CHAPTER 10

NOBLE METAL COMPLEXES IN CANCER CHEMOTHERAPY*

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ABSTRACT

Platinum coordination complexes form a new class of active anti-cancer agents in animals and man. Cis-dichlorodiammineplatinum(II), the most widely investigated drug, is now in experimental clinical use against a wide variety of cancers in man. The dose-limiting toxicity in man is renal tubular damage. Hydration of the patient and the use of osmotic diuretics have minimized this effect and allowed higher doses with largely improved responses. Combination chemotherapy with the drug has also produced significant response rates in a variety of cancers. The mode of action of the drug is not yet clear, but most likely involves a primary lesion on nuclear DNA and the stimulation of a host reaction to the cancer. So far, only square planar and octahedral complexes of platinum, with a variety of inorganic and organic ligands, have shown marked activity in animal studies.

* This manuscript is, in large part, taken from a review paper that appeared in Die Naturwissenschaften 60, Pages 399-406, in 1973. New sections and some revisions have been made, updating the data.
I. INTRODUCTION

The application of platinum coordination complexes to the treatment of tumors in animals and man arose from the discovery that cis-dichlorodiammineplatinum(II), and some analog structures were potent anti-tumor agents against sarcoma 180 and leukemia L1210 in mice. This was an unexpected finding. The history leading to the testing of its activity against tumors (a classic case of serendipity) has been described in earlier pages and does not bear repeating here. It is surprising and somewhat disconcerting that an entire sophisticated branch of chemistry, that of metal coordination complexes, had been largely ignored in the search for new drugs for cancer chemotherapy. Since 1970, however, the National Cancer Institute of the United States, the Chester Beatty Institute in England, and numerous other laboratories and institutes have been making extensive efforts to redress the balance. The literature is now large, and rapidly increasing. While the major motivations for these studies are the applications to cancer chemotherapy, some laboratories have shown a broader scope of biological activities of these complexes including bactericidal, viricidal, immunosuppressive, and anti-arthritic activities. Thus, we have a new, large class of chemical structures with a wide variety of potential biological and medical applications, the exploration of which has only just begun. I shall restrict this review only to some recent developments in the field of cancer chemotherapy with platinum coordination complexes.

Large numbers of square planar platinum(II) complexes now have been screened for anti-tumor activity and, from these results, some simple "rules of thumb" have emerged relating structure and in vivo activity. A variety of tumor systems in animals are used in such screening tests, and the number and types of tumor systems showing positive results suggest that these complexes are broad spectrum, anti-tumor agents. The retention times and distribution patterns of these complexes in animals and man are now becoming known. The sites of the primary lesions in the cells, leading to tumor destruction, are believed to be on the nuclear DNA. However, in vitro tests indicate a large number of possible modes of reaction of the complexes with the nucleic acid and its constituents. Events subsequent to the primary attack that lead to anti-tumor activity are largely unknown, but some evidence has been found suggesting the involvement of the host's immune response in the anti-tumor activity. The toxic side effects in animals and man primarily are damage to renal tubules, the gastrointestinal epithelium, and bone marrow; with the kidney damage being the dose-limiting effect in man. Recently, it has been found that hydration, with or without osmotic diuretics such as D-mannitol, decrease the renal toxicity without substantially depleting the drug from the body. Thus, at allowed higher doses, other side effects are enhanced, as is the