OCCUPATIONAL DISEASES

**ОДЕСЬКИЙ ДЕРЖАВНИЙ
МЕДИЧНИЙ УНІВЕРСИТЕТ**

**THE ODESSA STATE
MEDICAL UNIVERSITY**

*Бібліотека
студента-медика*

*Medical
Student's Library*

*Започатковано 1999 р. на честь 100-річчя
Одеського державного медичного університету
(1900–2000 рр.)*

*Initiated in 1999 to mark the Centenary
of the Odessa State Medical University
(1900–2000)*

OCCUPATIONAL DISEASES

Recommended
by the Central Methodical Committee
for Higher Medical Education of the
Ministry of Health of Ukraine as a manual
for students of higher medical educational establishments
of the IV level of accreditation using English

Odessa
The Odessa State Medical University
2009

Authors: O. M. Ignatyev, N. A. Matsegora, T. O. Yermolenko,
T. P. Oparina, K. A. Yarmula, Yu. M. Vorokhta

Reviewers: Professor G. A. Bondarenko, the head of the Department of
Occupational Diseases and Radiation Medicine of the Donetzk
Medical University named after M. Gorky, MD

Professor I. F. Kostyuk, the head of the Department of
Internal and Occupational Diseases of the Kharkiv State
Medical University, MD

This manual contains information about etiology, epidemiology, pathogenesis of occupational diseases, classifications, new methods of examination, clinical forms and presentation, differential diagnosis, complications and treatment. It includes the questions of prophylaxis, modern trends in treatment according to WHO adopted instructions, working capacity expert exam.

The represented material is composed according to occupational diseases study programme and it is recommended for the students of higher medical educational establishments of the IV accreditation standard and doctors of various specialities.

PREFACE

According to the best available estimates 100 million workers are injured and 200,000 die each year in occupational accidents and 68–157 million new cases of occupational disease are attributed to hazardous exposures or workloads. Such high numbers of severe health outcomes contribute to one of the most important impacts on the health of the world's population. Occupational injuries and diseases play an even more important role in developing countries where 70% of the working population of the world lives. By affecting the health of the working population, occupational injuries and diseases have profound effects on work productivity and on the economic and social well-being of workers, their families and dependents.

According to recent estimates, the cost of work-related health loss and associated productivity loss may amount to several per cent of the total gross national product of the countries of the world.

The formal workforce constitutes on average 50–60% of a country's total population. If informal work and work at home are also taken into account, the major part of the population is involved in work. This work products all economic and material values all other societal activities thus ensuring the socioeconomic development of countries.

The Constitution of the WHO, the WHO Global Strategy on Health for All, plus the JLO Conventions on Occupational Safety and Health and on Occupational Health Services stipulate among other issues the fundamental right of each worker to the highest attainable standard of health. To access to occupational health services should be ensured for all workers of the world irrespective of age, sex, nationality, occupation, type of employment, or size or location of the workplace.

Although effective occupational health and safety programmes and many structural changes have improved the conditions of work in some sectors, several hazardous agents and factors such as physical, chemical,

biological as well as psychosocial stress in addition to occupational accidents still threaten the health of workers in all countries continuing to cause occupational and work-related diseases and injuries throughout the world. In some economic sectors and in some countries occupational health indicators show even worse trends than in the past.

Although the transfer of healthy and safe technologies has had a positive impact on development, the transfer of hazardous technologies, substances and materials to developing countries, which have insufficient capacity to deal with such problems, constitute a threat both to the health of workers and the environment.

New developments in work, the work environment and work organization, the introduction of new technologies, new chemical substances and materials in all countries, and the growing mechanization and industrialization in developing countries can lead to new epidemics of occupational and work-related diseases and injuries. In addition, demographic changes in working populations call for new strategies and programmes for occupational health throughout the world.

The level of occupational health and safety, the socioeconomic development of the country and the quality of life and well-being of working people are closely linked with each other. This suggests that intellectual and economic inputs in occupational health are not a burden but have a positive and productive impact on the company and national economy. Some industries and countries have demonstrated that it is technically feasible and economically productive to prevent and minimize hazards at work. Thus occupational health is an important factor for sustainable socioeconomic development that enables workers to enjoy a healthy and productive life both throughout their active working years and beyond Way to a new healthy working life.

Governments should ensure the development of necessary infra-structures for effective implementation of occupational health programmes, including occupational health services, research programmes, training and education, information services and data banks. Networking of such infrastructures within and among the countries would substantially facilitate their efforts to implement national programmes.

It is a realistic long-term objective to organize well functioning and competent occupational health services for all workers to ensure healthy and safe workplaces as well as the required services for each individual worker. In order to be comprehensive such an occupational health service should include first of all a multidisciplinaly preventive element, including surveillance of the work environment and health of workers and, where appropriate, relevant curative and health promotion elements.

The focal point for practical occupational health activities is the workplace. Employers are responsible for planning and designing a safe and healthy work, workplace, work environment and work organization, as well as for maintaining and constantly improving health and safety at work. Workers in many countries are trained in occupational safety and health. They have the right to know the potential hazards and risks in their work and workplace, and they should, through appropriate mechanisms, participate in planning and decision-making concerning occupational health and other aspects of their own work, safety and health.

Introduction
TO OCCUPATIONAL DISEASES ———————

THE PLACE OF OCCUPATIONAL DISEASES IN THE TRAINING OF GENERAL PHYSICIANS ———————————

In the modern world a human being comes across with the greatest majority of harmful factors which can unfavourably influence on his health. The diseases caused by the influence on the human's body unfavourable factors of the industrial sphera are called occupational. A doctor should be aquainted with this group of diseases because they have special course and their social meaning is great as well. This group of diseases is learnt in a special unit of inner medicine, a so called occupational pathology.

Occupational pathology is a clinical discipline which studies the problems of etiology, pathogenesis, clinical course, diagnosis, treatment and prophylaxis of occupational diseases. Occupational pathology is a part of general clinical subjects and its meaning is closely connected with knowledge in other fields of medicine.

Occupational pathology is closely connected with hygienic subjects and especially with labour hygiene, toxicology, pathological physiology and other medical subjects. It goes without saying that the occupational pathology is connected with social points, labour protection and safety protection. The persons of different medical professions often come across with the consequences of a harmful influence of industrial factors on the human being's organism. That is why they should have some knowledge in the field of occupational pathology.

It refers to the general physicians as well as they should give medical aid on the enterprises and together with the doctor of sanitary and epidemiological stations to fulfil sanitary supervision, prevent harmful influence of industrial factors, treatment, reduction of general and occupational morbidity.

Labor is one of the human being's activity which has a favorable influence on his health and supplying the wellfare of the society. At the same

time some kinds of labor activity under certain conditions may lead to occupational diseases development. Insufficient and irregular technical equipment of the industrial objects, non-observance of sanitary and hygienic normae necessary may lead to the development of occupational pathology.

HISTORIC STAGES OF OCCUPATIONAL PATHOLOGY DEVELOPMENT _____

It was the labour activity of a human being which caused the idea about occupational diseases development. One can point out several historical stages in its development. We have very brief ideas about the ancient period of its development from the works of separate doctors and philosophers. In the ancient Greece and Roman literature in the works of Aristotel, Lucretius, Ovidius and Plutarch one can find notions to the severe diseases and high mortality rate among miners, slaves, working at the silver pits, leathers, metallurgists. Hippocrates (460–377 BC) gave a more detailed description. He was the first who paid attention to the harmful properties of lead dust and described the clinical picture of lead poisoning — "lead cramps".

Classification of Occupational Hazards and Dangers

I. Psychophysiologic factors
    1.1. Static and dynamic overstrains of locomotor apparatus.
    1.2. Hypodynamia.
    1.3. Overstrain of circulatory, respiratory systems, vocal cords.
    1.4. Neuropsychic overstrain.
II. Physical factors
    2.1. Lowing or rising of temperature, moisture, atmospheric pressure.
    2.2. A higher level of infrared, ultrasound, laser, ionizing, electromagnetic irradiation.
    2.3. High level of dust content.
    2.4. High level of noise, vibration, ultrasound.
    2.5. Disturbance of illumination.
III. Chemical factors
    3.1. Gases, steams, acids, alkali.
    3.2. Dissolvents, varnishes, paints.
    3.3. Pesticides.
IV. Biological factors
    4.1. Micro- and macroorganisms.
    4.2. Antibiotics, vitamins and other biologically active substances.
V. Danger of occupational trauma

Classification of Occupational Diseases (by Etiological Concept)

1. Diseases related to **industrial dust** exposure (pneumoconiosis, mechanic bronchitis, occupational bronchial asthma).

2. Diseases related to the exposure of **physical factors** of industrial environment (vibrational disease, damages caused by different types of irradiation, high or low temperature, etc.).

3. Diseases related to the exposure of **chemical factors** (acute and chronic intoxications).

4. Diseases related to the exposure of **biological factors** (infectious, parasitic and allergic diseases).

5. Occupational diseases caused by **overstrain** of separate organs and systems (locomotor system, peripheric nerves and muscles, etc.).

Hygienic Classification of Labour

For hygienic estimation of labour conditions and character at the working places "The hygienic classification of labour" has been developed. According to it they differentiate as follows:

A harmful industrial factor. This is a factor which influence on a person working under certain conditions, may cause a disease or a stable decrease of a working capacity.

A dangerous industrial factor. This is a factor which influence on a person working under certain conditions, may cause a trauma or another sudden acute worsening of health.

Heaviness of labour is a characteristic of labour process reflecting primary load upon a locomotor apparatus and functional systems (cardio-vascular, respiratory, etc.), providing its activity.

Strain of labour is a characteristics of a labour process reflecting a primary load upon the central nervous system.

ESTIMATION OF LABOUR CONDITIONS AND LABOUR CHARACTER

Principle of labour conditions and character differentiation is provided for the degree of industrial environment and labour process parameters deviation from the existing hygienic standards and influence on the functional state and health of the workers.

According to these indices they highlight three classes of labour conditions and character.

Class I — optimal labour conditions and character. An unfavourable influence of dangerous and hazard occupational factors on the workers are excluded. The requisites for high working capacity keeping are created.

Class II — acceptable labour conditions and character when the level of occupational dangers and hazards do not overpass the adopted hygienic standards on the working places and possible functional labour-related changes are recovered during regulated rest within the working day or the rest at home by the beginning of the next shift. There is no unfavourable influence on the condition of their health or health of their posterity in the nearest and remote period.

Class III — hazard and dangerous labour conditions when because of sanitary norm and rules violation the influence of occupational hazards and dangers is possible in the limits overpassing hygienic standards and psychophysiologic factors of labour activity and may cause functional changes of an organism leading to the resistant decrease of the capacity to the work and/or disturbances of health.

They highlight three degrees of dangerous and hazard labour conditions.

Degree I — labour conditions and character which cause functional disturbances of reversible character if they are detected or stopped at early stages.

Degree II — labour conditions and character which cause resistant functional disturbances, leading to the morbidity rate increase and sometimes to the appearance of light signs and forms of occupational diseases.

Degree III — labour conditions and character with the higher danger of occupatinal diseases development, higher morbidity rate.

The tasks of curable and prophylactic measures with occupational pathology:

— rendering a qualified medical aid to the workers of the industrial enterprises;

— regular medical examinations;

— prophylactic medical examinations;

— sanitary education;

— sanitative measures.

Prophylactic Medical Examination

The aim of prophylactic medical examination (PME) is to prevent diseases (including non-occupational) by regular medical observation after practically healthy persons and their labour conditions and way of life, detection of the earliest stages of disease and timely treatment. PME includes four stages:

1) definition of contingents for PME;

2) active indication of sick persons and correct organization of record-keeping;

3) active systematic observation of the groups under PME;

4) organization of public prophylactic measures.

PME includes annual profound medical examination of all working persons and conduction of a set scope of laboratory and instrumental investigations. This scope should include general blood analysis, examination of urine, determination of blood sugar and lipids, ECG and photofluorography. Those who needs should be examined additionally with the use of all modern methods. Simultaneously, risk-group persons should be determined as well as the persons with the diseases on early stages. PME provides for definition and individual estimation of health, working out and condition of a complex of the necessary medical and social measures and dynamic observation for the state of health of the persons working at a certain enterprise.

Chapter 1
DUST BRONCHITIS
AND OCCUPATIONAL
BRONCHIAL ASTHMA ⎯⎯⎯⎯⎯⎯⎯

DUST BRONCHITIS ⎯⎯⎯⎯⎯⎯⎯

Dust bronchitis and professional bronchial asthma are common diseases. The tendency to their absolute ratio increase had been recently observed. That is the result of the atmosphere pollution, frequent bronchitis and the changes of the organisms reactivity. Late diagnosing, inadequate therapy may cause invalidisation and complete professional disability, convertion of the disease into its chronical form, complications, other severe or even lethal diseases.

Long-term inspiration of the composite dust of medium agression rate produces dust bronchitis. Smoking, infections and weather factors are the additional factors adding to the main ethiological one — the dust itself.

In case of dust agression the nasal cavity suffers greatly. Primary irritation converts into the hypertrophic catarrh, hypersecretion starts. These changes cause poor nasal respiration to occur. Hypertrophy is followed by atrophy. Ciliar epithelium gets replaced by the flat one, small glands disappear. The nasal barrier function fails. Nasal irritation may cause the attacks of spastic coughing.

The pathogenic stages of dust bronchitis are the following: primary stage, inflammation stage, degeneration stage.

The clinical outline depends greatly on the inhaled dust type (mineral, organic, silicate or carbon dust types). Coughing is the main symptom of dust bronchitis. It's usually dry, scarce sputum can be found. Usually the onset term is long. The first symptoms appear after 5–10 years of constant professional contact (table 1.1).

Basic therapy:
1. Isolation from dust.
2. Regeneration of the bronchial passage — removing of spasm, edema and hypersecretion:
— sympathomimetics (salbutamole, berotek, ephedrine);
— purine or xanthine derivates (euphilline, teophilline);

Table 1.1. **Classification of dust bronchitis**

Form of bronchitis	Clinical symptoms
Mild bronchitis	2–3 years of coughing (dry or scarce sputum). Dyspnea after excercise. Harsh breathing. Single dry rales. Seldom attacks (1–2 times a year). Respiratory insufficiency (0–I)
Moderate bronchitis	Constant coughing, sputum present. Dyspnea after usual excercise, seldom attacks of choking. Harsh breathing, dry rales. Seldom moist rales in lower segments Attacks — 3–4 times a year. Respiratory insufficiency (I–II). Changes of X-ray film. Emphysema, symptoms of cor pulmonale
Complicated forms. Severe bronchitis	Constant coughing, excretion of sputum. Dyspnea at patient state, choking. Long-term frequent attacks. Combinations of pulmonary syndromes: asthmatic, infectious-inflammatory, diffused obstructive emphysema. Respiratory insufficiency (III–IV). Hypoxemia. X-ray — severe changes. Bronchial pneumosclerosis, bronchoectases. Pneumonic infiltration symptoms are found during the attacks. Severe emphysema. Cor pulmonale (compensated or decompensated)

— cholinolytics (atropine);
— expectorants (bromhexine, mucolytine);
— mucolytics (acethylcysteine, mucosolvine, solvine);
— antibacterial drugs (sulphanilamides, hemi-synthetic penicillines, cephalosporines);
— steroid glycosides;
— diuretics;
— oxygenation;
— physical therapy;
— respiratory training.

Medical Findings and Professional Abilities Examination
1st stage — poor clinical symphtoms, lungs functionally normal. Professional abilities stay unchanged. Treatment and prophylaxis are needed.
2nd stage — isolation from dust (the other job).
3rd stage — possible invalidisation (2nd group).

Prophylaxis:

— mechanisation;

— anti-dust means (dust sedimentation);

— ventilation;

— individual protection means;

— medical examinations (at least once a year — obligate X-ray shot of thorax).

OCCUPATIONAL AND ENVIRONMENTAL ASTHMA

Dramatic advancements in the understanding of bronchial asthma have taken place over the past decade, especially regarding the role of airway inflammation in asthma. However, for a longer period of time, a better cognition of asthma was evolving. There was stipulation of bronchial asthma as a distinct pulmonary entity, and different from other common lung conditions in 1688. In 1713, more than a quarter of a millennium ago, Ramazzini chronicled occupational asthma when observing urticaria and shortness of breath among grain sitters exposed to organic dusts. Over the next 200 years, and until the beginning of the XX century, there was a paucity of publications concerning occupational asthma. In 1911, there was the recognition of asthma due to platinum salts among photographic workers. There were recordings of asthma among workers producing oil from castor beans in 1928. More interest in the association between the workplace and asthma evolved in the late 1960s and 1970s. Clinical and research interests in occupational asthma substantially heightened in the 1980s. In the 1990s, occupational asthma is the most common type of occupational lung disease. The supporting data comes from information on morbidity, disability, and the occurrence of the total number of cases.

Bronchial asthma affects approximately 5% of persons of all ages in the general population. Asthma in the replace afflicts as many as 400,000 to 3 mln workers in the United States. These numbers may be an underestimation if we also consider workplace exacerbation of preexisting asthmatic states. Moving into the XXI century we are gleaning new scientific information to better explain asthma mechanisms and pathogenesis, especially the roles of bronchial mucosal injury and airway inflammation.

When we consider occupational asthma on a clinical basis, a conclusive diagnosis must be based on objective information that combines clinical, physiologic, and laboratory findings. Prevention of occupational asth-

ma is paramount and involves a variety of strategies, most importantly eliminating further workplace exposures of sensitized workers. A key socioeconomic concern is the attempt to preserve the worker's long-term ability to be productive and financially provide for his/her family. An important goal is to try to return affected workers to their workplace in a timely and prudent manner.

Definition of Occupational Asthma

Occupational asthma is an inflammatory disorder of the airways. There is episodic airflow limitation, usually accompanied by nonspecific bronchial hyperresponsiveness. The initiation of occupational asthma occurs after the inhalation of a substance or material that a worker may manufacture, use directly, or be exposed to incidentally at the work site. More than 200 different agents cause allergic sensitization and specific airway hyperresponsiveness. Nonallergic mechanisms also operate in the initiation of asthma. Thus, irritant exposures may initiate asthma and the induction of nonspecific airway hyperresponsiveness.

There has been difficulty formulating a precise definition of occupational asthma that is acceptable to the different groups and institutions having different agendas and requirements.

A definition of use as a surveillance strategy and triggering public health investigation or intervention is less restrictive than a definition appropriate for workers' compensation or legal purposes. Due to a diversity of opinions, various definitions of occupational asthma are propounded.

A simple definition of occupational asthma is "variable airflow limitation caused by a specific agent in the workplace". A definition stressing allergic pathogenesis is "variable airflow limitation caused by sensitization to a specific agent encountered at work and excluding other occupational causes of variable airflow limitation not due to sensitization". The Industrial Injuries Advisory Council in Great Britain defines occupational asthma as "asthma which develops after a variable period of symptomless exposure to a sensitizing agent at work". There are limits to the consideration of what is an acceptable sensitizing agent when the definition is applied for compensation purposes. Smith formulated a medico-legal definition of occupational asthma.

A definition of occupational asthma emphasizing a mechanism propounds that allergic occupational asthma is allergic/immunologic sensitization to a substance or material present in the work site. There is variable and work-related airflow limitation and the presence of both specific and nonspecific airway hyperresponsiveness. For this type of occupational

asthma, a key clinical feature is that asthma develops after the passage of a latent period, or a time span. During the latent period, exposure continues and allergy evolves. Eventually, there is the clinical manifestation of work-related airflow limitation and specific and nonspecific airway hyperresponsiveness. The specific airway hyperresponsiveness relates to allergic immunologic influences; the nonspecific airway hyperresponsiveness appears to be the sequela of bronchial mucosal injury and airway inflammation.

Nonspecific airway hyperresponsiveness is such a characteristic feature of allergic and nonallergic occupational asthma that its absence brings into question the very diagnosis of asthma. Nonetheless, there are cases of allergic-type occupational asthma without nonspecific airway hyperresponsiveness. There are also examples of allergic occupational asthma where latency is not a feature, In such single-exposure cases, both allergic and nonallergic mechanisms seem operative. Recurrent nocturnal attacks of asthma are reported after a single exposure to Western red cedar in a sensitized worker. Nonallergic occupational asthma occurs after a high level, workplace irritant exposure and develops abruptly and without a significant latent period. The exposure is characteristically singular and intense. Asthma also occurs after lesser exposures and over a longer (months to years) period of time. The absence of a latent perioid is a critical clinical feature, because it supports the contention that an allergic mechanism is not operative.

Types of Occupational Asthma

There are **two types** of occupational asthma, depending on the presence or absence of a preceding latency period before asthma:

The **first**, occupational asthma with a latency period, encompasses instances of occupational asthma for which an allergic/immunologic mechanism is identified.

The **second**, occupational asthma without a latency period, includes asthma developing rather suddenly and is best illustrated by the reactive airways dysfunction syndrome (RADS). Work-aggravated asthma, on the other hand, is not considered occupational asthma but refers to the presence of concurrent asthma worsened by irritants or physical stimuli in the workplace.

The true prevalence of irritant-induced asthma (e.g., asthma without latency) is unknown but is more common than previously perceived. In one investigation, 6% of workers assessed for occupational asthma had irritant-induced asthma (i.e., RADS) compared to 32% with allergic occupational asthma. Data from a community-based random sample of

3,606 adults, 40 to 69 years of age, residing in Beijing, China, examined the relationship between occupational exposures to dusts and irritant gases/fumes and physician's diagnosis of asthma. After adjusting for sex, age, education, residential areas, indoor coal combustion, and smoking status, the attributable risks of dust-related asthma was 1.7%, while the risk for asthma from irritant gases/fumes was 1.2%. Another study addressed several hundred adult patients with bronchial asthma belonging to three major races (Chinese, Malay, and Indian) and observed in five outpatient primary care polyclinics. The risks of asthma were generally elevated for service and manufacturing production workers, especially municipal cleaners and sweepers, textile workers, garment markers, electrical and electronic production workers, printers, and construction/renovation workers. Nonspecific irritation effects are more common than sensitization as the cause of work-related asthmatic symptoms in flour milling, baking, and other flour-based industries. Nonspecific respiratory irritation was the cause of asthma symptoms in 2.6% of workers, while sensitization was responsible for symptoms in 0.3%.

The Sentinel Event Notification System for Occupational Risks (SENSOR) Program, launched by the National Institute for Occupational Safety and Health (NIOSH) in 1987, provides state-based surveillance and intervention programs for occupational asthma. From 1988 through 1992, 328 cases met the SENSOR surveillance case definition for occupational asthma. There were 128 cases classified as possible occupational asthma; 42 were RADS; and 37 cases were work-aggravated asthma. In Michigan, more than 40% of the asthma case-patients worked in transportation equipment manufacturing. In another investigation, the prevalence of occupational asthma in Michigan was estimated to be between 3% and 20.2%. In New Jersey, 15% of asthma case-patients worked in manufacturing of chemicals and allied products. The SENSOR data confirmed that isocyanates are the most frequently reported asthma-causing agents (19.4% of cases).

The prevalence of occupational asthma varies with the extent of exposure and with occupation. For example, investigations note that approximately 4% of workers exposed to Western red cedar develop asthma (40); the prevalence for Eastern red cedar is 3.8% to 7%. About 4% to 5% of workers exposed to isocyanates develop occupational asthma. Asthma from the proteolytic enzymes occurs in 10% to 45% of workers. Occupational asthma caused by latex evolves in 2.5% of hospital employees. Wheat flour allergy appears in 25% of bakers and pastry cooks. About 9% of the bakery workers show positive skin prick tests to fungal amylase and 8% demonstrate elevated amylase-specific immunoglobulin E (IgE)

antibodies. About 41% of technicians report work-related symptoms provoked by laboratory animals. The prevalence of work-related asthma among factory employees manufacturing flux-cored solder containing colophony is 21% in the highest exposure group and is 4% in the lower exposure group. Malo and associates report that 23% of employees at a carpet-manufacturing plant that used guar gum to adhere the dye to the fiber have a history suggestive of occupational asthma. An investigation of asthma conducted on 619 cedar sawmill, 724 grain elevator, 399 pulp mill, 798 aluminum smelter, and 1,127 unexposed workers shows an overall prevalence of physician-diagnosed asthma of 4.6%. The prevalence of asthma is 3.9 times higher in cedar sawmill workers, 2.2 times higher in pulp mill and aluminum smelter workers, and 1.7 times higher in grain elevator workers compared with unexposed workers.

Risk Factors for the Development of Occupational Asthma

Exposure Characteristics

A variety of exposure characteristics influence asthma development or aggravate the disease once it is present. The chemical characteristic of an allergen influences its antigenicity and its ability to cause asthma. Such relevant characteristics as chemical type and reactivity, chemical sources, and concentration of an exposure are pertinent. The intensity of an exposure is critical. High levels are implicated in the pathogenesis of both types of occupational asthma, with and without latency. Massive exposures occur with RADS. Intermittent, high-level exposures are important in the pathogenesis of toluene 2.4-diisocyanate (TDI)-induced asthma, but also asthma without latency. Workers who are more frequently exposed to spills are more likely to report asthma symptoms and show alterations in lung function testing.

An unmistakable dose-response relationship exists for an exposure and the prevalence of allergic sensitization. This association is reported for Western red cedar, Eastern red cedar, isocyanates, colophony, baking products, and acid anhydrides. Symptoms of work-related asthma in red cedar workers are more common after 10 years of exposure, and levels of pulmonary function are lower with higher wood dust exposures.

Cumulative exposure may be important, as exemplified by the investigation of Jones and associates for TDI. The duration of an exposure may be influential as ascertained by the investigation of Di Stefano et al. In the latter study, comparisons of lobar bronchial biopsies findings between two TDI groups show that workers who develop asthma after a short-term exposure (e.g., 2.4±0.4 years) show significantly higher numbers of

mast cells in the airway mucosa compared to the subjects who develop asthma after long-term exposure to TDI (e.g., 21.6±3.1 years). Exposure indices may also be tied to the type of asthmatic response noted. The presence of a late asthmatic-response is shown to have a linear relationship to the logarithm of tetrachlorophthalic anhydride air exposure. The immediate asthmatic response does not closely relate to tetrachlorophthalic anhydride air exposure.

Poor working conditions are a good predictor for the development of adverse pulmonary outcomes. For example, work activity in a small, poorly regulated hemp mill, where there are routinely very high dust levels, is associated with reduced pulmonary function testing. An accelerated decline in forced expiratory volume in 1 sec (FEV) is noted in women workers, who are predominantly nonsmokers; this observation suggests an independent effect of hemp on the airways.

Exposures may be monitored using biomarkers. Thus, bronchial responsiveness in aluminum pot-room workers with asthma appear related to plasma levels of fluoride. Trimellitic anhydride (TMA) workers showing late-occurring asthma or late respiratory systemic syndrome improve after moving to lower exposure jobs. However, elevated IgE against TM-HSA is considered to be a marker for a subpopulation of workers with asthma and rhinitis that do not improve.

An industry factor is observed with TDI. Asthma is reported more often by workers employed in polyurethane processing than by employees of TDI manufacturing.

A mill effect or plant effect is described to explain differences in the frequency of byssinosis, and possibly of TDI asthma among workers with similar exposure. Hexa-methylene diisocyanate (HDI) and TDI display the same vapor pressures and are relatively volatile at room temperature; MDI has a lower vapor pressure and is not volatile at room temperature. MDI becomes volatile and is more likely to lead to asthma after heating when its vapor pressure increases. This circumstance is observed in such industrial processes as foundry work. The specific type of industrial process may influence the development of asthma. For example, asthma appears in about 5% of workers exposed to isocyanates; 10% to 45% of workers exposed to proteolytic enzymes; and 2% to 40% of workers exposed to grain dust, including millers and bakers.

Geographic and Climatic Factors

Weather conditions such as wind direction and humidity may be influential. In Barcelona, Spain grain dusts released by unloading soybeans caused asthma outbreaks. Apparently, the unloading of the soybeans gives rise to sudden, massive release of soybean dust that reaches the urban area owing to appropriate meteorological conditions and causes the epi-

demic. Asthma from red cedar is seen in the western United States. In the Great Lakes area, grain dusts and flour frequently cause asthma. Chemicals are indigenous to many areas, especially the industrial East and Midwest. Working in a cold environment may have an adverse effect on asthmatics who exert themselves.

Atopy

The presence of the atopic status may influence how an individual worker respond to a workplace allergen. The relationship between atopy and allergic sensitization is best established for agents of higher molecular weight (>1,000 daltons). This includes the detergent enzymes, laboratory animal allergens, certain insect proteins, and products such as gum acacia and flour. In a cross-sectional study, involving 178 bakery workers, α-amylase exposure and atopy were the most important determinants of α-amylase skin sensitization.

Atopy may also be important for certain low-molecular weight (< 1,000 daltons) compounds such as platinum salts, ethylene diamine, and dimethyl ethanolamine. Other low molecular weight agents, such as TDI, Western red cedar, trimellitic anhydride, phthalic anhydride, and formaldehyde, do not seem to be influenced by the atopic state. The conflicting data on atopic sensitization and an agent's molecular size suggest that other factors are important in determining allergic sensitization.

Pathogenesis

Immunologic disorders are the basic initiators of the disease. The immunologic stage includes the interaction of allergene and the antibodies binded to the cells of the sensibilized organism. Antibodies are immunoglobulines. The complexes of antibodies and antigenes are fixed to the respiratory tract mucous coat labrocytes. The latter degranulate, excreting histamine, serotonine, etc.

These compounds promote the bronchospasm, mucous coat edema, hypersecretion and the allergic inflammation. These factors produce choking attack — the main symptom of bronchial asthma. The process is also influenced by the neuro-regulative, endocrine and toxico-infectious mechanisms.

Symptoms:

1. Asthmoid bronchitis is a predecessor of asthma. It can pass without turning into choking attacks. Quinke's allergic edema and urticaria can be considered to be pre-asthma too.
2. Mild asthma.
3. Moderate asthma.
4. Severe asthma.

The symptoms of asthmoid bronchitis are dry coughing, harsh breathing, emphysema, dry whistling rales.

Mild asthma is characterised by scarce attacks which can be easily managed with broncholytics and anti-histamine drugs. The state of patients stays satisfactory. No complications are found at this period.

The isolation of patients from allergenes brings clinical reconvalescence.

Moderate asthma is characterised by frequent attacks of choking. These attacks can be hardly managed with broncholytics. Coughing and dry rales are found even at the remission period. Medium emphysema and cor pulmonale symptoms appear. The isolation of patient from the allergenes makes the choking attacks disappear, but dyspnea, coughing and dry rales still occur.

Severe asthma is characterized by very frequent attacks of choking which are hardly managed at all.

Status asthmaticus is a state of continuing asthmatic attacks (lasting for hours or even days) which can't be managed with usual means. Coughing, dyspnea, dry rales and cor pulmonale accompanies the severe form. The disease progresses. Isolation wouldn't bring any positive progress at all.

The tests of bronchial passage (functional vital capacity, Tiffeneau's test, pneumotachometry) indicate bronchospasm.

X-ray data: emphysema, low diaphragm, poor respiratory excursion, cor pulmonale.

Laboratory data: sputum — eosinophiles, Charcot — Leyden crystals, Curschmann's spirals. Blood: high alpha-2 and gamma globuline levels, dysproteinemia.

Therapy

Ethiologic therapy: determination of allergene and its isolation.

Pathogenetic therapy: specific desensibilization (subcutaneous injections of allergene). Immunodepressors and steroids.The most popular steroids are prednisolone, triamcinolone, dexamethasone and hydrocortisone.

Immunodepression: clone-blocking cytostatics (6-mercaptopurine; 4-aminochinoline derivates — resochine, delagile).

Anti-histamin drugs: diasoline, diprasine, suprastine, tavegil.

Broncholytics and bronchodilatators: euphilline, asthmopent, alupent, berotek.

Chiolinolytics — atropine, platyphilline.

Adrenaline and ephedrine for attacks management.

Status asthmaticus management: steroids (regeneration of the beta-receptors sensivity), intravenous infusions (4% glucose, natrium bicarbonate, etc.)

Complex therapy — physical therapy, gymnastics, SPA.

Prophylaxis and Professional Abilities Examination

Prophylaxis includes social and labour hygiene and improvement of technologic processes.

Special protective clothes is the obligate mean of protection.

Removing of high and low temperatures, moisture and dust from the technologic process improve the health prognosis.

Prophylactic examination and health control are needed. No contact with sensibilising compounds or irritants is allowed to patients no matter how good their state is.

Patients with mild asthma don't lose their professional abilities.

The medium form is usually followed by significant decrease of the professional abilities or their complete loss.

Severe asthma means complete loss of professional abilities (II and III group invalidisation).

TESTS _____

1. A woman, aged 45, has been working for 20 years at the chemist-pharmaceutical plant. She complains of asthma attacks, which occur against a background of "full health". Noisy, stridulous breathing, which is heard at a distance. Herewith a patient takes a forced sitting position. On examination the thorax is extended. The lips, nails' loges, skin are cyanotic. On percussion of the lungs — a band-box sound. Breathing is difficult, with prolonged exhalation, a big amount of diffuse dry rales on inhalation and exhalation are heard.

Make a probable diagnosis:
A. Chronic bronchitis.
B. Professional bronchial asthma.
C. Tuberculosis.
D. Acute pneumonia.
E. Tracheobronchitis.

2. A 32-year-old man has been working on the elevator for 10 years, complains of constant cough for 2 years. Cough is dry, sometimes with the small quantity of sputum. Heavy physical load causes dyspnea. Auscultation: harsh breathing, single dry rales. 1–2 times a year the patient notes exacerbation. X-ray revealed no changes. Signs of cardiac insufficiency are absent. A diagnosis was: dust bronchitis.

Define a degree of severity:
A. The I degree of severity.
B. The II degree of severity.
C. The III degree of severity.

3. A woman, aged 35, has been working at the flax-spinning production for over 5 years. During the preventive physical examination she complained of strong pertussoid cough, which was terminated by the discharge of a little amount of the viscous sputum, deterioration of condition during a week and during each day, attacks of asphyxia at the end of the week. Objectively: expiratory dyspnea, dry rales in the thorax on auscultation, reduction of FVCL, power of the exhalation, VCL, MVL.

What is the most probable cause of this condition?

A. Allergic alveolitis.

B. Dusty bronchitis.

C. Professional bronchial asthma.

D. Acute respiratory insufficiency.

E. Hypocapnia

4. A 35-year old man applied to the physician with complaints of the constant cough, dyspnea, separation of a swampy mucous sputum, seasonly appeared attacks of asphyxia last 6 months. In anamnesis — 10-year experience of work at the lacquer-paint plant. He noticed that attacks appear under overflowing of paints.

Objective: on the part of the respiratory system at the percussion — a band-box sound on the base of the lungs; dry diffused rales are auscultated. Laboratory data: moderate eosinophilia. X-ray — a reinforcement of a lung pattern and expansion of lungs' roots.

What is the most possible reason of this condition?

A. Chronic toxic bronchitis at the stage of intensification.

B. Bronchial asthma, mild degree of severity.

C. Chronic toxic bronchitis complicated by bronchial asthma, moderate degree of severity.

D. Bronchial asthma, moderate degree of severity.

E. Acute toxic alveolitis.

5. A woman, aged 50, has been working during 20 years at the chemical plant. She complains of attacks of asthma, appeared at work, noisy, stridulous breathing, which is heard at a distance, dyspnea. At the examination — the thorax is extended. The lips, nails' loges, skin are cyanotic. At the percussion — a band-box sound. Breathing is harsh, with the prolonged expiration, a big amount of diffuse dry rales on the inhalation and exhalation are auscultated.

What a pathology has this patient?

A. Chronic bronchitis.

B. Professional bronchial asthma.

C. Tuberculosis.

D. Acute pneumonia.

E. Tracheobronchitis.

Chapter 2
PNEUMOCONIOSIS ─────────────

Pneumoconiosis is a chronic disease of the lungs, which is connected with long term inhalation and dust deposit in the lungs and characterized by development of diffuse fibrosis. More specified formulation of the disease today is a chronic diffuse pneumonitis, which connected with inhalation of occupational dust and developing of fibrosis in the lungs.

Three patterns are distinguished in the new classification of pneumoconiosis: etiologic, roentgenologic and clinical-functional (Table 2.1).

The first pattern includes 5 groups of pneumoconiosis: silicosis (dust containing free dioxide of silicon), silicatosis (dust containing dioxide of silicon in the linked state), carboconiosis (dust containing carbonicum), metalconiosis (dust, containing primary metals possessing fybrogenum action), hypersensible pneumoconiosis (aerosols of toxic-allergic metals; organic dust of vegetable and animal origin; another toxic and allergic inorganic dust), code and type of pneumoconiosis.

The second pattern includes basic X-ray signs of pneumoconiosis, type of fibrosis, code of type, character of shadows, size, contours, degree of manifestation and area of spreading, localization.

The third pattern includes clinical course, types of external breathing violations of function (EBD) and developing of the disease.

Table 2.1. **Classification of pneumoconiosis**

*Pattern 1. **Etiologic***

a) Taking into account composition of production dust (aerosol)			
N	The name of the group	Code	The type of pneumoconiosis
1.	Silicosis (dust containing free dioxide of silicon)	J. 62 J. 62.8	1.1. Silicosis 1.2. Silicosilicatosis Silicosiderosis Silicoantracosis

N	The name of the group	Code	The type of pneumoconiosis
2.	Silicatosis (dust containing dioxide of silicon in the linked state)	J. 61 J. 62.0	2.1. Asbestosis 2.2. Caolinosis, olivinosis 2.3. Talcosis
3.	Carboconiosis (dust contain-ing carbonicum)	J. 60 J. 63.3	3.1. Antracosis 3.2. Graphitosis, diamond pneumoconiosis
4.	Metalconiosis (dust, contain-ing primary metals possessing fibrogenum action)	J. 63.4 J. 63	4.1. Siderosis, baritosis, manganoconiosis 4.2. Pneumoconiosis of electric welders, polishers
5.	Hypersensible pneumoconio-sis: — aerosols of toxic-allergic metals; — organic dust of vegetable and animal origin; — another toxic and allergic inorganic dust	J. 63.2 J. 63.8 J. 63.0	5.1. Pneumoconiosis under influence of beryllium, chrome, nickel, platinum. 5.2. Bissinosis, papricosis, exogenous allergic alveo-litis (EAA) 5.3. Pneumoconiosis (pneu-monitis) of plastic dust, drugs

Pattern 2. **Basic X-ray signs of pneumoconiosis**

Type of fibrosis	Code of type	Character of shadows, size, contours	Degree of mani-festation and area of spreading	Localisation
Primary pneumofibrosis	0	Some strengthening of pulmonary pic-ture	Not sharply pronounced	Mono- or bilateral
Interstisial	s	Little shadows of wrong form:	Not sharply pronounced	Bilateral (diffuse)
	t	— linear till 1.5 mm reticular shadows, 1.5–3.0 mm	Not sharply pronounced	
			Moderatly pronounced lung picture	
	u	— linear and ma-cular shadows, 3.0–10.0 mm	Moderately pronounced	
			Sharply pronounced plenty shadows	

26

Type of fibrosis	Code of type	Character of shadows, size, contours	Degree of manifestation and area of spreading	Localisation
Nodular	p q r	Small spheroid shadows (nodulars) on the background of interstitial fibrosis: — size until 1.5 mm — size from 1.5 till 3mm — size from 3 till 10 mm	1. Small amount 2. Moderate amount 3. Big amount	Bilateral
Nodular	A B C	Big spheroid shadows (nodes) on the background of interstitial and nodular fibrosis: — size 1–5 cm; — size 5–10 cm; — size over 10 cm	1. Area of expansion <50 mm; 2. Expansion less than area of the right pulmonary superior lobe 3. Expansion more than area of the right pulmonary superior lobe	Bilateral or monolateral

Pattern 3. **Clinical picture and function**

Stages of pneumo-coniosis	Clinical manifestations	Types of external breathing dysfunction (EBD)	Stages of the disease	Clinical course
I, II, III	1. Without complications 2. Complicated: — bronchitis (nonobstructive, obstructive) — pneumonia — bronchial asthma — bronchoectatic disease — tuberculosis — pulmonary bleeding — rheumatoid pneumoconiosis	1. Without violations EBD 2. With functional violations: — restrictive — obstructive — diffusive — mixed	1. Acute (period of work less than 5 years) 2. Quick (period of work less than 10 years) 3. Slow (period of work over 10 years) 4. Late (5 years and more after finished working with dust)	— progredient — slow — stable — regressive

27

SILICOSIS

Silicosis refers to a spectrum of pulmonary diseases attributed to the inhalation of various forms of free crystalline silicon dioxide or silica. A man-made disease, it is probably as old as human history and was known to the ancient Egyptians and Greeks. Although the prevalence of silicosis apparently peaked in the late XIX and early XX century when mechanized industry was just beginning, even in developed countries today sporadic yet preventable cases of silicosis occur.

Silicon dioxide or silica is the most abundant mineral on earth. It is formed from the elements silicon and oxygen under conditions of increased heat and pressure. Silica exists in the crystalline and amorphous forms. Crystalline forms are based on a tetrahedral structure in which the central atom is silicon, and the corners are occupied by oxygen. The structure of the crystal is such that two adjacent tetrahedrons share two oxygen atoms. Examples of crystalline silica are quartz, cristobalite, and tridymite. The most common form is quartz, a typical component of rocks. Some of the common quartz-containing materials in industry are granite, slate, and sandstone. Granite contains about 30% of free silica, slate — about 40%, and sandstone is almost pure silica. Crystobalite and tridymite occur naturally in lava and are formed when quartz or amorphous silica is subjected to very high temperatures. They may also be formed in silica bricks (refractory bricks) used in industrial furnaces.

Amorphous silica is noncrystalline and has relatively nontoxic pulmonary properties. It occurs as diatomite (skeletons of prehistoric marine organisms) or as vitreous silica (the result of carefully melting and then quickly cooling crystalline silica). Heating diatomite with or without alkali (a process known as calcining) forms cristobalite, a material that has the potential to be more toxic than quartz.

Crystalline silica that is not bound to other minerals is referred to as "free"; when it is bound to other minerals it is referred to as "combined." The latter are also known as silicates. Examples of silicates that have been widely used in industry include asbestos, talc $[(Mg_3Si_4)O_{10}(OH)_2]$, and kaolinite ($Al_2O_3SiO_2 \cdot H_2O$), a major component of china clay, or kaolin.

Workers at Risk for Silicosis

The knowledge that silicosis is associated with certain occupations is rooted in antiquity. Hippocrates reported that miners developed dyspnea with exertion. Ramazzini and Agricola were instrumental in recognizing the relationship between rock dust exposure and the development of dyspnea in those who worked in this trade.

The worst outbreak of silicosis in the United States occurred during the construction of the Gauley Bridge tunnel in West Virginia in 1930 and 1931. In this unfortunate but preventable disaster, more than 400 men of the estimated 2,000 engaged in rock drilling died, and about 1,500 contracted silicosis and were eventually disabled.

Occupations known to carry increased risk for silicosis and the pertinent sources of exposure in these trades are enumerated in Table 2.2.

It is difficult to obtain precise estimates of the prevalence of silicosis because of the many different occupations involved, the participation of transient workers, and the variability of disease detection methods (e.g., autopsy versus compensation or screening data) and reporting practices from place to place. In 1956 Trasko obtained estimates of silicosis prevalence by examining records of workers in 20 states who were compensated for silicosis. About 6,000 cases were identified. The largest numbers of silicosis cases were found among metal miners (1,637) and foundry workers (1,645). Because of the nature of case identifications, these numbers most likely underestimate the actual frequencies. Autopsy records of 3,365 underground miners revealed the presence of classical silicotic nodules in the lungs of 12.5% of the cases. In an investigation of worker health at two silica flour mills, 16 (26%) of the 61 workers who were exposed to micro-crystalline silica had radiographic evidence of simple silicosis, and 7 (11%) had progressive massive fibrosis.

Table 2.2. **Occupations of high risk for silicosis**

Occupation	Exposure hazard
Sandblaster	Shipbuilding and iron-working industries
Miner or tunneler	Underground miners are at risk during roof bolting, shot firing, and drilling; surface coal mine drillers are at high risk
Miller	Finely milled silica for fillers and abrasives; "silica flour workers"
Pottery workers	Crushing flint and fettling are the major exposures
Glassmaker	Sand used for polishing and enameling
Foundry worker	Silica is essential during mold making; exposure is during fettling
Quarry worker	Slate, sandstone, granite
Abrasives worker	Finely ground particles

Million workers outside of the mining industry are potentially exposed to crystalline silica. Compared to working conditions of 20 years ago, better methods of dust suppression and ventilation as well as respiratory protection have diminished the attack rate among workers. However, new cases of silicosis are still reported sporadically in both developed and developing countries, and silicosis is still very much a disease of modern days.

Pathology

On inspection, the silicotic lung is firm and blacker than normal. The surface is coarse and nodular. The visceral pleura has areas of fibrosis and may be covered by plaque like lesions. Peribronchial and hilar lymph nodes are typically enlarged. On sectioning, these enlarged nodes show concentrically arranged fibrous tissue. Cutting the lung reveals palpable intrapulmonary nodules, especially in the upper lobes. In simple silicosis these nodules are usually 2 to 6 mm in diameter. In conglomerate silicosis or progressive massive fibrosis, the lesions are typically 10 to 20 mm diameter, a result of the coalescence of smaller nodules. Nodules vary in color depending on the presence of other dusts. The extent of nodule calcification is also variable.

The earliest parenchymal lesion in workers with relatively low-dose, chronic exposure to free crystalline silica is a collection of dust-laden macrophages and loose reticulin fibers in the peribronchial, perivascular, and paraseptal or subpleural areas. Later, these lesions become more organized and may appear. The silicotic nodule, the pathologic hallmark of silicosis, has a histologic appearance analogous to tornado. The central zone, like the eye of the storm, shows little activity. It is hyalinized and composed of concentrically arranged collagen fibers. The peripheral zone is whorled and becomes less organized toward the edges. It contains macrophages, lymphocytes, and lesser amounts of loosely formed collagen. Under polarized light microscopy, a few weakly birefringent particles may be seen in the center of the nodule, likely the result of trapped crystalline silica mixed with other dusts. In the periphery of the nodule, the amount of dust and the degree of birefringence differ dramatically. Needle-shaped, strongly birefringent material is easily seen intermingled with cells and dust. The strongly birefringent crystals are silicates. This is the site of active enlargement of the nodule and of ongoing inflammation. As the disease progresses, the periphery of the silicotic nodule moves farther from the hyalinized center, enmeshing small airways, pleura, and blood and lymphatic vessels in the fibrotic process.

Coalescence of silicotic nodules form the progressive massive fibrotic (PMF) lesion, a mass of dense, hyalinized connective tissue with minimal silica content, a small amount of anthracotic pigment, minimal cellular infiltrate, and negligible vascularization. Typically, the centers of these conglomerate lesions cavitate, the result of mycobacterial infection or ischemic necrosis when they exceed a certain size.

The histologic pattern of acute silicosis differs from that of chronic silicosis. Silicotic nodules are rarely seen, and, if identified, are usually poorly developed. The interstitium is thickened with inflammatory cells. There is alveolar filling with proteinaceous material consisting largely of phospholipids or surfactant (or surfactant-like material) which stain with periodic acid-Schiff (PAS) reagent. Since the histologic appearance resembles that of idiopathic alveolar preteinosis, this process occurring in a clinical background of overwhelming silica exposure has also been called silicoproteinosis. On electron microscopic examination the alveoli are lined by prominent epithelial cells, the majority of which are hypertrophic type II pneumocytes. The alveolar exudate is most likely the result of overproduction of phospholipids and surfactant-associated proteins by these hypertrophic type II cells. In addition, desquamated pneumocytes, macrophages, and silica particles are found in the alveolar spaces. Typically a minimal amount of pulmonary fibrosis is present. Therefore, although the term silicoproteinosis may reflect one of the pathologic changes present, other features of acute alveolar damage syndromes and even of desquamative interstitial pneumonitis are a part of the recognized lung injury.

Pathogenesis

The majority of the existing information regarding the pulmonary cellular and molecular responses to silica comes from experimental animal models. Silicosis is induced in these models by tracheal instillation of silica or by inhalational exposure of animals over a few weeks to months. One therefore has to be concerned about correlates drawn between the development of the silicotic nodules in experimental animals after only 6 or 8 months' exposure to silica and the development of classic silicosis over 20 or more years in humans. The applicability of this information to humans is subject to speculation. Nevertheless, animal work has provided much insight into the pathogenesis of the illness.

The pathogenesis of silicosis begins with the inhalation of crystalline silica particles that have favorable characteristics for deposition in the alveolar spaces. The most important of these is size. Particles of a diameter smaller than 3 mm and greater than 0.5 mm have the best chances of

entering and being retained in the pulmonary acini. The key event in the genesis of silicosis is the interaction between the silica particle and the alveolar macrophage, the main phagocytic cell in the alveolar space. Early work on the pathogenesis of silica-induced lung injury focused on the injury and cell death that occurred after ingestion of silica by alveolar macrophages *in vitro* and *in vivo*. Lung injury was believed to be related to the release of intracellular proteolytic enzymes following the disruption of the alveolar macrophage. Intracellular silica released in this process was taken up by other macrophages. The recurrent cycle of macrophage phagocytosis, cell death, release of intracellular enzymes, and reuptake of silica perpetuated the inflammatory process. More recent studies suggest that cell injury may be a more crucial factor than cell death in the pathogenesis of silicosis.

The fibrogenic effect of silica may be due to elaboration of several inflammatory mediators by alveolar macrophages that have been activated by silica exposure or ingestion. The data supporting this come mainly from experiments wherein alveolar macrophages are harvested by bronchoalveolar lavage (BAL) from subjects or animals exposed to silica particles *in vivo,* or are collected directly after being exposed to silica particles *in vitro*. There are chemotaxis of neutrophils and macrophages when these cells were exposed to BAL fluid supernatant of silica-exposed guinea pigs. The recruitment of cells to the sites of particle deposition and cell injury promotes the amplification of the inflammatory response. Enhanced production of fibrogenic factors, specifically interleukin-1 (IL-1), tumor necrosis factor (TNF), and transforming growth factor, by silica-activated alveolar macrophages has been shown.

Clinical Presentation and Diagnosis

The clinical diagnosis of silicosis has three requisites:

1. The recognition by the physician that silica exposure adequate to cause this disease has occurred.

2. The presence of chest radiographic abnormalities consistent with silicosis.

3. The absence of other illnesses that may mimic silicosis. For example, miliary tuberculosis or pulmonary fungal infection may appear radiographically identical to silicosis. In such cases, an extensive history and microbiologic workup to identify infectious pathogens could help better understand the cause of the radiographic abnormalities. Open lung biopsy is not needed to make the diagnosis of silicosis in the great majority of cases. However, in cases where the exposures and clinical presentations

are atypical, biopsy, BAL, and scanning electron microscopy combined with analytic techniques such as energy-dispersive x-ray analysis may be needed for accurate diagnosis of the disease.

The presentation and severity of silicosis are influenced by multiple factors, principally the concentration of free crystalline silica in the workplace, the duration of exposure, and the physical characteristics and innate fibrogenic properties of the respirable dust (i.e., the fraction of crystalline silica in the dust). Genetic factors, cigarette smoking, and additional complicating pulmonary diseases are among the host factors that interact with the environment in an apparently complex and poorly understood fashion resulting in a spectrum of disease presentations. For these reasons it is critical to recognize the features of classic silicosis, acute silicosis, and accelerated silicosis.

Classic Silicosis

Classic silicosis is the most frequently recognized clinical presentation of silicosis. This results from low to moderate exposure to silica dust for 20 years or more, although cases where the exposure occurred for 10 years or less have been reported. The extent of classic silicosis is described by the degree of radiographic chest involvement. In the lesser radiographic categories, silicosis does not typically cause impairment, although patients may complain of cough, sputum production, and dyspnea as a result of industrial bronchitis or concurrent cigarette smoking. Only in the most advanced radiographic categories of classic silicosis without progressive massive fibrosis is respiratory impairment attributable to silica exposure. The primary health concerns associated with mild classic silicosis are a predisposition to mycobacterial infections and disabling progressive massive fibrosis.

Progressive massive fibrosis typically causes respiratory impairment. Large opacities develop in the upper lung zones, usually on an extensive background of small, rounded nodules. The result is restriction of lung volumes, decreased pulmonary compliance, and diminution of gas transfer. Initially dyspnea occurs with exercise, but the condition progresses to dyspnea at rest as more lung is involved. Cor pulmonale develops as the illness progresses. Mycobacterial infection is always a concern. Development of such an infectious process in this clinical setting can radically worsen chest symptoms, accelerate lung function decline, and alter the chest radiograph.

The stiff lungs and basilar emphysema associated with progressive massive fibrosis increase the risk of developing spontaneous pneumotho-

rax. This can result in a precipitous worsening of preexisting hypoxemia and could be life threatening. The problem is exacerbated by the impaired ability of the poorly compliant lung to reexpand. In complicated silicosis, death is commonly attributable to progressive respiratory insufficiency.

Accelerated Silicosis

Accelerated silicosis results from exposure to higher concentrations of silica over a period of 5 to 10 years. Progression is virtually certain, even if the worker is removed from the workplace. Furthermore, antinuclear antibodies and clinical autoimmune connective tissue diseases such as scleroderma, rheumatoid arthritis, and systemic lupus erythematosus are frequently associated with accelerated silicosis.

Acute Silicosis

Acute silicosis, the least frequent yet the most devastating form of this disease, results from exposure to overwhelmingly excessive concentrations of free crystalline silica for as little as a few years or even 1 year. It was described in Britain by Middleton in 1929 as a syndrome of rapidly progressing respiratory illness occurring after 2.5 to 4 years' exposure to silica dust. In 1930, MacDonald et al. reported on two young women in a London factory who packed a kind of cleaning powder containing ground silica. Both had also worked for brief periods in this industry and they died from silica-induced respiratory failure. At autopsy the patients' lungs were noted to be heavy. Microscopic examination revealed that the alveoli were filled with desquamated cells and an "albuminous" exudate. The authors proposed that the histologic changes resulted from the formation of colloidal silica and insoluble silicates.

The invariable downhill clinical course of acute silicosis includes relentless dyspnea, cor pulmonale, and pulmonary cachexia. Serial lung function tests show progressive restriction of lung volumes and impairment of diffusing capacity. This form of silicosis is fatal, and death is typically attributable to respiratory failure within several years of beginning exposure.

Radiology

The clinical presentation of silicosis (classic, accelerated, or acute) is based on the time course necessary for the development of disease. The type of chest radiographic lesions, however, does not seem to correlate well with the duration of exposure. For example, conglomerate lesions may be found in a worker exposed for only 5 years, whereas small roun-

ded opacities may be the only radiographic lesions in a worker who has been exposed for more than 20 years.

The characteristic radiographic pattern of simple silicosis is the presence of rounded opacities that range in size from 1 to 10 mm. Using the 1980 convention described by the International Labour Organization's (ILO) International Classification of Radiographs of the Pneumoconioses, these small rounded opacities are grouped into three diameter ranges designated as **p** (up to 1.5 mm), **q** (exceeding 1.5 and up to 3 mm), and **r** (exceeding 3 up to 10 mm). In the lower-profusion categories these opacities are most often in the upper lung zones. In the more advanced stages of the disease, the middle and lower lung zones typically are also involved.

In complicated or conglomerate silicosis, also described as progressive massive fibrosis, smaller lesions coalesce into large ones and opacities exceeding 10 mm in diameter are recognized on the chest radiograph. The 1980 ILO classification categorizes these as **A** (10 to 50 mm diameter or several opacities greater than 10 mm but less than 50 mm aggregate diameter), **B** (one or more opacities larger or more numerous than category A but not exceeding the equivalent of the right upper zone), and **C** (one or more large opacities whose combined area exceeds the equivalent of the right upper zone). These large opacities tend to retract toward the hilus, resulting in subpleural areas of air space enlargement. The clear area between the lateral border of the opacity and the chest wall appears as a bulla. Since coalescence of these nodules occurs in the upper zones, the result is loss of upper zone volume, elevation of both hila, and the development of basilar emphysematous changes. While cavitation of these coalesced lesions may be explained by ischemia, tuberculosis or carcinoma with necrosis should also be considered in the differential diagnosis. These distinctions are not always easy to make on a clinical basis.

