can be confidently used to determine if a mass represents thymic hyperplasia of the thymus after treatment or is a tumor will have to overcome a number of problems. The concentration of ^{201}Tl in lymphoma after treatment may be lower than that of ^{67}Ga (Fig. 1). Also, ^{201}Tl is clearly taken up by the thymus after chemotherapy as shown in Figure 2, where there was no disease in the mediastinum in a patient with osteosarcoma after chemotherapy.

One has to remember that ^{201}Tl is taken up by many normal tissues, such as striate muscle of the myocardium and hypermetabolic bone marrow, and by nonmalignant diseases, such as actinomycosis or candidiasis (*13–19*). It has to be shown in a sufficient number of patients with benign hyperplasia that there is indeed a marked difference in uptake between ^{67}Ga and ^{201}Tl. This difference has to be substantially more evident than that seen between ^{67}Ga and ^{201}Tl in cases where a lymphoma exists in order to differentiate benign and malignant masses after treatment. Determining when a difference in uptake indicates a benign or malignant lesion may be difficult. Moreover, the difference in uptake between ^{67}Ga and ^{201}Tl in hyperplasia in some patients may be less evident than in the case presented by Harris et al. (*3*).

A hyperplastic thymus is not the only problem. A relatively often observed but seldom discussed problem of ^{67}Ga scintigraphy is bilateral hilar uptake in adults that may sometimes appear unrelated to treatment (*20*). If parahilar uptake appears before treatment and CT is normal, this symmetric uptake is probably of no clinical significance (*20*). However, parahilar ^{67}Ga uptake in the chest is problematic after treatment, when the nature

Received April 23, 1993; accepted April 23, 1993.
For correspondence or reprints contact: Ora Israel, MD, Rambam Medical Center, Technion, Israel Institute of Technology, Rappaport Research Institute, Haifa 35254, Israel.

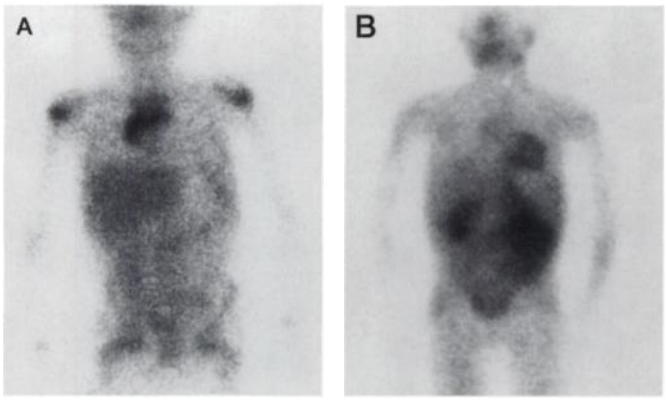

FIGURE 1. An 8-yr-old boy with Hodgkin's disease of the nodular sclerosis type. After completion of chemotherapy, there was still disease in the mediastinum and left parahilar region. Gallium-67 scintigraphy (A) shows abnormal uptake in the upper mediastinum and left parahilar region. Thallium-201 scintigraphy (B) shows uptake in the same region but of definite lower intensity. The difference in the intensity of uptake is similar to the difference in intensity of ^{201}Tl and ^{67}Ga scintigraphy seen in Figure 3 (*3*).

of a residual mass seen on CT has to be determined. An escape of treatment or recurrence may be the reason for ^{67}Ga uptake. If CT shows a marked improvement and ^{67}Ga scintigraphy has the characteristic appearance of low intensity symmetrical hilar uptake, it is probably not indicative of active lymphoma and the patient can be assumed to have achieved a complete clinical response. Evaluation of response on CT, however, may be difficult and there are variations in ^{67}Ga parahilar uptake intensity. A careful study to determine the value of ^{201}Tl uptake in adults in cases of bilateral hilar uptake of ^{67}Ga is still necessary.

