New Perspectives in Magnesium Research

Yoshiki Nishizawa, Hirotoshi Morii, and
Jean Durlach, Eds.

New Perspectives in Magnesium Research

Nutrition and Health

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Yoshiki Nishizawa, MD, PhD
Dean of Medicine
Professor of Internal Medicine
Department of Metabolism, Endocrinology and Molecular Medicine
Osaka City University Graduate School of Medicine
Osaka, Japan

Hirotoshi Morii, MD, PhD
Emeritus Professor
Osaka City University
Osaka, Japan

Jean Durlach, MD, PhD
President of the International Society for the Development of Research on Magnesium (SDRM)
Université Pierre et Marie Curie
Paris, France
and
Editor-in-Chief Magnesium Research journal

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Preface

Magnesium: New Vistas

Eighteen years after the 5th International Magnesium Symposium was held in Kyoto in 1988, the Japanese Society for Magnesium Research (JSMR) is organizing the 11th International Magnesium Symposium in ISE-Osaka. The vitality of the Japanese Society has been evidenced by the regular publication of its journal (Journal of the Japanese Society of Magnesium Research), which ensures regular updating of current Japanese research on magnesium, and by its participation in the activities of the international Society for the Development of Research on Magnesium (SDRM).

Thanks to the efficient management of Yoshiki Nishizawa, Hirotoshi Morii, and Masaaki Inaba, the publication of this book of proceedings provides new vistas on magnesium research in 2006. It comprises reports presented during the plenary sessions concerning the role of magnesium not only in physiology, chronobiology, nutrition, epidemiology, and internal medicine particularly, cardiology, neurology, rheumatology, gynecology, and nephrology, but also in stomatology, pharmacognosy, and veterinary medicine.

Unlike many books that promise more than their texts deliver, the multiplicity and interest of the discussed topics can but stimulate careful reading of this book, which gives a platform to authors originating from many parts of the world. Published 35 years after the 1st International Magnesium Symposium, it demonstrates that magnesium research stands the test of time and that a wide path remains open for further investigation.

Such as it is, this book provides a valuable tool for interdisciplinary research in the future.

Jean Durlach
September 2006

Preface

New Perspectives in Magnesium Research is published as a document of the 11th International Magnesium Symposium, a joint meeting of Japanese Society for Magnesium Research. Professor Jean Durlach has been President of International Society for Magnesium Research since it was established in 1970. There are international meetings every 2 to 3 years in many parts of the world. The last meeting hosted by the Japanese Society for Magnesium Research was in Kyoto in 1988, when the Society President was Professor Yoshinori Itokawa.

Magnesium is the most abundant cation, second only to potassium in the intracellular compartment and to calcium in bone tissues. One of the big differences between calcium and magnesium is the difference between intra- and extracellular levels. Extra- and intracellular ratio is 10,000 for calcium, but 0.33 for magnesium. Such facts have significance for maintenance of life. Intracellular space rich in magnesium is just like seawater, adequate for the origin of life and maintenance of life in sea animals and plants. Bone magnesium constitutes a part of hydroxyapatite and may be important in maintaining bone integrity.

In physiological situations, magnesium is involved in metabolism of fat, amino acids, and sugar. Magnesium plays an important role in PPAR (peroxisome proliferators-activated receptor)–mediated signaling pathways as a key cofactor in the protein phosphorylation.

In bone and calcium metabolism, magnesium seems to play roles as a constituent of bone. Experimentally, magnesium deficiency induces osteoporosis but there have not been definite evidences of correlation between osteoporosis and magnesium. In calcium- and magnesium-deficient animals, calcium restores the bone quality but magnesium only partially. Another aspect of role of magnesium is the regulation of calcium metabolism through calcium-sensing receptor, which requires magnesium for its action. Another point is how magnesium participates in vitamin D action. Vitamin D is another important factor, other than calcium-sensing receptor, that requires magnesium in its action. The correlation between calcium-sensing receptor and vitamin D receptor has been discussed. Thus, magnesium plays some roles in the regulation of calcium and bone metabolism.

Clinically, diabetes mellitus, atherosclerosis, hypertension, cardiovascular diseases, and hyperlipidemia are in some other ways influenced by magnesium. More evidence is needed to have a definite conclusion how to manage clinical problems, problems of public health, and individual nutrition.

Hirotoshi Morii
September 2006

Contents

Contributors

Y. Akiyama
Department of Pharmacology
Eisai Co., Ltd
Tokyo, Japan

Bella T. Altura, PhD
Physiology and Pharmacology
State University of New York
Downstate Medical Center
Brooklyn, NY, USA

Burton M. Altura, PhD
Physiology and Pharmacology, and Medicine
State University of New York
Downstate Medical Center
Brooklyn, NY, USA

Pilar Aranda, PhD
Department of Physiology
School of Pharmacy
University of Granada
Granada, Spain

Pierre Bac, PhD
Pharmacology Laboratory
Faculty of Pharmacy
F-Châtenay Malabry, France

Michel Bara, PhD
Physiology and Physiopathology Laboratory
Pierre and Marie Curie University
Paris, France

Mario Barbagallo, MD, PhD
Geriatric Unit
Department of Internal Medicine and Geriatrics
University of Palermo
Palermo, Italy

