cific nature of radioimmunotherapy. A set of parameters that are optimum under one set of conditions usually do not apply in general. The advantages of using antibody fragments to improve antibody targeting of solid tumors, for example, are not evident in targeting of micrometastatic disease since extravasation and diffusion of the antibody through the interstitial space are not required for targeting (*4*). One may anticipate that the currently popular radionuclide for radioimmunotherapy, ^{90}Y, will be inappropriate for targeting micrometastatic disease due to its long-range emissions. It is this case-specific nature of radioimmunotherapy that calls for the development of mathematical models and the application of computer simulations. By incorporating the salient features of a particular treatment protocol and accounting for the known biological parameters of a particular tumor and antibody-antigen combination, mathematical modeling analyses may help guide the experimental work and thereby reduce the scope of necessary human experimentation.

As the focus turns towards targeting of micrometastatic disease, mathematical modeling will become increasingly important in providing an assessment of potential therapeutic efficacy. Since it is not clinically feasible to determine the antibody concentration or the radioactivity associated with a microscopic cluster of metastatic cells, analytical techniques will be necessary to estimate antibody uptake and cell cluster absorbed dose, given the range of expected cluster sizes, their position relative to the vasculature (luminal versus interstitial) and blood pharmacokinetics.

Administering radiolabeled antibodies to patients that have no objective evidence of disease and without the ability to verify antibody targeting in vivo through external imaging may be unsettling to those accustomed to radioiodine therapy of thyroid disease or radioimmunotherapy of solid tumors. The potential for successful radioimmunotherapy in such a setting, along with the observation that chemotherapeutic trials have been undertaken with significantly less theoretical and experimental justification, should help overcome such reservations. Ultimate assessment of adjuvant or prophylactic radioimmunotherapy in the treatment of occult disease will require randomized trials with a 5-yr to 10-yr follow-up. Patience will therefore be required. The radioimmunotherapy community is well qualified in this regard.

REFERENCES

1. Sharkey RM, Blumenthal RD, Goldenberg DM. Radiolabeled antibodies as cancer therapeutics [Letter]. *J Nucl Med* 1993;34:1028.
2. Sgouros G. Plasmapheresis in radioimmunotherapy of micrometastases: a mathematical modeling and dosimetrical analysis. *J Nucl Med* 1992;33: 2167–2179.
3. Sharkey RM, Weadock KS, Natale A, et al. Successful radioimmunotherapy for lung metastases of human colonic cancer in nude mice. *J Natl Cancer Inst* 1991;83:627–632.
4. Blumenthal RD, Sharkey RM, Haywood L, et al. Targeted therapy of athymic mice bearing GW-39 human colonic cancer micrometastases with ^{131}I-labeled monoclonal antibodies. *Cancer Res* 1992;52:6036–6044.

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Diuretic Renography

TO THE EDITOR: The paper entitled "The Well Tempered Diuretic Renogram" (*1*), presented by the Society for Fetal Urology and the Pediatric Nuclear Medicine Council, appeared earlier in a more expanded form (*2*). In both presentations, one cannot quite distinguish whether the purpose is to explain the theoretical (physiopathological) basis for a procedure or to report on a technical methodology (e.g., region of interest (ROI) placement) which has been shown empirically to be superior to other methods. In the absence of either theoretical or empirical argumentation, on what exactly was consensus based?

For example, what is the physical meaning of a two-pixel wide background ROI? Even if we assume that the digital matrix will be in a 128 × 128 format, as recommended, two pixels would cover different sized regions, depending on detector size, zoom factor and the modulation transfer function of the imaging system.

It would have been useful to rationalize why separate sampling over the collecting system is necessary: if the collecting system is full, and if the compliance of the system has been exhausted, the obstruction must result in delayed cortical clearance, since fluid is not compressible. What interpretation is offered if cortical transit time and or diuretic response are normal, but are abnormal in the collecting system?

Third, to the extent that the kidney acts as a delay line, or even a mixing compartment, one should expect that clearance of the tracer from the kidney (or the output function) also reflects plasma clearance (or the input function) and not exclusively the transit function through the kidneys. This point has been made often and well (*3*), and its neglect in the discussion of interpretation is surprising.

Finally, the authors fail to describe what are or should be the criteria for success or failure of the test. Merely mentioning that there would be follow-up is hardly sufficient.

