Physiological Aspects of Copper

Copper in Organs and Systems

Charles A. Owen, Jr.

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Copper in Organs and Systems

by

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PHYSIOLOGICAL ASPECTS OF COPPER

COPPER IN BIOLOGY AND MEDICINE SERIES
in five volumes

by Charles A. Owen, Jr., M.D., Ph.D., D.Sc.

Copper Deficiency and Toxicity
Acquired and Inherited, in Plants, Animals, and Man

Wilson's Disease
The Etiology, Clinical Aspects, and Treatment of Inherited Copper Toxicosis

Biochemical Aspects of Copper
Copper Proteins, Ceruloplasmin, and Copper Protein Binding

Physiological Aspects of Copper
Copper in Organs and Systems

Biological Aspects of Copper
Occurrence, Assay and Interrelationships

To Bill, Bob, Carolyn, Curt, Elaine, Helen, Jane, Joe, Jauneita, Liz, Lloyd, Pat, Phyllis, Ruth, Steve, Sylvia and Zo.

Preface

When one considers the concentration of copper in any organ, the rate of uptake and release of the metal and the organic forms of the intracellular metal, it is quickly apparent that each organ is unique in its handling of copper. This might be expected when one reflects on the differing functions of the various organs. The liver generates ceruloplasmin and excretes excess copper into the bile. The intestine absorbs inorganic copper and the kidney excretes it.

Yet the basic metabolism of copper is remarkably similar in all cells. Low-molecular-weight proteins are involved in the uptake of copper by cells. The cells generate the self-protective enzyme superoxide dismutase as well as other copper enzymes. The heart, requiring excessive cytochrome oxidase, contains a greater than average concentration of the metal, for example. Why the locus coeruleus in the brain should concentrate so much copper is still unexplained.

Despite modern assay techniques, described in *Biological Aspects of Copper,* that have led to our knowledge of the concentrations of copper in whole organs as well as its subcellular distributions, most of what we know is still superficially descriptive. The functional pathways have yet to be worked out clearly. Even when that is accomplished we will have taken only the first step. How do deficiencies or excesses of copper *(Copper Deficiency and Toxicity)* distort these pathways, particularly in inherited disorders such as Wilson's disease *(Wilson's Disease)*? The answers lie in part with alterations of copper compounds within the body *(Biochemical Aspects of Copper).* For example, copper deficiency reduces lysyl oxidase resulting in impaired elastin and collagen formation. Arterial defects are a natural consequence. But does a deficiency of ceruloplasmin, or even of superoxide dismutase, impair metabolic functions significantly? Does an excess of ceruloplasmin, as occurs in patients with cancer or in women taking oral contraceptives, merely mirror the process responsible or is there some pathobiological significance?

It is gratifying to be able to review how much has been learned about the biology and chemistry of copper metabolism. It is frustrating to realize how much there is yet to be discovered.

The work with radiocopper has involved many of my associates. Dr. Norman Goldstein has continued as the central figure in the Wilson's disease program. Dr. Ray Randall, in Endocrinology, Dr. Rollie Dickson, in Gastroenterology, and Doctors Archie Baggenstoss and Juergen Ludwig in Anatomic Pathology, have contributed much from the viewpoint of their specialties. When I shifted from the clinical laboratories to the basic sciences my successors, Doctors Newlon Tauxe and Heinz Wahner, continued the clinical studies. Dr. John McCall and his able assistant Helen Sievers have furnished valuable advice in addition to copper assay facilities in Clinical Chemistry.

Graduate students are not only pleasant to associate with, and are usually hard-working, but stimulating because they ask naive, unanswerable questions. These have included Doctors James Maytum, Jane Hazelrig, Toshio Terao, Shanaz Ravanshad and Le-Chu Su.

The fact is that the day-in and day-out operation of a laboratory depends upon the loyalty of the technical staff. Over the years these have included Elaine Bay, Elizabeth Waldron, Phyllis Birden, Joseph Standing, Steve Ziesmer and Curtis Grabau. Jauneita Ogg and Robert Fountain functioned well in supervisory capacities. My associate, Dr. Gertrude Tyce, has been most encouraging and Zoanne Oliphant has cheerfully typewritten the many revisions of the text.

