

technology can be harnessed without exacerbating genetic erosion and further marginalizing small farmers. To enable the latter, the notion of equity will have to be included in the planning, use and practice of GM technology. Benefits must be shared with farming communi-

ties who have provided the base material for GM varieties. There will have to be much greater transparency in 'the system'. Data on GM research and GM products must be publicly available and debates on risks and benefits should be conducted in public.

Suggested reading

1. 'So far so good', *New Sci.*, 25 March 2000.
2. First editorial, *Nature*, 16 March 2000.

Rao named new Head of Third World Academy of Sciences

C. N. R. Rao, Honorary President of the Jawaharlal Nehru Centre for Advanced Scientific Research in Bangalore, India, has been named the new president of the Third World Academy of Sciences (TWAS). Rao succeeds José I. Vargas, who stepped down from the post after being appointed the Brazilian Ambassador to the United Nations Educational Scientific and Cultural Organization (UNESCO). Vargas has served as TWAS president since 1996.

TWAS membership currently consists of more than 500 distinguished scientists from 77 countries, mostly in the developing world. The Academy was founded

in 1983 by the late Nobel Laureate Abdus Salam and 40 distinguished scientists from the developing world. Its headquarters is in Trieste, Italy.

In a 7 May 2000 letter addressed to the TWAS Council, Vargas thanked the members for the 'high and unforgettable privilege' of serving the Academy over the past five years and anticipated that the goals of TWAS would continue to be advanced at a rapid pace 'under the competent and farsighted leadership of our most distinguished President-elect, scientist and world science statesman, C. N. R. Rao'.

TWAS Council members offered their sincere thanks for the contributions that Vargas has made to the Academy. They noted that his tireless efforts on behalf of the Academy have increased the strength and visibility of TWAS among both scientists and scientific policy makers across the globe. Council members agreed that Vargas's legacy would continue to shape the Academy's agenda in the years ahead and they wished him well in meeting his new challenges in Paris.

Rao will preside over the next General Meeting of TWAS to be held in Tehran, Iran, 21–26 October 2000.

RESEARCH NEWS

What's up with chelates

Rashmi Sanghi

The word chelation is derived from the Greek word 'chele' that means claw (like that of a scorpion or crab). The concept of chelation is based on the observation that when a certain amino acid complex like ethylene diamine tetra acetic acid (EDTA) comes in contact with certain positively charged metals and other substances such as lead, iron, copper, magnesium, zinc, platinum and manganese, it grabs them (hence the chele or claw), and removes them. Thus, chelation therapy is the process of removing from the body the undesirable ionic material by the infusion, or taking orally, of an organic compound which has suitable chelating properties.

Some of the problems of metal toxicity may be overcome by use of chelation therapy where chelating agents are used to remove toxic metals like lead and mercury or to reduce metals such as iron or copper to normal concentrations. Ideally, chelation therapy results in the removal, in the form of a metal chelate, of much of the toxic metal present in the blood stream. The subsequent removal from other parts of the body will depend primarily on the rate at which the metal becomes redistributed within the tissues. For use in chelation therapy, a chelating agent should be of low toxicity, not easily metabolized and capable of penetrating to metal storage sites. It should also be capable of

coordinating with a metal ion to form several chelate rings, that is, to give a highly stable complex and to be fairly selective in chelation.

