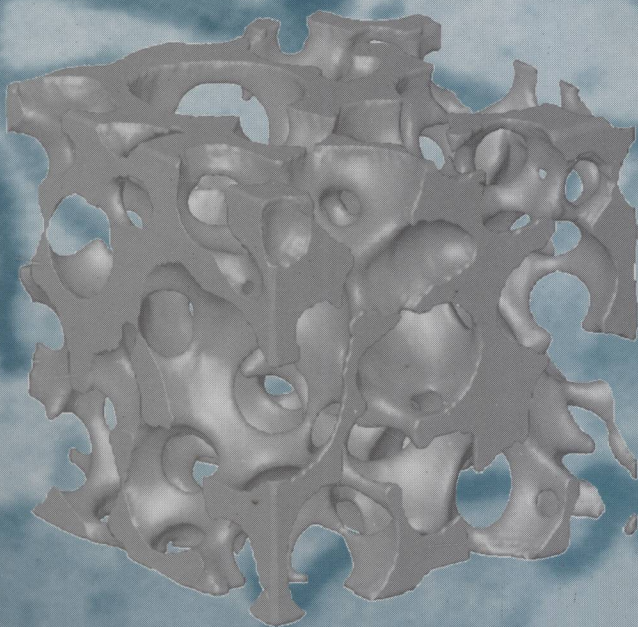


Biomaterials and Biomedical Engineering



Edited by W. Ahmed, N. Ali, A. Öchsner

R318
B615.4

Biomaterials and Biomedical Engineering

Edited by
W. Ahmed¹, N. Ali², A. Öchsner^{3,4}

¹ Advanced Digital Manufacturing Centre, School of Computing,
Engineering and Physical Sciences, University of Central Lancashire,
Preston PR1 2HE, UK
E-Mail: WAhmed4@uclan.co.uk

² Society of Nanoscience and Nanotechnology
Manchester, M85SF, UK
Current Address:
School of Mechanical and Manufacturing Engineering,
Dublin City University, Dublin, Ireland
E-Mail: n.ali@nano-society.org

³ Department of Applied Mechanics
Faculty of Mechanical Engineering
Technical University of Malaysia
81310 UTM Skudai, Johor
Malaysia

⁴ University Centre for Mass and Thermal Transport in Engineering Materials,
School of Engineering, The University of Newcastle,
Callaghan, New South Wales 2308, Australia
E-Mail: andreas.oechsner@gmail.com



E2009003290

ttp TRANS TECH PUBLICATIONS INC
Switzerland • UK • USA

Copyright © 2008 Trans Tech Publications Ltd, Switzerland

All rights reserved. No part of the contents of this book may be reproduced or transmitted in any form or by any means without the written permission of the publisher.

Trans Tech Publications Ltd
Laubisrutistr. 24
CH-8712 Stafa-Zuerich
Switzerland
<http://www.ttp.net>

ISBN 0-87849-480-4
ISBN-13: 978-0-87849-480-4

Volumes 41-43
Materials Science Foundations
ISSN 1422-3597

Distributed worldwide by

Trans Tech Publications Ltd
Laubisrutistr. 24
CH-8712 Stafa-Zuerich
Switzerland

and in the Americas by

Trans Tech Publications Inc.
PO Box 699, May Street
Enfield, NH 03748
USA

Biomaterials and Biomedical Engineering

Foreword

Biomedical engineering involves the application of the principles and techniques of engineering in order to enhance medical science in humans and animals. It involves an interdisciplinary approach to combine materials, mechanics, design, modelling and problem solving skills employed in engineering with medical and biological science to help improve health, lifestyle and quality of life of individuals. Biomedical engineering is a relatively new field and involves an array of disciplines covering bioinformatics, medical imaging, image processing, physiological signal processing, biomechanics, biomaterials and bioengineering, systems analysis, 3-D modelling, *etc.* By combining these disciplines systematically and in a synergistic way yield benefits much greater than the sum of the individual components added together. Some examples include the application of biomedical engineering involve the development and manufacture of biocompatible prostheses, medical devices, diagnostic devices and imaging equipment and pharmaceutical drugs.