Enlargement of hilar lymph nodes is common. In 5 to 10% of cases, the hilar nodes calcify circumferentially, producing the so-called eggshell pattern of calcification. This is not pathognomonic of silicosis, as it has also been described in sarcoidosis, postirradiation Hodgkin's disease, blastomycosis, scleroderma, amyloidosis, and histoplasmosis. However, the presence of eggshell hilar calcifications in the presence of typically distributed nodular parenchymal opacities reinforces the clinical impression of silicosis when there is an appropriate exposure history.

Acute silicosis or silicoproteinosis presents radiographically with varying degrees of air space filling. The radiographic differential diagnosis includes pneumonias and other pulmonary infections, pulmonary edema, alveolar hemorrhage, alveolar cell cancer, and idiopathic alveolar proteinosis. Several studies have examined the role of computed tomography (CT) of the thorax in the diagnosis of silicosis.

Pulmonary Function

It is difficult to make definite conclusions about the alterations in pulmonary function in workers with silicosis, since considerable variability in individual cases may be present, probably because of the multifactorial effects of concurrent cigarette smoking, the type of dusts involved in the exposure (mixed versus pure), the dose of dust and duration of exposure, and the presence of other pulmonary diseases such as tuberculosis.

In general, when the radiographs show only small rounded opacities of low profusion, no significant impairment in ventilatory capacity is associated. Abnormalities in spirometry can usually be explained by concurrent cigarette smoking or dust-induced bronchitis. Studies of different groups of workers tend to support this generalization, especially when care is taken to choose appropriate controls or to account for the effects of coexisting factors such as those mentioned above. When these precautions were taken, for example, no significant differences in forced vital capacity (FVC) or forced expiratory volume in 1 sec (FEV_1) were demonstrated in South African gold miners who had radiographic evidence of silicosis and those who did not. In a study of silicotic pottery workers in Hong Kong, there was no statistically significant gradient in percentage of predicted FEV_1 among the radiographic categories of simple silicosis in workers with and without symptoms of chronic bronchitis, although FEV_1 was lower in those with symptoms. FEV_1 was significantly lower as a percent predicted in those with conglomerate silicosis of B and C types compared to those who had simple silicosis. These trends were similar for those who had bronchitis and those who did not, though values were significantly lower for the former group. In this study, as in many others, significant impairment in total lung capacity, residual volume, and diffusion capacity tended to be associated with conglomerate disease. A similar patterns of pulmonary function abnormality was also shown in a study of silicotic sandblasters in Louisiana by Jones et al. Studies of lung mechanics in silicosis patients show abnormalities in lung compliance, which tends to decrease as the severity of radiographic involvement increases.

As a rule, rapid and progressive decline in pulmonary function accompanies acute silicosis. This is well illustrated in the case of a 34-year-old surface coal mine driller, who presented with progressive dyspnea, cough, weight loss, and bibasilar alveolar filling on the chest radiograph. His initial FVC was 3.47 L (63% of predicted), and the single-breath transfer factor was 6.32 ml/min/mm Hg (18% of predicted). After 10 months, the

FVC had further decreased to 1.77 L, and the patient was unable to perform the diffusing capacity test due to dyspnea. A radiographic picture of progressive massive fibrosis had developed from the initial alveolar pattern. This man died 26 months after his initial presentation.

Complications

Mycobacterial Infections

The association between silicosis and pulmonary tuberculosis is well accepted. Epidemiologic studies suggest that the risk of pulmonary and extrapulmonary tuberculosis is increased about threefold in workers who have silicosis compared to those who do not. The incidence of tuberculosis increases with the profusion of radiographic opacities. Only one study revealed an increased incidence of pulmonary tuberculosis in foundry workers who did not have radiographic evidence of silicosis but were employed in the industry longer than 25 years.

Mycobacterial infection should always be suspected when a silicosis patient experiences worsening of respiratory symptoms or chest radiographs. Yearly tuberculin tests are important in the follow-up of patients with silicosis. A positive result on an intermediate purified protein derivative (PPD) test or radiographic evidence of progression of the silicotic abnormalities mandates a search for mycobacteria. If acid-fast smears are negative in the presence of a positive tuberculin test, they recommend treatment with 300 mg of isoniazid daily for a year or a 4-month course of a mutlidrug regimen. Poor compliance and the concern of isoniazid resistance has generated interest in shorter, multidrug chemoprophylaxis regimens, and recent studies have highlighted the importance of directly observed therapy.

Smear or culture-positive silicotics should be treated with multiple antituberculous drugs. Effective regimens generally contain isoniazid, rifampin, and pyrazinamide. Older studies suggest that antituberculous chemotherapy should be given for an extended period, ranging from more than a year to a lifetime. Recent articles show successful outcomes and acceptable relapse rates with shorter treatment regimens. One study suggested that silicotics with tuberculosis do better when the usual multidrug regimen is given for 8 months. It is prudent, however, to guide therapy by frequent clinical and radiographic examinations as well as smear and culture responses.

Infections with atypical mycobacteria such as Mycobacterium kansasii and Mycobacterium avium-intracellulare have also been reported. The frequency at which these atypical mycobacterial infections are found is probably related to the geographic distribution of the organisms.

Immune-Mediated Complications

Associations between silicosis and progressive systemic sclerosis, scleroderma or rheumatoid arthritis are well described in the literature. Serologic studies show a high prevalence of antinuclear antibodies, rheumatoid factor, and other markers of an activated humoral immune system such as immune complexes and immunoglobulins. Whether and how these factors, or the immune system in general, plays a direct role in the genesis of silicotic lesions, and whether tissue injury related to silicosis predisposes a person to autoimmune disease are matters of speculation.

Renal Complications

A variety of renal complications have been described in association with silicosis. The clinical spectrum of silicon nephropathy includes glomerulonephritis, nephrotic syndrome, end-stage renal disease requiring dialysis, and in one report a presentation mimicking Fabry's disease. On light microscopy, glomerular sclerosis, hypercellularity, crescents, cellular inflammatory infiltrates, and tubule damage have been seen. Electron microscopic lesions include obliteration of foot processes, cytoplasmic dense lysosomes, electron-dense deposits, and myelinlike bodies. Evidence of immune system activation is frequently present in the glomeruli.

Cancer

Many animal and human epidemiologic studies have addressed the issue of whether exposure to crystalline silica plays a role in the development of pulmonary neoplasms. Animal studies have shown that rats given intrapleural silica develop malignant histiocytic lymphoma, and intratracheal administration can result in respiratory neoplasms that resemble human bronchogenic carcinoma. Older epidemiologic data reached conflicting conclusions regarding the association of silica exposure and lung cancer. The discrepancies in conclusions from these studies were thought to be related to sampling methods or to the fact that many of these studies did not account for the effects of cigarette smoke or radon exposure in underground mines.

The studies on refractory brick manufacturers in Genoa, Italy, and diatomaceous earth miners in California provide strong clues that exposure to crystalline silica itself may be linked to excess deaths from respiratory neoplasms.

Treatment

The diagnosis of silicosis, especially if it is progressive, is always a source of tremendous frustration for both clinician and patient, since there is no proven effective therapy for this disease. Symptomatic airflow obstruction is treated with inhaled bronchodilators. Antibiotics are empirically given to patients with acute bronchitis. Oxygen is used to manage hypoxemia and the associated pulmonary hypertension.

Numerous investigators have attempted to deal therapeutically with the primary problem in silicosis, the presence of free crystalline silica in the lung and the resulting inflammatory cascade, which is aggravated or perpetuated by cells or the fibrogenic mediators they produce. In patients with minimal disease, both lungs are lavaged sequentially in the same session. Those with more severe disease have each lung lavaged in separate sessions. Close auscultatory monitoring of the ventilated lung to prevent and detect overflow from the lung being lavaged, as well as positive pressure bag ventilation with 100% oxygen after infusion, are important safety measures.

Corticosteroids and immunosuppressive agents have been used to treat accelerated and acute silicosis. Although there is a suggestion that the inflammatory process is at least lessened, whether this pharmacologic approach affects long-term outcome is not clear. If steroid therapy is instituted, tuberculosis prophylaxis with isoniazid is probably prudent until cultures definitely show the absence of mycobacterial infection. In a 6-month trial of prednisolone for the treatment of chronic simple and complicated silicosis in 34 patients in northern India, there were statistically significant (although not clinically significant) improvements in lung volumes, diffusing capacity, and partial pressure of arterial oxygen (PaO_2), and a decrease in total cell count in BAL fluid.

Other therapies investigated in animal models and humans include inhalation of aluminum, and inhalational or parenteral administration of a polymer, polyvinyl pyridine N-oxide. Inhaled aluminum has not been shown to be effective in human disease and in a sheep model of chronic silicosis. While PVNO was shown to have some beneficial effects in some experimental models, there is some concern that it could be carcinogenic. More aggressive therapies have also been tried. A case of unilateral lung transplantation in a 23-year-old man suffering from acute silicosis was reported in 1972. The lung function and gas exchange improved and the patient survived 10 months. With the current advances in transplantation medicine, this option should therefore be considered seriously for individuals with far advanced silicosis.

In Chinese traditional medicine hanfangji, an extract of the root of the plant Stephania tetrandria, has been used to treat rheumatic diseases. The principal active component of the extract is tetrandrine, a bisbenzylisoquinoline. Tetrandrine has been shown to inhibit and even reverse pulmonary lesions in experimental silicosis. An open clinical trial showed clinical and radiographic improvement in patients with pulmonary fibrosis from silica inhalation. While the exact mechanism of the antifibrotic properties of tetrandrine is not established, it has *in vitro* antiphagocytic and antioxidant properties and inhibits human neutrophil and monocyte adherence. More recent work has demonstrated that tetrandrine is a potent inhibitor of particle-stimulated oxygen consumption, superoxide release, and hydrogen peroxide production by rat alveolar macrophages. The inhibition of these inflammatory mechanisms is strongly correlated with tetrandrine's binding affinity to alveolar macrophages.

Finally, the only reasonable way to deal with this man-made illness is to prevent it. As a consequence of reduced dust standards and better industrial hygiene practices, silicosis afflicts far fewer people that it did before.

Silicosis is preventable. The extent to which this can be realized depends on education of employers and employees, strict enforcement of industrial hygiene practices, and vigilance for circumstances where unacceptable exposures to respirable silica may happen. Further research on the mechanism of lung injury in silicosis and its modulation by pharmacologic agents will contribute to our therapeutic armamentarium for this disease.

ASBESTOS-RELATED DISEASE

The term asbestos refers to a group of six naturally occurring, fibrous hydrated silicates that share a common property of resistance to heat and fire. Chrysotile, or white asbestos, is characterized by serpentine fibrils and constitutes 90% of the asbestos that is employed in North America. Amosite, crocidolite, anthophyllite, tremolite, and actinolite are employed less often.

The health consequences of asbestos exposure are of great concern to public health officials. Between 1940 and 1979, estimated 27,500,000 individuals were occupationally exposed to this substance in the United States alone. This pattern of exposure and potential disease will continue through this century as the asbestos in place deteriorates and requires repair or removal. Exposure occurred most commonly in the occupations of asbestos mining and manufacturing; shipbuilding, repair, and refitting;

general construction; automobile maintenance; and railroad engine repair. In addition, an increased incidence of asbestos-related disease is found among family members of asbestos workers and among workers employed in the vicinity of asbestos workers ("bystander exposure"). Of note is that a significant risk for disease has not been reported among populations environmentally exposed to asbestos. It is unclear as to whether there is a safe level (i.e., a threshold) for asbestos exposure below which there is no increased risk for cancer. Extrapolation data suggest no minimal level; however, clinical studies indicate there may be a relatively safe level. Low-dose, long-term exposures are showing an increased incidence in asbestos-induced lung disease.

Asbestosis refers to parenchymal fibrosis and occurs in up to 78% of heavily exposed insulation workers and up to 30% in moderate exposures. Pathologically, asbestosis is characterized by the presence of interstitial fibrosis and an increased number of asbestos ferruginous "bodies" and uncoated asbestos fibers. The ferruginous body is an asbestos fiber coated with proteinaceous iron staining material; it is visible on light microscopy. Using lung digestion techniques, uncoated fibers may be identified and counted; levels should be compared to those found in lungs of unexposed individuals to assess the significance of possible exposure in an individual. The range is quite wide and does not appear to correlate well with the type or degree of disease. The difference between environmental and occupational exposures, however, is clear.

Asbestosis usually begins subpleurally in the lung bases. If it progresses, it may involve both lungs diffusely as a fine fibrosis. In the final stages, the lungs may acquire a cystic honeycomb appearance (i.e., honeycomb lung) and can be indistinguishable radiographically from other forms of interstitial fibrosis. Recent experimental data suggest the fibrogenic response to inhaled asbestos fibers begins within hours of exposure. It is followed by macrophage-mediated immunologic, inflammatory, mechanical, and chemical injury at the alveolar cellular level.

The clinical presentation of asbestosis is usually heralded by dyspnea. End-inspiratory rales and clubbing often are present. A clinical diagnosis of asbestosis requires an appropriate exposure history and a consistent latency period (i.e., the number of years from the initial exposure). The average minimal latency period for all forms of asbestos disease is approximately 20 years, but the latency may range from as low as 10–15 years, and there is no upper limit. Chest X-ray analysis using the International Labor Office system is useful to support a diagnosis; however, the lack of distinct findings does not exclude a diagnosis. Several clinicopathologic studies have demonstrated significant asbestosis on lung biopsy

in 10–20% of patients with normal chest X-rays. High-resolution thin-section computed tomography scans (HRCT) are valuable in providing objective evidence of interstitial disease in the presence of normal, equivocal, or mild parenchymal abnormalities on a chest X-ray. The path-correlate studies have clearly demonstrated a relationship between disease on HRCT and lung tissue. There has been demonstrated correlation between disease activity and gallium scans of the lung.

The laboratory is often helpful, although it occasionally demonstrates enigmatic findings. Pulmonary function tests (PFTs) may disclose diminished lung volumes (i.e., forced vital capacity and total lung capacity) and a decrease in carbon monoxide diffusing capacity. Such abnormalities may be confounded by the countervailing effect of severe airways disease, a condition that tends to raise total lung capacity and is found among a high percentage of asbestos workers due to their heavy tobacco exposure. The earliest PFT abnormality is a decline in compliance (i.e., increased stiffness). Exercise testing is useful in identifying clinically significant pulmonary disease among dyspneic individuals with relatively normal pulmonary function. The level of dyspnea often does not correlate with a single PFT value. The degree of impairment and disability should be noted according to subjective and objective criteria established by the American Thoracic Society and the American Medical Association.

Pleural disease or "pleural fibrosis" is the most common form of asbestos-related pulmonary injury. The incidence correlates primarily with the disease latency. Pathologically, there are localized areas of pleural scarring (the pleural plaque). Calcification may occur and appears to be primarily related to the latency period. Calcification of diaphragmatic pleural plaques is a sine qua non of asbestos-related pleural disease. Pleural plaques are usually bilateral and involve the middle and lower third of the thoracic cage. Pleural plaques are generally found on the parietal pleural surface. Recent data from CT studies indicate that fissural and mediastinal visceral plaques also may be present. The usual pleural plaque does not lead to an abnormal PFT; however, studies of groups of workers exposed to asbestos have shown a significant decrement in forced vital capacity and forced expiratory volume in 1 sec with asbestos exposure, asbestos pleural plaques, and asbestosis and asbestos pleural disease. Extensive pleural plaques may lead to restrictive lung disease, particularly if there is underlying parenchymal disease. Diffuse pleural thickening is a distinct process that leads to thickening or fibrosis of the visceral and parietal pleura. If extensive and severe enough, it results in lung entrapment and may lead to severe impairment and ventilatory failure. The most

likely etiology of "benign" diffuse pleural thickening is an initial asbestos-related pleural effusion. Subpleural fibrosis may also be present.

Rounded atelectasis is characterized by localized pleural thickening and lung entrapment. Prior to advances in CT scanning, pleural biopsy was necessary to distinguish this process from mesothelioma.

A variety of cancers are related to asbestos exposure. Lung cancer and mesothelioma are discussed in other chapters. In addition, there is an increased incidence of gastrointestinal cancers, particularly gastric, colon, pharyngeal, and renal cancers, and lymphomas. There is a dramatic synergistic relationship between asbestos and the risk for cancers of the lung excluding mesothelioma. Mesothelioma is reported with even minimal asbestos exposure. There is no specific therapy for asbestos-related pleural or pulmonary disease. Common sense dictates the avoidance of any further exposure once injury is recognized. Every effort should be made to eliminate smoking. Other measures include early treatment of lung infections, influenza and pneumonia vaccinations, careful surveillance, and treatment of complications of respiratory failure (e.g., hypoxemia, congestive heart failure).

Annual screening evaluations that include chest X-ray and PFTs are important for selected patients. In view of the marked increased risk for cancer, each patient should be fully evaluated for any change in cough pattern, hemoptysis, or suggestive radiographic changes.

COAL WORKERS' PNEUMOCONIOSIS

Coal workers' pneumoconiosis (CWP), formerly called anthracosis or anthracosilicosis, exists in two forms: simple and complicated, the latter being known as progressive massive fibrosis (PMF). Simple CWP is diagnosed by a history of exposure to coal dust and chest radiographs showing an increased profusion of small, round parenchymal densities (categories 0, 1, 2, and 3 as rated by the International Labor Office system for grading radiographs for pneumoconiosis). The diagnosis of PMF requires densities larger than 1 cm in diameter; some authorities require lesions larger than 2 cm.

The basic pathologic lesion in simple CWP is the coal macule. This is a collection of coal dust-laden macrophages, reticulin, and collagen located within the walls of respiratory bronchioles and adjacent alveoli. Macules range in size from 1–5 mm in diameter and are located predominantly in the upper lobes. As the number of macrophages grows, fibrosis increases, creating micronodules (< 7 mm) and macronodules (7–20 mm). A zone of focal emphysema is usually seen around macules and nodules,

possibly caused by mechanical traction on adjacent parenchyma or digestion of alveolar walls by proteolytic enzymes released from macrophages. There is a tendency for nodules to cluster and eventually to coalesce to produce PMF lesions.

The pathogenesis of CWP is unclear. Silica in coal dust was thought to be the cause; it is now recognized that CWP is a pathologic entity distinct from silicosis, though the two conditions can coexist in the same individual. Coal is composed predominantly of elemental carbon, together with varying amounts of minerals, metals, and organic compounds. Electrically charged surface radicals on coal dust damage biologic membranes; however, coal dust is much less cytotoxic than silica. The pulmonary macrophage plays a central role in the pathogenesis of CWP by releasing inflammatory factors, recruiting polymorphonuclear leukocytes into the lung, and stimulating fibroblast production of collagen.

A number of immunologic abnormalities have been found in miners with CWP. Their etiologic role, if any, is not known, and their prevalence has varied in different studies. Miners with CWP have elevated serum levels of IgA, IgG, C3, antinuclear antibodies, rheumatoid factor, and alpha1-proteinase inhibitor; similar findings are seen in other forms of pneumoconiosis. There is no clear correlation between these serologic factors and the risk or severity of CWP except for rheumatoid pneumoconiosis (Caplan's syndrome), which describes coal miners with rheumatoid arthritis. The characteristic radiographic features of rheumatoid pneumoconiosis are rapidly enlarging, evenly distributed nodules ranging in size from 0.3–5.0 cm in diameter, occurring in lungs that otherwise show little evidence of pneumoconiosis. Microscopically, the active lesions are similar to subcutaneous rheumatoid nodules; vasculitis is a common feature. Coal mining does not predispose to rheumatoid arthritis.

The risk of development and progression of CWP increases with greater cumulative dust exposure.

Higher rank (hardness) coals are associated with increased risk of simple CWP and PMF. Anthracite is the highest rank, followed by bituminous coal and lignite. Experimentally, high-rank coals are cleared more slowly from the lungs and are more cytotoxic. The attack rate for PMF rises with increasing total lung dust; PMF usually occurs in the setting of advanced simple CWP (categories 2 and 3). Increased silica content of inhaled dust also increases the incidence of PMF. Historically, tuberculosis has been considered as a risk factor for PMF; its role has diminished in recent decades, though this organism should always be sought in a patient with expanding upper lobe lesions. Cavitation of PMF lesions is usu-

ally due to tissue necrosis, not tuberculosis. Coal miners do not have a greater incidence of tuberculosis compared with the general population.

The issue of impairment and disability due to CWP has been controversial. Most authorities agree that clinically significant pulmonary impairment does not occur in nonsmoking patients with simple CWP, though small reductions in spirometric values are common. Conversely, PMF is associated with significant morbidity and premature death. Cough and sputum production, often described as industrial bronchitis, usually have little effect on lung function in the absence of smoking. Cigarette smoking, while responsible for the majority of pulmonary impairment among coal miners, does not increase the incidence of simple CWP or the risk of progression to PMF. The Federal Coal Mine Health and Safety Act and Black Lung Benefits Program established guidelines for rating disability based on reduction of the forced expiratory volume in 1 sec (FEV1) and maximal voluntary ventilation (MVV); decrements in spirometric values are based on a miner's height, but not his age, and do not consider the effects of smoking. Should a miner have either a normal ventilatory capacity or a slight decrement, he can still qualify for benefits if the PaO_2 is reduced below a certain level with an alveolar-arterial oxygen gradient greater than 45 mm Hg breathing room air at rest. Exercise testing is not included in the rating system.

Today, the life expectancy of a coal miner is approximately that of the general population. Excess deaths are seen for nonmalignant respiratory disease, accidents, and stomach cancer. Approximately 4% of coal miner deaths are directly attributable to pneumoconiosis, usually due to PMF; most studies have not shown an excess mortality for simple CWP. These excess deaths are counterbalanced by decreased mortalities from lung cancer and ischemic heart disease and by the "healthy worker effect." Cor pulmonale and right ventricular hypertrophy do not occur in the absence of cigarette smoking or PMF. There is no specific treatment for CWP except limiting dust exposure.

TESTS

1. A patient Y., 48 years old, has been working at the iron ore concentration factory during 20 years. At the medical examination he presented the following complaints: extended pains in the thorax in the manner of pricking, dyspnea during insignificant physical load, cough (mainly on mornings) with discharge of a small quantity of sputum. These complaints have been observed during 5 months. Objective: a band-box sound in the lower parts of the lungs, vague dry rale, at the interscapular space — a harsh brea-

thing. Excursion of the lower pulmonary margin on the middle axillar line — 3 cm. X-ray investigation: in the lower parts of the lungs on the right and on the left the pulmonary tissue is emphysematously changed, the lung pattern is intensificated, deformed, roots are extended, compacted and deformed. In the lower parts on the right and on the left there is a greater amount of small (< 0.5 cm) nodular shadows.

Preliminary diagnosis:

A. Fibrinous pleurisy.

B. Silicosis, the 2nd stage.

C. Silicosiderosis, the 2nd stage.

D. Idiopathic fibrosing alveolitis.

E. Chronic bronchitis.

2. In the course of routine medical examination, which was conducted among mining workers, it was chosen one of them, complained of dyspnea under the small physical load, pain in the thorax, dry cough. He has worked for 14 years. Objective: a band-box sound at percussion on the lower side areas of the lungs, reduction of the mobility of lower margins of the lungs. Auscultation: a harsh breathing, pleura friction noise. Factors of functions of the external respiration: reduction of vital capacity of the lungs and minute volume of the lungs, increase of residual volume of the lungs. Data of the roentgenologic examination: reinforcement and deformation of a lung pattern, node shades by the size 3–5 mm. The roots of the lungs are extended, compacted, of "cut" type. The pleura is slaked and deformed.

Probable diagnosis:

A. Silicosis, the 1st stage.

B. Silicosis, the 2nd stage.

C. Silicosis, the 3rd stage.

D. Dusty bronchitis.

E. Silicatosis.

3. A man, 40 years old, during 10 years has been working in the building material production and has a contact with oxides of silicon.

What disease is it necessary to exclude during the periodic medical examination?

A. Sarcoidosis of the lungs.

B. Syndrome of Hamman — Rich.

C. Tuberculosis.

D. Microlithiasis.

E. Pulmanory cancer.

4. A man, 42 years old, applied to the therapeutical department with complaints of pricking pains in scapulas' area, compression in the chest, dyspnea at the physical load, sometimes cough with separation of a small amount of the sputum. From anamnesis — during 10 years he has worked

in coal mining, has been ill for about 6 years; when these complaints appeared for the first time, there wasn't any therapy. Objective: at the percussion — a band-box sound in the lower parts. Auscultation: a harsh breathing. No heart pathology was revealed.

Possible diagnosis:

A. Pulmonary tuberculosis.

B. Silicosis.

C. Silicatosis.

D. Bronchiectatic disease.

E. Chronic bronchitis.

5. A man, 43 years old, has worked in coal industry over 10 years, complains of the loss of the working capacity, dyspnea, strong cough with a hard spitting sputum. Cough usually appears at the sharp changing of the body position, under the physical load, breathing in a cool air and is accompanied by asphyxia. Objective: auscultation — pleural dry and moist rales; barrel chest, limited respiratory excursion of the lungs; at percussion a band-box sound is defined. X-ray: an increase of transparency of the lung pattern, plaining of the cupula of diaphragm, expansion of intercostal spaces.

What is the most probable diagnosis?

A. Silicosis.

B. Microlithiasis.

C. Tuberculosis.

D. Dusty bronchitis.

E. Silicatosis.

6. A patient, 46 years old, is applied with complaints of dyspnea under insignificant physical load and sometimes at rest, appearance of cough, first dry, afterwards with the plantiful sputum discharge, pains in the thorax, which are vastly intensified during cough. During the examination: asthenic habitus, dirty grey colour of the skin, with cyanotic colour of the face and lips. There are distant rales in the lungs, the auxiliary musculature takes part in the act of breathing, intercostal spaces are extended. From anamnesis: he has worked for 17 years at the Odessa Cement Plant as a packedman. Beginning with the age of 28 the patient has been on the dispensary account in connection with the bronchial asthma, infectious-allergic form.

Establish diagnosis:

A. Bronchial asthma, an infectious-allergic form.

B. Bronchial asthma, an atopic form.

C. Chronic obstructive bronchitis.

D. Pneumoconiosis caused by cement dust, the 1st degree.

E. Pneumoconiosis coused by cement dust, the 2nd degree.

Chapter 3
AGRICULTURAL DUST-INDUCED LUNG DISEASE

Although not widely appreciated, the agricultural worker and possibly those living in rural environments are at increased risk of developing lung disease. The risk associated with progressive lung disease appears to be more than threefold greater among those who are more heavily exposed to dusts generated in the agricultural environment. Interestingly, cigarette smoking does not appear to account for this excess risk, since agricultural workers consistently have lower rates of cigarette smoking than other occupations. These general epidemiologic observations are supported by an increasing number of exposure-specific studies in agricultural workers, which are reviewed in this chapter. Lung disease caused by agricultural aerosols affects a large population, with more than five million agricultural workers in the United States and over 80% of the work force in developing countries involved in agriculture. Unlike other occupations, the agricultural worker usually lives in the same environment as he/she works in, with exposures occurring throughout the week, and children are commonly involved in agricultural work.

An agricultural worker and those living in a rural environment encounter a variety of inhaled organic dusts suspended in the atmosphere, including molds and pollens in the air, dusts generated in silos and barns, aeroalergens, silica from the soil, and general exposure to animal dandruf, grain dust, feed additives, and mite dust. While agricultural dusts generally have a large fraction (approximately 30% to 40%) of particles in the respirable range, these dusts differ tremendously in terms of their individual constituents. Dusts generated in the production of animals are obviously very different than dusts generated in the production and marketing of grain products. In fact, within the animal confinement setting, workers may be exposed to grain dust, gases (ammonia, hydrogen sulfide, and carbon monoxide) generated from the manure pit, microorganisms contaminating the manure, aerosolized fecal material, and animal proteins.

In all cases, these organic dusts are characterized by a complex mixture of vegetable particles and fragments, microorganisms and their toxic products, insects and insect fragments, feed additives including fish meal and antibiotics, avian and rodent proteins, pesticides, and adsorbed gases. While the vegetable dust and exposures resulting from contamination with microorganisms appear to be the primary respiratory pathogen, specific methods involved in the cultivation and storage of these products influence the type and degree of exposure. For example, irritant gases such as ammonia and oxides of nitrogen are generated in storage silos and may contribute to the respiratory symptoms experienced by these workers. Thus, the agricultural aerosol is complex and contains a variable mix of agents that may contribute to the development of lung disease.

This chapter discusses the clinical and occupational features of some of the most common forms of lung disease associated with exposure to agricultural dusts — asthma, chronic airway disease, and interstitial lung disease.

AGRICULTURAL ASTHMA

Asthma may either be caused or exacerbated by a specific exposure to agents in the agricultural environment. In both cases, agricultural asthma is characterized by variable and intermittent airflow obstruction initiated by specific exposures in the agricultural environment. The objective signs of airflow obstruction are often associated with symptoms of chest tightness, wheezing, coughing, and dyspnea. Since immediate and delayed (up to 12 h) airway responses may occur following these exposures, the specific agent causing the onset of airflow obstruction may not always be obvious.

Exposures to Plant-Derived Material

The largest and perhaps the most clinically relevant category of agents known to cause asthma in the agricultural setting are the plant-derived materials. Grain dust, cotton dust, and dusts generated from teas, tobacco, mushroom, chicory, and vegetable gums all represent a complex mixture of vegetable particles and fragments, microorganisms and their products, insects and insect fragments, feed additives including fish meal and antibiotics, avian and rodent proteins, and pesticides. The specific agents most likely to cause or exacerbate asthma from these plant products are the high molecular proteins that can act as allergens. However, other agents in these dusts, such as tannins, mycotoxins, endotoxin, pollens, and insect parts, may also contribute to the development of asthma in these individuals.

Exposures to Animal-Derived Material

Animal-derived proteins can cause asthma in agricultural workers. This form of asthma is much more common in atopic individuals who are capable of developing an immunoglobulin E (IgE) response to specific aerosolized animal proteins. Animal handlers, especially in sale barns and confinement units, may be intermittently exposed to high concentrations of animal-derived proteins, and are at particularly high risk of developing asthma. Arthropod-derived material from grain mites, honeybees, barn mites, and other arthropoda have been clearly shown to cause or exacerbate asthma in exposed populations. Since these are IgE-mediated responses, a period of sensitization is needed and onset of wheezing is usually immediate, often accompanied by rhinitis and other allergic symptoms.

Irritants

Low concentrations of irritants may result in airflow obstruction in workers with underlying asthma but do not usually cause asthma. Thus, chemicals common to the agricultural environment, including solvents, ammonia vapors, welding fumes, pesticides, herbicides, and fertilizers, may contribute to the exacerbation of airflow obstruction in individuals with preexisting asthma. An extreme form of irritant-induced asthma may occur following inhalation of high concentrations of fumes or vapors in the agricultural setting. In particular, noxious vapors, such as ammonia, may acutely cause extensive airway injury and result in recurrent episodes of airflow obstruction. Characteristically, irritant-induced asthma occurs only after an overwhelming exposure to irritating gases. The worker should be able to report a specific event where he/she was exposed to a high concentration of fumes that resulted in an acute respiratory illness. These exposures can acutely cause alveolar injury and result in pneumonia or adult respiratory distress syndrome. Subsequent to the acute illness, the worker may develop recurrent episodes of airflow obstruction that are caused by a variety of irritants.

Pharmacologic Agents

Two agents that are thought to cause asthma through pharmacologic mechanisms are organophosphate insecticides and vegetable dusts containing histamine. Organophosphates inhibit acetylcholinesterase and result in overstimulation of cholinergic receptors. This is thought to induce bronchospasm by increasing the concentration of guanosine $3',5'$-cyclic monophosphate (cGMP). Although many factors may account for the de-

velopment of asthma in individuals exposed to cotton dust and other vegetable dusts contain histamine, which may promote an allergic-like inflammatory process in the airway. The inflammatory response to inhaled histamine may, in part, be responsible for the development of asthma following inhalation of vegetable dusts containing histamine.

Occurrence

The prevalence of asthma caused by exposure to agricultural dusts and fumes is not known. Clearly, the prevalence of agricultural asthma depends on the exposure and the setting. However, occupational asthma is estimated to account for between 5% and 15% of the patients who are diagnosed with asthma. Among farmers, 15% were found to have symptoms consistent with either asthma or allergic rhinitis. Interestingly, the prevalence of asthma among grain workers is reported to be similar to a comparative population of unexposed workers. This apparent disparity may be explained by the factors that select workers into and out of the grain industry. Despite these inconsistencies, a recent review indicates that most studies in grain workers have shown approximately a twofold excess risk of wheezing among grain workers when compared to unexposed workers. The prevalence of chronic wheezing apart from a cold (37%) and in association with asthma exacerbations (11%) appears to be higher in hog-confinement workers who are exposed to both organic dusts and irritating fumes. Although data are sparse regarding the prevalence of agricultural asthma, absolutely no data are available concerning the incidence of asthma among agricultural workers and their family members who are often exposed to similar bioaerosols. Importantly, the prevalence of asthma among agricultural workers is dose related and appears to be influenced by host factors including preexisting asthma, airway hyperreactivity, and atopy. In addition to these factors, differences in specific products or processing may account for seasonal and geographic differences in the prevalence of asthma among agricultural workers.

Pathogenesis

The pathogenesis of asthma induced or exacerbated by exposures in the agricultural setting is highly variable and entirely dependent on the specific nature and intensity of the exposure. Airway narrowing caused by inflammation, edema, or hyperreactivity results in acute and reversible decreases in airflow. Allergic and nonallergic mechanisms of inflammation directly injure the airway epithelia. Recurrent episodes of inflammation

may result in chronic remodeling of the conducting airways and could be responsible for the development of progressive airflow obstruction.

Classical allergic mechanisms of airway inflammation involving mast cells, IgE, histamine, eosinophils, and lymphocytes may be responsible for the development of asthma following exposure to animal-derived proteins. In-patients with an IgE-mediated response, the symptoms and signs of asthma occur in close temporal proximity to the exposure. Patients can usually identify the specific agent responsible for their symptom, and these individuals have an atopic history. IgE-antigen interactions result in mast cell degranulation with the release of histamine. Importantly, histamine can stimulate bronchial obstruction by enhancing vascular permeability, increasing smooth muscle contraction and mucus secretion, and upregulating the production of prostaglandins.

Noxious gases and irritants may directly injure the airway epithelia, resulting in edema, inflammation, and cell death. In fact, the airway epithelia may prove to be an important mediator of the inflammatory response by producing and releasing chemotactic factors such as interleukin-8. Sloughing of the airway epithelia and thickening of the subepithelial region is common in asthma and has been reported in asthma associated with agricultural exposures. Thus, the airway epithelia may actually contribute to the edema and inflammation following inhalation of particularly irritating stimuli.

Direct pharmacologic effects of agents such as organophosphates and vegetable dusts containing histamine may cause asthma by modulating endogenous pathways associated with bronchial tone or airway inflammation. For instance, cotton dust containing sufficient concentrations of histamine, may have effects similar to endogenously produced histamine and may substantially influence airway inflammation. Similarly, organophosphate insecticides block acetylcholinesterase and can cause airflow obstruction by increasing bronchial tone and decreasing the caliber of the airways.

Clinical Features

The diagnosis of agricultural asthma is dependent on the demonstration of reversible airflow obstruction that occurs in conjunction with inhalation of specific agents that have been reported to cause or exacerbate asthma. Therefore, the physician should initially focus on the diagnosis of asthma and secondarily determine if there is an occupational etiology. Typical symptoms of asthma include recurrent episodes of a nonproductive cough, chest tightness, wheezing, and dyspnea. These respiratory symp-

toms may occur immediately after specific exposures or may develop several hours after the toxic exposure. Often these symptoms worsen during the workweek and improve on weekends and vacations.

The diagnosis of asthma is based on the demonstration of reversible airflow obstruction. Standard spirometry, reversible airflow obstruction after bronchodilators, and inducible airflow obstruction with nonspecific airway challenges are considered acceptable physiologic assessments of reversible airflow obstruction. Demonstration of a forced expiratory volume in 1 sec (FEV_1) to forced vital capacity (FVC) ratio of less than 75% is considered diagnostic of airflow obstruction. A decrease in the FEV_1/FVC ratio is usually associated with a low FEV_1 (less than 80% predicted or in the bottom tail of the 90% confidence interval) or a low forced expiratory flow after 25% to 75% of vital capacity has been expelled (FEF25-75) (less than 60% predicted). Variability in airflow obstruction is usually demonstrated by sequential spirometry but may be documented by improvement in airflow with bronchodilators (at least a 12% improvement in FEV_1 is considered significant) or enhanced bronchodilator responsiveness following inhalation of either histamine or methacholine. In many circumstances, spirometric measures of lung function are normal. The demonstration of nonspecific bronchial reactivity is an acceptable, objective measure of reversible airflow obstruction, which is useful in supporting the diagnosis of asthma.

The diagnosis of agricultural asthma requires the demonstration of a clear temporal relationship to specific exposures in the agricultural setting that are known to cause asthma. The history is often helpful in identifying an occupational etiology and should incorporate the following items:

— Presence of asthma-causing agents in the workplace
— New-onset asthma or worsening of previous asthma
— Exposure to an overwhelming concentration of ammonia or oxides of nitrogen
— Worsening of symptoms during times of more intense exposure
— Improvement of symptoms when away from work or seasonally

Agricultural workers usually work and live in the same environment, and some may work seven days a week. Thus, the temporal relationship between exposures and symptoms may be difficult to determine. Physiologic testing, either by spirometry, peak flow measurements, or periodic nonspecific bronchoprovocative challenges, can and should be used to critically evaluate the temporal relationship between occupational exposures and the development of airflow obstruction. For instance, demonstration of consistent decreases in FEV_1 of 15% when exposed to a spe-

cific agent in the agricultural setting not only helps establish the diagnosis of agricultural asthma, but may assist in identifying the offending agent.

Although peak flow measures are dependent on patient cooperation and are less reliable than traditional spirometric measures of airflow, peak flow measurements are the most convenient and often the only feasible approach to investigating work-induced asthma. Specific airway challenges are a definitive method of making the diagnosis of occupational asthma, however, these inhalation challenges are not entirely accurate, and very few centers are equipped to perform these exposure-response studies in a way that minimizes risk. On-site spirometric measures of airflow is the preferable method to establish a temporal relationship between specific exposures in the agricultural setting and the development of asthma.

Several immunologic tests have been proposed to evaluate patients with suspected or proven occupational asthma; however, their clinical utility is limited. Serologic or immunologic testing can assist in determining atopic status with respect to environmental allergens. Reactions to specific allergens are limited to the relatively few that have been completely purified such as extracts of flour and grain dusts, animal products, and certain chemicals. Serum IgG or IgE antibodies may be measured by radioimmunoassay or enzyme-linked immunosorbent assay (ELISA) methods. Unfortunately, these tests lack the sensitivity and specificity required for making a definitive diagnosis, but when used in conjunction with other testing methods and a careful patient history, these tests may help document a specific etiology. In the most limited context, immunologic tests may be helpful in farther documenting exposure and identifying the atopic status of the patient.

Among patients with occupational asthma, the majority continue to have asthma despite removal from the exposure. Remissions appear to be related to the duration and intensity of the disease, with earlier and less severe forms of asthma more likely to improve. Spontaneous recovery has not been reported among workers who remain exposed to the agent causing asthma. Thus, among agricultural workers, those with work-related asthma should be encouraged to modify their exposures by either changing jobs or reducing the concentration of inhaled dust and fumes. Although most agricultural workers will not change their occupation, substantial progress can be made by encouraging the use of a two-strap dust mask or, in some cases, using an airstream respirator. In fact, one study indicates that symptoms substantially improve by reducing the ambient concentration of dust through the use of respirators.

The treatment of agricultural asthma is similar to other forms of asthma and depends on the severity and frequency of symptoms. Antiinflam-

matory medications (preferably inhaled steroids) should be the mainstay of treatment, and bronchodilators should be used as needed.

Importantly, the use of inhaled steroids should be continued for at least 6 months after the patient has been free of any respiratory symptoms. Immunologic testing should not be used to definitively diagnose agricultural asthma.

CHRONIC AIRWAY DISEASE

Agricultural workers are at excess risk of developing chronic bronchitis and chronic obstructive lung disease. Among agricultural workers, accelerated declines in air-flow are significantly related to the concentration of dust and endotoxin in the bioaerosol, and the degree of airflow obstruction across the work shift or after challenge with nonspecific inhalants. Moreover, agricultural workers have a higher mortality from chronic pulmonary diseases than workers from other industrial sectors.

Occurrence

Chronic exposure to agricultural dusts can cause irreversible and progressive airway disease. Epidemiologic studies performed in North America, the United Kingdom, Egypt, and South Africa all demonstrate that workers chronically exposed to agricultural dust are at increased risk of developing chronic cough, phlegm production, wheeze, and dyspnea, irrespective of smoking habits. Moreover, long-term follow-up studies have shown that grain workers, as well as other agricultural workers, have accelerated decline in airflow that is directly related to the concentration of dust or duration of exposure. Although short-term experimental or occupational exposure to grain dust results in reversible airway symptoms and airflow obstruction, long-term occupational exposure to either grain dust or cotton dust causes irreversible and progressive airway disease.

Epidemiologic studies have shown that the acute airway response to grain dust and other organic dusts is predictive of the chronic airway response to these agents. Several epidemiologic studies have shown that the acute work-shift-related declines in airflow are independently associated with accelerated longitudinal declines in lung function among grain handlers, cotton workers, and agricultural workers. Although the work-shift response to organic dust may simply identify a cohort of individuals with a high intrinsic risk of airway disease, it is equally possible that the acute physiologic and biologic responses to inhaled organic dusts place workers at higher risk of developing progressive airway disease. In a hu-

man autopsy report of three grain workers, the significant pathologic findings included peri-bronchiolar fibrosis without bronchiectasis, patchy emphysema, and interstitial fibrosis; however, the smoking histories for these individuals were not mentioned in the report. Among cotton workers, chronic pathologic findings attributable to cotton dust include bronchitis and bronchiolitis with mucus gland hyperplasia and goblet cell metaplasia. In aggregate, these findings indicate that agricultural workers chronically exposed to organic dust are at risk for developing chronic airway disease, involving progressive airflow obstruction, persistent airway and alveolar inflammation, and remodeling of the airway architecture.

Pathogenesis

Animal inhalation studies demonstrate that inhalation of grain dust and other organic dusts cause acute and chronic inflammatory lesions primarily focusing on the airway and involving macrophages, neutrophils, and specific proinflammatory cytokines. Inhalation studies in mice have shown that following a single exposure to grain dust, neutrophils are rapidly recruited to the lung and proinflammatory cytokines [IL-1, 2, 3, tumor necrosis factor-α (TNF-α), and IL-6], and chemokines [macrophage inflammatory (MIP)-2] are produced and released for up to 48 h. Swiss mice exposed to grain dust for 16 weeks demonstrated increased neutrophils in the walls and lumin of small bronchi and clusters of neutrophils and macrophages in the ascini. Similarly, in rats exposed to grain dust for 8 weeks, histologic changes included subepithelial neutrophils in the bronchi and bronchioli, and dilated respiratory and alveolar ducts. In guinea pigs, chronic exposure to cotton dust for 1 year resulted in airflow obstruction, anatomic changes of the small airways consisting of hyperplasia of bronchiolar epithelium and type II cells, and thickening of the alveolar ducts and alveolar septa. A recent study in hamsters showed that 6-week intratracheal dosing with either cotton dust or endotoxin can cause mild centrilobular emphysema. However, the pathogenic mechanisms that result in chronic inflammation, irreversible airflow obstruction, and permanent airway remodeling are unknown.

Clinical Features

The diagnosis of chronic obstructive lung disease (COPD) is based on the physiologic assessment of air-flow. Patients with COPD have a reduced FEV_1 and a reduced FEV_1/FVC ratio. Although most of the patients with COPD may improve with bronchodilators, improvement in FEV_1 is usually less than 15% and the spirometric measures of airflow,

by definition, do not normalize. In addition, lung volumes may reveal air trapping and the diffusing capacity may identify those patients with emphysema.

The key, unanswered question is whether effective control of the acute inflammatory response to inhaled agricultural dusts will prevent the development of chronic airway disease. Studies have not been conducted to address this question. However, there is increasing evidence in asthmatics that control of the acute inflammatory response substantially improves airflow and chronic airway inflammation. Prolonged treatment of newly diagnosed mild asthmatics, chronic stable asthmatics, and severe asthmatics with inhaled corticosteroids resulted in significant improvement in airflow. Our recommendations currently include reducing the concentration of inhaled dust (better hygiene and use of a two-strap respirator) and using inhaled corticosteroids in individuals with recurrent episodes of agricultural dust-induced airflow obstruction.

INTERSTITIAL LUNG DISEASE

Agricultural workers are exposed to a wide variety of inorganic dusts, depending on their occupation and local geography. Although there is some evidence that asbestosis can be induced by inhalation of dust generated by agriculture in asbestos-mining regions, agricultural dust-associated pulmonary fibrosis is most closely associated with inhalation of inorganic silicate compounds. Most soils contain significant percentages of quartz and other silica dusts. These dusts are aerosolized in processes that disrupt the soil surface, such as tilling, sowing, and harvesting, particularly of root vegetables. Harvesting can also secondarily aerosolize dusts previously deposited on leaves and growing plants in harvesting and processing agricultural products such as grains and cotton. Workers who sort and clean produce following harvest may be at particular risk from secondary silica aerosolization. Farming activity causes significant particulate suspension, which may be exacerbated by factors such as erosion, flooding, and absent ground cover. The raising of livestock and other animals is also associated with significant dust exposure, caused both by the soil surface disruption and by contamination of livestock feed with inorganic dusts. In addition, silicosis may result from inhalation of biogenic silica. A number of plants are known to produce silica-containing fibers, including sugar cane and grains; ingestion of these plants is associated with the development of esophageal carcinoma, but no studies have demonstrated silicosis due to these fibers.

While the relationship between many occupations and pulmonary fibrosis has been closely studied, the association between agricultural exposure and pulmonary fibrosis has been less well examined. Although most studies have focused on the contribution of silicates to pulmonary fibrosis in agricultural settings, asbestos and biotoxin inhalation can also lead to fibrogenesis in the agricultural setting. Current exposure limits for silica have been set using mining and industrial exposures as benchmarks; the relevance of these limits for agricultural workers has not been established.

TESTS

1. A patient, 35 years old, an agriculturer, complains of a sharp sensation in the eyes, lacrimation, dryness and burning sensation in the nose at cleaning, hoarseness of the voice, sensation of compression and stethalgia, dry cough; nasal bleeding, headache. It's nessasary to prescribe for the treatment:
A. Unithiol + Calcium tetacini + Ascorbic acid.
B. Penicillamine + Pentacinum.
C. Sodium sulfacetamide (Albucidum) — 2 % solution of Sodium hydrocarbonate + 1 % solution of Novocainum.
D. Nootropil + Aktovegine + Cerebrolysin.
E. Methylene dark blue + Glucose + Ascorbic acid.

2. A patient C., was delivered to CDH with the complaints of headache, syncope, nausea, vomiting, abdominal pain. It was fixed that two hours before hospitalization he processed a field by methylmercaptophos. Objective: narrowing of the pupils, hyperhidrosis of the skin, bronchorrhea, bradycardia, fibrillation of separate muscles. What organs and systems suffer most of all as a result of this acute poisoning?
A. VNS.
B. Digestive organs.
C. Broncho-pulmonary system.
D. Locomotor system.
E. System of uropoiesis.

3. A patient A., 25 years old, works at the poultry factory during 5 years, complains of dry cough, dyspnea at the period of the working shift, temperature above 39°C. Objective: percussion sound with a band-box tone, weak vesicular breath, crepitation and fine bubbling rale on sepa-

rate areas of lungs. The type of the function of external breathing is re-strictive. Blood test: Hb — 130,0 g/l; L — $90 \cdot 10^9$/l; ESR — 30 mm/h. On X-Ray — diffuse enhancement and deformation of a lung pattern.

Establish diagnosis:

A. Croupous pneumonia.

B. Chronic bronchitis.

C. Exogenous allergic alveolitis.

D. Pneumoconiosis.

E. Bronchial asthma.

Chapter 4
ACUTE TOXIC IRRITATIONS ⎯⎯⎯⎯

RESPIRATORY TRACT IRRITANTS ⎯⎯⎯⎯

Respiratory tract irritants are agents that result in an inflammatory response or a physiologic response in the respiratory tract, because of either their chemical reactivity or physical properties. Respiratory irritants may be considered strong, weak, or relatively inert for the purposes of this discussion, although this terminology is not standard.

Strong irritants, which are the major emphasis of this chapter, consist of exposures that produce a stereotyped and acute pattern of damage in the respiratory tract; recovery is often associated with major sequelae and sometimes significant respiratory impairment. Strong irritants that are highly reactive are more likely to produce an immediate and sometimes life-threatening response. Examples of strong respiratory irritants, by any standard, would include acrolein, ammonia, chlorine, chlorine dioxide, phosphoric acid, and other chemical exposures described in the final section of this chapter.

Weak irritants tend to act by inducing chronic symptoms over a prolonged period of time and often by aggravating existing disease such as asthma and chronic bronchitis. It may be difficult to distinguish between sensitization to an agent and airways irritation due to the agent; this is sometimes a clinical problem with the isocyanates, for example. Examples of weak irritants include many common solvents (most potently the xylenes), and alcohols.

The Mechanism of the Lung's Response to Irritants

The lung is highly vulnerable to the effects of respiratory irritants. The respiratory tract is protected by many layers of host defense, but they are primarily effective against infectious agents. Chemical hazards may bypass most of these in the upper airway and penetrate deeply to air-

ways and alveoli. When this occurs, the effect of the agent on the respiratory tract is governed primarily by the degree of penetration, the characteristics of the agent, and the nature of the host defense mechanisms it encounters at the level affected.

The respiratory tract is saturated with water beyond the carina and is lined with a moist mucosa with a very large surface area. Inhaled gases that are soluble in water to any appreciable extent tend to be dissolved readily and removed from the airway very efficiently. Therefore, gases penetrate the respiratory tract more deeply the less soluble they are in water. Respiratory tract irritants that are chemically reactive but easily neutralized, such as formaldehyde or acetic acid, may induce upper respiratory tract irritation, sinusitis, and sneezing but rarely cause problems deeper in the respiratory tract. Relatively soluble gases, such as ammonia, chlorine, and sulfur dioxide, penetrate poorly and usually cause predominantly airways irritation, which manifests itself as bronchospasm or an acute bronchitis. Occasionally, the concentration at exposure is so high that a soluble gas can penetrate in significant quantities to the alveolar level because of sheer mass, but this is very uncommon. Relatively insoluble gases, such as phosgene, nitrogen dioxide, and ozone penetrate very deeply, to the terminal bronchiolar and alveolar regions. These gases are particularly dangerous because they can induce toxic pulmonary edema, an often fatal outcome resembling adult respiratory distress syndrome.

The response to respiratory irritants is highly variable, among the most unpredictable of occupational health outcomes in the individual case. Important factors include the circumstances of exposure, the level of exposure to the agent of interest, the constitutional susceptibility of the host (especially if there is a history of atopy or airways reactivity), recent personal history (such as recent respiratory tract infections), smoking history, and other recent exposures (including environmental tobacco smoke). In a few cases, especially involving chronic cough, there may be a behavioral component to the response and the cough itself may perpetuate the response by causing further inflammation. Although documentation appears to be lacking, there is at least an anecdotal impression among some clinicians that persons who smoked cigarettes and then quit are often more susceptible to low-grade airways irritants than persons who never smoked or who continue smoking. Empirical verification of this observation is needed.

Another important aspect of respiratory irritants is that an irritant that primarily affects deep structures often affects proximal structures on the way down. For example, ozone is primarily associated with changes at

the level of the terminal bronchiole and alveoli, where it may alter breathing reflexes in addition to a usually low-grade alveolitis. However, ozone may also induce a cough and inflammation in the larger airways and nasal irritation.

CLINICAL MANIFESTATIONS OF RESPIRATORY TRACT IRRITATION

The clinical effect produced depends on the level of penetration and what happens when the agent encounters the predominant host defense mechanisms at that level.

Gases that are very soluble and dusts that have a large aerodynamic diameter tend to produce upper airways effects, such as sinusitis and nasal irritation. They often aggravate or mimic hay fever and may cause symptoms to be pronounced in a previously quiescent atopic individual. Such symptoms are likely to be one important category of the "sick building syndrome" and an important manifestation of indoor air quality. Since approximately 15% of the adult population is atopic, it is clear why this is a common problem. It is perhaps most commonly a result of airborne dust alone. Such symptoms are also aggravated by low humidity, as occurs in northern climates in winter and particularly indoors in climate-control buildings.

Gases that are soluble and dusts that are somewhat larger than 10 μm may have their primary effect on a larger airways of the lower respiratory tract, causing cough or bronchoconstriction. In most cases, this effect transient or short-lived. Bronchoconstriction may be manifested as either acute bronchospasm or aggravation of airways reactivity, with more frequent and severe attacks in individuals with asthma. Occasionally, airways obstruction or cough may be pronounced in an individual without a history of asthma but with a personal family history of atopy and especially hay fever. In some situations, it is likely that the subclinical airways reactivity is enhanced by an inflammatory response to the irritant. This inflammatory response may be very low grade, unlikely to produce a response in an individual who is not susceptible, and rarely resulting in wheezing or productive cough. These responses are very variable depending on the individual, the exposure situation, the season, since the person affected may also responding to allergens.

Dusts of a diameter greater than 10 mm are very important in inducing responses in the upper airway and larger airways of the lower respiratory tract, especially inducing bronchospasm in an individual with exist reactive airways. Effects on small airways are usual silent because the

cross-sectional area at that level of respiratory tract is so large that there is a huge functional reserve and no obstruction is clinically apparent. The although there is evidence to suggest that some dusts induce fibrosis in this region and low-grade small ways disease, this does not seem to be a large effect. It is certainly a small response compared to induced by cigarette smoking. However, it may be significant in contributing to chronic obstructive pulmonary disease in the presence of other risk factors.

Particles that have a diameter less than 10 µm may penetrate the alveoli, deposit, and induce a pneumoconiosis. "Nuisance dusts," which are also called "particulates not otherwise classified/regulated" (PNOC), dusts that are rarely associated with obvious clinical disease and for which no separate regulatory standard exists in the United States. These dusts do not result in exuberant fibrosis associated with the clinically important pneumoconioses, such as silicosis and asbestosis the dysfunctional immune responses of hypersensitivity pneumonitis or beryllium disease. However, all such dusts may be associated with nonspecific responses at the alveolar level that induce a low-grade response, small amounts of focal fibrosis.

Gases that penetrate deeply may induce a general pattern of diffuse alveolar damage, which resemble: early pathology of adult respiratory distress syndrome. This response is very dangerous because it may lead to toxic pulmonary edema, described in greater detail below. This is a response to strong irritants and is clinically the most severe and most often life-threatening effect of respiratory irritants.

Toxic inhalation is a serious pattern of respiratory injury that results from diffuse alveolar damage and associated airway injury in an exposure that involves deep penetration of strong respiratory irritants. The most prominent feature of toxic inhalation is the risk of pulmonary edema. Parenchymal lesions may result in honeycombing (interstitial fibrosis), reflecting abnormally proliferative fibrosis. Airways effects may be prominent in toxic inhalation, among them acute bronchospasm, bronchiolitis obliterans, and reactive airways dysfunction syndrome. Toxic inhalation also involves substantial compromise of respiratory host defenses and a risk of infection and complications.

