Platinum Anti-Cancer Drugs

A DISCUSSION ON THE MECHANISM OF ACTION

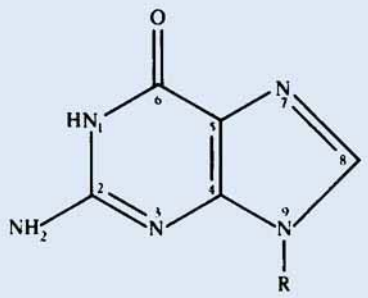
A conference to discuss the opportunities for inorganic biochemistry in the 1980s, organised by the Inorganic Biochemistry Group of the Dalton Division of the Royal Society of Chemistry, and held at Birkbeck College, London in December 1980, took as its theme the need to gain more knowledge of the biological distribution of metal and metalloid elements, in order to obtain a better understanding of their role in biological systems.

The final session of the conference was devoted to inorganic pharmacology, an area where much recent interest has been stimulated by the success of some platinum compounds, particularly *cis*-dichlorodiammineplatinum(II) (*cis*-Pt(II)), in treating certain types of cancer. This is now an approved drug, marketed under the registered trademarks Neoplatin and Platinol, in the U.K. and U.S.A. respectively. It was therefore appropriate that the first lecture in this session was given by Professor Barnett Rosenberg of Michigan State University, who was the first to report the anti-cancer activity of this compound in 1969 and who has done much to further its exploitation.

Following a brief description of the discovery, Professor Rosenberg discussed the aqueous chemistry of *cis*-Pt(II). In distilled water the chloride ligands are slowly displaced by water molecules, which may then deprotonate and react further to produce a variety of hydroxy species. Some of these have been separated and identified using high performance liquid chromatography.

In the clinic *cis*-Pt(II) is used in combination regimes with other anti-cancer agents, common examples being bleomycin, adriamycin and cyclophosphamide. Synergism, where the response to combination therapy is greater than would be expected from the response to the separate agents, is often observed. Tumours responding favourably include testicular, ovarian, head and neck, and bladder cancers. The drug has also been used successfully to treat primary brain tumours in children.

Professor Rosenberg then speculated on the mechanism of action of these platinum drugs. Molecular biology studies by several researchers indicate that *cis*-Pt(II) binds to DNA in cell nuclei, preventing replication. Normal cells have processes to repair such DNA damage, and it is widely believed that the breakdown of these repair processes is a major factor in the transformation from normal to cancerous cells. One particular DNA site, O-6 of guanosine has been linked with both carcinogenesis and the mechanism of anti-tumour action of platinum complexes.



Guanosine residue (R = sugar, linking into the sugar phosphate DNA backbone)

Rosenberg discussed preliminary results on the ability of tumour cells, both those sensitive and those resistant to *cis*-Pt(II), to repair DNA which has been methylated at this position. Present indications are that this type of DNA damage may be a major reason for the effectiveness of platinum drugs. An extension of this type of study may enable a relationship to be established between various types of DNA damage and cell transformation, and the anti-cancer activity of chemotherapeutic drugs. This could lead, in the long term, to optimised methods of treatment. C.F.J.B.