Biomaterials, due to their integral role in the fabrication of most of the current generation of medical implant devices are a critical component for the provision of advanced healthcare technologies. Indeed, the various medical implants that are now commonly used to replace and/or augment diseased or damaged tissues and organs in the human body owe much of their clinical success to the properties of the materials from which they are fabricated. Moreover, the function of such devices is critically dependent upon the interactions that occur at the interface between the surface of the implanted device/material and the biological environment in which it is placed. As such, the development of biomaterials that can direct and control specific cellular processes at this interface is a key consideration in furthering implant utility. This is particularly the case in the emerging areas of tissue engineering and regenerative medicine where the function of the product is dependent upon the nature and scale of the molecular and macromolecular interactions that occur within a scaffold or delivery system. The development of surface features that can direct such processes has the potential to improve tissue regenerative *in vivo* and thereby forms the basis of much of the developing technology in the area. An increasingly important aspect of such studies is the determination of those surface properties that will promote and support early stage bioprocesses that can lead to the formation of viable tissue. In this regard, the role of those effects that might be available at the nano-scale becomes an exciting proposition. The provision of targeted features (surface and/or bulk) in the region of ≤ 100 nm offers the opportunity for materials to interact directly with the molecular scale biochemistry on the sub-cellular level with the aim of directing a specific process that can lead to a targeted response *in vivo*. The opportunities that this approach offers have already been embraced in several areas of medicine, most specifically in the targeted treatment of cancerous cells by the use of nano-particles with the capability of releasing a highly targeted chemotherapy payload or by providing a target for their localized thermal inactivation *in vivo*. It is clear that the medical applications of nanotechnology will continue to expand rapidly and therefore the attendant materials science will need to develop in a concerted manner.

Specifically, the need to consider nano- and bio-materials in a way that provides for a process of convergence that results in a clear understanding of the role of the nano-scale is now evident.

The purpose of this book is to present research and development in the areas of biomedical engineering, biomaterials and nanomaterials science and to report on the application of such systems. Specific emphasis is given to the convergence of nano-scale effects, as they relate to the delivery of enhanced biofunctionality. The chapters presented in this book bring together a number of materials/engineering approaches that are currently being explored to deliver systems that can impart clinical benefits. As such, they represent many of the significant challenges that exist to our producing medical implants and therapies that are capable of achieving regeneration of viable tissues and organs for implantation. We hope that they will therefore serve as a key reference for those who wish to contribute to the global endeavor of improving clinical outcomes for the benefit of patients today and tomorrow.

Waqar Ahmed

Nasar Ali

Andreas Öchsner

Table of Contents

CHAPTER 1: Health Hazards of Manufactured, Natural Environmental and Other Anthropogenic Atmospheric Nanoparticulate Materials: Past, Present and Future

Lawrence E. Murr, Karla F. Soto, Kristine M. Garza 1

CHAPTER 2: Integration of Microfabrication and Surface Functionalization Strategies for Analysis of Cell-Surface Interactions

Nuttawee Niamsiri, Magnus Bergkvist, and Carl A. Batt57

CHAPTER 3: Mechanics of Biomimetic/Biological Vesicles

Isaac Kuo-Kang Liu and Kai-Tak Wan 115

CHAPTER 4: Engineered Titanium Surface Promoting Osseointegration

Yongxing Liu, Sangwon Park, Hyunseung Kim, Kwangmin Lee, Jeongtae Koh, Satoru Ken Nishimoto, Joel D. Bumgardner, Warren Haggard, Yunzhi Yang 135

CHAPTER 5: Electrospinning of Micro and Nano Fibers for Biomedical Applications

Souheil Zekri, Rahul Singhal, Nick Baksh, Ashok Kumar 167

CHAPTER 6: Bioactive Glasses, New Opportunities for Tissue Engineering

Jason Maroothyaden 217

CHAPTER 7: Ordered Nanoporous Silica Materials for Biomolecular Systems

Humphrey H.P. Yiu 251

CHAPTER 8: Biomaterials for Bone Regeneration: from Tissue Replacement to Tissue Engineering

Gadi Turgeman 283

CHAPTER 9: Biomimetic Approaches to Synthesize Mineral and Mineral/Organic Biomaterials

Sharon Segvich, Linh N. Luong, David H. Kohn 325

CHAPTER 10: Fluoridated Hydroxyapatite Coating on Metallic Implant for Stability

Yongsheng Wang, Sam Zhang, Xianting Zeng 375

CHAPTER 11: Physiological Insights of Pharmacokinetics and Host Response for Drug Delivery System Design

