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METALS, LIGANDS, AND CANCER

DAVID R. WILLIAMS

Department of Chemistry, University of St. Andrews, St. Andrews, Fife, Scotland

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Contents

I. Introduction

Although the human body is but 3% metals, life depends upon these elements far more than this figure suggests. For example, the transition series metals, even though some are present in only trace amounts, generally appear in the active centers of enzymes that catalyze substrates to form aggregate molecules, and so an understanding of the properties of multicomponent systems requires a knowledge not only of the biochemistries of these individual components but also of the metal complexes that marshall their conjoining. There have already been several reviews discussing our present knowledge of the roles of metal ions in biological systems.[1-4]

Paralleling these relatively new biochemical concepts, there ought to be an awareness of the usefulness of such discoveries in treating disease. Hence, the theory that metal complex formation is deeply involved in normal life processes has led to reviews such as "The Effects of Chelating Agents on Organisms",[5] "Chelation in Medicine",[6] "Metal Binding in Medicine",[7] "Metal Chelates in Biological Systems",[8] and "Structure and Bonding in Biochemistry".[9]

In essence, each *in vivo* complex involves the structural matching of a metal to a ligand. The mutual aims of this review are to draw attention to additional outlets for coordination chemistry researches and to focus upon metal complexes as being a new wide range of possibilities worthy of consideration by therapeutic researchers. Disease occurs when excesses or deficiencies of *in vivo* metals appear, when other metal pollutants enter the body (*e.g.*, the current controversies over cadimum, mercury, and lead), or when poisons or viruses enter into the metal–ligand competition. For our researches into metallotherapy, we have chosen to study a group of diseases called cancers.

Although some cancer problems have been partially solved, the diseases are still responsible for 20% of the deaths of the population, and there still remain groups of cancers that are increasing in occurrence (for example, leukemia and lung cancer).[10] Much research time and finance has been focused upon the mechanism of carcinogenesis, and a wide range of anticancer drugs is available. However, Stock has pointed out that simple modifications to already existing drugs are now unlikely to produce better anticancer reagents.[11] More dramatic measures are now necessary, and it is to satisfy this need that metal complexing is suggested as a possible means of exploiting the differences between normal and cancer cells to the detriment of the malignant cell.

Metallotherapy was first reported in 1500 B.C. when an aqueous–ethanolic suspension of rust was administered as a cure for impotence,[12-14] and the treatment of anemias using ferrous salts has long since been practiced. Nevertheless,

(1) R. J. P. Williams, *RIC (Roy. Inst. Chem.) Rev.*, 13 (1968).
(2) R. J. P. Williams, *Quart. Rev., Chem. Soc.*, **24**, 331 (1970).
(3) D. R. Williams, "The Metals of Life," Van Nostrand, London, 1971.
(4) H. Sigel and D. B. McCormick, *Accounts Chem. Res.*, **3**, 201 (1970).
(5) A. Albert, *Aust. J. Sci.*, **30**, 1 (1967).
(6) J. Schubert, *Sci. Amer.*, **214** (5), 40 (1966).
(7) M. J. Seven and L. A. Johnson, Ed., "Metal Binding in Medicine," Lippincott Co., Philadelphia, Pa., 1960.
(8) F. P. Dwyer and D. P. Mellor, Ed., "Chelating Agents and Metal Chelates," Academic Press, London, 1964, p 383.
(9) Collection of metalloenzyme reviews: *Struct. Bonding (Berlin)*, **8**, 1970.
(10) R. J. C. Harris, "Cancer," Allen and Unwin, London, 1970.
(11) E. J. Ambrose and F. J. C. Roe, Ed., "The Biology of Cancer," Van Nostrand, London, 1966.
(12) T. G. Spiro and P. Saltman, *Struct. Bonding (Berlin)*, **6**, 116 (1969).
(13) E. Beutler, V. F. Fairbanks, and J. L. Fahey, "Clinical Disorders of Iron Metabolism," Grune and Strattion, New York, N. Y., 1963.
(14) J. G. Frazer, "The Golden Bough," Macmillan, New York, N. Y., 1935.

apart from the reasonably widespread use of sodium, calcium, and magnesium salts for intestinal treatment and some use of mercury and of arsenic for syphilis and trypanosomes, metallotherapy has not developed parallel to, and at a rate comparable with, our understanding of the roles of metals *in vivo*.[15] The state of the subject up to 1960 was reviewed by Furst in a talk entitled "Chelation and Cancer—A Speculative Review," and even then he suggested that "chelation may be fundamental to the entire cancer problem."[16] We now propose to update his remarks.

II. Metals in Vivo

A. LIFE IN GENERAL

The 20 elements that are essential for life in our bodies are shown in Figure 1 in their correct positions in the periodic

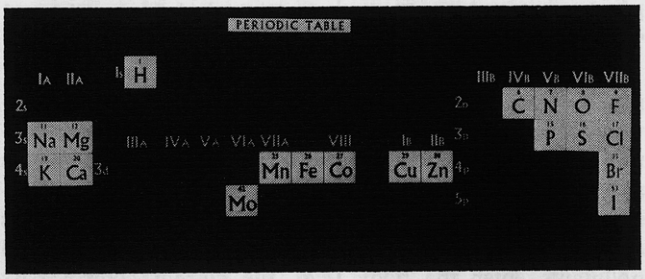

Figure 1. The 20 elements that are essential for life in the human body arranged in their correct periodic table positions.

table. In general, the elements shown follow the abundances of the elements in the earth's crust (*i.e.*, natural selection has removed organisms dependent upon less readily available elements). There are two exceptions to this generalization. (a) Some less well known species are dependent upon less abundant elements. The following "essential" elements have been mentioned in connection with nonhuman species: aluminum, arsenic, barium, boron, cadmium, chromium, lithium, nickel, niobium, rubidium, selenium, silicon, strontium, titanium, and vanadium. (For example, there are a whole range of silica- and phosphate-eating organisms that are to be found in the ocean[17] and also Ascidian, *Phallusia mamillata*, which require vanadium.[18-20]) Insufficient records exist to be able to extrapolate whether such minor species are going to die out or to thrive during the next few thousand years or so. (b) As more and more exotic catalysts, nuclear reactors, and heavy element compounds are used by our civilization, our world is becoming more polluted. If we accept the view that evolution and adaption permit elements to traverse the scheme poisons → tolerable impurities → useful elements → essential elements, the first new elements found to be useful will be those having chemical characteristics similar to the essential 20 (for example, in the main groups there are close relationships, often diagonal, among electronegativities, for example, S(2.44) = Se(2.44)).[21] Hence, the impurities arsenic, boron, and selenium may be found in place of iodine, phosphorus, or sulfur, respectively. Possibly, over a long time interval, adaption might occur and organisms will become dependent upon some of these new elements.

B. HUMAN LIFE

Turning our attentions to the essential ten metals, their essentialities are established beyond doubt,[1,2,4,22] and their biochemical roles are summarized in Table I. The metals fall into two broad classes: the main groups ions, which are ionic and mobile, and the transition series, which tend to be covalently bonded in the vicinity of the same donor groups.[4] In spite of these two convenient periodic classification groupings, the metals within each group are definitely not interchangeable. Each element has its own particular list of functions, and the optimum metal ion concentration for these functions is homeostatically controlled.