Mario Belvedere, MD
Department of Internal Medicine and Geriatrics
University of Palermo
Palermo, Italy

René J. Bindels, PhD
Department of Physiology
Radboud Univesity Nijmegen
Medical Centre
Nijmegen Centre for Molecular Life Sciences (NCMLS)
The Netherlands Nijmegen

Virna Brucato, MD
Department of Internal Medicine and Geriatrics
University of Palermo
Palermo, Italy

Giuseppe Costanza, MD
Department of Internal Medicine and Geriatrics
University of Palermo
Palermo, Italy

Ligia J. Dominguez, MD
Department of Internal Medicine and Geriatrics
University of Palermo
Palermo, Italy

Jean Durlach, MD, PhD
International Society for the Development of Research on Magnesium (SDRM)
Université Pierre et Marie Curie
Paris, France

Masanori Emoto, MD, PhD
Department of Metabolism, Endocrinology, and Molecular Medicine
Osaka City University Graduate School of Medicine
Osaka, Japan

Ginji Endo, MD, PhD
Department of Preventive Medicine and Environmental Medicine
Osaka City University
Osaka, Japan

Jesús F. Escanero, MD, PhD
Department of Pharmacology and Physiology
University of Zaragoza
Zaragoza, Spain

Anna Ferlisi, MD
Department of Internal Medicine and Geriatrics
University of Palermo
Palermo, Italy

Elisabeth M. Froschauer
Max F. Perutz Laboratories
University of Vienna
Vienna, Austria

Antonio Galioto, MD
Department of Internal Medicine and Geriatrics
University of Palermo
Palermo, Italy

Wouter M. Tiel Groenestege
Department of Physiology
Radboud University Nijmegen Medical Centre
Nijmegen Centre for Dalccular Life Sciences (NCMTS)
Nijmegen, the Netherlands

Fernando Guerrero-Romero, MD, PhD, FACP
Medical Research Unit in Clinical Epidemiology
Mexican Social Security Institute
and
Research Group on Diabetes and Chronic Illnesses
Durango, Mexico

Andrée Guiet-Bara, MD
Physiology and Physiopathology Laboratory
Pierre and Marie Curie University
Paris, France

K. Hara
Department of Pharmacology
Eisai Co., Ltd
Tokyo, Japan

Naoyuki Hasebe, MD, PhD
First Department of Medicine
Asahikawa Medical College
Asahikawa, Japan

Joost G.J. Hoenderop
Department of Physiology
Radboud University Nijmegen Redical Centre
Nijmegen Centre for Ralcular Life Scicuces (NCMLS)
Nijmegen, the Netherlands

Masaaki Inaba, MD, PhD
Metabolism, Endocrinology and Molecular Medicine
Osaka City University Graduate School of Medicine
Osaka, Japan

Takehisa Kawata, PhD
Pharmaceutical Division
Pharmaceutical Development Laboratories
Pharmacology Group, Nephrology
Kirin Brewery Co., Ltd
Takasaki, Japan

Kenjiro Kikuchi, MD, PhD
First Department of Medicine
Asahikawa Medical College
Asahikawa, Japan

Mieko Kimura, PhD
Takeda Research Institute of Life Science and Preventive Medicine
Kyoto, Japan

Hideaki Kitajima, PhD
Taisho Pharmaceutical Co. Ltd
Tokyo, Japan

Masatoshi Kobayashi, PhD
Department of Pharmacology
Eisai Co., Ltd
Tokyo, Japan

Naoko Kodama, RN
Laboratory of Clinical Nutrition
Tokyo Dietitian Academy
Tokyo, Japan

Martin Kolisek, PhD
Department of Veterinary-Physiology
Free University of Berlin
Berlin, Germany

Masato Konishi, MD, PhD
Department of Physiology
Tokyo Medical University
Tokyo, Japan

Yasuro Kumeda, MD, PhD
Department of Internal Medicine
Jyurakukai Ohno Memorial Hospita
Osaka, Japan

Maria José Laires, PhD
Biochemistry Laboratory
Faculdade de Motricidade Humana
Universidade Técnica de Lisboa
Lisbon, Portugal

Juan Llopis, PhD
Department of Physiology
School of Pharmacy
University of Granada
Granada, Spain

Linda K. Massey, PhD, RD
Human Nutrition
Food Science and Human Nutrition
Washington State University
Spokane, WA, USA

Tohru Matsui, PhD
Laboratory of Nutritional Science
Division of Applied Biosciences
Graduate School of Agriculture
Kyoto University
Kyoto, Japan

Ken-ichi Matsumoto
Sakai Institute of Public Health
Sakai, Japan

Nobue Matsuzaki, RN
Laboratory of Mineral Nutrition
Division of Human Nutrition
The Incorporated Administrative Agency of Health and Nutrition
Tokyo, Japan

Pierre Maurois, MD
Pharmacology Laboratory
Faculty of Pharmacy
F-Châtenay Malabry, France

Takami Miki, MD, PhD
Department of Geriatrics and Neurology
Graduate School of Osaka City University
Osaka, Japan