Acute toxic inhalation by irritant, and particularly by oxidant, gases is a complex process involving biochemical, morphologic, and functional changes. The severity and special features of toxic inhalation depend on the concentration inhaled, the duration of exposure, the redox potential and chemical characteristics (especially solubility) of the individual gas, and, as will be seen, other factors.

The pulmonary vascular endothelium is the primary target, and compromise of this tissue may lead to pulmonary edema. The pulmonary vas-

cular endothelium is a very active tissue that is susceptible to a variety of toxic injuries but is capable of only limited response. A specific problem of great complexity in oxidant gas injury is the behavior of fluid following damage to the endothelial barrier. Among the most important functions of the endothelium is the regulation of vascular tone by nitric oxide (NO), which acts as a local hormone on adjacent arterial smooth muscle. Its activity is kept strictly localized. This is an effective means of titrating the vascular response and rapidly adjusting the vascular tone to changing hemodynamics.

The presence of this endogenous, nitrate-based messenger system for vascular regulation robustly explains the therapeutic vasodilator action of nitrates, the alterations in lung perfusion observed with inhalation of nitrogen dioxide, and even the vasoconstriction response of the pulmonary vascular bed during hypoxia, resulting as it does from decreased NO activity. There is some evidence that vascular segments with impaired endothelium may be more sensitive to nitrates and NO-induced vasodilation than intact segments.

The apparent sensitivity of the pulmonary capillary endothelium may be a multifactorial phenomenon. The lung is the organ at highest local oxygen tension. The endothelium, despite its low turnover rate, is a very active tissue metabolically. Current theory suggests that much of the cytotoxicity induced by agents such as oxidant gases, ionizing radiation, and free radical-forming compounds (e.g., paraquat) is mediated by the superoxide radical. The pulmonary capillary endothelium is thus at maximum risk. Furthermore, secondary phenomena of inflammation may result in very localized superoxide injury to the endothelium, an "innocent bystander" effect, after stimulation of adjacent polymorphonuclear leukocytes (PMNs) by activated complement, specifically C5a. The concept is analogous to but distinct from the release of proteolytic enzymes by phagocytic cells, a process that may set the stage for damage persisting beyond the acute phase.

Another possible mechanism of injury is the release of vasoactive humoral factors to which the endothelium is specifically responsive or preferentially exposed by position. In the case of oxygen toxicity such metabolic abnormalities occur before visible evidence of cellular injury. Although humoral factors are undoubtedly involved, it is likely that the release of such factors, including bradykinin and the biogenic amines, contributes to the expression of injury more than the injury itself.

The presence of specific receptors that increase vascular permeability and induce pulmonary edema may be an important pharmacologic mechanism for the induction of pulmonary edema by toxic gases. This mecha-

nism provides an explanation for ontogenetic and phylogenetic differences in susceptibility, the phenomenon of tolerance, the action of neurogenic pathways, and the sympathetic appearance of edema in the contralateral lung after unilateral embolism. To date, the theory lacks empirical validation.

The pulmonary vascular endothelium is not a highly complex structure, and its responses to injury are limited by physiologic constraints on its function. Structural endothelial damage by toxic gases such as nitrogen dioxide or ozone or by irradiation include swelling, cytoplasmic changes, proliferation of microvilli, and cell surface redundancy. Vesicles become much more numerous and ultimately large vacuoles form. The cell may retract or slough, even leaving behind denuded areas of basement membrane. The functional results of this injury include loss of control of solute transport across the endothelium, resulting in increased permeability. This leads to interstitial and then alveolar edema.

Recent exposure to prior toxic inhalation, especially to phosgene, increases relative resistance to a later lethal challenge with another gas. This phenomenon of tolerance disappears within days but is remarkably strong while it lasts. Tolerance to repeated exposure to toxic gases, particularly the oxidant gases, is species-specific and inversely correlated with the age of the animal documented. It is usually explained on the basis of the regeneration of type I alveolar epithelial cells by the less susceptible type II cell. However, the role of the endothelium may be more important in the pathophysiology of toxic inhalation than previously realized.

The principal structural barrier to the passage of fluid is the alveolar capillary membrane, which may be as thin as 0.5 mm. The lung is highly vulnerable to flooding by plasma-derived fluid. Complex systems to control and contain the passage of fluid through the lungs act to protect it from edema and resultant substantial changes in gas exchange. These mechanisms that protect the lung include (a) the low pressure of the pulmonary circulation, (b) the surfactant system (which reduces intraalveolar surface tension), and (c) the lymphatic drainage system. The endothelium is the first barrier component encountered on the capillary side. Plasma water and smaller macromolecules are prevented from passing into the interstitium by intact endothelial junctions. These can be disrupted by circulatory overload, which stretches the intercellular junctions. Fluid may then enter the interstitium, where there are no barriers, and fluid collects as interstitial edema. At this point the barrier to further penetration is the alveolar epithelium, in which the junctions are tighter, more complex, and less susceptible to alteration by mechanical stress. The final phase of pulmonary edema, that of alveolar flooding, is thought to begin in the

corners of greatest curvature of the alveoli at a "critical configuration" of volume and geometry in which inflation pressure no longer balances surface tension and hydrostatic forces.

The pathways of resolution of toxic pulmonary edema have not been systematically studied. Most of the work has been done on cardiogenic (hydrostatic) edema and the capillary permeability type caused by sepsis or inflammatory mechanisms. The degree to which an irritant gas interferes with the process of resolution and repair may depend on its own intrinsic toxicity to other anatomical elements, particularly to the alveolar epithelium.

TESTS

1. A 35-year-old man applied to the physician with complaints of the constant cough, dyspnea, separation of a swampy mucous sputum, seasonly appearing attacks of asphyxia for the last 6 months. In anamnesis — a 10-year experience of work on the lacquer-paint plant. He noticed that attacks occur during exposure to paints.

Objective: on the part of respiratory system at the percussion — bandbox sound on the roots of the lungs; dry diffused rales. Laboratory data: moderate eosinophilia. X-ray — amplification of the lung pattern and retraction of the roots of lungs.

What is the most possible reason of this condition?

A. Chronic toxic bronchitis at the stage of intensification.

B. Bronchial asthma, mild degree of severity.

C. Chronic toxic bronchitis complicated by bronchial asthma, moderate degree of severity.

D. Bronchial asthma, moderate degree of severity.

E. Acute toxic alveolitis.

2. A woman, 50 years old, works at the chemical plant during 20 years, complains of attacks of asthma, appeared at work, noisy breathing, heard at a distance, dyspnea. At the examination — the thorax is extended. Lips, nails' loges, skin are cyanotic. At percussion — a band-box sound. Breathing is harsh, with prolong exhalation, pronounced diffuse dry rales during inhalation and exhalation are heard.

What a pathology has this patient?

A. Chronic bronchitis.

B. Professional bronchial asthma.

C. Tuberculosis.

D. Acute pneumonia.

E. Tracheobronchitis

3. A 40-year old man K. works at the chemical plant on the production of the sulfuric acid. Nitrogen dioxide escape took place as a result of incident at the plant. Through 15 min a sick man has felt a general malaise, which disappeared by itself after 1.5 h. In 10 hrs the condition of the patient sharply worsenned and he was hospitalized.

Objective: the condition is severe, cyanosis, bubbling breathing — 50 in 1 min, dyspnea, on auscultation — multiple dry and moist rales. Tones of the heart are deaf. Heart rate — 120 bpm, BP — 110/70 mm Hg.

It's possible to form the following diagnosis:

A. Acute poisoning with sulfuric acid.

B. Acute cardiovascular insufficiency.

C. Acute poisoning with ammonia.

D. Acute poisoning with nitrogases.

E. Cerebral haemorrhage.

4. A patient A., 32 years old, a worker of the Odessa sea port plant during 2 years, applied to the local polyclinic to the physician with complaints of headache, a tickling sensation in the throat, cough. At auscultation — dry rale in the lungs. Other changes are not revealed.

It's possible to expect the following diagnosis in this case:

A. Pharyngitis.

B. Acute rhinitis.

C. Poisoning by ammonia.

D. Bronchitis.

E. Acute respiratory disease.

5. A patient P., 44 years old, was delivered to the hospital by an ambulance with complaints of swoons, vomiting, pains in the epigastrium, a sensation of mist before the eyes, noise in the ears, frequent rare stool, a pain in the breastbone of compressing nature, a tickling sensation in the throat, dry cough, general weakness. Under the objective examination: pallor, hyperhydrosis, deaf tones of the heart, harsh breathing, dry rales. Mucous membrane of the rhinopharynx is dry, white cover of the tongue, the abdomen is inflated, palpation reveals a certain resistence in the epigastrium. In the blood test: leucocytosis, increased ESR. Other changes are not detected. Data from anamnesis: he worked with the process of enriching by ammonium water, used a respirator not regularly.

It is possible to suppose in this patient:

A. Food toxicoinfection.

B. Poisoning by phosphoric organic substances.

C. Lead intoxication.

D. Acute intoxication by ammonium water.

E. Pesticides' intoxication.

Chapter 5
CARBON MONOXIDE, METHEMOGLOBIN FORMERS, HYDROGEN ARSENIDE

Various physico-chemical substances are used in national economy of many countries of the world. They comprise nonorganic and organic compounds. They may form toxic compounds by themselves or in combination with other substances. According to the classification of toxicity and dangerous effect on the organism harmful substances may be divided into four classes (Table 5.1).

Table 5.1. **Classification of toxicity**

Indication	Class of toxicity			
	1	2	3	4
Average toxic dose: ingestion (mg/kg)	<15	15–150	151–5,000	>5,000
Percutanic action (mg/kg)	<100	100–500	501–1,500	>15,000
LC (mg/m³)	500	500–5,000	5000–50,000	>50,000

General Mechanism of Pathogenesis of Acute Occupational Poisonings (AOP)

Acute poisonings may occur in accidents, violations of production process technology. Depending on the properties of the toxic substance, acute poisoning may occur at once (for example, in inhalation of carbon monoxide of strong concentration) or after several exposures for a few hours (methyl bromide).

Disturbances of activity of a number of regulator ferments catalyzing porphyrin synthesis are very important for the course of AOP. Disturbance of porphyrin biosynthesis is more often in poisoning with carbon monoxide.

AOPs also influence the condition of receptor metabolic processes in the cell that effects the structure and function of the cellular membranes and condition of the cellular metabolism. Among primary mechanisms of membrane structure and function disturbance free radical oxidation is of special importance.

CARBON MONOXIDE

Sources and Exposure

Because of its many sources, carbon monoxide (CO) is a ubiquitous air pollutant in the urban environment. It is produced during the combustion of carbonaceous material, including gasoline, natural gas, oil, coal, wood, and tobacco. The principal source of carbon monoxide in outdoor air is motor vehicle emissions. In some areas of the country, wood burned for heating may be an important contributor to ambient levels. The concentrations of carbon monoxide in ambient air vary much, owing to the great spatial and temporal variability associated with its sources. Low ambient levels (less than 1 mg/m^3) are typically observed in outdoor settings away from active roadways, such as some parks and recreation areas. Outdoor concentrations tend to increase with motor vehicle density (e.g., downtown areas) and tend to be elevated in the air of the passenger compartments of motor vehicles. Exposure to carbon monoxide is greatest during commuting and in proximity to operating motor vehicles. The concentration in the passenger compartment of an automobile typically averages 5 mg/m^3. Outdoor levels near roadways and parking areas average 3 to 4 mg/m^3. Relatively higher levels may be encountered traveling in heavy traffic: peak levels to 50 mg/m^3 may occur in a background of approximately 10 mg/m^3. Because of the reliance on motor vehicles for transportation in urban areas, automobile exhaust represents the single greatest contributing source to total personal exposure.

In comparison to exposure during travel in automobiles, indoor levels in residences and public buildings are generally low. In the absence of unvented combustion appliances, indoor levels are usually equal to local outdoor concentrations. The most commonly used unvented natural gas appliance, the cooking range, is not a strong source, even if the residence is poorly ventilated. Neither has tobacco smoke been found to be an important source of carbon monoxide exposure in homes. Carbon monoxide can accumulate because of the presence of stronger sources, including improperly vented or malfunctioning furnaces, kerosene space heaters, and charcoal fires for heating. In public buildings concentrations of 2 to 4 mg/m^3 have been found to be typical. The fact that this level is slightly higher than those in private residences is probably attributable to the activity of motor vehicles in the areas immediately surrounding public buildings. Personal exposure to high levels of carbon monoxide in outdoor settings may occur during the use of equipment and appliances powered by small gasoline engines. Important sources include lawn mowers, edgers

and trimmers, chain saws, and snow blowers. These tools may be used for prolonged sessions of work, and because they are handheld, the user is close to the exhaust plume. Further, high concentrations of carbon monoxide may accumulate when such equipment is used in sheltered or partially enclosed areas. High levels have also been measured in the air of ice hockey rinks, which is contaminated by emissions from resurfacing machines.

Health Effects

When inhaled, carbon monoxide diffuses across the lung epithelium into the blood and reversibly binds to hemoglobin, taking over binding sites for oxygen. Hemoglobin's affinity for carbon monoxide is approximately 200 times greater than that for oxygen. Additionally, in the presence of carbon monoxide, allosteric changes take place on the hemoglobin molecule, causing leftward shift of the oxyhemoglobin dissociation curve. Thus, inhalation of carbon monoxide decreases the oxygen-carrying capacity of the blood and also the ability of tissues to extract oxygen from the hemoglobin at low partial pressures. Tissues that are most sensitive to low oxygen stress — the brain and the heart — are regarded as particularly vulnerable to hypoxia induced by the presence of carbon monoxide. Carbon monoxide may also interfere with intracellular oxygen transport in muscle.

Sustained exposure to high concentrations of carbon monoxide, particularly indoors, may lead to poisoning, and ultimately death. A carboxyhemoglobin saturation level of 50% is generally regarded as sufficient to cause coma and death. Analysis of death certificate data for 1977 through 1988 indicate that 11,547 deaths occurred nationally from carbon monoxide exposures that could not be attributed to suicide, homicide, or house fire. Most of these deaths were associated with asphyxiation by indoor exposures to exhaust from running autos, but 1,199 deaths were attributed to the use of coal, kerosene, or wood in a heating appliance (e.g., wood-burning stoves, kerosene space heaters), and another 1,047 deaths were attributed to carbon monoxide exposure from improperly vented furnaces and heaters using natural gas fuels. Fortunately, there appears to be a decreasing trend in the annual incidence rates of unintentional carbon monoxide poisoning associated with nonvehicular sources. The clinical manifestations of subacute poisoning (less than 50% saturation) reflect the underlying hypoxic processes associated with high carboxyhemoglobin levels. They range from headache, fatigue, and flu-like symptoms to chest pain, cardiac arrhythmia, and myocardial infarction.

The sequelae and diagnosis of subacute carbon monoxide poisoning are well described elsewhere.

Most outdoor levels are too low to produce clinical symptoms but outdoor carbon monoxide does penetrate indoors and can contribute to elevating carboxyhemoglobin saturation levels.

Low-level exposures have been the focus of most recent health effects studies. In particular, these studies have tended to focus on subpopulations whose cardiovascular or respiratory health is compromised. Susceptible groups include people with ischemic heart disease (IHD), peripheral vascular disease, and chronic obstructive pulmonary disease (COPD). For each of these groups, exercise testing has been used to evaluate exercise capacity after exposures to carbon monoxide sufficient to elevate carboxyhemoglobin levels into the 2% to 6% range. Most of the studies employed double-blind crossover experimental designs, comparing exercise performance after exposure to carbon monoxide to performance after exposure to clean air. The responses evaluated in heart patients include the interval to onset of angina pectoris and ST-segment depression on the electrocardiogram (ECG), and in patients with intermittent claudication, reduction in interval to leg pain. In the testing of COPD patients, the maximum distance walked during progressive treadmill exercise has been used. In most studies, the subject selection criteria have involved testing to demonstrate the reproducibility of the specific response during exercise testing and have excluded current smokers.

In patients with exertional angina, earlier onset of angina pectoris and ST-segment depression have been consistently observed at carboxyhemoglobin levels of 2% to 4% by several investigative teams. In the largest of these studies, the Health Effects Institute multicenter carbon monoxide study, 5% and 12% decreases in the time to onset of ST-segment depression were observed at carboxyhemoglobin levels of 2% and 4%, respectively. Significant decreases in time to onset of angina, 4% and 7%, were also demonstrated at these respective carboxyhemoglobin levels. Findings for the objective ECG end point and subjective end point of chest pain yielded consistent results and are compatible with the hypothesis that an elevated carboxyhemoglobin level impairs the response of the myocardium to increased metabolic demands.

Another manifestation of myocardial ischemia is ventricular arrhythmia. Myocardial hypoxia caused by carbon monoxide has been postulated to be a mechanism of sudden death. Animal models have provided limited and mixed information on the arrhythmogenic potential of carbon monoxide. The experimental design in these studies included induction of myocardial infarction followed by exposure to produce carboxyhemo-

globin levels as high as 20%. Current evidence suggests no effect at carboxyhemoglobin levels up to 5% to 6% in patients with coronary artery disease and no baseline ectopy at rest, but is inconclusive for patients with baseline ectopy. Clinical studies have used carboxyhemoglobin levels more typical of the urban exposure range. Sheps et al. investigated the arrhythmogenic potential of carbon monoxide in a group of 41 men and women with clinically established ischemic heart disease and a mixed history of ventricular ectopy. A 32% increase in the rates of ventricular arrhythmia during cycle exercise was observed after chamber exposure to 200 mg/m³ carbon monoxide for 1 hr (mean carboxyhemoglobin 5.3%) relative to filtered room air but not after exposure to 100 mg/m³ for 1 hr. At neither level of exposure was there a significant difference in the rate of ventricular ectopy as measured by ambulatory ECG during the 6 hrs after exposure and exercise.

Epidemiologic studies provide limited support for the hypothesis that ambient carbon monoxide aggravates myocardial ischemia. Several studies have reported associations between ambient carbon monoxide levels and hospital admissions for cardiorespiratory disease; however, causal inferences cannot confidently be made. Most of the investigations have relied on estimates of personal exposure derived from measurements made at outdoor monitoring stations. Because correlations between central site measurements and personal exposures are poor for carbon monoxide, substantial exposure misclassification probably occurred in these designs. Furthermore, the study designs may have been confounded by unknown or uncontrolled factors, including cigarette smoking and medications.

In an occupational study of tunnel and bridge workers in New York City, employment records and historical monitoring records were used to retrospectively classify exposure during the period 1952 to 1981. Exposure classification was validated by personal monitoring of contemporary workers. A standardized mortality ratio of 1.35 for cardiovascular causes of death was observed for the high exposure group (tunnel workers) when compared to the low exposure group (bridge workers). This statistical association was supported by the observed decrease in mortality among workers transferred from tunnels to bridges. The results of this study imply that short-term repeated carbon monoxide exposure may be associated with excess mortality from heart disease.

Controlled clinical studies have also been conducted on patients with COPD. Subjects with severe COPD are believed to be at risk for development of elevated carboxyhemoglobin levels because of reduced ability to eliminate carbon monoxide owing to decreased ventilatory capacity. However, the evidence for effects of carbon monoxide on exercise per-

formance in this potentially susceptible subgroup is limited. Calverley and co-workers observed a 7% reduction in the distance walked in 12 minutes after exposure to 200 mg/m³ carbon monoxide for 20 to 30 minutes; however, because the order of exposure and testing was not randomized, the effect could be attributed to fatigue.

Because of the sensitivity of the central nervous system to hypoxia, several clinical studies have evaluated the impairment of vigilance, perception, and the performance of complex tasks after exposure to low concentrations of carbon monoxide. The results of these investigations have been inconsistent and are potentially attributable to methodologic differences in the neurobehavioral end-point measurements and differences in carbon monoxide exposure protocols and measurement of carboxyhemoglobin levels. Varying effects on visual perception, auditory perception, manual dexterity, and vigilance have been reported, but in normal subjects clinically important neurobehavioral deficits have not been observed below 10% carboxyhemoglobin.

Finally, limited animal toxicology data have implicated carbon monoxide as an agent that causes lower birth weight and increased fetal and neonatal mortality. A case-control study of birth weight and maternal exposure to ambient carbon monoxide during the last trimester of pregnancy demonstrated an odds ratio of 1.5 at a mean neighborhood outdoor level of at least 3 mg/m³, compared to lower levels. The accuracy of this finding is limited by failure to control for maternal smoking and potential misclassification of personal exposure because outdoor monitoring data were used.

The findings of controlled exposure studies, when viewed with the evidence for widespread exposures to carbon monoxide in urban populations, suggest that several groups may be at risk for adverse, health effects. Although concentrations of carbon monoxide in the outdoor environment are generally low, the prolonged exposure may nevertheless lead to development of carboxyhemoglobin levels at which health effects have been clinically demonstrated for susceptible persons. Because of the prevalence of cardiovascular disease, chronic respiratory disease, and pregnancy in the population, these adverse health effects assume public health importance.

Carbon monoxide is a strong hemic poisoning by its toxic properties. Carboxihemoglobin (COH) is formed under its influence that results in hemoglobin blockade with transport disturbance of oxygen in blood causing hypoxemia and hypoxia. Connection of hemoglobin with carbon monoxide is 300 times more than with oxygen. It promotes very fast formation of COH when carbon monoxide gets into the organism and trans-

portation of hemoglobin into inactive form which is not able to transport oxygen into different tissues of the organism.

The cerebral tissue is the most sensitive to hypoxia and dies especially fast under such conditions. Carbon monoxide may exert pathologic effect on the peripheral nervous system.

There is increased permeability of the vascular walls, including capillaries which causes hemorrhage and dystrophicity up to necrosis in different organs and tissues — the brain, lungs, gastrointestinal tract.

Amido- and neurocompounds of benzene [methemoglobin formers (MHFs)] also cause severe changes in blood, CNS and parenchymatous organs. The processes of methemoglobin formation, oxygen deficiency, affections of the CNS prevail in acute intoxications. MHFs are strong oxidizers. In getting into blood they oxidize hemoglobin to methemoglobin. The latter is a rather stable compound, which is not dissociated.

Anoxemia and anoxia are the main pathologic signs which define most of intoxications symptoms that the nervous system is very sensitive to. The following parts are mostly affected: pyramidal ducts, striated body, the cerebral cortex as well as fibers of the peripheral nerves.

Hydrogen arsenide is extremely toxic. It penetrates into the organism through the respiratory organs without affection of the mucous membrane of the upper respiratory tracts. It is a hemolytic poison whose effect is manifested in 2.5–3 hrs after contract with it.

The results of active hemolysis are anemia, affection of the parenchymatous organs (kidneys, liver), nervous and cardiovascular systems. There may be observed metabolic changes characteristic of toxic conditions: increased amount of sugar and lactic acid in blood, hyperacetonuria, decrease of pool reservoirs of blood. Thus, development of anoxemia in intoxication of hemolytic character causes general hypoxia with its concomitant manifestations.

At the same time, severe dysfunction of the liver and kidneys can't be explained entirely by hemolysis. There are sings of toxic hepatitis in some cases. In severe cases there may be progressing renal failure and development of uremia. Changes in the cardiovascular system are to a great extent by hydremia and anemia.

There may be observed enlargement of the heart, tachycardia, some disturbances of conduction, arterial hypotension. The acute period of intoxication is characterized by headache, dizziness, something drowsiness or condition of dramatic excitation. Late damages of the peripheral nervous system should be emphasized, such as polyneuropathies with dramatic tenderness of the nervous trunks and parasthesias.

Clinical Manifestations and Peculiarities in Poisoning with Carbon Monoxide

Depending on the severity of the clinical manifestations there are three stages of intoxication (Table 5.2): mild, moderate and severe. The severity of intoxication depends on carbon monoxide concentration in the air, duration of exposure, individual sensitivity of the organism. Changes of the CNS are the first to develop.

The duration of coma over 48 hrs is a prognostically bad symptom.

In favorable course, the patients coming out of coma have a condition accompanied by motor excitation when they leap up, try to run, become aggressive. There may be catarrhal laryngitis, sometimes edema of the vocal fissure resulting in hoarseness and wheezing. There may be trophic disturbances on the skin. Erythema is most frequent, it gets pigmented later on. In some cases blisters develop on the background of erythema, filled with exudates which resemble burns.

Table 5.2. **Stages of poisoning with carbon monoxide**

Stage of poisoning	Symptoms	
	Subjective	Objective
Mild	Sensation of heaviness in the head, throbbing headache in the temples and forehead, tinnitus, weakness, nausea	Flashes in the eyes, palpitation, vomiting, trembling of the body, pink color of the mucous membranes and skin (caused by accumulation of carbox; hemoglobin in blood), tachypnoe. HbCO levels of 10–30%
Moderate	General weakness	Confusion, absence of critical evaluation of the situation, growing drowsiness. Reflexes are reduced. There is pathologic Babinsky's reflex. Rigidity of the occipital muscles. Ataxia. HbCO levels of 40–50%
Severe	—	Loss of consciousness with coma and fibrillar twitching of some muscular groups. There may be attacks of generalized convulsions of clonic and tonic character. The pupils are dilated, there is no reaction to light. Severe bronchopneumonia may develop on the 2nd–3rd day. HbCO levels of 60–70%. Death is likely at levels exceeding 70%

Blood analysis is characterized by erythrocytosis and increased content of hemoglobin, sometimes neutrophilic to the left shift leukocytosis, increased blood viscosity, decrease of ESR to 2–4 mm/hr. Carboxihemoglobin appears in blood at the highest level of intoxication.

Not infrequently poor memory, emotional instability, dysfunction of vision, smell, hearing and taste remain after acute poisoning. There may be central paralyses in some cases. Motor, hearing and trophic disorders may be observed as consequences of poisoning in the peripheral nervous system. The patient may also have anemia, amnestic aphasia, apraxia, agnosia, memory disturbances by Korsakov's syndrome type. There may be psychoses with hallucinations, phobias for several years after intoxication.

Treatment and Prophylaxis of Poisoning with Carbon Monoxide

Treatment consists of intensive supportive care and providing high-tissue oxygen levels to reduce cellular hypoxia and promote the elimination of CO. Under normobaric conditions, the elimination half-life of CO while breathing room air is approximately 6 hrs. This is decreased to about 90 min when breathing 100% oxygen. While breathing 100% oxygen under hyperbaric conditions at 3 atmospheres, the elimination half-life is approximately 20 min.

a) Oxygen. All patients should receive 100% oxygen until the HbCO level declines below 10%.

b) Endotracheal intubation is indicated for all patients with respiratory distress, inability to protect their airway (i.e., comatose, or seizing patients), or ARDS.

c) Hyperbaric oxygen (HBO) therapy is indicated for patients with evidence of end-organ toxicity, which includes significant neurologic deficits (e.g., confusion, coma, seizures), myocardial ischemia or infarction, and metabolic acidosis. In centers where neuropsychiatric testing is available, abnormal responses on the test battery can serve as an indication for HBO therapy. The indications for HBO therapy based on HbCO levels are less clear. Depending on the availability of an HBO chamber, persons with the HbCO level of 20–30% should be considered for HBO therapy. Pregnant women and patients at the extremes of age modify this value downward. Hyperbaric oxygen in itself is teratogenic but probably less so than the CO-induced hypoxia and inhibition of cellular respiration in the fetus. When the chamber is a significant distance from the patient and the patient is unstable, then the benefits versus risks must be considered.

Discharge. Patients with mild manifestations of Co poisoning may be discharged from the emergency department when the HbCO level has declined to less than 10% and they are asymptomatic. Patients who have major symptoms (usually association with HbCO levels >30%) or who remain symptomatic require hospitalization.

POISONING
WITH METHEMOGLOBIN FORMERS ⎯⎯⎯⎯

Amido- and nitrocompounds of benzene are widely used in industry to make dyes, pharmaceutical preparation, explosives, etc. The most important among them are anilin, nitroanilin, nitrobenzene, dinitrobenzene. Compounds of this group may cause both acute and chronic poisoning. They penetrate into the organism through the respiratory organs and undamaged skin.

The maximum permissible concentration of anilin and benzene nitrocompounds in the air of work premises is 3 mg/m^3. Changes in the CNS are the main ones in the clinical picture of acute intoxication. General cerebral signs include headache, dizziness, nausea, vomiting, dramatic weakness (the patients can hardly stand). Stupor with the following coma develops in severe cases.

However, the most characteristic sign of acute poisoning with MHFs is radial change of colour of the skin integument. On patient's examination there are grey-blue colour of the mucous membranes and skin integument and cyanosis.

Severe cases of acute poisoning are characterized by hyperactivity of knee-reflexes, development of clonuses and pathologic reflexes. The pupils reaction to light is flaccid. Coming out of the comatous condition is accompanied by motor excitation. During the first days after coma the patient suffers from intense headache, weakness, dizziness. In some cases there may be narrowing of visual field margins. Sometimes these signs may be accompanied by tenderness of the peripheral nerves, trigeminal in particular.

There may be noted elevation of tonicity of the parasympathetic part of the vegetative nervous system which is manifested by excessive sweating, stable scarlet dermographism, bradycardia. Methemoglobin is detected in blood. Depending on the severity, there are three stages of MHF intoxication (Table 5.3).

Treatment and prophylaxis of poisoning with MHFs are presented in table 5.4.

Table 5.3. **Degrees of intoxication with methemoglobin formers**

Degree of intoxication	Symptoms	
	Subjective	Objective
Mild	Headache, dizziness, weakness, drowsiness	Cyanosis of the mucous membranes and skin integument, ataxia, elevation of tendon reflexes, tachycardia with normal ABP. About 20–25% of methemoglobin in the blood. Duration of the disease is 2–4 days
Moderate	Intense headache, stunning condition, sometimes faint, marked muscular weakness	Cyanosis of the skin and mucous membranes with peculiar grey-slate tint. Not infrequently enlarged, somewhat tender liver is palpated. There are slight dilatation of the border, dull sounds and tachycardia in the cardiovascular system. The neurologic condition is characterized by tenderness of the nervous trunks, flaccid reaction of the pupils. The blood is chocolate-brown. The laboratory tests reveal 30–40 % methemoglobin in it. Elevated blood viscosity, reduced ESR, sometimes moderate neutrophilic leukocytosis. Hypoxia develops. The duration of clinical manifestation is 5–8 days
Severe	—	Conscious disturbances as stupor and even coma. Not infrequently there are convulsions. The pupils are dilated, no reaction to the light. There are no reflexes. Dramatic cyanosis of the mucous membrane and skin with slate tint. Subicterus of the cornea. Dilatation of the heart borders with dull sounds. Considerable tachycardia and arterial hypotension. The liver is enlarged and tender. Elevated amount of direct bilirubin in the blood. The blood is thick, viscotic, chocolate-brown with 60–70% of methemoglobin, there are a lot of Heinz-Erlich corpuscles. Test for paraaminophenol is negative

Table 5.4. **Measures in treatment
and prophylaxis of poisoning with MHFs**

N	Measures	Aim
1.	To take the man from the gas atmosphere	To prevent further penetration of the gas into the organism through the respiratory organs
2.	To take off the clothes and wash the skin with warm water	To prevent further penetration of MHFs through the skin
3.	To use oxygenotherapy	To struggle against respiratory and hemic hypoxia
4.	Intravenous dripping of solutions: — physiologic 400.0–500.0 ml or hemodesis 500.0 ml or 5% glucose 400.0–500.0 ml	For disintoxication and diminution of blood viscosity
5.	Intravenous stream introduction of 20–30 ml of 40% glucose solution	To achieve demethemoglobin effect
6.	Plasmapheresis	For disintoxication
7.	Cardiac drugs stimulating respiratory centres, neuropsychotropic drugs	To improve condition and function of the corresponding organs and systems

POISONING WITH HYDROGEN ARSENIDE ────────────

Hydrogen arsenide (HA) is a colourless gas, without smell but at moderate temperature it is rapidly decomposed with a garlic smell.

It is very important to purify zinc, iron and some other metals from arsenic. It is known that technician sulfuric and hydrochloric acids have some amount of arsenic in their composition.

It accounts for accidents in getting hydrogen at the chemical laboratories as well as production processes when interacted reaction, of mineral acids with metals are used: in galvanoplastics, tinning, soldering, production of anilin dyes, benzidine, acetylene, silver extraction from the zinc dust, etching of the sheet iron for further covering with zinc or tin. There may be cases of poisoning in cleansing of the tanks with sulfurous acid, in submarines as a result of HA appearance in accumulator premises where arsenic is in lead-antimonium alloy or in careless storage of arsenide preparations, which are in insecticide groups.

The maximum permissible HA concentration in the air of work premises is 0.3 mg/m³.

There are cases of everyday poisoning with HA which is caused by arsenic in blinds or oil dyes. HA is emitted into the air when moisture and mould fungi appear on such surfaces.

The onset of acute poisoning is sudden as the contact with poison may be imperceptible. This poisoning is complicated by the fact that characteristic garlic smell appears only after decomposition with formation of distilarsine when the patient already inhaled a toxic dose of poison.

The latent period depends on concentration of poison, duration of the contact, individual reaction of the organism. It lasts from 10–20 min to 3–8 hrs (in some cases even to 24 hrs). Acute intoxication is differentiated by degree of severity (Table 5.5).

Table 5.5. **Differentiated diagnosis of intoxication degree with hydrogen arsenide**

Degree of intoxication	Symptoms	
	Subjective	Objective
Mild	Weakness, headache, tiredness, nausea, vomiting, pain in the joints and back	Subicterus of the cornea and skin. Bloody urine. Jaundice and bilirubinemia in several days. Diminishing of erythrocyte number and elevation of reticulocytes. Recovery is in a few days, as a rule, not later than 1.5–2 weeks
Moderate	Bad headache. Increasing pain in the joints and back, chest, upper stomach, right subcostal area. Parasthesia	Chillness, elevation of temperature to 38–39°C, vomiting. Dark-brown urine. As a rule, jaundice is in 6–12 hrs and has a bronze tint. Bilirubin increases to 0.2–0.025 g/l. The amount of reticulocytes increases to 100%, basophilic granular erythrocytes appear and leukocytosis with increased amount of neutrophils and left shift. Reverse development lasts 4–6 weeks
Severe	Very intense headache, pain in the back, drowsiness	Chill, fever to 38–39°C, vomiting, already during the first hrs the urine becomes brown and contains a large amount of restored hemoglobin. Protein is detected in 20–30%. In future (on the 2nd day) progressive hemolysis develops. The bilirubin number in blood increases. There is a lot of urobilin in the urine. At the end of 2–3 days there are symptoms of hepatic affection, which become enlarged and tender. In progressing course of the disease, there develops renal failure with oliguria and increased level of residual nitrogen to 1 g/1 and higher. In further progress there is no excretion of urine, uremia develops and the patient dies. Death is often at the end of the 1st week

Treatment and Prophylaxis of Poisoning with Hydrogen Arsenide

The poisoned persons should be immediately hospitalized. They need rest. They should have a lot of liquid. Transfusion of blood and blood substitute should be made. Long-term inhalations of oxygen are administered. Diuretics are used when there are no signs of severe affection of the kidneys. When there is renal failure plasmapheresis and hemodialisis are used. Parenteral intake of unitiol is necessary during the first hours. Prophylaxis of HA poisoning in production consists of good control of arsenic use as well as effective airing of the working places.

TESTS

1. What contents of HbCO arises in the blood at the carbon oxide acute intoxication of moderate severity?
A. < 20–30%.
B. < 5%.
C. 35–40%.
D. 40–50%.
E. 10–20%.

2. What are the main preventive measures on warning of CO intoxication?
A. Special clothes.
B. Vaccination.
C. Encapsulating the processes connected with CO.
D. Ventilation.
E. Cessation of contact with the factor.

3. A patient M., 32 years old, occupied at production of viscous fibers, complains of headache, syncope, sometimes vomiting. Objective: shaky gait, tactile hallucinations.
What pathology is it necessary to think of?
A. Acute intoxication of carbon bisulfide, mild form.
B. Acute intoxication of carbon bisulfide, severe form.
C. Chronic intoxication, the 1st degree.
D. Chronic intoxication, the 2nd degree.
E. Chronic intoxication, the 3rd degree.

Chapter 6
ORGANIC SOLVENTS ⎯⎯⎯⎯⎯⎯⎯⎯

Solvents are simple organic substances that are (a) liquid at room temperature and under standard atmospheric conditions, (b) relatively nonreactive, and (c) able to dissolve a wide range of organic compounds (i.e., lipophilic). Most solvents are quite volatile. While exceptions to this definition can be found, it is applicable to the majority of solvents used in industry.

Solvents may be used for the selective dissolution of one substance from a mixture (i.e., chemical extraction), for reduction of the viscosity of another substance, or as feedstock for the production of synthetics. Some solvents, such as certain alcohols as well as gasoline and other aliphatic compounds, are used as fuels. A great variety of organic solvents are currently in use in industry. Commonly used organic solvents include the aliphatic, cyclic, aromatic, halogenated, ketone, aldehyde, alcohol, and ether classes. Solvents are constituents of, or are required in the production of, a wide variety of products, including paints, varnishes and other coatings, paint removers, fuels, glues, dyes and printing inks, degreasers and dry cleaning agents, plastics, agricultural products, and pharmaceuticals.

Solvents affect the nervous system, liver, kidneys, and skin. Several are known human carcinogens; others are animal carcinogens suspected of possessing carcinogenic activity in humans. The acute neurologic effects are related to the anesthetic property of solvents, manifesting as transient symptoms such as dizziness and light-headedness. A chronic, irreversible solvent syndrome that can include loss of intellectual function has been described. Solvents have a wide range of potency for the induction of liver disease. Classically, the halogenated hydrocarbons are capable of inducing fatty changes and cirrhosis. The renal toxicity of solvents includes both acute tubule necrosis and glomerulonephritis. Con-

tact dermatitis can occur in the setting of solvent exposure and is due to defatting of skin that has been in contact with organic solvents. Selected solvents have been related to cancer of the hematopoietic system and the lungs.

EXPOSURE

Because solvents are found in a wide range of products and processes, many workers are at risk of exposure. Solvent exposure is common among painters and others involved in surface coating or finishing, degreasers, printers, dry cleaners, petrochemical and refinery workers, and fiberglass laminators. In Western Europe in 1980, 43% of all organic solvents were used in paint and other surface coatings, 10% — for metal cleaning, 8.1% — in household products, 6.7% — in adhesives, 6.1% in pharmaceutical manufacturing, 3.9% — for dry cleaning, and 20% — for other uses. A detailed evaluation of organic solvent different solvents were used in industry, most commonly ethanol, gasoline, toluene, isopropanol, and acetone. In a related study, the highest exposures in Denmark were found to occur in the printing and chemical industries. It is important to note that many workers are at risk for solvent exposure, not just those in trades with known widespread exposure. For example, an automobile mechanic may be exposed intermittently to solvents if the work requires cleaning parts in a solvent bath, a common procedure in mechanical repair.

Most occupational solvent exposure is to solvent mixtures. Indeed, many solvents are provided as mixtures-paints, thinners, mineral spirits, kerosene, jet fuel, gasoline, and white spirit, the common name for a solvents mixture composed of aliphatics and aromatics. The frequent use of solvents is problematic when estimating solvent exposure or attempting to establish permissible limits.

Some authors distinguish two types of work activities, application and process, in occupational exposure to solvents. Application work involves the creation of an open surface from which solvents evaporate. It is usually associated with intermittent high-level exposure. Painting and degreasing are examples. Solvent exposure in these settings can be highly variable and is related to both the work setting and ventilation, work in confined spaces producing especially high and potentially acutely dangerous levels. Process work is often found in the petrochemical and pharmaceutical industries, where solvents typically are enclosed to reduce occupational exposure and prevent loss of product. In these settings solvent exposure occurs during leaks or other failures of the enclosure system, product transfer, or maintenance and repair.

Estimation of occupational exposure to solvents is problematic because (a) large variations in individual exposure can occur during the workday, with periods of high exposure interspersed with periods of low exposure; (b) much variability of exposure can exist between individuals, even those performing the same tasks; (c) there is potential for multiple routes of entry; (d) personal protective equipment may be used; (e) solvents are commonly used mixtures. Several methods are available for estimating occupational exposure to solvents, including environmental monitoring, biologic monitoring, and semiquantitative retrospective exposure estimation. The choice of methods depends on the exposure situation and the goals of the exposure assessment activities.

ENVIRONMENTAL BIOLOGIC MONITORING

Environmental monitoring involves measuring the concentration of solvent vapor in ambient air available for respiratory uptake by workers. Both direct reading and sampling methods are available. Direct reading equipment includes indicator tubes, portable gas chromatographs, and portable infrared analyzers, among others. This method of assessing exposure is most useful when the composition of the airborne solvent contaminants is well known. Sampling methods include the use of grab samples, collection of time-weighted average samples, use of solid adsorbents, and diffusion badges. Environmental measures of exposure can be obtained from fixed locations at the work site and are called area samples. Alternatively, breathing zone samples can be obtained by requiring the worker to wear a portable device that samples air near the nose and mouth. Breathing zone samples are considered more representative of individual exposure than area samples. Environmental monitoring can be performed for virtually any solvent in air.

Solvent uptake depends on several factors in addition to the concentration of solvent in air, including both dermal uptake and work load. A disadvantage of using environmental monitoring as the sole index of exposure is that the contribution of these other factors to solvent uptake is not measured, and therefore the actual dose may be poorly estimated.

Biologic monitoring is the evaluation of the internal exposure of the organism to a chemical agent (i.e., the internal dose) by a biologic method. "In practice, this means measuring the substance itself or its metabolites in various biologic media like blood, urine, expired air, hair, adipose

tissue, etc." Biologic monitoring methods have been described for a variety of industrial solvents, including benzene, toluene, xylene, styrene, trichlorethylene, tetrachlorethylene, trichlorethane, and dimethylformamide. The advantages of biologic monitoring are that (a) it accounts for all routes of absorption, (b) nonoccupational exposures are also assessed, and (c) individual differences in the rate of uptake due to either use of personal protection or differential uptake secondary to work load or other factors are accounted for. The disadvantages of biologic monitoring include (a) the need to obtain biologic media from workers, (b) limited understanding of the association between biologic exposure measures and worker health, and (c) the limited number of solvents for which biologic measures are available.

In epidemiologic study of the health effects of solvent exposure, it is often the case that neither environmental nor biologic exposure information is available. Frequently, exposure has occurred to a variety of solvents under variable conditions of exposure. Furthermore, measures of current exposure, environmental or biologic, may not represent past or cumulative exposure. In this circumstance the duration of exposure is often used by investigators as a substitute for actual total exposure. Typically, this variable is closely correlated with age, and it may be a confounder in exposure-effect analyses. Recent attempts have been made to develop a solvent exposure index for painters that utilizes information obtained by questionnaire in combination with a weighting scheme for factors that modify individual exposure, including respirator use, method of paint application, and ventilation.

With the exception of styrene, it is common for workers to be exposed to mixtures of solvents. This fact adds another level of complexity to the assessment of solvent exposure, as different solvents have different toxic potency. In an attempt to develop classification schemes for mixed solvent exposure that are more accurate than simple solvent-years, some authors have utilized a summary measure called the hygienic effect. The hygienic effect is the sum, for all solvents present in a mixture, of the actual exposure to each solvent divided by its maximum permissible exposure. The assumption underlying this index is that the health effect at the maximal permissible exposure level is equivalent for all solvents and that no synergy of effect occurs. He concluded that the assumption of "additive effects in the case of chemicals that share similar action in toxicity" was more accurate than were assumptions of independent action, potentiation, or antagonism, a conclusion that tends to support the hygienic effect concept.

TOXICOKINETICS

Inhalation and percutaneous absorption of solvents are the two routes of entry relevant to occupational medicine. Respiratory uptake of solvents depends on solvent concentration in inhaled air, the blood-air partition coefficient, alveolar ventilation, pulmonary perfusion, and the duration of exposure. Because both alveolar ventilation and pulmonary perfusion are functions of physical exertion or work load, manual labor can cause substantial variation in solvent absorption. Pulmonary uptake occurs via simple diffusion.

Dermal uptake is important only when liquid solvent is in contact with the skin, and it may be the predominant route of entry for solvents of low vapor pressure such as the glycol ethers. It is dependent on the surface area of the skin in contact with solvent, skin thickness and physical characteristics (cuts, abrasions, disease), and the duration of contact. Percutaneous absorption of solvent vapor is negligible.

The distribution of unchanged solvent in the body is a function the solvent's differential affinity for various target tissues, usually a function of the lipid content and vascularity of the tissue or organ. Metabolism of solvents occurs mainly in the liver and is typically mediated by the cytochrome P-450 mixed-function oxidase system. A water-soluble conjugate is produced that is subsequently excreted in the urine or bile. Biotransformation usually results in a biologically less active metabolite; however, it can produce a metabolite of greater toxicity than the parent compound, as in the case of metabolism of methyl-n-butyl ketone (MnBk) to 2.5-hexanedione, a peripheral neurotoxicant.

A great deal of recent research activity has concentrated on the development of pharmacokinetic models of solvent exposure. In these models, the body is represented as a set of compartments, and the interactions between compartments are described with differential equations. Such models may be useful for predicting the concentrations of solvents in various body tissues, and they also allow more precise estimation of dose-effect relationships. Models of increasing complexity are required when exposure to solvent mixtures is considered, when sources of variability such as work load, body build, liver function, and renal function are considered, when chronic toxicity is the outcome of interest and tissue repair processes mitigate the toxic effect of the solvent, or when bioactivation or repair mechanisms can become saturated. Pharmacokinetic models require extensive validation prior to acceptance.

Solvents are eliminated by exhalation of the unchanged parent compound or by urinary and biliary excretion of either the unchanged parent compound or its metabolites.

WORKER PROTECTION

A hierarchical approach is recommended for the reduction of workers' exposure to solvents. The initial step is to substitute less toxic solvents for more toxic ones. Substitution of toluene for the carcinogen benzene and of methylisobutyl ketone for the neurotoxicant MnBk are examples of this approach. In addition, changes in use in the paint industry from solvent-based paints to both water-based paints and solventless powder coatings represents substitution or elimination of potential solvent exposure.

In addition to the substitution of safer solvents for more toxic ones, effective ventilation and enclosure of solvent-based processes is useful for reduction of solvent exposure. The spray booth found in many spray-finishing facilities represents such a mechanism, both to isolate the spray-finishing process from uninvolved workers and to establish an environment in which air flow directs solvent vapors away from the breathing zone of the involved worker.

Respirators, either air-supply or air-purifying, are the least effective means of reducing workers' exposure to solvents. In addition, their use requires a comprehensive respirator program, including worker education, evaluation of worker fitness for use, fit testing, and regular maintenance.

Because some solvents are readily absorbed through the skin, an effective worker protection program must include measures to prevent skin contact. Gloves are often used and can be effective. However, many are permeable to a variety of solvents, so gloves must be selected carefully. Barrier creams, the least effective method of reducing percutaneous absorption of solvents, are not recommended. In addition to gloves, reduction of percutaneous exposure includes washing areas of skin contact with soap and water and removing solvent-contaminated clothing to prevent prolonged skin contact.

EFFECTS ON THE NERVOUS SYSTEM

Neurotoxicity induced by exposure to organic solvents has emerged as one of the most important issues in occupational health. Substantial concern stems from the essential life functions performed by the nervous system as well as the fact that damage to it may be irreversible. Although much work has been done, substantial uncertainty still exists, particularly with regard to the effects on the central nervous system of long-term, low-level exposure to solvents.

Solvents can cause depressant intoxication following acute exposure, which appears to be related to physical or chemical interactions with membranes or neurotransmitters. Long-term heavy exposure to solvents may also cause persistent, potentially irreversible impairment in cognitive function and affect, which may be associated with structural changes in neural tissue.

Solvents may exert their primary effect on the central nervous system (CNS), the peripheral nervous system (PNS), or both. CNS effects are typically investigated with behavioral tests or electrophysiologic evaluations. Information about the effects of occupational solvent exposure on the PNS has come from studies that utilize clinical evaluation, electrophysiologic examination, and histopathologic examination of biopsy specimens. The effects of occupational solvent exposure on the PNS are more clearly defined and easier to identify than those of the CNS, owing to the relative simplicity of both the structure and function of the PNS.

Peripheral Nervous System

Widespread agreement exists that the solvents n-hexane, MnBK, and carbon disulfide cause in humans peripheral neuropathy of the distal axonal type. Other solvents suspected of having peripheral nerve effects include styrene and tetrachloroethylene. In this section discussion is restricted to the peripheral nerve disorder induced by the hexacarbons n-hexane and MnBK. An excellent review of hexacarbon-induced peripheral neuropathy is provided by Schaumburg and co-workers.

The hexacarbon solvents n-hexane and MnBK have been used mainly in thinners, glues, paints, and specialized printing materials. The occupational toxicity of the hexacarbons was first recognized in the 1960s when an outbreak of peripheral neuropathy occurred in a shoe factory in Japan. Occupational disease has usually occurred among workers who use glues containing hexacarbons. Nonoccupational cases are mostly restricted to the deliberate inhalational abuse of glues.

Exposure to n-hexane and MnBK cause changes in peripheral nerves characterized initially by axonal swelling and focal demyelination in the distal regions of the longer, larger axons. With progression, degeneration of the entire axon occurs distal to the site of axonal swelling.

Both n-hexane and MnBK share a common metabolite, 2.5-hexanedione, universally believed to be the peripheral neurotoxicant responsible for hexacarbon-induced peripheral neuropathy. This substance has been shown in animals to produce in peripheral nerves pathologic changes that are virtually identical to those caused by administration of n-hexane and MnBK.

In the occupational setting the onset of symptoms is usually gradual. Deliberate inhalational abuse is associated with a more rapid onset of signs and symptoms and can lead to disabling disease within 2 months. The initial complaint is usually symmetric numbness of the fingers and toes. Loss of cutaneous sensibility to light touch, vibration, pin prick, and temperature are present on physical examination, as are proprioceptive abnormalities and loss of the Achilles tendon reflex. Severe disease can include motor weakness and atrophy.

Routine clinical laboratory test results are normal in patients with hexacarbon-induced peripheral neuropathy. Electrophysiologic evaluation discovers symmetric distal electromyographic abnormalities consistent with denervation as well as mild to moderate slowing of both motor and sensory nerve conduction velocity.

A characteristic feature of hexacarbon-induced peripheral neuropathy is the tendency for the disease to progress for up to 4 months following cessation of exposure. There are no specific treatments, and the degree of recovery is proportional to the severity of disease. Hexacarbon-induced peripheral neuropathy is indistinguishable from other toxic and metabolic neuropathies, so a careful occupational and social history is required to identify the causative agent.

Central Nervous System

A great deal of controversy exists regarding the toxic effects of solvents on the CNS. Much of the controversy is probably attributable to the use of confusing terminology and inconsistent diagnostic criteria to describe CNS impairment. Fortunately, some movement toward standardization of terminology used to describe the effects of solvents on the CNS has been made by the World Health Organization (WHO) and others. The first basic distinction in the classification scheme proposed by the WHO is acute versus chronic. Acute effects are graded as mild (acute intoxication) or severe (acute toxic encephalopathy). Chronic effects were classified as mild, consisting mainly of affective changes and loss of concentration (organic affective syndrome); moderate, with some impairment of neurobehavioral functioning (mild chronic toxic encephalopathy); or severe, with significant loss of intellectual function (severe chronic toxic encephalopathy). A second classification scheme is similar, except that specific names for the classifications are avoided (type 1, 2, and 3 are used instead) and the mild chronic condition is subdivided into those having primarily affective or primarily cognitive dysfunction.

Acute effects of exposure to solvents are pharmacologic and their intensity is generally proportional to their concentration in the brain. There

may be initial euphoria and disinhibition. Higher intensity exposure may result in prenarcosis symptoms such as dizziness, nausea and vomiting, incoordination, paresthesia, increased salivation, and tachycardia. The symptoms are generally transient, disappearing quickly after exposure is terminated. Overexposure can lead to seizures, coma, and death in severe cases. The likely mechanism is anoxia following depression of central control of respiration.

Severe cases of overexposure to solvents are not common under normal working conditions. Poisoning by simple chlorinated solvents appears more common than by aromatic solvents, and younger workers appear to be at greater risk than older ones. About half of all reported cases (loss of more than 3 days' work) resulted in loss of consciousness, and fewer than 5% were fatal. There have been numerous case reports of accidental poisoning to a variety of alcohols, acetates, and ketone solvents, but such cases are rare, perhaps owing to the respiratory irritant qualities of these solvents.

Some cases of acute industrial poisoning may be the result of volatile substance abuse (VSA), but the frequency of VSA among solvent-exposed workers is unknown and presumed to be low. The overwhelming majority of VSA cases are teenagers abusing solvents recreationally. Adhesives are the most abused products, and toluene is the solvent detected most frequently in the blood. Voluntary inhalation of gasoline carries additional hazard, since it may contain tetraethyl lead and ω-hexane.

Subclinical effects of acute exposure to solvents in humans can be studied in the laboratory under experimental control. It is not ethical to expose humans to agents or concentrations that are expected to produce severe or lasting effects, so this type of study yields information only on mild, transitory effects.

The most-studied solvents have been toluene, xylene, styrene, trichloroethylene, perchloroethylene, and methylene chloride. These studies have typically shown, at most, subtle effects of short-term exposure at the current exposure limit values. The acute effects of most solvents are narcotic; thus, performance decrements on tests of attention and reaction time have been reported most often. In addition to cognitive tests, quantitative measurement of postural stability may be a sensitive outcome for assessment of acute effects of solvents on the nervous system.

The nonspecific effects of long-term exposure to solvents range from a general negative affective state, to a subtle reduction in functional reserve capacity to perform well when fatigued or in a distracting environment, to mild slowing of psychomotor performance, to memory disturbance, and finally to severe intellectual deficits. The most severe condi-

tion, which has been called psychoorganic syndrome, presenile dementia, and severe chronic toxic encephalopathy, is also the most controversial. Although the existence of chronic solvent encephalopathy has been questioned, experts now generally agree that it occurs but do not agree on its prevalence. The extent to which these differences reflect differences in diagnostic criteria, past exposure, or other host factors is unknown.

A great number of epidemiologic investigations of CNS outcomes among various solvent-exposed groups have been conducted. Several international conferences have been held, and one critical review from a conservative perspective has been published. It is beyond the scope of this chapter to review all these studies. Rather, an orientation to the available literature and a discussion of the relevant issues are provided.

The epidemiologic studies have been either registry-based studies of neuropsychiatric disability or cross-sectional studies comparing exposed and unexposed groups for differences in prevalence of symptoms, neurobehavioral performance level, or prevalence of abnormality on neurologic or neurobehavioral tests. The results have been almost as heterogeneous as the exposures and the methods used to assess outcome. The reader is referred to a sample of well-conducted epidemiologic studies of multiple neurologic outcomes among solvent-exposed workers.

Neuropsychiatric Disability

A number of studies based on pension or disability registries in relation to solvent exposure have been published. In general, risk of disability award on the basis of neuropsychiatric illness was found to be elevated about twofold among solvent-exposed groups such as painters and floor layers relative to comparison groups such as carpenters and electricians, although there have been some exceptions to this trend. In addition to registry based studies, case-control studies of the association between occupational solvent exposure and (a) psychiatric disorders requiring hospitalization, (b) medical disability retirement resulting from chronic neurologic and psychiatric disease, and (c) organic brain damage have been published. Only in the study of organic brain damage was a significant association with solvent exposure observed. Interestingly, an interaction with alcohol consumption was observed, suggesting that alcohol consumption may modify (increase) the adverse effect of occupational solvent exposure on the central nervous system.

Symptoms

The rates of reporting of some symptoms were elevated above the rate reported by comparison groups in the vast majority of published epidemiologic studies of solvent-exposed workers. Those symptoms most often elevated were fatigue, irritability, depression, headaches, poor con-

centration, and forgetfulness. Terms such as neurasthenic syndrome and organic affective syndrome have been used to label this constellation of symptoms among solvent-exposed workers. Persistent expression of these symptoms has led some investigators to speak of personality changes or personality disturbances, which have been assessed with standardized personality tests.

