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EDITORIAL

Immunoscintigraphy of Colorectal Carcinoma and the Loch Ness Monster

What has Nessie, the legendary animal supposedly living in Loch Ness in the Scottish Highlands, in common with immunoscintigraphy? At first glance, there is no obvious relationship, but if one looks a bit closer one will notice that both are supported by firm believers on one side and attacked by convinced skeptics on the other. Who is right, who is wrong? I do not feel competent to give a definite answer to this question, but I shall try to discuss some reasons for the uncertainty of the status of immunoscintigraphy in the diagnostic work-up of patients with colorectal carcinoma.

First experiments in animals bearing human colon carcinoma grafts with excellent uptake of ^{131}I-labeled polyclonal antibodies directed against carcinoma-embryonic antigen (CEA) raised the hope of approaching the legendary concept of the magic bullet set up by Paul Ehrlich. The images obtained in patients with CEA-producing tumors were much less clear. The average nuclear medicine physician had some difficulties in accepting that a few white, red or yellow dots on a scan represent significant tumor uptake; and I guess that it was even more difficult for the average surgeon to accept. These pictures need the faith of the pioneers of immunoscintigraphy to be accepted in the same way that pictures of the Loch Ness Monster need the faith of those who have shot them to be interpreted.

The monoclonal antibody technique described by Köhler and Milstein in 1975 aroused the interest of the medical community in radioimmunodetection, which was expected to be followed very rapidly by efficient radioimmunotherapy. Again, we had to learn that even specific antibodies were still not magic bullets able to detect, visualize and destroy tumor cells wherever they were located in the body. Faith was confronted with the reality that macromolecules must first cross the capillary membrane before reaching the antigen on the tumor cells while swimming against the stream of high interstitial pressure (*1*). It is really magic that some of these antibodies finally reach their target! And they do: the article published by Haseman et al. in this issue of the *Journal*, as well as numerous other articles, which were reviewed extensively by Goldenberg and Larson (*2*), show that the faith in immunoscintigraphy of colorectal carcinomas was justified, even if many problems remain to be solved. Haseman et al. detected at least one tumor deposit in 75/95 patients (79%) whose clinical and radiological work-up was negative or equivocal at the time immunoscintigraphy was performed. This confirms the opinion of most of researchers involved in the field that immunoscintigraphy is able to visualize tumor foci before they are large enough to be shown by other methods. The technique takes advantage of the fact that uptake per gram tumor tissue in percent of injected activity is higher in smaller than in larger tumors. It thus has the potential to narrow the gap between the first doubts about a possible recurrence raised by subtle changes in a patient's symptoms or laboratory tests and treatment.

Despite many encouraging results, skepticism concerning the future of immunoscintigraphy and radioimmunotherapy remains. In fact, immunoscintigraphy is not yet considered a routine nuclear medicine procedure. Even if we know that antigens need not necessarily be tumor-specific as long as they are more abundant in tumor than in nontumor tissue or that antigen shed into circulation does not prevent from successful tumor imaging, it is not always easy to distinguish

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target from nontarget uptake. Imaging on multiple days as well as SPECT are helpful, but sometimes it is necessary to perform serial studies to confirm the presence or absence of tumor in equivocal lesions. Haseman et al. report, however, on a substantial increase of side effects after repeat immunoscintigraphy (18% in comparison with 1% after single injection). They did not measure human anti-mouse antibodies (HAMA) in the sera of their patients, nor did they state the quality of the scans in patients with adverse reactions. We find that the development of HAMA is one of the major drawbacks of the method. A diagnostic test, which cannot be repeated several times, has only restricted use in the routine follow-up of patients at risk of recurrence. This is especially true for colorectal carcinomas where early resection of local recurrence as well as of distant metastases (liver, lungs) offers the best chances of survival, because of the limited efficiency of chemo- and radiotherapy. Too few and contradictory data are available with chimeric or "humanized" antibodies to conclude on the incidence of anti-idiotype antibodies. Further studies and compounds are needed, which means additional expenses before definite conclusions on the utility of immunoscintigraphy in large scale patient management can be drawn.

Ongoing research may also produce unexpected effects: By the time a prospective study comes to its end, the compound may have already been improved. When the improvement only concerns a detail in production, the study often exceeds with the new product. In the present case, the authors do not explain why they reduced the protein dose from 42 to 5 mg when changing from ascites to cell culture-derived monoclonal antibody. This is particularly intriguing when one knows that previous publications on immunoscintigraphy with ^{111}In-labeled ZCE-025 strongly advocated the injection of large amounts of cold antibody to decrease nonspecific liver uptake of the labeled compound (*3*). Discussion of the reasons for changing the protocol during the study as well as details of results obtained in liver metastases, not just overall results, are unfortunately lacking.

The time between the beginning of clinical investigation and commercialization of a radionuclide antibody compound is usually even longer than that of prospective studies. The risk exists that at the moment of commercial release better compounds are already under evaluation. The short-term benefit should not obscure the final goal of being useful, not just for some selected cases, but for a majority of patients in the follow-up and treatment of colorectal carcinoma. This is a real challenge for industry in a period of recession and when several companies after major investments have either withdrawn from or reduced research in the diagnostic and therapeutic applications of radiolabeled monoclonal antibodies.

We still have only vague ideas of the real dimensions of immunoscintigraphy and even less of radioimmunotherapy. Each time we think the problem is solved we are confronted with new, often unexpected questions. Overall knowledge on the various factors affecting tumor uptake of radiolabeled antibodies has increased tremendously, but there is still no consensus on the most appropriate antibodies (nature, class, form) and radionuclides and labeling techniques (in vitro? in vivo?) for immunoscintigraphy of colorectal carcinomas. Tumor uptake remains poor, in most instances far less than 0.1% of injected dose per gram. It is important that individual teams study the multiple problems raised with radiolabeled monoclonal antibodies in the management of colorectal carcinoma, because it may be interesting to describe the tail, head or other body parts of a mythical animal. Our final goal, however, is to contribute to more efficient treatment of patients with recurrent colorectal tumors by immunoscintigraphy and radioimmunotherapy. Along with highly competitive research, this challenge also needs a certain humility, in that we must be able to recognize that the success of our own work is important only as part of the whole.

The results of Haseman et al. are excellent, but still not good enough. A great effort has to be made to present the data in a way that is meaningful for the surgeon when trying to remove a less than 1 cm tumor deposit embedded in postoperative scar tissue. It is urgent to develop techniques to fuse SPECT, CT or MR images in order to superimpose on the same tomographic slice functional and anatomic information. Furthermore, it is probable that in the day to day clinical routine with nonselected patients sensitivity and specificity will be less than 80% and equivocal results will be frequent in otherwise occult lesions. A method that does not fulfill the expectations of the clinicians might bring back the label of "unclear medicine" and confine us to the role of side-show imaging identifying curiosities such as Nessie, or making us court fools who are often right, but not always believed.

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