Tokuhiko Miki, MD
Osaka City University
Osaka, Japan

Cristina Monteiro, PhD
Biochemistry Laboratory
Faculdade de Motricidade Humana
Universidade Técnica de Lisboa
Lisbon Portugal

Carmen Mora-Fernández, MD
Research Unit
Hospital Universitario Nuestra Señora de Candelaria
and
Instituto Canario de Investigación Biomédica
Santa Cruz de Tenerife, Spain

Hirotoshi Morii, MD, PhD
Emeritus Professor Osaka City University
Osaka, Japan

Eiko Morikuni, RN
Laboratory of Mineral Nutrition
Division of Human Nutrition
The Incorporated Administrative Agency of Health and Nutrition
Tokyo, Japan

Chie Motonaga
Central Research Laboratories
Nichinichi Pharmaceutical Co., Ltd
Mie, Japan

Nobuo Nagano, PhD
Pharmaceutical Division
Pharmaceutical Development Laboratories
Pharmacology Group, Nephrology
Kirin Brewery Co., Ltd
Takasaki, Japan

Juan F. Navarro, MD
Nephrology Service and Research Unit
Hospital Universitario Nuestra Señora de Candelaria
and
Instituto Canario de Investigación Biomédica
Santa Cruz de Tenerife, Spain

Mihai Nechifor, MD, PhD
Department of Pharmacology
University of Medicine and Pharmacy "Gr. T. Popa"
Iasi, Romania

Mamoru Nishimuta, MD, PhD
Laboratory of Mineral Nutrition
Division of Human Nutrition
The Incorporated Administrative Agency of Health and Nutrition
Tokyo, Japan

Yoshiki Nishizawa, MD, PhD
Department of Metabolism, Endocrinology and Molecular Medicine
Osaka City University Graduate School of Medicine
Osaka, Japan

Takao Nohmi
Central Research Laboratories
Nichinichi Pharmaceutical Co., Ltd
Mie, Japan

Mariko Okamori
Central Research Laboratories
Nichinichi Pharmaceutical Co., Ltd
Mie, Japan

Masayuki Okazaki, PhD
Department of Biomaterials Science
Graduate School of Biomedical Sciences
Hiroshima University
Hiroshima, Japan

Senji Okuno, MD, PhD
Kidney Center
Shirasagi Clinic
Osaka, Japan

Nicole Pagès, PhD
Toxicology Laboratory
Faculty of Pharmacy
Illkirch-Graffenstaden, France

Antonella Pineo, MD
Department of Internal Medicine and Geriatrics
University of Palermo
Palermo, Italy

Elena Planells, PhD
Department of Physiology
School of Pharmacy
University of Granada
Granada, Spain

Ernesto Putignano, MD
Department of Internal Medicine and Geriatrics
University of Palermo
Palermo, Italy

Bartolomé Quintero
Department of Physical Chemistry
School of Pharmacy
University of Granada
Granada, Spain

Martha Rodríguez-Morán, MD, MSc, PhD
Medical Research Unit in Clinical Epidemiology
Mexican Social Security Institute
Durango, Mexico
Research Group on Diabetes and Chronic Illnesses
Durango, Mexico

C Sánchez
Department of Physiology
School of Pharmacy, University of Granada
Granada, Spain

Karl Peter Schlingmann, MD
Department of Pediatrics
University Children's Hospital
Philipps-University
Marburg, Germany

Monika Schweigel, PhD
Department of Nutritional Physiology "Oskar Kellner"
Research Institute for the Biology of Farm Animals – FBN
Dummerstorf, Germany

Rudolf J. Schweyen, PhD
Max F. Perutz Laboratories
University of Vienna
Vienna , Austria

Pedro Serrano, MD, PhD, FESC
Department of Pharmacology and Physiology
University of Zaragoza
Zaragoza, Spain

Takashi Shimada, PhD
Central Research Laboratories
Nichinichi Pharmaceutical Co., Ltd
Mie, Japan

Maríasol Soria, MD, PhD
Department of Pharmacology and Physiology
University of Zaragoza
Zaragoza, Spain

Yoshitomo Takaishi, DDS
Takaishi Dental Clinic
Himeji, Japan

Hidemaro Takeyama, PhD, RN
Graduate School of Medical Science
Nagoya City University
Nagoya City, Japan

Michiko Tashiro
Department of Physiology
Tokyo Medical University
Tokyo, Japan

Keiichi Torimitsu, PhD
Materials Science Laboratory
NTT Basic Research Laboratories
Atsugi, Japan

Ernesto Tranchina, MD
Department of Internal Medicine and Geriatrics
University of Palermo
Palermo, Italy

Andrzej Tukiendorf, PhD
Opole University of Technology
Opole, Poland

Renee J. Turner, BSc
Division of Pathology
School of Medical Sciences
University of Adelaide
Adelaide, SA, Australia

Pulat Tursun
Department of Physiology
Tokyo Medical University
Tokyo, Japan

Robert Vink, PhD
Neurosurgical Research
Division of Pathology
School of Medical Sciences
University of Adelaide
Adelaide, SA, Australia

Masaru Watanabe
Department of Physiology
Tokyo Medical University
Tokyo, Japan

Hideaki Yamada, RN
Mimasaka Women's University
Tsuyama City, Japan

Yayoi H. Yoshioka, RN
Laboratory of Mineral Nutrition
Division of Human Nutrition
The Incorporated Administrative Agency of Health and Nutrition
Tokyo, Japan

Overview

1
Overview of Magnesium Research: History and Current Trends

Jean Durlach

The lore of magnesium in medicine, starting as far back as the 17th century up to the first quarter of the 20th century, covers a large span of the chemical and pharmacological fields of knowledge.