1. Main Group Metals

These are found as solids (for example, in bones and teeth) and in solution (for example, the blood stream). Sodium and calcium are the main cations outside cells, and potassium and magnesium are the main ones within cells, there being active "ion pump" mechanisms for chemically pushing these ions in the required direction. Sodium and potassium take part in a multitude of roles: maintenance of osmotic pressure, transmission of nerve impulses, and as an essential cation for electroneutrality of anionic excretion. Few solubility difficulties arise from imbalances in the concentrations of these ions except possibly that the insoluble sodium salt of uric acid causes gout. Magnesium and calcium appear to fulfill all the ionic roles untouched by sodium and potassium. Group II ion characteristics include difficulty in passing through intestinal linings (Mg), production of depression and anesthesia in overdoses (Mg), dictation of the correct matrix in bone and teeth (Ca), precipitation of milk casein (Ca), maintenance of the correct rhythm of the heartbeat (Ca), and the conversion of fibrinogen into fibrin (Ca). The insolubility of calcium compounds is sometimes a nuisance (magnesium compounds are more soluble), and carbonate, fluoride, oxalate, and phosphate readily appear as precipitates in the bloodstream. (The blood is often supersaturated with calcium.) Ageing encourages such precipitation in the form of cataracts, gallstones, and the hardening of soft tissues and arterial walls.

2. Transition Metals

In general their role is one of catalysis, either redox or super acid, and this duty is performed in the active centers of enzymes. Metalloenzymes may either involve the metal ion being permanently attached to the active site (for example, the iron(II) in hemoglobin), or the metal coming and going as part of a coenzyme (for example, the cobalt(III) in vitamin B_{12} coenzyme). In general, metalloenzymes have three levels of sophistication of design: (a) the organic bulk which pro-

(15) F. Lembeck and K.-F. Sewing, "Pharmacological Facts and Figures," Springer-Verlag, Berlin, 1970.
(16) A. Furst in ref 7, Chapter 46.
(17) L. G. Sillén, *Svensk. Kem. Tidskrift*, **75** (4), 161 (1963).
(18) A. B. McNaught and R. Callander, "Illustrated Physiology," Livingston Ltd., Edinburgh, 1965.
(19) C. L. Comar and F. Bronner, Ed., "Mineral Metabolism," Vol. I and II, Academic Press, New York, N. Y., 1960.
(20) E. O. Walsh, "An Introduction to Biochemistry," 2nd ed, English Universities Press, Edinburgh, 1968.
(21) F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," 2nd ed, Interscience, London, 1966.
(22) R. J. P. Williams, *Endeavour*, **26**, 96 (1967).

Table I

Occurrence, *in Vivo* Roles, and Complexing Characteristics of the Metals That Are Essential to Human Life[3]

	Group IA (s^1)		*Group IIA (s^2)*		*Transition series (d^{1-9})*					*Group IIB (d^{10})*
	Na	*K*	*Mg*	*Ca*	*Mn*	*Fe*	*Co*	*Cu*	*Mo*	*Zn*
Position in periodic table	Main group I		Main group II		Transition metals					Subgroup II
Biological roles	Charge-carriers and osmotic balance		Structure formation and trigger reactions		Redox catalysis and enzyme structures					Super-acid catalysts
Location	Mobile		Semimobile		Static					Static
Oxidation states	I	I	II	II	II/III	II/III	II/III	I/II	V/VI	II
Donor atoms preferred	$-O^-$	$-O^-$	$-O^-$	$-O^-$	$-O^-$	N, $-O^-$	N, $-O^-$	N, $-S^-$	$-S^-$	N, $-S^-$
Type of complexes formed	Weak		Fairly strong		Strong					Strong
Rate of exchange between free and complexed ions	Very rapid		Moderately fast		No exchange					No exchange
Grams per 70 Kg man	70	250	42	1700	<1	7	<1	<1	<1	<1
Adult: total blood concn (μM)	85,200	44,500	1570	2420	2.18	8590	0.71	14.8		138.4

duces the correct shape of cleft to house the active site and also has ionic or hydrophobic groups on the outer surface of the enzyme to ensure water or membrane solubility, respectively; (b) the amino acid residues lining the active site (their arrangements are unique, and constructional errors have serious consequences; for example, sickle cell anemia and methemoglobinemia are both structural diseases[23,24]); (c) the immediate environment of the metal ion at the end of the active site. These ions are usually transition metal ions and have to be uniquely chosen. Gillard[25] has summarized the role of the metal ion as being to lock the geometry of the active site so that only certain substrates can be accommodated, to activate enzyme or substrate bonds through coordination, and, also *via* coordination, to change the shape of the substrate so that it can just fit into the active site. Not surprisingly, this high specificity requires several different metal ions and oxidation states to satisfy all the roles.

Manganese exists in solution in oxidation state II, and III if complexed. It is essential for several enzymes such as isocitrate dehydrogenase, malic enzyme, and pyruvate decarboxylase. Iron is the transition metal that occurs in highest concentrations in our systems. Depending upon the complexing ligand attached to the iron, the metal may be divalent (for example, myoglobin or hemoglobin), trivalent (for example, catalases and oxidases), or redoxing between both states (for example, cytochromes). Even within the same oxidation state it can have different electron arrangements (for example, the iron(II) in hemoglobin is high spin and in oxyhemoglobin is low spin). Cobalt is best known for being the central ion in cobalamins and cobamides (vitamin B_{12}, cobalt(III)). It is less well recognized that cobalt(II) complexes can carry molecular oxygen. Even simple complexes with ligands such as glycylglycine and histidine can perform this task. In general, cobalt(II) is associated with low symmetry sites in enzymes. Copper, using oxidation states I and II, and cuproproteins can also carry oxygen (for example, hemocyanin). With the exception of iron, copper is the best catalyst for such oxidation–reduction processes. In metalloproteins containing more than one metal ion, copper tends to occur as even numbers (for example, cerebrocuprein has two Cu, ceruloplasmin has eight Cu). Zinc exhibits but one oxidation state *in vivo*, but, nevertheless, it is still essential to several metalloenzymes (for example, carboxypeptidase A). Molybdenum, however, does enter into redox reactions (V ↔ VI) and even the III and IV oxidation states are suspected of being involved.[26] Its most notable role is in the xanthine and purine oxidases in milk (two Mo and eight Fe). We might note that molybdenum (atomic number 42) is the heaviest essential element *in vivo*.

III. Ligand Donor Groups in Vivo

A. DONOR ATOMS

All general textbooks of biochemistry review the structure of ligands *in vivo* even though the fact that the organic species are capable of reacting with metal ions or the words "ligand" or "complex" might never be mentioned. Fundamentally, any part of a molecule that happens to be more basic than the –C–H portions are potential electron donors. Amino acids, peptides, proteins, hormones, nucleoproteins, nucleic acids, carboxylic acids, carbohydrates, lipids, simple anions, administered drugs, and even the solvent water all contain some electron donor elements from the list nitrogen, oxygen, fluorine, phosphorus, sulfur, chlorine, bromine, and iodine. Quite recently even carbon has been shown to form bonds to metal ions (examples are (i) studies into vitamin B_{12} bonds to cobalt by Williams, *et al.*,[27] and (ii) the ease of converting mercury into methylmercury *in vivo*).

