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EDITORIAL

Imaging Inflammation: Current Role of Labeled Autologous Leukocytes

In the article by Cooper et al. (*1*), ^{99m}Tc-leukocyte scanning is shown to be accurate in the diagnosis of deep sternal wound infection following sternotomy for coronary by-pass grafting. This appears to be of real clinical value and represents another indication for leukocyte scanning to be added to the long list of specialized clinical settings for which the technique makes a significant contribution to patient management.

Currently, the main areas of controversy concerning the diagnosis of infection with radionuclides are: (1) the relative value of techniques which label either leukocytes or the inflammatory focus in vivo and do not, therefore, require autologous blood handling, and (2), perhaps of lesser importance compared with item 1, the relative merits of ^{99m}Tc and ^{111}In-labeled cells.

Agents which are thought to directly label the inflammatory focus include ^{67}Ga citrate, polyclonal immunoglobulin (HIG) (*2–4*), nanocolloids (*5,6*), porphyrins (*7*) and more recently streptavidin (*8*). Apart from ^{67}Ga, these have not been widely accepted. In experimental models of inflammation, most have given abscess-to-background ratios no greater than ^{67}Ga or radioiodinated serum albumin, and considerably less than autologous ^{111}In-labeled leukocytes (*9*). Radiolabeled monoclonal antibodies against neutrophil antigens are now available for labeling granulocytes in vivo. A considerable fraction of the antibody circulating in peripheral blood is not bound to cells, and, although the granulocyte-binding increases with time (*10*), there is a relatively small radioactivity signal from the spleen (*10,11*). These antibodies, in particular the one first described by the Swiss group (*12*) and the Behring monoclonal antibody, BW 250/183

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For reprints contact: A.M. Peters, Dept. of Diagnostic Radiology, Hammersmith Hospital, London, England W12 OHS.

(*10,13–16*), appear to label bone marrow myelocytic series (*17,18*). Bone marrow labeling exceeds peripheral granulocyte labeling by perhaps an order of magnitude, and, since circulating free antibody is in equilibrium with the entire cell-bound monoclonal antibody, mostly in the bone marrow, this could account for the apparently large amount of free circulating antibody. This raises potential problems for imaging, since if one has to wait for the labeled bone marrow granulocyte precursors to be released before sufficient radioactivity localizes in an inflammatory focus, then conditions such as inflammatory bowel disease (IBD), in which early imaging (within 3 hr) is critical, will be placed at a disadvantage. Furthermore, on the basis of delayed abscess labeling, ^{99m}Tc is not the logical radionuclide with which to label the monoclonal antibody. Nevertheless, as recently reported by the Barcelona group (*16*), the monoclonal antibody BW 250/183 detected involved bowel segments in IBD on 24 hr imaging as *proximally* as ^{111}In-oxine-labeled leukocytes did at 3 hr, suggesting that having become localized, the monoclonal antibody remains fixed at the site of the disease. Becker (*personal communication, 1991*) has offered several explanations for this phenomenon, for example binding of the Fc portion of the cell-bound monoclonal antibody to local Fc receptors in bowel mucosa (predominantly on macrophages and other, unlabeled, granulocytes). Free antibody in blood may, in addition, show some direct specific labeling of the inflammatory focus. This could be to non-viable granulocytes already localized in the inflammatory focus, as suggested by McAfee (*19*), or, in IBD, to CEA, the expression of which is increased in IBD (*20*). Nevertheless, the cynic might comment that localization of monoclonal antibody in inflammatory foci, is, like polyclonal immunoglobulin and nanocolloids, a nonspecific process, dependent on the circulating free protein, although the high accuracy figures quoted for BW 250/183 in the literature (*13–16*) and at recent nuclear medicine meetings (*21, 22*) would seem to deny this.

So, at present, autologous labeled cells, in spite of requiring in vitro blood handling, remain the agents of choice for imaging inflammation, at least in so far as they give the highest target-to-background ratios. Should we be using ^{99m}Tc or ^{111}In? Technetium-99m-HMPAO has now been widely investigated and offers advantages of improved image resolution, convenience and reduced radiation burden. Although in experimental studies, ^{99m}Tc-HMPAO has shown a lower target-to-background ratio than ^{111}In-labeled leukocytes (*23,24*), most (*25–27*) but not all (*28*) clinical comparisons have shown no significant difference. Currently, our own policy is to have both available and to choose whichever is the more appropriate for the clinical problem. Acute sepsis, for which an urgent answer is usually required, or IBD, can be satisfactorily studied with ^{99m}Tc-HMPAO. In spite of nonspecific bowel excretion, ^{99m}Tc-HMPAO is well-suited to imaging inflamed bowel, particularly for localizing ileal involvement (*29*). With the HMPAO on the shelf, a rapid response to the clinical request is possible. For more chronic processes, such as infected hip prostheses and likely pyogenic causes of fever of unknown origin, we prefer to use ^{111}In tropolonate-labeled granulocytes. In order to minimize cost, it should be possible to order ^{111}In electively for these indications. Since the turnover of granulocytes is likely to be slower in chronic foci, it becomes more critical to obtain images at 24 hr and to make full use not only of the longer physical half-life of ^{111}In but also its greater stability both in granulocytes and in the target inflammatory focus; recall that the amount of radiolabel incorporated into an inflammatory focus will be proportional to the area under the plasma labeled granulocyte-time concentration curve. Due to instability (rather than to cell toxicity), the effective half-time of ^{99m}Tc labeled leukocytes in blood is only about 4 hr (*25*) compared with about 7 hr for ^{111}In-labeled granulocytes (*30*). In addition, ^{99m}Tc-HMPAO almost certainly elutes from the target tissue following localization (*25*). We would elect, therefore, to use ^{111}In-tropolonate-labeled pure granulocytes for relatively chronic processes and for conditions in which a normal distribution of ^{99m}Tc-HMPAO (*25,29*) may obscure cell migration, such as renal sepsis and intraabdominal abscesses thought to be in communication with bowel lumen (*31*).

The choice of ^{99m}Tc in Cooper's study (*1*) is therefore somewhat surprising. A new diagnostic criterion seems to have been necessitated by the use of ^{99m}Tc-HMPAO in their study, namely an *increase* in activity at the sternotomy site between 4 and 24 hr. With ^{111}In, activity always increases between 4 and 24 hr in normal (except the spleen, *30*) and abnormal sites, unless, of course, there is spontaneous drainage as in intra-abdominal abscess communicating with bowel lumen (*31*). If, as seems likely, some ^{99m}Tc-HMPAO elutes from the abnormal sternum between 4 and 24 hr, then the diagnostic criterion of an increase between 4 and 24 hr introduces some uncertainty. However, any impact this potential problem may have had on the results of Cooper et al. (*1*) is doubtful since there were no false-negatives in their series. On the other hand, the two false-positives they encountered may have been correctly diagnosed as insignificant infections if ^{111}In-labeled cells had been used and if intensity of uptake, rather than an increase, had been adopted as the criterion for a positive scan. It is also worth pointing out that the time course of uptake in bone marrow probably parallels that in an inflammatory focus (*30*) and may, on the criterion of *increasing* uptake, be confused with osteomyelitis (*32*) and lead to a false-positive diagnosis of bone infection. It may be interesting, in the light of the paper by Cooper et al., to retrospectively review the criterion of increasing uptake with a view to evaluating it in other settings, including

other forms of osteomyelitis, and to compare ^{111}In with ^{99m}Tc-HMPAO.

A. M. Peters
Hammersmith Hospital
London, England

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