Man and the Elements of Groups 3 and 13

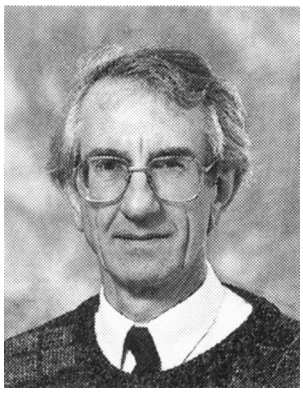
John Burgess
Department of Chemistry, University of Leicester LE1 7RH, UK

1 Introduction

This Review deals with interactions between compounds of the elements of Groups 3 and 13 of the Periodic Table, including the lanthanides and actinides, and the human body. It touches on their levels and role in healthy individuals and covers chemical aspects of their pharmacology, toxicology and control. Both the introduction and the elimination of metal-containing species, and their beneficial and harmful effects, will be considered. There will be specific illustrations of the multitude of ways in which these (and indeed many other) elements interact, favourably or unfavourably, with the metabolism and with malfunctioning of the human body. At appropriate points individual Groups 3/13 elements will be used to illustrate general features, such as the balance between essential traces and toxic excess and the tailoring of ligands for maximum effectiveness. Thus complex stability and selectivity will appear in the sections on aluminium and on the actinides, the hydro-philic/lipophilic balance (HLB) of complexes and its relevance to transport into and around the body will appear under the headings of aluminium and of gallium and indium, and the transformation of very labile metal centres into exceptionally inert species in the section on yttrium.

The abundances of the Group 3/13 elements in the Earth's crust, and in oceans and rivers, vary over an enormous range, from the ubiquitous aluminium (8.2% of the earth's crustal rocks) to the very scarce indium (perhaps 0.24 ppm in the earth's crust). Boron, gallium, scandium and yttrium occur at the 10—30 ppm level; these abundances are similar to that of, *e.g.*, cobalt or lead. Boron is the most abundant of the elements under discussion in the oceans, at a concentration of about 4.4 ppm. The concentration of aluminium in the oceans is only about 2×10^{-3} ppm; levels of the lanthanides are in the region of 10^{-6} ppm, with scandium and indium present at even lower concentrations. An average man contains about 0.05 g of boron, but vanishingly small amounts of the other Group 3/13 elements. These are present at levels less than, probably very much less than, 10^{-5} moles per person. Boron is an essential element, though toxic if taken in large amounts, but the other elements are all irrelevant to the normal workings of the human body – indeed many are toxic, some in very small amounts. But almost all these elements, often in the form of complexes of appropriate isotopes, are useful in diagnosis or therapy.[1–3] The following pages will illustrate these applications for this set of elements – a complementary discussion of the transition metals has appeared elsewhere.[4] References are mainly to reviews and to recently published articles; sources of detailed information can be tracked through the former.

John Burgess obtained his B.A., M.A. and Ph.D. degrees at the University of Cambridge. After two years at Fisons Fertilizers' R & D station at Levington he went to the University of Leicester in 1967. He has remained there ever since, and is now a Reader in Inorganic Chemistry. He has been interested for many years in medium and pressure effects on inorganic kinetics. More recently his interest in solvent effects on kinetic parameters has extended to solvation of inorganic complexes. One facet of this is the study of synthesis and solvation of hydroxypyranone and hydroxypyridinone ligands and their complexes, with particular reference to possible diagnostic and therapeutic rôles.



2 Boron

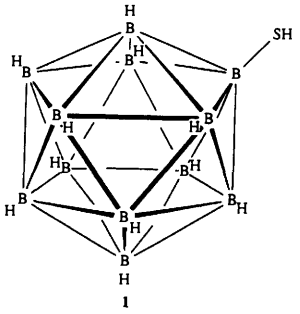
Boron was shown to be an essential element[5,6] for at least some plants in 1923. That it could play an important rôle in mammals was shown much later, in 1981, though the antibiotic boromycin had been produced from a new strain of *Streptomyces antibioticus* in 1967. Boron probably plays a part in calcium and phosphate metabolism, and in bone production and upkeep. It is also claimed to be involved in membrane function, and in nucleic acid and lignin biosynthesis. As for so many essential elements, an excess can be toxic; in the case of boron the fatal dose for an adult is as high as 15 to 20 g.

Boric acid and borax (sodium borate) were used medicinally by Persian alchemists. Boric acid is a mild antiseptic and astringent, being feebly bacteriostatic and fungistatic. Its aqueous solution is used as a mouthwash and as a skin lotion. It is also used in ointments, and in dusting powders in which it is combined with talc, starch or zinc oxide. The last combination is interesting in combining the antiseptic properties of the boric acid with the healing properties, still only dimly understood, of the zinc oxide. Boric acid has also been used in combination with a variety of other compounds, variously including mercury(II) chloride, 'mercuric oxycyanide,' zinc acetate, or borax in eye lotions. Perborate, a rather fragile peroxo-derivative of borate, has a significant usage in dental hygiene – both as an anti-gingivitis agent and in a cosmetic role. In the latter case it is acting as a bleach, removing unsightly yellow or brown coloration and stains, acting analogously to perborates in washing powders.

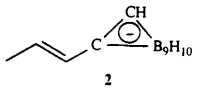
The possibility of utilising neutron capture by boron-10 to release α-particles

$$^{10}_{5}B+^{1}_{0}n\rightarrow^{7}_{3}Li+^{4}_{2}He \qquad (1)$$

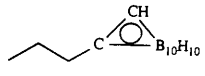
for the *in situ* destruction of cancerous cells seems to have been suggested almost 60 years ago. At that time there were neither suitable neutron sources nor suitable boron compounds, so boron neutron capture therapy was not actually attempted until the late 1950s. Severe problems were encountered then, with several fatalities resulting from insufficiently complete localisation of the boron-10; stray ^{10}B emitted α-particles in the wrong places, destroying essential tissues. In the past few years there has been a renaissance of boron neutron capture therapy, resulting from the refinement of the neutron beams available and the development of new boron compounds which can be delivered more efficiently to the required site. A large number of compounds, of a variety of types, are being assessed – pharmacological requirements, compounds, and methods of delivery have recently been fully documented.[7] Promising compounds include $H_3N^+BH_2^-CO_2H$, the boron analogue of glycine, and, more effective, (L)-4-boronophenylalanine. Many compounds containing polyhedral borane and carborane units have been evaluated, of which the best known is sodium borocaptate ('borolife') containing the anion **1**. Many related compounds are carborane derivatives of, *e.g.*, porphyrins, thiouracil and polyamines.[8] These contain substituents such as **2**,**3** or **4**; an anionic group such as *nido*-7,8-$C_2B_9H_{11}^-$, as in **2**, increase hydrophilicity. The most recent compound of this type is the dendritic or cascade species **5**, containing a multitude of sulfonate groups to confer water-solubility.[9]