Last, but far from least, the pieces of equipment needed for quantitating ^{64}Cu or ^{67}Cu or both in specimens have a degree of elegance beyond the capacity of many of us. Dr. Alan Orvis supervised the acquisition of our equipment, hand-built our first large solid probe detector and our first liquid scintillation counter. His assistants William Dunnette and Carolyn Kath have maintained a close liaison with the laboratory. With the help of Lloyd Meeker, from the Department of Engineering, a tape recorder was constructed that continuously monitored radioactivity in liver and blood during perfusions of isolated rat livers. Decay corrections were done by computer as were kinetic analyses under the direction of physicist-mathematician-computer specialist Dr. Jane Hazelrig.

A glance at this book will quickly indicate to the reader that an immense amount of library help was required. This was most generously furnished by Sylvia Haabala, Pat Erwin and Ruth Mann. Most particularly thanks are due to Jane Cabaya who devoted full time for several months to finding the more obscure articles or at least abstracts in English language abstracting journals. Help was furnished in Japanese papers by Dr. T. Yanagihara and in Russian papers by Dr. Ed Burke.

There is no uniformity among the scientific journals as to how to refer to a published paper: titles may be included or omitted, inclusive pages may be listed or only the first page, the number or month of the journal may or may not be included. Further, the abbreviations of journals vary. Should it be J.A.M.A. or J. Amer. Med. Ass.? The style used here generally follows the style of Current Contents. The importance of that journal in early identification of relevant papers cannot be overstated.

Certain problems in the listing of references have not been solved. Usually Archives is abbreviated as *Arch.* However, this abbreviation can also represent Archiv, Archiva, Archivii, Archivio, Archivo, Archivos, Archivum and Archiwum. Since the library files these journals alphabetically by their full names, and not by *Arch.*, one can spend a considerable amount of time trying to locate the

correct *Arch.* The same applies to Annallen, Annales, Annali, Annals, Annata and Annee, and so on.

A curious system has developed for listing a series of papers by the same first author. With some variations, the papers by this author alone are listed first, in chronological order. Then follow the papers by this author plus one or more coauthors, the order being determined by the alphabetical sequence of the coauthors' last names. Thus, one could find the following series of papers:

Able 1970
Able 1975
Able 1980
Able and Baker 1965
Able and Baker 1972
Able and Baker 1978
Able and Charlie 1960
Able and Charlie 1968
Able and Charlie 1977

There is no chronological flow in such a sequence so that reading the titles in this listing offers no guide as to the progression of the work in Able's laboratory. In this book I have listed all of Able's papers in chronological order regardless of coauthorship. This system still does not solve the problem of other papers coming from Able's laboratory in which Baker and Charlie were the first authors.

Since not all the papers referred to were examined in their original journals but in abstract form only, the latter have been identified by appending the following abbreviations to the references:

AA	Analytical Abstracts
BA	Biological Abstracts
CA	Chemical Abstracts
CAB	Commonwealth Agricultural Bureaux (Farnham House, Farnham Royal, Slough, England)
CCA	Cancer Chemotherapy Abstracts
EM	Exerpta Medica
GA	Gastroenterology Abstracts
NA	Nutrition Abstracts
OL	Ophthalmic Literature
VB	Veterinary Bulletin

Finally, my thanks to all those who assisted in the preparation and publication of this volume for putting up with these and other eccentricities and for their most valuable help.

Rochester, Minnesota
January 1982

Charles A. Owen, Jr.

ABOUT THE AUTHOR

Dr. Charles A. Owen, Jr. is Edmond A. and Marion F. Guggenheim Professor; Professor of Medicine (Medical Research) and Clinical Pathology at the Mayo Medical School, Rochester, Minnesota and the Graduate School of the University of Minnesota, Minneapolis, Minnesota. He is also Chairman of the Department of Biochemistry at the Mayo Clinic and Mayo Foundation. He was Chairman of the Department of Clinical Pathology and Head of the Diagnostic Radioisotopes Laboratory and Blood Coagulation Laboratory at the Mayo Clinic.