REFERENCES

1. The Society for Fetal Urology and The Pediatric Nuclear Medicine Council. The "well tempered" diuretic renogram: a standard method to examine the asymptomatic neonate with hydronephrosis or hydroureteronephrosis. *J Nucl Med* 1992;33:2047–2051.
2. Conway JJ. "Well tempered" diuresis renography: its historical development, physiological and technical pitfalls, and standardized technique protocol. *Semin Nucl Med* 1992;22:74–84.
3. Whitfield HN, Britton KE, Hendry WF, et al. Distinction between obstructive uropathy and nephropathy by radioisotope transit times. *Br J Urol* 1978;39:433–436.

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REPLY: Dr. Goris raises some interesting technical questions regarding our paper on "The Well Tempered Diuretic Renogram." His queries offer an opportunity to expand upon the reasons for and purpose of the Consortium report on the discussions which transpired during our initial meeting in 1989.

The Consortium of Nuclear Medicine Physicians was convened at the request of the Society for Fetal Urology (SFU). Members of the SFU had raised the concern that the diuretic renogram in the neonate as performed at their various institutions often did not correlate well with surgical findings. SFU members suggested that this might be related to variable methods of performing diuretic renography in their individual institutions.

The paper therefore is essentially a proceedings report from the meeting, which derived a consensus on the various methods of quantitatively measuring diuretic renogram response. The suggested methods should be utilized to gather data that eventually can be correlated with outcome and perhaps indicate which is the

most appropriate method for quantitation of diuretic renograms. However, the Consortium participants did not imply that any method was the most appropriate. It is impossible to describe in a proceedings report all of the theoretical or empirical argumentation that led to our consensus agreements. Suffice it to say, theoretical, empiric and literature evidence was used during our hours of discussion.

A consensus was reached that hydration should be used. The literature cited in the article indicates that hydration can profoundly affect the results of the diuretic renogram. The concept that the bladder should be kept empty during the procedure was based upon the group's empiric experience that a full bladder can impede drainage of the upper tracts. A standard dose of lasix should be administered to achieve some uniformity in performance of the technique among institutions since diuretic response is dose-dependent. Regarding the consensus on the methods proposed for determining regions of interest (ROIs), there is no evidence in the literature that any specific method for ROI selection is valid. Our suggested methods of ROI selection were only offered as an attempt to achieve some standard uniformity during examination of the neonate among different institutions. Of interest, one of our members (Reid B, *personal communication*, 1992) found an average of 6% variability in percent differential function when ROIs were blindly repeated on the same patient using the same method by the same operator. In our experience, quantitative results of diuretic renography can be manipulated significantly by simply altering the ROIs. At this time, no one knows which method is most valid.

Likewise, the decision to monitor parenchymal (cortical) transit time was based upon the work of Dr. Whitfield (*1*) who suggested that this is an excellent means to differentiate obstruction from nonobstruction. However, there was consensus among the participants based upon empiric experience that parenchymal transit times are not always accurate in defining obstruction versus nonobstruction, especially in the situation of chronic obstruction or renal failure. In addition, it was acknowledged that the proposed method for measurement of cortical regions provided only a "poor man's" parenchymal transit time. As an aside, our subsequent experience with the measurement of cortical ROIs shows little difference from the measurement of total renal ROIs, probably because the measurement interval is only between the 60–75 or 90-sec interval of the renogram. In this interval, there is little probability of collecting system interference from either method.

The failure to define criteria for success or failure of the test is based upon the lack of a definition of obstruction. It was revealing to the Consortium members that there are no surgical or histological criteria for defining obstruction. Therefore, such criteria as the endpoint of analysis need to be developed. That process is underway from a surgical as well as a pathological point of view among the SFU consortium members.

Ultimately, however, the results and analyses of the various data obtained will be based upon a blinded randomized prospective clinical trial of surgery versus observation in neonates with hydronephrosis. The eventual clinical outcome in these patients as monitored by diuretic renography in a standardized manner may define those criteria necessary for the diagnosis of significant obstruction. Such a trial is currently underway among SFU members.

It is recognized that this paper was not a scientific report but was intended to generate discussion and recognition that standardization of nuclear medicine procedures is desirable, if not essential, for correlating results with clinical outcomes.

REFERENCE

1. Whitfield HN, Britton KE, Hendry W, et al. Distinction between obstructive uropathy and nephropathy by radioisotope transit times. *Br J Urol* 1978;39:433–436.

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