The commoner electron donor groups employed in drugs are indicated in Figure 2.[3,15] The actual donor groups selected

(23) H. R. Mahler and E. H. Cordes, "Biological Chemistry," 2nd ed, Harper and Row, New York, N. Y., 1967.
(24) D. E. Green and R. F. Goldberger, "Molecular Insights into the Living Process," Academic Press, New York, N. Y., 1967.
(25) R. D. Gillard, *Inorg. Chim. Acta Rev.*, 69 (1967).
(26) J. T. Spence, *Coord. Chem. Rev.*, **4**, 475 (1969).
(27) H. A. O. Hill, J. M. Pratt, and R. J. P. Williams, *Chem. Brit.*, **5**, 156 (1969).

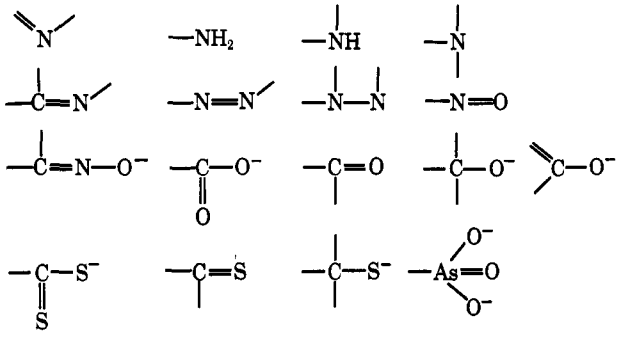

Figure 2. Donor groups commonly used in modern pharmaceuticals.

by the metal depend upon many factors that are conveniently discussed using the "hard and soft acids and bases" theory (see next section). These factors include the character of the metal, the nature of each donor group, and the type of supporting solvent. We consider there to be three types of solution chemistry *in vivo:* (a) aqueous, for example, the blood and lymphatic systems; (b) nonaqueous, for example, lipids in the membranes of cells; and (c) enzymic—the crevice leading to the active sites of enzymes may be quite different from both the supporting medium and the active site; for example, lysozyme has polar groups in its active site but the walls of the corridor leading to it are mainly hydrocarbon so that ionic substrates are not hindered while approaching this site.

It is noteworthy that although Figure 1 lists 20 of the lightest elements in the periodic table, all possibilities for bonding are still left open; for stability, the *number of extra electrons* required to complete a subshell and to produce a stable bond are *one* for hydrogen, *two* for oxygen, *three* for nitrogen, *four* for carbon, *three* or *five* for phosphorus, and *two* or *six* for sulfur. Finally, whichever the chosen donor groups and the ligand in question, the latter is usually asymmetric (for example, amino acids *in vivo* all have the L configuration). Naturally, the complexes formed with these ligands are also asymmetric, and Gillard has reviewed these possibilities.[25]

B. LIGAND–METAL BONDING CONSIDERED THROUGH THE HSAB APPROACH

The strengths of metal–ligand bonds are conveniently systematized using the theory of hard and soft acids and bases (HSAB).[28–33] This approach assumes that all bonds between heteroatoms may be considered as having an acid and a base portion. Essentially this acidity or basicity is decided by the number of valence electrons associated with a species and the ease with which they can be rearranged. Properties employed in classifying a species as hard or soft, acid or base, are summarized in Table II.

The main principle behind HSAB theory is that strong bonds are only formed between hard acids and hard bases or between soft acids and soft bases. Hard–soft bonds are either very weak or do not exist. Using these concepts, the commoner species encountered *in vivo* are included in Tables III and IV. In practice, it is found that the hard acid metals prefer ligand donor atoms of the first short period

$$N \gg P > As > Sb$$
$$O \gg S \sim Se > Te$$
$$F > Cl > Br > I$$

and soft acid metals prefer

$$N \ll P > As > Sb$$
$$O \ll S < Se \sim Te$$
$$F \ll Cl < Br < I$$

Such observations not only explain the distribution of metals on the earth's surface (for example, Mg^{2+}, Al^{3+}, and Ca^{2+} are found as ores of hard bases such as O^{2-} or CO_3^{2-}, and $Cu^{+/2+}$, Hg^{2+} or Hg^{+} or Pb^{2+} as ores of soft acid bases such as S^{2-}) but also the distribution of bonds *in vivo* (for example, see "donor atoms preferred" in Table I; as metal ion hardness decreases, there is a clear trend from O through to S).

From Tables III and IV, it is clear that the hardness of an element increases with its oxidation state. Hence, to stabilize an element in a high oxidation state it ought to be surrounded by hard bases, whereas stabilization of low oxidation states requires an environment of soft bases. Hence, metal ions undergoing redox reactions *in vivo* require an accompanying environmental change. When many ligands are concerned, the phenomenon of symbiosis needs also to be considered. This is the process whereby a hard (or soft) base on a metal ion encourages other hard (or soft) bases to join it. For example, zinc in carbonic anhydrase binds halide ions $I^- > Br^- > Cl^- > F^-$; *i.e.*, the enzyme environment has symbiotically rendered borderline Zn^{2+} as soft. However, in aqueous solution, Zn^{2+}_{aq} binds $F^- > Cl^- > Br^- > I^-$; *i.e.*, the hard solvation sphere has rendered Zn^{2+} hard. These metalloenzyme redox processes can be symbiotically poisoned because very hard or very soft ligands completely arrest the metal in one oxidation state. Examples of soft acid poisons are CH_3Hg^+ and Cd^{2+}, and, of soft base poisons, are CO, CN^-, and S^{2-}.

The relevance of HSAB to the design of therapeuticals is illustrated in Figure 3 and Table V. The most frequently used ligands for removing metal ions from human tissue are shown. The parallel increase in softness of the donor and of the metal ion removed is very evident. Many years of largely fruitless toil in selecting these ligands might have been saved had HSAB ideas had been more mature 30–40 years ago.

IV. Cancer

A. INTRODUCTION

Cancer rates among the top three causes of deaths in the West and in spite of press reports of amazing new cures, this rating is likely to increase as better cures are found for other fatal diseases. Roe has defined cancer as "a disease of multicellular organisms which is characterized by the seemingly uncontrolled multiplication and spread within the organism of apparently abnormal forms of the organism's own cells."[11] This term "cancer" actually embodies hundreds of different types of neoplastic diseases ranging from localized skin cancers to whole body leukemias with representative cure rates as high as 95% or as low as 0%. However, the cure rates for most cancers fall between these extremes.[34] There are a variety

(28) R. G. Pearson, *J. Chem. Educ.*, **45**, 581, 643 (1968).
(29) R. G. Pearson and R. S. Drago, *Chem. Brit.*, **3**, 103, 516 (1967).
(30) R. F. Hudson, *Coord. Chem. Rev.*, **1**, 89 (1966).
(31) F. Basolo and R. G. Pearson, "Mechanisms of Inorganic Reactions," 2nd ed, Wiley, New York, N. Y., 1971.
(32) S. Ahrland, *Struct. Bonding (Berlin)*, **1**, 207 (1966).
(33) S. Ahrland, *Helv. Chim. Acta*, **50**, 306 (1967).
(34) H. E. Skipper, *Sci. Horiz.*, **125**, 13 (1971).