Dr. Owen received his M.D. degree from the State University of Iowa, his Ph.D. from the University of Minnesota, and was awarded an honorary Doctor of Science degree by Monmouth College in 1958. For over twenty years, Dr. Owen has been involved in radiocopper studies of man and animals. In addition to being the author of two other books, *Diagnostic Radioisotopes* and *The Diagnosis of Bleeding Diseases* (now in its 2nd edition), he has published numerous scientific papers and abstracts on copper metabolism. He is a member of the American Association for the Advancement of Science, American Society of Clinical Pathology, American Society of Experimental Pathology, American Physiological Society, the Federation of American Societies for Experimental Biology and many others.

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Copper in Adipose Tissue

On a wet weight basis the copper content of fat is said to be 2.4 μg/g in the *mouse* (Schroeder 1966), 0.7 (Barber 1957) or 0.8 in the *pig* (Leibetseder 1977; Skalicky 1978), 1.2 in the *raccoon* (Schroeder 1966), 0.35 in the *rat* (Owen 1964) and 1.2 μg/g in the *whale* (Ármannsson 1979). There is said to be 3 μg Cu/g dry weight in the fat of a camel's hump (Khalifa 1973). In μg Cu/g ash of human omentum there are 80 (Forssén 1972) to 190 (Tipton 1963; Schroeder 1966). Ash represents 0.20% of the wet and dry weight of human fat (Tipton 1963).

Supplementing pigs' diets with 250 ppm copper is widely practiced. It has an effect on storage fat, however. The melting point is reduced (Christie 1969; Moore 1969; Amer and Elliot 1973a,b,c), the stearic acid/oleic ratio is reduced (Christie 1969; Moore 1969) and the increase in unsaturated fat can be demonstrated by a higher iodine number (DeGoey 1971). Interestingly, the softening of the porcine fat occurs only if the source of protein is of animal origin, not if it is of plant origin (Anonymous 1970).

The more fat is in human food, the greater the Zn/Cu ratio in the food. This is of interest because of the suggested relationship of coronary heart disease to abnormalities of the Zn/Cu ratio (Klevay 1974).

Some patients with Wilson's disease, but not all, have a steatorrhea (Gross 1967).

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–2–

Copper in the Alimentary Tract

SALIVARY GLANDS

In human glands the average concentration of copper is 5.5 μg/g dry weight in the parotid and 14.3 μg/g in the submaxillary gland (de Jorge 1964). Salivary glands in adult rats contained 2.8 μg Cu/g wet weight (Owen 1964). *Saliva* contains 2-22 μg Cu/dl (Munch-Petersen 1950), an average of 29 μg/dl (essentially the same in Wilson's disease) (Gollan 1971a,b,c), 25 to 32 μg/dl, all non-ceruloplasminic, (Dreizen 1952; de Jorge 1964) or 10 to 30 μg/dl in most persons (extreme range 1-75) (Rice 1966).

In human parotid saliva copper is associated with a protein smaller than 40,000 d (Langmyhr 1979).

TASTE

The nerve impulses stimulated by Cu^{2+} put on the tongue have been studied in the rat (Yamamoto 1971). Hypogeusia or reduction in sense of taste is fairly common in non-Wilsonian patients treated with penicillamine (23 of 73 in one series); it can be reversed by the administration of copper (Henkin 1967).

TEETH

Human teeth contain 1.3 to 6.8 (Oehme 1978), 7.6 (1.6 to 39.7) (Smith 1970), 9.8 (9.1 to 10.6 in 5 areas of Finland) (Lappalainen 1979), 10.1 (Liebscher 1968) or 12 to 30 μg of copper per gram (Brudewold 1955). Pinchin et al. (1978) reported 6 ppm for children's molars and less for their incisors, varying from 0.5 at the tip, 12.2 mesio to 3.4 distal and 1.8 at the root, for an overall value of 2.8 ppm. Modern teeth contain twice as much copper (22.9±22.4) as do teeth from seventeenth century skeletons (10.1±2.0 ppm) (Kuhnlein 1977).