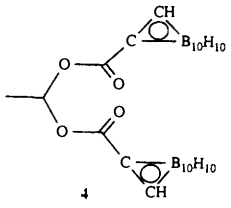
1



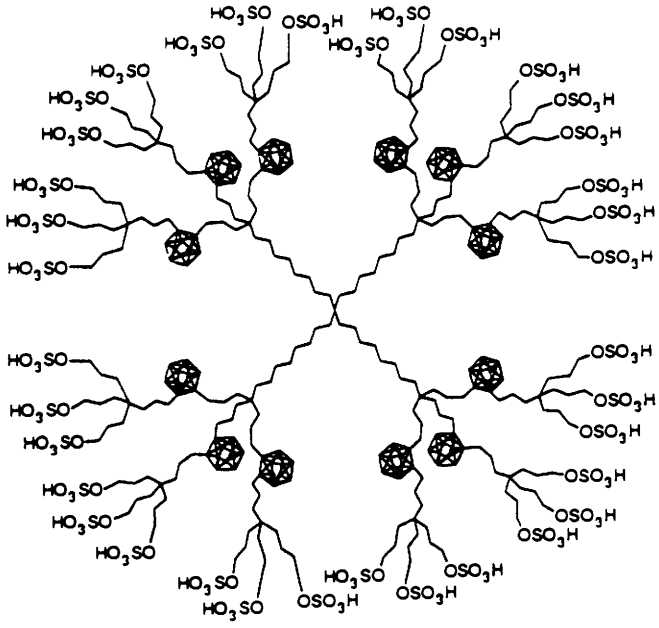
2



3



4



5

3 Aluminium

Aluminium compounds appear to have no useful role to play in human metabolism. Until recently it was generally believed that aluminium was irrelevant to the workings of the human body – a harmless, perhaps even benign, element. However, in view of the high charge density of Al^{3+} and the likelihood of strong interactions between Al^{3+} and 'hard' ligands such as phosphates, one might well be suspicious that it could be very harmful if it reached the wrong place. Stability constants for aluminium complexes of 'hard' oxoanions are generally several orders of magnitude higher than for analogous complexes of such biologically important metals as magnesium(II), calcium(II) and zinc(II), so there may be problems resulting from competition between Al^{3+} and Mg^{2+}, Ca^{2+}, or Zn^{2+}.

Nowadays everyone is aware of the connection between aluminium and various neurological malfunctions, especially Alzheimer's disease[10] and dialysis dementia. Aluminium is also implicated in some bone disorders, such as osteoporosis and osteomalacia. Whether aluminium causes or accelerates these problems – for example by interfering with calmodulin, the multifunctional calcium receptor that plays a central rôle in cell regulation, or with guanosine triphosphatase – seems still to be a matter of debate, though majority opinion at the moment seems to favour accumulation in the brain as a consequence rather than causative. Readers wishing to consult the voluminous literature may refer to several exhaustive reviews on aluminium and its role in food, medicine and biology.[11]

Fortunately the human gastrointestinal tract is extremely reluctant to allow simple Al^{3+}(aq.) and its hydroxo and polynuclear derivatives across. This is very important in view of several widespread uses of aluminium compounds, in water treatment, as food additives, and in everyday medicines. The use of aluminium salts in water treatment is primarily cosmetic, to give so-called 'polish' – to make it look clearer and more sparkling by using finely divided aluminium hydroxide to remove very fine suspensions of organic material, iron hydroxides, and the like. In recent years iron(III) salts have been replacing aluminium salts for this purpose, though in view of possible problems with long-term iron accumulation in the body this may not be the final solution. Simple aluminium salts, such as alum (potassium aluminium sulfate) were used for many years in foods such as pickles to give a sharper flavour, while the cooking of acidic fruits such as rhubarb or citrus fruits in aluminium saucepans must have added to the aluminium intake of innumerable people since the widespread superseding of enamel by aluminium for cooking vessels. Tea leaves have probably the highest aluminium content of any plant, up to 3% dry weight, so there have been concerns over the aluminium intake of heavy tea drinkers. A strong cup of tea may contain fifty times the EU-recommended maximum level of aluminium. There are a number of aluminium compounds in the lists of permitted food additives published by the Ministry of Agriculture, Fisheries, and Food and by the European Union. These include anticaking agents such as sodium and calcium aluminosilicates, used in some table salt, and sodium aluminium phosphate, used as a leavening agent in cakes and biscuits. Aluminium metal is dignified with an E-number, *viz.* E173, for its use in 'silvering' confectionery. Most of these permitted additives are so insoluble under physiological conditions as to preclude significant absorption in the body. Overall it does seem that the intake of aluminium from all these 'unnatural' sources adds only an insignificant amount to the daily intake of between 2 and 20 mg of aluminium in a normal diet.

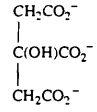
Aluminium compounds are extensively used in antacids. Aluminium acetate, hydroxide, phosphate, and silicate, and bismuth aluminate all feature in commonly used remedies for excessive acidity in the digestive regions. In most cases the aluminium-containing species are of fairly high relative molecular mass, which, coupled with their predominantly hydrophilic peripheries, means limitingly low absorption under almost all conditions – except when ingested immediately before or after consuming such materials as fruit juice or marmalade. There is some evidence for the absorption of aluminium in the form of complexes with fruit acid ligands such as citrate, **6**, or with vegetation-derived ligands such as humates and fulvates.

Oxalatoaluminates from the cooking of rhubarb in aluminium vessels (*cf.* previous paragraph), on the other hand, should be far too hydrophilic for significant absorption from the gastrointestinal tract. Basic magnesium compounds, such as the carbonate, have also long been used as antacids, often in conjunction with, *e.g.*, aluminium hydroxide. In view of magnesium's favourable, indeed essential, role in human metabolism, its compounds might well be deemed to be preferable alternatives to those of aluminium. The only drawback to the use of magnesium compounds in this respect is their significant laxative action – though in many cases that could be a distinct advantage! One needs to be aware that some drugs form stable complexes with Al^{3+} (and indeed with Mg^{2+}) – antacids can decrease absorption of such drugs significantly, sometimes to the point of making them totally ineffective. On the other hand, the buffering effects of antacids may improve absorption if a drug is absorbed more effectively from neutral rather than acidic media. It should be added here that aluminium can actually play a beneficial role in the treatment of peptic ulcers – 'Sucralfate', **7**, complexes through its aluminium to exposed protein, thereby protecting delicate tissue from stomach acid and promoting healing.

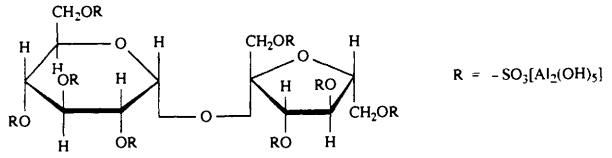
Aluminium compounds are applied, generally in the form of 'alum' – potassium aluminium sulfate – to the skin to staunch bleeding from minor scratches and cuts. They have also been used in face creams, and are very widely used in deodorants and anti-perspirants.[12] The first real anti-perspirant was aluminium chloride solution which, as it was messy, an irritant, and destroyed fabrics, found distinctly limited popularity. In the 1940s it was found that a number

of aluminium–hydroxide–chloride species, of precisely defined composition but unknown structure, were equally effective. Since then the formulation of this class of antiperspirant has been refined by the addition of some zirconium, and also often of glycine. All these mixtures probably result in no significant addition of aluminium to the body, since it is unlikely that any of their aluminium-containing species penetrate the skin. But the simple alum mentioned at the start of this paragraph is a different matter, since it is in contact with the blood and some complexation of Al^{3+} by transferrin seems likely.

