Nuclear Oncology

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IN THE BEGINNING

Since the beginning, nuclear medicine and oncology have been intimately connected. After the early physiologic tracer studies of the 1930s with radioactive iodine and phosphorus, the first clinical applications were for cancer therapy using ^{32}P for treatment of leukemia in 1937 (*1*) and radioactive iodine to treat thyroid cancer in 1942 (*2*). In the 1950s and '60s, a variety of radioelements and labeled compounds were studied as physiologic and organ specific markers and nuclear imaging developed to the point where the distribution of radionuclides in body organs could be delineated with some clarity. Consequently, diagnostic nuclear medicine took the forefront and the pursuit of cancer related diagnostic methods dominated the scene.

THE 1970s

When the Technologist Section of the Society of Nuclear Medicine was established in 1970, rectilinear scanning was the primary imaging tool, although the potential of the gamma camera was being recognized as the future method for nuclear imaging. Technetium-99m generators had become generally available and the radiochemists were working out the details of technetium's chemistry and methods for labeling new compounds for imaging.

At that time, scanning of the liver with ^{99m}Tc-sulfur colloid was a major activity, since this was the only practical and simple way to visualize the liver and see disruption of its internal structure. Thus, scanning for primary and particularly metastatic cancer in the liver was a major clinical tool of the oncologist. In the nuclear medicine clinic at the University of Washington, liver scanning accounted for 30% of total procedures. At M.D. Anderson Hospital in Houston, a more focused cancer center, a notice was posted to remind the technologists, "Do not schedule more than 40 liver scans per day."

The second major procedure used by the oncologists and neurosurgeons was the brain scan. Technetium-99m was the commonly used nuclide. Characteristic patterns were recognized for benign tumors such as meningioma versus high- and low-grade malignant glial cell tumors or metastatic tumors. Often brain scans were complemented by relatively crude, but fairly effective first-pass cerebral flow studies with the gamma camera. In most clinics, brain scanning also accounted for 30% or more of the diagnostic images.

This popularity of the brain scan was understandable since it was the first safe and widely applicable method developed to visualize the brain in vivo. This was considered a great advance compared to plain x-rays, more risky angiography, or x-ray pneumoencephalography, which required injection of large quantities of air into the cerebral fluid spaces and caused considerable discomfort and gave limited diagnostic information.

By contrast, in 1970 bone scanning, a procedure intimately related to management of cancer, was less frequently done. Strontium-85, ^{87m}Sr and ^{18}F were the radionuclides in use. However because of high-energy gamma rays and/or the low quantities of isotope administered, they were poorly adapted to rapid and high-resolution imaging. With the later introduction of the technetium phosphate bone scanning agents by Subramanian and McAfee, the use of the bone scan in oncology soared.

The only highly specific tumor marker available in 1970 continued to be, and probably still is, radioactive iodine which selectively localized in thyroid cancers. There was considerable cumulative experience using this as a therapeutic agent for thyroid cancer and hyperthyroidism.

About this time, Edwards and Hays at Oakridge introduced ^{67}Ga (carrier-free citrate) as a possible tumor-specific scanning agent (*3*). This is an interesting tale of serendipity. The Oakridge investigators were attempting to optimize a bone scanning agent using ^{67}Ga. When a patient with lymphoma was having a bone scan with a new carrier-free form of gallium, no bones were seen but the enlarged diseased lymph nodes in her neck showed dramatic gallium uptake. Although gallium was subsequently shown not to be tumor specific, it has found a

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continuing role in staging and following certain types of tumors, particularly Hodgkin's lymphoma.

On perusing the 1970 *Journal of Nuclear Medicine*, one gets a feeling for other issues on the leading edge of development. For instance, Donald Brown was discussing the reality of on-line computers in the nuclear medicine laboratories and David Kuhl was describing methods for tomographic transverse section scanning of the brain (*4,5*).

HERE COMES THE CAT SCAN

In the mid 1970s, a dramatic change began to take place in nuclear medicine and its relation to the practice of oncology—the development of computerized axial tomography (CAT). The first CAT scanners were introduced for imaging the brain and at once it was recognized they provided much improved anatomic definition compared to nuclear brain imaging. Soon rapid sequence CAT scanning of not only the brain but the whole body began. CAT scanning was rapidly implemented throughout the country and, by the early 1980s, essentially all of brain and liver nuclear imaging had been replaced by CAT. This accounted for at least 60% of nuclear medicine diagnostic examinations, the majority related to cancer diagnosis and staging.