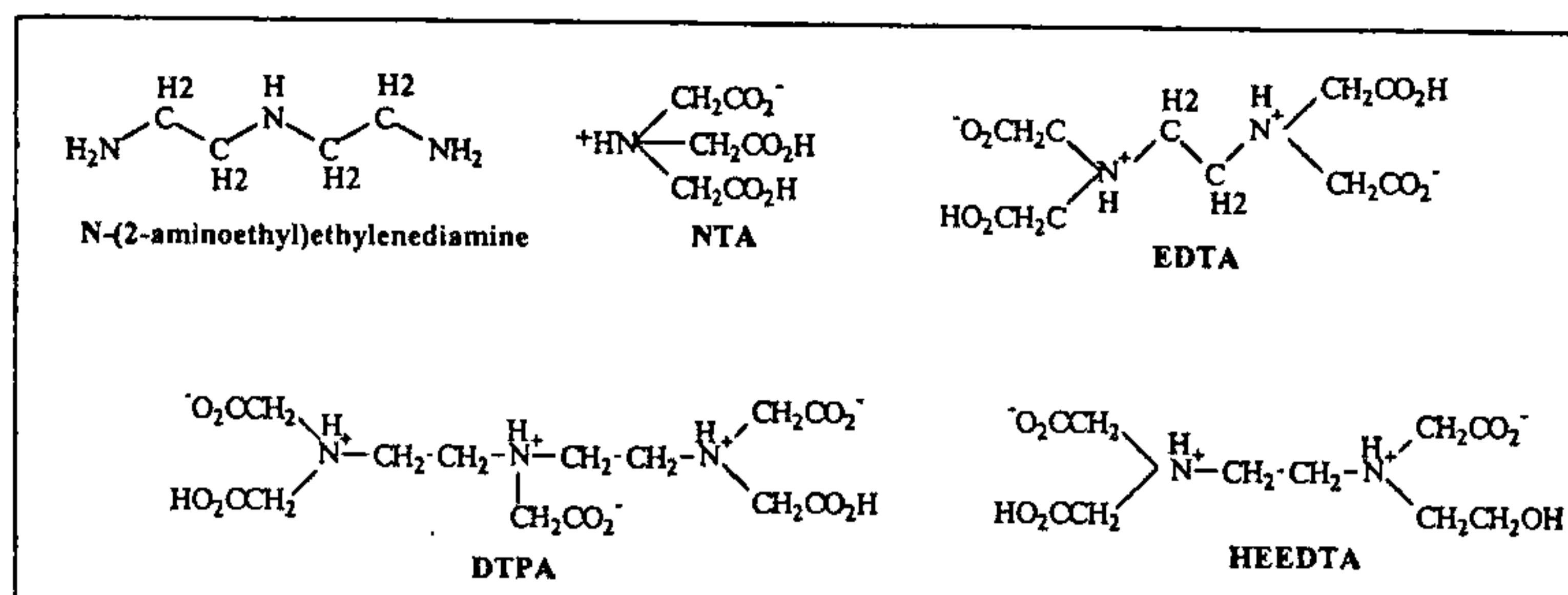
Chelation is very basic to all life. Chlorophyll which converts energy from the sun into everything we eat, is the chelation of magnesium by four molecules of porphyrin. Our human digestive process is a very good example of how chelation takes place. Digestion and assimilation of food involves the chelation of protein substances (amino acids) with minerals for transportation to their destinations, or in which blood cells latch on to, and thus acquire, iron. Haemoglobin is chelate of iron (as is the enzyme catalase, that is

used by our bodies to 'switch off' the free radical activity of hydrogen peroxide). When we eat meat or green vegetables which contain iron, after the digestive process has released the iron from the food in which it is bound it has to be combined (chelated) with amino acids (protein fractions) so that it can be carried through the intestinal mucous membranes into the blood stream.