Lei Shang, Sam Zhang, Subbu S Venkatraman, Hejun Du 419

CHAPTER 12: Biomedical Devices: Microbiological Aspects

Kathryn A. Whitehead and Joanna Verran..... 473

CHAPTER 13: Adsorption of Proteins and Amino Acids onto Surfaces

Mukhtar H. Ahmed and Waqar Ahmed 523

CHAPTER 1

Health Hazards of Manufactured, Natural Environmental and Other Anthropogenic Atmospheric Nanoparticulate Materials: Past, Present and Future

L.E. Murr,^a K.F. Soto,^{a*} K.M. Garza^b

^aDepartment of Metallurgical and Materials Engineering
The University of Texas at El Paso, El Paso TX 79968 USA

^{*}Now at Lockheed Martin Aeronautics Company,
Fort Worth, TX 76108 USA

^bDepartment of Biological Sciences
The University of Texas at El Paso, El Paso, TX 79968 USA

Table of Contents

1. Introduction.....	3
2. Examples of Nanomaterials in the Past Millennia: Applications, Benefits and Health Hazards.....	6
2.1 Chrysotile Asbestos: The Most Multifunctional Nanomaterial of All Time.....	6
2.2 Nanosilver: “The Wonder Drug Time Forgot”	9
3. Health Hazards of Environmental Dusts, Industrial PM and Other Atmospheric PM	12
3.1 Mineral Dusts and Human Health	12
3.2 Industrial and Other Atmospheric PM.....	13
3.3 Occupational and Indoor Environmental PM.....	19
3.3.1 Structures of Black Carbon (BC), Soots, Fullerenes and Carbon Nanotubes.....	21
3.3.2 Cumulative Indoor PM: House Dust.....	26
3.4 Health Effects and Health Hazards of Nanoparticulate Materials	27
3.4.1 Environmental and Occupational Health Risks of Contemporary, Manufactured Nano-PM	29

3.4.2	Environmental and Occupational Health Risks of Carbon Nanotubes and Related Carbonaceous PM.....	36
4.	Nanotechnology in the Future: Health Hazard Potential of Nanoparticulates and Lessons from the Past	43
5.	Summary	46
6.	Acknowledgements	46
7.	References	47

1. INTRODUCTION

Biomaterials and biomedical engineering are often associated with varieties of materials and materials systems involved in prosthetics and other implants, including total hip replacements (first performed by Dr. T. Mallory in 1971 at Columbus, Ohio, Mount Carmel Hospital), and the Jarvic 2000 Ti mechanical heart, about the size of a walnut; first invented by Dr. R. Jarvic as the Jarvic-7 and implanted in 1982. The latest mechanical heart, implanted in March, 2002, plugs into the left ventricle where the tiny pump pushes blood into the aorta, powered by a small external battery connected by a cochlear implant. While metals, alloys, polymers, ceramics, and various mixtures or composites serve as biomaterials, biological systems, including plant and animal systems, can serve multi-functional roles and applications as bio-materials [1]. These bio-materials provide models for biomaterials and biomedical materials engineering (biomimetics), as well as biological tools for engineering applications, such as bio-remediation, bio-extraction, bio-sorption, and a host of related biomedical engineering functions.

At the scale of living cells or sub-cell structures, biomaterials and bio-materials are dominated by the realm of nanomaterials or nanotechnology, where the understanding, control, or applications of matter focuses on the 1 to 100 nanometer (nm) dimension. The beginning of the Twenty-First Century heralded the “age of nanotechnology”, and in the U.S. a National Nanotechnology Initiative [2] was undertaken to promote and enhance nanotechnology, while similar initiatives were implemented in other parts of the world as well. Nanotechnology, with a prominent role to be played by engineered nanomaterials, was estimated to exceed the impact of the Industrial Revolution, and to command a \$1 trillion market by 2015 [2]. At this writing in late 2006, engineered nanomaterials, especially nanoparticulate materials, were being used in electronics, composite systems (including sporting good products), cosmetics and sunscreens, drug delivery systems, and many other products and applications totaling more than 200 commercial goods [3]. However many applications of nanomaterials are not new; simply a new awareness in the context of the nano-regime.