Neurobehavioral Tests

Tests of neurobehavioral function are aimed at noninvasively assessing the functional integrity of the CNS. Many standardized neurobehavioral tests have been used to assess CNS function in solvent-exposed workers. Because of the complexity of the human nervous system and the attendant wide range of functions that can potentially be affected, sets, or batteries, of tests are usually administered to the subjects in these studies. It is generally accepted that the tests administered should sample from the perceptual, motor, psychomotor, learning-memory, attentional, and affective functional domains.

In the last 15 years at least 16 epidemiologic studies of painters (car, industrial, construction, and combinations of the three) and four studies of paint-manufacturing workers exposed to mixed solvents have been published. At least 11 studies of fiberglass fabrication workers exposed almost exclusively to styrene and at least four studies of printers exposed primarily to toluene have been published. Many other epidemiologic studies of heterogeneous groups of solvent-exposed workers have been reported. Neurobehavioral performance was reported to be poorer in the solvent-exposed groups than in the referent groups in most of these studies.

The findings are far from consistent, however. Some studies have failed to observe differences in neurobehavioral performance level between solvent-exposed and referent groups, and even when differences between exposure groups were observed, the pattern of differences was often inconsistent across studies of presumably similar occupational groups. Different tests were administered in different studies, and tests intended to measure the same functions, or even those bearing the same name, were sometimes quite different in practice. Also, it should be noted that decrements in performance on neurobehavioral tests are nonspecific; performance is affected by a number of factors not related to exposure (e.g., age, education, native intellectual ability, and the motivation of the subject). Furthermore, the functional significance of performance differences between exposure groups (e.g., a mean difference in reaction time of 20 milliseconds) is not always apparent. Dose-response relationships have not been observed in many investigations, probably owing to imprecise estimation of exposure to the neurotoxic agents.

Other Tests

Testing of three sensory systems — olfactory, auditory, and visual — that may be early targets for solvent toxicity have received attention recently. Although a Swedish study failed to show differences in smell identification between painters and referents, loss of hearing has been associated with occupational exposure to solvents. In one study of self-reported hearing difficulty, a significant association was observed with self-reported occupational solvent exposure. Authors of another study, in which audiometry was performed to characterize auditory function, observed a strong effect of solvent exposure on hearing. In addition, a statistically significant interaction between solvent exposure and noise exposure was observed. Several reviews of the animal and human evidence in support of this hypothesis are available. Deficits in performance of a simple color vision test have been reported among several solvent-exposed groups; however, these results have not been replicated in other investigations. Changes in visual contrast sensitivity have also been reported for solvent-exposed microelectronics workers and a series of solvent-exposed patients.

Quantitative measurement of postural stability, or posturography, has been employed as an index of highly integrated CNS and PNS activity and findings have differed for solvent-exposed and referent groups.

Electrophysiologic outcomes such as electroencephalography and evoked potentials have been shown to differ on a group basis between solvent-exposed and referent groups. These methods are objective, but the findings are nonspecific and their relevance to health is usually unknown.

Computed tomography (CT) has been used as an index of cerebral atrophy among solvent-exposed workers and patients, but the results of such studies have been mixed. In addition to CT methods, several papers have been published in which single photon emission computed tomography (SPECT) was performed on solvent exposed subjects. Unfortunately, these studies are of poor methodologic quality, which severely limits inferences that can be made from them.

Effects of Solvents

Acute tubule necrosis (ATN) is a potentially life-threatening renal disorder characterized by azotemia and oliguria. It is one cause of acute renal failure. Short-term, high-level exposure to selected solvents is universally accepted as a cause of ATN. Solvents that have been described as causing ATN include the halogenated hydrocarbons (especially carbon tetrachloride), petroleum distillates, ethyiene glycol, ethylene glycol ethers,

diethylene glycol, dioxane, and toluene. ATN has been reported to follow both intentional inhalational exposure (volatile substance abuse) and unintentional occupational inhalational exposure. In addition, ATN has been described following dermal exposure (i.e., hand washing) to diesel fuel. The mechanism of solvent-induced tubule damage is poorly understood. Solvent-induced ATN is not associated with glomemlar disease.

When it occurs, ATN shortly follows solvent exposure, so the association with exposure is usually easy to establish. No studies are available in which the risk of solvent-associated ATN is estimated. Some authors have concluded that the risk of ATN associated with solvent exposure is low because few reports of solvent-induced acute renal failure are available despite the widespread use of solvents. Although in the past ATN was universally fatal, recovery is common now that renal dialysis is readily available. After the initial tubule changes associated with ATN have occurred, tubules regenerate in approximately 3 weeks. While complete recovery is possible, renal insufficiency may persist.

Glomerulonephritis is a disorder characterized by, either individually or in combination, hematuria, proteinuria, reduced glomerular filtration rate, and hypertension. It is caused by alterations in the structure and functional integrity of the glomerulus. Glomerulonephritis is the most common renal disease following long-term exposure to solvents.

Several comprehensive reviews of the literature relating solvent exposure to glomerulonephritis are currently available. All include a discussion of the many case reports of individual patients or series of patients with glomerular disease who have a history of exposure to solvents. Agreement exists that the results of these case series, while indicating the need for additional research, are not conclusive. In addition, they review the epidemiologic literature examining the association between glomerulonephritis and solvent exposure. Virtually all of the epidemiologic studies of the relationship between overt glomerulonephritis and solvent exposure have used a case-control design. One cross-sectional study of relevance to this issue examined both serum antiglomerular basement membrane and laminin antibody levels in relation to occupational solvent exposure.

The first comprehensive review included an evaluation of six studies in which a case-control design was used to determine whether glomerular disease was associated with solvent exposure. In five of the six studies reviewed, a significantly larger proportion of subjects with disease were exposed to solvents than were referents. In one study no association was found; however, several weaknesses in design that had the potential to bias the results of these studies have been noted: (a) inappropriate controls were used in three of the five positive studies, (b) blinding was a

94

concern in four, (c) recall bias was either possibly or probably present in all, and (d) measures of exposure were either poorly defined or not explained in all. One study was judged to be of substantially higher quality than the others; an odds ratio of 3.9 for the relationship between solvent exposure and glomerulonephritis was observed in this study. Churchill and colleagues concluded that additional studies were needed to clarify the relationship between solvents and glomerular disease.

The most carefully performed case-control studies of the relationship between glomerular disease and exposure to organic solvents controlled the above-mentioned sources of bias by (a) requiring that all cases be confirmed by biopsy, (b) using appropriate control groups, and (c) ensuring that interviewers were blinded to disease status of the subject. In addition, semiquantitative measures of exposure based on interview information obtained from subjects were incorporated into three studies. Of these five studies, a significant association between solvent exposure and glomerular disease was observed in three. In the one cross-sectional study of circulating antibodies considered to be potential preclinical indicators of glomerulonephritis, significant associations were observed between these indicators and occupational exposure to hydrocarbons and mixed solvents.

In summary, the body of research relating solvent exposure to glomerulonephritis is suggestive of an association, although not unequivocally. However, several well-performed case-referent studies have found significantly elevated odds ratios for exposure to solvents. Others have not, although their statistical power was limited. No cohort studies of glomerular disease among solvent-exposed subjects have been published to date. Given the low incidence of the outcome, such a study would be logistically difficult and require that a huge number of subjects be followed in order for it to have adequate power to detect even a relatively large effect.

Several cross-sectional studies of urinary excretion of proteins and cells in subjects occupationally exposed to organic solvents have been performed. The aim of these studies was to detect renal tubule and glomerular dysfunction at an early or subclinical stage. Outcomes of interest have included not only conventional clinical measures of renal function such as proteinuria, albuminuria, and the presence of cells in urine but also novel measures of renal function, such as excretion of low molecular weight enzymes and proteins, including I-acetylglucosaminidase, retinol-binding protein, and α-microglobulin. The results of such studies have been mixed, showing both mild tubule dysfunction and glomemlar effects. Studies in which no effect was found on a variety of measures of renal function have also been reported. In summary, some inconsistency

exists regarding the effects of solvents on measures of renal function among working populations exposed to solvents. However, currently, a preponderance of research findings suggest that mild tubular and glomemlar effects of unknown clinical significance are detectable in solvent-exposed workers.

Carbon tetrachloride, tetrachlorethane, and chloroform are well-known hepatotoxins, acutely causing hepatic necrosis and steatosis. In addition, hepatic cirrhosis has been observed following long-term exposure to carbon tetrachloride. Use of these substances has diminished over the past several decades, in large part because of their recognized hepatotoxicity and the availability of less toxic substitutes.

Evidence on human exposure to other halogenated hydrocarbon solvents such as methylene chloride, trichloroethylene, and trichloroethane suggests that they are substantially less hepatotoxic than carbon tetrachloride and chloroform. A relative paucity of data from carefully performed epidemiologic studies of exposed workers necessitates guarded conclusions, however. Case reports of diffuse liver disease, including hepatic necrosis and steatosis in workers exposed to trichloroethane and hepatic necrosis with fibrosis in solvent abusers heavily exposed to trichloroethylene, suggest that these chlorinated hydrocarbon solvents have hepatotoxic potential.

Few or no hepatotoxic effects have been observed in well-performed cross-sectional epidemiologic studies of subjects exposed to nonhalogenated solvents, including both aliphatics (kerosene, n-hexane, and others) and aromatics (xylene, toluene, styrene, and others). These studies have utilized conventional noninvasive laboratory methods, such as measurement of serum hepatocellular enzymes, including aspartate aminotransferase (AST) and alanine aminotransferase (ALT), to identify the potential hepatotoxic effects.

Outbreaks of liver disease in the occupational setting, such as the observation of liver disease due to dimethyl-formamide at a coated-fabric factory in the United States as well as in Taiwan and the case report of two workers with fulminant hepatic failure following exposure to 2-nitropropane, indicate that selected nonhalogenated hydrocarbon substances are capable of inducing acute and chronic liver disease in exposed populations. These outbreaks underscore the need to identify solvents that can induce hepatic disorders before they are made available for widespread use.

Carbon tetrachloride and chloroform are well-recognized hepatotoxins. Other chlorinated hydrocarbon solvents such as trichloroethylene and trichloroethane may also be hepatotoxic, although they appear to

be less potent. At this time the evidence for hepatotoxicity of these chlorinated hydrocarbon solvents in humans is limited to case studies of exposed workers and a few studies using relatively new methods of detecting hepatic effects. Evidence from high-quality epidemiologic studies incorporating appropriate comparison groups indicates that the commonly used nonhalogenated hydrocarbon solvents, including both aliphatic and aromatic compounds, have few, if any, measurable effects on conventional measures of hepatic injury (i.e., serum transaminase and bilirubin levels). Additional research is required to validate the newer methods that are being used to detect hepatic effects of solvent exposure.

Because of their ability to dissolve grease and fat, cutaneous exposure to solvents can deplete intact skin of lipids that are physiologically necessary for its functional integrity. This property of solvents results in an irritant contact dermatitis characterized by dryness, scaling, and fissuring of the skin, especially of the hands, in workers who have frequent dermal contact with solvents. This occurs either because the work requires manual handling of materials wet with solvents, as in the case of manual cleaning and degreasing, or in settings where solvents are used to wash the hands to remove glues, plastics, or other materials from the skin. These effects, which can be severe and require aggressive treatment with topical steroids, are reversible upon cessation of skin contact and are best prevented by avoiding direct skin contact with solvents.

Solvents can be irritating to all mucous membranes. This results in irritation of the eyes, nose, and respiratory tract for workers exposed unprotected to solvent vapor. Airways irritation resulting in both bronchial and tracheal irritation have been described among solvent-exposed groups.

The organic solvents benzene and the chloromethyl ethers, bischloromethyl ether (BCME) and technical-grade chloromethyl methyl ether (CMME), are well-established human carcinogens. Benzene is classified by the International Agency for Research on Cancer (IARC) as a group 1 carcinogen. It causes leukemia and other malignant hematopoietic disorders in humans. BCME is also classified by IARC as a group 1 carcinogen and is known to cause small cell carcinoma of the lung. It is used as an alkylating agent and solvent during the manufacture of polymers, ion-exchange resins, and waterproof coatings. Technical-grade CMME contains 1% to 7% BCME. Epidemiologic studies demonstrating excess small cell lung cancer in working populations exposed to BCME have come from the United States, the Federal Republic of Germany, and Japan.

The IARC has classified the solvent epichlorohydrin as "probably carcinogenic to humans" (group 2A), noting that the human evidence of car-

cinogenicity was inadequate at the time of evaluation but that evidence to declare it carcinogenic to animals was sufficient. Epichlorohydrin has been used in varnish, paint, and nail polish.

The halogenated hydrocarbons have been shown to be carcinogenic in animal systems; however, convincing human evidence is not available at this time. Reports of increased cancer of selected sites are available for many solvent-exposed cohorts: urologic malignancies and multiple myeloma in painters in New Zealand; esophageal and cervical cancers in dry cleaners; cancers of the lymphatic and hematopoietic system, colorectal cancer, and pancreatic cancer in commercial pressmen; lymphatic leukemia in rubber industry workers exposed to carbon tetrachloride and carbon disulfide; and primary liver cancer in solvent-exposed workers.

The goals of the clinical evaluation of solvent-exposed patients are to ascertain the presence of health effects attributable to solvent exposure, determine whether preexisting or underlying disease complicates the approach to the patient, and provide guidance on exposure reduction and periodic surveillance.

The evaluation of the symptomatic patient always begins with a review of presenting complaints. When a solvent-exposed worker presents for reasons other than current symptoms, such as periodic surveillance examination, a review of neurologic and dermatologic symptoms should be performed. Symptoms temporally related to exposure are a function of the anesthetic property of solvents. Specifically, dizziness, light-headedness, impaired concentration, and headache that have a temporal relationship to solvent exposure are likely the result of the acute CNS effects. In addition, unusual tiredness, sleep disturbance, appetite disturbance, mood changes, and other vegetative signs may also be related to solvent exposure, although in the absence of a close temporal association these very nonspecific symptoms may be difficult to attribute to solvent exposure in an individual case. Symptoms of dry, cracked, or itchy skin, especially of the hands, should be sought. In addition to symptoms of neurologic and dermatologic effects, symptoms of mucous membrane irritation manifesting as discomfort of the eyes, nose, and throat, should be elicited explicitly.

Review of past diagnoses or symptoms of neurologic, renal, hepatic, and dermatologic disease is required. The association between occupational solvent exposure and diagnosable conditions such as glomerulonephritis, contact dermatitis, cognitive impairment, and peripheral neuropathy may have been overlooked by other clinicians. In addition, the presence of such conditions, even if they are unrelated to current solvent exposure, may warrant more frequent medical surveillance or more aggres-

sive exposure reduction for individual patients. The use of alcohol or medications that can affect the target organ systems of solvents must be ascertained, especially in light of increasing research evidence that toxicologically important interactions between these agents and solvents may occur.

The occupational circumstances under which the solvent exposure occurred must be elicited from the patient. Clearly, this requires knowledge not only of the job title but of daily occupational activities and the setting in which solvent exposure occurs. Exposure from the activities of co-workers should not be overlooked. An assessment of ventilation should be made, if possible. Inquiries about enclosure of solvent-related processes, use of hoods or other specialized ventilation, and specialty equipment such as spray booths should be made. The specific constituents of the solvent-containing materials used must be ascertained. This may necessitate requests for material safety data sheets (MSDS) from employers, suppliers, or manufacturers. Use and type of personal protective devices should be determined, and an assessment of the effectiveness of the program evaluated, if possible. Specific inquiry about the extent of skin contact and measures taken to prevent its occurrence should be made. The occupational history should include a general assessment of the hygienic conditions of the occupational setting, including the availability of separate washing, changing, and eating facilities.

A complete physical examination, with emphasis on the skin and the nervous system, should be performed. The skin, especially of the hands, should be inspected for redness, drying, cracking, or fissuring. A mental status examination that includes evaluation of alertness, orientation, cognition, and short-term memory should be performed. Evaluation of peripheral nerve function by assessing proprioception, deep tendon reflexes, motor strength, postural stability (Romberg test), and cutaneous sensibility to vibration, light touch, and pin prick should always be included in the evaluation. Clinical assessment of liver size and tenderness should be performed as it can be done quickly, although the clinician must recognize that it is not very sensitive.

Routine laboratory evaluation should be guided, in part, by the known toxicity of the solvents. For example, liver function tests are more likely to be of value in patients exposed to halogenated hydrocarbon solvents than in those exposed to nonhalogenated solvents. The consumption of alcohol must be considered when interpreting liver function test results. Routine urinalysis and measures of renal function (blood urea nitrogen and serum creatinine) are also reasonable for inclusion in the laboratory evaluation of solvent-exposed workers, although, again, their utility is limited by modest test sensitivity for early renal changes. The choice of

additional tests must be guided by the clinical presentation of the patient. Those with complaints of persistent mood alteration or cognitive dysfunction, including memory loss, should be referred to a clinical neuropsychologist for evaluation, and a complete dementia workup should be considered. Those with persistent neuritic complaints, such as numbness, tingling, weakness, or pain, should be referred for neurologic consultation or electrophysiologic evaluation of peripheral nerve function (nerve conduction measurement and electromyography).

The health effects of exposure to organic solvents are nonspecific. Currently it is not known what proportion of neurologic, hepatic, renal, and dermatologic disease in exposed populations is attributable to solvents. Furthermore, the marked variety of exposures precludes sweeping generalization. Prior to making a diagnosis of solvent-related disease, other causes must be sought and their contribution to the current problem assessed. Organic brain syndrome secondary to solvent exposure is a diagnosis of exclusion. Substantial difficulties in estimating attribution of end-organ disease (e.g., peripheral neuropathy) due to solvent exposure occur when other disorders (e.g., diabetes) present at the same time could cause the same outcome.

Evaluation of the solvent-exposed worker provides an opportunity to address the exposure situation for the purpose of reducing exposures and preventing additional health effects for both the patient and co-workers. Unfortunately, access to the workplace may be limited, and often neither ambient nor biologic measures of exposure are available to allow quantification of the magnitude of exposure. In addition, patient confidentiality requirements may make workplace intervention difficult or impossible. Regardless, when the results of clinical evaluation suggest that biologically meaningful exposure is occurring, the clinician is obligated to explore avenues of exposure reduction within the confines of protection of patient confidentiality.

Much remains unknown about the rational approach to the solvent-exposed worker. Additional research is needed to clarify the clinical syndromes caused by solvent exposure, to provide guidance for treatment, and to attribute nonspecific outcomes to solvent exposure.

BENZENE

Benzene (C_6H_6) is the simplest and the prototypical aromatic hydrocarbon. It is a known cause of aplastic anemia, leukemia, and lymphoma. It is among the most widely used of all organic chemicals and has the highest production volume of all known human carcinogens. Historical-

ly, benzene was produced as a by-product of coal gasification and coke production. Today, however, it is produced principally by the petrochemical and petroleum-refining industries.

Benzene is a clear, colorless, noncorrosive, highly flammable liquid with a strong and rather pleasant odor. Its low boiling point and high vapor pressure cause rapid evaporation under ordinary atmospheric conditions; the resulting vapors are nearly three times heavier than air.

Human Exposure

Benzene is used as a solvent, a degreasing agent, and as a fundamental building block in many processes in the synthetic chemical industry. Occupational exposure occurs in the chemical, printing, rubber, paint, and petroleum industries. Particularly heavy exposure occurs in maintenance, clean-up, product sampling, and petroleum bulk transfer operations. Although benzene's use has recently declined in the United States and in other industrially developed nations, data from developing countries suggest that exposures there are widespread, especially in artisan work, shoe manufacture, small chemical industries, and work involving children.

Environmental exposure to benzene is extensive, because benzene is a constituent of both inhaled and environmental tobacco smoke. Also benzene constitutes 1% to 2% of unleaded gasoline by weight, exposure occurs during the pumping and handling of gasoline.

Occupational absorption of benzene occurs predominantly through inhalation of benzene vapor. Experimental studies indicate that approximately 50% of inhaled benzene is absorbed into the body and the remainder is exhaled. Ingested liquid benzene is rapidly absorbed through the gastrointestinal mucosa.

Benzene can also be absorbed through the skin. Dermal absorption is substantially enhanced when the skin is cracked, blistered, or abraded, as occurs in rubber workers engaged in tire building. It is estimated that a rubber worker who produces 150 tires a day using benzene-containing rubber solvent could absorb 6 mg of benzene through the skin; this compares with an estimated 14 mg absorbed by inhalation per 8-hr day in an atmosphere containing 1 mg/m^3 benzene vapor.

Metabolism and Mechanisms of Injury

Benzene is rapidly metabolized, principally in the liver. Its metabolic products are excreted, mainly as water-soluble metabolites in urine, within 48 hrs of absorption. The oxidative products of benzene include phenol, catechol, quinol, hydroxyquinol, and muconic acid.

Metabolism of benzene is required for toxicity. This metabolism occurs principally in the liver via the cytochrome P-450 and mixed-function oxidase systems. Production of benzene metabolites in the liver is followed by their transport to the bone marrow and other organs. Substantial evidence indicates that benzene per se is not myelotoxic, and that its toxicity is due to several of its metabolic products, particularly benzoquinone and muconaldehyde. These compounds have the ability to react with DNA to form adducts. Benzene metabolism is quantitatively different at different dose levels, and at low doses a relatively higher proportion of benzene is converted to hydroquinones and other more highly toxic metabolites than at higher doses; this finding suggests that linear extrapolation of risk from high-dose studies may underestimate the true risk of low-level benzene exposure.

Benzene itself is not mutagenic. However, various of its products are mutagenic in bacterial species. Presumably, these active products such as the quinones are involved in the causation of the chromosome damage, with increased numbers of strand breaks, hyperploidy, and deletions observed in humans and animal species exposed to benzene. It is hypothesized that these chromosomal aberrations induced by benzene may lead to inactivation of p53 or other tumor suppressor genes, and that these genomic events are involved in leukemogenesis. Recently, an association has been suggested between benzene exposure and deletion of the long arm of chromosome 5; this 5q-deletion is linked to myelodysplastic syndrome, a preleukemic condition, and the deletion is hypothesized to result in inactivation of a leukemia tumor suppressor gene, possibly the gene encoding pura, located at 5q31; the pura protein is involved in cell cycle control of DNA replication. The principal screening tool for clinical assessment of benzene toxicity is the complete blood count (CBC), including a platelet count and a white cell differential count as well as a red blood cell count, hemoglobin, hematocrit, and red blood cell indices. These hematologic indices do not appear to be sufficiently sensitive to detect toxic changes in workers whose exposures are within current exposure standards. However, at high levels of exposure, benzene is associated with significant decreases in white and red cell counts as well as in hemoglobin levels. Therefore, periodic hematologic testing of benzene workers may be useful to detect those who are exposed to higher-than-average ambient levels. Also, it is at least theoretically possible that periodic biologic monitoring of workers exposed to benzene may detect any who are unusually sensitive, although such sensitivity has not been well documented.

Chromosome aberrations have been seen in several studies of workers exposed to benzene, even at low levels. These changes consist of chro-

matid deletions and gaps as well as increased numbers of strand breaks and micronuclei. The utility of these cytogenetic abnormalities as quantitative screening tests for benzene exposure and toxicity is not yet established and will require prospective epidemiologic follow-up of exposed groups.

An important unmet need in benzene toxicology is for a stable biologic marker of exposure. There is need for a marker that better reflects cumulative exposure over time than the measurement of evanescent levels of benzene in exhaled breath or blood or the measurement of relatively rapidly excreted phenol in urine.

Exposure Monitoring

Occupational exposure to benzene is assessed principally through personal (breathing zone) air sampling. Measurement of the blood benzene level has traditionally been considered to be insensitive for occupational exposure monitoring; however, recent studies with new high-resolution gas chromatographic techniques suggest that blood sampling may be a useful indicator of current benzene exposure.

Timing is very important in the determination of the blood level of benzene because of the short half-life of the compound in blood. Measurement of benzene in exhaled breath is another sensitive means of assessing exposure. Approximately 50% of benzene is exhaled unmetabolized; this measurement also is very time dependent.

Urinary phenol determination is a good biologic marker of recent industrial benzene exposure. Recent studies in China and Japan indicate that there is a close quantitative relation between level of benzene vapor in workroom air and urine phenol level. By contrast, urinary markers are not useful as indicators of low-level benzene exposure in the general environment.

Toxicity

Immediate Effects

Central nervous system toxicity is the most important aspect of acute high-dose exposure to benzene. Like many solvents, benzene is readily soluble in lipids and rapidly crosses the blood-brain barrier to enter the central nervous system. Low-level neurologic exposure causes headache and nausea, whereas higher levels cause alteration of consciousness progressing to coma and respiratory arrest. Acute benzene exposure is toxic to the liver and kidneys; elevations in the serum creatinine level as well as in liver function enzymes and serum bilirubin can result. Benzene is

toxic to the skin. Direct contact may cause erythema and blistering. Long-term direct contact removes lipids from the skin tissue and may result in the development of a dry, scaly dermatitis. Benzene is poorly absorbed through intact skin but is readily absorbed through cracked, dry, or fissured skin. Immediate effects of ingestion of liquid benzene are local irritation of the mouth, throat, esophagus, and stomach. Subsequent absorption of ingested benzene into the blood leads to the signs and symptoms of systemic intoxication. High concentrations of benzene vapor are irritating to the mucous membranes of the eyes, nose, and respiratory tract.

Long-Term Effects

Aplastic anemia is the classic cause of death in chronic benzene poisoning, and the association between benzene exposure and bone marrow suppression has been recognized since 1897.

Leukemia in workers exposed occupationally to benzene was first recognized in the 1920s. Additional case reports and case series published from the 1920s to the 1960s repeatedly noted the association between leukemia and exposure to benzene. All types of leukemia are observed in reports of workers exposed to benzene. Myeloid and myelomonocytic leukemias are the cell types most commonly seen, but also acute and chronic lymphocytic leukemia are encountered. Additionally, benzene exposure has been linked in clinical and epidemiologic studies to lymphoma, including non-Hodgkin's lymphoma and multiple myeloma.

Initial analyses of mortality in this population were primarily qualitative, and they showed a significantly increased rate of deaths from leukemia in workers exposed to benzene as well as a particularly striking increase in leukemia mortality among workers employed for 5 or more years. Then, in the most recent study in this series, an extensive effort was made to examine quantitatively the dose-response relationship between benzene and leukemia.

Benzene-induced leukemia may develop in some cases in persons who previously have had aplastic anemia. In other cases, however, no preceding aplastic anemia is seen; thus aplastic anemia does not appear to be a necessary precursor to benzene-induced leukemia.

Prevention

The toxic effects of benzene are best prevented by replacing it with less toxic compounds and thus eliminating exposure. There are many solvents safer than benzene. If benzene cannot readily be replaced, for example in the synthetic chemical industry where it is used widely as a

basic chemical reagent, it is essential to provide safety of workers. The greatest risk of exposure in modern chemical factories is for maintenance and cleanup workers. Also there may be substantial risk to workers engaged in process sampling, laboratory analysis of process samples, and bulk transfer operations. Protective efforts should therefore be targeted at those specific job operations.

These early epidemiologic studies showed that occupational exposure to benzene was statistically associated with excess numbers of deaths from leukemia.

By merging industrial hygiene data with personnel records, cumulative benzene exposures (ppm-years) were calculated for each member of the work force. This approach provided a more directly quantitative index of exposure than analysis of length of employment and demonstrated a strong dose-response relationship.

TESTS

1. A man, born in 1948, was hospitalized to the urological department of regional hospital with profuse hematuria, which is accompanied with weak pain in the overpubic area. Anamnesis data: he has been working during 16 years at the dye-stuff production factory. Hystologically a tumor is revealed in the field of the anatomical triangle of the urinary bladder, its construction — pupillary cancer. After additional tests — metastases to regional lymph nodes. The most possible carcinogenic action of the following factors:

A. 3, 4-benzipren.
B. Benzidine, R-naftilamine.
C. Ionizing radiation.
D. Aflatoxin.
E. Retrovirus, contained RNA.

2. A 40-year-old man works at a varnish plant, was delivered to the hematological department of the region hospital with complaints of fatigue, bad headache, sickness, vomiting, weakness, imbalance, unconsciousness, depression, pain in the thorax. Under the objective study there were revealed: grey-blue colour of the skin integument and mucous membranes, blood is chocolate-brown, disorders of coordination, seasonly — a daydreaming. Narrowing of the visual field. Under the laboratory exam: anemia, poikilocytosis, anisocytosis, unconjugated bilirubine, leucocytosis with the left

shift. Increased viscosity of blood, increased amount of erythrocytes with basophilic granules.

Which poisonous substance do these data determine?

A. Carbon oxide.

B. TEL.

C. Nitrate of mercury.

D. Amino- and nitrobenzene.

E. Phosphorus.

3. A worker of the artificial resin production, 35 years old, was hospitalized with complaints of a whining pain in the right hypochondrium, weakness, fatigue, absence of the appetite, headache, sweating, pains in joints and muscles, sickness.

Objective: bilious-brown colouration of the skin of hands, cyanosis of the mucous membranes, painful liver at the palpation; blood test: hypochromic anemia, appearance of Heinz — Ehrlich's bodies till 3%.

What is the most possible reason of this condition?

A. Chronic intoxication by lead.

B. Chronic intoxication by nitro- and aminobenzene.

C. Chronic intoxication by metallic mercury.

D. Cancer of the liver.

E. Hepatic colic.

4. A workman of agriculture during a day inhered on the grape field, where took part in the work on the struggle with vermins of vineyards. At the end of a workday a man has felt a significant malaise, weakness, headache, feeling of fear in the eyes. Afterwards sickness, then — vomiting, hypersalivation, increased sweating joined. Then stomachache, diarrhea, pain in the field of the heart appeared. Skin integument is pale, the pupils of the eyes are dilated, spasm accomodation, weak pulsation. Pulse — 50 per min. There was observed a single fibrillar twitch of muscles of the face, bones.

Preliminary diagnosis:

A. Nitrofenolic pesticides intoxication.

B. Urea intoxication.

C. Arsenious intoxication.

D. Chlorine-organic compound intoxication.

E. Hydrargium-organic compound intoxication.

Chapter 7
INTOXICATION
BY CHEMICAL POISONS
IN AGRICULTURE

ACUTE AND CHRONIC INTOXICATIONS
WITH PESTICIDES

Pesticides are biocidal agents used to control a wide variety of organisms that pose a threat to health or compete for food or other materials. Selective toxicity is the principle of pesticide use, but because organisms are similar at the cellular or subcellular level, adverse human health effects may occur.

The earliest pesticides included metals such as arsenic, mercury, and lead. Other pesticides are inorganic chemicals, such as sulfur, and organic chemicals, such as nicotine derived from plants. After the discovery of dichlorodiphenyltrichloroethane (DDT) in 1939, the world has witnessed an unprecedented increase in the search for and production of synthetic organic pesticides. Production of inorganic pesticides such as arsenicals has steadily declined since the 1940s. The prolonged ecologic half-life and lack of species selectivity of DDT and other organochlorine pesticides was recognized in the 1960s. These pesticide characteristics and concern about the effects of accumulation of organo-chlorines in human adipose tissue caused the banning or severe restriction of most of these agents. In their place, newer synthetic pesticides, predominantly organophosphorus compounds, have been developed and are now widely used. These agents cause less environmental damage through accumulation but are more acutely toxic to humans and other animal species.

There are approximately 600 active pesticides ingredients, configured in more than 45,000 formulations in use today. More ominously, toxic organophosphates such as the nerve gas sarin have been used by terrorists to attack large numbers of people in cities in Japan.

Despite of temporary decrease of intensity of an agriculture, Ukraine is still a developed agrarian country. Ripe fine crops of grain, vegetables and fruit grow on our famous black earth. All this requires laborious work

and our hardworking people are ready to put the forces and soul in this ground to yield high crops, but it appears unsufficiently.

For saving a crop it is necessary to conduct struggle with the wreckers in agriculture. There are pesticides, used for this purpose, part of which represent threat to health of the man if one neglects rules of work with them.

This circumstance also causes actuality of the given theme. A future doctor should know a list of modern chemical poisons, which are applied in agriculture, mechanism of their pathogenic influence on an organism of a man, clinical pattern of acute and chronic poisoning, to be able to treat injured and train the agriculture workers in methods of prophylaxis of poisonings.

The development of a modern agriculture provides a wide use of fertilizers, agents of struggle with weeds, wreckers of cultural plants.

The pesticides or agricultural chemical poisons include agents of struggle with insects, originators of bacterial, fungic diseases of plants, with rodents, chemical drugs for destruction of weeds.

The pesticides are used for pollination and plants spraying, for dry and wet mordanting of seeds, for fumigation of ground, premises, sowing material. Airplaines, tractor, automobile, satchel and manual sprayers and pollinators are used for processing of plants. The mechanized methods of pollination or spraying, in particular air, reduce an opportunity of getting of chemical poisons on the skin, clothes and in organs of respiration of workers. The wide circle of the people working in agriculture, workers of depots, loaders, aviators, and also persons engaged in production of these toxicants are exposed to immediate influence of pesticides.

The influence of chemical poisons on the nature and people is one of the most actual problems of modernity.

Classification of Pesticides

1. Insecticides — for struggle with insects.
2. Fungicides — for treatment of plants for fungic diseases.
3. The insectofungicides — destroy both insects and originators of fungic diseases.
4. The defoliants — destroy leaves of weeds.
5. Herbicides — only for destruction of weeds.
6. Bactericides — destruction of bacteria.
7. Acaricides — destruction of mites.
8. Ovicides — destruction of eggs of insects and mites.

The following pesticides are used in agriculture: chlorine-organic, phosphorus-organic, hydrargyrum-organic, arsenous, nitrophenol, derivants of a carboline acid, drugs of copper and others.

Occupational Exposure

Humans are exposed to pesticides in a variety of occupational settings, including agriculture, structural pest control (e.g., buildings), public health pest eradication programs, manufacture and formulation, transportation industries such as railroads and trucking, the florist industry, and hazardous waste treatment and cleanup. Many commercial products such as paints, cotton, and wood products have fungicides added to prevent degeneration. Herbicides are used heavily in maintaining roads and highways in developed countries.

Assessing exposure to pesticides in an occupational setting is a complex task. A worker may be exposed unknowingly to clothing saturated with pesticides or by direct skin contact, but these amounts do not necessarily predict the actual dose, or amount absorbed into the body. Absorption may occur through inhalation, ingestion, or direct absorption on dermal surfaces. Detailed information on rates of absorption and knowledge of the pharmacokinetics of the compound in humans is often unavailable. Relating the absorbed dose to human health effects is often difficult or impossible. Work on biologic markers of pesticides may improve assessment of exposure and dose.

Accurate data do not exist on the incidence of acute illnesses secondary to pesticide poisoning, and even less is known about the chronic effects of pesticide exposure. While most acute pesticide-related illnesses and deaths in the past were caused by accidental agricultural exposure or attempted suicides, toxicologists and clinicians today must be alert to the illicit use of pesticides for criminal or militant activities. Health care providers must be able to recognize the immediate health effects of pesticides to establish diagnosis quickly and to begin treatment early. Worldwide estimates for pesticide poisoning suggest the problem of acute toxicity and death is much greater in developing countries than in developed ones.

Biomagnification of organochlorine compounds in the food chain lead to high residues, particularly in predaceous fish and birds. Elevated levels of DDT (and to a lesser degree, dieldrin) in several species of birds of prey lead to eggshell thinning and threatened species extinction. Because organochlorine compounds are not species-specific, large populations of animal species may be at risk of poisoning, which can lead to deleterious, long-term changes in the diversity of ecosystems in nature. Furthermore, pest species may develop increased tolerance or resistance to these specific pesticide compounds. Organochlorines have been largely replaced by organophosphates and carbamate compounds that rapidly hydrolyze

in soil and by plants. Although organophosphates and carbamates do not accumulate significantly in the environment, they remain extremely toxic if used indiscriminately.

Environmental exposures to pesticides in humans most often result from household or garden use. The World Health Organization (WHO) has estimated that more than 3 million cases of serious acute pesticide or insecticide poisoning occur worldwide annually, the majority being caused by organophosphates used for agriculture. There are an estimated 220,000 deaths annually from pesticides, and 99% of these are in developing countries. This grim total occurs despite the fact that only 20% to 25% of the global agrochemical use is in developing countries. The easy availability of pesticides in many developing countries makes them a common means of suicides.

Tolerance levels for pesticide residues in foods, the maximum residue levels allowed when pesticides are used according to the directions on the label, are set by the EPA. The levels are based on toxicologic studies that attempt to balance the risks and benefits associated with the use of pesticides on human foodstuffs.

Even though there is increasing public concern about pesticide residues in the food supply, residues detected in fresh and processed foods are generally low. Only a small percentage are found to have levels above tolerances, and most samples have no detectable residue. Results from these analyses indicate that in general the dietary intake of pesticide residues is within acceptable tolerance. When pesticides are used on crops for which their use is not approved or are applied in an unapproved manner, however, outbreaks of food-borne pesticide illness may occur.

Organophosphate Insecticides

Millions of pounds of organophosphate pesticides are used worldwide in commercial farming, gardening, structural pest management, and vector control programs. The development of these agents derive from the search for new chemical warfare or nerve gas agents in the 1930s. Although the organophosphate nerve agents such as sarin, tabun, and VX have not been used as insecticides, further research has shown that related, less potent compounds can be used successfully as insecticides. The worldwide use of these organophosphates compounds has increased over the last 20 years, owing to increased use in the Third World and because their use results in less severe environmental impacts than the organochlorine insecticides. Because the organophosphate insecticides are less

detrimental to the environment, they have largely replaced the organo-chlorine insecticides.

Examples of organophosphate insecticides include parathion, chlorfen-vinphos, diazinon, fenmion, diamethoate, monocrotophos, and malathion. These insecticides are commonly used in commercial farming, home gardening, pest control (e.g., flies), environmental control of vectors (e.g., mosquitoes), and the control of ectoparasites (e.g., fleas, lice). They may be combined with one or more other types of insecticides to potentiate their insecticidal action.

Organophosphate insecticides are efficiently absorbed by inhalation, ingestion, and skin penetration. Exposure by all three routes has been seen in occupational poisonings. The degree of toxicity varies considerably, depending on the route of exposure, and the exposure concentration and dose. Organophosphate insecticides vary in potency. For example, the median lethal dose (LD_{50}) for parathion in humans is estimated to be 3 mg/kg while that of malathion is 1,375 mg/kg.

The toxic manifestations of organophosphate insecticides result from the irreversible phosphorylation of the enzyme acetylcholinesterase (AchE) found at the nerve-nerve synapse or nerve-muscle motor end plate where anionic binding of acetylcholine normally occur. The loss of function of this enzyme allows flooding of the postsynaptic receptors with acetyl-choline, leading to a cholinergic crisis in severe cases.

Acute Signs and Symptoms

Patients acutely intoxicated with organophosphates often present with a set of signs and symptoms. Recognition of these "toxidromes" helps the astute clinician establish the chemical class of the toxicant quickly and allow vital treatment to begin early. All too often, the clinician has only a history of exposure or a toxidrome to suggest organophosphate insecticide poisoning. The dramatic accounts of the Matsumoto sarin attack in 1994 and the notorious Tokyo subway sarin attack in 1995 should serve as valuable lessons to emergency room and hospital staff and prompt simulated disaster drills to prepare health care providers.

The organophosphate insecticide toxidrome can develop during the chemical exposure or be delayed some 4 to 12 hrs after exposure. The key aspects of this toxidrome can be divided into muscarinic, nicotinic, and central nervous system overstimulation.

Muscarinic overstimulation leads to hyperactivity of the parasympathetic system, including miosis, bradycardia, and hypersecretion of salivary, lacrimal, digestive, and bronchial glands. Accumulation of acetyl-

choline at the nicotinic synapses leads to blockade of nerve impulses in the central nervous system, at the autonomic ganglia, and at the skeletal muscle-nerve junction. The latter effects lead to motor end plate dysfunction.

Nicotinic effects include muscle fasciculations that can be mistaken for seizure, cramps, and generalized muscle weakness. Depression of respiratory drive, delirium, loss of consciousness, and seizures are complications of central nervous system toxicity. The mnemonic DUMBELS (diarrhea, urination, miosis, bronchospasm, emesis, lacrimation, salivation) describes the signs of cholinergic (muscarinic) excess seen with organophosphate poisoning. A garlic odor may also be noted from the exposed patient or from the container of the pesticide. Recent data have suggested visual changes, pancreatitis, and psychiatric findings are seen with acute organophosphate poisoning more commonly than previously recognized.

Establishing a diagnosis from acute or chronic low-dose exposure is particularly difficult in children. The typical muscarinic and nicotinic signs and symptoms of an acute organophosphate poisoning are often absent. Patients may present with neurobehavorial changes, hypertonicity, and even acute psychosis. To establish a preliminary diagnosis, clinicians should be aware that reliable reference laboratories are capable of detecting alkylphosphate metabolites of organophosphates in urine, but the time necessary for this assay may limit its clinical usefulness.

Certain organophosphate insecticides have been associated with delayed and intermediate neurotoxicity syndromes. Characteristic manifestations include weakness, paralysis, and paresthesias in the distal lower extremities for the delayed syndrome, and weakness of proximal limb muscles and muscles of respiration, and cranial nerve paralysis in the intermediate syndrome. Development of the delayed neuropathy is not associated with inhibition of neural or neuromuscular cholinesterases, as is the acute toxicity. It has been correlated with initial phosphorylation or inhibition of the neurotoxic esterase enzyme (NTE). Symptoms usually occur within 2 to 3 weeks, with a denervation electromyographic pattern and a progressively irreversible to slowly reversible course over 6 to 12 months. The intermediate syndrome associated with organophosphate neurotoxicity was recently described in 10 patients.

The time of onset was between 1 and 4 days after significant organophosphate insecticide poisoning, with proximal limb, neck, cranial, and respiratory muscle involvement. The electromyogram (EMG) findings were described as tetanic fade. Recovery took between 4 and 18 days; seven often patients had respiratory difficulty and four often required mechanical ventilation. Most commonly, both delayed and intermediate neu-

rotoxicity have been seen in survivors of massive organophosphate insecticide poisonings coming from the Third World countries. Prolonged effects of muscle blocker agents have been reported in patients poisoned by organophosphate pesticides. Persistence of organophosphates measured in blood and in tissues at autopsy in humans has been demonstrated particularly for the most lipid soluble agents such as penthion and methidathion. The intermediate syndrome may represent delayed organophosphate absorption or prolonged tissue half-life.

Laboratory Findings

Confirmatory laboratory tests include measurements of plasma and red blood cell (RBC) cholinesterase activities, which provide a measure of the inhibition of two types of cholinesterase enzymes *in vivo.* However, these studies may be available in a limited number of diagnostic laboratories in addition to regional poison control centers. At least six different methods are available for measuring RBC and plasma cholinesterase levels. Consequently, interlaboratory variability may be great and this variability may complicate the interpretation of results.

Plasma cholinesterase (pseudocholinesterase) is produced by the liver. It is a phase-reactant enzyme with baseline fluctuations due to many variables. Falsely lowered activity may be due to chronic or acute liver disease, chronic alcoholism, pregnancy, malnutrition, dermatomyositis, or concomitant poisoning with carbon disulfide and organic mercury compounds. Plasma cholinesterase levels decline and return faster than RBC or "true" cholinesterase levels. The 3% of the population who are genetically deficient in this enzyme are particularly vulnerable to the neuromuscular blocker succinylcholine and may be hypersensitive to organophosphate insecticides. Regeneration of activity is normally related to synthesis by the liver of new enzymes and may take 7 to 60 days to return to levels found prior to organophosphate insecticide exposure. RBC cholinesterase activity regenerates even more slowly because new RBCs must be released from the bone marrow to replace those with inactivated cholinesterase enzyme. This slow rate of renewal (0.5% to 1% per day) can take 60 to 90 days for RBC cholinesterase levels to return to nearly baseline values.

Red blood cell cholinesterase is the preferred measurement for documenting exposure and monitoring when exposed workers can return to handling organophosphate insecticides. Generally, RBC cholinesterase levels should be greater than 75% of baseline before workers are allowed to return.

Sensitive blood and urine screens for the parent organophosphate insecticide compounds and excreted metabolites exist but they are not routinely available and often require detailed knowledge of the specific parent compound.

Symptoms of organophosphate insecticide toxicity are not usually seen until 50% of baseline cholinesterase activity is inhibited, although this is not a reliable threshold. The large variability in normal cholinesterase level also makes its interpretation difficult. Cases of poisoning and even deaths have been reported with depressions of less than 50%. Cholinesterase level is useful in clinical evaluation, but it must be done in association with a careful history and physical examination. Because baseline plasma cholinesterase levels are not usually available for an individual patient, serial determinations are useful in acute exposures. No clearly reliable association has been established between the magnitude of serum cholinesterase decrease and the severity of poisoning; it is simply a marker of organophosphate intoxication or poisoning. Nevertheless, most authorities consider mild exposure with minimal signs and symptoms to be associated with plasma cholinesterase levels 20% to 50% of baseline. Moderate exposure, usually resulting in muscle fasiculations and miosis, is associated with plasma cholinesterase levels of 10% to 20% of baseline. Severe poisoning with life-threatening symptoms is associated with plasma cholinesterase levels of 0% to 10% of baseline. Some authors reported that prolonged severe depression of plasma cholinesterase has been associated with poor clinical outcomes after organophosphate poisoning.

However, survival has been reported with extremely low plasma cholinesterase levels, leading some investigators to suggest that serum cholinesterase levels have no prognostic value in acute organophosphate poisoning. Identifying high-risk patients based on this enzyme measurement alone is not always reliable.

Leukocytosis with a leftward shift toward polymorphic neutrophils, hyperglycemia, ketoacidosis, glycosuria, albuminuria, and acetonuria have been reported with organophosphate poisoning, but these findings are not specific or sensitive enough for diagnostic purposes. Hyperamylasemia and other evidence of acute pancreatitis, such as computed tomographic imaging of the pancreas, have been reported following organophosphate poisoning. Recognition and appropriate therapy of acute pancreatitis when evident may lead to a better prognosis.

Large, short-term doses of organophosphates insecticides have resulted in prominent electroencephalographic (EEG) changes and convulsions in humans and other primates. Studies have shown long-term (1 to 6 years) spectral shifts in beta voltage in sarin-exposed primates or accidentally

exposed workers with serial EEG determinations. The usefulness, both in terms of specificity and sensitivity, of these EEG findings in the diagnosis of organophosphate poisoning has not been established. Cardiac toxicity can manifest as intraventricular conduction abnormalities, atrial dysrhythmias, and repetitive ventricular tachycardia such as torsades de pointes.

Treatment

The decision to treat a possible organophosphate poisoning is often based only on the history and physical examination findings. Initial management is directed at protecting and maintaining an open airway with respiratory support, including airway suctioning, endotracheal intubation, and mechanical ventilation with supplemental oxygen. Because organophosphates insecticides can easily cross the skin barrier, they pose a particularly insidious threat of secondary contamination to unprotected health care providers and emergency department personnel. Patients who arrive at an emergency department without having had appropriate decontamination should be decontaminated with large amounts of soap and water. Removing clothing potentially saturated with organophosphates is particularly important for both patient and health care provider. Clothing and other contaminated materials must be discarded as highly contaminated waste. Even waste water from field or hospital decontamination must be handled carefully. Gastric decontamination with lavage followed by repeated doses of activated charcoal is indicated for enteric exposure and can reduce total and continued organophosphate exposure. Hemoperfusion removes only minimal amounts of the organophosphate insecticides.

For acutely ill patients, atropine sulfate in doses sufficient to reverse cholinergic (muscarinic) signs and symptoms is the primary pharmacologic treatment. A specific dose limit or an arbitrary dose goal is not practical. Careful titration with atropine while monitoring reversal of excessive parasympathetic stimulation is the standard of care. Initial doses of 0.4 to 2.0 mg atropine intravenously (IV) are given every 15 minutes until evidence of "atropinization" or muscarinic blockade, such as flushing, dry mouth, dilated pupils, and tachycardia, is seen. Repeated doses or continuous infusion of atropine to maintain partial muscarinic blockade is needed. Evidence of cholinergic excess, including miosis, nausea, bradycardia, is used to govern atropine doses for several hours to days, depending on the severity of the organophosphate poisoning. Caution must be exercised when treating children with large doses of pre-mixed atropine sulfate because large amounts of preservatives (e.g., alcohols) used to in-

crease the shelf life of the drug can be toxic. Consultation with a pharmacist should allow formulation of a high-dose atropine sulfate solution that is preservative-free. Other anticholinergic agents such as glycopyrrolate have been shown to be as effective as atropine in the treatment of organophosphate poisoning.

N-Methyl Carbamates Insecticides

The carbamates, like the organophosphates, are used in commercial farming, home gardening, and control of domestic animal ectoparasites. Aldicarb, oxamyl, and methomyl are highly toxic carbamate insecticides; dioxacarb, carbaryl, and isoprocarb are less toxic. The carbamate insecticides are often used in combination with an organophosphate or pyrethroid insecticide.

Carbamate insecticides are readily absorbed by inhalation or ingestion through the skin. The N-methyl carbamate esters cause reversible inhibition of acetylcholinesterase. As in the case of organophosphates, postsynaptic cholinergic receptors are flooded with acetylcholine, resulting in a characteristic toxidrome. Unlike the phosphorylated enzyme, the carbamylated acetylcholinesterase enzyme can undergo spontaneous hydrolysis *in vivo,* which reactivates the enzyme. Less severe toxidromes of shorter duration can be expected from carbamate poisoning because of this hydrolysis.

Acute Signs and Symptoms

The diagnosis of carbamate poisoning is generally made by history and clinical presentation of the patient. The clinical toxidrome of carbamate poisoning is similar to that of organophosphates. Symptoms typically develop within 15 min to 2 hrs after exposure and usually last less than 24 hrs. Central nervous system toxicity is less predominant because the carbamates do not penetrate the blood-brain barrier well. However, carbamate poisoning in children was recently found to have a greater depressant effect on the central nervous system when compared to organophosphates. The cause of death is often acute respiratory failure from respiratory muscle fatigue, pulmonary edema, bronchorrhea, and bronchospasm. Central nervous system depression, seizures, and ventricular arrhythmias also increase morbidity and mortality. Carbamate insecticide poisoning has been responsible for causing trauma-related deaths and injuries. When dealing with farm injuries, the clinician must consider the possibility of occult pesticide poisoning.

Laboratory Findings

Plasma and RBC cholinesterase enzyme measurements are less useful in cases of carbamate poisoning. Symptomatic patients whose blood samples are drawn within a few hours of exposure and absorption can exhibit depressed cholinesterase levels if the enzyme measurement is done rapidly. Enzyme reactivation can occur *in vitro* as well as *in vivo,* causing a rise in the enzyme activity before measurement, which makes clinical interpretation extremely difficult. Urine and blood analyses for parent compounds and metabolites have been described but are not often available. A radioimmunoassay has been described for carbamate insecticides that may resolve these problems if the assay becomes commercially available.

Treatment

Symptomatic treatment of the patient poisoned by carbamate insecticide includes aggressive respiratory support and atropine to reverse severe muscarinic manifestations. Because of the shorter duration of effect from *in vivo* hydrolysis, atropine treatment is usually required for less than 24 hours. The most important difference in treatment for carbamate and organophosphate poisoning involves 2-PAM. The use of 2-PAM is relatively contraindicated in carbamate poisoning because it may enhance acetylcholinesterase inactivation. After mixed or combined exposures involving both organophosphates and carbamate insecticides or in severe poisonings with an unidentified anticholinesterase agent, it is reasonable to administer 2-PAM cautiously.

Organochlorine Insecticides

Most of the organochlorine pesticides have been banned in the United States, principally because of their long ecologic half-lives. Organochlorine insecticides can be classified by chemical structure.

Lindane (γ-hexachlorocyclohexane), currently the most commonly encountered organochlorine insecticide, will be used as the prototype compound for discussing acute toxicity. It is available as a garden spray, structural and environmental pest control product, and as a scabicide (Kwell). The mechanism of toxicity is related to the ability of the organochlorine to alter ion fluxes, principally in nerve tissue. Although its use is decreasing, it continues to be a source of human poisoning. Evidence suggests that lindane produces antagonism of λ-aminobutyric acid-mediated inhibition in the central nervous system.

Organochlorine insecticides are easily absorbed through the lungs, gastrointestinal tract, and skin. As much as 10% of a topical dose of lin-

dane is systemically absorbed. Because of the relatively large surface area-to-body weight ratio of infants, lindane poisoning has been reported to result from repeated therapeutic doses of lindane scabicide shampoo. The organochlorine insecticides are metabolized slowly and are excreted principally in the feces. Lindane accumulates in organs, including fat and tissue, but to a lesser extent than many of the other organochlorine insecticide. Lindane excretion takes several days, whereas most other organochlorine insecticides have much longer elimination half-lives. Lindane is partially dechlorinated and oxidized, yielding a series of conjugated chlorophenols and other oxidation products in the urine. Many of the organochlorine insecticides, including lindane and mirex, are capable of inducing liver microsomal enzymes, e.g., cytochrome P-450-dependent monooxygenase system.

Immediate Signs and Symptoms

The neural excitation caused by the organochlorine insecticides leads to their primary toxic manifestations. The toxidrome includes disturbances of sensation, coordination, and mental status. Anorexia, malaise, headaches, myoclonic jerking, lethargy, tremor, hyperreflexia, motor hyperexcitability, oral paresthesia after ingestion, and convulsions of organochlorine pesticides have been associated with increased myocardial irritability and cardiac arrhythmias. Lindane has been rarely associated with aplastic anemia, agranulocytosis, disseminated intravascular coagulation, and proximal myopathy with myoglobinuria. A singular case of self-poisoning with 1.0 ml of intravenous thiodan resulted in refractory grand mal seizures, increased liver enzyme levels, and acute rhabdomyolysis leading to proximal myopathy and acute renal failure. Motor seizures were controlled with IV midazolam and thiopentone. Both liver and renal dysfunction resolved with supportive ICU care. Hemodialysis was not required. The patient experienced a full recovery.

Laboratory Findings

Blood, tissue, and urine determinations of organochlorine pesticides and their metabolites are available from a limited number of laboratories. These levels are rarely useful in the clinical management of acute poisoning. The relatively rapid metabolism of lindane compared to many of the other organochlorine insecticides reduces the likelihood that the parent compound or metabolites will be detected in body fat, blood, urine, or human milk. Other organochlorine pesticides and their metabolites, such as DDT, dieldrin, mirex, and chlordecone, can remain in blood and tissue

(particularly fat) for weeks or months. Persons exposed to lindane long-term at work have had fat-to-serum concentration ratios of 220:1. Workers exposed to lindane had whole blood lindane levels of 0.02 to 0.45 mg/m^3. Symptoms are unlikely in patients with whole blood lindane levels as high as 20 to 30 mg/m^3. EEG abnormalities have been noted after brief or long-term organochlorine exposure.

Treatment

Gastrointestinal decontamination with activated charcoal should be used for acute oral poisoning with organochlorine pesticides. For any exposure, skin decontamination and removal of contaminated clothing is essential. Treatment of convulsions may require ventilatory support and anticonvulsants such as diazepam, phenobarbital, or phenytoin. The organic solvents used to dispense organochlorine insecticides may result in aspiration pneumonitis and even acute respiratory failure. Because of the very long half-life of some organochlorine insecticides, e.g., chlordecone, the resin cholestyramine (3 to 8 g four times daily) has been shown to disrupt enterohepatic recirculation and significantly reduce the total body half-life of these insecticides. Cholestyramine has been advocated in the treatment of lindane poisoning. Repeated doses of activated charcoal over days to weeks may have the same effect, but this approach remains unproven, specifically with organochlorine insecticides.

