ments resulting from the diagonal relationship in the periodic table [10]. Kinetic studies of magnesium dependant enzymes and investigation by NMR of interactions of lithium and magnesium with nucleotides [11], have shown only weak effects of lithium on magnesium regulated processes and the working hypothesis must therefore be reconsidered.

Lithium carbonate is a useful and inexpensive drug which has an important role to play in current therapeutics. Its mode of action is not well defined and much scope therefore remains for further study in this area of Inorganic Pharmacology.

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RT1.5 — MO

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CLINICAL APPLICATIONS OF PLATINUM METAL COMPLEXES

In the late 1960's ROSENBERG noted that the growth of bacteria exposed to an electric field became filamentous, suggesting the presence of an antiproliferative agent in the culture medium. This observation led to the identification of *cis*-dichloro-diammine platinum II (cisplatin) as a possible anticancer agent [1]. Subsequent clinical studies performed initially in the USA and England, but later throughout the world have established cisplatin as one of the most important new anticancer drugs to enter clinical practice in the last ten years [2]. Its use in combination in the treatment of testicular tumours has transformed the prognosis. Even for patients with disseminated disease cure rates in the region of 90% are now achieved in most major centres [3]. Cisplatin is also the prime agent in ovarian cancer [4] and is active in a variety of other tumours.

Cisplatin is capable of forming adducts to nucleophilic sites on biological molecules, the chorine atoms acting as leaving groups. In common with a number of other anticancer drugs, cisplatin will cross-link DNA via the guanine residues. The property of cisplatin which endows it with its special activity is not known. However, cisplatin is capable of forming intrastrand cross-links [5] and it is tempting to speculate that these differentiate its activity from that of other drugs. The analogue transplatin possesses most of the biological properties and toxicities of cisplatin but is both devoid of antitumour effect and incapable of forming intrastrand cross-links.

Although cisplatin has been one of the most active anticancer drugs to be introduced recently, it is also one of the most toxic. Cisplatin causes severe emesis and is toxic to the kidneys and the peripheral nervous system. It can also cause deafness, anaemia and convulsions, the latter mediated by hypomagnesaemia. The acute renal failure which occurred in the early trials of cisplatin may be averted by forced hydration and diureses, although a progressive decline in renal function still occurs and limits both the maximal single dose and the total dose which may be given. OZOLS *et al.* [6] have shown that hyperhydration and the administration of hypertonic saline will allow higher doses of cisplatin to be given without a marked decline in renal function, possibly due to a common ion effect in the renal tubule stabilising the leaving groups of cisplatin. However, the incidence of the other complications, particularly deafness and peripheral neuropathy, was markedly increased.

Another approach has been to search for analogues. In a collaborative programme with the Johnson Matthey Company we have evaluated about 300 analogues of cisplatin as potential alternatives to the parent drug. Of these, eight were selected which showed antitumour activity similar to that of cisplatin in experimental systems. An intensive toxicity study of these eight led to the selection of 2 analogues without nephrotoxicity. These were *cis*-diammine-1,1-cyclobutane dicarboxylate platinum II (JM8, CBDCA, Carboplatin) and *cis*-dichloro-trans-dihydroxy-diisopropylamine platinum IV (CHIP, JM9, Iproplatin) [7]. Carboplatin has been extensively evaluated in the Royal Marsden Hospital and latterly in other centres [8]. It has activity similar to that of cisplatin in carcinoma of the ovary, but is devoid of renal toxicity and ototoxicity [9]. It also causes significantly less emesis. Carboplatin is also highly active in small cell lung cancer [10] and has shown encouraging activity in a number of other tumours. The dose-limiting toxicity of carboplatin is to the bone-marrow. Iproplatin is at an earlier stage, but has been evaluated in Rosewell Park (USA) and Manchester (England). It also possesses reduced non-haematological toxicity compared to cisplatin and has shown encouraging signs of antitumour activity. It is interesting that there is some clinical evidence that Carboplatin and Iproplatin may be active in patients whose tumours are resistant to cisplatin [11]. These observations suggest that the pursuit of cisplatin analogues may lead to the discovery of drugs with an enhanced or different spectrum of antitumour activity in addition to having a more acceptable toxicity profile.