Table II

Classification of Hard and Soft Acids and Bases

Acid (electron acceptor)			*Base (electron donor)*		
Hard	*Property*[a]	*Soft*	*Hard*	*Property*[a]	*Soft*
Low	Polarizability	High	Low	Polarizability	High
High	Electropositivity	Low	High	Electronegativity	Low
Large	Positive charge or oxidation state	Small	Large	Negative charge	Small
Small	Size	Large	Small	Size	Large
Ionic, electrostatic	Types of bond usually associated with the acid	Covalent, π	Ionic, electrostatic	Types of bond usually associated with the base	Covalent, π
Few and not easily excited	Outer electrons on donor atoms	Several, easily excited	High energy and inaccessible	Available empty orbitals on donor atom	Low-lying and accessible

[a] These properties may be used as guide lines for classifying species. The whole column need not be satisfied for a species to be called hard or soft but the more properties that are true, the greater the degree of hardness or softness.

Table III

HSAB Classification of Acids[28] [a]

Hard	*Soft*
H^+, Li^+, *Na^+*, *K^+*	*Cu^+*, Ag^+, Au^+, Tl^+, Hg^+
Be^{2+}, *Mg^{2+}*, *Ca^{2+}*, Sr^{2+}, *Mn^{2+}*	Pd^{2+}, Cd^{2+}, Pt^{2+}, Hg^{2+}
	CH_3Hg^+, $Co(CN)_5^{2-}$, Pt^{4+}, Te^{4+}
Al^{3+}, Sc^{3+}, Ga^{3+}, In^{3+}, La^{3+}	Tl^{3+}, $Tl(CH_3)_3$, BH_3, $Ga(CH_3)_3$
N^{3+}, Cl^{3+}, Gd^{3+}, Lu^{3+}	$GaCl_3$, GaI_3, $InCl_3$
Cr^{3+}, *Co^{3+}*, *Fe^{3+}*, As^{3+}, CH_3Sn^{3+}	RS^+, RSe^+, RTe^+
Pu^{4+}, Ce^{3+}, Hf^{4+}	
UO_2^{2+}, $(CH_3)_2Sn^{2+}$, VO^{2+}, *MoO^{3+}*	I_2, Br_2, ICN, etc.
$BeMe_2$, BF_3, $B(OR)_3$	Trinitrobenzene, etc.
$Al(CH_3)_3$, $AlCl_3$, AlH_3	Chloranil, quinones, etc.
RPO_2^+, $ROPO_2^+$	Tetracyanoethylene, etc.
RSO_2^+, $ROSO_2^+$, SO_3	O, Cl, Br, I, N, $RO\cdot$, $RO_2\cdot$
I^{7+}, I^{5+}, Cl^{7+}, Cr^{6+}	M^0 (metal atoms)
RCO^+, CO_2, NC^+	Bulk materials
HX (hydrogen bonding molecules)	CH_2, carbenes
Borderline	
Fe^{2+}, *Co^{2+}*, Ni^{2+}, *Cu^{2+}*, *Zn^{2+}*, Pb^{2+}, Sn^{2+}, Sb^{3+}, Bi^{3+}, Rh^{3+}, Ir^{3+}, $B(CH_3)_3$, SO_2, NO^+, Ru^{2+}, Os^{2+}, R_3C^+, $C_6H_5^+$, GaH_3	

[a] Essential *in vivo* metal ions are italicized.

Table IV

HSAB Classification of Bases[28] [a]

Hard	*Soft*
H_2O, OH^-, F^-	R_2S, RSH, RS^-
$CH_3CO_2^-$, PO_4^{3-}, SO_4^{2-}	I^-, SCN^-, $S_2O_3^{2-}$
Cl^-, CO_3^{2-}, ClO_4^-, NO_3^-	R_3P, R_3As, $(RO)_3P$
ROH, RO^-, R_2O	CN^-, RNC, CO
NH_3, RNH_2, N_2H_4	C_2H_4, C_6H_6
	H^-, R^-
Borderline	
$C_6H_5NH_2$, C_6H_5N, N_3^-, Br^-, NO_2^-, SO_3^{2-}, N_2	

[a] The symbol R stands for an alkyl or aryl group.

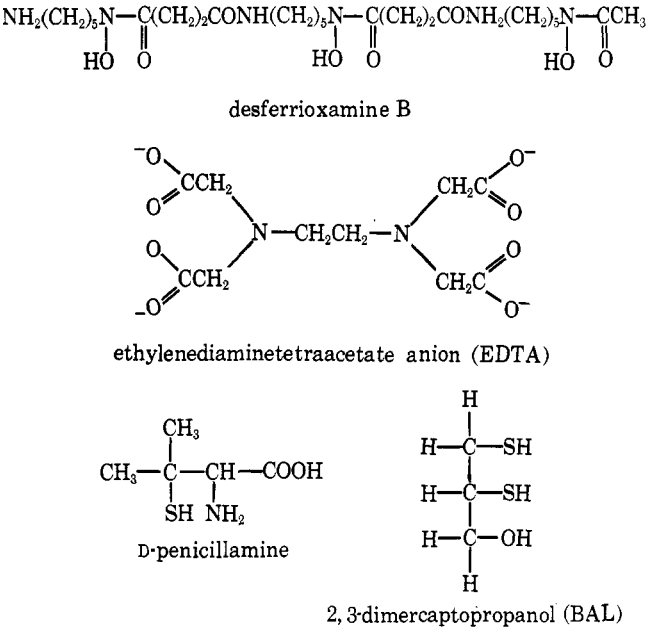

Figure 3. Earliest sequestering reagents for therapeutically treating metal ion excesses. Their applications are described in Table V.

of publications reviewing cancer research, and these are written for the layman,[10,34-36] biologist,[10,37] chemist,[38,39] therapeutical designer,[40-43] and researcher in general.[44] Hence, section B may be kept brief.

B. DESCRIPTION OF CANCER

Cancer is caused by carcinogens[38] which may be defined as substances that are capable of producing tumors in any test species by any route and at any dose level.[39] This

(35) H. W. Cook, "Tobacco Smoke and Lung Cancer," Vol. 5, Royal Institute of Chemistry, lecture series, 1961.

(36) *Sci. J.*, **10** (1969); *Sci. Res.*, 20 (Dec 22, 1969); *Chem. Eng. News*, 7 (March 30, 1970); 46 (April 20, 1970).

(37) P. Daudel and R. Daudel, "Chemical Carcinogenesis and Molecular Biology," Wiley, New York, N. Y., 1966.

(38) C. E. Searle, *Chem. Brit.*, 5 (1970).

(39) P. Grasso, *ibid.*, 17 (1970).

(40) J. A. Stock, "Experimental Chemotherapy," Vol. 4, Academic Press, New York, N. Y., 1966.

(41) J. A. Stock, *Chem. Brit.*, 11 (1970).

(42) P. A. Plattner, "Chemotherapy of Cancer," Elsevier, Amsterdam, 1964.

(43) J. Y. Bogue, *J. Chem. Educ.*, 458 (1969).

(44) Proceedings of the 6th National Cancer Conference, Denver, Colo., 1968," Lippincott Co., Philadelphia, Pa., 1970.