The modern period, from 1926—when the essential character of magnesium was demonstrated—up to the 1960s, laid the basis for the present development of magnesium research by opening new vistas in the epidemiological and clinical fields where magnesium was acknowledged as being involved.

Several leading ideas deserve to be mentioned: (1) magnesium concerns all areas of medical activities; (2) the main expression of chronic marginal deficit is long-term chronic magnesium deficiency; (3) the specific etiological treatment of the responsible illness is the specific therapeutic measure meant to correct secondary magnesium deficit; (4) atoxic physiological palliative oral magnesium therapy is basically different from potentially noxious pharmacological use of magnesium; (5) the importance of distinguishing between magnesium deficiency and magnesium depletion in case of magnesium deficit; and (6) the interest of studying the chronopathological forms of magnesium deficit with hyper- or hypofunction of the biological clock.

This overview on past, present, and future bears witness to the vitality of magnesium research in health and disease.

Magnesium, the second most important intracellular cation, is found in all tissues and may affect many functions in the body. Its multiple physiological actions have been discovered thanks to the numerous convergent efforts of multinational research.

The aim of this study is to sum up the history of magnesium research and to highlight the current trends with a special stress on the leading ideas developed at the XIth International Magnesium Symposium (ISE, Japan).

This overview, which first considers the early history of the subject during the 18th and 19th centuries and first quarter of the 20th century, is mainly an account of the development of chemical and pharmacological knowledge. The modern history follows, which includes an initial period ending in the 1970s, when physiological, analytical, and epidemiological data established a firm

background for the first clinical studies in the neurological and cardiovascular fields particularly.

The present period is characterized by an exponential development of magnesium research, as will be testified by the subjects of the multiple sessions at the ISE Osaka Symposium.

History[1–7]

One may consider the recognition by N. Grew, in 1695, of magnesium sulfate as one of the essential constituents of Epsom salts, as marking the entry of magnesium into medicine. N. Grew separated the solid salt in quantity from the bitter-tasting natural water of the Epsom spring. This latter was considered as an internal remedy and purifier of the blood and used by "a great store of citizens" and especially by "persons of quality," including Marie de Medicis in the 16th century. Other important springs also contained magnesium sulfate and Epsom salts, or sal anglicum, synonymous with Sedlitz, or Egra powder, or salt, to designate the first preparation of magnesium sulfate used in medicine, mainly as a purgative. It was considered as a typical saline cathartic.

In 1707, M.B. Valentini of Giessen processed "magnesia alba" from the mother liquors obtained in the manufacture of nitre. This by-product of the preparation of nitre was considered as "a panacea for all bodily ailments," but then magnesia alba and "calcareous earth" were confused. In 1755, J. Black of Edinburgh distinguished between magnesia and lime chemically.

In 1808, H. Davy of London isolated magnesium. Conducting his studies on alkali, that is, earth compounds, H. Davy succeeded in producing the amalgams of calcium, barium, strontium, and magnesium. He then isolated the metals by distilling off the mercury. As in the case of the alkali metals, he named these alkali–earth metals after their oxides: baryta, strontia, chalk, and magnesia, calling them barium, strontium, calcium, and magnium. Magnium has long been forgotten, however, and magnesium has been adopted by general usage for the element derived from magnesia.

In 1828, the French chemist A.A. Bussy, by reducting anhydrous magnesium chloride with potassium, prepared the metal in a state approximating purity.

In 1833, M. Faraday of London was the first to succeed in producing metallic magnesium by electrolysis of molten magnesium chloride. Electrolytic methods entirely superseded the older ones in the industrial production of magnesium until about 1941, when the carbothermic and ferrosilicon technique employing a thermal process came into use for a small proportion of magnesium production. In industry, magnesium was first used in photography and to make incendiary bombs; now it is in great demand for alloys and structural materials. Because of its lightness and abundance (2.1% of the earth's crust) "it has become the glamour metal of the space age." Aluminium, the nearest rival for structural purposes, is one and a half times as heavy.[1]

Two Nobel prizes are linked to work concerning the important role of magnesium in organic chemistry. V. Grignard was awarded his in 1912 for the description of organomagnesium compounds. Grignard reagents are those with the composition $RMgX$ (where R = an akyl or aryl group and X = a halogen). These compounds are primarily important as intermediates in a large scale of synthesis, in biology in the conversion of aldehyde or ketones to alcohols, as well as in organic chemistry in the production of silicones. R. Willstatter was awarded the Nobel prize in 1915 for demonstrating that the structure of chlorophyll consisted of the porphyrin system, the central magnesium atom with its complex linkage and the phytol radical.

These discoveries laid a scientific basis for the use of magnesium in fertilizers and for assessing its importance in phytophysiology.

