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Metal Compounds in Therapy and Diagnosis

Michael J. Abrams and Barry A. Murrer

There is increasing interest in the use of metal-containing compounds in medicine. This review describes several therapeutic applications, such as the use of platinum complexes in cancer chemotherapy, gold compounds in the treatment of arthritis, gallium in hypercalcemia, bismuth in anti-ulcer medication, and sodium nitroprusside in hypertension. The use of metal radionuclides in diagnosis and radiotherapy and the role of paramagnetic metal complexes as contrast agents in magnetic resonance imaging are also discussed.

Although most modern pharmaceuticals are purely organic compounds, the use of metal-containing agents for both therapy and diagnosis is of increasing interest. Perhaps it is not surprising that because of their unusual properties or value, or both, metals and metal compounds (such as preparations of iron, zinc, copper, gold, mercury, and bismuth) were used in medical practice from antiquity through the middle ages (*1*). In fact, the first modern chemotherapeutic agent was Erlich's arsphenamine, an organoarsenic compound. This drug, sold under the name Salvarsan, was introduced in 1910 and was the first effective treatment for syphilis (*2*).

The diverse therapeutic uses of metal compounds discussed in this article reflect the fact that most of these applications were discovered serendipitously. The discovery of diagnostic and radiotherapeutic agents containing metals has been the result of a somewhat more rational procedure in that specific chemistry was developed to take advantage of some physical characteristic of the metal atom such as radioactive decay or paramagnetism.

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Therapeutic Applications of Metal Compounds

Platinum antitumor drugs. The serendipitous aspect of inorganic drug research is nowhere better illustrated than in the discovery of platinum anticancer drugs. The observation in 1965 by Rosenberg (*3*) of the inhibition of bacterial division by cisplatin (Fig. 1) formed during electrolysis experiments with platinum electrodes in nutrient media led to the antiproliferative effects of the compound being applied to therapy of human tumors, and today platinum drugs are among the most active and widely used clinical agents for the treatment of advanced cancer. In testicular cancer, the addition of platinum drugs to treatment regimes has led to a dramatic increase in survival rate: Before cisplatin was available, only about 5% of patients were cured. Today 80 to 90% of patients can expect long-term disease-free survival. Platinum drugs also have clinical utility in the treatment of ovarian, bladder, head and neck, and small-cell lung cancer, and combination with other agents in these types of disease is still being explored. Proceedings of a recent international symposium summarize current developments (*4*).

The ultimate target for platinum antitumor drugs is DNA. The interactions of these drugs with DNA have been extensively reviewed (*5*), and it would appear that the Pt-GG intrastrand cross-link is the critical lesion that leads to cytotoxicity. Recently, proteins that bind to the Pt-DNA lesion have been identified that are homologous to the HMG1 protein, and indeed HMG1 itself can bind to the damaged area (*6*). Research continues to provide insight into the relevance of this discovery, which could lead to more specific and more active platinum drugs.