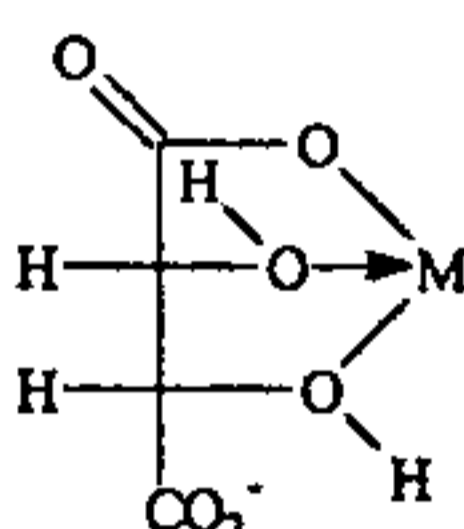
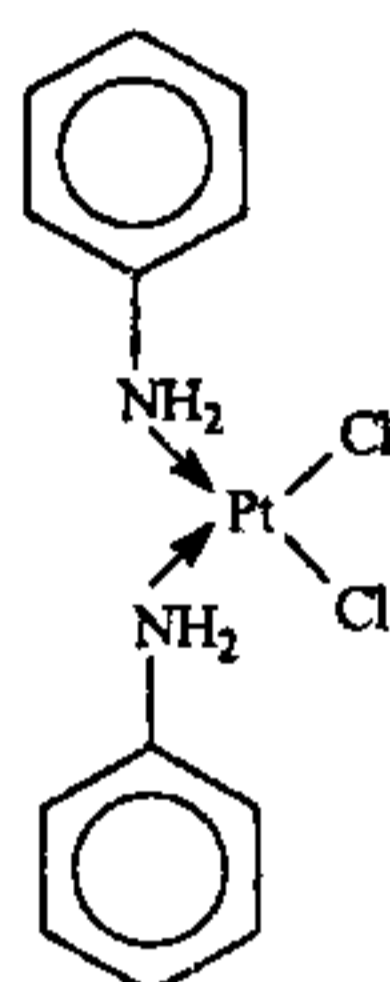
A chelating agent is a substance whose molecules can form several coordinate (or covalent) bonds to a single metal ion. That is, a chelating agent is a polydentate ligand. The most common and most widely used chelating agents are those that coordinate to metal ions through oxygen or nitrogen donor atoms, or through both. Chelating agents that coordinate through sulfur in the form of -SH (thiol or mercapto) groups are not as common in commercial applications, but they perform a significant role in complexing metal ions in biological systems. Three widely used chelating agents are ethylenediamine ($\text{H}_2\text{NCH}_2\text{CH}_2\text{NH}_2$), EDTA, and dimercaprol ($\text{HSCH}_2\text{CHSHCH}_2\text{OH}$).