Around 1900, the essentiality of magnesium was established by studies concerning several algae and inferior fungi.

The same notion concerning animals was demonstrated only after a further quarter of century. However, one can cite as a predecessor J. Gaube Du Gers who, more than a century ago, noticed in mice that a diet deficient in magnesium, that is, composed of bread devoid of magnesium and of distilled water, but also no doubt deficient in other nutrients, caused progressive sterility. Magnesium already appeared to Gaube Du Gers as "the metal of vital activity for what is most precious in life: reproduction and sensation."[1,3,7]

The first modern biological studies[1,2,4,6] concerning the pharmacodynamic properties of parenteral magnesium were carried out by the French.

In 1869, F. Jolyet showed that intravenous injection of magnesium in dogs induced a peripheral paralyzing action similar to that of curare. Unfortunately, these pertinent observations were considered physiological.

Thirty years later, the same misconstruction, through the assimilation of pharmacological and physiological data, was repeated by the American groups of J. Loeb, who included magnesium among the denominators of his coefficient in which the principal humoral factors controlling neuromuscular excitability were grouped, and of J. Meltzer, who analyzed the sedative pharmacological properties of magnesium. The latter also observed that the effects of intravenous administration of a solution of a calcium salt rapidly reversed the effects of magnesium given parenterally. Correspondingly, parenteral magnesium sulphate was used to treat tetanus and eclamptic, nephritic and tetanic convulsions. In cases of respiratory depression through magnesium therapeutic overload, calcium was administered as an antidote to magnesium intoxication.

Although these observations of the pharmacodynamic effects of high doses of oral or parenteral magnesium may have some interest per se, one should nevertheless not extrapolate from these pharmacodynamic effects to physiological properties. Evidence of the latter can be demonstrated only by the occurrence of symptoms due to magnesium deficiency followed by its specific control by administration of nutritional physiological oral doses of magnesium. One should however, note, the predictive character of hypotheses presented more than a century ago, and subsequently verified, on the etiological

and physiopathological role of magnesium in certain tetanies, convulsions, and cardiovascular or toxic problems. We have cited here only carefully chosen examples, where modern studies have proved past extrapolations to be well founded, and not any others. The latter have, on the contrary, been the source of a number of unwarranted attributions of paternity as to the etiology of magnesium deficit. For this reason few ions have generated as much enthusiasm and as much disdain. Heated zealots, such as the French P. Delbet, have seen in magnesium a sort of panacea, the lack of which plays a major role in the development of cancer, the spread of epidemics, and even in the frequency of suicides. To the skeptics, on the other hand, magnesium remained a trace element of unclear biological physiological and pathological importance.

Between these two extremes it is today possible to find a balance.

The Early Modern Period

Beginning with the seminal experiment of J. Leroy, who proved in 1926 the essential character of the ion in mice, this era ended in the 1960s. The physiological properties of magnesium were mainly revealed in the 1930s by the remarkable studies in the rat of the American groups of E.V. MacCollum and D.M. Greenberg, who showed the multiple effects of a lack of magnesium intake on development, reproduction, the neuromuscular apparatus, and humoral balance. The specific reversibility of such defects by oral loading of magnesium provided the experimental basis for the diagnostic test for magnesium deficiency by oral loading of nutritional physiological doses of magnesium.

These physiological data constituted the background for the first clinical observations establishing the importance of abnormalities in magnesium metabolism in the period between the 1930s and 1960s. These observations concerned acute syndromes, for example, in veterinary medicine according to the work of the Dutchman B. Sjollema in 1932 on grass tetany (in cows or ponies) and the tetany of milk-fed calves and human pathology, where Americans E.B. Flink and W.E.C. Wacker in particular led the way with reports of acute neurological manifestations of primary or secondary magnesium deficit due to alcoholism or endocrinometabolic disorders.

Epidemiological data introduced two major considerations. First, in the 1960s, the American M. Seelig, as well as J. Durlach in France, emphasized the fact that dietary magnesium in many regions appeared to be insufficient to meet daily needs. Indeed, it may be said that magnesium intake in developed countries is marginal. Previously, the Japanese J.A. Kobayashi (1957) and the American H.A. Schroeder (1958) stressed an inverse relation between total drinking water hardness and cardiovascular risk.

In 1955, the Australian A. Walsh reported the first application of atomic absorption spectrophotometry to the determination of magnesium. Henceforth magnesium could be measured with ease and accuracy.

Current Trends[2–8]

The first international symposium on magnesium deficit in human pathology (1971) may be considered as evidence of the present importance of magnesium research in medicine: 350 participants from 52 countries contributed to the publication of two heavy volumes of proceedings corresponding to a synthesis of more than 25,000 references and which still offer a wide range of valuable knowledge.

The first International Symposium on Magnesium fostered the creation of the Society for the Development of Research on Magnesium (SDRM), an international coordinating structure.

The Society for the Development of Research on Magnesium promoted the publication of magnesium books: volume of proceedings[2,3,5,11–13] and monographs.[6]

The Society for the Development of Research on Magnesium organized the publication of diverse magnesium journals. First of all, *Magnesium Research*, the official organ of the international Society for the Development of Research on Magnesium (18 volumes), but also national journals such as the *Journal of the Japanese Society for Magnesium Research* (Japan), the *Buletin informatic al societatii romane de cercetare a magneziului* (Romania), and the *Journal of Elementology* (Poland).