LONG-TERM HEALTH EFFECTS OR POISONINGS WITH PESTICIDES _____

Most acute effects of pesticide toxicity are well characterized, and the mechanisms of their pathogenesis have been established in many cases. Studies on long-term effects, which develop or persist long after the exposures that may have precipitated them, typically are less consistent in their findings and often raise more questions than they answer. The ability of pesticides to cause cancer, neurotoxicity, and adverse reproductive effects has been demonstrated in laboratory animals, but unambiguous clinical or epidemiologic evidence of effects in humans exists for only a few specific agents. For most pesticides, clinical or epidemiologic data are lacking on long-term health effects or the data do not yet support clear evidence of causality.

Epidemiologic studies have focused principally on pesticide formulators and applicators as representing heavily exposed populations. Several

population-based investigations have studied both cancer and reproductive outcomes, although most of these have been limited by ecologic methodology or poor estimates of pesticide exposure. In the remainder of this chapter we focus on epidemiologic studies, including pertinent laboratory and clinical results to clarify the effects of the various pesticides on health outcomes.

Issues of causation, particularly from long-term exposures, ideally require a combination of laboratory, clinical, and epidemiologic data. Laboratory studies may address the important question of biologic plausibility of associations observed in epidemiologic studies. The ability to assess exposure quantitatively through biomarkers will greatly improve the sensitivity and specificity of epidemiologic studies. Recognition of subcellular initial lesions that contribute to eventual development of degenerative diseases also will open new avenues to epidemiology. Until such studies are completed, prudent avoidance or minimization of exposure to all xenobiotics is the safest course.

Cancer

While farmers mortality rates are lower than the general population's for all causes combined and for smoking-related cancers, numerous studies of farmers have demonstrated above average death rates from particular cancers, most not related to smoking. These studies, from several regions in the United States as well as countries in Europe, have most commonly observed increases in leukemia, non-Hodgkin's lymphoma (NHL), and multiple myeloma. Fewer studies have observed increases in Hodgkin's lymphoma and cancers of the brain, stomach, prostate, skin, and connective tissue. While some of these studies have linked cancer rates to pesticide use or other agricultural practices, all of the studies have serious problems of exposure misclassification. In addition, most farmers and farm workers are exposed to numerous pesticides and other potentially harmul substances, further complicating the conclusions from epidemiologic studies. The observed associations should be regarded provisionally and sceptically. Despite these difficulties, hematopoietic and lymphatic cancers consistently have been associated with farming, and in some cases have been associated with geographic areas of higher pesticide use or with specific agricultural activities, such as corn production, associated with heavy pesticide use. More recently epidemiologic studies have estimated exposure to specific pesticides (e.g., phenoxyl herbicides) and evaluated their association with specific cancers (e.g., NHL).

A major epidemiologic approach to the question of pesticides and cancer has been to study occupational cohorts exposed to pesticides. Such

studies have included pesticide manufacturers, structural pest control applicators, and agricultural applicators. These studies lack exact measurements of pesticide exposure in individuals, and multiple pesticide exposures often occur, especially among applicators. They do, however, target populations that experience relatively frequent, intense, and prolonged exposures. Some show small increases in mortality due to cancer at various sites, although not always increasing with increasing exposure. An increase in lung cancer mortality among arsenical manufacturers is consistent with other epidemiologic data on the carcinogenicity of occupational arsenic exposure. No excess risk, however, could be detected for former users of lead arsenate (long since discontinued). Small increases in lung cancer mortality have also been observed among chlordane and other organochlorine manufacturers and among structural and agricultural applicators. Studies of these occupationally exposed cohorts generally have not shown increases in lymphatic or hematopoietic cancer mortality rates.

Recent indications that chlorinated pesticides and their contaminants may interact with hormone receptors (see Female Reproductive Effects, below) have led to speculation about a possible role in the development of cancer of the breast. This work was catalyzed by a case-control study showing increased DDE (a metabolite of DDT) in the sera of patients with breast cancer compared to controls. However, a larger nested case-control study conducted within a prospective cohort found no evidence of an association. The evidence remains contradictory and does not support a causal association.

In summary, there is consistent epidemiologic evidence for a small association of lung cancer with exposure to pesticides no longer used in developed countries. This association is established for arsenicals and is suggestive for the chlorinated hydrocarbons. Large prospective cohort studies now in progress are attempting to reduce the uncertainty now prevalent.

Neurotoxicity

In most cases of acute neurotoxicity from pesticides, recovery is complete unless convulsions or other acute injuries occur. However, there is evidence that long-term pesticide exposure may result in some chronic neurologic effects. DDT and the other organochlorines are stored in fat tissue, so cumulative exposure may occur. With DDT, symptoms of chronic and of acute toxicity are similar — anorexia, weakness, anxiety, and hyperexcitability. Persistent neurologic sequelae are most likely to follow acute organochlorine toxicity that is associated with convulsions. Polyneuropathy has been associated with chronic exposure to some organochlorine pesticides. Follow-up of adults and children years after chlordane

was sprayed around the apartment complex in which they lived indicated impairment of balance, reaction time, and immediate recall, among other test results.

The acute neurotoxic effects of the organophosphate and carbamate insecticides, and the recently recognized intermediate syndrome, have been discussed above. A delayed neuropathy has been observed in humans days to weeks following acute organophosphate insecticide exposure. The syndrome is manifest by involvement of the longest nerve fibers, and presents with progressive weakness, ataxia, and paralysis. Pathogenesis of this irreversible syndrome appears to involve inhibition of the neurotoxic esterase enzyme (NTE) rather than of neural acetylcholinesterase, although inhibition of acetylcholinesterase has been an inevitable concomitant. One study of neurologic sequelae following organophosphate poisoning found impaired visual attention and vibrotactile sensitivity among cases compared to controls. While this finding is provocative, it needs to be replicated with more complete follow-up and better estimates of exposure.

The possibility that pesticide exposure may contribute to development of Parkinson's disease has been suggested following observations that such exposure is more common among Parkinson's patients than among unaffected people from the same region. A similar suggestion with respect to Guillain — Barré syndrome has been reported only in the Chinese, in an English abstract. Both of these observed associations require further confirmation before they can be accepted as causal.

Studies of neuropsychologic effects in humans following acute organophosphate insecticide poisoning have indicated a fairly consistent constellation of subjective disturbance and subclinical deficits. Persistent symptoms following acute toxicity include headache, dizziness, nausea, visual disturbances, weakness, confusion, agitation, and insomnia. The most consistent of positive measurable results has been elevation of the threshold for vibratory sensation. These symptoms may last weeks to months following cessation of exposure, persisting long after resolution of cholinergic signs. Cholinesterase depression is only variably associated with these persistent symptoms.

A variety of neurobehavioral symptoms has been associated with chronic low-dose exposure to organophosphate insecticides, but careful, rigorous studies are generally lacking; some studies have failed to observe these effects. Symptoms observed among workers exposed long-term to organophosphate insecticides include fatigue, memory deficits, nervousness, malaise, vision disturbances, and loss of concentration. There is supportive evidence from animal studies for chronic neurologic effects of organophosphate insecticide exposure, but more carefully controlled studies are necessary in humans.

122

Reproductive Toxicity and Male Reproduction

Chlordecone (Kepone) was an insecticide and fungicide produced from 1958 to 1975, when production was stopped because of toxicity in production workers. In animal studies chlordecone causes testicular atrophy. Among the production workers in the Virginia Allied Chemical and Dye Corporation plant, chlordecone caused oligospermia and reduced sperm motility in several men, as well as neurotoxicity and several other clinical effects.

The study of infertility among men exposed to pesticides and other occupational agents is hindered by ignorance of the fundamental determinants and modifiers of spermatogenesis, the large individual and intraperson variability in semen parameters, and difficulty in conducting controlled epidemiologic investigations. Difficulties in obtaining accurate estimates of pesticide exposures further hamper studies of their potential adverse reproductive effects.

The possibility that environmental exposures including pesticides may adversely impact sexual development of the male fetus has been discussed seriously since publication of a study reporting decreasing semen quality over a 50-year period. Data for the earlier 30 years of the study period were sparse, and evaluation criteria may not have been comparable. Confirmatory and contradictory studies, including relatively strong evidence from observations of wildlife in contaminated areas, have been reviewed without reaching a firm conclusion. An important source of resistance to the idea of environmental hormone disruption has been the low potency of the implicated xenobiotics. An *in vitro* study on yeast genetically altered to express a human estrogen receptor suggests synergistic effects of combined exposures. The area of endocrine disruptors is one of current intensive research.

Female Reproductive Effects

Few human studies directly address the effect of pesticides on female reproductive outcomes. Most of the epidemiologic studies have been descriptive or ecologic and do not provide direct support for causal associations with potential pesticide exposure. Furthermore, studies that have evaluated associations between birth defects and agricultural activity or pesticide use have generally been ecologic analyses and have been inconsistent in their results. They thus have done little more than raise concern about the effects of pesticides on female reproduction.

Organochlorines, including DDT, have been implicated in a variety of adverse reproductive outcomes. The mechanism is generally thought to be interaction with estrogen receptors, either directly or indirectly by metabolism to estrogen agonists. Abnormal menses and impaired fertility have been suggested effects of the organochlorines. Epidemiologic evidence has also suggested, but not definitely implicated, DDT exposure in premature delivery and spontaneous abortion.

One study of a small but intense outbreak of congenital abnormalities provides persuasive evidence linking the event to consumption of fish treated for parasites with extraordinarily high doses of the organophosphates. Two case reports of malformations associated with prenatal exposure to organophosphates are anecdotal only, lacking any estimate of exposure magnitude.

TESTS

1. A patient C., 34 y. o., complains of laboured breathing. The mucous membrane of the nasopharynx is dry, tongue is white covered, the abdomen is inflated, at palpation some resistance in the epigastrium is defined, dry rhonchi at auscultation are revealed. Blood analysis: leukocytosis, increased ESR. He worked near aggregate of the enrichment by ammonium hydroxide, used an oxygen breathing apparatus irregularly. It is possible to suspect in this case:

A. An alimentary toxicoinfection.
B. Poisoning by POS.
C. Intoxication by lead.
D. Acute intoxication by ammonium hydroxide.
E. Intoxication by pesticides.

2. A patient C., 38 y. o., a horse breeder at the farm is delivered to CDH with the complaints of a sharp weakness, headache, nausea, vomiting, abdominal pain. It was fixed that 2 hrs before he was engaged in weeding of the field processed by methylmercaptophos. Objective: narrowing of the pupils, hyperhydrosis of the skin, miosis, bronchorrhea, bradycardia, fibrillation of some muscles.

Preliminary diagnosis:

A. Acute intoxication by POC, a mild degree.
B. Acute intoxications by POC, a moderate degree.
C. Acute intoxication by POC, a severe degree.
D. Chronic intoxication by POC, a moderate degree.

3. A patient H. works at the chemical industry on production of a phosphoric acid, complains of ostealgia.

What bones suffer most of all at chronic intoxication by phosphorus?

A. Bones of the backbone.

B. Bones of the arms.

C. Bones of the legs.

D. Pelvic bones.

E. Bones of the jaws.

4. A worker of the farm H. has applied for medical help because of an acute poisoning by POC after processing sowings on the field. What term should the cases of acute professional poisonings be investigated at?

A. 1 day.

B. A week.

C. 3 days.

D. 1 month.

E. 6 months.

Chapter 8
OCCUPATIONAL EXPOSURE
TO VIBRATION ⎯⎯⎯⎯⎯⎯⎯⎯

Probably since earliest time, when humans first took to the sea, the debilitating and incapacitating effects of vibrating motion have been known. With the beginning of the Industrial Revolution came vibrating hand tools and automated machinery. Raynaud's phenomenon first appeared in 1911 to 1918 in some workers who used vibrating hand tools. Post-World War II, with the introduction of modern aircraft, ships, vehicles, etc., emerged a myriad of studies to determine how vibration affects the ability of human beings to function and perform work. It is now apparent that occupational vibration affects the worker's health and the ability to work safely. Approximately 8 mln workers in the United States are exposed to occupational vibration. Of these, 6.8 mln are principally associated with vehicular operation (e.g., truck and bus driving, farming, construction) there vibration impinges on the entire body. The remaining 1.2 mln workers are users of gasoline powered tools (e.g., chain saws, brush cutters, etc.), and users of pneumatic and electrical hand tools. Vibration impinges locally and principally on the upper limbs when using the aforementioned tools. The former vibration is referred to as whole-body vibration (WBV), and is usually transmitted to the entire human body through some supporting structure, such as a vehicle seat or a building floor; the latter vibration is referred to as segmental or hand-arm vibration (HAV) and usually is applied locally to specific body parts, for example the hands, by a vibrating tool the generic term vibration refers to back-and-forth, up and down, side to side linear motion that emanates from and returns to some defined reference position. Rotational motion (pitch, yaw, and roll) also occurs, but is rarely measured in occupational situations. Although WBV and HAV are usually distinct, some workers may be exposed to both types of vibration, depending on the job. For example, a worker

using a pneumatic jackhammer or road ripper tool with outstretched arms receives principally HAV whereas if the worker operates the tool so that it is placed in contact with the abdomen, the vibration reverts to WBV.

A person who works at the same job with vibration exposure for 20 hrs per week, 50 weeks per year, for 30 years, that person can receive up to 30,000 hrs of cumulative vibration exposure. Thus it is imperative to monitor and minimize both the acute and chronic effects of the vibration exposure on workers.

TERMINOLOGY _____

To understand vibration's effects on humans it is important to be familiar with some terms. Vibration frequency, pronounced in Hertz (Hz), describes the cyclic nature of vibration. For WBV the 1-Hz to 80-Hz band (range) is of interest; for HAV the band is from 5 to 5,000 Hz. In the occupational setting, usually more than one vibration frequency is simultaneously present, thus constituting a "vibration spectrum" that must be analyzed. Vibration motion per second is characterized as a "vector quantity," which consists of both a direction and a magnitude. Three mutually perpendicular (linear) vectors at each vibrating point are usually measured. Each vector magnitude can be pronounced either as (a) vibration displacement, which refers to the distance traversed between the normal resting position of an object and its position at a given time in its vibratory cycle (in units of inches, feet, centimeters, millimeters, etc.); (b) velocity (speed) of a moving object, which refers to the time rate of change of displacement (in units of feet per second, meters per second, etc.); or (c) a moving object's speed, which usually changes over time; this time rate of change of speed or velocity is acceleration and is pronounced in gravitational units *(g),* or in meters per second per second (1g = 9.81 m/sec/sec). Acceleration has been the most frequently used measure of vibration intensity or magnitude, owing in part to its ease of measurement, and from this one parameter both vibration velocity and displacement can be mathematically derived. Resonance refers to the optimum condition of maximum transfer (or coupling) of vibration energy from the vibrating source to the receiver (e.g., the human body) accompanied by an actual amplification of the incoming vibration by the human body per se; thus in a resonant situation the body uncontrollably acts in concert with the incoming vibration, exacerbating the effects.

CLASSIFICATION
OF VIBRATION DISEASE _____

Whole-Body Vibration

I degree of severity:

    1) syndrome of vascular dystonia (cerebral or peripheral);

    2) vegetative-vestibular syndrome;

    3) syndrome of sensory (vegetative-sensory) polyneuropathy of lower extremities.

II degree of severity:

    1) cerebral-peripheral syndrome of vascular dystonia;

    2) syndrome of sensory (vegetative-sensory) polyneuropathy in combination:

        a) with polyradiculitis (syndrome of polyradiculoneuropathy);

        b) with the second lumbar radicular syndrome (lumbar osteochondrosis);

        c) with dysfunction of nervous system (syndrome of neurasthenia).

III degree of severity:

    1) syndrome of sensorimotoric polyneuropathy;

    2) syndrome of discirculatory encephalopathy in combination with peripheral neuropathy (syndrome of encephalopolyneuropathy).

Hand-Arm Vibration

I degree of severity:

    1) syndrome of peripheral vascular dystonia of upper extremities, including with the rare angiospasms of fingers;

    2) syndrome of sensory (vegetative-sensory) polyneuropathy of upper extremities.

II degree of severity:

    1) syndrome of peripheral vascular dystonia of upper extremities, including with the frequent angiospasms of fingers;

    2) syndrome of vegetative-sensory polyneuropathy of upper extremities:

        a) with the frequent angiospasms of fingers;

        b) with persistent vegetative-trophic disturbances on hands;

        c) with trophic disturbances of vehicle of locomotor system of upper extremities and shoulder girdle (myofibrosis, periarthrosis, arthrosis);

        d) with cervical and brachial plexopathy;

        e) with syndrome of cerebral vascular dystonia.

III degree of severity:

    1) syndrome of sensorimotoric polyneuropathy of upper extremities;

    2) syndrome of encephalopolyneuropathy;

    3) syndrome of polyneuropathy with generalized akrovasoconstriction.

WHOLE BODY VIBRATION ————————————

Epidemiology and laboratory studies have shown that WBV is a form of cumulative trauma; it can be regarded as a generalized stressor and may affect multiple body parts and organs, depending on the vibration stimuli characteristics. Thus vibration exposure time, direction, and intensity are important, and the human resonance is especially important since resonance represents the Achilles' heel of human response to vibration. When the vibration impinges vertically on the body, the principal WBV resonance occurs in the 4- to 8-Hz band (nominally 5 Hz). When the vibration impinges horizontally or laterally, WBV resonance occurs in the 1- to 2-Hz band. These resonances are due principally to the response of the upper trunk and torso. The head-shoulder system can resonate in the frequency range of 20 to 30 Hz, and the eyeballs can resonate in the 60- to 90-Hz range. The hand-arm system appears to resonate in the 150- to 200-Hz range. Other body parts can resonate at other frequencies.

The significance of resonance can best be described by a simple example. If a 5-Hz vibration magnitude of 1 g were applied to a human subject's buttocks, one could expect to measure as much as a 1.5 g vibratory magnitude at the cranial level. Thus the body has intensified the actual acceleration applied by a factor of 1.5. The concern is that many vehicles, for example, contain 5-Hz vibration components that reach the body, as do higher-frequency tool components that reach the resonance of the hand-arm system and can stimulate this response.

With regard to WBV medical effects, studies of human subjects have shown that during WBV exposure oxygen consumption and pulmonary ventilation increase. One study of 78 Russian concrete workers exposed to WBV showed marked changes in bone structure involving spine deformations, intervertebral osteochondrosis, and calcification of the intervertebral disks and Schmorl's nodes. Hypoglycemia, hypocholesterolemia, and low blood ascorbic acid levels in concrete workers exposed to WBV have also been reported. In an early study of agricultural and forestry workers, a rare clinical description of so-called WBV sickness is found:

"The first stage is marked by epigastralgia, distention, nausea, loss of weight, drop in visual acuity, insomnia, disorders of the labyrinth, colonic cramps, etc. The second stage is marked by more intense pain concentrated in the muscular and osteoarticular systems. Objective examinations of the workers disclosed muscular atrophy and tropic skin lesions, it is apparent that it is difficult to determine the critical moment at which pathologic changes set in, especially due to differences in individual sensitivity to vibration."

The study of bus drivers revealed a statistically significant excess of venous, bowel, respiratory, muscular, and back disorders in a population of 1,448 interstate bus drivers exposed to WBV who were compared to office workers and general population control groups. The study concluded that the combined effects of WBV, body posture, postural fatigue, and poor dietary habits contributed to the occurrence of these disorders. The study of truck drivers examined 3,205 drivers and a control group of unexposed air traffic controllers. The study conclusions indicated that WBV, forced body posture, cargo handling, and poor eating habits contributed to significant excesses of back pain, spine deformities, strains, sprains, and hemorrhoids among the truck drivers. The first study of heavy equipment operators found that WBV-exposed workers had an excess of certain musculoskeletal diseases, including slipped disks, limb fractures, male genital diseases (prostate), ischemic heart disease, and obesity of nonendocrine origin. A study of farm tractor drivers revealed that, in many cases, the effects of WBV were exacerbated by poor seats, poor seating posture, and long working hours. A recent critical review of WBV epidemiology studies with regard to the back concluded, "The most frequently reported adverse effects (of WBV) are: low back pain, early degeneration of the lumbar spinal system, and hemiated lumbar disks.... It must be concluded that long-term exposure to WBV is harmful to the spinal system". Particularly disturbing are recent reports suggesting that WBV-exposed female workers experience a high risk of menstrual disorders, abortion, varicosities, and hyperemesis gravidarum.

Most whole body vibration researchers would agree that hard-tissue (mostly lumbar) spinal disorders are the most frequently reported disorders associated with occupational WBV exposures. But these lumbar spine disorders must be tempered with the patient's work history of lifting heavy objects and related activities that can confound the diagnosis.

Finally, it is important to note that kinetosis can appear in the very low WBV frequency vibration range of 0.1 to 1 Hz and rarely there carry over effects on workers after the exposure ceases.

Through the years there have been many human performance studies of WBV. Most have used young, physically fit military personnel, such as jet aircraft pilots, for short time periods (up to 30 min) in simulated military situations. Studies of vibration have shown that the lowest subjective discomfort-tolerance level occurs around the 5-Hz resonance frequency. Manual tracking capability is also most seriously affected at 5 Hz. Visual acuity is severely impaired in the 1- to 25-Hz range. Performance of tasks such as pattern recognition, reaction time, and monitoring appear not to be affected by WBV exposure. Laboratory studies using simulated heavy equipment driving tasks that compared the effects of a mixture of multiple vibratory frequencies (i.e., a limited spectrum) showed that human subjects performed worse under the mixed-vibration conditions containing a 5-Hz resonant frequency gradually improving as the mixture was replaced by nonresonant single sinusoidal vibration.

HAND-ARM VIBRATION

Hand-arm vibration (HAV), or segmental vibration, unlike WBV, appears as locally applied cumulative trauma to the fingers and hands of exposed workers using gasoline powered, pneumatic, or electrical hand tools such as chain saws, chipping hammers, grinders, jack-hammers, jack-leg type drills, etc. Extensive use of such tools (especially in cold environments) has been causally linked to Raynaud's phenomenon of occupational origin, also variously called "dead hand" or "vibration white fingers" (VWF) and most recently termed hand-arm vibration syndrome (HAVS). This condition is characterized by tingling, numbness, and blanching of the fingers with probable loss of muscle control and reduction of sensitivity to heat and cold with accompanying pain on return of the circulation.

Historically, the condition of blanching, numbness, and tingling in the fingers of clinical patients was first reported in 1862 by the French physician Maurice Raynaud in his M.D. thesis, "Local Asphyxia and Symmetrical Gangrene of the Extremities", which describes "a condition, a local syncope, where persons, who are ordinary females, see under the least stimulus one or more fingers becoming white and cold all at once. The determining cause is often the impression of cold. The cutaneous sensibility also becomes blunted and then annihilated." This is primary Raynaud's disease. Raynaud's phenomenon affects up to 10% of the general population and 5% or 6% of the working male population. These blanching attacks usually affect the fingers symmetrically and are relatively trivial in the early stages of the disease. In later stages the attacks become se-

vere and painful, leading to blue, cold fingers wherein the skin becomes atrophic, later ulcerated, and finally gangrenous. Raynaud also noted that the number and severity of blanching attacks increased during times of emotional stress.

In 1911 Loriga in Italy first described the initial association of vibrating hand tools and Raynaud's symptoms in the hands of miners who used pneumatic hand tools. In 1918, the famous study of Dr. Alice Hamilton was reported. She studied stone cutters using pneumatic hammers in the Oolitic limestone quarries of Bedford, Indiana. She reported:

Among men who use the air hammer for cutting stone there appears very commonly a disturbance in the circulation of the hands which consists in spasmodic contraction of the blood vessels of certain fingers, making them blanched, shrunken, and numb. These attacks come on under the influence of cold, and are most marked, not while the man is at work with the hammer, but usually in the morning or after work. The fingers affected are numb and clumsy when the vascular spasm persists. As it passes over there may be decided discomfort and even pain, but the hands soon become normal in appearance and as a usual thing the men do not complain of discomfort between the attacks. ...The condition is undoubtedly caused by the use of the air hammer' it is most marked in those branches of stonework where the hammer is most continuously used and it is absent only where the air hammer is used little or not at all. Stonecutters who do not use the air hammer do not have this condition of the fingers. Men who have given up the use of the air hammer for many years may still have their fingers turn white and numb in cold weather. The trouble seems to be caused by three factors: long-continued muscular contraction of the fingers in holding the tool, the vibration of the tool, and cold. It is increased by too continuous use of the air hammer, by grasping the tool too tightly, by using a worn, loose hammer, and by cold in the working place. If these factors can be eliminated the trouble can probably be decidedly lessened.

In the 1930s, reports by Seyring, who studied fettlers in iron foundries, by Telford and co-workers, who described men working with electrically driven rotating tools in a warm environment, and by Hunt, who studied riveters using pneumatic tools, all showed that VWF was on the increase. In 1939, Leys reported diffuse scleroderma and Raynaud's phenomenon in a pneumatic hammer operator. In 1947, Agate and Druett examined 230 men who were grinding excess metal from small castings; of this total, 163 (71%) had a history of white fingers, later to be called VWF. With further research into VWF in the 1950s, signs and symptoms associated with vibrating tools were reported in other systems, such as the

peripheral nerves, bones, joints, and muscles. The association of VWF with these disabilities became known later as hand-arm vibration syndrome.

In 1962 and 1964, Ashe and colleagues at Ohio State University investigated a small group of hard-rock drillers from Saskatchewan, seven of whom were examined in the hospital. As part of these investigations, arteriography and biopsy of the digital arteries were performed. Results showed that, in the worst cases, extensive damage to the digital artery intima with narrowing of the lumen had occurred as a result of the vibration exposure.

From 1964 on, a significant number of vibration syndrome cases appeared in the United Kingdom, up to 90% in the logging and forestry industries, where gasoline-powered chain saws had been in widespread use for some 12 to 14 years. The clinical state of the hands of workers using these chain saws was deteriorating to such an extent that the British Forestry Commission, in 1971, issued workers newly designed antivibration (A/V) saws, which were based on the best available vibration criteria of the time for 6 to 7 hrs per day, 5 days per week exposure.

Medical Assessment

It is important that primary Raynaud's disease, as originally described by Raynaud, be distinguished from secondary Raynaud's phenomenon. Secondary Raynaud's may arise from (a) exposure to vibration; (b) trauma, such as lacerations and fractures of the fingers and hands; (c) frostbite; (d) occlusive vascular disease, such as arteriosclerosis; (e) intoxication, as from ergot or nicotine; and (f) neurogenic causes such as poliomyelitis. It is also necessary to exclude causes of reduced blood flow to the fingers from compression of the main blood vessels at the outlet of the thorax (e.g., cervical rib or "thoracic outlet" syndrome). In addition, connective tissue disorders, such as scleroderma, polyarteritis nodosa, and rheumatoid arthritis, may cause secondary Raynaud's phenomenon. It is recognized that it may not be possible to eliminate confounding conditions during the diagnostic process, since on occasion scleroderma and sclerodactyly with vibration induced Raynaud's have occurred simultaneously in patients as have carpal tunnel syndrome (CTS) and primary Raynaud's.

Some years ago Taylor and Pelmear developed a white finger grading system, which bears their names and became widely used in many countries. Their system tended to emphasize the vascular component of HAVS.

In 1986 a meeting was held in Stockholm, Sweden, at which a modified Taylor — Pelmear system was adopted with the concurrence of Drs. Taylor and Pelmear.

The modified system, called the Stockholm system, came about in recognition that although the majority of HAVS subjects have a combination of neurologic and vascular signs and symptoms, it became necessary to separate these two components and stage or classify each independently, since it is possible that the neurologic component of the syndrome can progress independently of the peripheral space vascular component in some patients.

Given that the Taylor—Pelmear system has been used for many years and that the literature is replete with studies that use it, and given the relative newness of the Stockholm system, both systems will be addressed here.

The Taylor—Pelmear system was developed for grading HAVS patients and uses the results of the physical examination, occupational health history, history of social impairment (as a direct consequence of induced white finger), and the degree of interference with hobbies; the HAVS patient is placed into one of the following categories. The initial symptoms of HAVS are tingling or numbness after vibration exposure. In stage 1, as vibration exposure time increases, finger blanching attacks begin and increase in number, duration, and severity. They occur at first mainly in cold temperatures, and especially during the early morning, either at home, with chores, or en route to work as a result of exposure to the elements (e.g., grasping a cold steering wheel, driving a motorcycle), or during morning rest breaks. Workers who work outside in all weather conditions (e.g., forestry workers) are most prone to early morning attacks. Workers may report interference both at work and during hobby and leisure activities (e.g., gardening, fishing, woodworking, auto maintenance, etc.). All such activities have one common factor: a reduced environmental temperature, which triggers an HAVS attack. The latent period to finger blanching is defined as the time interval from when the worker began using the vibrating tool(s) to the appearance of the first white fingertip; also note that thumbs generally do not blanch during an HAVS attack (Table 8.1).

In stage 2 there is a limitation of hobby activities. In stage 3, there is a definite cessation of hobby activities as well as interference with work, particularly in outdoor jobs such as forestry, and especially in the winter; difficulty with fine manual dexterity; difficulty in feeling and picking up small coins; difficulty in buttoning/unbuttoning clothing; finger clumsiness with increasing joint stiffness.

Table 8.1. **Exclusion criteria and differential diagnosis
for hand-arm vibration syndrome**

Primary (Raynaud's disease)	Constitutional white finger
Secondary (Raynaud's phenomenon)	
Connective-tissue disease	Scleroderma, systematic lupus erythematous, dermatomyositis, polyarteritis nodosa, mixed connective-tissue disease
Posttraumatic conditions	Following injury, fracture, or operation; occupational origin, vibration; frostbite and immersion syndrome
Occlusive vascular disease	Thoracic outlet syndrome (cervical rib, scalenus anterior muscle), costoclavicular and hyperabduction syndromes. Thromboangiitis obliterans, arteriosclerosis, embolism, thrombosis
Dysglobulinemia	Cold hemagglutination syndrome; cryoglobulinemia, macroglobulinemia
Intoxication	Acro-osteolysis, ergot, nicotine
Neurogenic	Poliomyelitis, hemiplegia, syringomyelia
Other	Carpal tunnel syndrome

In stage 4, the severity of the HAVS and interference with work, social activities, and hobbies are so intense that the patient changes occupation; tissue necrosis of the fingers can appear in rare instances with increased vibration and cold exposure in this stage.

It is to be noted that the preceding sequence of increasing stages of HAVS severity arises from the cumulative trauma effects of the impinging vibration on the hands, usually from prolonged and regular use of vibrating tools found in industry. The aforementioned latent interval is related to the vibration (acceleration) intensity; the shorter the latent interval, the more severe will be the HAVS if vibration exposure continues.

The Stockholm system is shown in Table 8.2 and requires the examining physician to do extensive work/hobby histories in order to estimate the patient's vibration dose. Vascular, neurologic, and musculoskeletal objective tests must be performed in order to separately stage each hand for neurologic and for vascular damage. The following tests for HAVS are recommended:

Table 8.2. **Stockholm-revised vibration syndrome classification system**

Stage/Grade	Description
Vascular component	
1. Mild	Occasional blanching attacks affecting tips of one or more fingers
2. Moderate	Occasional attacks in distal and middle phalanges of one or more fingers
3. Severe	Frequent attacks affecting all phalanges of most fingers
4. Very severe	As in stage 3 with trophic skin changes (tips)
Sensorineural component	
0SN	Vibration exposed — no symptoms
1SN	Intermittent or persistent numbness with or without tingling
2SN	As in 1SN with reduced sensory perception
3SN	As in 2SN with reduced tactile discrimination and manipulative dexterity

The staging is made for each hand. The final grade of the disorder is indicated by the stage and the number of affected fingers in each hand (e.g., stage/hand/no, of digits). This Stockholm Classification System is based on:

a) removal of the unquantifiable areas — difficulty at work, home, and hobby activities;

b) discarding the seasonal component;

c) the syndrome to be separated into two major areas — vascular and sensorineural;

d) separate staging of each hand.

Vascular component tests: cold provocation tests; Doppler artery delineation; Alien and Louis — Prusik tests.

Neurologic component tests: two-point discrimination and depth sense (aesthesiometry); vibrotactile threshold tests; light-touch, pain, and temperature appreciation and dexterity tests; Moberg and pinch tests.

Musculoskeletal tests: dynamometer grip force and pinch tests.

Differential diagnosis (neuropathy and polyneuropathy): Tinel's and Phalen's tests; nerve conduction velocity for median, ulnar, motor, and sensory nerves of the Tinel and Phalen tests (which indicate the degree of CTS symptoms).

Hand-Arm Vibration Control

It is beyond the scope of this presentation to describe in detail the various methods for controlling HAVS in the workplace except to briefly mention them. Totally controlling HAVS usually is multifaceted and involves several measures.

The first line of control is better tool design (or tool redesign) that incorporates the engineering principles of vibration damping and isolation together with good ergonomic design. Currently there are many reduced vibration or so-called antivibration (A/V) gasoline-powered chain saws and related forestry and professional landscaping tools available; unfortunately, this is not the case for most pneumatic tools, except for a single major Swedish company with virtually a complete line of effective A/V tools. Although new A/V tools employing ergonomic principles are beginning to appear on the market, most tool companies have a few A/V tools at most in their complete lines.

The second line of control is A/V gloves, which use special viscoelasic materials to damp a broad spectrum of vibration. These gloves are also intended to keep the hands warm and dry and prevent cuts and lacerations. The main design challenge is allowing sufficient sensory feedback and dexterity with a minimum grip strength (in order to reduce vibration coupling into the hand).

The third line of control is hand-arm vibration standards. Although all of these standards try to protect workers from the harmful effects of hand-arm vibration, these standards emphasize (weight) the lower vibration frequencies more than the high-frequency spectral components. As a result, some of these standards are in the process of being revised accordingly.

The fourth and final line of control is work practices and medical surveillance:

1. Any worker whose hands may be exposed to vibratory hand tools should, prior to employment, be physically examined and questioned about:

    a) Signs and symptoms of primary Raynaud's disease or Raynaud's phenomenon.

    b) Detailed history of vibration exposure (which should be recorded); on the basis of present medical evidence, it is not advisable to allow workers with primary Raynaud's disease to use vibratory hand tools.

2. A/V tools should be used when and where possible; all tools should be carefully maintained according to manufacturer's recommendations. Worn-out tools should be discarded and replaced with new ones, preferably A/V tools.

3. Workers are advised as follows:
   a) Use only full-finger A/V gloves at all times when using vibrating hand-tools. A/V gloves with fingertip material removed expose the fingertips to vibration and thus do not adequately protect the finger-hand system despite the fact that finger dexterity is improved.
   b) Wear adequate clothing to keep the body core temperature at a stable, acceptable level.
   c) Keep the hands warm before and during work.
   d) Do not allow the hands to become wet and chilled. Should this happen, dry and warm the hands and put on a pair of dry, warm A/V gloves. This may require carrying an extra pair of gloves.
   e) Do not smoke while using vibrating hand tools. Nicotine acts as a vasoconstrictor, reducing the blood supply to the fingers and hands.
   f) Let the tool do the work, grasping it as lightly as it is safe to do so, allowing the tool to rest on the workpiece where and when possible.
   g) Use only ergonomically designed A/V tools where and when possible.
   h) Use the tool only when absolutely necessary, operating at reduced speed when possible.
   i) Should signs of tingling, numbness, or white or blue fingers occur, see a physician promptly.

4. The hazard of HAVS can be reduced if continuous vibration exposure over long time periods is avoided. Therefore, a 10-minute vibration-free rest break for every hour of continuous vibration exposure is recommended.

TESTS

1. A woman, aged 50, a farmer, noted a headache during several weeks, "a faint condition". It was noted a vegetatic neuralgia of the upper limbs. Diagnosis: vibration disease.

Determine a functional degree of the disease on the basis of these symptoms:
   A. I.
   B. II.
   C. III.
   D. IV.
   E. V.

2. A man, aged 40, a farmer, complains of the headache of constant nature, a short faint condition. There were noted a vegetatic-sensitive polyneuropathy of the limbs, the diencephalon syndrome.

A possible diagnosis and degree of the disease are following:

A.Vibration disease, the 1st degree.

B. Vibration disease, the 2nd degree.

C. Vibration disease, the 3rd degree.

D. Vibration disease, the 4th degree.

E. NCD.

3. A man, aged 40 y. o., works at the metallurgical industry. He applied to the physician with complaints of severe night aching pain in hands, numbness of the fingers of the hands, general painfulness, extended headache, strong pain in the heart area, palpitation.

What kind of the disease has this patient?

A. Vibration disease, local.

B. Vibration disease, general.

C. Raynaud's syndrome.

D. Syringomyelia.

E. NCD.

4. A man, 35 y. o., has worked as a driller over 13 years. During a preventive physical examination he complained of general sweating, headache, which is accompanied by the noise and sonitus, memory impairment, sleepiness, pain in the field of the heart. Objective: flutter of the fingers and hands, oppressing of the pharynx, conjuctive and corneal reflexes, instability in the pose of Romberg, distal and general hyperhydrosis, bright steadfast dermographism.

What is the most possible reason of this condition?

A. Radiation disease.

B. Vibration disease.

C. Action of production noise.

D. Change of the atmospheric pressure.

E. Meniere's disease.

5. A patient, 50 y. o., a mechanical engineer in the turbine shop of the power plant, complains of the steady headache in the forehead area, increased petulance. Besides, he notes a cold snap of limbs, pallor, seasonly cyanosis, increased sweating of the palms and foots. During the examination — a reduction of the pulsation of dorsal arteries of feet on both sides, bone power reduction.

Establish diagnosis:
A. Raynauld's disease.
B. Atherosclerosis of the lower limbs' vessels.
C. Vibration disease action of the general vibrations.
D. Vibration disease caused by the action of the local vibrations.
E. Polyneuritis.

Chapter 9
DYSBARISM ─────────────────

Dysbarism is the collective term used to describe the pathologic changes that occur when the human body is exposed to environmental pressure changes (alternobaric exposure). Those altered pressures are translated into unphysiologic behavior of gases in organs and tissues. Failure to adequately or timely adapt to those changes, can generate (depending on a number of exposure and individual factors) the different clinical syndromes of dysbarism. Altemobaric exposure is a concern in a number of occupational and recreational activities, such as diving, compressed air work (as in tunnel construction and caisson work), as well as in aviation, mountain climbing, and high-altitude flying.

HISTORICAL PERSPECTIVE ──────────────

Diving has been an important human activity since antiquity and, as such, the quest for increased depths and durations has been ongoing since then. Although reports of dysbaric disorders began earlier, their experimental study was not possible until the XVII century, when diving bells were introduced for salvage operations. In 1650, von Guericke developed the air pump, which permitted simulation of high-altitude environments in special gas chambers. Sir Robert Boyle (1627–1691) experimented with live animals exposed to this gas chambers and noted bubbles floating in the vitreous humor of their eyes. In 1667, Redi, an Italian naturalist, reported on the death of animals when air was injected into neck veins. In the XIX century, Augustus Siebe manufactured the first diving suit with a surface air supply, and Ammussat observed that the speed of death of air-injected animals was related to the size of the injured vein and the relationship of this vein to the heart when air was injected. In 1818, Bauchene reported the first case of fatal air embolism in a human. In the

1840s, decompression sickness (DCS) was first recognized in France in men who were working in the compressed air environments of tunnels and caissons. A French scientist, Paul Bert (1833–1886), was the first to hypothesize that "caisson disease" resulted from the development of air bubbles in body tissues and fluids after decompression from a hyperbaric exposure. Bert also determined that the gas in those bubbles was nitrogen. In 1930, a Dutch physician named Jongbloed recognized that the joint symptoms that he experienced after self-experimenting with hyperbaric exposure were the same as those observed in men after rapid decompression from diving or caisson work. During World War II, Jacques Cousteau and Emile Gagnon developed a demand regulator that automatically delivered breaths at any depth, the self-contained underwater breathing apparatus ("scuba"). Hyperbaric chamber treatment techniques were also refined during World War II because of the demands of submarine technology and higher flying aviation. At the same time, Behnke recognized that the symptoms felt at high altitude were analogous to those associated with caisson work, thus identifying a link between aviation and diving hazards. By 1960, a classification scheme for decompression sickness based on symptoms experienced by tunnel workers had been formulated.

ALTERNOBARIC EXPOSURES

Exposure to altered environmental pressures followed by a return to atmospheric pressure occurs in a number of settings. When the rapidity of the pressure changes exceeds that of the compensatory and adaptive mechanisms of the human body, dysbaric disorders can result, depending in part on interindividual differences in responses and susceptibility. This chapter focuses on compressed air work and diving.

Compressed air work is carried out during tunnel construction and caisson work. A caisson is a watertight chamber used in construction work to construct bridge and tunnel foundations under water. The chamber is placed over the site of the proposed underwater foundation, and air is pumped in at a pressure sufficient to displace the water and allow work to be performed under dry conditions (Fig. 9.1). In the United States, working pressures for compressed air have varied from 3.1 to as high as 6.1 atmosphere absolute (ATA). Part of this work can now be done with mechanical devices.

There are three main diving methods, which have been sequentially developed during man's quest for deeper and more prolonged dives: breath-hold diving, scuba diving, and saturation diving. Breath-hold diving is the simplest and oldest of all. Once the diver holds his breath and de-

scends, the increased pressure that he is exposed to is applied to his entire body. The duration of the dive is limited by that of the breath-hold, and specifically the rate of $PaCO_2$ rise.

Scuba-diving allows descent deeper into the water for a considerable longer duration than breath-hold diving Scubas provide a breathing mixture (air, oxygen, helium-oxygen, helium-nitrogen-oxygen, hydrogen-nitrogen-oxigen) upon demand at the ambient pressure to which the diver is exposed. This allows the maintenance of ambient pressure within the respiratory tract. Dive computers calculate saturation and desaturation of tissues. Their purpose is to maximize the time underwater by pushing dives to the limit of a decompression model different from the more conservative one used to derive decompress tables. They therefore decrease safety margins and increase in the probability of dysbarism. Recreation scuba diving has gained immense popularity in many industrialized countries, where it is by far more widespread than commercial and military diving. Recreation diving is currently restricted to depths of 39 m.

Saturation diving was developed to permit commercial divers, especially in the oil industry, to perform complex and economically profitable tasks during prolonged periods and at increased depths. Saturation diving allows for an increase in the ratio of time spent underwater to the total diving time, which is the sum of underwater plus decompression time. In this modality, divers descend in diving bell where they are gradually compressed to pressure level encountered at the depths where they are released (which usually exceed 200 to 300 m). Breathing mixtures have high partial pressures of inspired oxygen, and an inert gas other than nitrogen (usually helium) is added. The compression and descent phase of this diving modality is long enough for the diver's tissue to be-
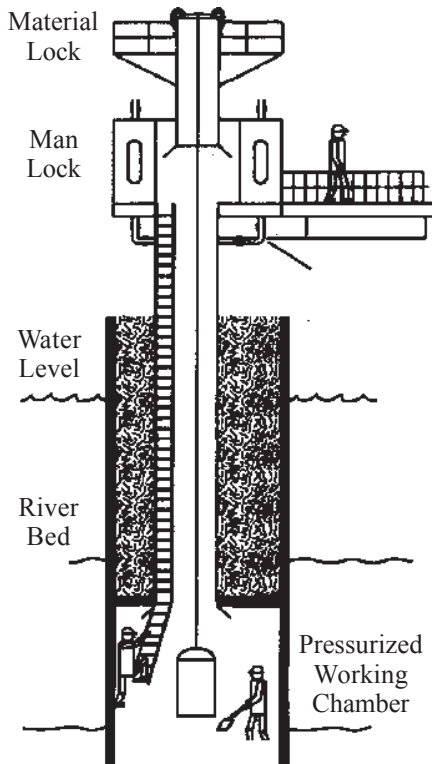
Fig. 9.1. Scheme of a caisson

come fully saturated with the inert gas that is being breathed. Once saturated, the diver can remain underwater for an indefinitely long period, without further increasing his obligated decompression time. Stays of 1 to 14 days are usual, with decompressions of approximately the same duration.

The technical refinements of scuba and saturation diving have allowed increased human activity underway under hyperbaric conditions. With these modalities, divers are exposed to breathing mixtures that are usually hyperbaric, hyperoxic, and have an increased gas density. Furthermore, the surrounding environment can be hypothermic, physical activity can be strenuous, and the specific tasks performed underwater may also expose commercial or technical divers to potentially injurious toxins and physical agents. The compromises that are mad are felt to be "acceptable," although long-term, close follow-up is necessary to exclude unforeseen deleterious consequences.

PATHOPHYSIOLOGY OF DYSBARISM

Whereas body tissues are nearly incompressible, the physical behavior of gases is affected by three factors: pressure, volume, and temperature. The interrelationship between these factors is determined by Boyle's, Dalton's, and Henry's laws, three fundamental gas laws. Comprehension of these concepts is essential to the understanding of dysbaric disorders, which in this chapter are classified according to their pathophysiology.

Pressure is defined as force applied per unit area. Commonly used units and equivalent pressures are 1 atmosphere (atm), 760 mm Hg, 10 m of sea water. The sea of air under which we normally reside is defined (at sea level) as 1 atmosphere (atm) of barometric pressure. Hyperbaric exposures add to the ambient pressure and hypobaric exposures subtract from it. Absolute pressure is the sum of ambient pressure plus any additionally applied pressure. It is measured in atmosphere absolute (ATA) units. For instance, under 10 m of sea water, 1 atm is added to the ambient pressure and the absolute pressure is 2 ATA.

The Boyle's law states that the volume (V) of a given mass of gas is inversely proportional to its pressure (P): $PV = K$ (a constant). In the human body, hyperbaric exposures (compression, diving descent) cause a contraction in gas volume, and hypobaric exposures (decompression, ascent after diving) cause an expansion. A doubling of pressure to 2 ATA results in the volume being halved; similarly, a decrease of pressure to

0.5 ATA is associated with a doubling of volume. The diameter of a sphere or bubble is also affected by the pressure change but to a lesser extent than volume. Whereas the volume change is more important in predicting barotrauma, the bubble diameter change is the important factor for restoring circulation to embolized areas during recompression therapy.

The Dalton's law states that the total pressure (P1) exerted by a mixture of gases is the absolute sum of each individual gas: $PT = P_1 + P_2 + P_3 + ... + P_n$. This law forms the physical principle of hyperbaric (recompression) therapy and the hypoxemia that occurs under hypobaric conditions (Table 9.1; 9.2).

Table 9.1. **Effects of gas laws on hypo-
and hyperbaric exposures**

Distance from sea level, m	Ambient pressure		PO_2 (mm Hg)	Bubble volume	Diameter
	(ATA)	(PSI)			
+6,000	0.5	7.35	380	200%	126%
+2,000	0.8	11.76	608	125%	107%
0	1	14.70	760	100%	100%
−10,0	2	29.40	1,520	50%	79%
−20,0	3	44.1	2,280	33%	69%
−30,0	4	58.8	3,040	25%	63%
−40,0	5	73.5	3,800	20%	59%
−50,0	6	88.2	4,560	17%	55%

Table 9.2. **Gas pressures under hypo-
and hyperbaric conditions**

Distance from sea level, m	Pressure (ATA)	PO_2 (mm Hg)	PN (mm Hg)	PT (mm Hg)
+8,000	0.388	62	233	295
+1,700	0.743	119	446	565
0	1.0	160	600	760
−10,0	2.0	320	1,200	1,520
−20,0	3.0	480	1,800	2,280
−30,0	4.0	640	2,400	3,040
−40,0	5.0	800	3,000	3,800
−50,0	6.0	960	3,600	4,560

The Henry's law provides the physiologic basis for understanding decompression sickness, nitrogen narcosis, and the formation of bubbles when a bottle of champagne is uncorked. This law states that the amount of gas that dissolves in a liquid at a given temperature is directly proportional to the partial pressure of that gas. The Boyle's, Dalton's, and Henry's law together describe the ideal gas law:

$$PV = nRT,$$

where P — pressure; V — volume; n — number of moles of gas; R — universal gas constant, T — absolute temperature.

This law allows the prediction of the behavior of gases in response to changes in environmental pressures.

Behavior of Gases During Compression and Decompression

As predicted by the gas laws, the volume of gases within the body change during hyperbaric and hypobaric exposures. If the gas volume changes provoked exceed compensatory mechanisms of the body, the major dysbaric disorders — decompression sickness (DCS) and barotrauma — may result. In both conditions pathologic changes result from the formation of gas bubbles. In barotrauma, changes in gas volumes within air-filled anatomic structures are involved, and gas may be directly injected into arteries. In DCS gas bubbles form within tissues and their vasculature, where they cause most of the damage.

Gases in the body under these circumstances takes into account the phenomena of compression versus decompression, and gas behavior at the level of tissues and of air-filled organs.

Compression in a hyperbaric environment causes tissue uptake and saturation with gases. When ambient pressure rises, the partial pressure of a given gas (e.g., nitrogen) in a tissue and the total pressure of gas in an air-filled organ rise proportionally. Compression of gas in the latter is the direct cause of barotrauma of descent. Compression also results in the development of a gradient that causes a net flow of nitrogen from pulmonary alveoli to the blood and subsequently into body tissues. The rate of gas uptake is most rapid immediately following a pressure increase and reaches a plateau as tissue saturation is approached. The time that it takes to achieve equilibrium in gas uptake is a function of (a) the solubility of the gas in the tissue and (b) the rate at which the gas is delivered to that tissue by blood. Tissue perfusion varies. Well-perfused tissues such as the brain can achieve equilibrium with a gas within minutes; they are relatively "fast" tissues. On the other hand, poorly perfused tissues such

as adipose tissue, joints, and tendons, which also have a high solubility for gases, require more time to reach equilibrium and are called "slow" tissues. Tissues acquire gases exponentially, and a range of half-times (from 5 to 75 minutes) has been estimated to describe that process in different body tissues. Much longer half-times, however, are believed to occur for some tissues under specific circumstances. The latter is important, because decompression tables are based on those half-time estimates. Increased tissue perfusion, and thus gas uptake, as observed during exercise, active heating, immersion, and supine position, may all increase the risk for dysbarism (in particular DCS).

When ambient pressure is lowered during decompression, the rate of escape of gas from tissue is believed to be similar to the rate of uptake, but in reverse, as long as bubbles do not form. If the reduction of ambient pressure to a level lower than the total gas pressure in tissues is too rapid, formation of microbubbles within tissues is favored. These bubbles immediately appear because the pressure of the dissolved gas cannot decrease fast enough by diffusion alone. Reversal of tissue supersaturation with gas must therefore be controlled during ascent (decompression) in order to minimize bubble formation and growth, the development of DCS, gas expansion within air-filled organs, and barotrauma of ascent.

In the case of barotrauma of ascent, gas bubbles are formed from the injection of rapidly expanding gas into the arteries. In the case of DCS, the exact site of initial bubble formation and the microcirculatory events related to intravascular bubbles following rapid decompression remain unclear. Formation of bubbles primarily in the venous circulation, tissues themselves, and/or arteries, have been hypothesized. Bubbles are thought to originate on preformed bubble nuclei. The latter may exist in microscopic hydrophobic spaces (e.g., between endothelial cells), or be generated by shear forces exerted on moving tissues. Once bubbles develop on those nuclei, their size can increase as a function of several factors, including exchange of gas with adjacent blood, presence of surfactant, and coalescence or disintegration of bubbles resulting from collision. The high fat content of the nervous tissue, combined with the high liposolubility of nitrogen, may account for its vulnerability. Histologic studies on rapidly decompressed animals demonstrated relative abundance of intravascular gas bubbles in fat-rich tissues and organs. In the spinal cord, the white matter, rather than the gray matter, is usually affected. A number of observations have established the presence of bubbles in almost all tissues, intra- and extravascularly, and even intracellularly. Progressive stages of bubble formation in fat tissue range from the enlargement of fat cells by inclusions of microbubbles to the rupture of gas-filled cells generating extracellular and extravascular pockets of gas in the tissue.

Regardless of the origin of the gas bubbles three main interrelated mechanisms have been invoked to explain their pathologic effects in tissues: (a) mechanical obstruction with reduced blood flow, (b) surface activity at the gas-liquid interface of the bubbles, and (c) injury of vascular endothelia. These three mechanisms can trigger local and systemic inflammatory effects. Bubbles have been shown to have surface activity due to the abnormal gas-liquid interface. Denaturation and reorientation of globular plasma proteins are believed to occur upon contact with that interface and be associated with loss of function, aggregation of proteins, and coating of blood cells that favor their aggregation. Those phenomena may explain several of the observed changes in the blood during decompression, which include sludging and rouleaux formation of red cells in small vessels, neutrophil aggregation, platelet clumping, and a decrease in the number of circulating red and white cells and platelets. In addition, and possibly through activation of kinin and complement pathways, several inflammatory phenomena may result, such as increased capillary permeability and fluid extravasation. All these alterations contribute to producing microcirculatory compromise, endothelial damage, and local inflammatory tissue damage.

Some of the manifestations of DCS are similar to those of systemic inflammatory conditions characterized by complement activation. This led some to hypothesize that complement activation may mediate DCS, perhaps underlie intel-individual differences in susceptibility to it, and possibly even explain its occasional recurrence after initially successful resolution with hyperbaric treatment. Complement activation may also mediate some of the observed changes in blood elements and vascular endothelial injury. In animal studies, air bubbles have been observed to activate complement by the alternative pathway. In humans, activation of complement by the alternative pathway has also been demonstrated in plasma samples incubated with air and nitrogen bubbles, and in individuals subjected to decompression. Furthermore, subjecting some of those individuals to a series of pressure profiles severe enough to cause bubble formation in blood vessels revealed that complement-activation seemed to correlate with susceptibility to DCS. The functional and clinical relevance of decompression-associated complement activation, however, remains to be determined.

Cardiovascular and Pulmonary Effects of Gas Embolization

The physiologic consequences of gas embolization to the heart and lungs is due to mechanical factors as well as secondary effects of released mediators (as described above). Cardiovascular collapse may ensue due to a combination of acute right heart failure and hypoxemia-related myo-

cardial infarction. If even a small amount (< 0.1 ml) of air enters a coronary artery, ventricular fibrillation and infarct can result. Ultimately, poor oxygen delivery results in multisystem organ failure and death.

Mechanical obstruction of the pulmonary arterial system and the right heart may result from simple lodging of bubbles causing an "air-lock" phenomenon. Vortex flow round a partially obstructing embolus is postulated to cause a "whipping" type action that results in a blood-froth mixture. The latter enhances platelet aggregation, fibrin formation, and coalescence of intravascular fat. Proximal deposition of these fibrin strands interspersed with conglomerations of red cells may play a major role in the obstruction of the pulmonary vasculature. Transient pulmonary vasoconstriction has also been detected in a canine model of venous gas emboli. These mechanisms resulted in a brisk rise in pulmonary vascular resistance (PVR) prior to a fall in cardiac output when bubbles were injected into the venous system of sheep. This sequence of events lends further support to the hypothesis that vasoactive mediators may be involved in the subsequent changes following gas emboli.

In the lungs, airways resistance (Raw) increases when gas emboli are composed of air, oxygen, or nitrogen but not when they contain only carbon dioxide (CO_2) or the inert gases helium, neon, argon, or xenon. As a result of the significant increases in Raw, lung water, and PVR, there is maldistribution of ventilation relative to perfusion. The ventilation/perfusion (V/Q) ratio imbalances result in hypoxemia due to low V/Q areas as well as areas of physiologic shunting (V/Q = 0). The V/Q maldistribution that occurs during venous gas embolism also causes increased areas of dead space (elevated V/Q ratios). This explains the finding of a drop in end-tidal CO_2 concentration (ET CO_2) following venous gas embolization as areas of high V/Q experience a "washout" of CO_2 from the poorly or nonperfused alveoli. The decrease in $ETCO_2$ is exaggerated when the cardiac output is also decreased.

Cardiopulmonary Effects of Diving

The physiologic effects of submersion have been studied in a head-out immersion model during which the subject is submersed up to the neck. This induces an asymmetric pressure on the subject's body that is proportional to the vertical distance that is immersed. Venous return is augmented due to compression of the extremities by the relative high density of water and an increase in abdominal pressure relative to intrathoracic pressure. Right atrial pressure rises, which stimulates release of atrial natriuretic factor (ANF), which contributes to the diuresis and natriuresis

that usually accompanies head-out immersion. However, this shift can acutely reduce circulating blood volume, which is further compromised by sweating, the cold pressor response, and any associated alcohol intake.