Sources of metal contamination

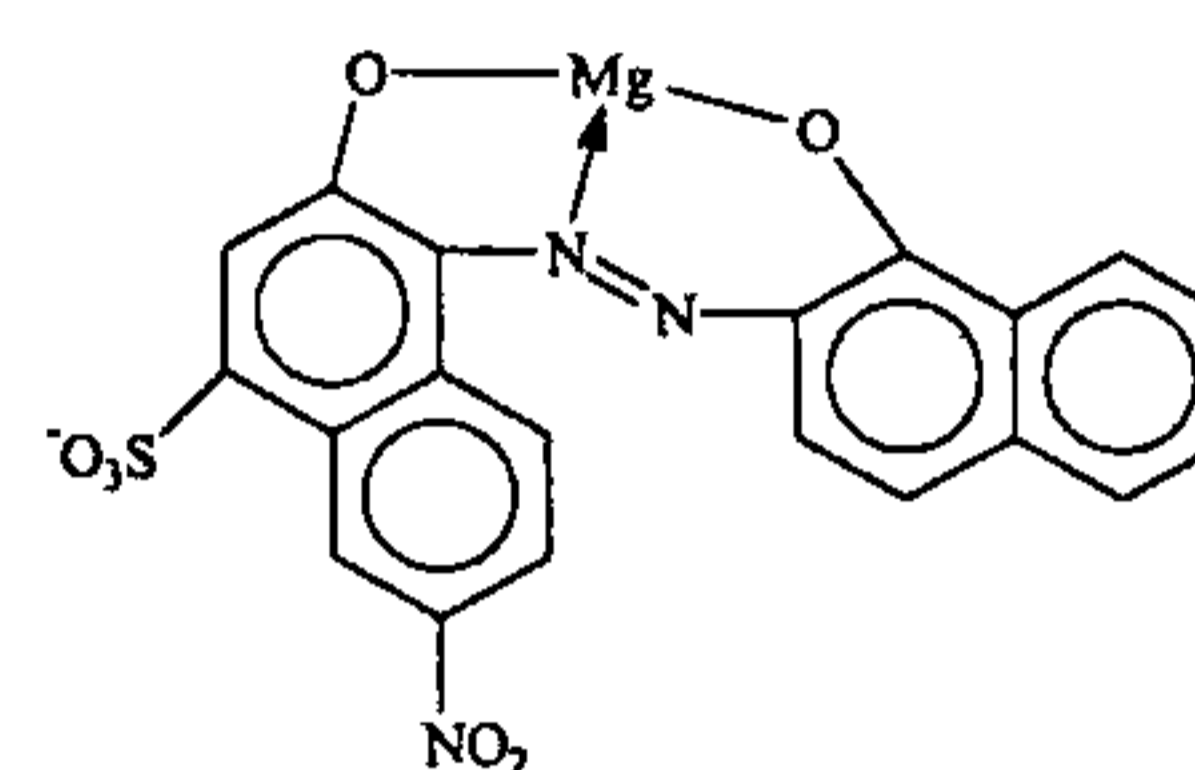
In many industrial processes the presence of adventitious metal ions causes problems because of the adverse effects these can have on product quality¹. Such difficulties can be avoided if the concentration of the free metal ion is reduced to such a level that at least some of its chemical reactions are no longer observed. An effective means of achieving this is by the addition of a suitable chelating agent which, by complexing with the metal ion, masks its characteristic reactions. Most of the raw materials used by industry contain metal ions. For example, natural water used so extensively for washing operations and as a medium for chemical reactions, contains dissolved metal salts, especially those of calcium and magnesium, which are chief contributors to the hardness of water. Raw materials originating in plants always contain metals, such as magnesium and manganese that are essential for growth. Most naturally occurring organic materials used industrially are, by their constitution, good chelating agents, and provide sources of metal ions. For example, wood is a complex protein containing coordinating groups such as -OH, -NH₂, -CO, -NH-, -COOH, -SH and -S-S-. It has a



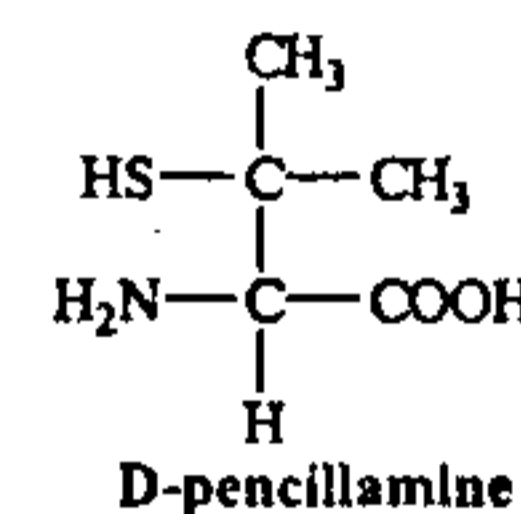
Some examples:



tartrate chelated to a metal ion



Eriochrome Black T chelated with magnesium



D-penicillamine

capacity for binding metal ions comparable with that of some synthetic ion-exchange resins.

Mineral substances used industrially are also normally contaminated with metallic salt impurities. For example, lime commonly employed for neutralization purposes contains at least traces of some other metal ions besides calcium. Corrosion of industrial equipment is a common source of contamination by iron and to lesser extent by metals such as zinc, tin, aluminium, lead, copper, nickel and cobalt.

The process by which a soluble complex of a metal is produced so that it is no longer precipitated by anions which form sparingly soluble salts with the free metal ion, is known as sequestration and the complexing species which cause this process are called *sequestering agents*. Unless steps are taken to sequester metal ions introduced from any of the sources, a number of deleterious consequences can follow, including the formation of slightly soluble metal salts which could lead to difficulties. Other examples include textile processing operations like bleaching

and dyeing or deposition and build-up of scale in boilers, the catalysis of unwanted side-reactions, such as the oxidation of fats or oils to produce rancidity, poor colour stability and general deterioration or reaction with chemicals subsequently introduced as in case of many dyestuffs used in the textile industry which themselves behave as chelating agents and can react with metal ion impurities to give undesired coloured products or precipitates.

