

an excellent agent for skeletal imaging. The diphosphonate is a stable chemical in aqueous solutions, and there is still no evidence that it is metabolized in vivo, unlike linear polyphosphates. Despite the increasing number of publications on the pharmacology and toxicity of diphosphonates, most of these have reported results of oral or subcutaneous administrations, and there is still a paucity of information on intravenous toxicity. In our laboratory, the  $LD_{50/30}$  for EHDP administered intravenously as a tin complex was 45–50 mg EHDP/kg body weight in albino mice and 40–45 mg/kg in New Zealand adult rabbits compared with 100 mg/kg in both mice and rabbits for linear polyphosphate. Recent measurements of the long-term retention of  $^{99m}\text{Tc}$ -EHDP in beagles by total-body counting and radioassay of excreta have revealed a slow component with a biological half-time of 72 days for 15% of the administered activity (5). Although the effects of subcutaneously administered diphosphonates on ionizable serum calcium and the histological appearance of bone have been studied in dogs (6), similar information following intravenous injection has not been reported. The human experience on the administration of large doses of EHDP for the treatment of Paget's disease and other skeletal lesions is probably not closely related to single or repeated intravenous administrations since only about 3% of these therapeutic doses administered orally are absorbed. The small quantities of diphosphonates currently used for radioisotope imaging studies appear to be considerably below levels of demonstrable toxicity; however, the evidence to date suggests that their skeletal concentration depends on the degree of dilution, the diphosphonate-to-tin molar ratio,

and the chemical dose administered. Therefore, more experimental data are needed to define better the optimal diagnostic dose and the minimal dose for undesirable effects following intravenous administration.

Since the introduction of the  $^{99m}\text{Tc}$ -Sn complex of linear polyphosphate (MW 5,000), other polyphosphates, pyrophosphate, and several diphosphonates have been developed recently as successful skeletal imaging agents at various centers. More experience will be needed to determine which of these will be the most satisfactory agent; at the present time, it is the authors' opinion that one of the labeled diphosphonates may prove to be "the best".

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## FREQUENCY OF EARLY SKULL METASTASIS IN BREAST CANCER

Since we began using  $^{99m}\text{Tc}$  as our bone-imaging agent, we have noted a high frequency of skull metastases in breast cancer patients. In 31 patients studied so far, 16 (53%) have had skull involvement in addition to other bone metastases, principally in the axial skeleton. In ten (32%) patients with early bone metastases, i.e., those with positive scintiphotos and negative roentgenograms, the skull was the first site of involvement. In each case the scintiphoto findings were confirmed by subsequent roentgenographic changes. We had not noted a similar frequency of skull metastases when using  $^{18}\text{F}$  (1,2) and have attributed its appearance to the superior scintiphotos obtained with  $^{99m}\text{Tc}$ . Our limited experience suggests that the frequency of early skull metastasis in breast cancer may be greater than heretofore recognized (3) and stresses the need for rou-

tine skull views. We would be interested in knowing if others have made a similar observation.

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