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 shon 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

Net Efficacy =

= Survival Ratio – Relative Brain Cadmium/n,

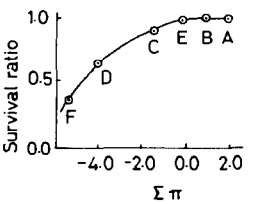

Fig. 1. Relative Survival Ratio *vs.* $\Sigma\pi$.

TABLE I. Antidotal Behavior of Dithiocarbamates ($^{-}S_2CNR_1R_2$).

Compd.	R_1	R_2	Relative[a] Survival Ratio	Relative[b] Brain Cd	$\Sigma\pi$
A	C_2H_5	C_2H_5	1.00	1.00	2.04
B	CH_3	CH_3	1.00	0.88	1.12
C	C_2H_4OH	C_2H_4OH	0.88	0.30	−1.54
D	CH_3	CH_2COO^-	0.63	0.14	−4.16
E	CH_3	C_2H_4OH	1.00	0.00	−0.21
F	CH_2COO^-	CH_2COOH	0.38	0.02	−5.44

[a]Relative Survival Ratio = Survival Rate/Survival Rate for A.

[b]Relative Brain Cd = Brain Cd/Brain Cd for A.

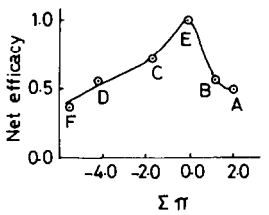

Fig. 2. Net Efficacy *vs.* $\Sigma\pi$.

then such a net efficacy (with n = 2), as plotted in Fig. 2, can be seen to reach a maximum in the region $\Sigma\pi \approx 0$. It is possible that such correlations will prove useful in the development of optimal chelating agents for the removal of intracellularly deposited metal ions.

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V6

Interaction of DNA with Chiral Cisplatin Analogues

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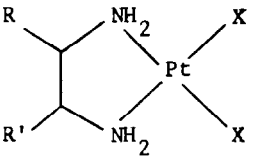
The *in vivo* target of the anticancer drug *cis*-$[Pt(NH_3)_2Cl_2]$ (cisplatin) is believed to be DNA [1]. As this is a chiral substrate, it could be expected that cisplatin analogues, in which the two ammonia ligands have been substituted by chiral chelating diamines [2] (see Scheme), should be discriminated according to the absolute configuration of the diamine. A number of these analogues has been synthesised and tested against leukemia P388 in mice, but, contrary to the expectations and to some early independent reports [3], only marginal, ill detectable differences in the activity of the enantiomeric compounds were observed.

In agreement with this observation, we have found that the chiroptical properties of the adducts of the chiral cisplatin analogues with calf thymus DNA are independent of the absolute configuration of the diamines; moreover an electrophoretic study has also shown that the conformational changes of supercoiled and nicked PM2 DNA do not depend on the configuration of the cisplatin analogues [5].

This set of results indicates the absence of relevant diastereoisomeric effects in the cisplatin DNA interaction. However, when model systems were investigated, a more complicated behaviour was observed. The compounds of general formula $[(diam)Pt(guo)_n]$



R = R', ethylenediamine, en.
R = H, R' = CH_3, propylenediamine, pn.
R = R' = CH_3, butanediamine, bn.
R = R' = ½$(CH_2)_4$, cyclohexanediamine, chxn.
The diamines are in the *R*-, *S*-, or *meso*-configuration.
X = Cl, ½$SO_4^{=}$.
In the model compounds X = guo.

Scheme.

and $[(diam)Pt\{guo(-H)\}_n]$ (diam = chiral diamine; guo = guanosine; n = 1, 2) were synthesised and studied by ^1H and ^{13}C NMR and circular dichroism spectroscopy. It appears that when two guo are