Nuclear medicine techniques in oncology are useful only when they can add a dimension that imaging techniques such as CT or MRI cannot provide. This appears to be the case in monitoring the response to treatment of lymphoma or the recent attempt to determine the nature of a breast mass with ^{201}Tl (*21*). On the other hand, CT and MRI provide suitable sensitivity and specificity for diagnosis and staging of most tumors.

Over the years, many radiopharmaceuticals have been suggested as "tumor-seeking" or "tumor-specific" agents. It is not yet clear, however, that a tumor-specific agent really exists, not even when theoretically it is a "magic bullet" (*22,23*). There are reports that ^{201}Tl is taken up by a number of tumors, including lymphomas (*13,24–31*). If this uptake is indeed specific and ^{201}Tl is not taken up by normal tissue or benign disease, it could provide a clinically valuable diagnostic tool. Specifically, ^{201}Tl scintigraphy could be useful in determining the nature of a mass after treatment of lymphoma. There has been no evidence, however, for any specific mechanism which makes ^{201}Tl a "tumor-specific" agent.

The expectation that MRI might be able to differentiate in vivo between neoplastic and normal tissue has not been realized, and it is not clear if it will be realized using nuclear medicine techniques. Heterogeneity is a hallmark of cancer (*32*) and overlap between normal tissue and cancer is large. For the highest prospective yield, only areas which do not overlap should be explored with radiopharmaceuticals. For evaluation of mediastinal and parahilar disease after treatment, a careful, objective evaluation in a large number of patients of the difference in uptake between ^{67}Ga and ^{201}Tl in lymphoma and in nontumor tissue will be necessary to establish the value of these radiopharmaceuticals.

FIGURE 2. A 15-yr-old girl with osteogenic sarcoma of the right leg after chemotherapy. Thallium-201 scintigraphy shows increased uptake in the thymus. There was no evidence of disease in the mediastinum.

Ora Israel
Dov Front
Rambam Medical Center
Technion, Israel Institute of Technology
Rappaport Research Institute
Haifa, Israel

REFERENCES

1. Iosilevsky G, Front D, Bettman L, et al. Uptake of ^{67}Ga citrate and (2 H-3)deoxyglucose in the tumor model, following chemotherapy and radiotherapy. *J Nucl Med* 1985;26:278–284.
2. Israel O, Front D, Lam M, et al. Gallium-67 imaging in monitoring lymphoma response to treatment. *Cancer* 1988;61:2439–2443.
3. Harris EW, Rakow JI, Weiner M, et al. Thalli-