Synonymous with the realization, and further economic speculation of engineered nanomaterials, especially nanoparticulate materials, has been the prospect for adverse health effects on a wide range of biological systems; especially humans. Indeed, these concerns are also not necessarily new, but rather a resurgence of safety and health issues in the context of nanotechnology. In addition, there has been mounting evidence over the past decade that nanoparticulates in the environment are associated with adverse respiratory health, in spite of efforts worldwide to reduce atmospheric particulate levels, and the realization that the prevalence of asthma and related respiratory diseases is increasing dramatically, especially in industrialized countries [4-6]. The case has been made, for both *in vitro* and *in vivo*, studies, that ultrafine particulate matter (PM) (for particle diameters $<0.1\ \mu\text{m}$) is notably more toxic

or cytotoxic than fine PM (where particle diameters are between 1 and 2.5 μm) [7-12]. This realization has fueled numerous calls for moratoriums on nanotechnology-related research, especially nanoparticulate production, manufacturing, and use [13,14]. More recently, Friends of the Earth produced a report [15] describing nanoparticulates composing more than 100 cosmetic and skin care products, which also called for a moratorium on the commercial release of products containing nanomaterials until they have been subjected to rigorous health and environmental safety assessment. Of course, many such products have contained nanoparticulates, and have historically produced irritation and allergic responses in susceptible individuals.

Perhaps the most ubiquitous of the nanoparticulates in the environment are various combustion soots or carbonaceous particulate matter (PM). These include complex, aggregated soots composed of spherules of graphene fragments often intercalated with polycyclic aromatic hydrocarbons (PAHs) which range in size (diameter) from <10 nm to 100 nm. Commercial black carbon (BC), news print ink, wood soot, diesel and other internal combustion engine soot, tire burning soot, and soot produced by natural gas combustion (including liquid natural gas sources), food cooking soots, and candle soots all contribute to indoor and outdoor air pollution, often symbiotically with accompanying gases such as CO , NO_x , ozone (O_3), etc., as well as other nanoparticulates, which can include plant and animal-related aerosols such as pollens and natural mineral dusts, or degradation products from paints, coatings, corrosion products, etc.

Several localized, soot-related episodes have occurred in the last century where significant numbers of people were killed. Notable among these was the Donora, Pennsylvania, USA event associated with steel mill and related soot emissions trapped in an atmospheric inversion in October, 1948. This caused 20 deaths and hundreds of respiratory-related illnesses. This event led to the U.S. Air Pollution Control Act of 1955. This U.S. event was followed by 4 days of heavy soot produced by fire place burning of coal and wood in London, England in December, 1952. Thousands of people died from lung overload and thousands more suffered respiratory illnesses in this event. This prompted passage of Great Britain's first Clean Air Act in 1956. Both events were marked by particulate mass concentrations in milligrams/ m^3 .

Andreae [16] has estimated that while mineral PM composes approximately 16.8 Tg (1 Tg = 10^{12} g or 10^6 metric tons) mass abundance of the global atmospheric aerosol, industrial sources, including soot PM production contribute nearly 10 percent additional PM, or 1.4 Tg mass abundance. But more recent soot or black carbon (BC) PM estimates by Chameides and Bergin [17] show the soot or BC mass abundance to be ~ 7 Tg; with the U.S. contributing 0.32 Tg of BC in contrast to 1.2 Tg of BC for China. In addition to contributing to suspended particle haze and air pollution, which can vary by orders of magnitude from urban-industrial

areas to remote and rural locations, the BC contribution to global warming may be second only to that of CO₂. This occurs by the BC PM absorbing sunlight.