During this transition, however, bone imaging increased dramatically, because of the new technetium phosphonate agents, and cardiovascular imaging of perfusion and function was on the rise. Bone scanning increased from approximately 10% of all studies in 1970 to 35–45% of the diagnostic procedures today. Approximately 60% of the bone scans performed are related to cancer diagnosis and staging. Cardiovascular imaging represents 30% of nuclear medicine procedures today and about one-third of these are related to the practice of oncology.

DEVELOPMENT OF TUMOR MARKERS IN NUCLEAR ONCOLOGY

The Adrenals

Of the radiopharmaceuticals used to delineate the functional parameters of the adrenals, ^{131}I-labeled cholesterol and MIBG are prime examples of the results of directed research to create tumor markers from substrates that follow a well-defined metabolic pathway. This work was originated by William Beierwaltes and his coworkers at the University of Michigan (*6*).

Radioiodinated cholesterol, a precursor to the cortical steroids, is extremely useful in delineating hyperfunctioning adrenal tumors, such as cortisol producing adenomas and aldosteronomas. Malignant forms of primary adrenal cortical tumors are rare, but on occasion radioiodinated cholesterol has been effective in delineating extra adrenal metastases (*7*).

MIBG localizes in neurosecretory granules and can confirm the diagnosis of pheochromocytoma and delineate the extent of disease in malignant pheochromocytoma and neuroblastoma. Because of its selective localization, high doses of ^{131}I-MIBG have been successfully used for palliative therapy of these diseases (*8*).

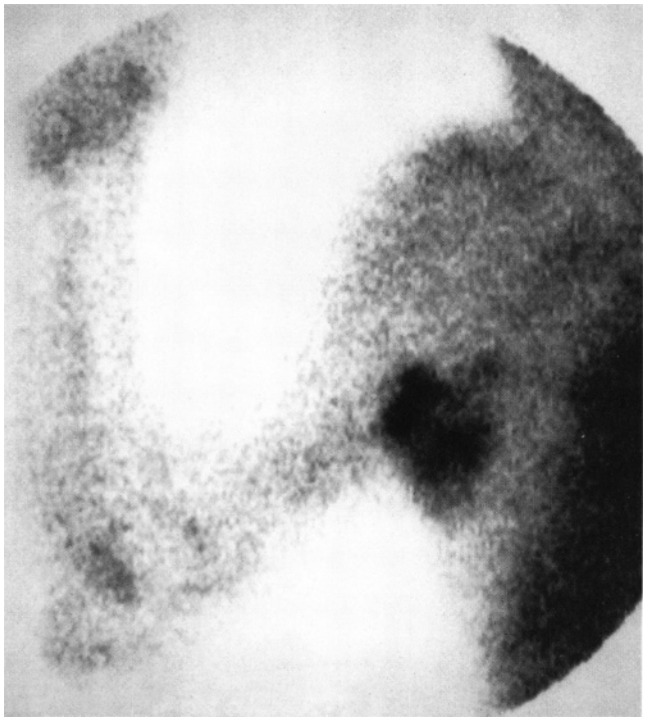

FIGURE 1. Image of the axilla showing intense concentration of ^{99m}Tc antimelanoma antibody (NRML-05-NeoRx Corp.) in metastases in lymph nodes. Imaged 6 hr after injection.

Antitumor Antibodies

There has been long-time interest in using radiolabeled antibodies directed against tumor antigens for tissue-specific cancer diagnosis and potentially for therapy, if given with large amounts of radioactivity (*9,10*). The production and purification of antibodies was greatly facilitated by the work of Kohler and Milstein. In 1975 they described methods for the production of highly specific monoclonal antibodies derived from cells harvested and cultured from the mouse spleen. Various cell line hybridomas now have been identified. These can produce large quantities of highly purified antibodies directed against specific antigens present on the cells of a number of important human cancers.