There was for a time yet another possible route for the introduction of aluminium, through the use of aluminium-containing water supplies in dialysis treatment for kidney malfunction. The resultant dialysis dementia is now avoided by ensuring vanishingly small levels of aluminium in water used for such treatments.



6



7

For several years there have been discussions as to the possibility of slowing, halting, or reversing the inexorable progress of senile dementias by decreasing, or at least controlling, aluminium levels in the body. There are two problems here. The first is that it has proved well-nigh impossible to reproduce Alzheimer-type neurofibrillary tangles in the laboratory, making *in vitro* tests of aluminium-control drugs impossible. The second is that it is actually very difficult to diagnose Alzheimer's disease—definitive proof is only available through a post-mortem autopsy! It is therefore difficult to assess the effectiveness of chelation therapy. Moreover there is always the concern that a chelator might mobilise aluminium and transfer it to an even more undesirable site rather than transport it through the excretion system. The choice and tailoring of potential chelators for the control of aluminium levels provides an interesting illustration of drug design and development. It starts with the observation of the similarity between stability constants for aluminium(III) and iron(III) complexes. There is a marked correlation between stability constants for respective pairs of aluminium(III) and iron(III) complexes, as shown in Fig. 1. Iron(III) complexes are almost always the more stable – all the points in Fig. 1 are on the same side of the line corresponding to equal stability constants for Al and Fe complexes. Therefore one has to be careful not to remove iron rather than aluminium. Some simple carboxylates and hydroxycarboxylates have been tried for chelation therapy – succinate, **8**, and malate **9**, were claimed to be of some value, citrate **6**, of rather less. The tris-hydroxamate chelator desferrioxamine **10** (R=H), so important and well-tried for control of iron levels in the body, is another obvious reagent to try. It has been used in tests for control of aluminium levels since 1980, with several claims that it can produce a significant retardation of deterioration of mental faculties. But its cost is high, its availability is relatively limited, its administration is not totally straightforward, and it often has undesirable side effects on sight and hearing (though admittedly these are thought to be reversible). Nonetheless it was, in early 1993, the only aluminium chelator approved for long term administration to humans. What is really needed is a cheap orally-administrable drug. Again it is profitable to start with iron(III) chemistry, though for that metal there were two complementary objectives – to get iron efficiently into anaemic people, and, later, to try to get iron out of people with iron overload, *i.e.* the very large number of patients suffering from such diseases as haemochromatosis and thallasaemia.

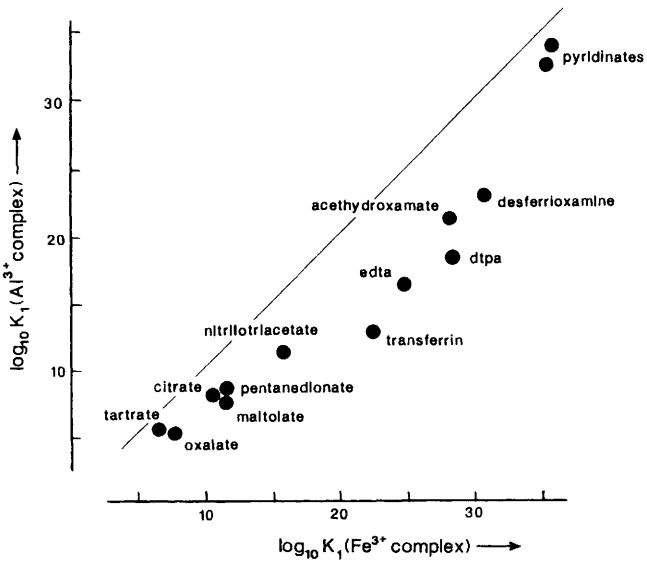


Figure 1 Correlation between stability constants for aluminium(III) and iron(III) complexes. The line corresponds to equal stability constants for complexes of the two cations.

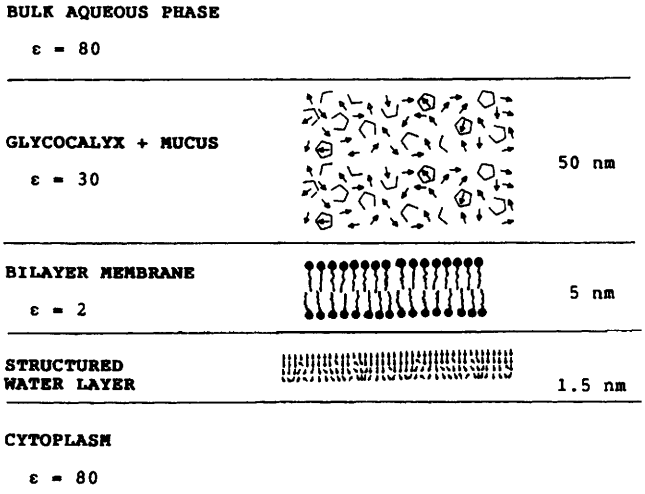
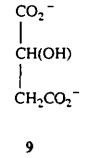


Figure 2 Simplified representation of the barrier to absorption from the gastrointestinal tract. The values of ϵ are estimates of the relative permittivity for each layer.

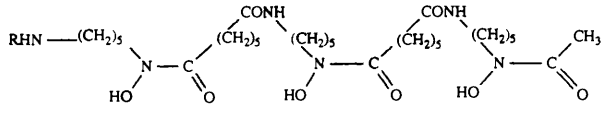
The pyranones **11** and **12**, maltol and ethylmaltol respectively, are both good chelators for iron(III). Moreover they have the great advantage of being permitted food additives, widely used in the baking industry. Reaction of these pyranones with a range of primary amines gives the series of pyridinones **13**, which form even more stable complexes (log $\beta_3 \sim 36$) with iron(III), and whose solvation properties (hydrophilic/lipophilic balance, or HLB) can be tailored according to the nature of the group R′. Such solvation tailoring is particularly important for chelators for metal removal. The ligand needs sufficient water solubility for successful oral administration, but sufficient lipophilicity to be absorbed on passage through the gastrointestinal tract (GIT), and to be able to cross the cell wall to reach intracellular iron. The complex formed then needs the right HLB to leave the cell and make its way successfully down the excretion pathway. Fig. 2 shows a much simplified version of the barrier to absorption from the GIT. The ligand has to proceed from one aqueous medium to another through the membrane bilayer whose central region is essentially hydrocarbon and an ill-defined intervening layer of intermediate properties. Unless there happens to be a specific transmembrane transport mechanism, the species crossing such a barrier needs sufficient hydrophilicity to dissolve in the aqueous media and sufficient lipophilicity to transverse the fatty centre of the bilayer membrane.