The increase in intrathoracic pressure during head-out immersion experiments induces several pulmonary changes, including:

a) a 70% decrease in expiratory reserve volume (ERV);

b) smaller reductions in vital capacity, since there is an increase in inspiratory capacity that partially compensates for the large decrease in ERV;

c) a small, but statistically significant, decrease in residual volume caused by an increase in intrathoracic blood volume;

d) a 60% increase in the work of breathing partly due to an increase in nonelastic airways resistance;

e) a form of "negative-pressure ventilation," since the thorax and lungs experience greater than 1 ATA while the oropharynx and nose are surrounded by only 1 ATA (at sea level).

During breath-hold diving, the entire body is exposed to the increased ambient pressure. Breath-hold diving is associated with decreased intrathoracic pressure (relative to ambient pressure) and chest elastic recoil, and increased work of breathing. Increased venous return to the heart also results, which causes an increase in cardiac output that probably contributes to counteracting the pressure exerted on the thoracic cage. Distribution of pulmonary perfusion may also improve. At the end of a prolonged dive, marked hypoxemia and hypercapnia occur, the latter being the usual stimulus for resumption of ventilation. Ventilatory responses to hypercapnia and hypoxia have been shown to be altered in elite breath-hold divers, Japanese pearl divers, and submarine escape training instructors. Most studies have described a blunted response to hypercapnia with variable tolerance to hypoxia. Whether these traits are genetic or adaptive has not been determined, but they do contribute to the breath-hold diver's longer underwater performance. Hyperventilation before a dive produces a larger depletion of the body CO_2 reserves than increases in those of O_2. By retarding the hypercapnic stimulus, predive hyperventilation prolongs the apnea time and favors the development of a more severe hypoxemia than would result otherwise, thus increasing the risk of syncope and death.

By contrast, scubas maintain atmospheric pressure within the respiratory tract. They expose the lungs, however, to breathing mixtures that are more dense, hyperbaric, and hyperoxic in comparison to atmospheric air. The increased work of breathing, with decreased expiratory flow rates in direct proportion to the ambient pressure, has been well documented by several investigators in the past. Furthermore, mouthpieces, masks, and helmets all add dead space (i.e., increased pulmonary ventilation/perfusion

ratio) to the total ventilation required for adequate respiratory gas exchange.

Different studies have documented pulmonary functional changes in scuba divers and, more recently, in saturation divers. The results generally suggest definite but mild degrees of overinflation and obstructive impairment. Cross-sectional ventilatory functional studies in divers with prolonged exposure to hyperbaric environments demonstrated significant increases in forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV$_1$). Other studies detected decreases in air flow rates at low lung volumes suggestive of obstructive impairment, and decreased diffusion capacity uncorrected or corrected for alveolar volume (DL/VA). Hyperoxia, hyperbaria, and venous gas microembolism appear to be independent contributors to the described pulmonary functional changes. Although these changes may result (at least in part) from occupational self-selection or from respiratory muscle training, they have also been suggested to indicate small airways dysfunction.

NITROGEN NARCOSIS AND HIGH-PRESSURE NERVOUS SYNDROME (HPNS)

Nitrogen narcosis has been most commonly described in deep diving while breathing compressed air. It has also been described in compressed air workers. The resulting increased partial pressure of nitrogen in compressed air generates a large additional nitrogen load, which (due to its lipid solubility) easily saturates the brain tissue. This allows nitrogen to exert narcotic effects, which have also been described for other "inert" gases (e.g., hydrogen) in close correlation with their lipid solubility. The term inert gas narcosis is sometimes used when referring to this condition, which sets clear limits on compressed air diving to depths of about 50 m.

The clinical syndrome of nitrogen narcosis is quite similar to alcohol intoxication, and Cousteau coined the term "l'ivresse des grandes profondeurs" (or "rapture of the depths") to describe it. It is characterized by the development of abnormal behavior, euphoria, as well as impaired judgment, intellectual functions, neuromuscular coordination, and performance. The symptoms may begin at depths of 20 to 30 m. At depths greater than 90 m (10 ATA) loss of consciousness can occur. The risk for drowning accidents and death is very high, particularly because of the euphoria and impaired judgment. Individual susceptibility to this condition va-

ries, and there is also some evidence for adaptation from frequent exposures. The narcotic effect is believed to be exacerbated by cold water, hypercarbia, fatigue, strenuous activity, and alcohol consumption. Upon decompression (ascent), rapid and complete recovery occurs.

High-pressure neurologic syndrome (HPNS) was described when breathing mixes of helium-oxygen began to be used to allow deep dives (exceeding depths of 100 m) while avoiding the development of nitrogen narcosis. Increased environmental pressure by itself causes HPNS, although there are interindividual differences in susceptibility. HPNS is characterized by hyperexcitability of the central nervous system. Clinically, symptoms include opsoclonus, headache, vertigo, fatigue, euphoria, nausea, and vomiting. Signs include decreased manual dexterity, tremors of the hands and arms, myoclonus, dysmetria, and hyperreflexia.

The pathogenesis of HPNS is still unclear, but it involves a number of disturbances in neural transmission, in particular enhanced subcortical release of glutamate (with excitation of V-methyl-D-aspartate receptors) and decreased serotoninergic activity. Electroencephalography reveals increased θ-activity. At compressions of more than 30 ATA sleep disturbances are observed consisting of awake periods, increased sleep stages I and II, and decreased REM periods. Brain stem auditory evoked potential studies during saturation dives have demonstrated increased neural transmission times, suggestive of enhanced synaptic excitability. A puzzling observation has been that the effects of high environmental pressure (which explains HPNS) and anesthesia (which nitrogen narcosis resembles) are mutually antagonistic.

Prevention of HPNS may be achieved by reducing the speed of compression, and by adding nitrogen (5–10%) or hydrogen to the heliox breathing mixture. Although anticonvulsants (especially barbiturates) have anti-HPNS activity, they are of no practical use in diving. Serotonin receptor antagonists may provide an additional approach to the prevention of HPNS. Resolution without long-term sequelae seems to be the rule.

DECOMPRESSION SICKNESS

Decompression sickness (DCS) is probably the most frequent dysbaric disorder. DCS occurs upon return from ahyperbaric (e.g., during a diver's ascent) or from a hypobaric exposure (hypobaric or altitude DCS, e.g., in aviators). DCS is a probabilistic phenomenon with clear interindividual differences in susceptibility.

Decompression sickness symptoms are frequently concurrent, and sometimes difficult to differentiate clinically from those of barotrauma of ascent. This is not surprising, given that both conditions result from the

formation and the pathologic effects of gas bubbles. Furthermore, treatment for the two conditions is essentially the same. The terms decompression illness and decompression disorders are being increasingly used to include both DCS and barotrauma. A descriptive clinical classification has been recently proposed that does not attempt to differentiate between these two entities or ascribe the observed clinical features to a given disease mechanism. This chapter, however, follows the traditional approach of discussing these two entities separately.

Clinical Manifestations

Decompression sickness encompasses a broad spectrum of clinical disorders, involving several organ systems with different degrees of severity. The diagnosis of DCS is a clinical one. Multiple organ involvement is more frequent in DCS than in barotrauma of ascent, but the signs and symptoms of both conditions can be quite similar and often occur concurrently. Although symptoms of DCS usually occur within 6 hrs from ascent, they are frequently not present immediately upon surfacing, and delayed presentations (24 hrs) have been described. In contrast, symptoms of barotrauma and arterial gas embolism have a sudden and rapid onset upon surfacing. In practice, any neurologic or cardiovascular symptom or sign that occurs within 15 min of reaching the surface should be assumed to be due to barotrauma and arterial gas embolism until proven otherwise. Both conditions can relapse after initial successful hyperbaric treatment, but this occurs slightly more frequently with DCS than with barotrauma.

On the basis of severity of clinical presentation and the presence or absence of neurologic involvement, decompression sickness has been traditionally classified into two types: type I (mild; peripheral limb and joint pain, cutaneous involvement, no neurologic symptoms), and type II (serious; primarily neurologic including vestibular, cerebral, and spinal involvement, as well as other systemic symptoms). The symptoms of type I disease may mask or antedate the more serious type II manifestations. Although studies differ widely on the relative frequency of the two types of disease, type II disease probably occurs in as many as 80% of DCS patients.

Spinal Cord and Brain

Central nervous system (CNS) manifestations of decompression sickness reflect potentially very ominous complications resulting in permanent neurologic damage. The spinal cord, particularly the lower thoracic and upper lumbar (T_{12}-L_1) segments and its dorsal and lateral columns, is

by far the most frequently affected CNS structure. There is some evidence, however, that cerebral damage may be more prevalent in DCS than was once thought. The predilection for spinal cord in DCS remains unexplained, and it sharply contrasts with the predilection of barotrauma with arterial gas embolism for the brain.

Morphologic studies in humans with DCS have been limited. Four stages of damage to the spinal cord have been described in humans: hyperacute, acute, subacute, and chronic. In the hyperacute phase, abrupt decreases in external pressure and formation of bubbles within tissues leads to an explosive effect. If the pressure changes are less severe, gradual accumulation of bubbles in the white matter may be seen instead. The acute stage generally occurs 10 to 48 hrs following rapid decompression. Infarcts are found in the lateral, ventral, and dorsal columns of the white matter. Early myelin degeneration, and changes in the structure of neurons in the gray matter are also observed at this stage, with associated vascular injury and microthrombi. The subacute stage is characterized by lipid phagocytosis, replacement of cells by astrocytes, and progressive nerve fiber (wallerian) degeneration.

The chronic stage is marked by the progressive organization of white matter infarcts.

The typical presentation of DCS in the CNS begins with transient back pain radiated to the anterior chest or abdomen soon after rapid decompression. Multifocal lesions probably explain the frequently observed combinations of sensory and motor deficits at multiple sites. Subsequently, paresthesias and hyperesthesias develop in the legs. Without medical intervention this situation progresses to urinary retention, lower extremity paresis, and eventually paralysis. Detection of sub-clinical neurophysiologic abnormalities may be possible by using somatosensory evoked potentials (SSEPs).

Although neurologic DCS has been regarded as predominantly a spinal cord disease, on rare occasions it involves the brain. Clinically detectable manifestations of brain damage include visual disturbances, hemiplegia, and unconsciousness. Patients with classic spinal cord manifestations have been reported to have concomitant cerebral perfusion defects. A recent study using single photon emission tomography (SPET) reported statistically significant abnormal brain textures in divers who had experienced DCS in the past, compared to divers who had not. Overlapping results between the two groups, however, were evident, and the significance of these findings remains unclear.

Pulmonary System

Under normal conditions the lungs work well in filtering out most gas microbubbles. In most cases of DCS, no pulmonary symptoms occur, even though bubbles may be detected in the venous circulation. However, the relationship between degree of pulmonary embolization and pulmonary symptoms remains unknown. Morphologic studies of the lungs' response to decompression showed no alteration in the bronchoscopic and histologic appearance of the airway mucosa. Pulmonary edema has been noted on histologic examination of the lung parenchyma. In addition, small autopsy series of patients who succumbed to acute decompression sickness frequently demonstrated fat emboli to the lungs and peripheral organs.

The pulmonary syndrome, called "the chokes" by divers, develops in 2% to 8% of DCS patients and is characterized by paroxysmal cough, substemal chest pain, and dyspnea. Early physical signs include respiratory distress, tachypnea, cyanosis, and in severe cases, hypotension and shock.

Without appropriate therapeutic intervention (i.e., recompression) patients suffering from this syndrome may progress to noncardiogenic pulmonary edema, circulatory collapse, and death. Recompression results in essentially complete reversal of symptoms, usually within minutes. In a case report, complete radiographic resolution of pulmonary edema was documented to occur within a few hours of recompression treatment.

Osteoarticular System

It has been said that bone is the organ that limits human exposures to compressed air. Indeed, involvement of bones in DCS occurs very frequently, and includes an acute pain condition (known as the "bends"), and the late, chronic complication of dysbaric osteonecrosis or aseptic bone necrosis.

The bends are one of the most frequent and typical manifestation of decompression sickness. They consist of pain felt in the joints, or in both muscles and bones. The pain has been described as dull, throbbing, gradual in onset, variable in progression and severity, and occasionally preceded by paresthesias. The affected extremity is usually held in a semiflexed position, and less intense pains are referred to by divers as the "niggles." It is believed that the bends are caused by air embolism most likely affecting the bone marrow, and to be related to later development of chronic dysbaric osteonecrosis. The diagnosis of this condition is based on its clinical features. Evaluation includes a search for involvement of other organ systems, and treatment is the same as for all DCS (as discussed below).

Dysbaric osteonecrosis (caisson disease) is a late and chronic complication of exposure to hyperbaric environments. Caisson disease was first recognized at the beginning of the century in men who had worked in caissons. It was later described in divers and, rarely, in aviators exposed to hypobaric environments. Adherence to recognized decompression procedures does not completely prevent bone necrosis. The lack of early symptoms (and few late ones) and its long latency (months or even years after the initial exposure) also contribute to the persistence of this occupational hazard.

Incidence and prevalence of dysbaric osteonecrosis among occupationally exposed workers have varied over time. In divers, prevalence seems to correlate with exposure dose (e.g., in terms of amount of pressure, and number and duration of dives). Statistically significant correlations have also been suggested between the presence of definite osteonecrotic lesions and number of episodes of decompression sickness, as well as body weight. In the United Kingdom, the Medical Research Council Decompression Sickness Registry, based on 10-year longitudinal data on 4,980 commercial divers, estimated the prevalence of dysbaric osteonecrosis at 4.2%, and the highest incidence at 6/1,000/year of diving experience. When the comparison has been possible, dysbaric osteonecrosis has been found more frequently in compressed air workers than in divers. Among compressed air workers the incidence of bone lesions also appears to be related to exposure dose (intensity of hyperbaric exposure and number of hyperbaric experiences). No lesions have been reported in workers exposed to less than 2.4 ATA, and osteonecrosis is most common when the pressure exceeds 3.6 ATA. At least 50% of experienced compressed air workers who have been exposed for many years have bone lesions. Yet, there is evidence that even a single hyperbaric exposure can result in osteonecrosis. Men without previous exposure to compressed air who suffered at least one attack of the bends were more likely to have a bone lesion than those who had not suffered such attacks. Conversely, not all men with radiographic evidence of osteonecrosis were thought to have experienced acute decompression sickness. Furthermore, in the absence of any additional hyperbaric exposure, new lesions may develop in previously normal areas, and existing lesions may progress.

Dysbaric osteonecrosis usually develops only in portions of long bones and in sites where fatty bone marrow is found in mature adults. The most common sites are the distal end of the femur and the proximal end of the humerus, tibia, and femur (Fig. 9.2). At each of these sites two types of lesions can occur. Juxtaarticular (JA) lesions are situated adjacent to the joint surface, more frequently in the femoral and humeral heads and sel-
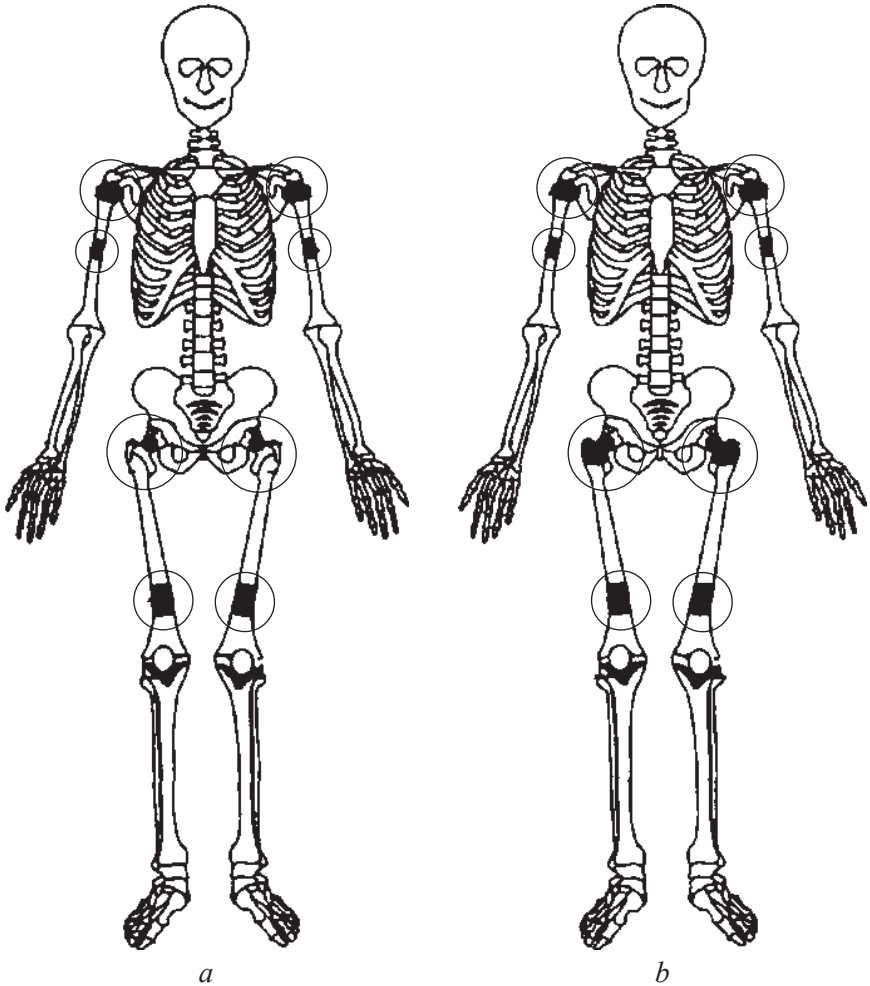
Fig. 9.2. Distribution of bone lesions
in compressed air workers (*a*) and commercial divers (*b*)

dom near the articular surfaces of the knee or elbow joints. The head, neck, or shaft (HNS) lesions, are situated in the remaining parts of the bone that lie at a distance from the joint surface. HNS lesions most frequently affect the medullary cavity of the lower femoral and upper tibial shaft, but may involve the neck and head of the femur and humerus and are often bilateral and symmetric. While HNS lesions usually remain symp-

tom free, JA lesions may cause pain and limitation of movement due to damage to the adjacent joint surface. Structural failure of the joint may result, and osteoarthritis may develop, causing marked disability. In divers, joint damage was estimated to occur in 14.5% of previously identified JA lesions.

While the characteristics of the osteonecrotic lesions that occur in divers and compressed air workers are essentially indistinguishable, their emphasis and distribution varies in the two groups. JA lesions have been described to occur more commonly in compressed air workers than in divers and have a predilection for the femoral head. In contrast, JA lesions in divers occur more frequently in the humeral head. When HNS lesions occur, their location is more often in the humerus in compressed air workers and in the lower femur in divers.

The precise cause of dysbaric osteonecrosis is not known. It is believed to result from occlusion of multiple end arteries in the bones by intravascular gas bubbles that develop during decompression; experimental evidence, however, is insufficient. Alternatively, it has been hypothesized that rapidly expanding nitrogen gas would cause bone marrow adipose tissue damage with disruption of lipids and lipoproteins. The latter would then lead to local release of intravascular procoagulant factors and the blood changes discussed before.

No satisfactory experimental animal model exists for dysbaric osteonecrosis. Within just a few hours of arterial occlusion, the absence of osteocytes from the bone lacunae can be recognized.

As repair of a necrotic area takes place, granulation tissue grows from the living bone into the necrotic area and new bone is laid over the dead trabeculae without prior resorption of latter. This formation of new bone and failure of resorption creates an area of thickened trabeculae that is separate from the dead bone and marrow. If the area of bone necrosis is not too extensive, it may be completely repaired. This buildup of the trabeculae takes at least 5 months after the ischemic episode to appear and is the first point at which radiographic changes appear. As time passes the changes become more pronounced, the dense areas growing larger. Structural failure of the articular surface, easily detectable by radiography, may eventually occur and can lead to secondary osteoarthritis. The time from the first radiographic indication to the point of structural failure can range from several months to a few years; the patient remains symptom free until the articular surface is no longer intact. If bone death is not extensive and complete repair occurs, the radiographs return to normal.

Mesenchymal malignancies have very rarely been reported in association with preexisting osteonecrosis, regardless of the etiology. In the

majority of reported cases (including all of those associated with dysbaric disorders), malignant fibrous hystiocytomas have been the histologic type. Tumors have developed in the distal femur, femoral head, and distal tibia, and all reported cases have been associated with HNS lesions, with long (about 20-year period) latencies between last exposure and diagnosis.

Because the first changes leading to osteonecrosis are only slightly different from the normal variation in the trabeculae, early radiographic diagnosis requires high-quality radiographs and skilled interpretation. Routine bone surveys should include the proximal ends of the humerus and femur and the shafts of the femur and tibia. The most common radiographic abnormalities (in order of descending frequency) are calcified areas in the shaft of the bone, juxtaarticular dense areas and spherical seg-mental opacities, and linear opacities. A generally accepted classification developed by the British Medical Research Council Decompression Sickness Registry is used for clinical and surveillance purposes. It first classifies the lesions according to their location (JA or HNS), and then describes the patterns of altered bone density and structural failure.

On radiographs, some difficulty may be experienced in distinguishing dense areas of aseptic bone necrosis from the bone islands that are commonly found in the normal skeleton. However, bone islands are usually composed of uniformly dense compact bone and are ovoid or oblong. Lesions of aseptic osteonecrosis are usually irregular and have thickened trabeculae running through them. Also, as mentioned previously, they are often multiple and bilateral. Radiographic changes due to dysbaric osteonecrosis must also be differentiated from those of other conditions such as Gaucher's disease, sickle cell anemia, the arthropathy of steroid therapy, alcoholism, radiotherapy, some hemoglobinopathies, and osteoblastic metastases. Most of these causes of bone necrosis are rare in relatively young and healthy persons; therefore, when osteonecrosis occurs in a person exposed to a hyperbaric environment, as long as the other causes are ruled out, it can be attributed to work.

Additional imaging techniques may be useful in the diagnosis of dysbaric osteonecrosis. These include computed tomography (CT), bone scintigraphy, and magnetic resonance imaging (MRI). CT gives much better definition than conventional radiography. In the early stages of osteonecrosis, CT allows clearer identification of the thickened trabeculae. Structural failure is also more easily identified with CT. Bone scintigraphy with "technetium-labeled" diphosphonate seems more sensitive than traditional radiographic methods. With bone scintigraphy the necrotic area of bone produces a "cold" lesion resulting from decreased or absent uptake of radioisotope from the hypometabolic area. During revascularization, radioiso-

tope uptake increases, producing a "hot" lesion. While bone scintigraphy is a powerful tool in that it can identify areas of osteonecrosis within several weeks of ischemia, it is not without limitations. What bone scintigraphy possesses in sensitivity, it lacks in predictive value. Many bone diseases show the characteristic hot spots that occur in osteonecrosis. Moreover, fewer than half the lesions shown by bone scintigraphy progress to positive radiographic evidence of osteonecrosis. MRI has enhanced the detection of osteonecrosis thanks to its ability to image in multiple planes and to more clearly identify soft tissue and bone marrow. On MRI necrotic areas appear as homogeneous areas of decreased signal intensity in the JA area within just a few days. As revascularization occurs, so does an increase in the signal intensity. MRI can be helpful in the detection of early lesions. However, like bone scintigraphy, MRI lacks positive predictive value. Therefore, traditional radiography, in conjunction with CT, still remains the easiest, most readily available method of diagnosing dysbaric osteonecrosis. Bone scintigraphy may prove to be useful in early detection and thus have a role in periodic surveillance. MRI may be useful in clarifying equivocal radiographic appearances. Further work will determine the role of bone scintigraphy and MRI in early detection.

Other Involved Systems

The skin is very frequently affected in DCS. Cutaneous pruritus, erythema, nonspecific macular eruptions, and cutis marmorata are common presentations of cutaneous DCS. Inner ear decompression sickness is more common when helium-oxygen breathing mixtures are used for diving. Symptoms usually begin during decompression (ascent) or shortly after surfacing from a dive. Those symptoms include sensorineural hearing loss, tinnitus, and/or vertigo during or shortly after decompression, which are similar to those of inner ear barotrauma (discussed below). The latter, however, usually occurs during compression or after a shallow dive, and may be associated with middle ear barotrauma. Treatment is the opposite for both conditions (recompression for inner ear DCS but not for barotrauma). Explosion of teeth, especially if they have been previously repaired, has been described after rapid decompression and it is more frequently consider a form of barotrauma of ascent. Ocular signs and symptoms occur in about 7% of all DCS cases, and may include nystagmus, diplopia, visual field defects, cortical blindness, convergence insufficiency, central retinal artery occlusion, and optic neuropathy. Fluorescein angiography findings similar in appearance to those of choroidal ischemia have been documented in divers, but their significance remains to be es-

tablished. The hematopoietic system is affected even beyond the intravascular changes in blood components and plasma volume that have been discussed above. Bone marrow infarction has been recognized as a complication of decompression sickness. This is a consequence of bubble-induced swelling of fat cells in the marrow rather than direct toxicity to the hematopoietic series. Nephrotic syndrome due to minimal-change glomerulonephritis was described in association with DCS in one case report.

Treatment and Prognosis

Ideally, DCS should be prevented by decompression schedules that estimate the degree and duration of safe decompression to be allowed for gas equilibration during return to a normobaric environment. Those schedules are developed and revised according to both empiric data and mathematical models of gas elimination in the body. Not surprisingly, current schedules, even when strictly followed, do not completely prevent DCS. Furthermore, it may be impossible to eliminate the risk. Surveillance with periodic radiographic examinations is necessary for persons at risk for dysbaric osteonecrosis.

Decompression sickness is a true medical emergency, especially when neurologic manifestations occur. The primary treatment for decompression sickness (as well as barotrauma) is to administer hyperbaric therapy accompanied by 100% oxygen. The recompression pressure causes bubbles to become smaller, and breathing pure oxygen produces a gradient by which inert gas in bubbles and tissues can diffuse out of the body. Treatment protocols (decompression tables) usually consist of series of timed exposures to increased atmospheric pressure with alternating 100% oxygen and air breathing (to avoid oxygen toxicity). The use of helium-oxygen mixes during recompression seems promising and may be used more frequently in the future. Rapid transport of the victim to a recompression facility is the single most important measure, and the probability of recovery greatly decreases with delays. If transportation is by air, either pressurized or low-flying unpressurized aircraft are preferred. Portable one-person recompression chambers have been devised to initiate treatment immediately while transporting the patients, but are not widely available. If transportation delays cannot be avoided, intermittent administration of 100% oxygen and air is recommended. Additional supportive measures include the use of corticosteroids to reduce nerve tissue edema and volume expansion (intravenous fluids). Their beneficial effects, however, have not yet been substantiated.

Treatment can be extremely effective if begun early, when symptoms are just developing, and tissue damage is only mild. Hyperbaric oxygen therapy has achieved successful results in as many as 98% of cases of neurologic DCS. If treatment is delayed, tissue damage increases; even if all bubbles disappear with hyperbaric therapy, healing requires days to weeks and may not be complete. By a still unknown mechanism, however, some patients (30–50%) relapse after having responded favorably to recompression treatment, long after bubbles may have persisted. Repeated recompression treatment is indicated in case of relapses, or until no further clinical improvement is observed. Somatosensory evoked potential testing may provide a tool to monitor neurophysiologic improvement during recompression treatment.

In most cases the aftereffects of decompression sickness resolve within weeks of initial treatment, yet little is known of subsequent health complications of this disorder. Permanent neurologic defects can result, even with prompt and adequate recompression. In a study of U.S. Navy divers that compared postdecompression sickness hospitalization rates with those for a matched sample of divers who had no recorded diving accidents, divers who had suffered from decompression sickness had significantly higher rates than matched controls for total hospitalizations, symptoms (vertigo, abnormal involuntary movement, limb or joint pain, chest pain, abdominal pain, syncope, and headache), and disorders of the arteries and veins (arterial embolism and thrombosis, phlebitis and thrombophlebitis, occlusion of precerebral arteries, and aneurysm). Other manifestations may not appear for many years. There is controversy, however, about the nature, frequency, and extent of neurologic sequelae of neurologic DCS and arterial gas embolism, which may be difficult to document objectively.

At the present time, there is still no consensus about recommendations for divers who have had DCS. It is probably advisable that diving not be resumed until 4 weeks after an episode of DCS and that it be discontinued if long-term sequelae remain after treatment.

Treatment of dysbaric osteonecrosis is mainly symptomatic. Attempts at repairing and revascularizing necrotic areas of bone in the femoral and humeral heads have been largely unsuccessful. Patients with severe structural failure frequently require prosthetic articular replacement. Workers with definite JA osteonecrotic lesions should be advised to stop their exposures, and should be followed even if they do. On the other hand, data does not support a similar recommendation for workers with definite HNS lesions. The probability of neoplastic transformation in the site of bone infarction needs to be kept in mind during long-term follow-up.

162

BAROTRAUMA

Barotrauma is the second leading cause of death in scuba divers (drowning is the first). Barotrauma may occur during descent or ascent whenever a gas-filled space, such as pulmonary alveoli, middle ear, paranasal sinuses, stomach, or dental fillings, fails to equalize its internal pressure relative to changes in ambient pressure. The most dramatic changes in pressure and volume occur under hyperbaric conditions, but the hypobaric environment of aviation and space flight can also predispose the aviator to complications of barotrauma. Manifestations of barotrauma of descent are usually referred to as "squeeze," and those of barotrauma of ascent as "reverse squeeze." Recreational divers refer to the pulmonary complications of barotrauma as "bubble trouble."

Barotrauma of Descent

The middle ear is commonly affected in divers and air travelers. As the ambient pressure is altered by high altitude or diving, the tympanic membrane (TM) is displaced outward or forced inward because of the compressibility of middle ear air. If the pressure across the TM is equalized by normally patent eustachian tubes, or by forcing air into the tubes by a controlled Valsalva maneuver, there will be no net displacement of the TM and no barotrauma. If the eustachian tube or sinus osmium is blocked, it is not possible to restore gas pressure equilibrium across the TM and intense pain and hemorrhage can result. Blockage is most frequently due to mucosal edema from infections or allergies. Middle ear barotrauma can be associated with usually transient peripheral facial nerve paralysis due to compression of *vasa nervorum* and neurapraxia. If the inner ear is affected, perforation of the oval window may result in symptoms of tinnitus, vertigo, hearing loss, and nystagmus. Temporal relation with the characteristics of the dive help differentiate this inner ear barotrauma from inner ear DCS (see above), which is important in view of their different treatments.

Together with the middle ear, the paranasal sinuses are the most common targets of barotrauma in divers, and the frontal sinuses are more frequently affected. Symptoms of sinus barotrauma include severe pain overlying the sinus or adjacent teeth, sometimes associated with bloody nasal discharge. Submucosal hemorrhage in the ear or paranasal sinuses may be severe enough that surgical drainage is required. Prevention of these conditions can be accomplished by the judicious use of systemic or nasal decongestant and antiinflammatory steroid sprays. Unsatisfactory symp-

tom control and/or failure to equalize middle ear pressure by a Valsalva maneuver contra-indicate a hyperbaric exposure.

During descent, facial barotrauma (face squeeze) can occur if the diver does not exhale through his nose into the mask. The latter allows equalization of the gas pressure in the space between the mask and the face, and the ambient pressure. The manifestations include facial mucocutaneous edema and/or ecchymosis, which does not require treatment. Dental barotrauma, characterized by implosion of teeth (especially poorly filled ones), can also occur during descent.

Barotrauma of Ascent

The ears are rarely affected on ascent because the eustachian tubes normally function as one-way valves, allowing air to escape from the middle ear but not to enter it. Although less frequent than barotrauma of descent, barotrauma of ascent is associated with the most serious and potentially lethal complications: pulmonary barotrauma and arterial gas embolism (AGE).

When transpulmonary (intratracheal minus alveolar) pressure exceeds 100 cm H_2O, gas can escape along perivascular sheaths and rupture into the pulmonary interstitial tissue (interstitial emphysema), mediastinum (pneumomediastinum), pleural spaces (pneumothorax), subcutaneous tissues (subcutaneous emphysema), or the pulmonary veins or the left atrium (paradoxically through a patent foramen ovale) causing arterial gas embolism. Excessive transpulmonary pressure gradients are most common under hyperbaric conditions, such as scuba diving, during which the scuba apparatus allows the diver to maintain near-normal lung volumes despite being exposed to hyperbaric intraalveolar pressures. According to Boyle's law, if a scuba diver ascends from a salt water dive of only 33 feet too rapidly or without exhaling, alveolar volume will double. This differs from breath-hold diving during which the volume cannot exceed total lung capacity at sea level. Less significant volume expansion occurs at altitude. However, even small volume changes may cause barotrauma if individual lung units have prolonged time constants (resistance × compliance) due to obstruction or bronchospasm or if the diver fails to exhale during ascent.

Short of rupturing, overdistention of the lung with resulting local injury results in the relatively mild pulmonary overinflation syndrome. Patients may complain of hemoptysis, with or without chest pain. Chest radiographs may reveal a small pleural effusion. Injury is localized to the overdistended area and requires only symptomatic treatment.

Symptoms of mediastinal emphysema include dysphagia, cough, dyspnea, and pleuritic chest pain that may radiate to the shoulders. Mediastinal emphysema can only be detected radiographically, unless it extends to the subcutaneous tissues of the neck (subcutaneous emphysema). A pneumothorax, especially if under tension, is clinically detectable by a characteristic physical examination: diminished ipsilateral breath sounds, hyperresonance to percussion, and deviation of the trachea to the contralateral side. Concomitant signs include tachypnea, tachycardia, hypertension, and cyanosis. If a pneumo-pericardium is also present, a harsh pericardial rub (Hamman's "crunch") may be auscultated. Treatment of a pneumothorax involves administering high-flow oxygen and placement of a chest tube. Concomitant injuries may require hyperbaric oxygen therapy.

AGE is the most life-threatening syndrome of barotrauma. AGE and decompression sickness share similar pathophysiology (formation of arterial gas bubbles) and treatment (decompression). However, they differ in the source of the gas bubbles, and in that DCS requires a transition to an environment with lower ambient pressure, whereas AGE occurs isobarically. Although it is much less frequent than DCS, AGE accounts for a disproportionately higher number of deaths from diving.

Clinically, there are two main presentations of AGE:

a) isolated CNS symptoms;

b) cardiovascular collapse. In divers, the CNS manifestations predominate (95% of reported cases of AGE). Cardiovascular collapse is thought to be due to either acute myocardial ischemia after coronary artery embolization or neurogenic-mediated hypertension and cardiac dysrhythmias if the embolus lodges within the cerebral arterial circulation.

The neurologic manifestations of AGE are diverse. In contrast to DCS, the brain is the most frequent target of AGE, and symptoms and signs are noticed immediately upon surfacing, almost without exception. Simultaneous embolization of multiple brain arteries occurs, and this explains the diversity of the neurologic clinical findings. Symptoms include vertigo, a feeling of apprehension, confusion, and faintness. Signs progress rapidly and range from sensory disturbances and aphasia to hemiplegia, cortical blindness, hemianopias, confusion, coma, and seizures. Rare, but classic, signs include marbling of the skin of the upper torso, gas in the retinal arteries, and sharply demarcated areas of pallor on the tongue (Leiber — Meister's sign).

Five percent of individuals with AGE die almost immediately and 35% stabilize or deteriorate. The majority (60%) improve within minutes because of redistribution of emboli to the venous circulation. Interestingly,

within 1 hour of initial embolization, approximately 15% of AGE cases recover completely, but frequently relapse. Relapse may be due to the interactions between air and blood elements, and triggering of the inflammatory mediator cascades discussed above.

Treatment is very similar to that of DCS. Despite the severity of AGE manifestations, recompression in a hyperbaric chamber frequently reverses them. Delays in transporting patients to a treatment facility is directly proportional to mortality and frequency of long-term sequelae. A few issues are relevant to the treatment of AGE. Patients are transported in a head-down and left lateral decubitus position and that position is also maintained during hyperbaric treatment. The recommended starting compression is usually higher in AGE than in DCS, to ensure immediate bubble size reduction. Relapse after an initial complete recompression treatment is frequent (about 30%), although usually less so in AGE patients than in those with DCS. Hyperbaric treatment is indicated for relapses, and is continued daily until there is no evidence of further improvement. Although administration of large doses of corticosteroids has been recommended in the treatment of AGE, its therapeutic value is unclear. Cardiac antiarrhythmic medication infusions are being increasingly used. Chest radiograph to exclude tension pneumothorax and continuous ECG monitoring during hyperbaric treatment are also indicated.

As with DCS, there is no agreement on the nature, extent, and frequency of long-term neurologic sequelae from episodes of AGE. Long-term follow-up should include careful neuropsychological assessments. All individuals who have suffered AGE should permanently refrain from diving.

Other Dysbaric Disorders

Oxygen-diving-induced middle ear underaeration is a condition of unknown pathogenic mechanism, believed to be different from middle ear barotrauma. It occurs in divers in the morning hours after diving the previous day with a pure oxygen breathing mixture. The pathogenesis is still unclear. Middle ear negative pressure has been demonstrated by tympanography. Transient pain and hearing deficit are the usual complaints, and effusions can be observed by otoscopic examination. The process is self-limited.

Medical Evaluation of Prospective Divers

Diving requires strenuous activity in an alien, hyperbaric environment. The medical evaluation of individuals wishing to dive needs to focus on conditions that either limit the ability to exercise, are exacerbated by exercise, or can be provoked or worsened by alterations of ambient pressure,

volume, or temperature. Any contraindication for hyperbaric treatment also contraindicates diving. Table 9.3 lists those conditions that are believed to be disqualifying for diving. The major diseases that require exclusion are obstructive lung disease and cardiac conditions. The type of diving (recreational versus commercial) influences the rigidity of the standards used to evaluate candidates.

The elderly should undergo appropriate cardiopulmonary exercise testing prior to diving. The older diver should also be warned about an increased risk of hypothermia.

Obstructive lung disease or previous pulmonary barotrauma place the diver at risk because of hyperinflation, which may occur during ascent, and because of limited exercise tolerance. Similarly, exercise-induced cardiac dysrhythmias are a potential danger for divers. Intracardiac shunts predispose to paradoxical venous emboli followed by arterial gas embolization. Unfortunately, patent foramen ovale (demonstrated by echocardiography during a Valsalva maneuver) is a very common condition in the general population. One study noted a prevalence of 24% in a group of divers who had no symptoms of decompression sickness, compared to two-thirds of divers who had.

Asthma poses a problem when an afflicted individual wants to dive. Exercise or hyperventilation of cold, dry air may provoke airway constriction that can cause nonuniform ventilation distribution and localized pulmonary hyperinflation. Even when asymptomatic and well controlled, asthmatics show evidence of abnormal ventilation distribution as assessed by frequency dependence of compliance testing. Hyperinflation and air trapping theoretically predispose the diver to barotrauma during ascent. Whether the hypothetical concerns of increased risk of barotrauma in asthmatics translates into an increased number of diving accidents in asthmatic divers has not been conclusively documented, and remains a controversial issue. Until recently, most experts disqualified diving candidates who had an asthma attack after the age of 12. Recently, various arguments have questioned this dictum based on epidemiologic data. Of 100 scuba diving fatalities in New Zealand and Australia, 7% occurred in asthmatics, whereas the incidence of asthma in those countries is 12% to 20%. However, there was a strong bias during the decade studied (1980–1990) to exclude asthmatics from the dying population, which may explain the underrepresentation of asthmatics in mortality figures. In a questionnaire study of 10,400 certified divers, 8.3% had a history of asthma and 3.3% currently had asthma at the time of the study. In studies of active asthmatic divers, Farrell and Glanville reported no statistically increased incidence of barotrauma compared to nonasthmatic divers.

Table 9.3. **Medical conditions
that may disqualify individuals from diving**

Pulmonary disease (e. g. Obstructive lung disease)
Asthma (see text)
Bullous or cystic lung disease
Bronchiectasis
Cystic fibrosis
Chronic obstructive pulmonary disease
Predisposition to pulmonary barotrauma
Previous pneumothorax
Previous thoracic surgery
Eosinophilic granuloma
Pulmonary lymphangioleiomyomatosis
Pulmonary hemorrhage
Cardiac diseases
Intracardiac shunts, unrepaired
Coronary artery disease
Exercise-induced tachyarrhythmias
Dysmythmias, not controlled
Neurologic diseases
History of seizure disorder (except febrile seizures in infancy)
Recurrent episodes of syncope
Ophthalmologic and otolaryngologic conditions
Meniere's disease
Middle ear prosthesis
Visual disturbance, severe
External ear canal obstruction
Unilateral vestibular organ damage
Failure to voluntarily equalize middle ear pressures (e.g., by Valsalva maneuver)
Recent eye surgery
Presence of hollow orbital implant
Obstructed nasal and paranasal passages (e.g., upper respiratory infections)
Miscellaneous
Previous episode AGE or sequelae from DCS
Poor physical conditioning
Psychological instability
Clinical dependency
Insulin-dependent diabetes mellitus
Sickle-cell disease or trait
Caries (including poorly filled ones)

The estimated risk ratio for arterial gas embolism was 1.25 (95% confidence interval 0.8–2.1) for asthmatic divers, and 1.65 (0.8–3.6) for current asthmatics. However, a small sample size may have limited the ability to detect statistically significant risk ratios. Asthmatics would therefore face a less than twofold increase in risk of a very infrequent event.

Realizing that a significant number of recreational and commercial divers have active or past history of asthma, the Undersea and Hyperbaric Medical Society recently sponsored a conference on asthmatic divers. Given the fact that many asthmatics dive without experiencing the theoretically increased risk of dysbarism, the experts focused on identifying which asthmatics should be excluded from diving. The panel concluded that:

a) previous policies that excluded all asthmatics from diving may paradoxically increase the risk of dysbarism in asthmatic divers by discouraging them from obtaining an appropriate assessment of their fitness to dive;

b) pulmonary function testing (PFT) is the best method of evaluating an asthmatic's fitness to dive;

c) asthma that is controlled (no symptoms, normal PFT), even if inhaled (not systemic) steroids are required, does not preclude safe diving;

d) acute asthma, as evidenced by symptoms (dyspnea, chest tightness, cough, nocturnal awakenings), signs (wheezing, coughing), or PFT abnormalities, would preclude diving until the symptoms have normalized and returned to the individual's baseline for a minimum of 3 weeks.

Airway hyperreactivity, a physiologic hallmark of asthma, may be best assessed in divers by bronchoprovocation testing with exercise (which simulates the activity of diving); inhalation of cold dry air, methacholine, or histamine are other available methods.

Most experts discourage diving during pregnancy. Pregnant women may incur difficulties when diving due to the physiologic changes that they undergo. Congested mucous membranes may prevent equilibration of the middle ear and sinuses. Abnormal temperature regulation may predispose to hypothermia. In addition, the increase in body fat may predispose to decompression sickness. Of more concern is the fate of the fetus, which can be adversely affected by a decrease in oxygen delivery. Surveys of women who scuba dived during their pregnancies showed a fetal complication rate similar to the general population but statistically increased when compared to women divers who refrained from diving when pregnant.

A previous history of dysbaric disorder is also a consideration. Divers who have suffered DCS should refrain from any diving until 4 weeks after complete recovery. Divers who have sequelae from DCS or who have experienced AGE (with or without sequelae) should not dive at all.

TESTS

1. A man, 48 y. o., spent a holiday at the mountain health resort. After good breakfast he climbed on the height of 800 m with a group of sportsmen at a rapid pace. At the end of the climbing nausea, giddiness appeared, dyspnea, palpitation, and in some hours epistaxis appeared, the pain sensations in joints and their tumescence increased. From anamnesis it is known that he has suffered from hypertension of 1st degree for 10 years. Establish diagnosis:

A. Alimentary toxicoinfection.
B. Hypertonic crisis
C. Rheumatic disease.
D. Mountain disease.
E. General cooling.

2. After skiing in the highlands a man of 40 years old felt fast fatigue, weakness, dyspnea, palpitation, pain in joints, nasal bleeding, vomiting with blood impurity. At slow descent down to the valley these signs decreased, and then disappeared absolutely.

Establish the diagnosis:

A. Disorder of the nervous system.
B. Hypobarism.
C. Coronary disease.
D. Rheumatoid attack.
E. Peptic ulcer.

3. A patient, 34 years old, a diver, complains of pain in the ears, "enflated abdomen", sensation of cold, articular pain (knee and humeral), skin itching ("caisson scabies"). Objective: the pain in nerve trunks, muscles and joints are defined at palpation. The edema of periarticular tissue is marked.

Put the diagnosis:

A. Acute caisson disease of moderate severity.
B. Acute caisson disease, a severe form.
C. Acute caisson disease, a mild form.
D. Chronic decompressive disease.
E. Intoxication with hydrogen sulfide.

4. A patient, 29 years old, a diver. While ascending from the depth, in connection with breakage of the compressor he was compelled to increase the rise. In 2 hours the complaints of sharp weakness, sansation of heaviness and pains in the head appeared. Then sonitus, "fly flashing" before

eyes appeared. The vomiting, strong abdominal pains, often defecations added. Objective: mydriatic pupils, reaction to light is reduced, horizontal nystagmus, bradycardia, intense stomach, painful palpation.

What pathology is meant?

A. Ulcer of the stomach.

B. Acute compressed-air disease, a moderate form.

C. A poisoning with a respiratory admixture.

D. An acute compressed-air disease, a mild form.

E. Hypertensic crisis.

5. A man C., 46, a pilot with a 5-year experience on the preventive examination marks, that in last 3 months in the flight, continued more than 1 hr a desire to yawn, hypersalivation, nausea, sometimes swoon or headaches, strong sweating have appeared. After the flight a malaise still was not kept for a long time. Objective: BP — 140/95 mmHg, heart rate — 80 bpm.

The preliminary diagnosis:

A. NCD, hypertonic type.

B. Vibration disease.

C. Altitude sickness.

D. Cochlear neuritis of a mild degree.

E. AH, the 1st degree.

Chapter 10
OCCUPATIONAL EXPOSURE TO NOISE ——————————

Damage to human hearing from exposure to noise can take two forms: acute, which is secondary to a loud noise such as a blast, and chronic, which is due to long-term exposure to hazardous noise levels. Noises hazardous to human hearing are present in a variety of environments, including military service, civilian occupations, especially manufacturing, and leisure-time pursuits. Noise-induced hearing loss (NIHL) was recognized as early as the publication of Bernardo Ramazini's text on diseases of workers in the XVIII century.

Recent estimates indicate that many people in the Ukraine work where noise exposure levels of 80 dB or greater may present a hazard to hearing and approximately 3.2% of people had some degree of hearing loss. The proportion of those with hearing loss increased with age; within age groups, rates were consistently greater for those who worked in industries defined as noisy.

Clearly, noise is a major occupational health risk. We recommended the following measures to prevent hearing loss:

1. Develop new technology that leads to quieter processes.

2. Develop noise control strategies at the source of existing operations.

3. Develop hearing conservation programs and effective hearing protection devices.

NOISE AND HEALTH ——————————————————

In occupational medical practice, noise presents three fundamental risks to health:

1. Acutely, through blasts, explosions, or other high-impulse noises that lead to hearing deficits.

2. Chronically, through continued exposure to unsafe levels of noise that lead to sensorineural hearing impairment.

3. Through extraauditory effects, including alterations in blood pressure and adverse influences on existing illnesses such as hyperlipoproteinemia and diabetes.

Acute Acoustic Trauma

Exposure to intense levels of noise can cause permanent damage to the middle and inner ear. In one review of 52 cases of acute acoustic trauma (AAT), the most common symptoms were hearing loss (95%) and tinnitus (70%). Most of the cases were thought to have been exposed to noise levels in the range of 140 to 160 dB. Military service accounted for the majority (45%); about one in four had bilateral damage.

Results of audiometric evaluation in AAT may reflect conductive hearing loss secondary to traumatic rupture of the tympanic membrane, disruption of the ossicular chain, and mechanical damage to the oval window, as well as sensorineural loss from cochlear hair cell disruption. Higher-frequency pure tone hearing loss is more common in AAT, with frequencies between 4,000 and 8,000 Hz most affected. A period of weeks to months may be required for hearing to stabilize; the pathologic process resulting in progression of hearing loss from AAT appears not to extend beyond a year unless other factors are present. Even if the audiometric results return to normal, however, permanent damage may have occurred to the sensory cells of the inner ear, and continued exposure to noise may result in further deterioration of hearing. An interesting finding of evaluations of AAT is that most people do not seek medical attention immediately following the blast explosion or traumatic event. It appears that tinnitus, rather than pain or decreased hearing acuity, was the symptom most likely to prompt people to seek a medical evaluation.

Military operations present the greatest risks for suffering an acute injury to the ear. A survey of World War II casualties indicated that aural injuries accounted for 5.8% of the patients treated at a U.S. military hospital in Paris. Relatively little information is available on the extent of occupationally related acute hearing damage that progresses to the sensorineural pattern typical of NIHL.

Unusual explosions have also occurred in certain settings, especially in concert with terrorist activities. One such event in Belfast, Northern Ireland was described. Nearly a year after an explosive blast in a restaurant, 30% of those present suffered from high-frequency sensorineural hearing loss. (Hearing loss was defined as > 30 dB at 4,000 and 8,000 Hz in one or both ears.)

In the Falkland Islands war, military personnel who operated heavier weapons suffered greater hearing loss than those not so exposed. Soldiers operating the heavier artillery, on average, had at least 5 dB loss in each ear at certain frequencies. Blast injuries are particularly difficult to prevent in military operations because of the reluctance of personnel to wear

hearing protection devices for fear that they will interfere with communications and place their lives at risk.

On physical examination the ear is usually normal unless the tympanic membrane is ruptured, which occurs in approximately a third of cases of AAT. Damage to the cochlea, vestibular system, and ossicles of the inner ear can also occur. The diagnostic use of the auditory brain stem response has been found to be effective in the clinical evaluation of a blast injury to the ear. Note that it is not necessarily the ear exposed to the blast that sustains the injury, since blast waves may bounce off walls and surrounding objects to cause an injury in the ear not directly exposed to the source.

Complications following such injuries include persistent perforation of the tympanic membrane, permanent hearing loss, and cholesteatoma. About 10% to 20% of tympanic membrane ruptures require surgical correction, with the remainder generally healing without intervention. The patient with a persistent perforation should be advised to keep water, foreign bodies, and other potential contaminants out of the external auditory meatus. Large perforations and those that appear not to be healing mandate referral to an otolaryngologist.

Although prevention of AAT should be emphasized, these injuries can rarely be predicted. Where prevention fails, proper treatment depends on access to medical care. A number of treatment measures have been attempted that are based on the premise that the blast has caused metabolic disturbances in the sensory cells of the inner ear. Evaluation of the effectiveness of medications, however, is impeded by the lack of preexposure audiometric values.

In a review of medicinal therapy for AAT, no convincing evidence was noted to support the use of vitamin A, B, or E, nicotinic acid, papaverine hydrochloride, or a number of other substances. Dextran has been widely used by the German military with variable results, which may have been in part due to better pre-treatment thresholds in the treated subjects. Reports suggest that following the injury, treatment must be given promptly if the intervention is to be effective. More recent reports indicate a lack of efficacy of dextran. The strength of these claims is difficult to evaluate in light of the absence of clinically controlled double-blind evaluations.

A thorough understanding of the mechanisms of AAT would enhance both prevention and treatment. Animal studies have suggested that certain pathologic features are consistent within species, especially the acute mechanical failure associated with AAT. Consistent findings include separation of the organ of Corti from the basilar membrane and disturbances in function of the tympanic membrane and ossicles. In an attempt to un-

174

derstand the effect of various military operations on the hearing of troops, the U. S. Army sponsored an evaluation of 67 sheep and pigs that were exposed to military operations while they were positioned in an armored vehicle. Tympanic membrane rupture was a consistent finding in the animals; the authors concluded, "The prevalence and severity of ear drum injury is greater for large anti-armor artillery and that the injury correlated with increasing peak pressure" and therefore blast intensity.

Chronic Hearing Loss

Prolonged exposure to noise primarily damages the inner ear, especially the hair cells of the organ of Corti. Cochlear blood vessels, the stria vascularis, and nerve endings associated with the hair cells can also be damaged. Initially, the hair cells of the basal turn of the cochlea are affected; this area is responsible for perception of higher-frequency sound. Eventually, disruption of the medial and apical areas occurs as well.

Although the risk of suffering NIHL tends to increase with advancing age as well as with length of employment, most noise-related effects occur within the early phases of exposure to noise. In fact, most of the damage that occurs to the hearing mechanism tends to occur within the first 10 years. Presbycusis, the impairment of hearing due to advancing age, results in diminished hearing ability usually beginning in the mid-40s and continuing thereafter. People who suffer from sensorineural hearing loss, however, do not usually recognize early changes in their ability to hear. Nonetheless, early changes can usually be documented by audiometric monitoring. A study of army helicopter pilots indicated that only one of four who exhibit decrements on audiometric monitoring was aware of any hearing deficit. Early symptoms of NIHL reflect a person's ability to distinguish higher-pitched consonant sounds. Speech is recognized as less intelligible as opposed to lower in volume. This latter point accounts for the lack of efficacy of hearing amplification devices in the treatment of people whose hearing is impaired due to noise.

Risk Factors

The major risk factor for suffering noise-induced hearing loss is prolonged unprotected exposure to levels of noise beyond 85 dB. A number of other risk factors, however, have been proposed, including hyperlipoproteinemia, diabetes, solvents, cigarette smoking, eye color, and thyroid abnormalities.

The contribution to hearing loss from lipid abnormalities remains uncertain. A review of 100 patients with bilateral sensorineural deficit found

the prevalence of hyperlipoproteinemia to be lower than in the general population. These results, however, differ from other, later results indicating a significant correlation of elevated low-density-lipoprotein cholesterol with noise-induced hearing loss.

A significant issue in occupational medicine is whether workers with diabetes are at greater risk of NIHL. Non-insulin-dependent diabetes may increase the risk of severe hearing loss in those with occupational exposure to noise. Imprecise data, especially regarding the duration and severity of disease, and small sample sizes of workers with insulin-dependent diabetes mellitus (IDDM), have hampered attempts to draw a link between IDDM and NIHL. The cause of diabetes-induced hearing loss, however, is yet to be fully determined, but it appears to be due to metabolic disturbances that affect nerve function. Despite the possibility of increased risk of NIHL among diabetic patients, most occupational physicians do not feel that scientific evidence warrants restricting people with this disorder from noisy work if appropriate measures for reducing noise exposure are followed.

An investigation of more than 2,000 noise-exposed white males in an aerospace company indicated that cigarette smokers have an approximately 40% greater risk of NIHL. In fact, the major risk factors for this cohort were smoking, a noisy hobby such as guns, and number of years worked at a noisy plant. These results give credence to the theory that susceptibility to NIHL may be due to relative ischemia of the vasculature of the inner ear. The contribution of ischemia, however, to the development of NIHL is difficult to discern in light of conflicting scientific evidence, especially regarding people with diabetes. For example, patients with diabetic retinopathy had no greater prevalence of sensorineural hearing impairment than controls. Other studies assessing the contribution of cigarette smoking to the development of NIHL have shown mixed results. Some evaluations have shown a strong association between smoking and NIHL, others a dose-response relationship significant only at heavy smoking levels, and still others demonstrate no association.

After noise, the exposure of most concern in the workplace setting is industrial solvent exposure. Selective midfrequency hearing deficits have been demonstrated in rats exposed to toluene, styrene, xylenes, and trichloroethylene. Solvent abusers, with exposure primarily to toluene, have also demonstrated balance disorders and hearing impairment. Epidemiologic studies of hearing loss in solvent-exposed workers have been more variable, possibly because of the role of other factors, such as workplace noise, aging, and smoking, on the results. High-frequency hearing loss has been described in workers exposed to mixed solvents and noise. Seve-

ral cohorts of workers exposed to solvents in the absence of noise have also shown abnormalities on pure-tone audiometry or on evoked cortical response audiometry, indicating an effect on more central pathways of the auditory response.