Table V

Earliest Sequestering Reagents for Therapeutically Treating Metal Ion Excesses[a]

Ligand	*Donor atoms*	*Metals removed*	*HSAB classification*
Desferrioxamine B	Several O	Fe(III)	Hard
EDTA	4 O, 2 N	Pb(II)/Co(II)	Borderline
D-Penicillamine	S, N, O	Cu(II)/Cu(I)	Borderline/soft
British antilewisite (BAL)	2 S	Arsenicals/ Au(I)/Hg-(II)/Hg(I)	Soft

[a] The chemical formulas are given in Figure 3. As one descends the table, increasing softness of donor atoms is paralleled by increasing softness of the acid removed.

term includes quite inert materials such as gold, silver, sodium chloride, or plastics which can cause cancer by localized irritation, but, in general, it refers to the more widely recognized carcinogens summarized in Table VI. Carcinogens first

Table VI

Classification of Agents Known to Cause Cancer[11]

Chemical	*Physical*
Aromatic hydrocarbons and amines	Ionizing radiation
Aromatic heterocyclic ring compounds	Ultraviolet radiation
4-Nitroquinoline oxide	Burns
Nitrosamines	
Azo compounds	*Other*
Alkylating agents	Chromosomal abnormalities
Urethanes	
Polymers	Viruses

come to light during epidemiological studies, and then the carcinogenicity of the suspect chemicals are measured using animal experiments. Difficulties that arise include (a) the extrapolation between one animal species and another, (b) the choice of the age of the animals (for example, new born have less capabilities of developing immunological rejection reactions than older animals), and (c) the classification of identified carcinogenic chemicals into initiators or promoters (cocarcinogens; see later).

The molecular mechanism of cancer induction is still mainly embodied in tentative theories. Because cancer cells cannot be turned back into the forms of their parent normal cells, the following hypotheses are at present in vogue: (a) carcinogens may be metabolized into more active reagents, (b) the hereditary mechanism of the cell is then involved either by the carcinogen reacting with nuclear DNA (for example, sulfur mustard is thought to increase the cross-linking between juxtapositioned DNA strands) or by similar but more extensive reactions with cytoplasmic proteins. The significance of these carcinogen–protein interactions is still vague, but one view (the protein deletion hypothesis) is that these proteins usually suppress some chromosomes present in the normal cell; but when a carcinogen is bound to the proteins, the repression is not present and so new cell characteristics arise. There are many variations of these two mechanisms.[10] The carcinogen so far may also be called an "initiator". However, there are some 20 or so more stages in the mechanism of our one abnormal cell appearing as a malignant tumour. Reactants required for these subsequent stages are called "promoters," or "cocarcinogens" (for example, cigarette smoke). Substances that provide initiators and promoters may be called "complete carcinogens." Two points worthy of note are that the speed and direction of cancer development are promoter dependent and that promoters themselves cannot cause cancer. Having been formed, the primary tumor metastasizes into secondary tumors either by direct contact and invasion or by cells from the primary tumor entering the blood and lymph streams and being carried to other parts of the body.

The popular view of cancer is of a painful, fast-growing lump which spreads to the surrounding tissues. In fact, the majority of cancers are at first present without a lump, and, as newly formed malignant tissue contains no nerve endings, pain need not be felt until pressure is built up in some normal tissue. As far as the speed of growth is concerned, tumors usually grow more slowly than normal tissues *can* grow; however, the normal tissues are under homeostatic control and, except during childhood, do not demonstrate their maximum growth rates. Thus, the first symptoms of cancer are usually imitations of more innocent disorders (for example, a persistent cough). Clinical symptoms include the cancer tending to form at a source of irritation, a suppressed bone marrow activity, and a lower intercell adhesion. Microscopic analysis of tissue samples is the safest method of differentiating between benign and malignant growths because cancer cells can be perceived to differ from normal cells in their infinite range of shapes, sizes, and structures.

Once having diagnosed cancer in the primary locus and checked for growths in suspected secondary sites (for example, the lungs) by tissue sample analysis, a pattern of treatment is selected from chemotherapy, radiotherapy, and surgery. The radiotherapist's beam is used to kill the tumor and some surrounding tissues in an effort to prevent the spread of the disease. Radiotherapy is most effective in the presence of a host reaction; *i.e.*, the radiation effects and the antibodies synergistically aid each other. Surgery is limited by the impossibility of removing vital organs until organ transplants become easier.

Chemotherapy of cancer has been practiced for 70 years but has remained fairly unsuccessful until the last 2 decades.[41,42] Even now the treatment is not always successful, and the field is beset with innumerable difficulties; for example, only a proportion of cases respond to any one drug. Nevertheless, there have been fertile regions of discovery. Before discussing the range of drugs available, some of the problems associated with them will be mentioned. Frequently tumors have inadequate blood supplies and so the drug has to be applied topically or injected right into the tumor rather than taken orally. Problems arise in defining the best kind of animal screening tests for potential new drugs. Yet another problem occurs when a tumor builds up a resistance to a drug and so a different chemical has to be administered for a while. Finally, we ought not to underestimate the alarming side effects of these "anticancer" drugs. In fact, the drugs are less specific than the term implies and are really antigrowth reagents. Hence (a) slow-growing tumors do not respond well to them; (b) normal healthy rapidly multiplying parts of the body (for example, the bone marrow and stomach linings) are attacked by these drugs; and (c) in common with radiotherapy, chemotherapy depresses the number of lymphocytes, and so, even if

cured of cancer, the organism is much more likely to contract some other form of serious disease.

Anticancer therapeuticals fall into four broad classifications.

(a) The alkylating reagents are based upon nitrogen mustard (*e.g.*, triethylenemelamine and myleran). They are sometimes called radiomimetic reagents as their biological effects resemble those of radiation. Hence they are useful in treating leukemias. Unfortunately their high-antitumor activities are accompanied by high toxicities.

(b) The antimetabolites have formulas very similar to a chemical that is essential for tumor growth. The tumor, mistakenly, builds its new cell using the administered antimetabolite and this hinders further growth. Possibly the most famous pair are aminopterin (antimetabolite of folic acid) and ethionine (antimetabolite of methionine).

(c) Enzymes can also be used in treating cancers. For example, some cancer cells are asparagine dependent but cannot synthesize their own asparagine and so rely upon a supply from normal cells being passed to them *via* the blood stream. The enzyme asparaginase removes this blood-borne asparagine and so the malignant cell is starved.

(d) Hormone treatment is the area of chemotherapy having the highest success rate to date. It is mainly used in the treatment of tumors of the breast, uterus, and prostate because these organs, being under hormonal control, support tumors that respond to the opposite hormones. Unfortunate side effects include masculinization in females and feminization in males. Researchers in chemotherapy must aim at making existing therapies more specific and searching for new families of therapeuticals.[43]

In general, future research is aimed (a) at discovering new anticancer and antiviral vaccines and new methods of early cancer detection, and (b) at improving our attempts to remove environmental carcinogens, our knowledge of nucleic acid or protein carcinogen interactions, our matching of dose levels and spacings to tumor growth characteristics, and our synergistic combinations of treatments.[34]

We shall now demonstrate the metal dependency of cancer by reviewing the metals that are involved in the promotion and inhibition of some cancers, those known carcinogens and cancer drugs that are powerful metal chelating ligands, and the metal chelates that have been used as carcinostatic agents.