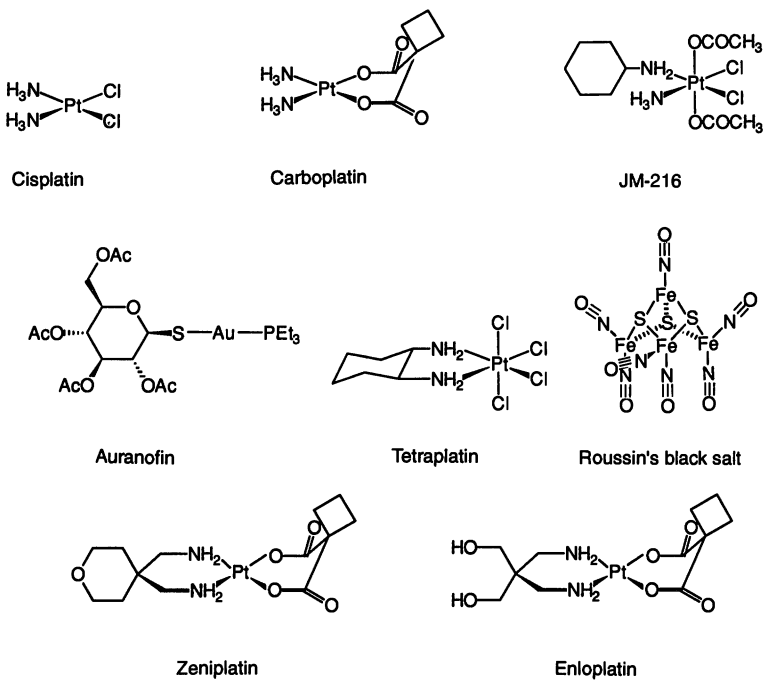
During early clinical trials it was clear that although cisplatin was an active antitumor agent, it was also extremely toxic; nephrotoxicity is now less of a problem, as intravenous hydration is usually given with a course of cisplatin. Nausea and vomiting are substantially controlled by the new generation of serotonin antagonists, leaving neurotoxicity as the major dose-limiting effect. An alternative approach has been to control the toxicities of cisplatin by design of a "second generation" drug. Antitumor testing of a series of analogs and kinetic studies on the loss of their leaving groups (chloride in the case of cisplatin) showed that antitumor activity was retained across a range of reactivity, but that the toxic side effects were directly related to the rate of ligand loss. This discovery led to preparation of a series of substituted malonate derivatives with reduced reactivity as compared with cisplatin, from which carbo-

platin (Fig. 1) was selected for clinical evaluation (*7*). Preclinical predictions were entirely confirmed in these studies: no nephrotoxicity was observed, nausea and vomiting were much reduced, and the dose-limiting toxicity effect was thrombocytopenia. Randomized phase III trials established equivalent antitumor activity to cisplatin, and carboplatin was approved for use in the United Kingdom in 1984 and subsequently elsewhere.

It is often possible to give carboplatin on an outpatient basis, as intravenous hydration is no longer required. A further objective in treatment of cancer would be development of a drug capable of oral administration, as neither cisplatin nor carboplatin is effective when given by mouth. Recently a new class of Pt(IV) dicarboxylate complexes has been described, of which JM216 (Fig. 1) is an example, where the lipophilic nature of the compounds, coupled with the inertness to substitution of the Pt(IV) center, allows good absorption. After absorption, these compounds are reduced to Pt(II) species that can bind to DNA in a manner similar to cisplatin (*8*). Preclinical studies show that these compounds are effective antitumor agents when given orally to nude mice bearing human tumor xenografts (*9*), and JM216 is currently in clinical trials in the United Kingdom.

About 10 other platinum analogs are currently, or have recently been, in clinical trials in various countries (*10*). With the exception of tetraplatin (Fig. 1), all are Pt(II) complexes with leaving groups of reduced lability as compared with cisplatin; indeed, several have the same cyclobutane-1,1-dicarboxylate ligand as carboplatin. It is not always the case that such compounds have the same toxicity profile as carboplatin, however, as both zeniplatin [2,2-bis-(aminomethyl)-1,3-propanediol-*N,N'*)(cyclobutane-1,1-dicarboxylato-*O,O'*) platinum-(II)] (Fig. 1) and enloplatin [cyclobutane-1,1-dicarboxylato-*O,O'*)(tetrahydro-4*H*-pyran-4,4-dimethanamine-*N,N'*) platinum(II)] (Fig. 1) caused nephrotoxicity during phase I trials. Many of these compounds, and tetraplatin in particular, were selected on the basis of their activity against murine tumors that had become resistant to cisplatin. Such resistance is a major problem in the clinic, as many patients initially respond and then relapse; however, the relevance of murine models is controversial. Recently a much better understanding has been developed of how tumor cells become resistant to platinum drugs (*11*), and chemical efforts are under way to design new compounds that circumvent acquired resistance.