Mechanisms of Noise-Induced Hearing Loss

How noise actually damages hearing has been the subject of a variety of research efforts. Most investigations have been conducted on animals and have attempted to determine the cellular and vascular damage secondary to noise. The first detailed description of abnormalities in the inner ear associated with sensorineural hearing loss was published in 1934. Since then, research has indicated that the effects of noise tend to occur in the organ of Corti, within the cochlea of the inner ear. This structure has three outer rows and one inner row of hair cells, with the tectorial membrane suspended above them. The hair cells contain cilia that project toward the tectorial membrane. The energy transmitted from the tympanic membrane via the ossicles to the cochlea vibrates the cilia and is then coded into nerve impulses in the acoustic nerve. The hair cells are quite susceptible to the trauma of loud noise. The cell bodies swell with repeated exposure to loud noise and ultimately the hair cells are destroyed. Studies have indicated that the vascular supply of the basilar membrane is disrupted when high noise levels are applied. Capillary vasoconstriction in response to loud noise may result in diminished oxygen tension and local hypoxia within the cochlea.

A variety of animal investigations have been performed that confirm the mechanisms described above. In a transmission electron microscopic study, edema and swelling of the afferent nerve endings below the inner hair cells were noted. Following an acute reaction, in which the hair cell was distended, a cytoplasmic protrusion occurred that indicated cell damage. These changes to the afferent nerve fibers were also noted in an investigation of guinea pigs. In general, most investigators agree that a combination of mechanical, metabolic, and vascular factors are involved in the destructive changes that lead to NIHL. Eventually, the organ of Corti breaks down with separation of segments of sensory cells from the basilar membrane, leading to elimination of sensory structures and replacement by a single flat cell layer.

In a study of rats, mean cochlear blood flow was much lower in noise-exposed groups than in those not exposed to noise. In fact, an interesting finding of potential clinical application was noted: rats that were spontaneously hypertensive tended to have a greater decrease in blood supply

than those that were not hypertensive. This finding may have some relevance in evaluating the extraauditory health risks associated with noise, such as hypertension. This observed reduction in cochlear blood flow could lead to hypoxia, and ultimately disruption in inner ear metabolism. This finding that hypertensive rats were at greater risk for NIHL was confirmed by another study. It remains unclear, however, whether the decrease in blood supply associated with impaired hearing is either a primary or secondary pathologic response. Another animal investigation noted vasoconstriction of the cochlear blood vessels in response to exposure to high noise levels. These authors also proposed impaired blood flow in the inner ear capillary as the major mechanism leading to NIHL.

According to some authors, the pathologic abnormalities associated with NIHL can be differentiated from those due to presbycusis. Certain morphologic abnormalities, for example, appear to be different. Noise disrupts the outer and inner hair cells of the organ of Corti; ultimately degeneration of nerve fibers and ganglion cells occurs. Presbycusis, by contrast, causes abnormalities over the entire auditory system.

Extra-auditory Effects of Noise

The extraauditory effects of noise, most notably hypertension, remain an area of active interest regarding health implications of noise. Investigative results, however, have varied regarding the relationship to hypertension of long-term noise exposure. The basis of the proposed relationship between noise and hypertension is grounded in the stress response, that is, as a result of noise, release of adrenocortical hormones and sympathomimetic mediators leads to increased heart rate and eventually higher blood pressure. Investigations have been hampered because the prevalence of hypertension and presbycusis, as well as NIHL, tends to increase with age.

A number of investigations have been conducted into the relationship between noise and hypertension. One approach involves correlating noise levels with blood pressure measurements, which has been attempted in some cross-sectional evaluations. For example, the blood pressure of certain noise-exposed groups can be compared to a similarly matched group of workers not exposed to loud noise. Another approach is to evaluate the blood pressure of people with sensorineural hearing loss and compare their measurements to those of matched controls without NIHL. An investigation of nearly 200 workers in a quiet plant (less than 81 dB) in comparison to others in a noisy plant (greater than 90 dB) observed no difference in mean systolic or diastolic blood pressure. A strong relation-

ship, however, was noted between severe NIHL (defined as a hearing threshold of 65 dB or more at 3,000, 4,000, 6,000, and 8,000 Hz) and high blood pressure (defined as diastolic pressure more than 90 mm Hg or a physician's prescribing hypertensive medication). The rate of hypertension among older workers with severe NIHL was twice as great as for those without hearing loss. The authors noted the clinical difficulties in distinguishing presbycusis from sensorineural hearing loss. They found that subjects with NIHL were impaired in both ear — and bone-conducted sound and exhibited the traditional 4,000-Hz dip on audiometric evaluation. This study, however, was the first effort in which NIHL proved to be a biologic marker for hypertension, even when traditional risk factors were controlled. These results are consistent with other evaluations that suggest that the duration of noise exposure required to cause hypertension is greater than that needed to cause NIHL.

A study of 245 retired metal assembly workers showed a significant relationship between hypertension and NIHL (defined as more than 65 dB loss at 3,000, 4,000, or 6,000 Hz). Note that these definitions of severe NIHL are not identical to standard threshold shifts that may be detected in audiometric evaluations. The authors also suggested that a threshold of occupational noise exposure may be necessary to increase the risk of hypertension. High-frequency hearing loss has also been associated with elevations in serum cholesterol, which may lead to impaired blood supply to the inner ear. In fact, a model for an apparent interaction between hypercholesterolemia and NIHL has been proposed.

An investigation of automotive workers, however, found no relationship between mean blood pressure and hearing loss at 4,000 Hz among white workers. Among the 119 blacks in the study a higher prevalence of hypertension (32%) was noted than in the 150 whites (22%).

The authors noted other interesting findings. In particular, they found no correlation between years of exposure and hearing loss; as a result of this finding, they suggested that the exposure years may not accurately reflect cumulative noise exposure. Moreover, because of blacks' higher risk of hypertension, the authors suggested they may also be more susceptible to sensorineural hearing loss. A study of nearly 500 people who worked in a textile plant and were exposed to levels of noise beyond 100 dB revealed that approximately a third had hypertension. The authors noted, however, that the relation of arterial hypertension to noise exposure was not strong. Studies of human volunteers have tended to support a relationship between noise and diastolic blood pressure elevations in both normotensive and hypertensive volunteers.

Fifteen healthy normotensive medical students exposed to 95 dB noise for 20 min exhibited significant elevations in diastolic blood pressure. This elevation in diastolic blood pressure secondary to noise is confirmed by other investigations. The authors proposed that noise activates the sympathetic nervous system and elevates blood pressure by increasing total peripheral resistance. Animal studies support the concept that vasoconstriction of the cochlear vessels plays an important role in causing NIHL. An interesting aspect of this mechanism is that different strains of rats have marked differences in susceptibility for contracting hypertension due to noise. In a review of the animal literature, Pillsbury claimed a significant relationship between hypertension, noise, hyperlipoproteinemia, and hearing loss.

Various hormonal responses have also been described secondary to noise; effects range from increased levels of urinary catecholamines to increased concentration of 17-hydroxycorticoids. Increased postshift urinary cortisol excretion has been noted in workers exposed to high ambient noise levels compared with those wearing hearing protection equipment. These findings bolster the hypothesis that noise acts as a general stressor in the setting of normal work demands.

Pregnancy and Noise

Exposure to noise has resulted in teratogenic effects on laboratory rats, including reduced fertility and enlargement of the ovaries. In a case-control study in Finland, approximately 1,200 women were evaluated. Results showed no relationship between occupational noise exposure (greater than 80 dB) and risk of either premature birth or low birth weight. Only approximately 3% of the study group, however, reported any exposure to noise at work during their pregnancy. Moreover, approximately two-thirds of the noise-exposed women were on sick leave during their pregnancy.

It is unclear what effect exposure to noise during pregnancy may have on the unborn child, in terms of increased rate of miscarriage, low birth weight, or prematurity. Most evaluations have been conducted on women living in the vicinity of airports. Exposure to noise in utero may affect hearing later in life. In a study of 131 offspring of Quebec women, there was a threefold increase in the risk of high-frequency hearing loss in the children whose mothers were exposed in utero to noise in the range of 85 to 95 dB, and a significant increase in the risk of hearing loss at 4,000 Hz when there was a strong component of low-frequency noise exposure.

Clinical Evaluation of Hearing Impairment

Physicians who practice occupational medicine are likely to find themselves asked to assess hearing impairment, prevent further deterioration of hearing, and recommend patients for further evaluation and treatment. Human hearing has a remarkable capability for differentiating sounds ranging from a rustling leaf to the blast of armaments. In fact, the ear can hear frequencies as low as 20 Hz and as high as approximately 20,000 Hz.

The early symptoms of NIHL tend to be subtle and may not be readily recognized by the patient. As NIHL progresses, the person's ability to distinguish softer sounds is usually disrupted first. For example, the sounds of birds and other high-frequency sounds such as voices may be difficult to discern. People with high-pitched voices, such as children and some women, may speak in a way that presents difficulties for a person with NIHL. In general, the amplitude of the sound is not affected as much as its clarity. As noted earlier, people with NIHL initially have difficulty with higher-pitched sibilant consonant sounds, such as distinguishing the word fish from fist.

Since the primary effect of NIHL is on the inner ear, the astute physician must be aware of other symptoms of inner ear disease, especially vertigo. Vertigo is often the first symptom of inner ear disorders. Both vertigo and high-pitched tinnitus can be early signs of acoustic neuroma. Its presence may also suggest Meniere's disease.

Vertigo, however, is seldom associated with NIHL or presbycusis. Nevertheless, NIHL rarely, if ever, produces profound deafness, but the condition tends to be progressive. Hearing handicaps are usually noticed when the threshold hearing level of important (speech frequencies such as 500, 1,000, 2,000, and 3,000 Hz) averages more than 25 dB.

The diagnosis of NIHL is straightforward when the physician incorporates a clear occupational history of noise exposure with the results of an audiometric evaluation. The audiometric results may indicate the need for further evaluation with more detailed diagnostic studies. The major pathologic entities in the differential diagnosis of NIHL are presbycusis and ototoxicity, although more than 40 genetic and metabolic syndromes can cause deafness. Physicians evaluating the contribution of workplace noise to hearing loss should also consider nonoccupational causes such as target shooting, motorcycle riding, hunting, loud music, and portable radios. It has been shown, for example, that personal stereos with headphones can generate noise levels well beyond OSHA standards. The major drugs associated with deafness include furosemide and aminoglycoside antibiotics (gentamicin, for example). Analgesics, such as salicylates

and antihistamines, as well as tricyclic antidepressants have been associated with ototoxicity. Salicylates, in particular, are well known to cause reversible tinnitus.

In evaluating a hearing-impaired person, the physician is advised to review the results of pure-tone audiometric testing, which assesses the ability to hear various standardized frequencies. During the test, tone levels are increased in volume until the person recognizes the sound. The decibel reading at which the person first recognizes the sound at each frequency is recorded; this value is termed the hearing threshold for that frequency. Threshold levels above 25 dB are abnormal, and are especially important when the speech frequency ranges (500 to 4,000 Hz) are affected.

Early impairment due to NIHL tends to occur at 4,000 Hz, with preservation of hearing at higher frequencies (8,000 Hz). These findings are typical of NIHL, with this 4,000-Hz notch persisting and deepening with increased hearing loss secondary to noise. With presbycusis, the audiometric pattern has a similar decrement in the 4,000-Hz range; however, the loss tends to be greater still in the 8,000-Hz range, and no notch is noted. The audiometric findings of hearing loss due to ototoxicity are similar to those of presbycusis.

Despite the differences described for audiometric results, differentiating NIHL from presbycusis can be a difficult exercise. Moreover, presbycusis and NIHL can act concurrently to affect hearing. People with NIHL, however, tend to show high-frequency hearing deficits for both ear and bone conduction of sound, reflecting the sensorineural character of the hearing loss.

Other diagnostic and screening tools used to identify hearing impairment and distinguish between differing etiologies have been described. To assess the degree of hearing impairment among people over 65 years of age, a handheld audioscope was combined with the Hearing Handicap Inventory for the Elderly (HHIE), a self-administered ten-item questionnaire designed to assess emotional and social problems associated with impaired hearing. The audioscope can be inserted into the ear and delivers a 40-dB tone at frequencies of 500, 1,000, 2,000, and 4,000 Hz. In this evaluation of 178 patients, the audioscope proved to be a sensitive and reliable test for the detection of hearing impairment in persons older than 65 years. The same study, when coupled with the HHIE, was 83% accurate in diagnosing NIHL.

After reviewing diagnostic studies, especially the audiometric evaluation, the physician can formulate an opinion as to the cause of hearing loss and whether therapy may be effective. Unfortunately, treatment mea-

182

sures for NIHL tend to be ineffective, since the primary problem is not the amplification of sound but the distinguishing of various types of sounds. Thus, amplification devices that correct other types of hearing impairment by increasing transmission of sound in the middle ear are largely ineffective. Nonetheless, the physician should be aware of the need for otologic referral in evaluating hearing loss. Consultation with an otolaryngologist may be necessary when reviewing audiometric monitoring tests of a hearing conservation program or for clinical evaluation of individual patients. Some points to remember in the evaluation of suspected NIHL include the following:

1. Chronic NIHL is usually symmetric; other otologic disorders, especially the more serious, as well as treatable, types, are often asymmetric.

2. NIHL usually develops gradually; other otologic disorders may progress rapidly.

3. NIHL usually causes high-frequency threshold shifts.

4. Regardless of the cause, a pure-tone threshold average in excess of 25 dB in either ear is likely to cause hearing difficulties.

Noise-Level Assessment

The first step in assessing the need for an HCP is to measure the ambient noise level. Assessments are customarily performed by an industrial hygienist or a similar professional. Measurements performed in the occupational setting usually consist of overall levels that are obtained either through a sound-level meter or a noise dosimeter. Monitoring of certain areas of a facility that generate noise is required to identify employees who need to be enrolled in the HCP or who require hearing protection. These measurements can also be effective in determining the amount of attenuation required of the hearing-protection devices may be used. Moreover, noise assessments help to acquaint employees and employers with the level of noise in the facility. When area surveys are not appropriate, individual measurements must be made with a personal dosimeter. This particular approach, although capable of yielding more accurate results, tends to be more time-consuming and complicated. Generally, an employee wears the noise dosimeter on the shirt collar throughout a work shift. Accurate measurements depend on reliable calibration of the monitoring device. In certain circumstances it is worthwhile to assess noise at the ear. An approach to monitoring noise exposure in workers who wear communication headsets has also recently been introduced. This first step, assessing the noise levels encountered in work, is one of the more critical determinants in evaluating the need for an HCP. Once noise levels are

determined, they need to be reevaluated at intervals, especially if new processes or plant equipment are introduced into an operation. The occupational physician who is asked to participate in an audiometric monitoring program should obtain results of noise level assessments, the date of the measurements, and an assessment of whether they reflect normal operations.

In work settings where noise levels exceed 90 dB, engineering controls should be employed. Machinery design, enclosures, and noise-control products can be effective in reducing noise at its source. The importance of noise-control measures cannot be overemphasized. One author, for example, has claimed that "prevention of occupational deafness, if it is to be taken seriously, requires a decisive shift to engineering noise control".

Hearing Protection Devices

The fundamental approach to reducing the risk of NIHL is to control noise at its source. In some cases, however, this approach is not feasible, so it is essential to provide hearing-protection devices. These are of three basis types: insert, which are devices inserted directly into the ear canal; semiinsert, which are devices that cover entry into the ear canal; and muffs, which completely encapsulate the ear itself. Hearing-protection devices provide various levels of attenuation (noise reduction). No single type of hearing protection can be considered the single best choice for all users; different workers will choose different devices because of such factors as personal comfort and variations in the anatomic structure of their ears. Thus it is essential to offer employees a variety of hearing-protection devices, to ensure that all can comfortably wear them. During the audiometric evaluation it is worthwhile to acquaint or reeducate the employee in the proper use of the hearing-protection device. When such a device is fitted at the time of the audiometric evaluation, the external canal can be evaluated more thoroughly.

Most hearing-protection devices provide 15 — to 30-dB attenuation. When insert plugs are combined with muffs, an additional 10 — to 15-dB protection can be obtained, a result noted clinically in a study of army helicopter pilots. A noise reduction rating (NRR), which reflects attenuation of environmental noise, must be assigned by the manufacturer of the hearing protection device. Efficacy of these devices in the workplace, however, is dependent on many variables, and attenuation of noise under actual working conditions may be 25% to 75% of the labeled NRR. For a comprehensive review of hearing-protection devices, including selection, fitting, and care, the best source remains Berger.

Education and Training

Physicians may also participate in various educational and training programs designed to acquaint managers and employees with the health implications of long-term exposure to high noise levels. Such educational sessions can be of great benefit in motivating employers and supervisors, and impressing on them the importance of noise control measures and proper use of hearing-protection devices. Employees also need to be apprised of the nature and consequences of NIHL, and of the importance of wearing hearing-protection devices and participating in annual audiometric monitoring programs.

TESTS

1. A man, 49 years old, has worked during 15 years as the tester of engines. What complaints does the man have during a preventive medical examination?
A. Sweating.
B. Headache.
C. Memory impairment.
D. Sonitus.
E. Hearing impairment.

2. A man, 45 years old, visited a polyclinic with complaints of headache, weakness, working ability and sleep disorder, unpleasant sensation in the heart area, sonitus, palpitation, hearing impairment. From anamnesis it is known that the patient during 15 years has worked as a technologist at the water-pump station. Some months ago he had a lincomycine course, a week ago he suffered from influenza. Objective: BP — 140/90 mm Hg. The lability of the nervous system is found. The audiogram reveales an increased level of sound perception.
Establish the diagnosis:
A. Idiopathic hypertension.
B. NCD
C. Infectious cochlear neuritis.
D. Hearing impairment owing to the use of lincomycine.
E. Hearing impairment owing to influence of industrial noise.

3. A man, 49 years old, has worked as a conductor during 20 years. Last 2 months he hasn't heard some music tones. There are a headache, swoons periodically. General otoscopy revealed no changes. At the audio-

gram: rising of sensitivity level. Whispering speech he catches normally. Roentgenogram of the skull bones isn't changed.

Establish the diagnosis:

A. Cochlear neuritis, phase of adaptation.

B. Cochlear neuritis, phase of decompensation.

C. Latent encephalitis.

D. Otosclerosis.

E. Tumor of the brain.

4. A man, 29 years old, a professional DJ, complains of blunt headache, feeling of heaviness and noise in the head, sonitus, hearing impairment, swoons at change of the body position, acrimony, dicrease of attention, infringement of the sleep rhythm, unpleasant sensations in the heart area, palpitation, change of pulse and BP.

Establish the preliminary diagnosis:

A. Neuroinfection.

B. Cochlear neuritis, the 2nd degree.

C. Transient impairment of the cerebral circulation.

D. Cochlear neuritis, the 1st degree.

E. Idiopathic hypertension.

5. A patient, 48 years old, has worked during 10 years at the Belyaevka Water Distributing Station, in the turbine shop, complains on hearing impairment, feeling of heaviness and noise in the head, occured at the end of the duty; muscle weakness, increased sweating, pricking pain in the heart area appeared also. Objective: tremor of fingers of the extended arms, decrease of tendinous reflexes, BP — 140/70 mmHg, Heart rate — 78 bpm. Other tests: hearing loss on 4,000 Hz — 65 dB, perception of whispering speech on 2 m. All kinds of sensitivity are preserved.

What pathology is it possible to think of?

A. Cochlear neuritis with 1st degree of the hearing impairment.

B. Vibration disease, the 2nd degree.

C. Acute otitis.

D. Sound vegetative polyneuropathy

E. Craniopharyngioma.

Chapter 11

INTOXICATION WITH SALTS OF HEAVY METALS (LEAD, MERCURY, MANGANESE) AND THEIR COMPOUNDS ____

The materials having toxic properties are often applied at the industry. Various chemical substances, inorganic and organic compounds, entering an organism in small amounts belong to toxic substances, participate in biochemical reactions in cells and tissues, break the normal processes of metabolism and cause their dysfunction.

Such substances may be initial, intermediate and end products of the chemical industry, different solvents, lacquers, paints, some dopes, components used in engineering and exploitation of gears, as well as pesticides, insecticides and other components used in agriculture.

Toxic ability is a property of chemical compounds to cause harmful action. It is defined as size to absolute meaning of an average lethal doze or concentration: $1/DL_{50}$; $1/CL_{50}$. The first one indicates the doze provoking the death of 50 % of laboratory animals, the second one determines the concentration of the substance. By the level of toxic ability all chemical substances are divided into 5 classes.

The 1st class — extremely toxic substances. It is the most dangerous industrial poisons and insecticides, forbidden to the usage in Ukraine. They are derivative of cyanhydric acids, compounds of lead, mercury, arsenic, etc. For the 1st class the maximally admitted concentration (MAC) of such substances makes up less than 0.1 mg/m^3 in the air of the working area.

The 2nd class — very toxic substances, e.g. methanol, carbon tetrachloride, etc.). MAC is from 0.1 to 1.0 mg/m^3.

The 3rd class — moderately toxic substances, e.g. aromatic hydrocarbon. MAC — 1.1–10 mg/m^3.

The 4th class — low toxic substances, e.g. derivative of urea, etc. MAC — over 10 mg/m^3.

The basic route of exposure of industrial poisons are inhalatory (gases, steams and aerosoles), through the skin and less often — through the gastrointestinal tract. The inhalatory route of exposure to industrial poi-

sons in an organism is basic and the most dangerous (the area of alveolar membranes exceeds 100 m^2).

The toxic substances, well dissolving in fats and lipids, easily penetrate the unprotected skin: organic solvents, aromatic compounds, tetraethyl lead etc.

Some poisons are soaked up already in the mouth cavity. Thus their toxic ability grows. From the gastrointestinal tract through the portal vein toxic substances fall in the liver where they are neutrolized. Therefore MAC of many chemical agents at entering through the stomach can be 100–150 times higher than at inhalation route.

The distribution in an organism of industrial doses depends on their physicochemical properties and can be irregular. For example, poisons dissolving in lipoids are to greater extent are stored in subcutaneous-fat layer. The salts of heavy metals accumulate in the osteal tissue.

The toxic substances accumulate basically in the liver, where they subject to oxidation reactions, reduction, deamination, acetylation, connection with other substances.

Some toxic substances have capacity to be stored in the tissues, forming a deposit. The concentration of the drug in the blood is reduced, but the deposited compound is not decontaminated and under certain conditions can act in the blood again, rendering a harmful effect.

The toxic substances are excreted both in changed and unchanged way through the kidneys, the lungs, the gastrointestinal tract, the skin, the salivary and mammary glands. The nature of toxic action of the substance is determined by its physicochemical features determining specificity of biochemical violations and organ damage. The sex, the age, the personal sensitivity to a poison, the disease in the life history, condition of target-organs are very important. The toxic influence of industrial poisons can be increased by unfavourable factors of manufacturing surroundings, overheating, increase of humidity, physical stress.

INTOXICATION WITH LEAD AND ITS COMPAUNDS

Lead (Pb), a bluish gray metal, is distributed in the earth's crust in a large number of minerals. The most important of these, in terms of extraction of lead, is galena (PbS), which consists of 85% lead metal. Two other significant lead minerals are cerussite ($PbCO_3$) and anglesite ($PbSO_4$).

Galena is usually accompanied by sulfides of silver, antimony, copper, bismuth, and tin. Lead is also found combined with zinc in sphalerite. Lead is a member of group IVB in the periodic table and has a melting point of 327°C. It has two oxidation states, Pb(II) and PB(IV) in addition to its elemental stage Pb(0). The metal is extracted from the ore by concentration of the sulfide, heating (roasting), and reduction. The metal then undergoes refining to remove other metal constituents in the ore. Because of its widespread use, lead and some of its chemical compounds are nearly ubiquitous in the human environment and can be found in plants, oceans, rivers, drinking water, soil, and in various food items. Lead is also present in the air and attaches to dust particles. Consequently, the possibility of human exposure to some form of lead is great. It can be said that the presence of lead in blood and other body fluids serves as an indicator of industrial development and activities; its presence always reflects environmental pollution, whether it originates from the general or occupational environment. Lead is one of the ancient metals, produced by humans and used as early as 6,000 years ago in Asia Minor. Both its use and toxic effects can be traced to the cradle of human civilization. The numerous applications of lead throughout the ages have been as varied as the human mind can envision. To mention a few examples, the Egyptians used leaden tools and vessels, and a leaden statuette in the British Museum in London gives testimony to the fact that lead was also used by the Egyptians in the arts and crafts around 3500 B.C. The Israelites made the candelabrum in the Second Temple of an alloy containing lead; in the Hanging Gardens of Babylon plants were kept in leaden pots to retain moisture, while the Romans drank sapa, wines, and ciders sweetened and preserved with lead. The habit of drinking such beverages was prevalent among the Roman aristocracy and, according to some historians, might have been an important contributing factor to the fall of the Roman Empire.

Although lead may have had a major impact on society as early as two millennia ago, it is only during the past two decades that drastic measures have been taken in many industrialized countries to minimize human exposure to lead. In this respect, the United States has been in the vanguard in controlling both occupational and environmental lead exposure.

Some of the toxic effects of lead were probably known to both the Greeks and the Romans. Hippocrates (circa 370 B.C.) describes a severe attack of abdominal pain (possibly "lead colic") in a man who extracted metals, while Nicander, in the second century B.C., noted an association between exposure to lead and symptoms such as pallor, constipation, colic, and paralysis. Pliny (79 A.C.) mentions that lead-based paint was used on ships and that lead poisoning occurred among shipbuilders in his time.

The numerous epidemics of lead poisoning that occurred in the Middle Ages throughout Europe are of great historic and epidemiologic interest. The ancient Roman practice of improving the taste of poor vintages with additives containing lead was common during the Middle Ages. The many episodes of lead poisoning that occurred during this period were in fact the result of this practice. This was primarily discovered by Eberhard Gockel, an alert physician in the German city of Ulm, who realized that the severe clinical symptoms known as colica Pictonum (the colic of Poitou) that occurred among monks in monasteries in Ulm were caused by drinking wines treated with lead oxide (litharge). His findings were published in 1697. Poitou was the region in France where the habit of adding lead to wines was so prevalent that the colic of Poitou was synonymous with lead colic.

Moreover, another probable cause of intoxication was drinking acidic beverages that had either been stored in lead-glazed earthenware or been contaminated with lead during manufacturing. Thus, Sir George Baker, in his classic description of the Devonshire colic in 1767, traced the disease to cider that had been contaminated with lead. Subsequently, in this episode, other lead-induced clinical effects (e.g., gout) were also associated with exposure.

In 1839 Tanquerel des Planches published a famous study of 1,217 cases of lead poisoning, and his clinical observations contributed much to our current knowledge of the clinical signs and symptoms of this occupational disease, including effects on the central nervous system. He realized that most cases of occupational lead poisoning were caused by inhalation of lead dust and fumes. He also suggested an association between lead exposure and renal disease. In Great Britain, great efforts to control occupational lead poisoning were introduced during the last decade of the 19th century. The pioneering work by Sir Thomas Legge, the first medical inspector of factories, resulted in strict legislation, including declaring lead poisoning a notifiable disease, in 1899.

The adverse clinical effects of lead were not confined to the European continent but occurred in colonial America as well. Symptoms of lead colic were caused by drinking rum distilled in leaden vessels, and in 1723 legislation was passed in Massachusetts "preventing abuses in distilling of rum and other strong liquors with leaden heads or pipes". Serious concern over occupational lead poisoning in the United States began in 1910, with the investigations of several lead-related industries by Alice Hamilton, a pioneer in the field of American occupational medicine. Detailed studies of the clinical and biochemical aspects of lead poisoning were conducted during subsequent decades.

Since lead does not serve any biologic function in the body, its presence has always been taken as a sign of environmental pollution. Despite its known toxic effects and long history of lead-associated diseases, there is evidence that compounds of this metal were used for medicinal purposes, especially during the XVIII century in France. The surgeon Thomas Goulard (circa 1784), a member of the famous medical faculty in Montpellier, used extract of Saturn (a concoction of lead monoxide in wine vinegar) externally to treat a number of conditions: inflammations, sprains, joint stiffness, ligament injuries, and gunshot wounds. Although Goulard did not recommend internal administration of lead, other medical authorities in the XVIII and XIX centuries advocated taking lead acetate per os for epilepsy. It is interesting to note that these physicians were indeed aware of the "side effects" of such treatment, which included abdominal cramps (lead colic).

Although some sources of environmental lead pollution prevalent in modern society are different from those of the Middle Ages, many of the symptoms associated with excessive lead exposure remained consistent over time. Control of lead exposure achieved by legislation and modern technology has undoubtedly made acute lead poisoning a much rarer disease; however, certain neurologic and gastrointestinal symptoms, known for centuries to be lead related, are still common symptoms causing persons exposed to lead to seek medical attention.

During the past two decades much concern has been voiced over the potential health consequences of exposure to lead in both occupational and general environments. During this period several investigators have examined the effects of environmental lead exposure, particularly among infants and young children, who are most sensitive to the effects of lead in society. Through these studies it has become increasingly clear that adverse health effects are seen at levels of exposure that during previous decades were considered safe. Of greater concern is the fact that the levels of environmental exposure at which adverse health effects can be detected have become progressively lower and the magnitude of the lead-related public health risk to children may be greater than was hitherto estimated. Major efforts to reduce exposure to lead have been made or are in progress in many industrialized countries.

Lead and its many compounds will be used in effecting some alloys, accumulators, solders, chemical instrumentation, crystal, for manufacturing of safety devices from irradiation, and also in effecting paints, glazes etc. The contact is most dangerous to those by connections of lead, which one well solve in biomediums of an organism. Basic of them are shown in the table 11.1.

Table 11.1. **Toxic compounds of lead**

Metallic lead — Pb
Lead acetate: (Lead sugar) — Pb $(CH_3COO)_2 \times 3H_2O$
Lead Acetate — Pb $(CH_3COO)_2$
Basic lead carbonate (White lead) — $PbCO_3$
Lead chloride — $PbCl_2$
Lead tetraethyl — Pb $(C_2H_5)_4$

The route of lead and its compounds exposure depends on plant conditions. It takes place basically through the respiratory tract by the way of dust, aerosol or vapors. Less often — through the gastrointestinal tract (by swallowing of spit or at random intoxication) and through the skin at a contact to liposoluble compounds of lead.

The respiratory route is the most dangerous as it acts directly in the blood. Here-in-after it circulates in connection with proteins of plasma, being step-by-step deposited different organs, predominantly bones, displacing calcium. The deposited lead under unfavorable conditions intensively excretes again in the blood, that creates conditions for peaking to intoxication, and quite often long after contact with it.

Sources and forms:
A. Oral ingestion
B. Inhalation
C. Dermal absorption
D. Intravenous route

Pharmacokinetics
A. Absorption
1. Oral exposure. About 300 mcg are ingested each day in the normal adult diet, 10% of which are absorbed. Children absorb 50% of ingested lead. However, absorption after ingestion of organolead, such as tetraethyl lead in gasoline, may be as high as 75%.

2. Inhalation. Absorption is greater and more rapid by the pulmonary route.

3. Dermal exposure. Absorption is poor except in the case of organic lead.

4. Dietary deficiencies of calcium, iron, and zinc enhance lead absorption as well as its tissue storage.

B. Metabolism
1. Although poisoning is generally chronic (months to years), symptoms arise acutely. When exposure is by inhalation or intravenously, symptoms develop far more quickly than if the lead is ingested.

2. Half-life: 32 years in the bones; 7 years in the kidneys.

3. Once absorbed from the digestive tract, lead is distributed to the viscera, chiefly the kidneys and liver; it is then taken up by the skeletal system and stored as the insoluble, biologically inert tertiary lead phosphate. Lead is also deposited in the bones, kidneys, and teeth.

4. Excretion of lead occurs by way of bile, urine, exfoliation of epithelial tissue, and sweat.

5. Accumulation and toxicity occur if > 0.5 mg/day are absorbed.

6. A dose of 0.5 g of absorbed lead is estimated to represent a fatal dose.

Lead and its compounds fall into to poisons rendering polytropic action.

Pathogenesis of Lead Intoxication

1. Disturbance of biosynthesis of porphyrins and heme with development of hypochromia, hypersyderemical anemia.

2. Damage of the nervous system (astenovegetative syndrome, polyneurites, encephalopathy).

3. Damage of the digestive tube (lead line on the gums, gastroduodenitis, lead colic).

4. Disturbance of lipid, carbohydrate and mineral metabolism, sex glands.

One of the basic developments of intoxication by lead compounds is the development of a peculiar "lead" anemia owing to disturbance of biosynthesis of porphyrins and heme.

As it is known, the process of synthesis of porphyrins passes a series of stages. Initial products are glycine and succinic acid. Then as a result of a series of enzymatic reactions the protoporphyrin IX will be derivated, which one after actuation in it divalent iron transforms to a heme. Major intermediate products are aminolevulinolic acid and coproporphyrinogen. A feature of toxic action of lead is depressing activity of the enzymes participating in the subsequent transformations of indicated intermediate connections at the expense of blocking of their sulfhydryl groups. As a result of accumulation of the indicated products their contents in urine is augmented. At the same time lack of formation of heme leads to formation of a peculiar hypochromic anemia. Thus the contents of iron in the blood is heightened, in erythrocytes is stored unused in synthesis of heme protoporphyrins and iron. The lead also renders direct effect on erythrocytes, that results in a decrease of their elasticity, abbreviation of duration of their life and accelerated destruction. Outcome it is the activating of erythrogenesis pronounced in reticulocytosis and appearance of erythrocytes with a basophilic stippling.

The pathogenesis of changes on the part of nervous system at a lead intoxication is connected to disturbance of exchange because of enzymatic disturbance, and also direct operating of lead and its compounds on nervous tissue. Already at early stages of lead intoxication acid-base balance is disturbed. The processes of excitation dominate over inhibition.

Clinical Manifestations

Disturbance of the blood and nervous system is most typical in clinical picture of chronic lead intoxication.

Hematological signs of lead intoxication satumism are:

Hypochromic anemia, with the normal or heightened contents of iron in serum, reticulocytosis, basophilic stippling of erythrocytes. Their degree of manifestation as a whole corresponds to gravity of lead intoxication. The earliest and authentic sign of intoxication is the disturbance of porphyrinic exchange manifested in increased allocation with urine aminolevulinolic acid and coproporphyrin.

The changes on the part of the nervous system at effect of lead and its compounds are shown by the asthenic syndrome, polyneuropathy and encephalopathy. The most mild form is asthenic or asthenovegetative syndrome with its typical features (weakness, heightened fatigue, irritability, headache, decrease of memory and capacity for work).

The polyneuritic syndrome manifests at early stage as sensory distresses, then the condition deteriorates. The hands and feet, and characteristically primary impairment of extensor muscles (e.g. wristdrop) are affected to the greatest extent. The vegetative-vascular disturbances (cyanosis, sweating, decrease of dermal temperature) are frequent. With severe forms of intoxication the mixed forms with considerable increase of an affected zone prevail.

Encephalopathy is characterized by organic changes in the CNS. Clinically the dysarthrias, hyperkinesis, ataxia, tremor, cramps, anisocoria, nystagmus are clinically manifested.

On the part of the digestive organs the changes are observed in secretory and motor disturbance of the gastrointestinal tract. The inclination to hypersecretion of gastric juice, spasticoatonic phenomenon in the intestine, instability of stool, disturbance of taste are marked, etc. In the most pronounced form all these phenomena manifest as lead colic. The sign for the given intoxication is a leaden line. Its appearance is connected to deposit of lead sulphide which is generated due to hydrogen sulphite for people with paradontosis and caries of teeth.

194

An often mark is dyskinesia of the bile duct. There are data about disturbance of lipide, mineral and hormonal exchange.

According to the degree of manifestation the initial, mild and pronounced forms are distinguished.

At the initial form only the laboratory signs of lead intoxication take place: reticulocytosis up to 25%, basophilic stippling of erythrocytes up to 4%, increase of excretion with a urine aminolevulinolic acid up to 15 mg, coproporphyrine up to 300 mcg by 1 g of creatinine.

At the **mild form** alongside with aggravation of laboratory parameters approximately 1.5–2.0 times as much as compared to previous, mild anemia and initial neurologic symptomatology are already determined.

At the pronounced form all the clinical and laboratory symptomes are sharply manifested.

The duration of lead intoxication depends on expressiveness and nature of syndromes. The initial and mild forms usually have the favourable prognosis. After the termination of contact with lead and treatment the parameters normalize. At the severe form the irreversible residual changes are possible. It is important to remember that exacerbation of lead intoxication could occur due to periodic entry of lead from deposit.

A. The gastrointestinal effects
1. Anorexia.
2. Abdominal pain, colic.

Leaden colic is the most frequent manifestation of lead poisoning in adults. The patient is anorectic and constipated, and often has nausea and vomiting. There is abdominal pain but no tenderness. Characteristically, the patient presses on the abdomen to relieve the discomfort. Lead colic generally accompanies lead encephalopathy in children.

3. Intermittent vomiting.
4. Constipation.

B. The CNS effects
1. Irritability.
2. Learning disability and regression.
3. Drowsiness.
4. Persistent vomiting.
5. Incoordination, weakness, paralysis.
6. Headache.
7. Peripheral neuropathy — rare in children, but foot drop characteristic; in adults, wrist drop is characteristic.

Neuromuscular form. Slowing of motor nerve conduction velocity is an early sign of lead poisoning in children; symptomatic neuropathy is

rare. In adults, however, symptomatic neuropathy is frequent in lead poisoning. Typically, lead neuropathy produces weakness, but paresthesias and sensory changes may occur. Extensors are weakened before flexors, and the most-used muscle groups (usually the extensors of the wrist) are involved the first.

8. Stupor.

9. Convulsions.

10. Ataxia.

11. Papilledema, optic atrophy, or both.

12. Retinal pigmentation.

13. Cranial nerve paralysis.

Encephalopathy — more common in children than in adults. Lead encephalopathy occurs in children who ingest large amounts of lead salts. It occurs only rarely in adults and only in those exposed to tetraethyl lead, which is lipid soluble and reaches high levels in the CNS. In children, it is usually accompanied by pica, and it is most frequent between the ages of 1 to 3 years. For unexplained reasons, lead encephalopathy is more common in summer than in winter.

The usual symptoms of lead encephalopathy are personality change, lethargy, and irritability progressing to somnolence and ataxia, and finally, seizures, coma, and death. In children, acute episodes of lead encephalopathy may recur, superimposed on a state of chronic lead intoxication.

The mortality of acute lead encephalopathy is less than 5% at the best, but 40% of victims are left with permanent and significant residual neurologic deficits, which may include dementia, ataxia, spasticity, and seizures.

C. Acute and chronic ingestions

Lead ingestion can be divided into acute and chronic ingestions.

1. Chronic lead ingestion

a) signs and symptoms: nonspecific, vague aches and pains, wrist and ankle drop, chronic nephritis;

b) history: environmental source, family history;

c) laboratory tests: anemia (Hgb < 100 g/l), basophilic stippling, increased urinary ALA, blood level (0.3–0,6 mg/l), erythrocyte protoporphyrin less than 7 times normal;

d) radiography: lead lines, opacities on abdominal films.

2. Acute lead ingestion:

a) signs and symptoms: anorexia, constipation, abdominal pain, behavioral changes, vomiting, lethargy, hyperactivity, clumsiness, ataxia, convulsions, coma;

b) history: same as for chronic lead ingestion;

c) laboratory tests: same as for chronic lead ingestion; also increased urinary coproporphyrins, blood lead level > 0.6 mg/l, erythrocyte protoporphyrin > 1.9 mg/l or > 7–10 times normal;

d) Roentgenography: the same as for chronic ingestion.

D. Less severe symptomatology

Less severe symptomatology may be exhibited in patients who have blood lead levels below the "toxic" level.

E. Differential diagnosis

The differential diagnosis of lead poisoning includes encephalitis, porphyria, peripheral neuropathies (e.g., diabetes mellitus), brain abscess, brain tumor, Reyes syndrome, meningitis (particularly tuberculous meningitis), and other toxic ingestions (e.g., cadmium, zinc, salicylates).

Poisoning with Organic Lead Compounds

Tetraethyl lead was introduced commercially in 1923 and has been used since the 1960s as a supplementary antiknock agent in gasoline. During combustion in the engine, the compound is broken down to inorganic lead compounds such as carbonates, oxycarbonates, and oxides, which constitute most important sources of lead pollution in the general environment. However, some organic lead may also be present in automobile exhaust fumes if the compound has not undergone combustion. The organic lead compounds are colorless liquids that are insoluble in water but soluble in organic solvents. Exposure to these compounds occurs principally during synthesis, transport, and mixing with gasoline. Tetraethyl lead is normally added to gasoline together with other organic halogen compounds such as ethylene dibromide, the latter acting as a scavenger for the removal of lead after combustion. Current world production is estimated to be 300,000 tons per year.

The toxicity of organic lead compounds was recognized soon after they were first employed, and in the 1920s several cases of severe poisoning were described. Stricter industrial hygiene regulations were introduced in 1926, and a considerable reduction in the number of cases with clinical intoxication followed.

The toxicity of organic lead differs markedly from that of inorganic lead compounds. Tetraethyl lead is fat soluble and easily absorbed through the skin; in contrast to the inorganic lead compounds, the organic lead substances can cause lead poisoning by absorption through the skin. It should be noted that penetration of the skin usually occurs without causing local injury. Inhalation of vapor is another important route of entry

into the body for organic lead compounds. Tetraethyl lead is converted to triethyl lead in the liver, and triethyl lead is the active toxic derivative.

Because of the solubility of organic lead in fat, accumulation occurs in the central nervous system, and symptoms of intoxication are referable primarily to this organ system. One of the early symptoms is insomnia, and it can be accompanied by headache, anxiety, restlessness, and excitation of the nervous system. In more severe cases, encephalopathy occurs with a variety of symptoms, including hallucinations, convulsions, and acute psychosis. The gastrointestinal symptoms are usually mild and include abdominal discomfort and anorexia, but the abdominal cramps (colic), so typical of inorganic lead poisoning, usually do not occur. Muscle, hepatic, and renal damage has also been observed in cases of organic lead poisoning from gasoline sniffing. A history of exposure to organic lead compounds and subsequent development of encephalopathy suggest the diagnosis.

The blood lead level is slightly elevated, but the degree of elevation usually does not correspond to the severity of clinical symptoms. Erythrocyte protoporphyrin, urine aminolevulinic acid, and urine coproporphyrin levels may remain within normal range. A high level of lead in urine supports the diagnosis.

Laboratory findings

A. Blood cells analysis

1. *Anemia* is not a common finding. Hemoglobin levels of < 100 g/l due to lead toxicity are normochromic and normocytic in nature, resulting from interference with enzymes responsible for heme synthesis. Bone marrow findings of erythroid hypoplasia and ringed sideroblasts have been reported and are suggestive of interference of RBC synthesis. Lead attaches to RBC membranes, causing increased friability and decreased survival time. This phenomenon is believed to be due to interference with the RBC membrane sodium-potassium pump. Patients with a predominantly hemolytic pattern are more likely to present with more severe anemias than those with a predominantly hypoproliferative pattern, who usually develop only mild anemia.

2. *Reticulocytosis* results from early release of immature RBCs. Myeloid sources attempt to compensate for deceased RBC survival and decreased heme synthesis. Reticulocytosis is not present in iron deficiency anemia and so is valuable for differentiating the two forms of anemia.

3. *Basophilic stippling* of erythrocytes on Wright stain of peripheral blood has been observed to be a less frequent occurrence than anemia. This finding is also nonspecific to lead poisoning and may be seen with thalassemia and pyrimidine 5'-nucleotidase deficiency.

4. *Eosinophilia* is a more common finding than basophilic stippling but is also nonspecific. It has been shown not to be dose-related.

B. Serum lead level

1. Levels of 0.3–0.6 mg/l are regarded as significant for lead toxicity, although levels of 0.6 mg/l in children and 0.8 mg/l in adults may be necessary before clinical symptoms manifest. Atomic absorption spectrometry (AAS) is the most commonly utilized method for measuring blood lead levels.

2. Levels below the toxic range do not rule out toxicity because 90% of lead is stored in bone. Blood levels may be lower after a steady state has been reached and recent exposure levels have been low. A toxic lead level is a strong indication that toxic lead exposure has occurred recently.

3. Unexpectedly high lead levels may be due to contamination of the blood specimen with lead prior to laboratory analysis. Samples must be taken with lead-free needles and vacutainers, and must be placed in lead-free containers to avoid this problem. A second specimen must be analyzed to confirm the high blood lead levels.

C. Erythrocyte protoporphyrin (EPP)

1. This test is often referred to as FEP, or free erythrocyte protoporphyrin. Protoporphyrin accumulates as a result of the lead inhibition of the enzyme ferrochelatase, which binds iron to protophyrin, forming hemoglobin.

2. EPP is regarded as the foremost test for chronic lead poisoning, as it reflects the soft-tissue lead levels and total body lead burden. EPP usually corresponds well with blood lead concentration after the first 2 months of exposure. This lag is due to the time required for EPP to build up in the erythrocytes after interference with hemoglobin synthesis.

3. EPP should be performed in conjunction with blood lead levels to obtain a more accurate picture of total body burden. Iron deficiency anemia also causes elevation of the EPP, but here blood lead levels are normal.

4. EPP is the most widely utilized screening test. A fingerstick specimen can be used with a fluorometer to perform the test. EPP analysis with a fluorometer is a simpler technique than protoporphyrin analysis using Delves cup AAS. The Centers for Disease Control (CDC) has recommended use of EPP to screen all children between the age of 9 months and 6 years.

D. Delta-aminolevulinate dehydratase (ALA-D) activity

1. Lead decreases the activity of this enzyme, which is present in the erythrocyte. This test is more sensitive than measurement of protopor-

phyrin levels. ALA-D activity is affected with blood lead levels of 0.5 mcmol/l; almost complete enzyme inhibition occurs at 2.0 mcmol/l, whereas porphyrin levels remain low when blood levels are <1.5 mcmol/l.

2. Blood protoporphyrin measurements with a portable fluorometer are recommended over ALA-D measurements for screening because the ALA-D assay is more complicated to perform and requires a service laboratory.

E. Urinary ALA and coproporphyrin III

1. Urinary levels of ALA are increased owing to lead inhibiting the enzyme delta-aminolevulinic acid dehydratase (ALA-D).

2. Lead inhibition of the enzyme coproporphyrinogen oxidase has been proposed as a cause for increased coproporphyrin III.

3. Quantification of urinary ALA and coproporphyrin has been used for surveillance of lead toxicity in exposed individuals. Blood fluorometric erythrocyte protoporphyrin analysis has largely supplanted these tests.

F. Calcium disodium versenate (CaNa$_2$-EDTA) provocation test

1. CaNa$_2$-EDTA is administered to evaluate chelatable lead stores. Because serum lead levels may become elevated, it is not recommended for patients who are symptomatic or have blood lead levels > 0.7 mg/l.

2. Patients with lead nephropathy may have falsely low results because urinary lead is the measured parameter.

3. Procedure

a) administer CaNa$_2$-EDTA 500 mg/m^2 intramuscularly or dilute this amount in 250 ml distilled water and administer intravenously over 1 hr;

b) copious fluids are encouraged;

c) urine is procured for lead analysis: an 8-hour specimen from children and a 24-hour specimen from adults;

d) lead excretion ratio: urine lead (mcg) divided by CaNa$_2$-EDTA (mg):

— positive result in children: > 0.6;

— positive result in adults: > 1.0.

G. Indications for serologic evaluation

1. Erythrocyte protoporphyrin is recommended by the CDC for screening and is the primary test used for surveillance of lead toxicity.

2. ALA-D may also be used for screening, but the test costs more and requires special instrumentation.

3. CBC and serum lead level must be determined for all patients who are being evaluated for lead toxicity. Serum lead determinations help guide subsequent management.

4. Urinary ALA and coproporphyrin III may be used for surveillance of continued lead exposure but have largely been replaced by erythrocyte protoporphyrin.

5. CaNa$_2$-EDTA provocation test is used to evaluate the patient for chelatable lead stores and would be indicated for asymptomatic patients with levels between 0.25 and 0.55 mg/l to determine if treatment is indicated.

H. Roentgenography
1. Abdominal flat plate:

a) may show lead densities in the GI tract if the ingestion was within the previous 36 hrs;

b) a negative film does not rule out lead toxicity.

c) a positive film showing densities in the GI tract gives additional evidence for lead toxicity.

2. Long bone films:

a) lead lines are areas of increased density at the distal ends of growing bones, where rapid growth of bone occurs:

— lead lines are present only if there has been heavy chronic poisoning (minimum 4 weeks);

— the width and density of the lines increase with the duration of the exposure;

— multiple lead lines indicate repeated episodes of toxicity;

— lead lines are most commonly seen between the ages of 2 and 5 years when bone is growing rapidly;

b) use as a screening test is poor because roentgenograms are usually negative.

I. Hair and tooth lead
1. It is not useful for diagnosis and treatment of lead toxicity.
2. It is best used for population studies.

J. Additional testing
Additional testing should be directed to the specific organs that may develop pathology as a direct result of lead toxicity.

1. Neurologic effects:

a) intelligence testing;

b) psychological testing;

c) motor strength;

d) lumbar puncture for opening pressure;

e) cerebrospinal fluid (CSF) for WBCs and protein;

f) peripheral motor nerve conduction velocity.

2. Renal effects:
   a) serum creatinine;
   b) urinalysis;
   c) 24-hour urine for creatinine, protein, and uric acid.
3. Reproductive and endocrine effects:
   a) sperm counts;
   b) serum testosterone;
   c) metapyrone challenge test;
   d) serum thyroxine;
   e) thyroid-binding proteins.
4. GI effects:
   a) SGOT;
   b) SGPT.

Treatment is started from the termination of a contact with lead. For removal of compounds of lead from an organism complexons are used. Tetacinum-calcium is administered in the dosage under 20 ml with 10% sol. daily within 3–4 days with an interval of 4–5 days, only 2–3 cycles. Pentacinum is used in the dosage of 20 ml in 5% sol. after the same scheme. D-Penicillaminum Skuprenil is also used by 150–300 mg 3 times per day within 2–4 weeks. With the asthenoneurological syndrome vitaminized drugs, adaptogenes, tranquilizers, soporific (under the indications) are expedient. Vitamine medicines, and also balmeotherapy, massage, resort therapy are applied with polyneurites.

Expertise of Capacity for Work
with the Initial Form of Lead Intoxication

The transfer to work outside the connection with lead for 1–2 months with vigorous therapy (see above) in out-patient conditions is mandatory. In subsequence probable returning to former activity. With the mild form the treatment in the hospital is prescribed, for 1–2 months transfer to work outside the contact with lead and only then (under condition of normalization of parameters) they can return to former activity.

With the pronounced form all yardsticks are hardened — prolong treatment without return to former activity. These people are provided with a job or transferred to a group of physical inability. The preventive maintenance actuates a complex of technical and sanitary-hygienic measures preventing lead poisoning. The medical contraindications for activity with lead including anemias, pathology of the central and peripheric nervous system, disease of vessels and others are established.

INTOXICATION WITH MERCURY AND ITS INORGANIC COMPOUNDS _____

Mercury (Hg) is a metal and a natural component of the ocean and earth's crust. Compared to other elements, mercury is not a major component of the biosphere. The weather and human industry release mercury into the air and water, resulting in its redistribution and increasing the risk of human exposure.

When mercury becomes concentrated in the air, water, or foods as a result of human activity, it is considered to be a pollutant. Modern techniques can detect mercury in parts per billion (mcg/m^3) concentrations in the air or water. Mankind has used mercury since history began, most recently as a germicide and preservative, (e.g., in eye drops), for production of paper pulp, in chemical processes such as alkaline-chlorine plants, and in the manufacturing of vinyl. Mercury is released from burning of fossil fuels and waste materials. Monitoring of environmental contamination may employ chemical analyses of sentinel animals or plant species that accumulate mercury from air or water, as well as specimens taken directly from humans. These monitoring strategies are discussed below.

Mercury exists in three forms: elemental (a liquid commonly known as quicksilver), inorganic mercury compounds, and organic compounds. Although all forms of mercury are toxic, the specific form of mercury influences how mercury moves through the environment and within the body. Both elemental and organic mercury are volatile and absorption by inhalation is significant. The gastrointestinal tract accounts for the most significant absorption of inorganic mercury salts, and for nonoccupational exposures to organic mercury via the ingestion of foods.

The toxicity of mercury compounds is the result of their affinity for sulfur and sulfhydryl groups; this affinity facilitates mercury binding with proteins, which in turn results in cytotoxicity. Alkylmercurials, the most toxic form of mercury, have a high absorbance from the gastrointestinal tract and a slow rate of elimination from the body. These properties cause alkylmercurials to accumulate in both soft and hard tissue with continued exposure, even if the daily exposure is rather low. Details of the uptake, binding, distribution, and metabolism of mercury have been well described.

Epidemiology

Occupational exposure represents a significant portion of mercury poisoning cases. Miners extracting gold from mercury, or extracting mercury ore (mercuric sulfide, cinnabar, is the most prevalent form) provided early cases of occupational poisoning. Exposure is mostly by inhalation.

Respiratory problems dominate the effects of short-term inhalation exposures. Longer-term exposures bring on signs of nervous system disorders (see indices of exposure below). Miners may have neurobehavioral deficits that persist for more than 10 years after the end of exposure.

The dental profession conveys higher risk of mercury poisoning because mercury-silver amalgams have been extensively used to fill dental caries. Exposure is by inhalation and dermal routes. Procedures for handling mercury in dentistry have improved along with increasing awareness of the health hazards of low-level exposure to mercury, and mercury amalgams are now used in only half of the dental restorations of Americans. Dental personnel may have higher levels of mercury in their bodies and may have higher incidence of nervous system impairment than employees of similar socioeconomic status who do not work with mercury. Female dental assistants whose work involved substantial use of mercury amalgams and who practiced "poor mercury hygiene" were less fertile than others who used less mercury in their work. Oddly, the women who used small amounts of amalgam in their work were more fertile than the control group who worked in dental offices that did not use amalgams. These results illustrate that more research is needed before we can fully understand the effects of low-level exposure to mercury.

Mercury is also used in the calibration of glass, in fluorescent lamps, and in thermometers and electrical switches. Workers who had used elemental mercury to calibrate glassware illustrate the onset and recovery from mercury-induced tremor. Other current industrial uses are in paper pulp processing and in alkaline-chlorine factories.

Mercury in the Food Chain

Ingestion of mercury in food is responsible for the largest number of nonoccupational exposures. mercury is taken up by terrestrial and aquatic plants, which become food for humans and other animals. Inorganic mercury is converted to the more toxic organomercurial compounds, primarily by methylation by anaerobic microorganisms in the sedimentary layers of seas and lakes. As larger animal species feed on the plants or smaller animals, the content of mercury in the tissues becomes concentrated, reaching its highest levels in large fish such as tuna, and other predators at the top of the food chain. The major portion of mercury in fish is methylmercury. The risk from heavy consumption of these fish has caused public authorities to regulate the marketing of seafood having > 1 mg/kg mercury. Some seafoods contain significant amounts of selenium. Experiments indicate that selenium binds some of the mercury and thus redu-

ces the toxicity that would occur with a given concentration of mercury without selenium.

The most profound examples of people poisoned by environmental mercury were in Iraq, where thousands of people were poisoned after making bread from seed grain that had been treated with methylmercury as a fungicide and in Minamata, Japan. The Japanese episode illustrated the conversion of inorganic mercury to the more toxic organic forms, by aquatic organisms. Mercury was discharged from a factory that used mercuric chloride in the manufacture of vinyl chloride. The effluent from the factory drained into a bay. Seafood was a principal part of the diet of the local people. The complex path of the runoff of inorganic mercury pollution from land to sea, its conversion to the highly toxic methylmercury, accumulation in the food chain, and finally the delayed manifestations of neurotoxicity among people made it difficult to trace the cause. The tragedies in Iraq and Japan also illustrated the fetus's higher vulnerability to mercury, with the most severe cases becoming apparent at birth but others displaying more subtle deficits later in the developmental process.