C. METALS AS CARCINOGENS

Pure metals that are reported to have caused cancer are aluminum, chromium, cobalt, gold, iron, mercury, nickel, selenium, silver, tin, and zinc.[7,45-55] These, in common with other widely used materials such as glucose, iron–dextran complexes, or even sodium chloride, sometimes have produced cancers following their subcutaneous implantation in test animals.[56] During this process of carcinogenesis, if the metals dissolve in hard solvents (for example, the blood) the higher oxidation states are likely, whereas in soft solvents (for example, lipids or enzymes) the lower oxidation states probably occur. However, at the present time, it appears that the technique employed for implantation (pieces, powders, or perforated sheets, etc.) is the important factor in determining whether the material will be carcinogenic. For the occasions when carcinogenesis does occur, Furst has suggested that the metals penetrate living cells[7] and either advance or retard the kinetics of anabolic or catabolic enzymes by instigating a competition between the invading and normal metals.[57] He further suggested that viruses may aid cell penetration by these metals.

Metals of any oxidation state, whether complexed or not, if present as unstable isotopes emit ionizing radiations that can cause cross mutations and eventually cancer. A well-known group of radioprotective drugs (for example, cysteamine or mercaptoalkylamine) are specific copper-binding ligands that protect copper(I)-containing enzymes.[6] Without such protection, irradiated mammals exude iron and copper from most organs.[58]

The ions of metals and their complexes have been widely reported to have been involved in carcinogenesis. One of the first reports was that of excesses of ingested iron from iron cooking pots causing liver cancers.[59] The process of ageing permits a wide range of soil and plant impurities to accumulate in various organs. For example, it has been found that the well-researched tobacco plant contains aluminum, barium, calcium, cobalt, copper, iron, lead, lithium, magnesium, manganese, molybdenum, nickel, sodium, strontium, tin, titanium, vanadium, and zinc.[60] In laboratory experiments, hamster carcinogenesis has been definitely shown to be zinc dependent, but the mechanism is still under investigation because, on the one hand, DeWys, *et al.*, report dietary zinc *deficiencies* as inhibiting cancer,[61] whereas, on the other hand, Poswillo and Cohen report zinc sulfate *excesses* as inhibiting cancer, some of this excess zinc appearing in the newly healed tissues.[62] In humans, high zinc (and chromium) soil contents have been correlated with the regional incidences of stomach cancer.[63]

Sometimes metal ions have the power of determining whether a carcinogen is active or not; for example, cyclohexylsulfamic acid and its sodium and calcium salts. Both salts are more than 98% ionized in aqueous solution at neutral pH. However, in animal experiments, under the most severe conditions, the sodium salt only manages to produce a mild self-limiting lesion whereas just traces of the calcium salt produce progressive lesions.[39] Analogously, in the crystalline state also it is usually the calcium salts that produce cancers (for example, calcium oxalate crystals produce bladder tumors by chronic irritation). All metals ions are inherently involved in the pH gradients that exist within the body[11] and

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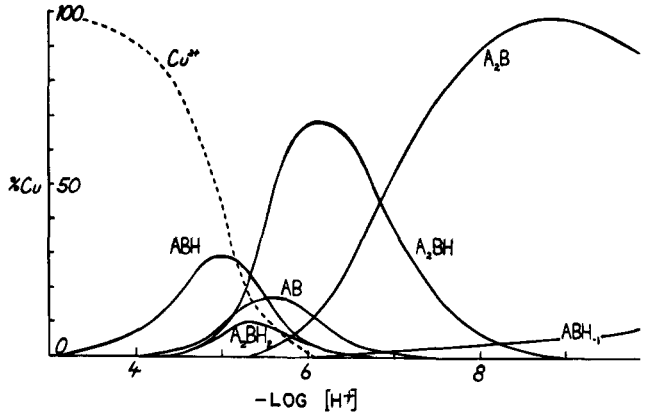

Figure 4. An example of the pH dependence of metal–amino acid complexes: A = anion of histidine (*i.e.*, histidyl$^-$), B = Cu^{2+}, H = H^+. The conditions refer to blood plasma total concentrations of A (74 μM) and B (18 μM): D. R. Williams, *J. Chem. Soc.*, in press.

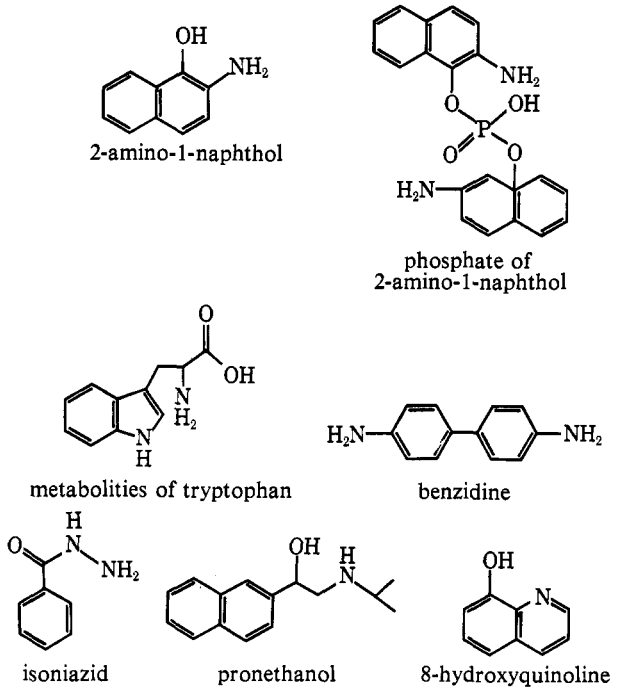

Figure 5. Ligand donor groups of known and suspected carcinogens.

in the tendency of cancer cells to migrate from low pH toward neutral regions.[64] Further, the pH within tumor masses is lower than in normal comparable tissues. This has been suggested as a means of powering the spread of cancer cells.[65] It is important to remember that (a) the amount of metal hydroxy complexes present is pH dependent and, conversely, the type of metal determines the pH. This means that the free concentrations of metal ions are pH dependent also. (b) The distribution of the metal between the available complexes is pH dependent (an example is given in Figure 4). Here it is pertinent to realize that varying the pH changes the complexes present and that not all complexes can penetrate cell walls, for example, 8-hydroxyquinoline–Fe(III) complexes: the mono and bis forms are toxic and cannot penetrate cell walls; the tris form is nontoxic and can penetrate cells because it is uncharged.[8] (c) The number of protons associated with a ligand is pH dependent and proton ionizations from the active site of enzymes mean that enzyme catalysis is also pH dependent.

D. CARCINOGENS AS LIGANDS

Some carcinogens are capable of acting directly as powerful ligands, either in an aqueous or in a nonaqueous environment, and others can react indirectly by undergoing metabolism into strong ligands. We shall discuss the subject under three headings: (a) the ligand donor atoms of known carcinogens, (b) is there an increase in the amount of ligands (*i.e.*, a sequestering of metals) when cancer occurs?, and (c) correlations between ligand deficiencies and cancer.

