The assumption that an environmental system is at equilibrium is only valid if equilibrium between all species is reached very quickly. However, if some reactions are very slow, the equilibrium between the species involved can sometimes be ignored. The extent to which reactions with intermediate rates are a problem depends on the application.

The inclusion of equilibria involving complex macromolecular species such as fulvic and humic acids has been either avoided or approximated by making use of conditional stability constants [10, 11]. However, a new method, whereby concentrations of many individual metal binding sites on the macromolecules can be estimated from 'random' computer generated fulvic acid molecules, does provide more detailed insight into the mode of metal binding by these substances [12].

Equilibrium calculations on large systems have received widespread application. The sea has been studied for many years [13, 14]. Fresh water, lakes and river systems have been investigated [7, 10] as well as the so-called 'soil solution' [15]. Other important areas include human blood plasma [6] and plant xylem fluid [16].

Computer models, nevertheless, must be judged on their ability to predict real behaviour [17]. They should be supported, wherever possible, by experimental investigations, the direction of which can often be indicated by the results of the model itself. The current trend of investigations into the identity of important naturally occurring ligands and the determination of their formation constants with metal ions needs also to continue unabated.

1 T. M. Florence, *Talanta, 29,* 345 (1982).
2 P. Benes, E. T. Gjessing and E. Steinnes, *Water Res., 10,* 711 (1976).
3 T. A. O'Shea and K. H. Mancy, *Water Res., 12,* 703 (1978).
4 D. Midgley, *Ion-Selec. Elect. Rev., 3,* 43 (1981).
5 S. V. Mattigod and G. Sposito, in E. A. Jenne (ed.), 'Chemical Modelling in Aqueous Systems', ACS Symposium Series No. 93, Washington, D.C., 837 (1979).
6 P. M. May, P. W. Linder and D. R. Williams, *J. Chem. Soc. Dalton Trans.,* 588 (1977).
7 A. H. Truesdell and B. F. Jones, *J. Res. U. S. Geol. Surv., 2,* 233 (1974).
8 U. Forstner and G. T. W. Wittmann, 'Metal Pollution in the Aquatic Environment', Springer-Verlag, New York, 1979.
9 A. E. Martell and R. M. Smith, 'Critical Stability Constants', Plenum Press, New York, Vol. 5, 1982.
10 R. F. S. Mantoura, A. Dickson and J. P. Riley, *Estuarine Coastal Mar. Sci., 16,* 387 (1978).
11 R. Wagemann and J. Barica, *Water Res., 13,* 515 (1979).
12 K. Murray and P. W. Linder, *J. Soil Sci.,* submitted (1982).
13 L. G. Sillén, *Chem. Br.,* 291, July (1967).
14 N. Stumm and J. J. Morgan, 'Aquatic Chemistry', Wiley–Interscience, New York (1970).
15 W. L. Lindsay, 'Chemical Equilibria in Soils', Wiley, New York (1979).
16 W. C. White, F. D. Baker, R. L. Chaney and A. M. Decker, *Plant Physiol., 67,* 301 (1981).
17 G. Berthon, C. Matuchansky and P. M. May, *J. Inorg. Biochem., 13,* 63 (1980).

D4

Copper Complexes: A Physiologic Approach to the Treatment of 'Inflammatory Diseases'

JOHN R. J. SORENSON[1,2*], LARRY W. OBERLEY[3], VIMAL KISHORE[1], SUSAN W. C. LEUTHAUSER[3], TERRY D. OBERLEY[4], and ABBAS PEZESHK[1]

[1]*Department of Biopharmaceutical Sciences, College of Pharmacy and* [2]*Department of Pharmacology, College of Medicine, University of Arkansas for Medical Sciences,* [3]*Radiation Research Laboratory, University of Iowa, and* [4]*Department of Pathology, College of Medicine, University of Wisconsin, U.S.A.*

Copper is an 'essential' metalloelement and as such it is required for life. Since none of the essential metalloelements can be synthesized *in vivo* it is required that they be obtained in the diet. If, following absorption, copper is not utilized immediately in the synthesis of copper-dependent enzymes it is either stored in the liver or excreted in a homeostatic fashion.

It is well established that copper-dependent enzymes are required for cellular utilization of oxygen; dismutation of superoxide; cross-linking of collagen and elastin; synthesis of dihydroxyphenylalanine, melanin, norepinephrine, and epinephrine; metabolism of monoamines; and mobilization of stored iron for hematopoeisis. Other biochemical processes which are less well understood concerning the involvement of copper are: modulation of prostaglandin synthesis, lysosomal membrane permeability, modulation of histamine activity, angiogenesis, enhancement of synaptic vesicle attachment to neuronal plasma membranes, uptake and release of monoamines by synaptosomes, and activation of brain adenylate cyclase.