In a living system, the concentrations of metal ions and their complexes are controlled within narrow limits. If the natural balance of these concentrations is disturbed by internal or external causes then the organism can no longer behave normally and disorders result. A number of major diseases are associated with changes in the concentration of the trace metal ions in certain tissues and body fluids. For example, in patients suffering from *Wilson's disease*, a disorder of the liver which affects the central nervous system, the natural mechanism for the control of copper concentrations is disturbed. Copper is stored in the liver in the form of copper proteins and it app-

ears that accumulation of free copper ions is the result of a deficiency of the copper protein *ceruloplasmin*.

Organisms cannot tolerate unusually high concentration of those metals which perform useful biological functions. Iron poisoning commonly results from the ingestion of excess iron compounds, leading to the condition known as *siderosis*. Again, if the extracellular concentration of potassium ion is increased to double the normal amount, heart disorders and possibly even death results, as this increase disturbs the osmotic balance of the electrolyte between the exterior and interior of the cell. The presence of some metals, such as lead, arsenic and mercury which apparently have no beneficial biological action causes well-known toxic effects. In these cases, poisoning results in a big increase in the amount of copper and zinc excreted.

Application

The role of chelating agents for the prevention, intervention and treatment of exposure to toxic metals was the topic of a conference held at the National Institute of Environmental Health Sciences in 1994. The objective of the conference was to review experimental and clinical studies concerned with the effectiveness and potential toxicity of chelating agents used to reduce the body burden of various metals and to identify research needs in the area of chelation.

Chelating therapy² is widely used for the treatment of *atherosclerosis* and other chronic degenerative diseases involving the circulatory system. It also has other side-effects. Most of the scientists agree that the beneficial effect of chelation treatment is from the removal of metallic catalysts that causes excessive oxygen-free radical proliferation, thus reducing the lipid peroxidation of the cell membranes, DNA, enzyme system and lipoproteins. Chelation prevents the bad effects of these and initiates the body's healing process and very often reverses the damage. By removing the calcium and copper anions from the blood, the plaque lining the artery walls may be made porous and brittle and eventually may be dislodged. Even if only a microscopic layer of the plaque is removed, it, along with a smoothening of the artery wall due to the healing of the cells that line the arteries, can improve the blood flow to the artery

muscles substantially. This can prevent artery spasm and thus minimize or prevent angina pain. Many patients who could not walk due to muscle pain or angina pain were able to walk without pain after chelation therapy.

Chelation extraction of heavy metals from contaminated soil has recently been seen as a method of treatment³. Chelating agents incorporate phosphonate, carboxylate and a variety of soft-donor atoms in geometries that foster high selectivity for targeted metal ions. New ligands enhance metal separations, waste water treatment, corrosion inhibition, scale removal, radioactive waste disposal and surface decontamination⁴. The problem of scale deposition is well known in the oil industry, as well as in other fields like gas field operations and desalination plants. As the oil reserves decrease, the conditions of production get more severe, favouring the formation of scales like that of CaCO_3 , CaSO_4 and BaSO_4 . A semi-quantitative study⁵ has been successfully conducted on coordination compounds containing calcium/magnesium and polydentate ligands suitable as sequestering agents for scale removal.

Chelates serve in a myriad of products and processes from cosmetics and pharmaceuticals to institutional and industrial cleaners⁶. In pulp and paper processes, chelates enhance the stability of oxidizing compounds, such as hydrogen peroxide. The ban on chromates in water treatment has spurred the demand for phosphates. In aqueous processes, chelating agents are routinely called upon to immobilize metal ions, that left unchecked can cause unwanted reactions, and result in product degradation, discolouration and other problems. Gas scrubbing processes based on ferric EDTA are also a small but growing market for chelates. Chelates on the basis of amino carboxylic acids are offered for cleaning, photography, pulp bleaching foodstuffs, detergents and cosmetics as metal complexing agents.