Gold compounds in arthritis. Although gold compounds have been used in therapy since the 1920s, initially against tuberculosis and later against arthritis, the fate of the administered gold and the mechanism of action are still not well understood. The older drugs such as myochrisin (sodium gold thiomalate) and solganol (sodium gold thioglucose) are mixtures of polymers that are not light stable. Modern analytical techniques have done much to elucidate the composition of these mixtures, and it is clear that in vivo these injectable compounds break up very quickly, and gold becomes bound to thiol groups or blood proteins and is extensively distributed around the body. Beneficial results are usually seen only after long-term treatment, and clearance of gold is slow. Although there are undoubtedly cases where treatment with gold compounds is beneficial, there are concerns over the empirical nature of the treatment and its toxicity. There have been calls to discontinue the use of gold in treatment of rheumatoid arthritis (*12*). Inorganic chemists have resolved some of the problems associated with the injectable gold drugs by design of Auranofin [(1-thio-β-D-glucopyranose 2,3,4,6-tetracetato-*S*)(triethylphosphine)gold (I)] (Fig. 1), which is a single, well-defined compound. The ligands used impart sufficient stability and lipophilicity to the drug to allow oral administration, although on absorption the acetate groups are hydrolyzed, and eventually the resulting thioglucose ligand is lost and the triethylphosphine ligand is oxidized to triethylphosphine oxide (*13*). It seems likely that the final range of gold protein thiol adducts is the same as those arising from treatment with injectable gold compounds, although blood gold concentrations may be lower. As an additional complication to treatment with any antiarthritic gold compound, blood gold concentrations have no correlation with clinical response or toxicity. There has been much work aimed at understanding the mechanism of action of gold in arthritis, much of it pointing toward gold blocking a critical thiol group. Results discussed in a recent article (*14*) suggest that gold may inhibit the production of reactive oxygen species such as superoxide ion and hydroxyl and peroxyl radicals in cell membranes and plasma but enhance the site-specific generation of such species within target cells. A better understanding of the speciation of gold in vivo and



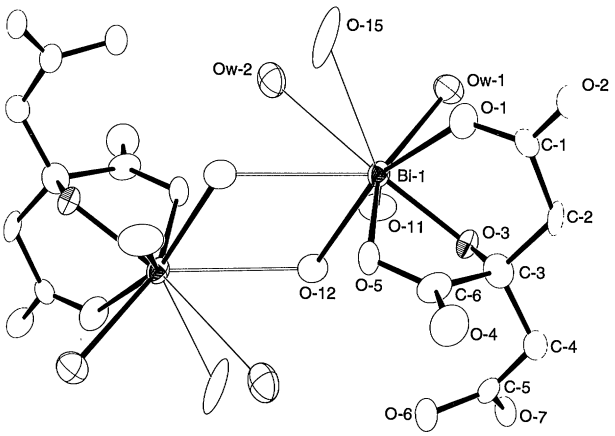


Fig. 1 (left). Chemical structures of some metal-containing therapeutic compounds described in the text. **Fig. 2 (right).** Representative section of the three-dimensional network in the crystal structure of potassium bismuth citrate $KBi(C_6H_4O_7)_3 \cdot 3H_2O$. [Reprinted from (*28*) with permission, American Chemical Society]

a more precise knowledge of its molecular target would allow a more specific and less toxic agent to be designed. The problems in gaining the required level of understanding are, however, immense, and it is likely that less empirical forms of treatment for rheumatoid arthritis will eventually lead to the demise of chrysotherapy.