Over the past decade, carbon nanotubes have emerged as one of the more promising engineered multifunctional nanomaterials, either as single wall carbon nanotube (SWCNT) configurations or multiwall carbon nanotube configurations, which have evolved from industrial efforts to develop carbon fibers, including graphite fibers and carbon nanotube fibers [18-20]. At the turn of the Century (2000), hundreds of tons of MWCNTs were already used in composite applications to strengthen plastic products [21, 22], and the purported strength of SWCNTs at ~100 times the strength of steel at 1/6th the weight, along with other thermal and electrical properties led nanotechnology proponents to predict proliferation of SWCNTs and MWCNTs in a variety of structures, even artificial muscles [22,23]. But this multifunctional material prospect seems to be a drawback to a previous era of engineered nanomaterials development; namely asbestos. Indeed, asbestos-based products, evolving since at least 300 BC [24-25], were celebrated at the 1939 New York World's Fair where the Johns-Manville Company highlighted asbestos' "service to humanity". Like SWCNTs, asbestos fibers and nanotubes are also stronger than steel, and are estimated to have been involved in about 4000 products, mostly commercial, over the past 2000 years. Even at the turn of the Century (2000), it is estimated that nearly 2 million tons of chrysotile asbestos (the most popular, nanotube form of asbestos) was processed worldwide, mostly in the form of asbestos-cement (composite material) products outside the U.S. [24, 26]. Asbestos-cement pipe use in the U.S. alone since 1930 is nearly enough to reach from the moon and back to Earth twice. But by 1931, reports of fibrotic lung damage amongst asbestos workers in British asbestos milling and manufacturing operations led to the enactment of industry regulations which served as a precursor to asbestos becoming the most notorious and feared contaminant on earth. However, Strabo and the Greek historian Pliny-the-Elder both described the horrors of asbestos quarry slaves in terms of the "disease of slaves" long before [26].

Asbestos was not the first environmentally associated health risk leading to cancer and death amongst occupational workers in nanotechnology or nanomaterials. The first cancer-causing, environmental nanomaterial was wood soot and soot-related deposits in chimneys, which caused cancer of the scrotum in 9 to 12 year-old, nude boys bought from orphanages and used by chimney sweeps for centuries to clean chimneys. In 1775, Percival Potts, a British medical doctor, recognized the cause and effect [27]. Similarly, at the turn of the 20th century, nasal, throat, and lung cancers were observed in nickel mine workers exposed to NiO dust [28]. This was followed by a variety of graphite and other carbon industry worker diseases, coal dust-related ailments, including silicosis, which began to establish fine particle respiratory health issues amongst a wide range of industrial and manufacturing occupational environments [29, 30].

These examples, few amongst so many worldwide, illustrate that to a large extent, the mindset for thousands of years has been to produce and use materials until they are proven to be a severe health hazard. Even then, for expedience, profit, or political concerns the use continues. A good example is cigarette smoking, a well known health risk which can result in death and which continues to kill tens of thousands in the U.S. alone. The mandate for the future success of nanotechnology, especially biomaterials and nanomaterials engineering and applications, must include a recognition of the potential for health hazards, and to demonstrate that there are no significant risks either to public health or the ecology.

In this chapter we explore current knowledge of the health hazards of nanoparticulate materials: engineered, manufactured, and environmental including indoor and outdoor pollutants. We also review fundamental microstructures and properties of some prominent nanoparticulate materials, and their toxicities and potential for occupational and environmental health risks. We explore the health benefits of several nanoparticulate materials in contrast to their complex, systemic human and animal toxicities, and the implications for biomaterials and biomedical engineering and applications; especially in the context of medicine and public health.

2. EXAMPLES OF NANOMATERIALS IN THE PAST MILLENNIA: APPLICATIONS, BENEFITS AND HEALTH HAZARDS

2.1 CHRYSOTILE ASBESTOS: THE MOST MULTIFUNCTIONAL NANOMATERIAL OF ALL TIME

Chrysotile ($\text{Mg}_3\text{Si}_2\text{O}_5(\text{OH})_4$) is the most unique and versatile of the many asbestos fiber family members. It is the only cylindrical asbestos with a hollow core, a nanotube, which can have lengths of many centimeters. Its nanotube structure is similar to halosite, one of few hollow core natural mineral nanotubes. Its snake-like nanotube structure led to its designation as serpentine. Other prominent asbestos fiber minerals include the so-called amphibolic forms: amosite, or “brown” asbestos ($(\text{Fe}^{2+}, \text{Mg})_7\text{Si}_8\text{O}_{22}(\text{OH})_2$), and crocidolite, or “blue” asbestos ($\text{Na}_2\text{Fe}^{2+}_3\text{Fe}^{3+}_2\text{Si}_8\text{O}_{22}(\text{OH}, \text{F})_2$) which accounted for about 5 percent of the commercial use of asbestos; with chrysotile accounting for the remaining 95 percent. Other amphibolic asbestos fibers include anthrophyllite, tremolite and actinolite as well as palygorskite (or attapulgite), a hydrated clay mineral nanofiber mass ($(\text{Mg}, \text{Al})_4\text{Si}_8(\text{O}, \text{OH}, \text{H}_2\text{O})_{24}$) used in antiquity in Maya (blue) wall paints [31,32], and other contemporary commercial applications, and often referred to as “Mountain Leather” [33].