A 2 to 3 fold increase in plasma or serum copper concentration is observed as a general response to infectious, inflammatory, and stress related diseases. It is well documented that blood copper concentrations increase in arthritic diseases, seizures, and neoplastic diseases and it is likely that there is a similar elevation with ulcers and diabetes. These elevations are viewed as a general acute phase physiologic response which facilitates remission. In the event that this physiologic response is impaired remission does not occur.

Copper-containing components in blood are: ceruloplasmin which contains 6 atoms of copper and has a molecular weight of 132,000, a copper–albumin complex with a molecular weight of 69,000, and a variety of amino acid complexes with molecular weights in the range of 300 to 400. While there is

always a highly significant correlation between the plasma copper increase and the increase in ceruloplasmin, further studies are needed to determine the relative change in concentration of each of the copper-containing components in the physiologic response to disease.

This same increase in plasma copper concentration occurs in a variety of animal models of inflammation. Since treatment of these inflammations with exogenous low-molecular-weight copper complexes produces antiinflammatory effects the use of copper complexes may be viewed as a physiological approach to treatment. Low-molecular-weight copper complexes have been shown to have antiarthritic effects in man.

In addition to being effective antiinflammatory agents copper complexes have been shown to be effective antiulcer, anticonvulsant, anticancer, and antidiabetic agents. This seeming diverse variety of pharmacologic effects are unified with the hypothesis that copper complexes facilitate or promote tissue repair processes involving copper-dependent enzymes and that arthritis, ulcers, seizures, neoplasia, and diabetes are diseases of specific tissues in disrepair. The corollary to this hypothesis is that the loss or reduction of copper-dependent enzyme mediated processes leads to tissue disfunction which may be re-established with copper complex therapy.

Evidence will be presented to show that non-toxic doses of copper complexes have antiinflammatory activity in recognized models of inflammation and that copper complexes of antiinflammatory drugs are more effective than the parent drugs.

Data will also be presented to show that copper complexes have antiulcer activity and that copper complexes of antiinflammatory drugs, which are well known ulcerogens, are also potent antiulcer agents. This observation supports the view that copper complexes of antiinflammatory drugs are less toxic than the parent drugs and suggests that complexation may have a role in ulcerogenesis.

Anticonvulsant activity of copper complexes in two recognized models of seizure will be presented to show that complexes of non-anticonvulsant and convulsant ligands are effective anticonvulsant agents. In addition, data obtained with a copper complex of an antiepileptic drug suggests that the active form of these drugs may be their copper complexes.

Recognition that neoplastic cells have reduced superoxide dismutase (SOD) activity and that copper complexes have SOD-like activity lead to the investigation of copper complexes as anticancer agents. Data will be presented to show that small molecular weight copper complexes inhibit solid Ehrlich tumor growth and increase survival.

Following the observation that SOD inhibited streptozotocin-induced diabetes, small molecular weight copper complexes were studied and found to inhibit streptozotocin-induced diabetes as well. This observation will be presented in support of a possible role for copper complexes in the treatment of diabetes.

Acknowledgments. This work was supported by grants from American Diabetes Association, The Arthur Armbrust Cancer Research Foundation, The International Copper Research Association, The National Institutes of Health (GM-17574), The National Cancer Institute (5T32 CAO9125), and the National Science Foundation (SPI-8025702).

D5

Total Parenteral Nutrition (TPN) as a Cause of Depletion of Trace Metal Ions. Computer-based Interpretation and Treatment

GUY BERTHON

Laboratoire de Chimie Bioinorganique du Centre de Technologie Biomédicale de l'INSERM (SC 13), Université Paul Sabatier, 38, rue des 36 Ponts, 31400 Toulouse, France

Clinical Observations

During the past decade, various clinical data have brought out the compelling evidence that total parenteral nutrition (TPN) does induce abnormal losses of essential trace metal ions [1–3].

Among the latter, special attention has been drawn to zinc and copper. Urinary excretion of zinc rises spectacularly as soon as TPN is started, and plasma levels are eventually affected in long-term patients [4–6], notably after the reversal of the catabolic phase [7–9]. For copper, the urinary loss is less significant than that observed for zinc [6, 10], but the plasma level has been reported to fall rapidly and consistently [4].

These extra-losses are more especially injurious to the patient since zinc and copper are among the main trace metals essential to living systems. Zinc deficiency results in various abnormalities such as central nervous system disturbances, skin lesions [7], impaired immunity, growth retardation [9], and impairment of insulin response [9]. Retarded wound healing and tissue repair are also well documented [11], which constitutes an aggravating factor for patients with trauma [6], surgery [1] or burns [12]. The syndromes of copper deficiency are characterized by anemia, leukopenia, neutropenia, with severe bone demineralisation in infants [1].

Compared to enteral nutrition, TPN is known to promote specific extra losses in metals. It is thereby presumed that specific mechanisms inducing metal deficiency are involved [8].