But the indicated requirement of both hydrophilic and lipophilic areas on the surface of the species may mean that synergic solvation in the intermediate region or at the membrane interface makes the species particularly well solvated there, such that it is strongly absorbed and does not complete its passage through the membrane. A fine balance has to be achieved, for the entering ligand and for the leaving complex. Despite these complications, this type of ligand has been successful in the treatment of iron overload and thus has led to their testing for the control of aluminium levels. Definitive results are awaited on the two key questions – do such ligands reduce aluminium levels at key sites, by excretion and not by moving the aluminium elsewhere in the body, and is there a significant improvement in memory and other deteriorated mental powers?

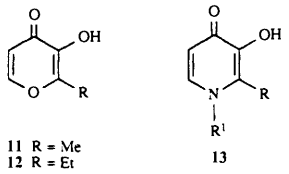
8



9



10



11 R = Me
12 R = Et

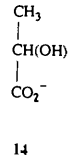
13

There may well be a purely inorganic means of controlling aluminium levels, as suggested by Birchall, who has been particularly interested in the role of silicon in the body. There are strong indications that silicon may be an essential trace element, and it could be that silicon is not essential in itself, but that it may, through the intermediacy of hydroxyaluminosilicates, play a part in the control of aluminium levels.[13]

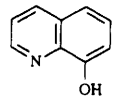
4 Gallium and Indium

These elements can conveniently be considered together. They have very similar chemistry; neither has a natural metabolic role. A few simple gallium compounds, *e.g.* nitrate and citrate, have been tested for anti-tumour activity, but showed no significant advantages over current treatments. Indium nitrate was similarly tested, but only briefly since it is a more toxic compound than its gallium analogue. Gallium nitrate, under the name 'Ganite', has been used in Japan for the treatment of cancer-associated hypercalcæmia. The great importance of these elements in relation to inorganic species in medicine is that both have isotopes useful for diagnosis or therapy.

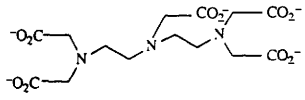
The various isotopes of gallium and indium which have at one time or another been suggested, investigated, or used for radiopharmaceutical purposes are listed in Table 1. Of these isotopes, ^{67}Ga, ^{68}Ga and ^{111}In are the most important. ^{67}Ga and ^{111}In have been widely used for many years; ^{68}Ga has recently become much more readily available, from ^{68}Ge/^{68}Ga generators. This may be expected to result in much increased use of this isotope, for positron emission tomography (PET). ^{67}Ga is used in the related γ-ray imaging technique of single photon emission computed tomography (SPECT–PET, SPECT, and other terms relevant to the use of inorganic complexes in imaging and therapy are succinctly explained in ref. 1). ^{67}Ga and ^{68}Ga are both used for scanning; both have $t_{\frac{1}{2}}$ suitable for medical usage – long enough to dose the patient and to carry out the appropriate scans, but short enough to avoid problems which may arise from long-term irradiation. ^{67}Ga imaging has in recent years been used for imaging soft tissue tumours and inflammatory lesions. The half-life of ^{67}Ga is particularly appropriate for introduction *via* monoclonal antibody techniques. ^{99m}Tc, very widely used for imaging a variety of parts of the body, has a half-life which is rather too short (6.05 h) for introduction this way. ^{111}In is used for evaluation of cerebral spinal fluid pathways, for biliary reflux studies, for imaging intra-abdominal abscesses, for monitoring thrombosis, and for early warning of transplant rejection. ^{114m}In has been used in the treatment of leukaemia. Of the other, much less important, isotopes in Table 1, ^{113m}In has recently found use as a tracer (*vide infra*), while ^{72}Ga was used in the early 1950s to look for bone tumours. It was found to be somewhat less unsuitable than ^{45}Ca and ^{47}Ca, but was soon superseded by isotopes better suited to this purpose.



14



15



16

^{67}Ga was first administered as a lactate (**14**) complex. The radionuclides of gallium and indium have in recent years usually been administered complexed with citrate (**6**), oxine (8-hydroxyquinolinato, **15**), or dtpa (**16**; the abbreviation is derived from its long-established trivial name diethylenetriaminepentaacetate). The citrate species are of relatively low stability, and readily give up Ga^{3+} or In^{3+} to transferrin, as does the indium chloride which has occasionally been administered. The radionuclides then localise in sites where iron tends to concentrate – *e.g.* the liver, spleen and kidneys, and in soft tissue tumours and lesions. The dtpa complexes are somewhat more stable, and are transported around the body with a markedly different distribution pattern. The oxine complexes are water-insoluble and thus more difficult to administer, though their lipophilicity is an advantage in crossing cell membranes and thus assists their introduction into cells. They are used to label white and red blood cells, which then take the radionuclide to the required site. Although it is relatively difficult to get the radionuclide to the right place to begin with, once there it tends to stay – hydrophobicity and low solubility in aqueous media help to minimise washout. At the other end of the HLB range, ^{111}In-labelling of haemoglobin is possible, through the intermediacy of the water-soluble derivative of *meso*-protoporphyrin IX.

Another method of administration is through attachment to monoclonal antibodies. Dtpa has recently been used as the chelating moiety to link $^{111}In^{3+}$ to monoclonal antibodies to improve localisation at the required site. Species of this type have been approved for myocardial imaging and are being developed for possible application in detecting colorectal tumours. The problem now is that the ^{111}In-containing species has a high relative molecular mass and slowly dissociates, so that the ^{111}In accumulates in the liver. Efforts are therefore currently being made to see if a fragment of the complete monoclonal antibody, or even simply a short polypeptide chain, is sufficient to direct the ^{111}In to the required site, and to bind the indium into a more powerful chelating moiety from which it will dissociate at a much slower rate.

Most of the vehicles for administration mentioned in the preceding paragraphs have some disadvantages, so other types of complexes are at various stages of testing to find a better method for the

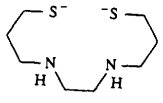
Table 1 Isotopes of gallium and indium of actual or potential radiopharmacological importance; the most importance are in bold type[a]

Isotope	Decay mode	Half-life	Isotope	Decay mode	Half-life
^{66}Ga	EC; β^+	9.5 hours	^{110}In	EC; β^+	1.15 hours
^{67}Ga	EC; γ	78.1 hours	**^{111}In**	EC; γ	67.4 hours
^{68}Ga	EC; β^+; γ	1.13 hours	^{113m}In	IT; γ	1.66 hours
^{72}Ga	β^-; γ	14.1 hours	^{114m}In	IT; EC; γ	49.5 days

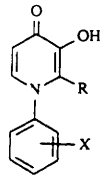
[a] Abbreviations: EC = electron capture; IT = isomeric transition.

introduction of gallium and indium radiopharmaceuticals into the body, and for their specific localisation in the tissue or organ to be imaged Several approaches are outlined in the following paragraphs