Gallium and hypercalcemia. Gallium nitrate [$Ga(NO_3)_3$] has recently been approved in the United States for the treatment of hypercalcemia of malignancy. This use is based on experience gained from the clinical use of gallium compounds dating back to the 1960s when the radioisotope ^{67}Ga was used in diagnostic bone scans. During these procedures it was noted that the isotope also accumulated in certain non-osseus malignancies (*15*), particularly lymphomas, and it is still used for imaging tumors. The carrier-free isotope is supplied in a solution containing high levels of citrate to suppress hydrolysis to $Ga(OH)_3$. When the gallium compound is injected into a patient, blood levels are between 1 and 100 pmol. At these concentrations, essentially all of the radioisotope is bound to transferrin (*16*), and it is the labeled transferrin that is taken up by, and accumulates in, the tumor. These early tumor localization studies, combined with renewed interest in metal-based antitumor agents after the discovery of the activity of cisplatin, led to the testing of nonradioactive $Ga(NO_3)_3$ for antitumor activity in rodent models by workers at the National Cancer Institute (*17*). They found that the salt showed good activity in a number of transplantable solid rodent tumor models but no activity in the P388 and L1210 murine leukemias. Although the doses used (up to 60 mg kg^{-1} day^{-1}) were very much greater than those used for diagnostic imaging, it is still likely that gallium bound to transferrin is an important species: addition of transferrin to tumor cells in vitro enhanced the cytotoxicity of gallium nitrate, whereas on addition of iron(III) sulfate it was reduced (*18*). The fate of the gallium transferrin complex inside the tumor cell and the mechanism of action are still not clear; there appears to be no specific organelle accumulation, and although gallium ions inhibit DNA- and RNA-dependent polymerases, this inhibition is incomplete at concentrations well above those attained in vivo. An alternative mechanism is suggested by the observation that treatment of tumor cells with gallium ions decreases calcium uptake, possibly through inhibition of the Ca–adenosine triphosphatase pump (*19*).

In view of the promising antitumor activity in rodent models, human studies were initiated, and early clinical trials with $Ga(NO_3)_3$ have been summarized (*20*). Definite single-agent activity was demonstrated in patients with Hodgkin's and non-Hodgkin's lymphoma, although there was no clear correlation between response to $Ga(NO_3)_3$ therapy and ^{67}Ga uptake by the patient's tumor during imaging procedures. When given $Ga(NO_3)_3$ as a 7-day continuous infusion in an attempt to increase the therapeutic index of the compound, two-thirds of the patients developed hypocalcemia (*21*). This observation suggested a role for $Ga(NO_3)_3$ in the treatment of cancer-related hypercalcemia. This is a very common problem in the management of patients with advanced cancer where accelerated bone resorption takes place, often precipitously, leading to release of skeletal calcium that overwhelms the main excretory pathway through the kidneys and leads to dehydration, stupor, and coma. Clinical trials in hypercalcemic patients quickly established that the compound was safe and effective in restoring calcium levels to normal (*22*). In vitro calcium loss from bone is inhibited directly. The mechanism is unclear, but bone calcium levels are increased and x-ray diffraction studies of hydroxyapatite from bone of treated rats show a difference in crystallite size and perfection over untreated controls (*23*).

Bismuth compounds in peptic ulcer disease. Bismuth compounds have been used in treatment of gastrointestinal disorders for about two centuries, but there has recently been an increased interest in their mode of action and in their structural characterization. This work was prompted in 1982 by the discovery of a Gram-negative bacterium from the gastric mucosa of patients suffering from gastritis (*24*). Originally named *Campylobacter pyloridis*, then C. *pylori*, the accepted name is now *Helicobacter pylori*. It seems that *H. pylori* is associated with chronic gastritis, which then predisposes the patient toward peptic ulcer formation and duodenal inflammation. Antacids based on bismuth have been shown to promote healing of peptic ulcers, and this effect has been ascribed in part to their selective antibacterial action. The compound that has been most studied is "colloidal bismuth subcitrate" (CBS), sold as De-Nol, and modes of action have been reviewed (*25*). This compound exerts a direct antimicrobial effect against *H. pylori* in vitro (minimum inhibitory concentration 4 to 25 μg/ml), and treated bacteria show deposits of bismuth on their surface and internally, although the ultimate target leading to the inhibition is not yet known. The chemical properties of CBS also contribute to its antiulcer effect: the initial colloidal solution of the material precipitates in the acidic environment of the stomach as bismuth oxychloride and bismuth citrate, and it has been estimated that about 90% of this precipitation occurs in the ulcer craters of gastric ulcer patients. Surrounding normal mucosal tissue is essentially unaffected. The protective coating so formed may prevent back-diffusion of H^+ and hence promote reepithelialization. There is also evidence that CBS promotes the ability of the gastric mucosa to produce prostaglandin E_2, which could lead to protection against noxious substances.