(a) Ligand donor atoms of carcinogens. Figure 5 shows the most likely ligand donor atoms of known and suspected carcinogens. In general, the molecules may be described as (i) lipid soluble, and (ii) consisting of coplanar rings. Furst has suggested that a third characteristic should be added, that of being (iii) a metal binding compound or capable of being metabolized into one.[7] Even if we restrict the choice of ions to those of the ten metals essential to life in humans, the range is broad enough to provide strongly complexing ions for all these ligands. Donor atoms separated by two or three other atoms are especially favored as they give rise to five- or six-membered chelate rings.

(b) Increases in ligand and decreases in metal concentrations accompanying carcinogenesis. Normal liver cells have different homeostatic control mechanisms compared to malignant cells; *e.g.*, animals fed on a tryptophan-rich diet usually adapt and develop extra tryptophan pyrollase in their livers and consequently the ligand excess is removed. However, the Morris 5123 experimental rat hepatoma does not do this, and so an excess of the amino acid accumulates in the animal.[66] We must also remember that tumor cells have to compete with normal cells for essential nutrients and that some of these latter are metals or metal containing. It is conceivable that the metals can be won by the malignant cell by using more or stronger ligands than normal cells.

Holmberg has suggested yet another manner in which the ligands can be used by malignant cells to defeat normal cells.[67] A variety of cancer cells that he studied excreted a toxin (a polypeptide of Gly, Cys, Glu, Arg, Val, Leu, Tyr, Ala; mol wt = 1900) that occurred at such a concentration that it did not affect the malignant cell but did poison the normal cell. It is thought that this toxin interferes with the S stage in the manufacture of DNA. The mechanism of poisoning by the toxin can be blocked by nucleosides such as deoxycytidine. Tumors are rich in deoxycytidine, and this is why they need so much higher concentrations of toxin before they are poisoned. On the other hand, normal cells have subprotective concentrations of deoxycytidine and so are selectively poisoned. Experiments have shown that the toxin, liberated from tumor cells when they die and break up, shortens the average lifetime of red blood cells by up to 20%.[67]

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(c) Ligand deficiencies leading to cancer.[11] It was shown in (b) that ligand excesses and carcinogenesis are interdependent. However, it also appears that deficiencies can also cause cancer. In general, starvation leads to (i) less waste products of metabolism, some of which might be carcinogenic, and (ii) malnutrition which lowers one's body resistance to invasion by diseases in general. Choline- and methionine-deficient diets lead to cancer of the liver in rats, mice, and chickens. However, treatment of nonmalignant psoriasis by using a tryptophan-deficient diet is also well known. Tryptophan is further coupled with bladder cancer in that its metabolites (for example, 3-hydroxyanthranilic acid) cause tumors.[60,68-78] Ligand deficiencies must also occur during the later stages of carcinogenesis when cell breakdown is reported to increase the blood copper concentration two- or threefold.[6]

E. ANTICANCER DRUGS AS LIGANDS

Figure 6 demonstrates that cancer drugs are viable ligands and illustrates the donor atoms probably involved in metal ion binding. Some of these drugs have an increased anticancer activity when administered as metal complexes[5,6,74,75] (see section IV.F). As with carcinogens, drugs incapable of being strong complexing ligands are usually metabolized into ligand species. Indeed, for nitrogen mustards it has been possible to correlate the rate at which the ligand (ethanolamine) was formed by metabolism with the extent of their therapeutic action (*i.e.*, a N–C–C–Cl species was metabolized into the more powerful N–C–C–O or N–C–C–N ligands that form stable complexes with charged metal ions in aqueous solution). HSAB considerations of metals of low or zero charge and other solvents may also produce useful drugs.

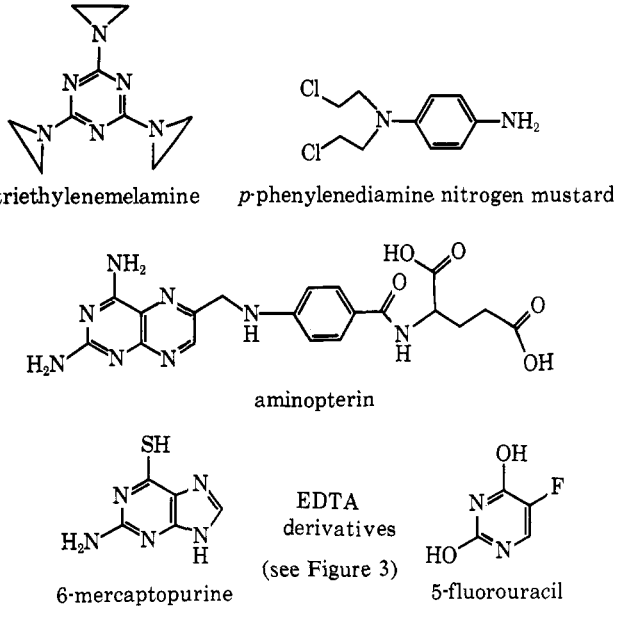
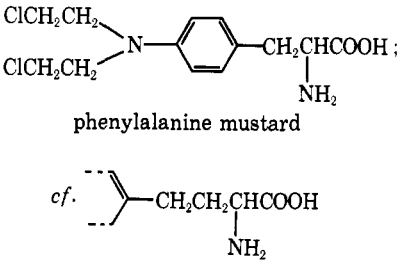


Figure 6. Ligand donor groups of cancer therapeuticals.

Once having formed a ligand, the actual mechanism of anticancer activity is still open to speculation. In general, such hypotheses center around deactivating either carcinogenic metals (as in section IV.C) or all enzymes necessary for rapid growth (both healthy and malignant).[7,76]

In selecting a therapeutic it is important to pick the correct stereoisomer; the amino acids in our bodies all have the L configuration. However, D isomers have been investigated as possible carriers for the mustard group of therapeuticals; *e.g.*, the Chester Beatty Institute found with phenylalanine mustard that the L isomer was an active drug (called melphalan) and was five times as active as the D isomer.[11] As might be expected, the DL racemate was as active as the amount of L it contained. Chemically, were cancer therapy of myeloma to be nonstereospecific, all three forms would have had equal activities. The finesse of this stereotherapy is further illustrated by examining the next isomer in the phenylalanine mustard homologous series.



Whereas the L isomer of phenylalanine mustard is more active than the D, it is the D isomer of aminochlorambucil that is the more active form. Phenylalanine is not the only amino acid used as a carrier; lysine and tryptophan have also been used.

Assuming that a D amino acid is not rejected by the body's defense mechanisms and that it is to complex with a metal ion that is already complexed with an L amino acid (or residue), there are thermodynamic reasons for mixed D–L complexes being energetically preferable with some tridentate ligands. For example, bonds involving histidine and first transition series metal ions such as Ni^{2+} and Zn^{2+} are stronger for D–L bis complexes than for D–D or L–L (for example, for Zn(D-His)-(L-His), $\Delta H_f^\circ = -49.2$ kJ mol^{-1}, whereas for Zn(D-His)-(D-His) or Zn(L-His)(L-His) $\Delta H_f^\circ = -47.7$–8 kJ mol^{-1}). These differences were determined calorimetrically.[77] These ΔH° differences also show up in the amounts of complex formed because of accompanying variations in formation constants, β ($-RT \ln \beta = \Delta H^\circ - T\Delta S^\circ$).