Gallium and indium complexes of pyranones and pyridinones (see formulae **11**—**13** in the section on aluminium above) have high stabilities (log β_3 for the complexes of **13** with R=R′=Me are 35 8 and 31 7 respectively), and offer the possibility of oral administration Their partition coefficients are rather smaller than ideal, but they can be tailored, *e g* by having an X-aryl-N-substituent (**17**) This increases their lipophilicity, which reduces washout with its concomitant over-rapid elimination Considerably increased lipophilicity can also render them suitable for myocardial monitoring Further, there is the possibility of including a peptide or ester linkage in the N-substituent, which may undergo hydrolysis at the site of action to give a derivative with a different HLB which may have more difficulty crossing membranes and may therefore stay at the required site for a longer period The main disadvantage of this class of ligand is the presence of phenolate donor groups, since even in mildly acid media these donor centres may become protonated and thus separated from the metal ion



18

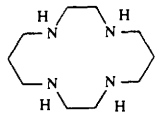


17

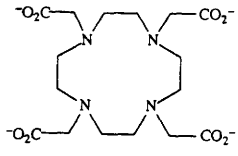
Ligands with an N_2S_2 donor set, for example with the framework **18**, were shown several years ago to be useful vehicles for the introduction of ^{99m}Tc into the body They, and N_2S_3 analogues, are now being assessed for the introduction of Ga and In In particular a lipophilic tetraethyl derivative has been proposed as a ligand for ^{111}In, to provide a new myocardial imaging agent Interestingly, ^{113m}In proved a useful tracer in assessing this diagnostic approach

Increased stability may be introduced in the form of the macrocyclic effect, familiar to inorganic solution chemists in the guise of the greater stability of complexes of, *e g* the cyclic ligand **19** than of its open chain (garland) analogue $H_2NCH_2CH_2NHCH_2CH_2NHCH_2CH_2NH_2$ Obviously it is even better to add further chelate rings and have the one ligand molecule encapsulating the metal ion and occupying all coordination positions An example of a ligand of this type is dota, **20**, whose carboxylate pendant arms provide extra chelating units Dota, with its eight potential donor sites, is a powerful and popular ligand, but has the slight disadvantage that its complex with a 3+ ion will have a nett negative charge, which will militate somewhat against passage across biological membranes One way around this problem is to replace carboxylate, $-CO_2^-$, by an alcohol function, $-OH$, another is to go from the tetraaza-ring of dota to the triaza ring of nota, **21** [14] This ligand has the added advantage of being hexadentate, and thus neatly occupying the six coordination sites of the Ga^{3+} or In^{3+} as well as giving an uncharged complex with 3+ cations Fine tuning and optimisation of nota have recently led to the synthesis and study of the derivative **22**, in which the simple carboxylate pendant arms of the parent ligand have been replaced by derivatised phenoxides (the $-O^-$ donors having a particularly high affinity for M^{3+}) with methyl substituents modifying the HLB of the complex

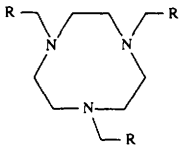
More recently, phosphinate groups have been incorporated into the pendant arms These ligands form considerably more stable complexes then dtpa (*vide supra*), though it should be mentioned that stability and inertness of polyaminocarboxylate complexes of the dtpa and edta type have been considerably increased by moving to anions of **23** Tailoring of properties is possible here, for example by the use of R=CH_3 or CH_2OH for fine tuning of the HLB The anionic ligand derived from the phenolic aminocarboxylic acid **24** is claimed to be unusually selective for gallium *vs* indium, with log K_1 values of 37 7 and 27 9 for its Ga^{3+} and In^{3+} complexes respectively, natural carriers such as transferrin exhibit very little differentiation, with a difference of only 10-fold between the stability constants for its Ga^{3+} and In^{3+} complexes

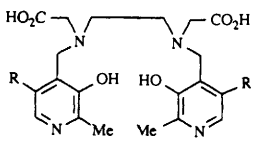


19

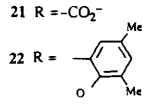


20



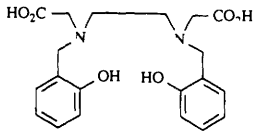


23



21 R = $-CO_2^-$

22 R =



24

The majority of the applications described in this section have been in diagnosis Effective radioimmunotherapy usually needs a more aggressive radionuclide, such as ^{90}Y (*vide infra*) Indeed ^{111}In/^{90}Y constitute a diagnosis/therapy pair, as analogous complexes with a given ligand have similar tumour affinities An alternative mode of tumour treatment is photodynamic therapy, for which sulfonated gallium phthalocyanines containing *tert*-butyl groups have been evaluated as photosensitisers The lipophilicity of the *tert*-butyl groups is balanced by the hydrophilicity of the sulfonate groups to provide an HLB suitable for cell uptake

5 Thallium

Thallium salts are poisonous – Tl^+ is absorbed efficiently from the human gastrointestinal tract About 1 g is sufficient to cause death, which usually occurs, from heart failure, 3 to 4 weeks after ingestion Earlier symptoms and effects include nausea, insomnia, mental confusion, and swelling of the feet and legs However the best-known effect of thallium poisoning is that on the hair of the victim At first the hair can be pulled out without pain, after some days it falls out anyway These phenomena have been detailed in, apart from the normal sources of reference, Agatha Christie's 'The Pale Horse', whose plot centres on thallium poisoning [15,16] The toxicity of thallium compounds was recognised soon after the discovery of this element, but was for a long time greatly underestimated There was much use of thallium compounds as depilatory agents, for example in preparation for treatment of ringworm, while thallium(I) acetate was at one time used for the treatment of tuberculosis By 1934 the number of fatalities recorded, as a result of 692 cases of medical (mis)use, had reached 31 However the main cause of thallium poisoning was the use of thallium sulfate and other salts in insecticides and rodenticides The thallium salts were often incorporated into syrups which, not surprisingly, formed a temptation to children At least the fact that death occurs many days after ingestion allows some scope for chelation therapy, though thallium does distribute itself around the body rapidly after absorption Dimercaprol (BAL **25**) is an effective antidote, potassium chloride also helps, as it promotes excretion of thallium through the kidneys

25

^{201}Tl (decay mode EC,γ-emitter of relatively low toxicity, t =72 hours) has been much used for tumour and, especially, myocardial imaging However it has now been superseded in this latter role by ^{99m}Tc ^{201}Tl is generally administered simply as TlCl ^{201}Tl works as good probe as a result of the fairly close similarities between Tl^+ and K^+, with the distribution of ^{210}Tl reflecting blood flow and tissue viability It accumulates in the viable myocardium *via* the Na–K–ATPase pump Thus the $^{201}Tl^+$ localises naturally where it is wanted without the need for specific tailoring of complexes It has to be administered to the patient under stress, either from exercise or drug-induced (*e g* by dipyridamole/persantin), as a resting study only shows up long-standing scars and damage, not current problems Images are taken immediately after stressing, and again 3 to 4 hours later, with the dif ferences pinpointing the problem sites

Sometimes comparison of scans for two different isotopes can provide valuable information An example of this is provided by the simultaneous use of ^{210}Tl (as TlCl) and ^{99m}Tc (as TcO_4^-) for parathyroid imaging Subtraction of the ^{99m}Tc image from the ^{201}Tl image reveals the site of an adenoma, since uptake of the two elements differs appropriately