Colloidal bismuth subcitrate is now very widely used clinically in the treatment of peptic ulcer disease (*26*). Randomized trials have established similar efficacy to the H_2-antagonists cimetidine and ranitidine, and there appears to be less of a tendency toward relapse with CBS treatment. Whether this is due to eradication of *H. pylori* remains controversial.

The structure of CBS has only recently been investigated: the approximate formula by analysis is often given as $K_3(NH_4)_2Bi_6O_3(OH)_5(Hcit)_4$. By variation of the pH and ratios of initial reactants, five different bismuth citrate complexes have been isolated and characterized (*27*). X-ray crystal structures have been obtained for $K_{4.75}(NH_4)_{0.25}[Bi_2(cit)_2](H_2O)_{13}$ and $(NH_4)_4[Bi(cit)(Hcit)(H_2O)_2]H_2O$. The structure of $K[Bi(cit)](H_2O)_3$, which crystallizes from solutions of CBS at low temperatures, has also been determined (*28*). A section of the three-dimensional network is shown in Fig. 2. Both the high coordination number (eight) for bismuth and the aggregation of $[Bi(cit)]^-$ subunits to form channels could account for the high solubility of the compound in water. The covalent bonds between citrate alkoxide groups and bismuth may confer extra stability on bismuth citrate subunits in gastric juices, which allows selective precipitation in ulcers: other bismuth compounds such as "basic bismuth salicylate" do not survive in the stomach intact and do not form protective coatings. There is still much to be understood about how the structure of CBS is responsible for its activity, but these studies represent a sound foundation. It may be possible to design new bismuth compounds with additional advantages; indeed, clinical studies have recently been carried out in the United Kingdom with GR122311X, a compound formed by reaction of bismuth citrate with the H_2-receptor antagonist ranitidine, so that the gastric antisecretory activity of ranitidine and the antibacterial effects of bismuth can be combined in one treatment. It appears so far that bismuth absorption is low and that the compound has similar acidity-suppressing properties to ranitidine hydrochloride (*29*).

Sodium nitroprusside and nitric oxide. Sodium nitroprusside {[SNP, $Na_2[Fe(CN)_5NO]$, sodium pentacyanonitrosylferrate(II)]} has been used since the 1950s in the treatment of hypertensive emergencies and during surgery on major blood vessels. Infusion gives rise to rapid vascular muscle relax-

ation, leading to a drop in blood pressure, which can be titrated against SNP concentration. On cessation of the infusion, blood pressure rapidly returns to normal. The drug is commonly described as a nitrovasodilator, along with the widely used organic nitrites and nitrates such as amyl nitrite, isosorbide-dinitrate, and glyceryl trinitrate. Although there are differences in their behavior in vivo (organic nitrates induce tolerance on repeated treatment, whereas SNP does not), it has recently become apparent that all of these compounds act at the same target, namely, they activate guanylate cyclase by nitric oxide, which is formed spontaneously, or by metabolism of the nitrovasodilator. It was known in 1977 that nitric oxide activates guanylate cyclase in vitro (*30*), but the true biological significance of this molecule has only been revealed in recent years, principally by Moncada's group at Wellcome, who demonstrated in 1987 the enzymic formation of nitric oxide from arginine in vascular endothelial cells and its equivalence to the so-called endothelium-derived relaxing factor EDRF. Nitric oxide is also essential in platelet aggregation and neurotransmission and is an important effector molecule produced in immune reactions. The biological roles of nitric oxide have been comprehensively reviewed (*31*).

