Cisplatin in the Treatment of Cancer

THE FIRST METAL ANTI-TUMOUR DRUG

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A platinum compound, cis-diamminedichloroplatinum (II)—known as cisplatin—has recently received the approval of the governments of the United States of America and the United Kingdom for chemotherapy of specific cancers. This paper gives a brief account of the discovery of the physiological activity of certain platinum co-ordination complexes by Professor Barnett Rosenberg and his colleagues, and of the clinical development and testing that has now resulted in its acceptance. While work is continuing to develop superior drugs of this type, and to find a better understanding of their modes of action, it is anticipated that this first generation metal anti-cancer drug will be used for many years to come.

Cancer chemotherapy was born in the late 1940s and early 1950s when mustine hydrochloride (mustard gas) was found to have anti-tumour and anti-leukaemic properties. The finding was an extension of research done during the 1939-45 World War into poisonous gases. This discovery that a drug could affect the natural history of a malignant tumour was followed by an enthusiastic search for other compounds and many "nitrogen mustard" derivatives were made. All these agents appeared to act by preventing cell division and the mechanism by which this was affected was, and is, thought to be by alkylation of nuclear DNA. Unfortunately by the late 1950s it seemed likely that all alkylating agents would have the same spectrum of anti-cancer action: that is, they would be useful only against some of the rarer tumours such as Hodgkin's disease and lymphoma, but would be very toxic to the developing bone marrow cells. By 1960 it was clear that alkylating agents on their own, even when given over long periods, would not cure any cancer and that it was necessary to find and test agents with different anti-tumour actions and therapeutic spectra. The involvement of inorganic metal based compounds was very limited until the discovery of potent anti-cancer activity in certain platinum co-ordination compounds by Rosenberg and Van Camp in 1969 (1). The world of clinical oncology was initially not too enthusiastic about the potential usefulness of the first platinum drug; this was perhaps not surprising as medical scientists tend to regard all heavy metal compounds as non-selective poisons. However, the platinum discovery heralded the arrival of metal co-ordination compounds as a new class of potential anti-tumour drugs and some researchers such as the late Sir Alex Haddow at the Institute of Cancer Research, London, persevered with platinum in the belief that such a new group would emerge from Rosenberg's discovery.

After some toxicological problems the first platinum drug, cisplatin, has now become a useful first line treatment for several tumours and has been approved by the U.K. and U.S.A. governments. This paper gives an account of its discovery and clinical development.

As for many other major developments the discovery of anti-tumour activity in platinum ammine complexes was somewhat fortuitous (2). The major investigator, Professor Barnett Rosenberg of Michigan State University, was a physicist by training and was fascinated by

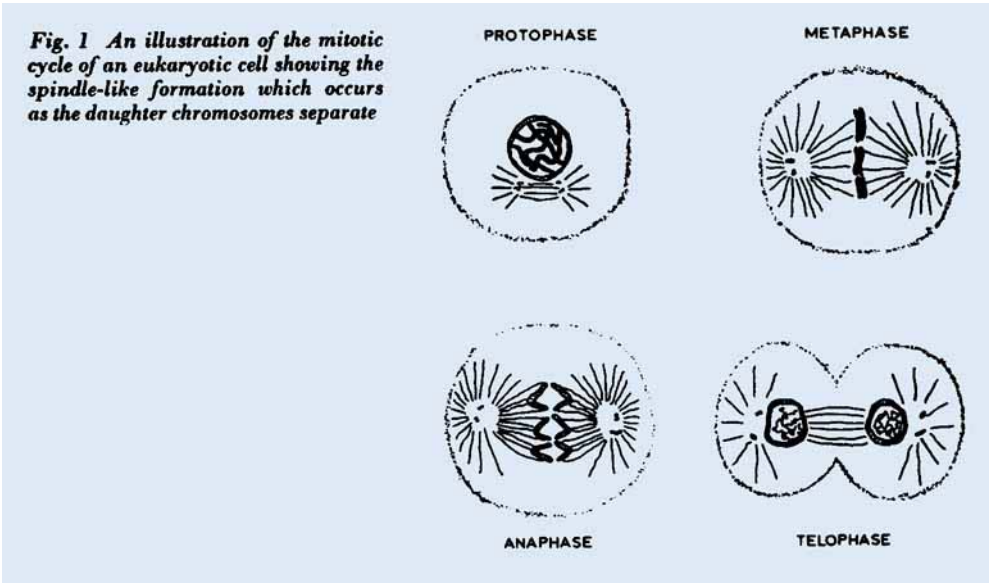

Fig. 1 An illustration of the mitotic cycle of an eukaryotic cell showing the spindle-like formation which occurs as the daughter chromosomes separate