The most common commercially used chelating agents are aminopolycarboxylics including EDTA, *N*-hydroxy ethylene diamine triacetic acid (HEDTA), diethylene triamine pentaacetic acid (DTPA), and nitrilo triacetic acid (NTA). NTA has an economic advantage over EDTA that on a weight basis, less of it is needed to complex cations in a 1 : 1 mole ratio and also the raw materials from which it is

manufactured are less expensive than those required for EDTA.

EDTA is a synthetic amino acid first used in the 1940s for the treatment of heavy metal poisoning. It is now effectively used in emergency treatment of hypercalcemia and the control of ventricular arrhythmias associated with digitalis toxicity. Studies by the National Academy of Sciences/National Research Council in the late 1960s indicated that EDTA was considered to be effective in the treatment of occlusive vascular disorders caused by arteriosclerosis. EDTA grabs metallic cations such as lead or calcium from the body and forms a stable compound that is then excreted from the systems. The stability of this bond is vital to success in chelation therapy. If the bond is weak, other chemicals can break this bond to form their own compounds.

EDTA, NTA and DTPA are being used for remediation of heavy metal contaminated soil. In these applications, the contaminated soil is treated with selected chelating agents to extract metals from the soil phase to the aqueous phase. In fact the average annual demand grew by 4% during 1989–1994 to 372 million pounds in the United States, Western Europe and Japan⁷. Stricter limits on omission of sulphur dioxide and nitrogen oxide are expected to generate more interest in chelates. Replacement of chlorine in pulp and paper bleaching with hydrogen peroxide and sodium hydrosulphite, led to increased use of aminopolycarboxylics. Less stable than chlorine, these alternative oxidizing agents are more dependent on EDTA-type chelates. Chelates help prevent decomposition of these bleaching agents by complexing trace metals that can otherwise catalyse the decomposition reactions.

Organophosphonates had an average annual demand growth of 2.4% during 1989–1994 to 89 million pounds for the United States, Western Europe and Japan. The water treatment sector has continued to grow strongly since organophosphonates became a replacement choice for chromates in the United States; chromates were banned in 1985 as scale inhibitors in cooling tower application. Chelates in the hydroxycarboxylic group are beneficiaries to eliminate phosphates in detergents and cleaners. With the increased emphasis in proper recycling in the United States, there is a growing demand for gluconates and gluconic acid.

This has led to an increase in chelate consumption, as they are used in the deinking stage to prevent the decomposition of the deinking agent, like hydrogen peroxide. Preferences for milder, environmentally friendly cleaners and personal care products favour gluconates over EDTA. Gluconates, a member of the hydroxycarboxylic group of chelating agents, could see some demand growth because of biodegradability concerns in Europe. Average annual demand growth in gluconates was 8% during 1989–1994 to 78 million pounds for the United States, Western Europe and Japan. Growth came mainly as a result of their increased use in industrial cleaners to replace phosphates as more environmentally friendly and biodegradable compounds. Furthermore, cleaner formulations have been trending toward higher alkalinity due to perceptions of improved environmental friendliness. Since the aminopolycarboxylics are less effective in this higher pH range, gluconates have become one of the popular replacement choices. A new generation of polymer agents based on materials such as acrylic acid, maleic anhydride and methacrylic acid and polymer–phosphonate blends are emerging.

For the relief of symptoms of lead poisoning⁸, which can even cause brain damage in children, the most effective chelating agent is EDTA and other polycarboxylic acids. The monocalcium disodium salt of EDTA is used in the standard procedure for the treatment of lead poisoning. Addition of calcium with the chelating agent avoids problems of calcium-ion depletion due to the tendency to form a stable water-soluble Ca-EDTA complex.