As a mined, hardrock mineral, chrysotile asbestos is noticeably softer and more flexible than other asbestos fiber types. As shown in Fig. 1(a) its cotton-like features have allowed it to be spun into continuous fibers to make an array of fire-proof fabrics for 2000 years. Mixed with cement and other matrix materials, it has found wide use in roofing, ceiling, and floor tiles, structural (concrete beam) members, and thousands of other heat insulating and fire

preventing products, including spray coatings on steel structural members, such as the Twin Towers in New York City; which was removed prior to the September 11, 2001 terrorist attack. An estimated 20 percent of U.S. buildings still contain a variety of products, including insulations, made from chrysotile asbestos [26].

As shown in Fig. 1(b) and (c) the cylindrical chrysotile nanofibers consist of curved layers of magnesium hydroxide connected to SiO_4 tetrahedra, with layers spaced 7.5 \AA apart [34]. Typical fibers (Fig. 1(b)) consist of up to 17 concentric, elongated, crystalline layers around an 80 \AA (8 nm) hollow core. These crystalline layers give rise to the streaking in the selected-area electron diffraction pattern, perpendicular to the fiber axis, shown in Fig 1(b) [35]. Single nanotube diameters can range from 15 to 30 nm. These nanotube fibers also often exhibit hemispherical caps as shown in Fig. 1(b) (arrow) [36].

Beginning with the British Asbestos Industry Regulations in 1931, and especially with notable asbestos-related diseases amongst shipyard workers in the U.S. after World War II, it became increasingly apparent in the 1960's that even low concentrations of chrysotile asbestos posed significant health risks, and this prompted a series of manufacturing and product bans, including remediation. Serious concerns of asbestos in drinking water were raised, but a comprehensive study of water systems with and without asbestos-cement pipe concluded that the largest concentrations of asbestos in drinking water originated from natural mineral deposits [32]. Concerns for asbestos-contaminated talc as an irritant and even chronic inflammation issue led to cosmetic talc (45 kilotons of cosmetic talc in 1998) being listed as a carcinogen, with concerns continuing even today [38].