Several leading ideas expressed in the course of the modern period of magnesium research deserve special mention:

- In the organism, all the systems and all the functions are involved. Therefore, magnesium research is not only relevant in certain fields but in all areas of medical activity.
- The main expression of primary magnesium deficit is closely linked with the consequences of long-term chronic marginal deficiency. Experimentally, it has been widely studied after the seminal report of O. Heroux in 1972. Clinical forms of chronic magnesium deficit are better and better identified, particularly in the neuromuscular system: for example, normocalcaemic latent tetany with or without mitral valve prolapse, and in the cardiovascular system, where the importance of magnesium deficit is recognized among cardiovascular risk factors.
- Specific therapeutic measures that seek to correct secondary magnesium deficit are justified only if the etiological treatment of the responsible illness is either impossible or ineffective. Such measures are then adjuvant treatments only justified by the ultimate importance of the secondary magnesium deficits in the physiopathology of the original illness.

Pharmacological effects of magnesium are observed irrespective of the magnesium status. They are established either in vitro, in situ, or in vivo when a parenteral or an oral intake is high enough to exceed any homeostatic capacity that may prevent magnesium overload. These basic differences between pharmacological and physiological magnesium actions lead us to discriminate

between the two types of magnesium load tests. Clinical efficiency of parenteral magnesium administration should not be used as a diagnostic tool attesting to magnesium deficiency. Conversely, physiological oral doses of magnesium are totally devoid of the pharmacodynamic effects of parenteral magnesium and without clinical effects when magnesium status is normal. Correction of symptoms by this oral magnesium load constitutes the best proof that they were due to magnesium deficiency.

But the main consequence of the differentiation between the pharmacological properties of magnesium is to allow us to distinguish between two different types of therapy with magnesium: atoxic physiological oral therapy and pharmacological magnesium therapy that may induce toxicity. Today the main form of magnesium therapy is oral magnesium physiological nutritional supplementation of magnesium deficiency. The palliative oral doses meant to balance magnesium deficiency are obviously devoid of any toxicity because their purpose is to restore to normal the insufficiency of the magnesium intake. In order to use the pharmacological properties of magnesium, no matter what the magnesium status is, it is necessary to go beyond the mechanisms of magnesium homeostasis to induce a therapeutic magnesium overload. Large doses of magnesium given orally are advisable when there are chronic indications and the parenteral route suitable for acute applications. Both types of pharmacological magnesium treatment are capable of inducing toxicity. It is a real scientific fraud and an ethical misconduct to fail to differentiate between the absent toxic consequences of a physiological magnesium supplementation and the effects of high pharmacological magnesium doses that are potentially dangerous.

In the case of magnesium deficit it is important to differentiate *magnesium deficiency*, where the disorder corresponds to a negative balance, and which merely requires an increased intake of magnesium as treatment, from *magnesium depletion*, where the disorder is related to a dysregulation of the control mechanisms of magnesium metabolism, and which requires appropriate correction. Modern research is concerned with the analysis of the neuro–endocrino–metabolic factors that control or disturb magnesium metabolism associated with genetic factors either linked with major leucocyte complex or studied as an etiopathogenic factor of various congenital hypomagnesemia.[6,18] The nervous forms of magnesium deficit may be considered as typical examples.

The nervous form of primary chronic magnesium deficiency represents the best documented experimental and clinical aspect of chronic magnesium deficit. This neurotic, neuromuscular, and autonomic nervous form induced by magnesium deficiency merely requires nutritional oral physiological magnesium supplementation.[4,10,13]

In the case of neurodegenerative diseases linked with various types of magnesium depletion, simple nutritional magnesium supplementation is inefficient. Magnesium depletion requires more or less specific correction of its causal disregulation. Amyotrophic Lateral Sclerosis/Parkinsonism/Dementia complex (ALSPDC) may be considered as the type of a neurodegenerative

disease linked with magnesium depletion due to the sum of magnesium- (and calcium-) deficient intake plus slow neurotoxins (either inorganic, i.e., Al, or organic, particularly cycad neurotoxins). Cycad seeds can be directly eaten or indirectly through traditional feasting on flying foxes (with possible biomagnification of neurotoxins).[6,12–15]

Both in clinical forms and in animal experiments, the dysregulation mechanism of magnesium depletion associates a reduced magnesium intake with various types of stress. Among these are the biological clock dysrhythmias with two opposite groups: (1) with a biological clock hyperfunction and (2) with a biological clock hypofunction. These symmetrical physiopathologies lead to opposed therapies: phototherapy in cases of a biological clock hyperfunction and scototherapy in cases of a biological clock hypofunction.[11,16–18]

Conclusion

Upon the initiative of SDRM and of Hirotoshi Morii, President of the Japanese Society for the Development of Research on Magnesium, the Eleventh International Magnesium Symposium will be held in ISE Osaka (October 24–28, 2006) under Yoshiki Nishizawa and Mieko Kimura. Once again, after the remarkable meeting organized 18 years ago in Kyoto (1988) by Yoshinori Itokawa, the Japanese branch of SDRM is organizing a meeting testifying to the exponential development of research on magnesium covering not only basic research (cellular and subcellular channels particularly), nutrition, epidemiology, and metabolic diseases, but also multifaceted clinical forms: cardiovascular, neuromuscular, psychiatric, rhumatologic, nephrologic, and even in dental and sport medicine.

