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.

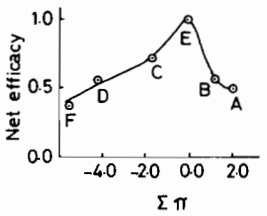

Fig. 2. Net Efficacy *vs.* $\Sigma\pi$.

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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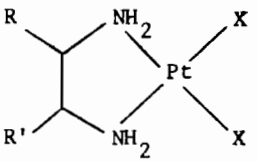
The *in vivo* target of the anticancer drug *cis*-$[Pt(NH_3)_2Cl_2]$ (cisplatin) is believed to be DNA [1]. As this is a chiral substrate, it could be expected that cisplatin analogues, in which the two ammonia ligands have been substituted by chiral chelating diamines [2] (see Scheme), should be discriminated 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

bound to platinum they arrange stereospecifically in a propeller-like structure in which strong and spatially oriented hydrogen bonds between O(6) of guo and the NH_2 groups of the diamine stabilize the structure, but only with diamines of *S*-absolute configuration [6]. Deprotonation of guo at N(1), which occurs at a pH lower than in free guo ($pK_a = 7.9$ vs 9.25 [7]) and leads to the enol tautomer, is accompanied by profound changes in the conformation of these complexes. At least in one instance, [{(*R*,*R*)-chxn}Pt-{guo(-H)}$_2$], the propeller-like structure is completely lost.

In the case of the monoguanosine complexes [(diam)Pt(guo)]$^{2+}$ and [(diam)Pt{guo(-H)}]$^+$ neither the configuration of the diamine, nor deprotonation of guo have great influence on the chiroptical properties of the complexes. It has been proposed that in these complexes guo is chelated to Pt through N(7) and O(6) [8]. However, although some shifts in the frequencies of ν(C=O) and of ν(C(4)=C(5) + (C(5)–C(6)) in the IR spectra suggest a perturbation of O(6), we failed to detect the expected coupling of C(6) with ^{195}Pt in the ^{13}C NMR spectra. It could be, therefore, that chelation is achieved via an outer sphere coordination of O(6) through a bridging water molecule directly coordinated to the metal as found in some instances [9].

The absence of chiral discrimination observed in the interaction with DNA does not agree with the results obtained with our model compounds. It can be suggested that the cisplatin-DNA interaction modifies the essential conformational features of DNA, at least in the neighbourhood of the site of attack, in such a way that makes any chiral recognition irrelevant.

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V7

Chelates of Indium-111 as Agents for Labelling Human Granulocytes for Clinical Use

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Chelates of the cyclotron produced radionuclide indium-111 ($t_{½}$ 2.8d) with 8-hydroxyquinoline [1] (oxine) and acetylacetone [2, 3] (acac) have been used for labelling human blood cells in diagnostic nuclear medicine [4, 5]. However, before labelling cells with oxine or acac complexes, the cells must be washed free from plasma before efficient labelling can be achieved. This may result in damage to the cells. Consequently we introduced the clinical use of tropolone (2-hydroxy-cycloheptatrien-1-one) with ^{111}In as an alternative cell labelling agent [6]. Indium tropolonate has the advantage of being able to label cells efficiently in the presence of plasma. Thus the time and degree of manipulation required for labelling is reduced and enhanced clinical results are also being obtained using granulocytes labelled with ^{111}In-tropolonate [7, 8].

Although tropolone offers considerable advantage over oxine and acac, all three still label blood cells non-selectively. It would be highly desirable clinically to find a ligand for ^{111}In which would selectively label only the cell type of interest. Labelling could then be carried out in whole blood, obviating the need for tedious cell separations and concomittant risk of cell damage. As part of a study to understand the mechanisms involved in cell-labelling and to produce more efficient and possibly more specific labelling agents, we have examined a series of indium-111 tris chelates with bidentate ligands for their ability to label granulocytes with ^{111}In.

Experimental

Materials. The following chemicals were used as supplied. Tropolone (2-hydroxy-cycloheptatrien-1-one); N,N′-dimethyldithiocarbamate; N,N′-diethyldithiocarbamate (Fluka). Acetylacetone (Sigma) was distilled before use. β-thujaplicin (4-iso-propyltropolone) (Roth) was converted to the more water soluble sodium salt [9] and recrystallised from water as the dihydrate. 8-hydroxyquinoline sulphate (Sigma) was recrystallised from water/ethanol. Purpurogallin (Aldrich) was recrystallised from anisole. The following coumpounds were synthesised according to reported methods; 7-carboxy-6-carboxymethyltropolone [10]; 6-methyltropolone [10]; ammonium 5-sulphonyltropolone [11].