

skimming or count addition should not modify those numerical results. Gross modulation of the images by count-correction circuits can only lead to less confidence in numerical analysis of those images.

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Ureterovaginal Fistula Detected by Tc-99m DTPA Scintigraphy

A 33-year-old woman underwent a hysterectomy for a cervical laceration and atonic bleeding.

In her 7th postoperative week, she complained of a watery vaginal discharge. She could also pass urine by urethra. Speculum examination revealed urine issuing from the vaginal vault. After intravenous injection of indigo carmine, no blue stain was observed on vaginal gauze. Intravenous pyelography revealed a left hydronephrosis, delayed visualization of the mid portion of the left ureter but no visualization of its lower portion (Fig. 1, left). The right kidney and ureter were normal, and no extravasation was demonstrated. Retrograde ureterography showed complete obstruction of the left ureter without extravasation (Fig. 1, right).

Renal scintigraphy following 10 mCi administered i.v. of technetium-99m diethylenetriaminepentacetic acid (DTPA) revealed abnormal radioactivity near the lower portion of the left ureter, suggesting extravasation (Fig. 2). Radioactivity on the gauze placed in the vagina was about 200 times background. To rule out extravasation from the urinary bladder, 200 ml water containing 10 mCi Tc-99m human serum albumin (HSA) was instilled into it through a Foley catheter, which was clamped for 2 hr. A scintigram of the bladder after release of the clamp showed no urinary extravasation (Fig. 3).

The incidence of ureteric fistula is extremely low (1). It usually occurs by accident, most often following injury to the urinary tract during pelvic surgery for gynecological conditions (1-3), or because of necrosis resulting from an impaired blood supply (1). The diagnosis of ureterovaginal fistula is generally confirmed by demonstrating urinary extravasation and/or a fistula by excretory or retrograde urography (1,4). A dye test can also confirm the diagnosis (1). A radionuclide study may be helpful in searching

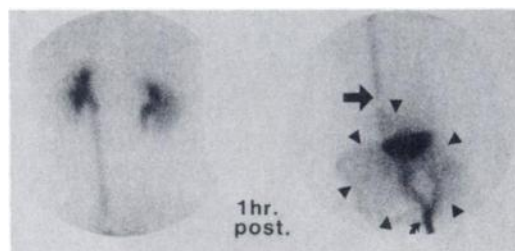


FIG. 2. Posterior views of Tc-99m DTPA study show extravasation of labeled urine into true pelvis (arrowheads) from distal end of dilated left ureter (arrow). Radioactivity is also present in Foley catheter (curved arrow).

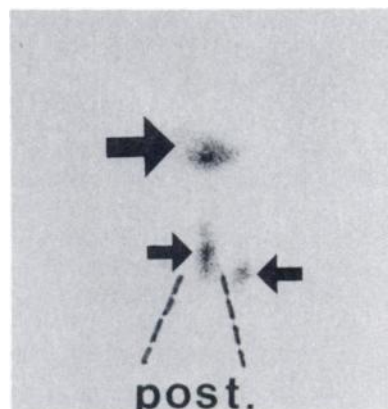


FIG. 3. Scintigram of urinary bladder after retrograde administration of Tc-99m HSA shows no extravasation of labeled urine. Large arrow indicates urinary bladder; small arrows, contamination.

for the urinary extravasation, and Tc-99m DTPA is the preferred radiopharmaceutical to assess glomerular filtration (5) because of its ideal physical properties and the simplicity of DTPA labeling. As in this case, when other methods fail to demonstrate the ureterovaginal fistula, renal scintigraphy using Tc-99m DTPA should be performed.