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2
Magnesium and Calcium in Drinking Water

Hirotoshi Morii, Ken-ichi Matsumoto, Ginji Endo, Mieko Kimura, and Yoshitomo Takaishi

While magnesium is one of the elements that supports life, many studies have been performed regarding physiological functions as well as correlation with diseases. Seelig and Rosanoff reviewed interesting data describing correlations between magnesium deficiency and disease.[1] Magnesium deficiency causes arrythmia, overactivity to stress hormones (adrenalin), overproduction of cholesterol, blood clotting in blood vessels, constriction of blood vessels, high sodium–potassium ratio, insulin resistance, coronary atherosclerosis, and vulnerability to oxidative stress. Thus, Seelig and Rosanoff showed that magnesium content in hearts from cadavers of those who died of heart disease were much less than controls. Cadaver hearts from people who had lived in areas with hard drinking water had higher amounts of magnesium than cadaver hearts from soft-water areas. In 1957, Kobayashi indicated that the hardness of drinking water is related to the incidence of apoplexy.[2]

Materials and Methods

Water samples were collected from various sources in the world: hotel aqueduct, river, spring, and other sources. Countries included the United States, France, Belgium, Turkey, Greece, Chili, Egypt, China, Korea, Mongol, Indonesia, and Japan. Mineral content was measured at Sakai Institute of Public Health, Sakai, Japan, and Takeda Research Institute Life Science and Preventive Medicine, Kyoto, Japan.

Results

Calcium and magnesium as well as calcium/magnesium in drinking water showed considerably different levels in various parts of the world. Generally speaking, both calcium and magnesium levels are higher in Europe compared to other areas. Mineral content in Pamukkale in Turkey was the highest among sampled water. Contrexville in France had high levels of calcium and

magnesium. In Asian countries, some areas showed relatively higher levels of calcium and magnesium. Sang Sa Village has been known as a longevity village in Korea and has its own spring from which drinking water is obtained. Zhoukoudian area, located 50 kilometers southwest of Beijing, where Peking man (*Sinanthropus pekinensis*) was discovered, has wells nearby still being utilized by neighborhood populations; water from one had calcium and magnesium levels that were remarkably high. Marie Eugene Francois Thomas Dubois (1858–1940) discovered fossils of *Pithecanthropus* near Solo River in 1890. Drinking water was collected in this region and compared with that collected near Jakarta, Indonesia. Calcium and magnesium content in the former was higher compared with the latter. In Japan, calcium and magnesium content are not so high compared with other areas in the world, especially in comparison with those in Europe.

Discussion

Cardiovascular Disease and Mineral Content

Regarding the effect of both magnesium and calcium on blood pressure and incidence of cardiovascular disease, there have been many studies that are contradictory.[1] However, Seelig and Rosanoff showed that cardiovascular and overall rates were found to be lower in hard-water areas than in soft-water areas. Deaths rates from coronary heart disease are approximately 300 per 1,000,000 people in Lincoln, Nebraska, where water hardness level was 147 ppm, a little more than 600 in Washington, DC, where water hardness level was 96 ppm, and more than 800 in Savannah, Georgia, where water hardness level was 41 ppm.

Recent statistics in the United States (Table 2.1)[3] indicate that areas with high incidence of total death (as well as cardiovascular deaths) are located in the southeastern part of the country, including approximately 10 states. Among the top 10 areas with high mortality rates for both total deaths and cardiovascular deaths, six area are included for both causes of death: Mississippi, the District of Columbia, Kentucky, Alabama, Tennessee, and Oklahoma (Table 2.1). In the state of Tennessee, the water hardness is not so high in the present study.

Water hardness in France seems to be high compared with other countries outside Europe. The idea of a French paradox has been proposed for the low incidence of cardiovascular deaths in France compared with some neighboring countries in Europe.[4] One of the contributing factors was ascribed to the high consumption of polyphenol supplied from red wine, but the water hardness could be another factor. Marque collected information about all deaths of 14,311 individuals in 69 parishes of southwest France from 1990–1996. A significant relationship was observed between calcium and cardiovascular mortality with relative risk (RR) = 0.90 for noncerebrovascular causes and

Table 2.1. Number of total and heart disease deaths in the United States in 2002.[3]