the appearance of spindle cell formation during the mitotic cycle of cells, shown in Figure 1. These appeared to him to resemble lines of magnetic force such as is seen with iron filings round a bar magnet. Thus a study was initiated to see if an external electromagnetic field would influence cell division, and the setting up of these experiments involved two pieces of fortune. First a.c. current was passed through Escherichia coli bacteria in a growth chamber via a set of platinum electrodes on the assumption that platinum was inert in a biologic environment. Second, the bacteria were supported in a nutrient medium containing ammonium chloride as the nitrogenous source (C medium—NH_4Cl 2 g/l, Na_2HPO_4 6 g/l, KH_2PO_4 3 g/l, NaCl 3 g/l, $MgCl_2$ 0.01 g/l, Na_2SO_4 0.026 g/l). E. coli and prokaryotic cells in general do not show mitotic figures in division and were only being used to test the proper functioning of the equipment prior to using mammalian cells; this was another piece of fortune. Under the influence of the current bacteria underwent filamentous growth. Bacterial rods are normally some 2 to 5 microns in length and about 1 micron in diameter, however, the filamentous strands formed were up to some 300 times the usual length. Thus cell division was inhibited while cell growth was unaffected. Further tests showed that gram negative rods were most sensitive with gram positive much less so and spherical bacilli (cocci) unaffected.

Filamentation effects had previously been noted for physical agents such as UV light, osmotic pressure or temperature changes, transfer to an unaccustomed medium, and a few organic compounds including methylene blue and penicillin. A long series of control experiments showed that the current itself was not causing the filamentous growth, but it was causing some 10 ppm of platinum to dissolve electrolytically into the C medium from the platinum electrodes. The species formed during the electrolysis was identified as $[PtCl_6]^{2-}$, which is present in part as the ammonium salt in C medium. Fresh solutions of $(NH_4)_2[PtCl_6]$ are bacteriostatic and inhibit cell growth at these concentrations, approximately 10 ppm. Van Camp and co-workers noticed that aged solutions (2 to 3 days) were very effective in producing filaments at low platinum concentrations (3). Spectroscopic and ionophoretic studies both

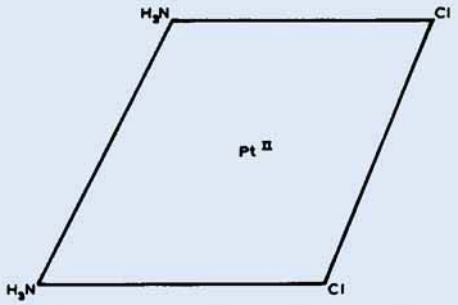

Fig. 2 The molecular structure of cisplatin, a simple co-ordination complex with platinum in the (II) oxidation state and adjacent (cis) ammonia and chloride ligands bound in a square planar configuration

confirmed the photochemical reaction:

$$[PtCl_6]^{2-} + nNH_4^+ \longrightarrow cis\text{-}[PtCl_{6-n}(NH_3)_n]^{(2-n)-} + nH^+ + nCl^-$$

which in the time period studied did not proceed much beyond the n=2 stage. The pentachloro species, $[PtCl_5(NH_3)]^-$, is neither an effective growth inhibitor nor cell division inhibitor, but as it readily converts to the neutral species in the presence of C medium and light it does appear to force filamentous growth. The neutral species *cis*-$[PtCl_4(NH_3)_2]$ is a potent inhibitor of cell division while having only a small inhibitory effect on the growth rate. Testing of synthesised *cis* and *trans* isomers confirmed that the *cis* species is biologically active while the *trans* isomer has relatively little effect on the cell growth processes. At the same time the corresponding *cis* and *trans* Pt^{II} species, $[PtCl_2(NH_3)_2]$, were tested and again only the *cis* compound caused filamentation. This is also likely to be formed in small quantities during the electrolytic and photochemical reactions due to reduction of *cis*-$[PtCl_4(NH_3)_2]$.