6 Scandium

Scandium is a widely distributed but extremely thinly spread element, whose aqueous solution chemistry has been somewhat neglected and is still rather incompletely characterised Thus, despite confident assertions that the hydration number of Sc^{3+} in aqueous solution is six, this has yet to be established Indeed there has been no X-ray crystal structure determination of a simple hydrated Sc^{3+} salt containing octahedral $Sc(OH_2)_6^{3+}$, or $Sc(OH_2)_7^{3+}$ (which would be uniquely interesting), or $Sc(OH_2)_8^{3+}$ [*cf* $Y(OH_2)_8^{3+}$ below] for that matter * There is not even a stable scandium alum, $Cs_2SO_4\ Sc_2(SO_4)_3\ 24H_2O$ has been reported, but is only stable below 0 °C

At present the nearest thing to interaction of scandium compounds with humans is their use in some forms of lighting used in public transport vehicles and department stores However scandium salts and their solutions have been reported to be bacteriostatic or bacteriocidal, probably through their affecting iron-enterobactin interactions [2] There have been hints of their use for specific delivery of bacteriocides in specialised applications, but cost (scandium salts start at around £20/$30 per gram) precludes widespread use Two radioisotopes are available from generators, *viz* ^{44}Sc (EC, β^+, γ, t =3 9 hours) and ^{47}Sc(β^-, γ, t =3 4 days) These might one day prove to have some radiopharmocological usefulness ^{46}Sc(also a β^- emitter) in the form of citrate, has also been briefly assessed for tumour imaging in rats However it seems to have no particular advantages to offset the disadvantage of its long half-life, of 84 days

7 Yttrium

Yttrium is another rare element which has no role in the human body Information on the solution chemistry of Y^{3+} is again limited, but at least, in contrast to $Sc^{3+}(aq)$ there are well-characterised aqua-yttrium(III) ions, as in $[Y(OH_2)_8][Tc_2Cl_8]$

$^{90}Y(\beta^-, t$ =64 hours) has been suggested for relatively minor applications, such as the treatment of arthritic joints, and, more substantially, for the *in situ* irradiation of malignant growths in the pleural and peritoneal cavities ^{90}Y is potentially valuable for radioimmunotherapy, but is one of the very few non actinide isotopes to come into the 'very high toxicity' category It must therefore be administered in a very stable and inert complex which can be deliv ered cleanly and accurately to the required site of action If ^{90}Y becomes free as $Y^{3+}(aq)$ it is liable to settle in bone tissue, substituting for Ca^{2+}, and cause serious problems $^{90}Y_2O_3$ incorporated in rods or in polythene sheet has been used for implantation in the pituitary In this form the ^{90}Y is unlikely to escape[1] The main problem associated with its use in the pleural and peritoneal cavities is that of obtaining a stable colloidal preparation, though yttrium silicate colloids have been used with some success The problem with other aspects of its use is one of ligand design – both for maximum stability and for maximum inertness, so that any very slight dissociation that does take place occurs extremely slowly As the characteristic timescale for substitution by simple monodentate ligands at the very labile $Y^{3+}(aq)$ is of the order of a microsecond, to judge from the rate constant established for water exchange at $Y^{3+}(aq)$, the inhibition required is enormous However it can be achieved by suitable ligand design and modification, as illustrated in Fig 3 The familiar multidentate polyaminocarboxylate ligand dtpa **16** reduces dissociation rates dramatically, though not quite sufficiently The half-life for release of Y^3 from its complex with the *n*-butyl amide derivative of dtpa is more than two days, but the incorporation of a 4-nitrobenzyl substituent in the dtpa skeleton leads to an increase in dissociation half-life to a matter of weeks Going from garland ligands to pendant-arm macrocycles gives a further large increase in inertness, as shown by the plot for the 4-nitrobenzyl-substituted dota complex in Fig 3 By this stage the half-life for dissociation, more than 200 days at 37 °C, is considerably longer than the half-life of the ^{90}Y, so there is negligible risk of harm arising from leakage of ^{90}Y from the administered complex into other parts of the body

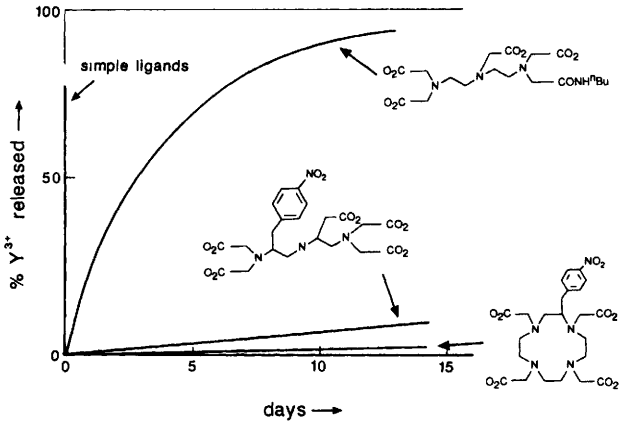


Figure 3 Inertness and lability of yttrium(III) complexes

8 Lanthanum and the Lanthanides

None of the lanthanides is an essential element for humans La^{3+} has been used from time to time as a Ca^{2+} substitute or antagonist to probe mechanisms of calcium action in the body The fluorescence of Eu^{3+} complexes has similarly found application in monitoring the functions of such ions as Ca^{2+} There has been some investigation of the possibility of the therapeutic use of lanthanum salts in the treatment of disorders of calcium metabolism or action There have also been experiments, mainly in Japan, on the replacement or reinforcement of calcium in teeth by lanthanum Prolonged treatment – La^{3+}/edta is better than $La^{3+}(aq)$ – gives a lanthanum phosphate coating on the enamel which is claimed to provide significant protection against dental caries In these and other applications it has to be borne in mind that several of the lanthanides are fairly poisonous, so for the administration of large or repeated doses it is advisable to have the required ion firmly complexed in a chelate which is both very stable and very inert In the latter respect it should be mentioned that rate constants for substitution of simple ligands at lanthanide(3+) ions are high, in the region of 10^7–10^9 $dm^3\ mol^{-1}\ s^{-1}$ under normal experimental conditions

Purely chemotherapeutic applications are thus very rare, but the magnetic and radiochemical properties of several of the lanthanides have important and wide-ranging applications in the diagnosis and treatment of disease Probably the most important application is in