The exact mechanism of conversion of SNP to NO is still not clear. It is often claimed that NO is released spontaneously, but in aqueous solution in the absence of light it is stable for at least 6 months (*32*). On photolysis NO is released, but this is unlikely in vivo. Recent studies of bovine blood vessel extracts have found proteins capable of releasing NO from SNP (*33, 34*). A deeper understanding of the generation of NO and the chemistry of inorganic nitrosyl compounds may lead to more effective nitrovasodilators; one interesting example is Roussin's black [heptanitrosyl-tri-μ3-thioxotetraferrate(1-)] (Fig. 1), which in a perfused rat tail artery model of vasodilation localizes in endothelial cells and slowly releases NO, giving rise to a sustained vasodilation (*35*). Of possibly even greater interest is the use of metal compounds to intervene in other physiological processes mediated by nitric oxide; as our understanding increases, we can expect major new therapeutic advances on the basis of nitric oxide chemistry.

Metal Compounds as Diagnostic and Radiotherapeutic Agents

In diagnostic nuclear medicine, a radiopharmaceutical containing a nuclide that emits γ radiation is administered to a patient and the resulting distribution of radioactivity is imaged with a γ-detecting camera. Nuclear medicine procedures are very useful in measuring biological function, and a wide variety of radiopharmaceutical agents are available to assist in the diagnosis of many medical problems, such as cardiovascular, bone, kidney, and liver disease, infection, and cancer. The most commonly used radionuclide (more than 90% of all studies) is technetium-99m (^{99m}Tc) (*36*). The preeminence of ^{99m}Tc is based in part on its favorable physical characteristics: it emits a single 140-keV γ photon, which is well suited for detection by a gamma camera, without significant radiotoxic α or β emissions. Its 6-hour half-life provides sufficient time for most imaging studies without exposing the patient to excessive radiation. Also, technetium as the pertechnetate ion TcO_4^- can be produced in a radionuclide generator, which contributes to its wide availability and low cost. These considerations left radiopharmaceutical scientists with the task of devising useful radiodiagnostic agents based on an element that was largely unavailable on Earth before the discovery of nuclear fission. Technetium is a congener of manganese, and its rich coordination chemistry has been explored in great detail in recent years (*37*). A number of useful technetium radiopharmaceuticals, however, were discovered in the 1970s despite a lack of knowledge about their chemical structure. In this work, generator eluent containing $^{99m}TcO_4^-$ was mixed with a reductant (commonly stannous ion) and a complexing agent. The biodistribution of the resulting preparation was then evaluated in animals. In this manner, agents for bone scanning (Tc-diphosphonates), kidney imaging (Tc-DTPA and Tc-glucoheptonate), and for measuring hepatobiliary function (Tc-HIDA) were developed (*38*).

Many of these preparations contain technetium complexes (and in some cases, mixtures of complexes) of unknown chemical structure and are still widely used in the practice of clinical nuclear medicine. As technetium chemistry became more defined in the 1980s, new agents of known chemical structure were introduced. These include Tc-MIBI (Cardiolite), and $TcCl(CDO)_3$-MeB (Cardiotec) for evaluating myocardial perfusion, Tc-HMPAO (Ceretec) and Tc-ECD (Neurolite) for cerebral perfusion, and Tc-MAG_3 (TechneScan MAG_3) for kidney function. The structures of these complexes are shown in Fig. 3 (*36, 39*). An example of the clinical information obtainable with a radiopharmaceutical is shown in Fig. 4, which compares Neurolite SPECT (single-photon emission computerized tomography) imaging with conventional CT in the evaluation of stroke.

The development of new technetium-based radiopharmaceuticals to probe more subtle and complex biochemical processes poses a challenging problem. Unlike the

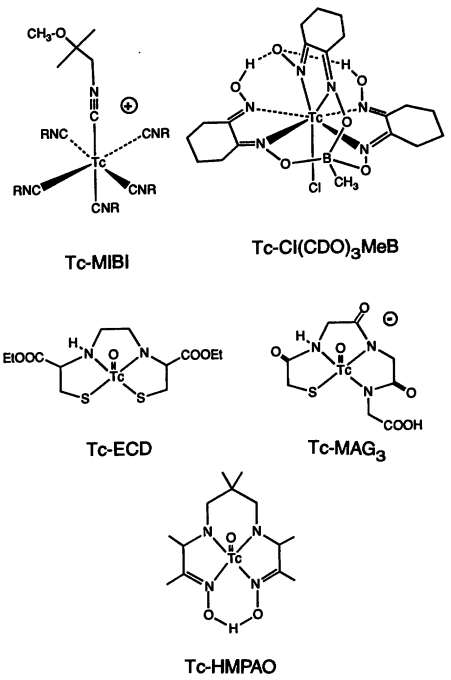


Fig. 3. Some technetium radiopharmaceuticals of known chemical structure.