um-201 scintigraphy for assessment of a gallium-67-avid mediastinal mass following therapy for Hodgkin's disease. *J Nucl Med* 1993;34: 1326–1330.
4. Peylan-Ramu N, Hardy TB, Jones E. High frequency of benign mediastinal uptake of gallium-67 after completion of chemotherapy in children with high-grade non-Hodgkin's lymphoma. *J Clin Oncol* 1989;7:1800–1806.
5. Cohen M, Hill CA, Cangir A, et al. Thymic rebound after treatment of childhood tumors. *Am J Roentgenol* 1980;135:151–156.
6. Donahue DM, Leonard JC, Basmadjian GP, et al. Thymic gallium-67 localization in pediatric patients on chemotherapy: concise communication. *J Nucl Med* 1981;22:1043–1048.
7. Shin MS, Ho KJ. Diffuse thymic hyperplasia following chemotherapy for nodular sclerosing Hodgkin's disease. An immunologic rebound phenomenon? *Cancer* 1983;51:30–33.
8. Bell BA, Esseltine DW, Azouz EM. Rebound thymic hyperplasia in a child with cancer. *Med Ped Oncol* 1984;12:144–147.
9. Tartas NE, Korin J, Dengra CS. Diffuse thymic enlargement in Hodgkin's disease. *JAMA* 1985; 254:406.
10. Choyke PL, Zeman RK, Gootenberg JE, et al. Thymic atrophy and regrowth in response to chemotherapy: CT evaluation. *Am J Roentgenol* 1987;149:269–272.
11. Chertoff J, Barth RA, Dickerman JD. Rebound thymic hyperplasia five years after chemotherapy for Wilm's tumor. *Pediatr Radiol* 1991;21: 596–597.
12. Leibundgut K, Willi U, Puss HJ. Thymic rebound following successful chemotherapy of B-lymphoma in an adolescent boy. *Eur J Pediatr* 1992;151:95–97.
13. Krasnow AZ, Collier BD, Isitman AT, et al. The clinical significance of unusual sites of thallium-201 uptake. *Semin Nucl Med* 1988;18:350–357.
14. Ando A, Ando I, Katayama M, et al. Biodistributions of Tl-201 in tumor-bearing animals and inflammatory lesions induced animals. *Eur J Nucl Med* 1987;12:567–572.
15. Tonami N, Matsuda H, Ooba H, et al. Thallium-201 accumulation in cerebral candidiasis. Unexpected finding on SPECT. *Clin Nucl Med* 1990;6:397–400.
16. Aktolun C, Deminel D, Kir M, et al. Technetium-99m-MIBI and thallium-201 uptake in pulmonary actinomycosis. *J Nucl Med* 1991;32: 1429–1431.
17. Krishna L, Slizofski WJ, Kastetos CD, et al. Abnormal intracerebral thallium localization in a bacterial brain abscess. *J Nucl Med* 1992;33: 2017–2019.
18. Bordlee RP, Ware RW. Thallium-201 accumulation by epidermoid inclusion cyst. *J Nucl Med* 1992;33:1857–1858.
19. Abdel-Dayem HM, Sanchez J, Al-Mohannadi S, et al. Diffuse thallium-201-chloride uptake in hypermetabolic bone marrow following treatment with granulocyte stimulating factor. *J Nucl Med* 1992;33:2014–2016.
20. Champion PE, Groshar D, Hooper HR, et al. Does gallium uptake in the pulmonary hila predict involvement by non-Hodgkin's lymphoma? *Nucl Med Commun* 1992;13:730–737.
21. Waxman AD, Ramana L, Memsic LD, et al. Thallium scintigraphy in the evaluation of mass abnormalities of the breast. *J Nucl Med* 1993; 34:18–23.
22. Fischman AJ. When magic bullets ricochet [Editorial]. *J Nucl Med* 1990;31:32–33.
23. Delaloye AB. Immunoscintigraphy of colorectal carcinoma and the Loch Ness monster [Editorial]. *J Nucl Med* 1992;33:1756–1757.
24. Salvatore M, Carratii L, Porta E. Thallium-201 as a positive indicator for lung neoplasms: preliminary experiments. *Radiology* 1976;121:487–488.
25. Hisada K, Tonami N, Miyame T, et al. Clinical evaluation of tumor imaging with thallium-201 chloride. *Radiology* 1978;129:497–500.
26. Fukuchi M, Tochibane K, Kwata K, et al. Thallium-201 imaging in thyroid carcinoma: appearance of a lymph node metastasis. *J Nucl Med* 1978;19:195–196.
27. Togawa T, Suzuki A, Kato K, et al. Relationship between thallium-201 to gallium-67 uptake ratio and histological type in primary lung cancer. *Eur J Cancer Clin Oncol* 1985;21:925–930.
28. Arnstein NB, Juni JE, Sisson JC, et al. Recurrent medullary carcinoma of the thyroid demonstrated by thallium-201 scintigraphy. *J Nucl Med* 1986;27:1564–1568.
29. Winzelberg GG, Melada GA, Hydovitz JD. False-positive thallium-201 parathyroid scan of the mediastinum in Hodgkin's lymphoma. *Am J Roentgenol* 1986;147:819–821.
30. Linde R, Basso L. Hodgkin's disease with hypercalcemia detected by thallium-201 scintigraphy. *J Nucl Med* 1987;28:112–115.
31. Waxman AD. Thallium-201 in nuclear oncology. In: Freeman L, ed. *Nuclear medicine annual 1991.* New York: Raven Press; 1991:193–209.
32. Schnipper LE. Clinical implications of tumor cell heterogeneity. *N Engl J Med* 1986;314: 1423–1431.