Arsenic is another element that has characteristic toxic effects on human organisms. Arsenic disturbs the pyruvate oxidase system by chelating with suitably arranged thiol groups on the enzyme. This causes biochemical lesions like formation of skin blisters. Recognition of the preference of arsenic to bond with sulphur, led to the development of the chelating ligand 2,3-dimercaptopropanol. This reacts with arsenic and other heavy metals like mercury to form a five-membered chelate ring and effectively prevents its interaction with the essential thiol group of enzymes such as pyruvate oxidase.

The D-isomer of penicillamine is the most effective chelating agent for the

removal of toxic excess of copper. This is able to coordinate to a metal via sulphur, nitrogen, and oxygen donors. It is water-soluble and stable and appears to be able to remove excess copper in the form of soluble complexes without depletion of the normal stores of copper ion within the body.

The discovery that some of the coordination complexes of platinum are very effective inhibitors for the growth of tumours supports the link between chelation and cancer. Most chemotherapeutic agents effective against cancer are actually chelating agents. 2,2'-bipyridyl and 1,10-phenanthroline are known to possess anti-tumour activity. It follows that most chemicals which have been implicated in the development of cancer are also chelating agents. These include azodyes such as *p*-dimethylaminoazobenzene or their metabolic products, which may become carcinogenic by the chelation mechanism. Platinum (II) complexes showing anti-tumour activity, *cis*-diammino dichloro platinum (II) and *cis*-diaminotetrachloro-platinum (IV), have *cis* arrangement of identical ligands. This stereochemistry appears to be essential for anti-tumour activity, as the *trans* isomers are not active. In the *cis*-isomer, because the two chlorine atoms are less firmly bound than the two ammonia ligands, their replacement by a chelating agent is possible. The number of uncharged *cis* platinum complexes, which can be used clinically with diametric effect for treatment of terminal cancer, is severely limited because they are toxic. Possibly the toxic effects of platinum complexes could be minimized by administering them in small amounts concurrently with another anti-tumour agent.

We need to design and develop still newer chelating agents for reducing the body burden of toxic metals and the radioactive actinide elements. Jones *et al.*⁹ are developing new chelating agents to enhance the elimination of cadmium in chronic cadmium intoxication. For this they have prepared a large number of compounds like monoesters of meso-2,3-dimercaptosuccinic acid, a bis dithiocarbamate containing two dithiocarbamate groups, which may coordinate to the same cadmium ion and monoamides of meso-2,3-dimercaptosuccinic acid. These compounds are capable of removing intracellular cadmium from the liver and the kidneys. Jones *et al.* have also shown

some chelating agents active against a culture form of *Trypanosoma cruzi*, the agent responsible for Chaga's disease and against a culture form of drug resistant *Leishmania major* which causes leishmaniasis.

Natural chelates

The chelating polymers can be obtained from the enormous amount of natural raw materials presently discharged to the sea as waste from the marine canning factories¹⁰. These natural chelating agents have caught the attention of analytical chemists and have found applications in the field of chromatography and trace metal separation. Polysaccharides and their breakdown products such as humic and fulvic acids present in the soil humus are important in chelation and exchange reactions involving active constituents such as the ursonic acids. Most of the principal chelating groups (amino, imino, hydroxy, thioether, carboxylate and phosphonate) are present in compounds isolated from soil organic matter. These organic polymeric molecules are complexed to some extent with naturally occurring metal ions. Amino acid derivatives like nucleic acids are known to interact with various divalent metal ions.

Cellulose can be used in certain cases to collect metal ions, particularly when organic solvents are used. For instance, traces of antimony could be separated from gram amounts of iron and manganese in ethyl-ether-nitric acid as well as from gram amounts of mercuric chloride, uranyl nitrate and tetrachloroauric acid. Similarly alginic acid and chitin and chitosan are naturally occurring chelating polymers. Alginic acid is a polyuronide found in brown seaweeds, and is present as a mixed salt of cations mostly calcium and the alginate in the seaweeds that behaves as a base exchange material.