Bacterial tests on a variety of platinum amine species showed that neutral complexes as opposed to charged species tended to inhibit cell division and cause filamentation; *cis* configurations were active and *trans* inactive. Forming a filament was not a terminal event, on removal of the platinum complex from solution, or on transfer of the filaments to a normal medium suitable for growth, the filaments divide into normal bacteria. This appears to be a different form of filamentation from that caused by chemicals such as nitrogen mustards and penicillin where it is a terminal event.

Renshaw and Thomson (4) studied the distribution of platinum, from UV irradiated $(NH_4)_2[PtCl_6]$ containing *cis*-$[PtCl_4(NH_3)_2]$, in E. coli and two gram-positive bacteria B. cereus and S. aureus. In the latter case most of the platinum was bound to metabolic intermediates, whereas in E. coli it was distributed amongst the cytoplasmic proteins and nucleic acids. A clue to the mode of action was given by a comparison with the distribution of platinum from a fresh $(NH_4)_2[PtCl_6]$ solution, which is bacteriocidal, where nearly all the platinum was in the cytoplasmic protein and very little was associated with the nucleic acid.

The property of inhibiting cell division but not cell growth suggested that these compounds might have anti-tumour properties and this was emphasised by the fact that other anti-tumour agents, for example alkylating agents, actinomycin D, also caused elongation in certain bacteria. Initially four compounds, *cis*-$[PtCl_4(NH_3)_2]$, *cis*-$[PtCl_2(NH_3)_2]$, which is shown in Figure 2, $[PtCl_4(en)]$ and $[PtCl_2(en)]$ (where en is used to denote ethylenediammine), were tested against Sarcoma 180 in the ICR strain of mice and were found to be effective in inhibiting the tumour growth (1), leaving some animals tumour-free. As had been predicted by the bacteriological results, neither of the *trans* isomers of Pt^{II} and Pt^{IV} showed any appreciable activity. The two *cis* compounds were submitted to the U.S. National Cancer Institute and were screened against L. 1210 leukaemia in mice (1). They showed potent anti-tumour activity and effected several cures with single injections at the therapeutic dose of 8 mg per kg of body weight. Rosenberg and Van Camp went on to show that *cis*-$[PtCl_2(NH_3)_2]$ was capable of regressing large solid Sarcoma 180 tumours

(8 days old) in Swiss white mice (5). A single intraperitoneal dose of 8 mg per kg caused the complete regression of at least 60 per cent of the tumours. *Cis*-$[PtCl_2(NH_3)_2]$, now referred to in the pharmaceutical industry as cisplatin, appeared to be the more potent of the original compounds and has since been tested against a wide variety of transplanted animal tumours and has proved to have a wide spectrum of activity. It was not always particularly successful when compared with established drugs but fortunately, many clinicians and some researchers had become disenchanted with the predictive ability of these experimental, usually transplanted tumour screens and continued to show interest in compounds of less value against animal tumours providing that they also showed different or minimal toxicity for normal tissues. In the 1960s the importance of toxicity in the clinic had increased for two reasons. First, it was clear that no single agent was of lasting benefit and resistance developed quickly to all anti-tumour agents. Second, combinations of drugs were much more beneficial and might produce cures in some cases. The use of several drugs together was possible only if the toxicities were not additive, while it was essential that the therapeutic benefit must be at least additive. It was therefore of great interest to the clinician that cisplatin had only a minor toxic effect on bone marrow cells—a feature rare in the group of cytotoxic agents so far produced for cancer treatment; other examples include hormones and bleomycin.

