Editorial: When Magic Bullets Ricochet

Every major scientific advance is accompanied by great expectations, which are rarely if ever realized at the rate predicted by the seminal contributors. In 1929, renowned physicist P.A.M. Dirac stated in the first edition of his classic text on quantum mechanics that "the underlying physical laws necessary for the mathematical theory of . . . the whole of chemistry are thus completely known, and the difficulty is only that the exact application of these laws leads to equations much too complicated to be soluble" (*1*).

In 1957, the first reports of successful radioimmune imaging were heralded as a "quantum leap" in disease detection, characterization, and therapy (*2,3,4*). Today, for all of its initial promise, experience with this technique suggests that radioimmune imaging will require a long maturation period before gaining a place in the daily diagnostic armamentarium (*5*).

While antibodies were considered to be the ultimate "magic bullet," combining the desirable properties of high in vitro affinity and specificity for the antigens under study, the in vivo application of these reagents has been plagued with severe and possibly insurmountable problems. One extremely important problem is nonantigen-specific tissue localization.

Data presented by Kairemo and his colleagues in this issue of the *Journal*, is an important and timely example of nonantigen-specific localization by an antibody fragment (*6*). Their results demonstrate that ^{111}In-labeled anti-myosin Fab localized to an extent sufficient for external imaging in 18/19 patients with soft-tissue sarcomas (target-to-background ratio: 1.1–2.6). The presence of cardiac myosin was detected by immunocytochemistry in only 1/10 tumors tested. Since the antibody preparation employed in these studies is highly specific for cardiac myosin, these data clearly establish that localization is by nonspecific mechanisms.

While studies directed at establishing the mechanism of localization were not presented in this report, the results of a previous investigation by O'Connor and Bale are helpful in understanding the process (*7*). In that study, the accessibility of circulating ^{125}I-labeled immunoglobulin G (IgG) to the extravascular compartment of three syngeneic rat fibrosarcomas as well as normal rat skin, muscle, lung and kidney was determined. Using a simple kinetic model, it was shown that tumor and normal tissue accumulation of IgG could be described as follows:

$$T(t) = A_0 k_1 (e^{-\alpha t} - e^{-k2t})/(k_2 - \alpha) \quad k_2 > \alpha \quad (1)$$

where

T(t) = extravascular cpm/g of tissue at time t
A_0 = initial blood activity
k_1 = influx rate constant
k_2 = efflux rate constant
α = blood decay rate constant.

Taking the limit as t goes to ∞ and dividing by B(t) (blood activity) and its equivalent A_0e^{-at} yields:

$$\frac{T(t)}{B(t)} = k_1/(k_2 - \alpha). \quad (2)$$

Using similar equations for normal tissue, the target-to-background ratio is:

$$T(t)/B_k(t) = k_1^T(k_2^B - \alpha)/k_1^B(k_2^T - \alpha), \quad (3)$$

where k_1^T and k_2^T are the influx and efflux rate constants for target tissue, and k_1^B and k_2^B are the influx and efflux rate constants for the background tissue.

Based on Equation 3, maximum target-to-background ratios for radiolabeled nonspecific polyclonal IgG can be approximated for tumors implanted in different anatomic sites: muscle ~ 11:1, kidney ~ 6:1, skin ~ 3:1, and lung ~ 2:1. In usual practice, these target-to-background ratios will be smaller due to blood radioactivity in the tumor and surrounding tissue as well as the mass of tissue between the tumor and the face of the gamma camera. Clearly, these effects will be most pronounced for highly vascular background tissues such as lung, kidney and liver, as well as for deep structures. By similar reasoning, for fixed values of k_1 and k_2, the target-to-background ratio will be elevated in highly vascular tumors. The recent reports that ^{111}In-labeled nonspecific polyclonal IgG is an effective agent for imaging focal sites of infection and several types of tumors in humans supports these predictions (*8,9*). Similarly, the range of target-to-background ratios reported by Kalevi et al. are consistent with these predictions, suggesting that the modeling results obtained with intact IgG can, at least qualitatively, be extended to Fab fragments.

It is essential that nonspecific lesion localization of radiolabeled antibodies be considered as the matrix over which specific targeting is evaluated. This is equally important for the extension of a previously established immunoscintigraphic technique to new clinical indications as it is in the initial evaluation of new antibodies. It is all too easy to assume that if an antibody localizes primarily by specific antigen-antibody interaction in one clinical circumstance, this mechanism can be generalized to all circumstances in which positive images

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are obtained. *Demonstrating* the presence of antigen in a lesion for which a diagnostic image was obtained, *though necessary, is* not sufficient evidence to reach this conclusion. The recent extension of anti-myosin imaging from the detection of myocardial infarction (*10*) to the evaluation of diffuse types of cardiac disease such as myocarditis and heart transplant rejection (*11, 12*) provides an excellent example. Currently, it is firmly established that the mechanism of anti-myosin localization at sites of myocardial infarction is specific antigen-antibody interaction. However, this has not been proven in diffuse cardiac disease. While, myocardial necrosis has been demonstrated in these diseases, the concentration of exposed antigen is at least an order of magnitude lower than after acute myocardial infarction. Thus nonspecific mechanisms of localization must be considered, particularly if imaging techniques are to be employed to quantitate the degree of myocardial necrosis as a means of monitoring progression of disease or response to therapy.

It appears that tumor accumulation of antibodies by nonantigen-specific mechanisms is a "double-edged sword," reducing the specificity of specific antigen-directed antibodies but also providing more general methods of lesion detection.

Like Dirac, we are gazing, with admiration, at a dazzling array of modern scientific weapons. However, we have not figured out from which end the bullets will come.

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