Rank		Total deaths		Heart disease deaths	
1		Mississippi		Mississippi	
2	1037		326.9		
3		District of Columbia		Oklahoma	
4	1027.4		307.1		
5		Louisiana		District of Columbia	293.5
6	1001.1			Kentucky	
7		Kentucky	288.9		
8	1000.6			West Virginia	
9		Alabama	288.0		
10	999.9			Alabama	
11		West Virginia	286.3		
12	991.7			Tennessee	
13		Tennessee	283.7		
14	985.5			Arkansas	
15		Oklahoma	279.5		
16	976.2			New York	
17		Arkansas	277.6		
18	966.9			Missouri	
19		Georgia	270.6		
20	953.4			Louisiana	
21		South Carolina	269.6		
22	949.5			Michigan	
23		Nevada	265.7		
24	919.1			Georgia	
25		Missouri	263.0		
26	917.1			Ohio	
27		Ohio	258.0		
28	907.8			Texas	
29		North Carolina	252.7		
30	907.5			Pennsylvania	250.6
31		Indiana		Indiana	248.0
32	919.1			Illinois	246.4
33		Texas		Nevada	246
34	878.4			South Carolina	244.7
35		Michigan		New Jersey	244.4
36	875.8			Rhode Island	240.3
37		Wyoming		Maryland	238.7
38	868.0			Delaware	236.7
39		Pennsylvania		North Carolina	235.6
40	863.5			Virginia	226.6
41		Maryland		California	225.9
42	863.5			Florida	222.3
43		Illinois		Kansas	221.0
44	855.8			New Hampshire	220.1
45		Virginia		Iowa	
46	855.6		219.1		
47		Maine		Conneicut	216.9
48	848.3			Wisconsin	216.4
49		Montana		Nebraska	213.5
50	848.3			Wyoming	211.3
51		Kansas		South Dakota	209.9
	845.1			Maine	209.0

Table 2.1. *Continued*

Rank	Total deaths	Heart disease deaths	
	Delaware	Vermont	208.2
840.9		Arizona	204.2
	Oregon	Massachusetts	202.3
832.6		Idaho	200.9
	New Mexico	North Dakota	200.8
817.7		New Mexico	194.1
	Nebraska	Washington	193.1
814.6		Oregon	191.9
	Rhode Island	Montana	190.6
813.3		Hawaii	187.7
	New Jersey	Utah	186.0
811.2		Colorado	180.3
	Arizona	Alaska	167.0
800.5		Minnesota	163.9
	Wisconsin		
799.3			
	Massachusetts		
796.1			
	Colorado		
795.7			
	Alaska		
794.1			
	Florida		
787.8			
	Utah		
785.8			
	Idaho		
785.7			
	Washington		
784.4			
	New York		
783.3			
	New Hampshire		
781.1			
	Vermont		
774.2			
	Iowa		
773.3			
	South Dakota		
771.7			
	Conneticut		
760.3			
	California		
758.1			
	North Dakota		
748.3			
	Minnesota		
743.8			
	Hawaii		
659.6			

RR = 0.86 for cerebrovascular deaths when calcium is higher than 94 mg/L. There was a protective effect of magnesium between 4 and 11 mg/L with RR = 0.92 for noncerebrovascular and RR = 0.77 for cerebrovascular mortality at concentration lower than 4 mg/L.[5]

Cardiovascular deaths in Japan are much less compared with those in western countries: 85.8 in males and 48.5 in females per 100,000 people in 2000, although the rank is the second next to neoplastic diseases.[6] Hardness of water is less in most of the areas in Japan compared with countries in Europe and North America (Table 2.2). But there are still differences in mineral content among areas in Japan. One of areas in Kyushu Island showed the higher level of calcium and magnesium compared to other areas (Table 2.2). This area belongs to Miyazaki Prefecture, where the cardiovascular death rate was shown to be lower than average. There are so many factors other than minerals that effect the incidence of cardiovascular death.

Mineral Intake of Prehistoric Man

Mineral content in the well of Zhoukoudian area, where the Peking man fossils were discovered, showed very high levels compared with those in Beijing City water and in the Yong Ding Hu river (Table 2.2). In Indonesia, calcium and magnesium content in natural water were not so high. However, in nearby Solo River, near where Java man was discovered 1859 by Dubois, mineral content was higher than in another area near Jakarta (Table 2.2).

Mineral intake will be influenced by mineral content in drinking water, contributing to the requirement of minerals. Total amount of minerals ingested from drinking water not only supplement the dietary allowances, but also modulates mineral metabolism by affecting various factors depending on the concentration of minerals. Meunier compared serum parathyroid hormone and biochemical markers of bone remodeling between females ingesting high- (596 mg/L) and low- (10 mg/L) calcium drinking water. One hundred and eighty healthy postmenopausal women with mean age of 70.1 ± 4.0 years and with daily average intake of calcium less than 700 mg were studied, and 152 completed the 6-month trial. There was a significant 14.1% decrease of PTH, osteocalcin (−8.6%), bone alkaline phosphatase (−11.5%), serum (−16.3%), and urine (−13.0%) type-1 collagen C-telopeptide in those who ingested high-calcium drinking water compared with control group. The additive effect of vitamin D supplement at a dose of 400 IU was not significant.[7] Regarding the effect of magnesium, Marie demonstrated that in weanling male mice, magnesium supplementation in drinking water increased serum and urinary magnesium concentrations and bone magnesium content and that both calcification rate and the extent of tetracycline double-labeled osteoid surface increased progressively in magnesium-treated mice.[8]

These data indicate that calcium and magnesium content in drinking water, as well as in diet, influence calcium and bone metabolism, thus helping to adjust individuals to the environment depending on the quantity of minerals