Clinical Development

By 1973 early clinical studies were ready for publication and were reported at an international symposium held in Oxford on platinum co-ordination complexes in cancer chemotherapy (6). Eight clinical reports were given concerning the use of cisplatin in patients for whom no other treatment was available and from such studies the main concern was to define toxicity, to examine the pharmacology and to give guidance for dose and scheduling of drugs in any future therapeutic investigation. This early clinical work confirmed the toxic features predicted from studies on dogs and monkeys. The principal side effect was severe nausea and vomiting at doses greater than 5 to 10 mg/m^2, this dose relating to the body surface area. Major toxicities were kidney (renal) tubular damage, 8th nerve damage (hearing loss) and some bone marrow suppression, principally involving red cell production, leading to anaemia. Dose schedules were also defined and most workers believed that up to 100 mg/m^2 could be given in a single dose or 15 mg/m^2 daily for 5 days. However, almost all clinicians were extremely concerned about renal toxicity especially with repeated treatments. In Phase I studies therapeutic effectiveness is not sought, but for this drug several responses were seen, in particular, by Wallace and Higby in testicular tumours and by Wiltshaw in adenocarcinoma of the ovary. There were also reports of occasional responses in urinary tract cancer, lung cancer and tumours of the head and neck area.

Delegates went home from that conference with the impression that cisplatin was a potentially useful anti-cancer drug, but that kidney toxicity was a serious limitation of its usefulness, especially in long term treatment.

Further Phase I studies confirmed this impression and showed that at doses of 20 to 100 mg/m^2 symptoms of kidney toxicity such as increases in blood urea nitrogen and/or serum creatinine were to be expected in 32 per cent of patients. It was clear that this degree of toxicity was unacceptable but some clinicians took steps to overcome the problem. In particular Cvitkovic and his co-workers at the Memorial Sloan-Kettering Cancer Centre in New York pioneered the use of intravenous hydration with normal saline for some hours before and after cisplatin administration, and included mannitol to induce diuresis (7) (8). This was successful and quickly adopted by other clinicians both with and without the diuretic addition. Both methods were surprisingly effective and renal toxicity was reduced to around 5 to 10 per cent, and at

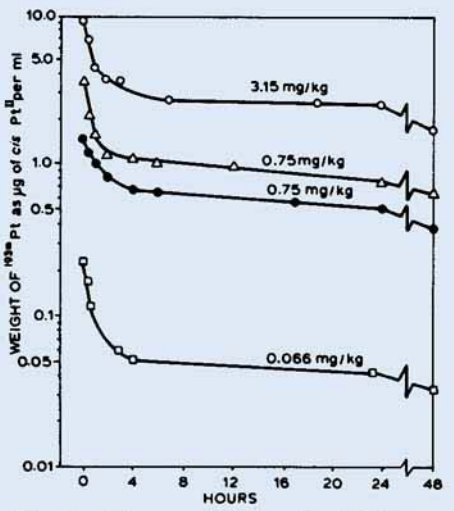

Fig. 3 The rate of removal of ^{193m}Pt, injected as cisplatin, from human blood plasma at different doses, as determined by R. C. DeConti, B. R. Toftness, R. C. Lange and W. A. Creasey* (Cancer Res., *1973*, **33**, *(6), 1310). Clearance occurs in a biphasic mode. The initial phase is fast and corresponds to the uptake of unbound platinum while the slow second phase involves platinum bound to blood constituents

doses below 50 mg/m² renal toxicity was rare even with repeated doses over one year at monthly intervals. Later the use of lower doses of cisplatin in combination therapy also helped to alleviate renal toxicity problems.

The next phase in the testing of a new anti-cancer compound involves its use in certain tumours with a view to documenting the number and quality of the response in each cancer type. These Phase II trials really got underway in 1975 when the renal problem had been reduced. Some of these studies on platinum complexes in cancer chemotherapy were reported at the next symposium held at the Wadley Institute of Molecular Medicine in Dallas. At that conference several relatively large scale trials confirmed the value of cisplatin in ovarian and testicular tumours, and also showed that responses could be obtained in squamous carcinomas of the head and neck areas, the bladder and the lung (9).

Squamous cell carcinomas have been relatively resistant tumours to treatment, either with drugs or radiotherapy, and any additional useful weapon against them is greatly to be welcomed. Also we were now entering the area of common tumours in man where benefit might be expected for large numbers of patients. Thus it was exciting to hear at this meeting that a large number of trials were being supported by the National Cancer Institute and that shortly we should know of the major areas of value of this compound in cancer management.