F. METAL CHELATES AS ANTIVIRAL AND CARCINOSTATIC AGENTS[3,8]

Many cancers have viruses associated with them and some animal, and a few human cancers are now believed to be caused by viruses. Hence, an anticancer drug may actually be an antiviral agent although the converse is not necessarily true.

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The protein and nucleic acid portions of viruses are particularly good coordinators, and the aim of the metallotherapeutical designer is to alter the virus by metal complexation so that the viral activity is diminished.[74] Kirschner has noted that the metal introduced must be "appropriate" in that (a) the metal ion must not be free enough to complex with simpler nonviral sites such as amino acids or enzymes (hence, moderately stable chelates are needed as drugs; for example, Pd and Pt complexes of 6-mercaptopurine destroy some adenocarcinomas), (b) these same ligands ought to be sufficiently weakly bonded to be displaced by the virus, and (c) the metal ion exploits the differences between benign and malignant viruses. As yet these differences are largely unknown so they cannot be capitalized upon.

A further interesting suggestion is that of using the virus to direct the toxic ligand into the tumor. This would involve the anticancer drug's metal complex giving its metal to the virus and liberating the toxic drug in the immediate vicinity. Such localization using metals is the converse of the practice employed in antibiotics whereby the metal is added to facilitate spread of the drug throughout the body. Clearly, such factors are dependent upon the choice of metal and the means of administration.

Albert has suggested that there ought to be two classes of anticancer metallotherapeuticals—those acting outside the cell (for example, those that attack viruses *en route* to the cells) and those acting inside the cell. These latter would need to be lipophilic or must closely resemble a known nutrient for which a specific uptake process already exists.[5] Compounds of the elements of group VIII in the d block have been particularly successful in destroying cells. (a) Livingstone has reported a series of nickel, palladium, and platinum dialkyldithiophosphates which are capable of reducing mice tumors to 69%.[75] (b) Rosenberg has reviewed[78] a range of platinum complexes that are capable of being bacteriocidal if negatively charged (for example, hexachloroplatinate(IV) anion), of blocking the division but not the growth of a cell if neutral (for example, *cis*-tetrachlorodiammineplatinum(IV)), and of being antitumor and lysogenic if cis (for example, *cis*-dichlorodiammineplatinum(II)).[79-81] The complexes produced increased survival rates, complete cures, and future immunity to tumors introduced by transplants, carcinogens, or viruses.[81-83] Further, they had promising synergistic effects when combined with other drugs, and any cytotoxic damage produced in normal tissue was reversible.[84] Their mode of action appears to be through forming *intra*strand links in a DNA chain. (c) Similar characteristics are to be expected for rhodium and iridium complexes.[84,85] The important chemistry of nucleic acid–transition metal ion bonding has been reviewed by Weser.[86]

Since tumors growing in a hormone environment are usually susceptible to hormone therapy, it is not unreasonable to postulate that tumors existing in a ligand environment, such as the bloodstream, might, in the future, be susceptible to complexometric therapy. An example can be found amid the treatment of lymphatic leukemia using the enzyme asparaginase.[87-90] Neoplastic cells usually have unrestrained growth, provided all the components for their proliferation are present. One of many components is the amino acid asparagine, and if this is only supplied in limited quantities, the growth may be controlled. Normal cells can synthesize their own asparagine using asparagine synthetase and so they are unaffected by a reduced supply. Fortunately, some varieties of leukemic cells are incapable of accomplishing this synthesis, and, because asparaginase has a greater affinity for asparagine than do malignant cells, the malignant cell is starved of an essential ingredient. However, there are problems both in the supply and in the side effects of asparaginase. Such difficulties can be circumnavigated using inorganic channels based upon asparagine's powerful metal complexing properties. Figure 7 shows that asparagine can form a selection of bonds to metal ions dependent upon the HSAB type of metal ion used.[91-106] Further, the metal ions in these complexes still have some vacant coordinating positions, and so a second, different ligand (D or L) can also be accommodated. Such mixed-ligand complexes may be designed so that malignant cell penetration is difficult but that complex removal by nephron is possible. Alternatively, just a small metal ion can be complexed with the asparagine so that it still penetrates the cell and there arrests further cell production by the antimetabolite approach. (This can be augmented by selecting a radioactive metal.[40]) The selection of a second ligand and of a metal ion need not be as difficult as it first appears since a wealth of literature already exists concerning the design of ligands to remove unwanted metal ions.[107] The concepts merely require converting

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(107) D. D. Perrin, "Masking and Demasking of Chemical Reactions," Interscience, New York, N. Y., 1970.

to suit the choice of a metal ion to remove an already available ligand.

It is important not to place an excessive emphasis upon the thermodynamic stability of metal–ligand bonds to the detriment of kinetic considerations. Cancer growth demands that the reproduction of malignant cells has a kinetic advantage over the body's defense mechanisms. Clearly, if chemotherapy is to reinforce these mechanisms, any metal complexes involved ought to be sufficiently labile to outpace the cancer growth. Reslova, *et al.*, have discussed the kinetic stabilities of platinum anticancer complexes in terms of the geometry of the complex, the oxidation state of the metal involved, and the type of ligands participating.[108] They conclude by suggesting that the best drug production may involve playing the kinetic and thermodynamic stabilities against each other.

V. Concluding Remarks

We have drawn attention to the fact that metals are essential to life in our bodies and this suggests that disease might also be influenced using metals. Figures 5 and 6 show that both carcinogens and anticancer drugs are capable of complexing with metal ions. This, in turn, suggests metallotherapy as means of attacking carcinogenesis and of extending the scope of available cancer treatments.

In compiling this review, it has been encouraging to note how frequently the mechanisms of carcinogenesis, cancer therapy and virus invasion are interdependent. For example, myeloid leukemia cells are dependent upon an external source of serine and we have already mentioned asparagine dependent leukemias. Possibly, a cancer will soon be found that is arginine dependent. Then Shope's virus can be introduced instead of a drug because this particular virus lowers the arginine concentration in man (*i.e.*, the virus is a treatment looking for a disease).

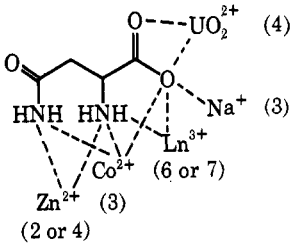

Figure 7. Suggested bonds formed between the asparagine anion and a variety of metal ions covering the periodic table. The numbers in parentheses denote the numbers of vacant bonds on these complexed metal ions that can possibly be used by the second ligand mentioned in the text.

The most important conclusions from this review are (a) that some of the major questions concerning neoplastic diseases can best be answered by cancer researchers and inorganic biochemists synergistically discussing and attacking these questions. Clearly, the most optimistic of us would only hope for one or two cures or prophylactics at the most. Roe and Ambrose[11] suggest that ignorance of the exact mechanisms of carcinogenesis need not prevent cancer therapy developments; the lack of knowledge of the cause of an accident does not rule out the development of new and better means of treating the injured. (b) As new ideas concerning the aforementioned causes are put forward, the patterns of metallotherapy researches are continually being modified; for example, as more viruses are found to cause cancers, this focusses deeper attention onto the already established metallotherapy of such infections. (c) All ligand-users ought to respect their possible carcinogeneity.

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(108) S. Reslova, A. J. Thomson, and R. J. P. Williams, *Struct. Bonding (Berlin)*, in press.