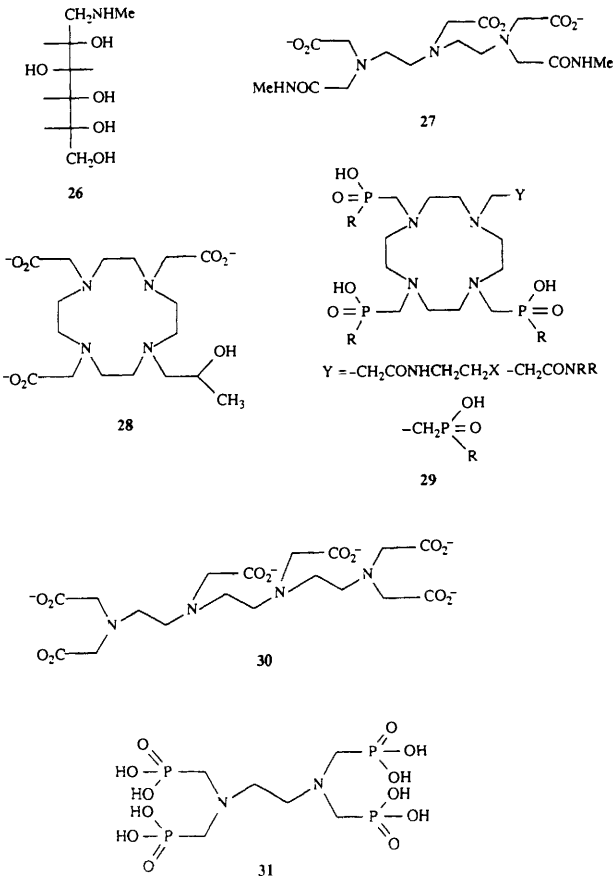
*Since this Review was written X ray diffraction studies have established $Sc(OH_2)_9^{3+}$ in hydrated scandium triflate

magnetic resonance imaging (MRI), which concerns mainly gadolinium This topic will be covered first, followed by a selection of uses of lanthanide radioisotopes

MRI in essence involves running the NMR spectrum of the appropriate part of the human body The aim is to detect and locate problems by picking up differences between the signals from protons in healthy and in diseased tissue This is achieved through comparing relaxation times (T_1, T_2) for water protons in the two environments As the differences can be very small, the effects are amplified by the addition of appropriate paragmagnetic ions – so-called contrast enhancement agents, which increase signal intensity by enhancing relaxation These ions operate by affecting the relaxation time of water molecules in their immediate vicinity, in particular water molecules which enter their normally very labile primary coordination spheres The best ions are the symmetrical half-filled shell d^5 or f^7 ions Mn^{2+}, Fe^{3+} or Gd^{3+} Compounds of manganese and iron were used first, gadolinium compounds were then found to be better Dtpa (**16**) complexes have generally been used for the introduction of gadolinium, indeed $[Gd(dtpa)]^{2-}$, as its *N*-methylglucamine (**26**) salt ('Gadopentetate/Magnevist'), was the first complex approved for use in MRI for tumour detection, about a decade ago It has proved valuable in diagnosis of problems affecting parts of the central nervous system The dtpa complex is stable, but is rather labile [17] Now new ligands, many very similar to those discussed above in connection with yttrium, are being designed and assessed for the required kinetic inertness of the chelating ligand [18] The complex with dota (**20**) has, for example, been found to have the requisite stability and inertness *in vivo* Complexes need to retain at least one water ligand in the coordination shell of the Gd^{3+} to permit rapid exchange between free and coordinated water so that all the water in the part of the system accessible to the Gd^{3+} feels its paramagnetism at first hand It is also desirable that the complexes are non-ionic, as such complexes are effective in smaller amounts and cause less pain on injection Two recently-approved complexes are 'Gadodiamide/Omniscan' and 'Gadoteridol/ProHance,' whose ligands are an amide derivative (**27**) of dtpa (**16**) and a hydroxypropyl derivative (**28**) of dota (**20**) respectively Phosphinate analogues are also promising, especially as they can be tailored by variation of no fewer than four groups, *viz* R,R′,R″ and X in **29** Tailoring of ligands with incorporation of lipophilic groups such as $-CH_2OCH_2C_6H_5$ and $-CH_2OC_6H_4CH_2CH_3$ is leading to agents which may localise in the liver, gall bladder and bile duct

Gd^{3+}, with its half-filled shell f^7 configuration and long electronic relaxation time, causes so much line-broadening that conventional ^1H NMR spectra are not obtainable The other lanthanides, with their much shorter electronic relaxation times, generally give large shifts without significant line broadening – hence their wide use, especially in organic chemistry, as shift reagents This complementary behaviour has also proved to have some medical value Several Dy^{3+} complexes, including those with tripolyphosphate and with ttha (triethylenetetraminehexaacetate, **30**) have been assessed for use as shift reagents in *in vivo* NMR, but a more promising development is the investigation of Dy^{3+} complexes as magnetic susceptibility contrast agents [19] Dysprosium is the element of choice here as it has the highest magnetic moment of the lanthanides Its complex with **27** ('Sprodiamide') is under development as a heart and brain imaging agent Thulium complexes are also being assessed for imaging, Tm^{3+} engenders shifts in the opposite direction from Dy^{3+}

Many radioisotopes of the lanthanides are available from nuclear reactors (*e g* ^{153}Gd, ^{169}Yb), from generators (*e g* ^{134}La, ^{140}Pr), or from cyclotrons (*e g* ^{157}Dy, ^{167}Tm, ^{169}Yb) [20] Several lanthanide radioisotopes are of actual or potential value in diagnosis or therapy A selection of these[2] is given in Table 2, β^- -emitting radionuclides of samarium, dysprosium, holmium and ytterbium have proved the most useful [3] Samarium, in the guise of ^{153}Sm, has considerable clinical potential,[21] it concentrates in bone tissue, like ^{89}Sr and ^{32}P[2] Phosphonate and aminocarboxylate complexes of ^{153}Sm have been used in palliative treatment of painful bone metastases in terminally ill patients As over 50% of patients with lung, breast or prostate cancer develop bone metastases, it is important to be able to alleviate the consequent pain Complexes of the smaller aminocarboxylate ligands are insufficiently well localised, but the complex with the anion of the tetrakis-phosphonic acid analogue of edta, edtmp (**31**), is very promising The relatively short half-life of ^{153}Sm permits treatment to be carried out in several discrete stages, thereby spreading the radiation burden on the patient Other radionuclides, again generally administered as aminocarboxylate complexes, though sometimes in colloidal form as coprecipitates with iron(III) hydroxide, have found employment in bone imaging, in the treatment of arthritic joints, in dental radiography, and in infiltration treatment of the lymph node To connect with applications mentioned earlier in this section, ^{153}Gd has been used to track the gadolinium administered for MRI purposes To link back to the section on boron, several lanthanide isotopes have been suggested for use in neutron capture therapy, including ^{157}Gd (which has a high nuclear cross-section), ^{155}Gd, ^{149}Sm and ^{151}Eu [68] However development of this approach has been severely hindered by the difficulty of localising a large enough number of atoms at the tumour cell site



9 Actinides

Their chemistry, applications, and interactions with man are dominated by their radioactivity There are few favourable features, apart from radiotherapy for cancer, though a century ago or so uranium nitrate was used in treating diabetes The main chemical problem is efficient detoxification, as such isotopes as ^{227}Ac(a naturally occurring isotope, identified in a uranium mineral as long ago as 1899), ^{228}Th, ^{231}Pa, ^{233}U, ^{239}Pu, ^{241}Am, and ^{242}Cm are all α, γ emitters and come into the 'very high toxicity' category It is essential to remove them reasonably soon after exposure, to prevent them being incorporated into bone There is particular concern about plutonium, as it is particularly toxic and is also now widely distributed – there are probably several hundred tons around the world There are also in existence considerable quantities of some of the other actinides, perhaps about 10 tons each of neptunium and americium The widespread investigation and application of a number of the actinides, with the consequent certainty of accidents, encouraged the early