The proper use of anti-cancer agents usually takes many years to accomplish and some that have been in clinical practice for over 10 years are still being studied. The difficulty here is our lack of knowledge of the methods of entry of a drug into the human cancer cell in vivo and of the interactions of one drug upon another. In this regard animal and tissue culture studies have not been helpful since studies in animals have often shown that more therapeutic benefit could be obtained by giving a compound in a particular way, but this has not been confirmed by human therapeutic trials. Thus it is not surprising that the best method of giving cisplatin is still under discussion and it may well be that different schedules will be necessary for different tumour types. One other complication has arisen with the newer cytotoxic drugs and that is the reluctance of clinicians to study the agent fully on its own before embarking on therapeutic trials involving combinations of cytotoxic drugs (cytotoxic cocktails).

What then is the present position of cisplatin in cancer treatment? Where studies have been done in depth over several years its place is assured for some time to come and it seems likely that the drug will add to the total cure rate of these tumours. The tumours involved are testicular tumours and ovarian adenocarcinoma and cisplatin is now recommended as first line chemotherapy to be employed in established combination regimes

with other approved chemotherapeutic agents. For testicular cancers an established combination therapy consists of cisplatin, bleomycin and vinblastine sulphate. In ovarian cancers combinations with both adriamycin and chloroambucil have been successful.

Testicular Tumours

It has been known for some years that testicular tumour masses frequently regress following exposure to a variety of drugs, but with all single agents the regression is followed by a very rapid recurrence and the patient does not benefit.

In 1975 Samuels described a combination chemotherapy using high doses of vinblastine and bleomycin which produce good and sometimes lasting regressions in 75 per cent of cases (10). This treatment was a great step forward in the management of advanced disease since good regressions allowed further treatment with radio-therapy or surgery to produce complete apparent disappearance of tumour with the prospect of cures. However, the therapy was extremely toxic and a significant proportion of the young men died due to treatment. Variations of this treatment incorporating other drugs produced similar results. When cisplatin was incorporated into testicular tumour therapy together with vinblastine, bleomycin and, in some cases, adriamycin, the toxicity of the therapy was much reduced and deaths due to the drug combination were rare. In addition a number of studies have shown a complete regression rate of 60 to 75 per cent with most of the remaining cases showing partial regression, that is overall responses of between 85 and 100 per cent. If complete regression can be maintained for two years or more then cure is likely. As a result the management of testicular tumours has been dramatically altered. Perhaps an example is the best way to show what can now be achieved. A young man in his twenties attends the clinic with a testicular tumour and a large abdominal mass of metastatic disease. The tumour is producing excess quantities of alpha feto protein which is a marker for the overall amount of tumour in the body. Treatment with bleomycin, vinblastine and cisplatin is started, following surgical removal of the testicular mass. Over a 12 week period the abdominal tumour disappears and the alpha feto protein level falls to normal levels. At this point three methods of approach are possible. First, continuation with chemotherapy alone can be used but this is only rarely effective in producing long term disease-free periods or cures. A better approach in this case is either surgical removal of residual disease within the abdomen or radical radiotherapy to the areas of previous involvement. Using this combined approach to the elimination of tumour, even patients with lung and brain metastatic disease may be rendered tumour-free; Einhorn (11) and his colleagues are claiming 57 per cent of patients presenting with advanced tumours survive and remain disease-free more than two years after treatment.

Ovarian Adenocarcinoma

Ovarian carcinoma is the most fatal gynaecological malignancy and at present it is estimated that one in every hundred women in the U.S.A. will die of it. Unfortunately, the death rate is very high since more than 60 per cent of patients have advanced pelvic and abdominal tumour when first diagnosed. When the disease is advanced, referred to as stages III and IV, the median survival is of the order of 18 months and the 5 year survival about 10 per cent. Cytotoxic therapy has been used in advanced disease for more than 10 years, but although response rates have been high, usually around 50 per cent, the median period for remission when there is a measurable disease is only 9 to 12 months. In these tumours alkylating agents have been most useful and curiously there has been little evidence that combinations of drugs have improved therapeutic benefit. It is also rare to see second remissions after previous chemotherapy has failed. Wiltshaw (12) first showed that remissions could be seen with cisplatin in 26 per cent of cases of far advanced

ovarian disease following previous chemotherapy. Later she and Bruckner (13) independently produced 60 per cent overall remissions and 30 per cent complete regressions when cisplatin was used as first line treatment in combination with chlorambucil or adriamycin, respectively. The overall response rate was not significantly higher than with alkylating agents, but the complete regression rate was impressively high. Because of this high complete regression rate second operations have been possible in previously inoperable cases of advanced ovarian cancer. These second operations have made possible radical surgery for advanced disease in a significant proportion of cases (14), a situation not achieved by any other form of chemotherapy on this tumour. In about half of the operated cases no evidence of residual tumour has been found on histological examination of the removed previously involved tissues. All this is encouraging, for the goal is cures of ovarian cancer, but long term results are not yet available.