radiohalogens (such as ^{18}F and ^{123}I), which can be readily incorporated into active metabolic substates (such as [^{18}F]deoxyglucose), the chemistry of technetium, a transition metal, does not readily lend itself to such treatment. Recent efforts to circumvent this problem include the preparation of technetium-labeled progestins for the imaging of steroid receptor–positive breast tumors and technetium-labeled nitroimidazoles for hypoxia imaging (*40, 41*).

Another approach for obtaining biological specificity in metal-based imaging agents is to exploit the targeting properties of immunological molecules such as monoclonal antibodies. A stable coordination site for the metal ion must be provided that is sufficiently removed from the antigen binding site of the antibody to prevent loss of the antibody's immunoreactivity. A compound of this type, OncoScint CR/OV, a monoclonal immunoglobulin G (B72.3) labeled with ^{111}In, was approved at the end of 1992 by the Food and Drug Administration (FDA) for the evaluation of colorectal and ovarian cancer (*42*).

If radionuclides with α or energetic β emissions can be targeted to disease sites, radiotherapeutic agents can be obtained. Sufficient radioactivity must be deposited in the target tissue to kill the desired cells while the uptake in nontarget tissues is kept to a minimum. In several cases targeting was established with the use of an imaging isotope, and the chemistry was adapted to a therapeutic nuclide. For example, the ability of ^{99m}Tc diphosphonates to accumulate in the skeletal metastases of cancer patients

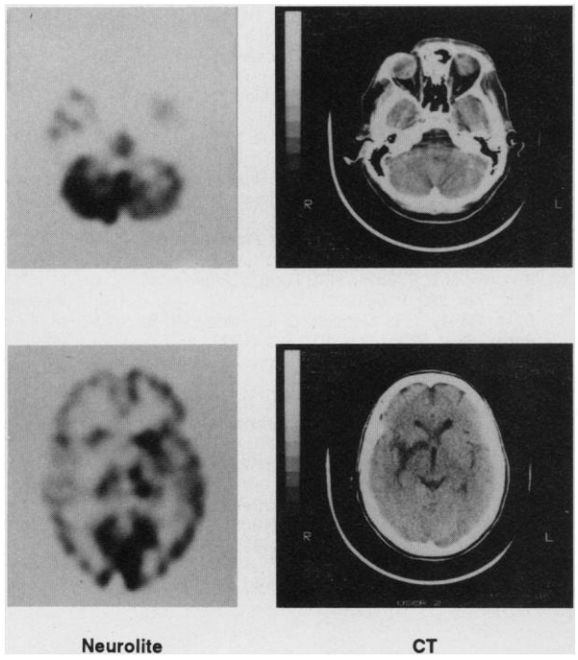


Fig. 4. Tomographic brain images of a stroke patient. Neurolite SPECT brain perfusion images on the left were obtained 15 days after stroke, and CT images on the right were obtained 3 days after stroke. Note the decrease in perfusion in the right frontal, partial-temporal, and subcortical regions that correspond to a smaller CT lesion. In contrast, the left cerebellar hypoperfusion (crossed cerebellar diaschisis) was observed in the presence of a normal cerebellar CT. (Imaging studies with permission from Hellman and Tikofsky, Section of Nuclear Medicine, Medical College of Wisconsin.)