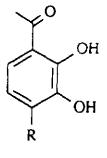
Table 2 Lanthanide isotopes used in diagnosis and therapy

	Isotope	Decay mode	Half life		Isotope	Decay mode	Half life
Samarium	^{153}Sm	β , γ	47 hours	Thulium	^{167}Tm	EC, γ	9 2 days
Terbium	^{161}Tb	β	6 9 days		^{170}Tm	EC, β , γ	134 days
Dysprosium	^{153}Dy	EC, β^+	6 3 hours	Ytterbium	^{169}Yb	EC, γ	32 days
	^{157}Dy	EC, γ	8 1 hours	Lutetium	^{177}Lu	β , γ	6 7 days
	^{165}Dy	β	2 3 hours				
Erbium	^{169}Er	β , γ	9 4 days				
	^{171}Er	β , γ	7 5 hours				

establishment of detoxification agents and procedures As long ago as 1981 some thirty chelating agents had been assessed for removal of plutonium, many more have been developed since then [22]

Transferrin binds plutonium, and several other actinides, strongly Despite this, detoxification simply with (bi)carbonate is claimed to be quite effective for, *e g* removal of ingested uranium However, treatment with appropriate polydentate organic ligands is much more effective Use of diethylenetriaminepentaacetate, **16**, in the form of Na_3Zn(dtpa), is the preferred treatment for removing transuranium elements after exposure as a result of industrial incidents Dtpa has the advantage over edta of being potentially octadentate It is thus more selective for the actinide cations, which favour coordination numbers higher than six, in comparison with ions such as Mg^{2+} or Zn^{2+} which it is undesirable to remove Triethylenetetraminehexaacetate (ttha, **30**), next up the series from dtpa (**16**) and potentially decadentate, has been developed as a potential oral decorporation agent for transuranic elements Polyaminocarboxylates containing long hydrocarbon chains, *e g* $C_{12}H_{25}$ or $C_{22}H_{45}$ derivatives of triethylenetetraminepentaacetate, are effective for removal of plutonium and americium, even of aged deposits They can be administered orally, presumably the hydrocarbon chains assist in the transport of ligands and complexes across the various membranes which have to be traversed [23] Desferrioxamine (**10**), so important for the removal of excess body burdens of aluminium (*vide supra*) and iron, is also effective for plutonium mobilisation Its set of six hard donor atoms are appropriate for the removal of a hard ion such as Pu^{4+}, but it lacks the possibility of selectivity *versus* the essential 2+ cations which is a feature of the high denticity polyaminocarboxylates

New ligands are still being developed, to maximise effectiveness, stability, inertness and selectivity [24] Thus, for example, catechol (1,2-dihydroxybenzene) and pyridinone (**13**) units are being grafted onto appropriate backbones to maximise the desirable properties A good example is provided by the modification of desferrioxamine **10**, with the moieties shown as **32**, to give particularly promising chelating agents [25]



R = H CO_2H CONHMe

32

10 Conclusions

Compounds and complexes of the Group 3 and Group 13 elements can interact in many ways, favourable and unfavourable, with human metabolism A selection of examples has appeared in this short review, the interested reader will find a much greater depth of treatment and a greater variety and range of examples in the general review articles cited, and in several of the multi-volume treatises published in recent years

10 References

1 D Parker, *Chem Br*, 1994, 818
2 R C Hider and A D Hall, *Progr Med Chem*, 1991 **28**, 41
3 S Jurisson, D Berning, Wei Jia, and Dangshe Ma, *Chem Rev*, 1993, **93**, 1137
4 J Burgess, *Transition Met Chem*, 1993, **18**, 439
5 See, *e g*, R J P Williams, *Coord Chem Rev*, 1987, **79**, 175
6 P J Sadler, *Adv Inorg Chem*, 1991, **36**, 1
7 M F Hawthorne, *Angew Chem Int Ed Engl*, 1993, **32**, 950
8 J R Hariharan, I M Wyzlic and A H Soloway, *Polyhedron*, 1995, **14**, 823
9 G R Newkome, C N Moorefield, J M Keith, G R Baker and G H Escamilla, *Angew Chem Int Ed Engl*, 1994, **33**, 666
10 R Doll, *Age Ageing*, 1993, **22**, 138
11 P O Ganrot, *Environ Health Persp*, 1986, **65**, 363, H Sigel and A Sigel (ed), *Metal Ions in Biological Systems Vol 24 Aluminium and its Rôle in Biology* Marcel Dekker, New York 1988, R C Massey (ed), *Aluminium in Food and the Environment*, RSC, London, 1989, T E Lewis (ed), *Environmental Chemistry and Toxicology of Aluminium* (ACS Symposium, New Orleans, 1987), Lewis Publishers, Chelsea Michigan, D J Chadwick and J Whelan (ed), *Aluminium in Biology and Medicine* (Ciba Foundation Symposium 169, 1991), Wiley, Chichester, 1992, R A Yokel, *J Toxicol Env Health*, 1994, **41**, 131
12 T Schamper, *J Chem Educ*, 1993, **70**, 242
13 J D Birchall, *Chem Br*, 1990, 141, *Chem Soc Rev*, 1995, 351
14 C J Broan, J P L Cox, A S Craig, R Kataky, D Parker, A Harrison, A M Randall and G Ferguson, *J Chem Soc Perkin Trans 2*, 1991, 87
15 A Christie, *The Pale Horse*, Collins, 1961, see, *e g* ch 22
16 D A Labianca, *J Chem Educ*, 1990, **67**, 1019
17 R B Lauffer, *Chem Rev*, 1987, **87**, 901
18 K Kumar and M F Tweedle, *Pure Appl Chem*, 1993, **65**, 515, D Parker, K Pulukkody, T J Norman, A Harrison, L Roule and C Walker, *J Chem Soc Chem Commun*, 1992, 1441
19 C A Chang, *Eur J Solid State Chem*, 1991, **28**, 237, A D Watson, *J Alloys Cpd*, 1994, **207/8**, 14
20 G V S Rayudu, *Sem Nucl Med*, 1990, **20**, 100
21 A Singh, R A Holmes and M Farhangi, *J Nucl Med* 1989, **30**, 1814, P Sorby, *J Lab Cpd Radiopharm*, 1989, **26**, 492, R A Holmes, *Sem Nucl Med*, 1992, **22**, 41
22 K N Raymond and W L Smith, *Struct Bonding* 1981, **43**, 159 R A Bulman, *Struct Bonding*, 1987, **67**, 91
23 F W Bruenger, G Kuswik Rabiega and S C Miller, *J Med Chem* 1992, **35**, 112
24 F L Weitl and K N Raymond, *J Am Chem Soc*, 1980, **102**, 2289, K N Raymond, G E Freeman and M J Kappel, *Inorg Chim Acta*, 1984 **94**, 193
25 Zhiguo Hou, D W Whisenhunt, Jide Xu and K N Raymond, *J Am Chem Soc*, 1994, **116**, 840