By the late 1970s, nuclear medicine investigators were exploring radiolabeled monoclonal antibodies as unique diagnostic tools. When injected into the human body, they could specifically attach to tumor cells where tumor antigens were present in high concentration. Studies of the diagnostic potential of radiolabeled antibodies have been directed at a variety of malignancies such as melanoma, lung, colon, ovary, prostate, leukemia and lymphoma.

The magic bullet does indeed show promise and can delineate primary and metastatic disease quite successfully in certain cases. For example, antimelanoma antibody labeled with ^{99m}Tc may show dramatic deposition of antibody in tumor with high target to nontarget ratios (Fig. 1). Figure 2 shows an abdominal planar image of an antiprostate cancer antibody (Cytogen Corporation, Princeton, NJ) labeled with ^{111}In.

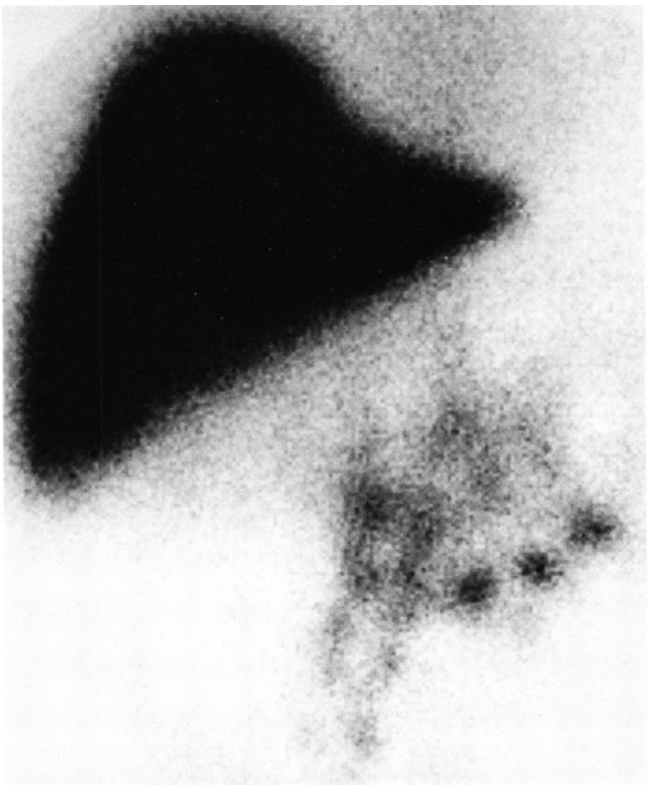

FIGURE 2. Anterior image of abdomen showing ^{111}In antiprostate antibody (Cytogen Corp.) in normal-sized diseased lymph nodes. Activity in liver is normal biodistribution at 48 hr after injection.

There is discrete deposition of antibody in diseased normal-sized lymph nodes in the upper pelvis and mesentery. The patient had previously been surgically treated for prostate cancer, was asymptomatic, had a normal diagnostic staging workup including a normal bone scan, but had a rising PSA.

Another antibody that shows considerable diagnostic promise and is reportedly soon to be released as a commercial product, is an antilung antibody called NR-LU-10 and developed by NeoRx Corporation (Seattle, WA). Extensive clinical trials have been completed for staging patients with small-cell lung cancer at the time of initial diagnosis. Using the Fab fragment of the antibody labeled with ^{99m}Tc, the ability for a single total-body antibody image to correctly stage patients prior to therapy was excellent. The antibody alone, as a single test, could stage patients with extensive disease with a positive predictive value of 97%. Since this single test was comparable in all ways to the standard staging methods (i.e., CAT scanning of the brain, chest and abdomen, combined with chest x-rays, bone scans and bone marrow aspiration), to which it was compared, it will be cost effective and useful as a primary staging tool (*11*).

The only antibody to date approved by the FDA for diagnostic imaging is an antibody directed against colon and ovarian carcinoma, also produced and marketed by the Cytogen Corporation. This antibody, called B72.3, is marketed under the trade name of OncoScint CR/OV and is labeled with ^{111}In. It is indicated for determining the extent and location of extrahepatic malignant disease in patients with known colorectal or ovarian cancer. The antibody provides ancillary information that is complementary to the usual standard diagnostic tests (*12*).