Other Tumours

Preliminary encouraging results have been reported in bladder cancer from several centres. This tumour is very resistant to chemotherapeutic attack with all known agents so that partial regressions in about 35 per cent of cases using cisplatin as a single agent is not as depressing as it might appear. Similarly, in advanced carcinoma of the head and neck an overall response rate of 32 per cent has been seen in several studies. The role of cisplatin in the treatment of lung cancer is less clear, but good responses have been seen in adenocarcinoma at this site.

One tumour where chemotherapy may improve survival in the future and where the cure rate has remained around 20 per cent for the last 50 years, is osteosarcoma. This tumour is seen only rarely, but usually occurs in young people. Chemotherapy with very high doses of methotrexate or adriamycin were reported to reduce the very high tendency of the tumour to spread (metastasise) immediately after surgery or radiotherapy, if the drugs were given soon after diagnosis. Unfortunately, while early results were very exciting metastases do appear in most patients, although the chemotherapy may delay their growth. The search for other effective drugs for this disease is therefore particularly important. So far only a few patients have been treated with cisplatin, but partial regressions have occurred, when other chemotherapy has failed, in about 45 per cent of cases. So this drug will be a good candidate for use in early stage disease, either as a single agent or combined with other drugs.

Preliminary studies also suggest that a proportion of remissions can be produced by cisplatin in prostatic cancer, melanoma, lymphoma and some childhood tumours.

Conversely some tumours seem to be refractory to treatment with cisplatin and these include breast cancer and gastrointestinal tumours. The reasons for sensitivity of one tumour to the drug as opposed to resistance of another is entirely unknown, but this ignorance is common to a lot of chemotherapeutic agents. Many other tumours remain without adequate testing, but one can state with confidence that the list of tumours responsive to cisplatin is not yet complete.

Pharmacokinetics

Animal studies on the distribution of cisplatin showed that the highest concentrations were in the excretory organs, the ovary and the uterus while the lowest concentrations were in the brain (15, 16, 17). Human studies with radioactive platinum, ^{193m}Pt, showed high uptake in the kidneys, liver and intestine (18). Brain scans and brain tissue samples confirmed the animal results and suggested poor penetration of the drug into the central nervous system (19). Blood levels of ^{193m}Pt decayed in a biphasic manner with an initial half-life of 25 to 49 minutes and a terminal half-life of 58 to 73 hours (20), see Figure 3.

Platinum was rapidly cleared from the blood after initial injection with more than 90 per cent of the radioactive platinum in the

post distribution phase being protein bound (20). A recent study using an atomic absorption ultrafiltration technique indicated that no unbound platinum was present seven hours after administration (21). This is important as only unbound *cis*-$[Pt(NH_3)_2Cl_2]$ may be anti-tumour active.

Platinum is largely excreted via urine although urinary excretion only represents 27 to 43 per cent of the administered dose over the first five days, the remainder being excreted slowly over a long period (20, 22).

Cis-$[Pt(NH_3)_2Cl_2]$ is produced in bulk quantities in a governmentally approved clean room at Matthey Bishop Inc. in the U.S.A. Several purification steps are involved to ensure a pharmaceutical quality product. The bulk product is formulated by Bristol-Myers Co Ltd. by freeze drying a solution of the drug containing saline and mannitol to make the preparation isotonic. The vials, shown in Figure 4, are reconstituted with water when required for intravenous use.

