

## V4

### Fate of Gallium *in vivo* and its Significance in Tumour Diagnosis and Therapy respectively with Gallium-67 and Cold Gallium

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Of the 105 elements known today, gallium is the only one which lends itself to both non-invasive diagnosis and therapy of tumours. Although the first report on the clinical application of gallium dates as far back as 1931 [1], the observation by Edwards and Hayes [2] in 1969 that gallium-67 concentrates in several soft tissue tumours aroused great interest in

this radionuclide, and today it has become the most widely used radiopharmaceutical in the imaging of a wide variety of tumours [3]. Two years later Hart

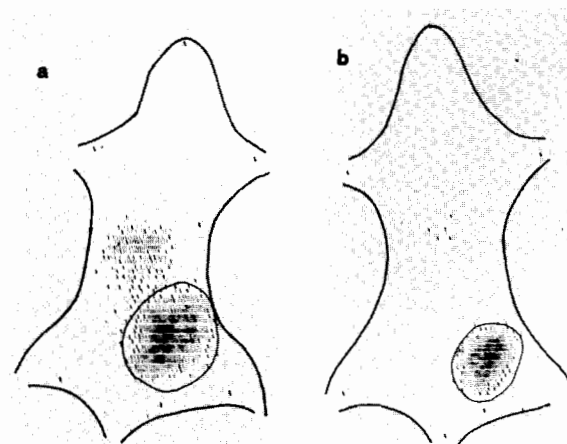


Fig. 1. Gallium-67 distribution in a Morris-hepatoma-3924A-bearing rat injected with (a) commercial gallium-67 citrate brought in the formulation 0.88 mg/ml Na-citrate + 7.94 mg/ml NaCl; (b) tumour specific gallium-67 made loosely bound before injection.

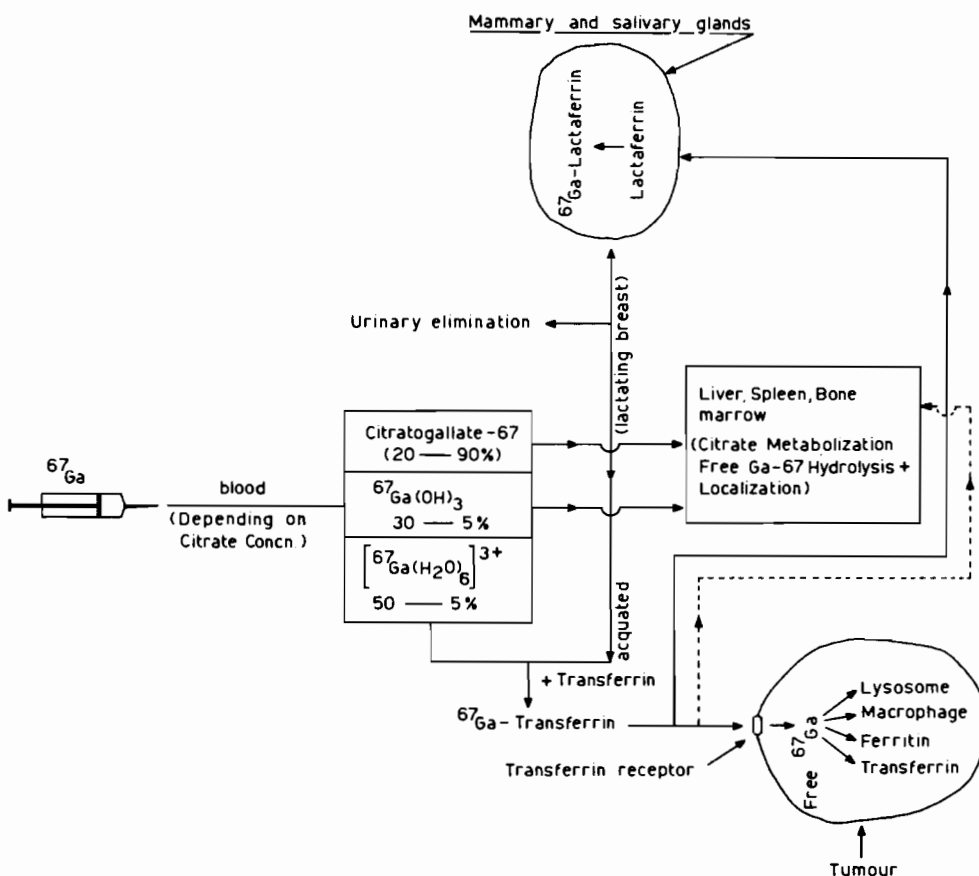


Fig. 2. Mechanism of gallium distribution in healthy and tumour bearing subjects.