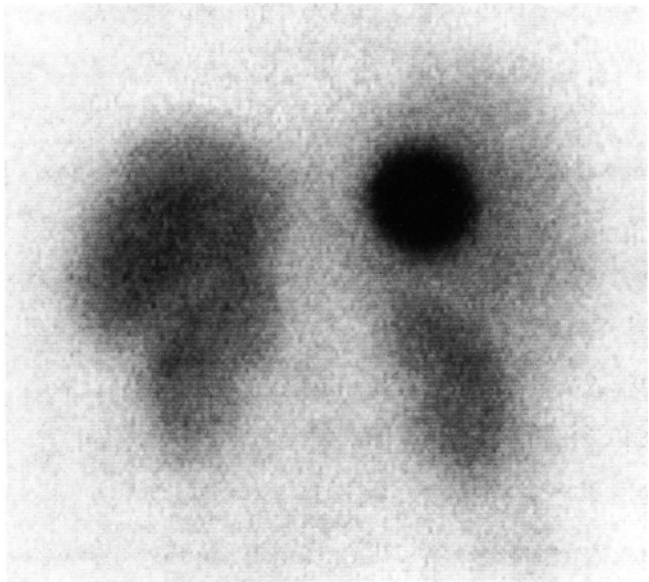

FIGURE 3. Posterior image 4 hr after injection of ^{111}In OctreoScan. The focal activity is a gastrinoma in the liver, thought to be a primary lesion.

Following injection of mouse protein, some recipients will mount an antigenic response, producing a human antibody against the mouse antibody (HAMA). In the case of the antilung antibody NR-LU-10, only 6% of the time was this observed. With other antibodies, including OncoScint CR/OV, HAMA response may be higher and in the range of 30–40%. This theoretically limits the use of the antibody a second time, since in certain individuals if circulating HAMA persists (it ordinarily disappears after 10–20 wk), it could attach to the antibody at the second injection and interfere with its distribution to tumor.

Somatostatin Receptors

Another exciting specific radiolabeled receptor imaging agent is ^{111}In Octreotide. This small molecular weight peptide binds to somatostatin receptors. Most neuroendocrine tumors, such as carcinoid, gastrinoma, insulinoma, neuroblastoma and medullary thyroid carcinomas, may have high concentrations of somatostatin receptors and thus ^{111}In Octreotide can delineate these tumors in vivo (Fig. 3). This agent has recently been approved by the FDA for clinical use (OctreoScan, Mallinckrodt Medical, Inc., St. Louis, MO). It is of interest that somatostatin receptors also are present on certain lung cancers and lymphomas, and it is anticipated that ^{111}In Octreotide imaging also could be useful in staging these more common diseases. Octreotide does not incite an antigenic response (*13*).

Thallium and MIBI

For some time, ^{201}Tl has been known to concentrate in tumors such as parathyroid adenomas and thyroid cancers.

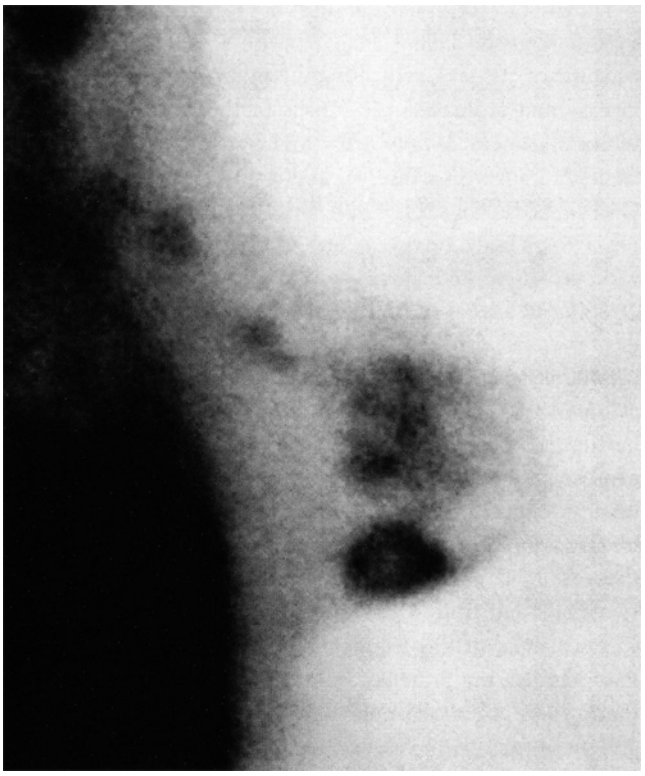

FIGURE 4. Right lateral image of the breast, liver and thorax, 15 min after injecting ^{99m}Tc-sestamibi. Note the localization of MIBI in the large infiltrating ductal carcinoma of the breast and in diseased axillary lymph nodes.