Chitin, a derivative of cellulose, poly-N-acetyl-D-glucosamine, occurs widely in lower animals like fungi, etc. The enormous amount of chitin which falls to the sea bottom collects metallic elements by various mechanisms, adsorption–exchange chelation, and in the light of the long time available for this process to occur, it is quite probable that this will prove to be a major factor in the transport of transition metal ions in the sea.

Metallothionein (MT) was discovered in 1975 as a cadmium-binding protein in

the renal cortex of the horse and is characterized by its low molecular weight (> 9000 Da), cysteine-rich, metal-binding protein. Mammalian MT contains 61 amino acids. Metals bind to MT in metal-thiolate complexes exhibiting tetrahedral (cadmium, zinc) or trigonal (copper) geometry. The toxicity of the cadmium-metlothionein complex precludes any consideration of the clinical use of this natural metal ligand to enhance excretion of metals.

In addition, there are many other natural polymers exhibiting chelating ability. They can immobilize metals ions, which can cause chemicals to decompose and are highly toxic to the ecosystem. In

short, we can say 'chelates, can't live with 'em, can't do without 'em'¹¹.

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HYPOTHESIS

Anoxia during the Late Permian binary mass extinction and dark matter

Samar Abbas, Afsar Abbas and Shukadev Mohanty

Recent evidence quite convincingly indicates that the Late Permian biotic crisis was in fact a binary extinction with a distinct end-Guadalupian extinction pulse preceding the major terminal end-Permian Tartarian event by 5 m.y. In addition, anoxia appears to be closely associated with each of these end-Palaeozoic binary extinctions. Most leading models cannot explain both anoxia and the binary characteristic of this crisis. In this paper we show that the recently proposed volcanogenic dark matter scenario succeeds in doing this.

Recently, Knoll *et al.*¹ have suggested a new model wherein the overturn of anoxic deep oceans and the consequent introduction of carbon dioxide into surficial environments led to the end-Permian Tartarian extinction. This model could explain the selectivity of the extinction, with organisms tolerant to elevated carbon dioxide levels exhibiting higher degrees of survival across the P/T boundary. The C-isotope record also indicates that another anoxic event occurred at the end of the Guadalupian, approximately 5 m.y. before the Tartarian extinction. Knoll *et al.* state that it is possible that the Siberian flood basalt volcanic episode² could have led to the Tartarian overturn by means of tectonic realignment³. It has also been realized that this P/T extinction was in fact a double extinction⁴, with each extinction apparently associated with an anoxic

event, and the work of Knoll *et al.* is consistent with this fact. In this paper we extend the recently proposed idea of volcanogenic dark matter⁵ to consistently explain the binary nature of the extinction and the associated anoxia.

Dark matter may constitute more than 90 per cent of the matter of the universe, and ample evidence in favour of its existence occurs in the form of galactic rotation curves, the stability of galactic clusters, etc. Several candidates for the enigmatic dark matter have been proposed^{6,7}. This dark matter envelopes galaxies in a uniform halo. However, the nature of the dark matter is unknown, with candidates ranging from neutrinos to Jupiter-sized brown dwarfs. This paper considers the class of dark matter candidates generally known as WIMPs (weakly interacting massive particles). In addition, it is very

likely to form compact clusters as well. During the occasional passage of such a 'clump' through the earth, dark matter would accumulate in the core and annihilate, producing vast quantities of heat⁸. Abbas and Abbas⁵ estimate that the heat output can exceed present-day terrestrial heat production by five orders of magnitude. These large quantities of heat would lead to the creation of a superplume that initiates, upon arrival at the surface, a flood basalt volcanic episode, of which Siberia is an example⁵. Inherent in this model is the concept that all giant flood basalt provinces, including the Deccan, Parana and Ethiopian plateaus, were produced in this manner. This volcanism may lead to changes in oceanic circulation patterns by tectonic realignment or the creation of new oceanic plumes above submarine eruption sites. Such a change