and co-workers [4, 5] reported the potential usefulness of cold gallium nitrate for treatment of solid tumours in both rodents and humans. Although the literature reports less work on the antitumour activity of cold gallium as compared to that on the diagnostic properties of gallium-67, it has been felt that if the aqueous solution chemistry of both gallium-67 and cold gallium is well studied, gallium has a promising future in the early diagnosis and treatment of cancer [6].

Many studies have been reported to show that transferrin *in vivo* plays an important role in the transport of gallium from the site of its administration to the tumour [6]. There is little agreement on the role of ion storage protein, ferritin, on the biological behaviour of gallium and on its tumour affinity [7]. We have studied chromatographically and electrophoretically the relative stability of gallium complexes with citrate ion, transferrin, and ferritin. The stability of the complexes follows the order gallium-ferritin complex  $\gg$  citratogallate  $>$  gallium-transferrin complex. All three complexes are anionic.

Based on these results, and on those on the distribution of gallium-67 and of cold gallium in healthy and tumour-bearing subjects (Fig. 1), we proposed a mechanism (Fig. 2) of the uptake of gallium from different formulations. It has been found that only free or loosely bound gallium easily binds to transferrin which transports it to the tumour site, where a transferrin receptor in the tumour cell membrane sequesters transferrin and allows free gallium to diffuse into the cell to be bound firmly to ferritin, found in high concentration in malignant tissue cells [9]. We could succeed in making gallium-67 uptake tumour-specific and have also obtained encouraging results on the treatment of experimental mammary tumours (TGS) by administration of weakly bound cold gallium.

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## V5

## Structure-Activity Relationships with Therapeutic Chelating Agents

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Although the vast majority of therapeutic chelating agents are water soluble rather than lipid soluble (*e.g.* EDTA, D-penicillamine, DTPA, desferrioxamine and unithiol, among others), recent studies [1, 2] have shown that lipid soluble chelating agents and those that give lipid soluble metal chelates, may be the only effective means of mobilizing intracellular deposits of certain metals. This has been shown most strikingly in the case of cadmium present in the kidney (as metallothionein). Such deposits can be mobilized by both BAL and sodium diethyldithiocarbamate. Because it is possible to synthesize derivatives of sodium diethyldithiocarbamate with varying lipophilicity, we have undertaken to prepare some of these compounds and examine their behavior as antidotes for acute cadmium intoxication. The animal experiments have been carried out using the procedure of Gale *et al.* [2, 3], while syntheses have been done using published procedures [4]. The dithiocarbamates prepared and examined are shown in Table I, together with information on their efficacy as antidotes.

The behavior of these compounds as antidotes can be correlated using the  $\pi$  substituent constants of Hansch, as tabulated by Chu [5]. For each compound the relative hydrophobic nature can be estimated as the sum of the  $\pi$  substituent constants of  $R_1$  and  $R_2$ . These sums are shown in the last column of Table I. Figure 1 below shows the survival ratio variation with  $\Sigma\pi$ . One of the adverse effects of such dithiocarbamates is their ability to transport cadmium to the brain, an effect which is also related to the lipophilicity of the chelating agent. If the Net Efficacy of the chelating agent is defined as

$$\text{Net Efficacy} = \text{Survival Ratio} - \text{Relative Brain Cadmium}/n,$$

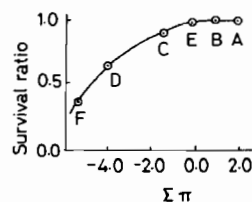


Fig. 1. Relative Survival Ratio vs.  $\Sigma\pi$ .