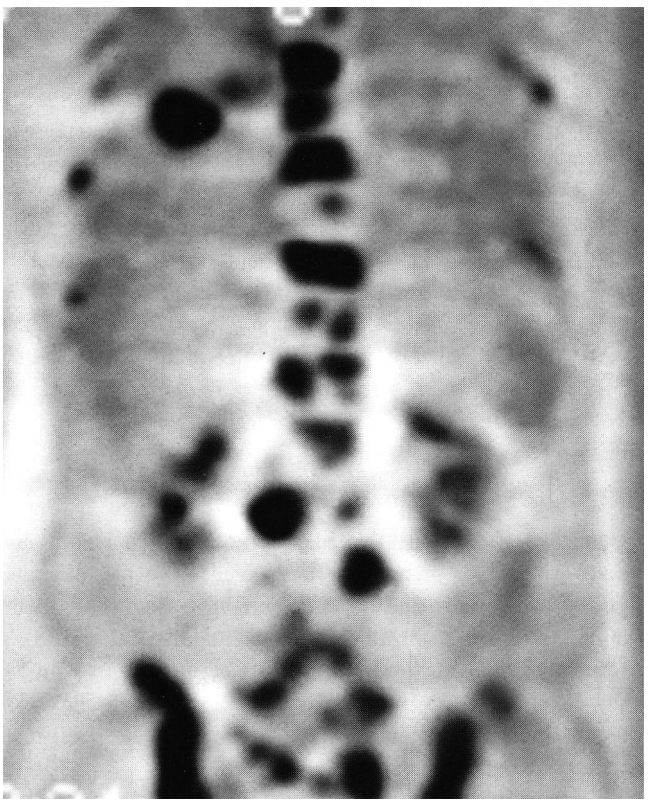

FIGURE 5. Coronal PET image 1.5-cm thick through the mid-pelvic region and thoracic spine. The image was acquired 1 hr after giving 10 mCi of ^{18}F-FDG to a patient with small-cell lung cancer. Note the intense FDG accumulation in tumored marrow (^{99m}Tc-phosphate bone scan was normal) and in diseased lymph nodes. The primary lung lesion is seen in the upper left. There is FDG activity in the kidneys, the normal route of excretion.

More recently, interest has centered on its ability to concentrate in malignant tumors of the brain, to help determine if residual abnormalities seen by brain imaging on MRI or CT are due to scar tissue resulting from the previous surgery and x-ray therapy (thallium negative), or whether it represents the persistence or reemergence of new tumor (thallium positive). This particular problem has also been approached by using ^{99m}Tc-labeled sestamibi, which also demonstrates higher concentration in tumor cells.

Another potential use of ^{99m}Tc-labeled sestamibi is imaging lesions in the breast to help differentiate benign from malignant tumors (*14,15*) (Fig. 4). There is substantial evidence accumulating to suggest that focal concentration of MIBI in palpable breast lesions indicates cancer and, hopefully, the same would be true for nonpalpable lesions seen by screening with x-ray mammography. It is quite clear that initial screening for breast carcinoma using MIBI would not be cost effective, compared to mammography, but imaging lesions with MIBI which by mammography are suspicious for cancer may be cost effective. If this proves true patients with positive MIBI scans could proceed to excisional surgery without going through an intermediate biopsy step (*16*).

PET and Cancer Diagnosis

Diagnostic procedures for using PET in oncology currently are under intense investigation and show much promise. One very promising area is tumor identification with ^{18}F-deoxyglucose (FDG). In most tumors the rate of glucose utilization, and FDG trapping, is considerably higher than that in surrounding normal tissues, and positive concentrations of radioactive FDG easily are seen in tumor sites. FDG is being used effectively with PET to determine the viability of malignant tumors in the brain, as opposed to residual scar after surgery and radiation therapy. This is similar to the previously mentioned uses of thallium and sestamibi. A positive image with FDG in a region of known brain tumor is very consistent with tumor regrowth or persistence. A negative study suggests the absence of tumor. In other malignancies, such as carcinoma of the breast or lung, staging or screening for the extent of cancer by PET can be done using directed examinations or total body surveys. The technique is quite sensitive and results can be quite spectacular, as seen in Figure 5 (*17*).