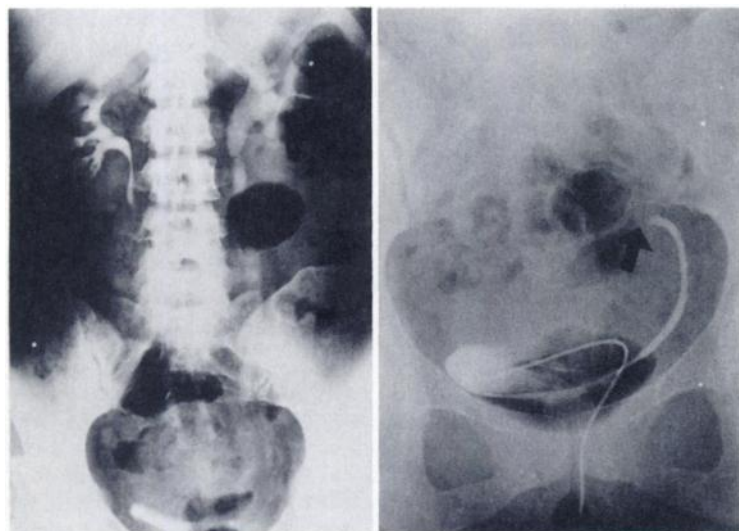


FIG. 1. Excretory urogram 210 min after i.v. injection of contrast medium shows left hydronephrosis and distended left ureter as far as the stenosis in lower portion of ureter, but without extravasation (left). Retrograde ureterogram shows complete obstruction of lower portion of left ureter (arrow), without extravasation (right).

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Re:Activity and Protein Levels in Studies of Monoclonal Antibody Imaging

The recent imaging article by Khaw et al. (1) is to be recommended for its thoroughness regarding monoclonal antibody research with the nude-mouse model, but there are pertinent questions that the authors fail to discuss. These concern the relatively large amounts of indium-111 and protein given to the animals. It seems that their experiments pertain more to monoclonal-associated radiation therapy than to diagnosis.

Khaw et al. (1) report injection of 200 μCi of In-111-labeled antibody into ~ 20 g of mouse. The activity was attached, in the case of their intact monoclonal 10-3D2, to 20 μg of IgG. If one assumes a 70-kg human and scales these values upward by a factor equal to the ratio of human to mouse masses, rather unacceptable levels of activity and protein are obtained. Amounts approaching a curie of In-111 and 100 mg of mouse-derived protein would probably not be permitted in a human imaging study. A reduction in these levels by approximately two orders of magnitude would be clinically realistic.

The obvious question arises as to the resultant murine biodistributions with such appropriately lowered amounts of activity and tracer. With a relatively small number of antibodies and no sloughing of tumor-associated antigens (1), it is possible that the tumor uptake, measured in % injected dose/g, could be significantly increased. On the other hand, if the antigen does enter the circulation to some degree, it is likely that lowering the amount of injected antibody would reduce the injected dose/g lodging in the tumor (2). Other opposing effects can occur. In the related therapy situation, Order (3) has described prolonging by several days the human tumor retention of a labeled monoclonal IgG by raising the total protein dose to approximately 200 mg. The additional carrier protein appeared to retard sloughing of labeled monoclonal complexes and thus to enhance radiotherapeutic ef-

fects. At any rate, it is unclear that if the amounts of In-111 and IgG were reduced, there would be consistency in the levels of tumor uptake and figures of merit reported in the recent article.

Questions regarding dose-level effects on pharmacokinetics are also involved in the conclusions reached by Khaw et al (1). Using signal-to-noise criteria, they report optimal BT-20 tumor localization of 10-3D2 at 4 days after i.v. injection in the nude-mouse model. This result might not recur, however, with decreased amounts of activity and protein. In fact, imaging out to 7 days, as reported by these authors, may not even be possible with In-111 levels reduced by a factor of 100.

It seems that drug-dose effects need to be addressed by researchers in monoclonal imaging. One cannot simply assume that the amount of radiopharmaceutical given to a particular species has no effect on the biodistribution. Differential tissue uptake is generally going to be a function of the amount of material injected per unit mass of the animal used in the experiment. Clearly, diagnostic animal research should concern activity levels less than 10 mCi/70 kg or 140 $\mu\text{Ci/g}$ —i.e., be equivalent to the maximum human dose levels. Similarly, the amount of protein should be restricted to less than 500 $\mu\text{g}/70$ kg or 7 ng/g of test animal so as to reduce the likelihood of antimouse antibody production with serial studies. Published reports involving polyclonal (4) and monoclonal (5) human imaging trials are in good agreement with these limits.

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Reply

My colleagues and I thank Dr. Williams for his thoughtful comments on our article (1). We disagree, however, with his suggestion that the concentration of monoclonal antibody and the amount of In-111 reported in our manuscript were excessive, amounting to what he describes as "monoclonal-associated radiation therapy." These quantities were selected for the following reasons: (a) the amount of antigen expected on the surface of the tumor; (b) the physical constraints involved in imaging small animals; (c) the radionuclide used; and (d) the assumption that use of approximately 0.2% murine antibody in a murine model would not interfere with the circulation of the injected antibody.

Dr. Williams suggests that one can extrapolate from the antibody concentration and radiation doses used in our nude-mouse model to those used for a 70-kg patient with mammary carcinoma.