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2. *Environmental Bioinorganic Chemistry*
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RT2.1 — MO

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ENVIRONMENTAL ASPECTS OF NICKEL TRANSPORT AND NICKEL TOXICITY IN SELECTED ALGAL SPECIES

More than ten years ago it was shown that nickel can function as an essential element by Zerner's group in Queensland, Australia. In a series of seven papers in Biochemistry, a detailed study of the structure, kinetics and mechanism of Jack Bean urease was reported by this group who showed that nickel is present at the active site of this enzyme. Since that time nickel has been found to play a very important role in the metabolism of carbon-1 (C_1) compounds in the anaerobic bacteria. Nickel containing coenzymes function in the active sites of the enzymes which fix molecular hydrogen (*i.e.* the hydrogenases), in the terminal enzyme for methane biosynthesis (*i.e.* a nickel--containing B_{12}-analog or nirrin macrocycle), and in the hydration of carbon monoxide by those organisms which utilize CO as sole carbon and energy source.

In sediments nickel forms stable and insoluble complexes with sulfide ions and with thiolates to give nickel sulfides and stable oxidization complexes with organic compounds which contain thiol--groups. However, at the sediment/water interface, nickel forms weaker coordination complexes with oxygen donors such as carboxylate, hydroxyl, and other oxy-ligands (*e.g.* humic acids, fulvic acids, clays, metal oxides, *etc.*). Slightly stronger complexes are formed with oxygen donors at the cell surfaces of bacteria and algae which have many anionic functional groups from both proteins and polysaccharides (*e.g.* polygalacturonic acids at the surface of green algae). These complexes, to the weaker oxygen donors, are unstable enough for nickel to be exchanged with the fast exchange ions Ca^{2+} and Mg^{2+} releasing Ni^{2+} into the water. Thus, Ni^{2+} has an intermediate exchange rate with Ca^{2+} and Mg^{2+}, and so Ni^{2+} cannot be removed entirely from industrial wastewater by traditional treatment methods.

Since algae are known to bioaccumulate nickel directly from the aqueous environment, we conducted a basic study to determine some of the parameters necessary for nickel removal by, and nickel resistance in, these photosynthetic organisms. I shall present here a summary of the results of this study by selecting two axenic cultures of cyanobacteria, (*Synechococcus* ATCC 17146 and *Oscillatoria* UTEX 1270) compared with two strains of green algae (*Scenedesmus* ATCC 11460 and *Chlamydomonas* UTEX 89). Nickel tolerance was found to vary widely among these four species, with the two species of green algae (*Eukaryotes*) being much more resistant to nickel poisoning than the two species of cyanobacteria (*Prokaryotes*). Using $^{63}Ni^{2+}$, and a microplate technique, we examined nickel transport through cell membranes, nickel complexation at the cell surface, as well as inside cells, and nickel efflux from cells in these four algal species. Also we examined a variety of environmental factors which regulate nickel bioaccumulation and toxicity. *Chlamydomonas* tolerates up to 10 ppm of Ni^{2+} without any effect on its growth rate. In fact this organism will even grow slowly in the presence of up to 150 ppm Ni^{2+}. *Scenedesmus* tolerates up to 5 ppm, but *Oscillatoria* only tolerates 1 ppm and *Synechococcus* is very sensitive accepting only 0.02 ppm. With the exception of *Chlamydomonas*, these algae all accumulate Ni^{2+} optimally at pH 8.0. *Chlamydomonas* does not accumulate Ni^{2+} in the pH range 7.0 to 9.0. A detailed study of Ni^{2+} bioaccumulation in *Scenedesmus* indicated that Ni^{2+} uptake is not affected by either competing cations or competing anions, however, the rate of Ni^{2+} uptake was affected by the age of the culture and by light *versus* dark conditions. Ni^{2+} was found to be primarily complexed at the cell surfa-