THERAPY WITH RADIOPHARMACEUTICALS

Thyroid Cancer

Iodine-131 therapy of thyroid cancer continues to be the primary therapeutic tool, in those tumors (the majority) that retain the ability to take up radioiodine. If we only had other

radiolabeled substances with such selective and good tumor targeting.

Treating Bone Pain

A new nuclear medicine therapeutic agent was introduced into the marketplace in 1993 for the palliative treatment for diffuse metastatic bone pain, such as seen in carcinoma of the prostate or breast. This was the first new therapeutic agent in more than 30 years. This substance, beta-emitting ^{89}Sr (Metastron, International Amersham, England), has proven to be quite effective in most patients, giving temporary, and in some cases prolonged, relief of bone pain. Interestingly ^{89}Sr was first considered for this type of therapy in 1940. At the therapeutic levels prescribed, ^{89}Sr does not severely affect bone marrow function (*18*).

Antibodies—Radioimmunotherapy

It has been the hope that high doses of radiolabeled antibodies (i.e., radioimmunotherapy) could provide effective therapy for certain cancers. Encouraging results have been obtained by direct installation of radiolabeled anti-ovarian cancer antibodies in the peritoneal space in patients with locally disseminated ovarian cancers. A decrease in ascites production and considerable clinical improvement has been seen in a number of these patients.

Intravenous radioimmunotherapy has been attempted with relatively high radiation doses for a variety of solid tumors. Although there are encouraging partial responses in some individuals, the amount of radiation delivered to the tumor, compared to normal cells is relatively low and the bone marrow has been at considerable risk.

With highly radiosensitive tumors, such as lymphoma, the results of therapy with radiolabeled antibodies are much more encouraging. Iodine-131-labeled antilymphoma antibody has been given in relatively small amounts in single or repetitive doses (30–100 mCi) that do not severely affect the marrow function. Sufficient antibody localizes in the lymphoma so that major responses and even complete clinical remissions have occurred after treatment. It is clear that this form of therapy has produced an improved quality of life and most likely an increased duration of life (*19,20*).

A more aggressive approach to lymphoma therapy has been to give much higher doses of ^{131}I antilymphoma antibody (up to 750 mCi). In this case, the bone marrow can be severely damaged. Consequently, the patient will have a bone marrow or peripheral stem cell harvest prior to the therapy, and the marrow or stem cells are returned to the patient several days following therapy. Thus, much higher doses of radiation can be delivered to the lymphoma and the bone marrow, although severely damaged by the radiation, is repopulated and can fully recover. With this method, the majority of patients achieve a complete clinical remission that may be maintained for an extended period of time (*21*).

WHAT IS AHEAD?

The practice of nuclear oncology has changed considerably in the last 25 years. What can we predict for the future?

The use of PET in nuclear oncology is being established and should flourish. Tumor imaging with FDG is very exciting because of its sensitivity for determining the extent of the disease and evaluating the effects of therapy, such as is the tumor still metabolically active? The staging of cancer today frequently involves extensive and expensive imaging, such as CAT or MRI. Thus, PET with the attractive feature of providing a total body survey in one examination, will likely find widespread use and should be cost effective.

With the advent of molecular biology and advances in molecular engineering, it is probable that a variety of molecules will be designed that are capable of binding to specific tumor cell markers. Today antibodies are produced by growing cells, mostly of mouse origin, in culture media and harvesting the protein antibody produced. This is a technically demanding process and the purified antibody may be immunogenic. In the long run, molecular engineering will solve these problems and there will be engineered antibody-like materials with high specificity and little or no immunogenicity. Octreotide is an early example of this technology. At the turn of the century, Paul Ehrlich, the father of immunology, said that antibodies, then called antisera, would have a role in ameliorating the growth of tumors. In essence, we have pursued Ehrlich's concepts in nuclear oncology and the next step is to fashion the molecular subsets of the antisera into radiolabeled units for diagnosis and therapy.

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