The Future of Cisplatin in Cancer Treatment

In December 1978 *cis*-$[PtCl_2(NH_3)_2]$ received U.S. Food and Drug Authority approval as an anti-cancer drug for testicular and ovarian cancers. The formulated drug containing sodium chloride and mannitol is marketed under the name of Platinol™. The bulk *cis*-$[PtCl_2(NH_3)_2]$ is referred to as cisplatin. In the U.K. the drug is known as Neoplatin™, and this received approval in March 1979 while applications are pending in many other countries; a number of European approvals are expected during 1979.

While the strong position of cisplatin in the management of two tumours, namely testis and ovary is certain, its position has yet to be established in other diseases. The drug has several advantages over many other cytotoxic drugs namely that it is relatively non-toxic to the bone marrow and gastrointestinal tract and does not produce hair loss (alopecia). Major disadvantages are renal toxicity, now limited to higher doses only, and some peripheral neurological toxicity, both of which may be life threatening without suitable supporting treatment. Even if these dangers were entirely overcome it would still be extremely unpleasant therapy for patients because of its accompanying nausea and vomiting, although this also occurs with some other types of cancer therapy. Despite these disadvantages the author has no doubt that it will benefit patients in the future and will be widely used in cancer treatment for many years to come.

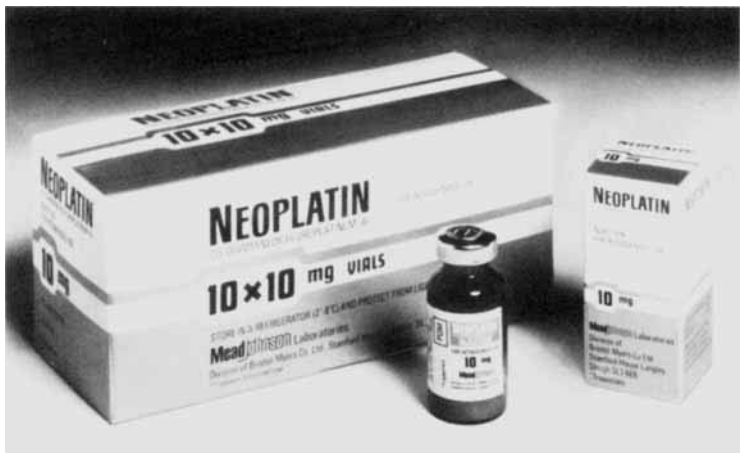

Fig. 4 Cisplatin is being marketed in the United Kingdom under the name Neoplatin and in the United States as Platinol. It is available on prescription in vials containing 10 mg lyophilised cis-*diamminedichloroplatinum for intravenous injection*

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A Symposium on Cancer Therapy

Following the governmental approval of cisplatin for the treatment of certain types of cancer a symposium for the medical profession was organised in London by the manufacturers, the Mead Johnson division of the Bristol-Myers Company. The chair was taken by Dr. Eve Wiltshaw, Royal Marsden Hospital, London, who introduced Dr. M. J. Cleare of the Johnson Matthey Research Centre, the author of the opening paper on the development of platinum anti-cancer agents.

After describing the initial experiments which led to the identification of anti-cancer activity in platinum compounds, Dr. Cleare detailed the techniques of quality control exercised in the preparation of the first platinum drug, cisplatin. These included the examination of the infra-red and ultra-violet spectra and the use of thin-layer chromatography and of high performance liquid chromatography. These methods of quality control of the first metal co-ordination compound to find application in therapy were essentially the same as those employed with organic preparations.

Having emphasised the pronounced and prolonged effect of cisplatin on DNA synthesis, Dr. Cleare described the screening of several hundred platinum compounds for potential usefulness. Research on these compounds was directed towards finding those giving less toxicity and with a wider spectrum of anti-tumour properties. It was indicated that success, particularly with regard to toxicity, seemed quite probable.

There followed several papers reporting on the degree of success so far established with cisplatin. Dr. R. B. Golbey of the Memorial Sloan Kettering Cancer Center, New York, dealt with cisplatin in the management of testicular cancer and Mr. G. H. Barker, Registrar at the Royal Marsden Hospital, with the treatment of ovarian cancer. Further reports were presented by Dr. R. T. D. Oliver of the Institute of Urology, London, and by Dr. R. E. Wittes, also from the Memorial Sloan Kettering Cancer Center.

A lengthy general discussion on the practical aspects of patient management during cisplatinum therapy indicated a high degree of interest among the medical profession.