was established in the 1970s (*43*). These agents presumably function by exploiting the affinity of the diphosphonate group for the hydroxyapatite structure of the bone with the preference for metastatic lesions, which reflects a difference in relative metabolism (*44*). By incorporation of the appropriate β-emitting isotopes into diphosphonate complexes, agents for the palliation of bone cancer pain have been prepared such as ^{186}Re-HEDP (hydroxyethylidene diphosphonate) and ^{153}Sm EDTMP (ethylenediaminetetramethylene-phosphonate) (*45, 46*). Another bone-seeking radiopharmaceutical, $^{89}SrCl_2$ (Metastron), has been approved in some countries for the treatment of skeletal metastases (*47*). There is also continued interest in the use of monoclonal antibodies to deliver cytotoxic β-emitters (such as ^{90}Y) and α-emitters (such as ^{212}Bi) to tumors (*48, 49*).

Another physical property of metal ions of great interest to medicine is paramagnetism. Magnetic resonance imaging (MRI) is an important diagnostic tool that exploits the differences in relaxation rates of water protons in different tissues, translating these differences into three-dimensional anatomic information. Paramagnetic metal complexes can shorten proton relaxation times and, depending on their biodistribution, provide improved tissue contrast when administered in vivo (*50*). The metal ions currently favored for this application are Gd^{3+}, Fe^{3+}, and Mn^{2+}. Coordination complexes used as MRI contrast agents must have high in vivo stability to prevent the release of toxic metal ions (such as Gd^{3+}), yet must also have open coordination sites for rapidly exchanging water ligands in order to enhance proton relaxation (*51*). There are currently two FDA-approved gadolinium-based MRI contrast agents, Magnevist (the Gd complex of diethylene-triaminepentaacetic acid) and ProHance [the Gd complex of 1,4,7-triscarboxymethyl-10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane] (*52*). These compounds are injected intravenously and are confined to extracellular space. Their major clinical application is in imaging of the central nervous system. The use of an MRI contrast agent to provide clinically useful information is shown in Fig. 5. There is currently great interest in identifying more organ-specific agents, particularly for the hepatobiliary system (*53*).

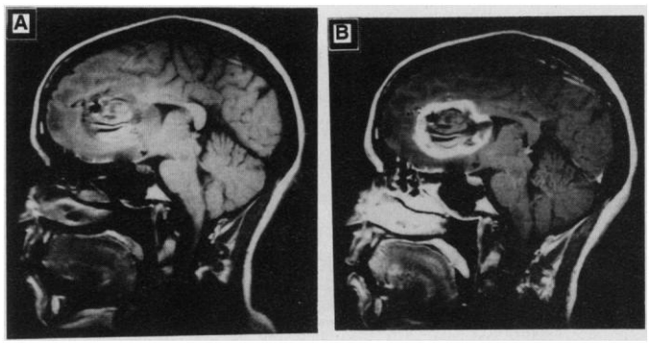


Fig. 5. Sagittal slices (weighted by time constant T_1) (**A**) before and (**B**) after intravenous administration of ProHance (0.1 mmol/kg). The enhanced area indicates a defect in the blood-brain barrier.

Prospects for the Future

If this review has seemed like a disjointed tour of the periodic table, then that accurately reflects the current state of medicinal inorganic chemistry. There are many important applications but few principles tying the field together. Further, if metal chemistry is to have a continuing role in the discovery of new drugs, attempts must be made to use the properties of metal compounds in different ways. For example, the Lewis acidity of lanthanide ions may be useful in the design of complexes to catalyze the hydrolysis of messenger RNA (*54*). Conjugates of such complexes to oligonucleotides might improve the potency of antisense drugs. Perhaps the rich oxidation-reduction chemistry of the transition metals may be useful in the design of drugs to protect tissue from oxidative damage.

Lastly, it must be appreciated that whereas this review has emphasized the medicinal role of administering metal containing compounds, there exists the somewhat larger realm of drugs that modulate the biochemistry of endogenous metals. For example, captopril, an important drug for the control of hypertension, is a sulfhydryl-containing compound that inhibits the Zn^{2+} hydrolase angiotensin-converting enzyme (ACE) by binding to the zinc site (*55*). It is perhaps in this area that medicinal coordination chemists will make their greatest contributions in the future.

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