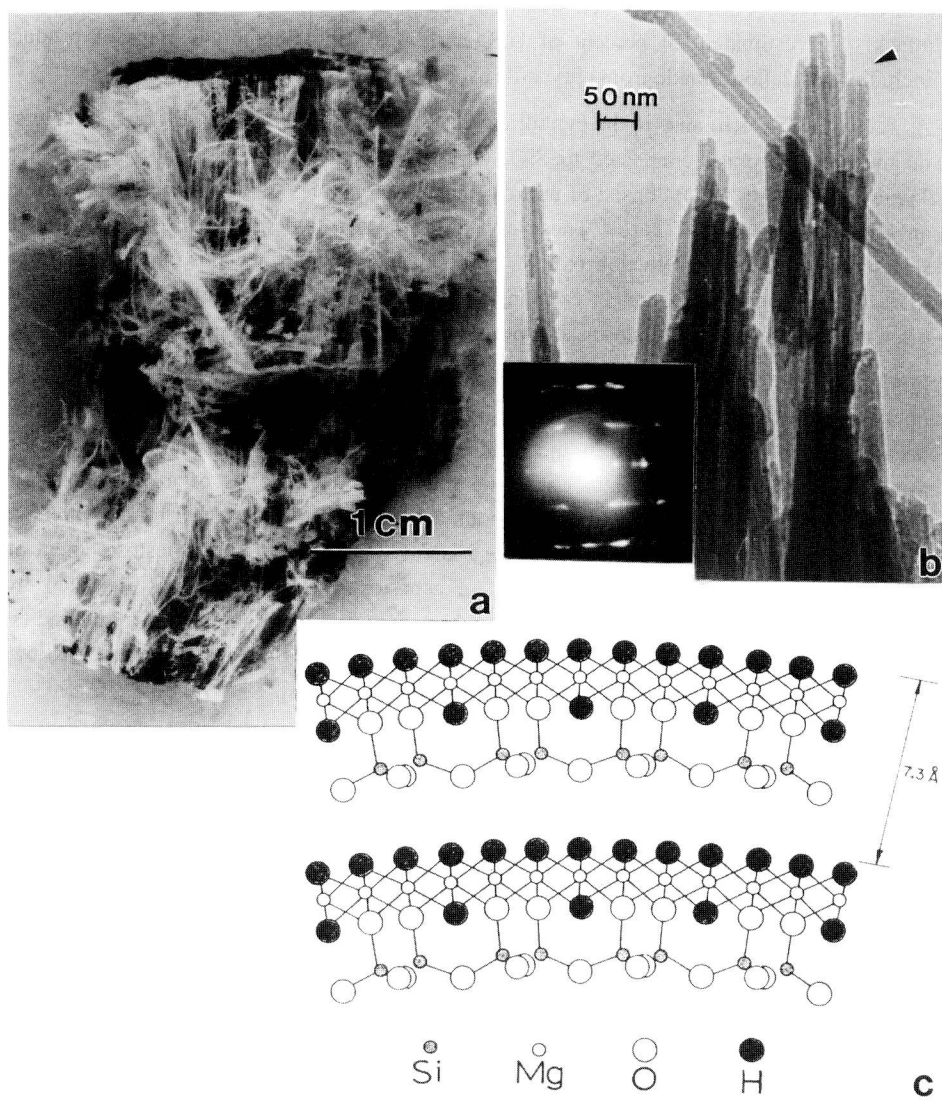


Fig. 1. Chrysotile asbestos. (a) Sample from large mine in Quebec, Canada. (b) TEM view of individual asbestos nanotubes, some with caps (arrow) and SAED pattern insert. (After Murr and Soto [36]). (c) Curved layer sections with 7.5 Å spacing, looking down the nanotube axis (After De Souza Santos [34]).

Chrysotile contaminated, talc-coated rice was also suspected in notable, segregated geographical cases of stomach cancer [39].

Animal studies and epidemiology assessments in humans have now shown that inhalation of asbestos can result in pulmonary fibrosis, lung cancer, mesothelioma, and other, related pleuropulmonary disorders, especially after occupational exposure at high concentrations. The pathogenesis of asbestos-related diseases is associated with persistent inflammatory responses initiated directly or indirectly by reactive oxygen species (ROS), among other factors generated by lung cell phagocytosis [40, 41]. The U.S. National Institutes of Health (NIH) in 1978 estimated that between 1940 and 1978 (a 38 year period) 11 million individuals in the U.S. had been exposed to asbestos. The Work-Related Lung Disease Surveillance Report, published by the U.S. National Institute for Occupational Safety and Health (NIOSH) in 1999 determined that between 1987 and 1996, more than 9000 deaths were associated with asbestos exposure, of which more than 5000 deaths were from malignant neoplasms of the pleura.

Despite the horrific numbers of asbestos-related deaths and related diseases, and the lifting of the U.S. Environmental Protection Agency (EPA) ban on all forms of asbestos in 1991, asbestos, particularly chrysotile asbestos, is not ubiquitous in the environment. It is rarely detected in traffic-congested regions which prior to the 1970's accounted for millions of tons of asbestos wear debris. Indeed chrysotile asbestos remains to this day an essential element of global technologies which, as a consequence of intense scrutiny and research, are now amongst the safest uses of nanoparticulate material.

2.2 NANOSILVER: “THE WONDER CURE TIME FORGOT” [42]

In a recent revision of a book titled the quoted subtitle above, d'Raye [42] recounts how colloidal (nano) silver was used to treat some 650 infectious conditions prior to the discovery of penicillin in 1938, which heralded the age of antibiotics. Silver was observed to possess what is now recognized as an antibacterial effect prior to recorded history, when silver vessels for storing and carrying water were observed to keep the water purer for long periods of time. In 1893, as a realization that even small quantities of silver or silver compounds had a powerful effect in water purification and even open wounds, Von Nageli coined the term “oligodynamic” from the Greek oligas (small) and dynamics (power) [43]. About the same time (circa 1897), Credé introduced an ointment base containing colloidal silver (as silver citrate) for use in the treatment of wounds and skin diseases [44]. Silver foil and “wet packs” of silver powder were also applied to wounds to eliminate pathogenic bacteria. Silver powder was also ingested to treat ulcers and other ailments and after continued ingestion in large amounts, a condition called argyria occurred where the persons' hair and skin became discolored, giving a silvery appearance.