Attention has now shifted to children of fish-eating populations. Residents on islands (Seychelles, Faroes) where sea fish are the main component of the diet have slightly higher concentrations of mercury in their blood and hair than do other populations. These studies showed that mothers can transmit mercury to their fetus through their blood supply, and to their infant through maternal milk. Clear evidence of toxic effects is being sought for these relatively low exposures.

Mercury Exposure from Dental Amalgams

Metallic mercury accounts for about 50% of the material in most dental fillings, and small amounts of mercury vapor are released from fillings. The World Health Organization recently concluded that mercury-silver amalgams, used in dentistry for about 150 years, offer several advantages over alternative materials for dental restorations; they provide a desirably hard surface, and are inexpensive and long-lasting. Most dentists believe that amalgams present the patient with no more health risk than that associated with alternative materials. However, people with mercury amalgams exhale increased levels of mercury after brushing teeth or chewing gum and have higher levels of mercury in their blood or maternal milk than persons with few fillings. Mercury from amalgams may be absorbed into the body through the buccal mucosa, the lung or the digestive tract. Mercury appears in the nervous system and kidney of laboratory animals after they were given dental amalgams. These data demonst-

rate the uptake of mercury from amalgams into the body, but do not indicate whether the amount of mercury absorbed from amalgams contributes to health impairment.

Long-term exposure to mercury from dental amalgams can be quantified by the number of amalgam surfaces in the mouth. The level of mercury in the urine represents primarily recent exposure, but urinary mercury levels may be proportional to the number of amalgams. Mercury content of the blood and urine of adults with amalgam restorations is quite low, but mercury is known to accumulate in the kidney and nervous system, where it is less easily measured. Thus, there has been considerable speculation that accumulated mercury from dental amalgams may contribute to health problems (see "Chelation therapy" below).

There is little solid evidence of deleterious health effects that can be traced unambiguously to amalgam. The largest body of research on health effects of amalgams has been done in Sweden. Large epidemiologic studies of adults found no significant impairment of renal or immune systems related to amalgams. One study reported no relationship between amalgams and children's allergic problems. However, there is sufficient concern about mercury from amalgams affecting the more vulnerable, juvenile population to cause the National Institute of Dental Research to begin prospective clinical trials, the strongest experimental design for identifying health hazards from amalgams. At present, the large-scale replacement of an individual's amalgam fillings with nonmetallic materials seems unjustified because the drilling releases mercury and thus worsens the patient's exposure. Occult religions and alternative medical practices lead to some mercury poisonings. Santeria, a quasi-religious practice that has been transplanted from the Caribbean islands, employs elemental mercury in potions that are thought capable of banishing evil forces from a person or their home. It is not surprising that exuberant use of such potions may result in accidental poisoning, but the extent of poisoning attributable to folk remedies is not known.

Indices of Exposure

Exposures to mercury in the workplace have become lower, and fewer cases of mercury poisoning are reported after governmental regulation of many organo-Hg compounds. Exposure to mercury in the ambient air can be documented with personal monitoring devices.

Indices of human body burden are obtained by mercury content of hair, blood, and urine. Most cases of mercury toxicity are associated with detec-

table mercury in the urine. Exposure to metallic mercury vapor and inorganic mercury can be monitored in urinary mercury concentration, after adjustment for creatinine content. Exposure to methyl mercury is best indicated by the concentration of mercury in whole blood, where it is sequestered in the red cells. Blood mercury concentration is a better index of recent exposure to methylmercury than is urinary mercury. The elimination of mercury from blood and urine is much more rapid than from the whole body. Thus, blood and urine mercury concentrations are most influenced by recent exposures (e.g., within a week) and provide less evidence of past exposures.

A more extended chronology of past exposure to methyl mercury can be determined from the analysis of the concentration gradient of mercury along a strand of hair. Analysis of mercury in maternal hair may provide good evidence of fetal exposure during the various gestational stages. The hair and the finger nails are useful indicator media for two reasons: these tissues are composed mostly of keratin, a protein that is formed from many sulfhydryl groups that can bind mercury during the growth process, and because cells of hair and nails survive for a relatively long time. However, care is required to avoid contamination of hair and nails with mercury external to the body, e.g., in dusts and cosmetic products.

Biologic specimens can be analyzed for total mercury content by atomic absorption methods. Cold vapor atomic absorption spectrometry is the most commonly used method to measure mercury in biologic samples. Digestion of the specimen may be required to liberate ionic mercury from the chemical matrix in which mercury is bound. Total mercury may be further analyzed into its organic and inorganic components, if gas chromatography is combined with the atomic absorption method. Other methods and their suitability, depending on the expected concentration of mercury in the specimen and the matrix in which mercury has been found, have been reviewed frequently.

Many new methods are being assessed for their ability to detect molecular or cellular changes that can be shown to indicate exposure to, or effects of, toxicants including mercury. Of particular relevance for mercury is the suggestion that evidence of nervous system damage caused by mercury may be seen in the peripheral blood, in the form of autoantibodies produced in response to fragments of damaged nervous system cells. N-acetyl-p-D-glucosaminidase (NAG) is one of a number of possible markers of renal changes in mercury-exposed workers. Elevation of urinary

porphyrins, one of the earliest indices of chronic exposure to mercury in lab experiments, was also observed in dentists.

Traditional indices of mercury effects, involving measures of behavioral and physiologic processes, are described below.

The clinical picture of a chronic mercury intoxication arises for working at a long-lived contact to mercury. The rates of growth and expressiveness depend on specific features of an organism, dose and time of effect. The basic directivity — primary damage of the nervous system.

The list of the basic clinical signs is shown in table 11.2.

There are distinguished 3 stages of chronic mercury intoxication according to the degree of manifestation.

The initial stage (the stage of "mercury nervosism") is characterised by fewer symptoms and fast reversibility. Alongside with asthenic phenomena emotional instability, frightening dreams, dyspeptic distress (metallic taste in the mouth, hypersalivation, diarrhea), tremor of the limbs are observed. At well-timed relief from the contact with mercury and treatment all the signs of disease completely disappear.

Stage of the moderately pronounced changes takes place at the long-lived experience of activity with mercury, delayed recognition of initial developments. Asthenovegetative disorders rise, the depression combines with excitation and aggressiveness. Mercury eretism, psychopathologic condition take place, as well as endocrine-vegetative dysfunctions, hyperthyroidism, goiter), tachycardia, arterial hypertension. The changes strengthen on the part of the digestive channel and oral cavity, parodontosis, colitis). The diencephalic crisises can take place.

Table 11.2. **The basic clinical signs
of chronic mercury intoxication**

1. Symptom-complex of irritable weakness (or "mercury nervosism").
2. Asthenoneurotic or asthenovegetative syndrome, possible psychopathologic distresses.
3. Tremor of fingers, sometimes heads, legs.
4. Increase of an excitability of sympathetic department of the vegetative nervous system (dermographism, sweating, hyperthermia).
5. Distress on the part of the endocrine glands.
6. Ulitis, stomatitis, gastritisþ
7. Trophic disturbance (loss of hair, brittleness of the nails).
8. Hematological violations (lymphocytosis, monocytosis, anemia).
9. Damage of the eyes.

The convalescence in this stage also is possible at well-timed and steady treatment, and also prevention from activity with mercury. The stage of the pronounced changes is characterized by signs of toxic encephalopathy, the memory and intellect is reduced, hallucinations are possible. The tremor of fingers and arms becomes generalized. The microorganic symptomatology, anizopria, flattening of the nasolabial fold, distinction in tendon reflexes, dysartheria, hypomimia, schizophrenical syndrome are possible.

The diagnosis is established taking into account clinical symptomatology, data and sanitary-hygienic characteristic of working conditions. Diagnosis is confirmed by the definition of mercury in urine (0.02–0.9 mg/l) and in feces.

Chelation Therapy

Chelating agents have been used clinically as an antidote for severe toxicity of mercury. However, there is limited evidence of the safety and efficiency of chelating drugs to warrant their use for extended durations, for less severe cases, or for prophylactic treatment. Most studies have evaluated chelation outcome in terms of the metal's concentration in blood and other exposure indices; there is less evidence to indicate that chelation restores impaired function in the renal or nervous system toxicity of mercury. Many of the neurobehavioral sequelae of mercury poisoning appear to be irreversible, and the severity of neurotoxicity is influenced by the duration of exposure as well as the magnitude of exposure. Thus, chelation or rehabilitation therapies may be useful only if administered in the early stages of intoxication, before irreversible changes occur. Numerous clinical case reports tell of apparently irreversible neurotoxicity of mercury that survives brief chelation treatment.

The most promising chelators are the dimercaprol derivatives, meso-2,3-dimercaptsuccinic acid (DMSA, succimer) and dimercaptopropanesulfonate (DMPS, Dimaval). DMSA and DMPS have advantages over chelating agents used previously for the treatment of mercury toxicity, e.g., BAL (British anti-Lewisite, dimercaprol), EDTA (ethylenediaminetetraacetic acid), and D-penicillamine. DMSA and DMPS are water-soluble derivatives of BAL and thus may be administered orally; they are less toxic than most other chelators, and are effective in reducing metal concentrations in experimental studies, and in reports of clinical efficacy. It is not yet clear whether DMPS or DMSA may be the more effective. More evidence is needed to determine if chelators are capable of reversing the toxic effects of metals in the brain and kidney.

The treatment of mercury intoxications should be complex, with allowance for degrees of manifestation. For the ascent of mercury the antidotes and symptomatic means (Table 11.3) will be used.

The expertise of capacity for work is carried out is differentiated depending on the stage of the process (Table 11.4).

Table 11.3. **Principles of treatment of chronic mercury intoxication**

1. Application of antidotes — Unithiolum — 5 % sol., 5–10 ml intramuscularly, 1st day 2–4 times per day, then once within 6–7 days — Natrium thiosulfuricum — 30% sol. i.v. slowly 5–10 ml daily — Succimerum — at the highly severe forms of 0.3 g is dissolved in 6 ml with 5% sol. of soda: 1st day — 4 injections i. m., 2nd day — 3 injections, 3rd–7th days till 1–2 injections; in mild forms — tab. $0.5 \times \times 3$ times per day within 7 days. — D-Penicillaminum $\sim 0.15 \times \times 2$–3 times a day — 1-st day 2nd day 0.15×1 time, then on alternate days by 0.15 2. Metabolic drugs neurotropic — Aminalonum, Cerebrolysinum, Nootropilum — Stugeronum, Cinnarizinum — Vitamins of group B (B_1, B_{12}) 3. Tranquilizers, small doses of soporifics 4. Hydroprocedures (pine needle baths), MPE, psychotherapy

Table 11.4. **Expertise of capacity for work at chronic mercury intoxication**

1. Initial stage — Temporary break of contact with mercury — Transfer to the other activity for the period of 1–2 months under the labor medical certificate — with improvement of health condition a worker can return to former activity under a careful medical monitoring 2. Manifested stage — The activity in conditions of mercury influence is contraindicated — Transfer to the activity without any toxic substances — The expertise of work ability is necessary 3. At toxic encephalopathy the patients are disabled

The preventive actions are directed on replacement of mercury by less harmful materials, creation of effective ventilation, equipment of opaque surfaces for mercury, air cooling up to 10°C. Periodic medical examinations of the people working with mercury in open condition (mining, smelting of mercury, effecting of mercury paints, etc.) are carried out once 12 months; for working with mercury in a closed condition (devices, pharmaceutical and cosmetic industry) — once 24 months. In realization of physical examinations the participation of therapeutist and neuropathologist is necessary. All inspected carried out definition of the mercury contents in urine.

The additional medical contraindications at employment in the contact to mercury and its compounds include the chronic diseases of the CNS (psychosises), peripheric and vegetative nervous system, diseases of the digestive organs, skin, toxicomania. The indicated limitations allow avoiding of intoxications development in people of high risk group.

INTOXICATIONS WITH MANGANESE

Manganese (Mn) is a reddish-gray or silvery soft metal, a member of group VII elements of the periodic table. Manganese minerals are widely spread. Ores containing manganese (e.g. pyrolusite, braunite, manganite, hauserite, manganesespat, tephroite, and rhodochrosite) could be found on the bottom of the oceans. Most manganese is obtained from ores found in Australia, Russia, Ukraine, India, and Brazil. Manganese is used to form many important alloys. In steel, manganese improves rolling qualities, and malleability, hardness, strength, and mild resistance. Manganese, with aluminum, antimony, and small amounts of copper, can form a highly ferromagnetic alloy. Manganese metal is reactive chemically and decomposes cold water slowly. Many steel and iron manufacturing processes need the addition of manganese to molten iron to reduce its iron oxide content by the formation of manganese oxide. Manganese compounds are used in the manufacture of dry cell batteries, and in paints, bleaching agents, and disinfectants. Manganese is also used as a colorizer and coloring agent in the manufacture of glass and ceramics. Potassium permanganate is a powerful oxidizing agent and is employed in quantitative chemical analysis and in medicine as anticeptic. Manganese is an essential trace element, and is required for the activity of the enzymes mitochondrial superoxide dismutase, galactosyltransferase, and glutamate synthetase.

Manganese is very toxic, therefore in all industries, where the manganese is applied, and also at its mining from ores there is a potential danger of originating of manganese intoxications.

Manganese penetrates an organism through the lungs, to a lesser degree — through the gastrointestinal tract and skin.

Manganese oxides are fast digested. In blood the manganese circulates as a non-persistent complex with serum proteins. It deposites in the bones, the brain, the parenchymatous organs by the way of slightly soluble sodium phosphate. It excretes with feces and to a lesser degree with urine. People exposed to manganese compounds for a long time, if they are not keeping safety precautions could get chronic intoxication with a primary damage to CNS. Manganese is haptene capable to invoke bronchial asthma, eczema. The combined exposure to manganese and silicon dust can be observed. This condition is called manganoconiosis.

Pathogenesis

The manganese, being a trace element, participates in biological processes. It enters the tissues structure, influences metabolism, e.g. oppresses activity of cholinesterase, upsetting synaptic conduction, causes changes in metabolism of serotonin.

With long and systematic exposure manganese causes direct damage to the nervous tissue, and invokes vascular disturbance increasing permeability of capillary tubes. There are data about direct influencing of manganese on the processes of oxidative phosphorylation, excitability of N-cholinergic and adrenergic systems. It changes activity of monoaminoxidases of nerve cells, oppresses a biosynthesis of catecholamins, increases an intensity of protein metabolism. The manganese is capable selectively to strike the nervous system, predominantly its subcortical formations. In initial stages of intoxication the disturbance of cortical activity, and hereinafter — distress of the motor analyzer develop.

Diffused excitation is spread to cortical zones. Simultaneous synergists, excitation of antagonists muscles results in musculation rigidity. It is established that the pathological locuses, developing in the subcortex, invoke excitation in the cortical zone of the motor analyzer. In other words chronic manganese poisoning causes pyramid insufficiency. But this agent also influences the emotions.

Therefore, with chronic manganese intoxication along with structural changes the important role in its genesis is played by complex neurodynamic shifts in majority of CNS's parts stipulating a clinical development of the disease. The manganese changes the functions of the thyroid gland, the cardiovascular system, the gastrointestinal tract, the liver, etc.

Clinical Manifestations

The symptomatology of a chronic manganese intoxication develops step-by-step, that invokes definite difficulties in diagnosis of its initial forms.

The basic signs of intoxication are the functional disturbance of the CNS, which has a progradient course and can turn to organic changes. The damage of a striopallidal system is specific, that in the pronounced stages shows akineticorigid (amiostatic) syndrome and phenomena of parkinsonism. Besides of neurologic symptomatology the disease is characterised by hypertention and dyspeptic signs. Quite often even at early stages of the disease the functional disturbance of the thyroid gland can be marked. Chronic intoxication by manganese has three stages.

The initial stage is characterized by functional changes of the CNS: fast fatigue, sleepiness, headache, which often occurs at the end of a labour shift, decrease of functionability, weakness, loss of appetite. The salivation is sometimes increased, there are nausea and stomach aches associated with eating. Quite often already at this stage there are marked paresthesia and pain in distal parts of the limbs. Patients, as a rule, do not present much symptoms. The disease has a latent course. At further development of intoxication it is possible to reveal functional disturbance of the nervous system and phenomena of the polyneuritic syndrome; hypoalgesia, moderate decrease of muscular force, minor pain at a palpation of muscles of limbs ate typical. There are hypomyotonia, mild exophthalm and "ophthalmic signs", erectile dysfuncion, menstrual disorders. There are marked fast appearance and fading of pilomotor jerk, poured bright red dermographism, distal hyperhidrosis. The mechanical excitability of muscles is increased. In peripheric blood in the onset of intoxication can be watched inclination to hyperglobulinemia, lymphocytosis and monocytosis, left shift can be observed.

At development of the next stage of intoxication the initial phenomena of toxic encephalopathy develop. The positive signs of an oral automatism (Marinesko's and proboscis sign) are marked. The muscle tone is increased. The transition of the 1st stage into the 2nd one sometimes passes very fast. The cerebellar syndrome is characterised for the 2nd stage of chronic manganese intoxication. There are observed inability to fulfil the finger-nose test and instability in the Romberg's test. The gait changes, there can be disturbance of motions of arms at walking. Abdominal reflexes are asymetric and exhaust fast. There is a generalized tremor and more pronounced polyneuritic syndrome with development of trophic dermal changes and considerable impairment of sensitivity. The crisises of

diencephalic nature are sometimes observed. The blood pressure is not stable, the changes on the ECG of extracardial nature associated with described neurologic symptomatology.

The third stage — manganese parkinsonism. A characteristic diffuse damage to the brain with primary increase of extrapyramidal signs. In this stage a masked face is observed, the motions are retarded and bound; from time to time there is an emotional explosibility accompanying with violent cry or by laugh. Intellect is reduced. The gait becomes disordered (tiptoes), there is possible retro and propulsion; monotonic muffled speech. The deep reflexes are high, there are marked clonuses of feet. Unlike to postencephalic parkinsonism the manganese intoxication is not accompanied with pronounced hyperkinesias and cranial nerves dysfunction.

Besides of the indicated changes on the part of the CNS, which are specific for chronic intoxication with manganese chronic gastritis with dicreased gastral secretion, hepatomegaly and disturbance of protein-synthesizing function and changes of carbohydrate and vitamin exchange.

Feature of clinical course of a chronic manganese intoxication is its progredient development, independent on the termination of a contact with metal. The aggravation of symptoms manifests in gait disorder increase.

Diagnosis

The special attention is payed to early diagnosis of chronic intoxication by manganese. Depending on working conditions, time of a contact with manganese the risk of manganese intoxication could be determined. Then detailed examination of the patient directed to specifying symptomatology of damage to the nervous system and other signs is conducted for establishing a diagnosis. If necessary, the health providers conduct prolonged dynamic medical supervision or even advanced clinical examination in the hospital.

Treatment

At mild stage of intoxication with manganese they are prescribed general treatment directed on the increase of body resistance (gymnastics, hydrotherapeutic procedures etc.), vitamins B_1, B_6, ascorbic acid and other medications. In more advanced stages they apply central cholinolytics, improving a metabolism and blood supply of the brain (Nootropil, Aminolon, Scopolamin, Arpenal, etc.). If signs of parkinsonism occured, it is necessary to prescribe cholinolytics (Norakin, Amedin, Tropacin, Corbella, etc.).

214

Expertise of Capacity for Work

If we suspect manganese intoxication, it is necessary to change temporarily (for 1–2 months) the occupation into the one without exposure to manganese. The decision on return to the previous job is made by an expert comission.

At the advanced stages of disease patients are disabled. They can work only in the special facilities. The expertise of work ability should be focused on the issues of medical and social-labor rehabilitation. They recommend treatment in sanatoria and resorts, repeated courses of maintenance therapy and dynamic surveillance of patients.

Preventive Maintenance

It is necessary to equip work places with mechanisation and reduce the manganese dust concentration by hermetic sealing of equipment and provision of exhausted ventilation. The preliminary and periodic medical examinations should be conducted regularly.

The neuropathologist and therapeutist, otolaryngologist, dermatologist participate in medical examinations. They assess the function of external respiration, conduct electromyography of the skeletal muscles, a large picture frame photo roentgenophotography, blood count (Hb, RBC, WBC, ESR).

Terms of periodic medical examinations depend on the occupation and intensity of exposure to manganese. Thus, for example, workers employed at the enterprises where manganese is provided would be examined 1 time per 6 months, on an ore mining of manganese mixtures — 1 time per 12 months, on welding — 1 time per 24 months.

Contraindications to contact with manganese are following: chronic diseases of the peripheral nervous system; mental disorders; pronounced vegetative dysfunction; pronounced forms of chronic bronchitis, asthma, chronic pneumonia, and other respiratory diseases.

TESTS

1. A woman came to the internist with complaints of dull spasmodic stomach ache, constipation, moderate raising of blood pressure. Fatigue, general weakness, increased petulance, headache. It's known from anamnesis that the woman during 2 years had been working at the lacquer-paint plant.

Define the type of intoxication:

A. Oxides of carbon.

B. TEL.

C. Lead.

D. Mercury and its inorganic compounds.

E. Manganese.

2. A 52-year old man has been working during 12 years on assembling the batteries at the factory. He presents complaints of the weakness, quick fatigue, headaches, petulance, pains in the hands and legs, hyperhidrosis and disturbed movement of fingers; thirst, bad appetite, spasmoid stomach aches. At the examination: skin is cool, humid, on the mucous membranes of gums — a grey line. In the morning he had breakfast. In blood test — reticulocytosis, Hb — 109 g/l, in coprogram — increased amount of coproporphyrin before 500 mcg on 1 g of creatinine.

Your diagnosis:

A. Acute poisoning with mercury.

B. Food toxicoinfection.

C. Poisoning with sulfuric acid

D Chronic poisoning with lead.

E. Intensification of chronic gastritis.

3. A man, 43 years old, a driver of a cargo car, has done several gulps of gasoline during transfusion from one car to another one. In several hours he felt a strong headache, weakness, itching, feeling of hair in the mouth; unexplained awe, salivation has appeared. He applied to the polyclinic, where physician has found tremor of fingers, unstability in the Romberg's pose, nystagmus, dysarthria, ataxic unsteady gait, increased tendinous reflexes. ABP — 90/60 mmHg, temperature — 34.5°C, heart rate — 52 bpm.

Your diagnosis:

A. Poisoning with lead.

B. Poisoning with nitrochlorine benzene.

C. Poisoning with benzene.

D. Poisoning with TEL.

E. Poisoning with oxide of carbohydrate.

4. A patient, 52 years old, applied to the internist with complaints of general weakness, quick fatigue, dizziness, weakness in the limbs, change of a taste and reduction of vision. In the mouth — sensation of metallic taste, bad appetite, periodic spasmoid stomach ache. From anamnesis — he has worked during 20 years on the battery production. Laboratory tests: reticulocytosis (> 40‰) increased amount of erythrocytes with basophilic

granulosity (> 60%), Hb — 125 g/l. In urine the contents of δ-aminolevulinic acid and coproporphyrin are increased.

Your diagnosis:

A. Hyperacidic gastritis.

B. Food toxicoinfection.

C. Chronic lead intoxication.

D. Poisoning with manganese.

E. Poisoning with mercury.

5. A patient during 20 years works at the battery production. He complains of general weakness, petulance, swoons, muscular weakness and pain in hands and legs, memory impairment and dicreased working capacity, increased sweating. Objective: tremor of fingers of stretching hands, pains at the palpation on the length of nerves. Laboratory examinations: anemia, reticulosis, erythrocytosis with basophilic granulosity.

Which compounds' toxic action caused these clinic manifestations?

A. Mercury.

B. Manganese.

C. Lead.

D. Chromium.

E. Chlorine.

Chapter 12
IONIZING RADIATION

Within weeks after Roentgen's discovery of the X-ray in 1895, radiation injuries began to be encountered in those working with the early radiation equipment.

During the century since then, the study of such injuries has received continuing impetus from the expanding uses of radiation in medicine, science, industry, and nuclear energy. In historical perspective, the effects of ionizing radiation have received more study than those of any other hazardous environmental agent. As a result, our experience with radiation has been strategically important in addressing other environmental and occupational causes of the disease.

NATURE AND PROPERTIES OF IONIZING RADIATION

Ionizing radiations are of two broad types: **electromagnetic and particulate**. The electromagnetic radiations include roentgen rays (or X-rays) and gamma rays, which possess no mass or charge and which are characterized by extremely short wave length and high frequency. The particulate radiations consist of electrons, protons, neutrons, alpha particles, negative pi-mesons, heavy charged ions, and other atomic particles varying in mass and charge. Both types of ionizing radiation differ from other forms of radiant energy in being able to disrupt the atoms and molecules on which they impinge, thereby producing ions, free radicals, and, in turn, biochemical lesions.

As ionizing radiation penetrates matter, it gives up its energy by colliding with atoms and molecules in its path.

Such collisions are clustered so closely together along the path of an alpha particle that the particle typically has only enough energy to traverse a few cells, whereas the collisions are separated so far apart along the

path of an X-ray that the radiation can traverse the entire body. The average rate at which energy is deposited per unit length of path, i.e., the linear energy transfer (LET) of the radiation, is customarily pronounced in kiloelectron volts per micrometer (keV/µm).

In general, the higher the LET of the radiation, the more likely it is to deposit enough energy in a critical site within the cell, e.g., a deoxyribonucleic acid (DNA) molecule or a chromosome, to cause an irreparable molecular lesion. Alpha particles and other high-LET radiations are typically more potent, therefore, than low-LET radiations such as X-rays.

Within the body, the distribution and retention of each internally deposited radionuclide is governed by its physical and chemical properties, i.e., the amount of radioactivity remaining in situ decreases with time through both physical decay and biologic removal. The physical half-lives of radionuclides vary from less than a second in the case of some radionuclides to billions of years in the case of others. Biologic half-lives also vary, tending to be longer for bone-seeking radionuclides (such as radium, strontium, or plutonium) than for radionuclides that are deposited predominantly in soft tissue (such as iodine, cesium, or tritium).

Quantities and Units of Measure

Following the recommendation of the International Commission on Radiological Units and Measurements the International System (SI) of units has come into increasingly wide use in place of the centimeter-gram-second (cgs) system. The SI unit for expressing the dose of radiation that is absorbed in tissue is the gray (Gy): 1 Gy = 1 joule per kilogram of tissue. The corresponding cgs unit is the radiation absorbed dose (rad): 1 rad = 100 erg per gram of tissue = 0.01 Gy.

To enable doses of radiations of differing potencies to be normalized in terms of risk, another unit, i.e., the equivalent dose, also is used in radiologic protection. This unit is the sievert (Sv): 1 sievert is equivalent to the dose in gray multiplied by an appropriate relative biological effectiveness (RBE)-dependent quality factor (Q), so that, in principle, 1 Sv of any given type of radiation represents the dose that is equivalent in biologic effectiveness to 1 Gy of gamma rays. The corresponding cgs unit is the rem: 1 rem = 0.01 Sv.

The unit for expressing the collective effective dose to a population is the person-Sv; 1 sievert to each of 100 people = 100 person-Sv = = 10,000 person-rem.

The unit for expressing the amount of radioactivity in a given sample of matter is the becquerel (Bq); 1 Bq corresponds to that quantity of radio-

activity in which there is one atomic disintegration per second. The cgs unit used for the same purpose is the curie (Ci); one Ci represents that quantity of radioactivity in which there are 3.7×1010 atomic disintegrations per second (1 Ci = 3.7×1010 Bq).

Historically, the unit used for measuring exposure to X-rays is the roentgen. One roentgen (R), defined loosely, is the amount of X-radiation that produces one electrostatic unit of charge in 1 cubic centimeter of air under standard conditions of temperature and pressure. Exposure of the surface of the skin to 1 R of X-rays typically deposits a dose of slightly less than 10 mGy (1 rad) in the underlying epidermis.

Sources and Levels of Ionizing Radiation in the Environment

Ionizing radiation from natural, as well as artificial, sources is ubiquitous in the human environment. Natural background radiation comes from three main sources: cosmic rays, which originate in outer space; terrestrial radiation, which emanates from radium and other radioactive elements in the earth's crust; and internal radiation, which is emitted by potassium-40 and other naturally occurring radionuclides normally present in the body. The dose received from all three sources by a person living at sea level in the United States averages about 0.94 mSv per year to all soft tissues other than the lung. The intensity of cosmic radiation varies with altitude by a factor of two or more, however, so that a person residing at a high elevation (e.g., Denver) may receive twice as large a dose from this source as one who resides at sea level. The radiation from the earth's crust also varies markedly from one geographic region to another, depending on local variations in the content of radioactive material in soil and subterranean rock. The doses from these sources are far smaller in any event than the average dose to the bronchial epithelium from radon in indoor air; in heavy smokers, moreover, portions of the respiratory tract may also receive as much as 200 mSv additional radiation per year from the polonium that is normally present in tobacco smoke. Fertilizers and building materials, atomic weapons fallout, nuclear power production, and consumer products (color television sets, smoke detectors, luminescent clock and instrument dials, etc.).

Workers in various occupations are exposed to additional ionizing radiation, doses of which vary with the nature of the occupation, particular work assignment, and working conditions. The annual dose equivalent received occupationally in different countries averages less than 20 mSv (200 mrem), and less than 0.1% of radiation workers exceed the maximum permissible dose limit (50 mSv) in any given year.

Nature and Types of Radiation Injuries

For purposes of radiologic protection, it is customary to distinguish between radiation injuries that have dose thresholds and those that are assumed to lack dose thresholds. The former (so-called nonstochastic or deterministic effects) include various acute and chronic tissue reactions (e.g., erythema of the skin, depression of the blood count, oligospermia, cataract of the lens) that result from the killing of large numbers of cells in affected organs. Injuries of the latter type, on the other hand, include mutagenic and carcinogenic effects, which are viewed as stochastic, or probabilistic, effects that can result from radiation-induced changes in single cells within affected organs.

Effects of Radiation at the Cellular Level Gene Mutation

Of the various molecules that radiation may damage within the cell, DNA is the most critical, since damage to a single gene may irreparably alter or kill the cell. A dose of radiation large enough to kill the average dividing cell (1 or 2 Sv) suffices to cause dozens of lesions in its DNA, most of which are reparable, depending on the effectiveness of the cell's DNA repair processes. In fact, thousands of such lesions are thought to be produced each day in the DNA of every cell by natural background radiation, oxidative metabolic reactions, and other causes.

Mutagenic effects of radiation have not yet been documented in human germ cells, but they have been investigated extensively in human somatic cells and in the germ cells of many other species, in which their frequency approximates 10^5 to 10^6 per locus per Sv, depending on the locus in question and the conditions of irradiation. The magnitude of the increase per unit dose is so small that the absence of detectable mutagenic effects on the children of the atomic bomb survivors is not surprising in view of the limited numbers of such children and the comparatively small average gonadal dose received by their parents. On the basis of present knowledge, the dose of ionizing radiation that would be required to double the frequency of heritable mutations in the human population is estimated to exceed 1 Sv, from which it is inferred that less than 1% of the total burden of genetically related human diseases is attributable to natural background irradiation.

Chromosome Aberrations

By breaking chromosomes and/or interfering with their normal segregation to daughter cells at the time of cell division, irradiation can alter the number and structure of chromosomes in the cell. If two or more chromosome breaks occur close enough together in space and time, the

broken ends from one break point may be joined incorrectly with those from another, giving rise to translocations, inversions, rings, dicentrics, and other types of chromosome rearrangements. With high-LET irradiation, the frequency of such "two-event" aberrations increases steeply as a linear function of the dose and is virtually independent of the dose rate, whereas with low-LET irradiation it increases less abruptly, as a linear-quadratic function of the dose, and is highly dependent on the dose rate, i.e., the linear dose term predominates at low doses and low dose rates, whereas the quadratic term predominates at high doses and high dose rates.

In human lymphocytes irradiated in culture, the frequency of two-event chromosome aberrations approximates 0.1 aberration per cell per seivert in the low-to-intermediate dose range. It is not astonishing, therefore, that the frequency of such aberrations has been observed to be increased in radiation workers and persons residing in areas of high natural background radiation, as well as in persons exposed accidentally or therapeutically to large doses of radiation, for whom it can serve as a crude biologic dosimeter.

Cytotoxic Effects

In general, the radiosensitivity of cells varies in proportion to their rate of proliferation and inversely in relation to their degree of differentiation, as noted early in this century by Bergonie and Tribondeau. Relatively few types of cells (e.g., lymphocytes and oocytes) are radiosensitive in a nonproliferative state. Although any cell can be killed by a large-enough dose of radiation (hundreds or thousands of gray), a dose of only 1 to 2 Gy suffices to render most human clonogenic cells incapable of proliferating.

The survival of cells, as measured by their ability to proliferate, tends to decrease exponentially with increasing dose. With high-LET radiation, the dose-survival curve is characteristically steeper than with low-LET radiation and is relatively independent of the dose rate, whereas with low-LET radiation the curve usually has an initial shoulder in the low-dose region, which reappears between successive exposures as a result of repair of radiation damage during the interim.

Effects on Tissues and Organs

Tissues in which cells proliferate rapidly are generally the first to manifest injury. Mitotic inhibition is typically detectable within minutes after intensive irradiation, in contrast to scarring, tissue breakdown, and other degenerative changes, which may not appear until months or years later. If a dose of radiation is absorbed gradually enough, its damaging effects

may be offset to varying degrees by the compensatory proliferation of stem cells that escape injury, so that a larger dose of radiation can be tolerated if it is spread out in time than if it is absorbed in a single brief exposure.

Because of the great multiplicity and diversity of ways in which irradiation can affect different organs, only those effects that are of particular relevance to occupational and accidental irradiation are described in the following sections.

Skin

The earliest outward reaction of the skin is erythema, which results from dilatation of blood capillaries by substances released from injured cells in the overlying epidermis. The severity of the erythema increases with the area as well as the depth of the skin that is irradiated. The threshold dose for erythema in an area greater than 10 cm^2 varies from about 6 to 8 Gy delivered in a single, brief exposure to more than 30 Gy delivered in multiple exposures over a period of several weeks. After rapid exposure to a dose of 6 Gy, the erythema may become evident within hours, typically lasts only a few hours, and is followed 2 to 4 weeks later by one or more waves of deeper and more persistent erythema.

For epilation, the threshold is lower: a dose of 3 to 5 Gy delivered in a single, brief exposure suffices to cause temporary shedding of hair from the scalp.

Blood-Forming Tissues

Hematopoietic cells are highly radiosensitive, undergoing degenerative changes within minutes after a dose of 1 Sv, while mature leukocytes, erythrocytes, and platelets are radioresistant. A dose of 3 to 5 Sv acute whole-body irradiation suffices to kill enough hematopoietic cells to cause profound depression of the white blood cells and platelet counts within 3 to 5 weeks, whereas a dose of 0.5 to 1.0 Sv is not large enough to depress the count severely. A dose of 10 Sv of whole-body irradiation, which is lethal when received within minutes or days, can be tolerated when accumulated gradually over a period of weeks or months or when delivered to only a small fraction of the hematopoietic marrow.

Lymphocytes like hematopoietic cells, are highly radiosensitive. A dose of 3 to 5 Sv of intensive whole-body irradiation suffices to cause prompt lymphopenia, with profound depression of the immune response.

Gastrointestinal Tract

Germinative cells in the epithelium of the small intestine can be killed in sufficient numbers by intensive irradiation to cause denudation and ulceration of the overlying mucosa. When a large part of the small intestine is exposed acutely to a dose in excess of 10 Gy, a fulminating dysentery-like reaction is produced, which may terminate fatally within several days.

Reproductive Organs

Immature spermatogonia are among the most radiosensitive cells in the body. As a result, rapid exposure of both testes to a dose of only 0.15 Sv suffices to depress the sperm count temporarily, and permanent sterility may result from a dose in excess of 4 Sv.

Oocytes also are radiosensitive. A dose of 1.5 to 2.0 Sv to both ovaries may cause temporary sterility, and a dose of 2.0 to 3.0 Sv — permanent sterility, depending on the age at the time of irradiation.

Lens of the Eye

Irradiation of the lens can cause the formation of lens opacities within a matter of months, depending on the dose. Although a posterior subcapsular opacity may become detectable microscopically after a dose of 0.6 to 1 Sv received in a single, brief exposure, the threshold for a vision-impairing cataract is estimated to vary from about 2 to 3 Sv if received in a few minutes to as much as 5.5 to 14 Sv if received over a period of months. The occurrence of radiation cataracts in pioneer cyclotron physicists provided the first evidence of the relatively high cataractogenic effectiveness of neutrons.

THE ACUTE RADIATION SYNDROME

Intensive irradiation of the major part of the hematopoietic system, the gastrointestinal tract, the lung, or the brain can cause the acute radiation syndrome. The prodromal symptoms — anorexia, nausea, and vomiting — typically begin within a few hours after irradiation. Except at the highest doses, these symptoms usually subside by the end of the first day and are followed by a symptom-free interval until the onset of the main phase of the illness.

In the intestinal form of the syndrome, the main phase of the illness characteristically begins 2 to 3 days after irradiation, with abdominal pain, fever, and increasingly severe diarrhea, dehydration, prostration, and toxemia. The reaction progresses rapidly, culminating within several days in a fatal, shocklike state.

In the hematopoietic form of the syndrome, the main phase of the illness is related to leukopenia and thrombocytopenia, which typically do not give rise to symptoms until the second to third week after irradiation. When injury of the marrow is sufficiently extensive, death from infection or hemorrhage may result during the fourth to sixth week after irradiation.

In the pulmonary form, an acute pneumonitis develops in the irradiated area within 1 to 3 months after a dose of 6 to 10 Sv to the lung. If extensive, the process may terminate in respiratory failure, or it may lead to pulmonary fibrosis and cor pulmonale months or years later.

A fourth form of radiation sickness, the cerebral form, can result from acute exposure of the brain to a dose in excess of 50 Sv. In this reaction, anorexia, nausea, and vomiting begin almost immediately after irradiation, to be followed within minutes or hours by increasing drowsiness, confusion, ataxia, convulsions, loss of consciousness, and death.

CARCINOGENIC EFFECTS

Irradiation has been observed to increase the incidence of cancers of various types in radiotherapy patients, early radiologists, radium dial painters, underground hardrock miners, and atomic bomb survivors, depending on the conditions of exposure. Such cancers have not appeared until years or decades after irradiation, however, and none has shown features identifying it as having resulted from radiation specifically, as opposed to some other cause. These findings, are complemented by extensive experimental data on radiation carcinogenesis in laboratory animals.

Excesses of many types of malignancy are evident in atomic bomb survivors, in whom the overall incidence of cancer appears to have increased in proportion to the radiation dose. However, the data do not suffice to define precisely the shape of the dose-incidence curve in the low-dose domain. Hence the carcinogenic risks of low-level irradiation can be estimated only by extrapolation, based on assumptions about the relationship between incidence and dose. Of the available dose-incidence data for the various cancers, the most extensive pertain to leukemia, cancer of the female breast, and cancer of the thyroid gland.

Leukemia

All major forms of leukemia, except the chronic lymphocytic form, have been observed to be increased in frequency after irradiation of the whole body or a large part of the hematopoietic system. The increase has typically appeared within 2 to 5 years after irradiation, has been dose de-

pendent, and has persisted 15 years or longer, depending on the hematologic type of leukemia and the age at irradiation. In atomic bomb survivors, patients treated with spinal irradiation for ankylosing spondylitis, and women treated with pelvic irradiation for menorrhagia, the overall excess of all forms of leukemia (other than the chronic lymphocytic form) averaged over the first 25 years after irradiation has approximated 1 to 3 cases per 10,000 persons per year per sievert to the bone marrow. A comparable excess has been observed in occupationally exposed workers, based on combined analyses of the data from several different cohorts. The data do not suffice to define the shape of the dose-incidence curve unambiguously, but they appear to be most consistent with a linear-quadratic dose-incidence relationship.

Leukemia has also been observed to be increased in frequency in British and American children who were exposed prenatally during radiographic examination of their mothers, the excess corresponding roughly to a 5% increase in the relative risk of childhood leukemia per millisievert, or to approximately 25 cases per 10,000 children at risk per sievert per year during the first 10 years of life. Although no such increase was evident in Japanese children exposed prenatally to atomic bomb radiation, the lack of an excess in this population is not incompatible with the increase noted above, in view of the limited numbers of children in question.

The possibility that the excesses of leukemias and lymphomas in children residing in the vicinity of some of the nuclear plants in the United Kingdom may have been caused by heritable oncogenic effects resulting from the occupational irradiation of their fathers has been suggested by a case-control study, but arguing against this hypothesis are:

a) the lack of any comparable excess in larger numbers of children born outside of Seascale, England, to fathers who had received similar or even larger doses of occupational radiation at the same facility;

b) the lack of similar excesses in French, Canadian, or Scottish children born to fathers with comparable occupational exposures;

c) the lack of an excess in the children of atomic bomb survivors;

d) the lack of excesses in U.S. counties containing nuclear plants.

Cancer of the Breast

A dose-dependent increase in the incidence of cancer of the breast has been observed in women who survived atomic bomb irradiation, women who were given radiation therapy to the breast for acute postpartum mastitis or other benign diseases, women who were examined repeatedly by fluoroscopy of the chest during treatment for pulmonary tuberculosis with

artificial pneumothorax, and women who worked as radium dial painters. In all four groups of women, the incidence of carcinoma of the breast was observed to become elevated within 5 to 10 years after irradiation, depending on the age at exposure, and to remain elevated for the duration of follow-up. Averaged over all ages, the magnitude of the dose-dependent excess is similar in each group, in spite of marked differences among the groups in the rapidity with which the total doses were received. The observation of comparably large carcinogenic effects in the women who accumulated their doses in many small and widely separated increments implies that successive exposures are additive in their cancer-causing effects on the breast and that there may be little or no threshold for such effects.

Susceptibility appears to be highest in childhood and to decrease markedly with the age at the time of irradiation, little if any cancer excess being detectable in women exposed after the age 40. Furthermore, in atomic bomb survivors of any given cohort whose tumors appeared relatively early, the excess was larger than in those whose tumors appeared later, suggesting that the former may have constituted a genetically susceptible subgroup. In women irradiated during infancy or childhood, the excess did not become evident until 30 to 40 years later, implying that expression of the carcinogenic effects of radiation on the breast depended on their being promoted by age-related hormonal stimulation.

Thyroid Gland

Tumors of the thyroid gland have been observed to be increased in frequency in atomic bomb survivors, patients given radiation therapy to the neck in infancy for thymic enlargement and other non-neoplastic conditions, patients given X-ray therapy to the scalp in childhood for treatment of tinea capitis, Marshall islanders exposed to radioactive fallout from a weapons test in 1954, children exposed to fallout from nuclear weapons detonated at the Nevada test site, children exposed to radioactivity released in the Chernobyl accident, and other populations exposed to external irradiation of the thyroid. The induced neoplasms have consisted chiefly of papillary adenomas and carcinomas, have caused a relatively low rate of mortality, and have been preceded by latent periods of 10 to 25 years or longer. Susceptibility to the induction of such tumors appears to be appreciably higher in females than in males, and to be markedly higher in childhood than in adult life.

In persons who received X-ray therapy to the neck in infancy, the incidence of thyroid cancer has been observed to be increased after a dose

as low as 65 mSv, and the observed dose-incidence relationship appears to be consistent with a linear, nonthreshold function, corresponding to an excess of approximately 4 cancers per 10,000 person-yr-Sv. No excess has been evident, however, in patients who have received as much as 0.5 Gy to the thyroid from iodine-131 administered for diagnostic purposes, implying that such radiation is substantially less carcinogenic to the thyroid than external X- or gamma-radiation, possibly because of spatial and temporal differences in the distribution of the radiation within the gland.

Radiation Accidents

In spite of elaborate precautions, some 285 nuclear reactor accidents (excluding the Chernobyl accident) were reported between 1945 and 1987 in various countries, causing more than 1,350 persons to be irradiated, 33 of whom were injured fatally. The Chernobyl accident itself, owing to inadequate containment of the reactor and other design and operating flaws, released enough radioactivity to necessitate the evacuation of thousands of people and farm animals from the surrounding area, and it caused radiation sickness and burns in more than 200 emergency personnel and firefighters, injuring 31 fatally. Accidents involving medical and industrial gamma ray sources, which have been more numerous than reactor accidents, also have also resulted in injuries and loss of life. In 1987, for example, the improper disposal of a cesium-137 radiotherapy source in Goiania, Brazil, led to the irradiation of dozens of unsuspecting victims, four of whom were injured fatally as a result.

From the foregoing, it follows that in any situation where people may be irradiated accidentally, plans for coping with such an accident should be in place. The plans should include delineation of lines of authority for managing an accident, knowledge of the local medical facilities capable of evaluating and treating radiation accident victims, plans for handling and transporting radioactive victims, and some instruction on the hazards of radiation for those employed at the site.

In managing the radiation accident victim, sound medical judgment should come first. Thus, even victims who are heavily irradiated or contaminated should be evaluated for other forms of injury, such as burns, mechanical trauma, or smoke inhalation. In addition, persons who handle or examine a potentially contaminated victim should wear gloves, mask, and other protective clothing, to guard against self-contamination with radioactivity. Detailed records should be kept of all examinations, measurements, procedures, findings, personnel, and times involved.

228

If radioactive contamination is detected, the victim should be isolated and the contaminated area sealed off as soon as possible. Contaminated clothing should be removed promptly, isolated in a plastic bag, and labeled to denote radioactivity. Contaminated parts of the body should be isolated with paper or plastic, monitored for radioactivity, rinsed thoroughly, and monitored again. During the rinsing, care should be taken to avoid abrading contaminated skin, and the rinse water should be isolated as radioactive waste. If radioactive material may have been inhaled, the victim should rinse the oral and nasal cavities with water, taking care not to inhale or swallow more radioactivity in the process; the rinse water and any other secretions should be collected in plastic bags, labeled, and isolated for subsequent examination.

The management of radiation injuries themselves depends on the severity of the injuries and the organs that are affected. Because the signs and symptoms of radiation injury are nonspecific, pertinent information from the victim's exposure record, medical history, physical examination, and laboratory data must be synthesized and integrated. Inasmuch as the nature and severity of injury depend inevitably on the size and anatomic distribution of the radiation dose, evaluation of the latter is paramount. In the absence of physical dosimetry, cytogenetic analysis of circulating lymphocytes can serve as a useful biologic dosimeter (Table 12.1).

Table 12.1. **Responses to acute whole-body irradiation**

Whole-body dose		Response
Sv	rem	
0.05–1.0	5–100	Asymptomatic. Minor depression of leukocytes and platelets* in a few persons. Chromosome aberrations.
1.0–2.0	100–200	Mild anorexia, nausea, vomiting, and fatigue of <24 hrs' duration in most persons. Depression of leukocytes and platelets* in most persons, with lymphocytes declining by about 50% within 48 hrs.
2.0–4.0	200–400	Symptomatic course with nausea and vomiting lasting 2-4 days in most persons. Skin erythema and subsequent epilation. Marked reduction in leukocytes and platelets.* Some deaths within 60 days due to infection.
4.0–6.0	400–600	Serious illness with nausea and vomiting occurring within a few hours and diarrhea. Severe hematopoietic changes.* Approximately 50% mortality, usually within 30 days (LD[50] = 450 rem).

Whole-body dose		Response
Sv	rem	
6.0–10.0	600–1000	Accelerated version of acute radiation syndrome with severe nausea, vomiting, and diarrhea starting within a few hours and culminating in gastrointestinal hemorrhage and severe fluid and electrolyte loss. Lymphocyte depression to <500/mcl by 48 hrs. High mortality, usually within 14 days.
>10.0	>1000	Fulminant course with rapid onset of gastrointestinal, CNS, and cardiovascular manifestations and complications. Lymphocytes decline to 0 within 48 hrs. Mortality of 100%, usually within 72 hrs.

Note. * — maximum depression of lymphocytes usually occurs within 48 hrs, whereas maximum depression of neutrophils and thrombocytes usually takes 3–4 weeks.

TESTS

1. Define an approximate dose of the radiation and degree of severity of ARS, caused by external radiation.There were observed in a damaged man at a period of primary reactions: single vomiting in 3 hrs after injury, small general weakness, short headache, not changed consciousness; skin and visible mucous membranes are not changed, temperature of the body is 36.8°C. A term from the injury to primary reactions — 10 hrs.
Define the doze of radiation:
A. Dose of radiation 2–4 Gy, moderate degree of severity.
B. Dose of radiation 1–2 Gy, mild degree of severity.
C. Dose of radiation 4–6 Gy, severe degree.
D. Dose of radiation more than 6 Gy, extremely severe degree.

2. Define an approximate dose of the radiation and degree of severity of ARS, caused by an external radiation. Among clinical manifestations in a damaged man at a period of primary reactions there are following: frequent vomiting, which has appeared in 2 hrs after the radiation, general weakness, headache; consciousness is not changed, mild hyperemia of the skin covers and mucous membranes, temperature of the body — 37.5°C. These changes were observed during the first day.
A. Dose of radiation more than 6 Gr, extremely heavy degree of severity.
B. Dose of radiation 1–2 Gy, mild degree of severity.
C. Dose of radiation 2–4 Gy, moderate degree of severity.
D. Dose of radiation 4–6 Gy, severe degree.

3. A patient, aged 32 years, 5 hrs after the Chornobyl disaster, where he had been the operator during 2 years, was delivered to the rehabilitation department. Objective: the confused consciousness, cramps, instability of BP, temperature of the body — 39°C. In the blood —leukopenia, thrombocytopenia.

Establish the diagnosis:

A. Acute alcoholic poisoning.

B. Chronic radiation syndrome.

C. Acute radiation syndrome, the cerebral form.

D. Chronic radiation syndrome, the intestinal form.

E. Medicamental poisoning.

4. A man, aged 43 years old, at the examination presented the complaints of weakness, headaches, dysability, decrease of memory and potency, abaissement of hair, gums' bleeding, sweating, often nasal bleedings. Objective: on an internal surface of the femur and brachiums the dermal petechias, positive pinch sign, stomatitis are observed. Changes in the blood: leukopenia $0.2 \cdot 10^9$/l; thrombocytopenia — $120 \cdot 10^3$. Occupational anamnesis: during 2 years he works as the driver on uranic mine.

The preliminary diagnosis:

A. Chronic radiation syndrome, 1st degree of severity.

B. An acute radiation syndrome.

C. The Werlhof's disease.

D. Chronic radiation syndrome, 2nd degree of severity.

E. Scurvy.

5. A woman, aged 37 years, a researcher, complains of general weakness, malaise, headache, fall of a working capacity, appetite and sleep disorders, bleeding of gums, the dyspeptical phenomenon, infringement of menstrual function, hypotonia, concussion, nasal bleedings.

The preliminary diagnosis:

A. Pregnancy.

B. Cancer.

C. Chronic radiation syndrome, 2nd degree of severity.

D. Vegetatovascular dystonia.

E. Toxicoinfection.

Chapter 13
MUSCULOSKELETAL DISORDERS ———

Musculoskeletal disorders (MSDs) were recognized as having occupational etiologic factors as early as the beginning of the 18th century. However, it was not until the 1970s that occupational factors were examined using epidemiologic methods, and the work-relatedness of these conditions began appearing regularly in the international scientific literature. Since then the literature has increased dramatically; more than six thousand scientific articles addressing ergonomics in the workplace have been published. Yet, the relationship between MSDs and work-related factors remains the subject of considerable debate.

The term musculoskeletal disorders (MSDs) refers to conditions that involve the nerves, tendons, muscles, and supporting structures of the body. Because the relationship between exposure to physical work factors and the development and prognosis of a particular disorder may be modified by psychosocial factors, the literature about psychosocial factors and the presence of musculoskeletal symptoms or disorders is also reviewed.

Understanding these associations and relating them to the cause of disease is critical for identifying exposures amenable to preventive and therapeutic interventions. By the official data 32% of MSDs cases are the result of overexertion or repetitive motion. In the OSHD survey amongst **367,424** injuries due to overexertion in lifting there were 65% cases affected the back. Due to implementation of new technologies in the industry the incidence rate of overexertion (in lifting) declined from 52.1 per 10,000 workers in 1992 to 41.1 in 1995; the incidence rate for repetitive motion disorders declined from 11.8 per 10,000 workers in 1992 to 10.1 in 1995 in the developed countries. These declines are similar to those seen for cases involving days away from work from all causes of injury and illness. However, the prevalence and incidence of MSDs are still high.

Musculoskeletal disorders (MSDs) can affect the body's muscles, joints, tendons, ligaments and nerves. Most work-related MSDs develop

over time and are caused either by the work itself or by the employees' working environment. They can also result from fractures sustained in an accident. Typically, MSDs affect the back, neck, shoulders and upper limbs; less often they affect the lower limbs.

Health problems range from discomfort, minor aches and pains, to more serious medical conditions requiring time off work and even medical treatment. In more chronic cases, treatment and recovery are often unsatisfactory — the result could be permanent disability and loss of employment.

Many problems can be prevented or greatly reduced by complying with existing safety and health law and following guidance on good practice. Unfortunately, MSDs are an increasing problem. For the employee, they cause personal suffering and loss of income; for the employer, they reduce business efficiency; and for government, they increase social security costs. MSDs are a priority for the EU in its Community strategy. Reducing the musculoskeletal load of work is part of the 'Lisbon objective', which aims to create 'quality jobs' by:

— enabling workers to stay in employment; and

— ensuring that work and workplaces are suitable for a diverse population.

A number of factors can influence a person's response to risk factors for MSDs in the workplace

The prevalence of MSDs increases as people enter their working years. By the age of 35, most people have had their first episode of back pain. Once in their working years (ages 25 to 65), however, the prevalence is relatively consistent. Musculoskeletal impairments are among the most prevalent and symptomatic health problems of middle and old age. Nonetheless, age groups with the highest rates of compensable back pain and strains are the 20–24 age group for men, and 30–34 age group for women. In addition to decreases in musculoskeletal function due to the development of age-related degenerative disorders, loss of tissue strength with age may increase the probability or severity of soft tissue damage from a given insult.

Another problem is that advancing age and increasing number of years on the job are usually highly correlated. Age is a true confounder with years of employment, so that these factors must be adjusted for when determining relationship to work. Many of the epidemiologic studies that looked at populations with a wide age variance have controlled for age by statistical methods. Several studies found age to be an important factor associated with MSDs, others have not. Although older workers have been found to have less strength than younger workers, Mathiowetz et al. demonstrated that hand strength did not decline with aging; average hand

pinch and grip scores remained relatively stable in their population with a range of 29 to 59 years. Torell et al. found no correlation between age and the prevalence of MSDs in a population of shipyard workers. They found a strong relationship between workload (categorized as low, medium, or heavy) and symptoms or diagnosis of MSDs.

Some studies have found a higher prevalence of some MSDs in women. A male to female ratio of 1:3 was described for carpal tunnel syndrome (CTS) in a population study in which occupation was not evaluated.

The relationship of physical activity and MSDs is more complicated than just "cause and effect." Physical activity may cause injury. However, the lack of physical activity may increase susceptibility to injury, and after injury, the threshold for further injury is reduced. In construction workers, more B-5 frequent leisure time was related to healthy lower backs and severe low back pain was related to less leisure time activity. On the other hand, some standard treatment regimes have found that musculoskeletal symptoms are often relieved by physical activity.

Having good physical condition may not protect workers from risk of MSDs. Persons with high aerobic capacity may be fit for jobs that require high oxygen uptake, but will not necessarily be fit for jobs that require high static and dynamic strengths and vice versa. When physical fitness is examined as a risk factor for MSDs, results are mixed. For example, some early case series reported an increased risk of MSDs associated with playing professional sports, or with physical fitness and exercise while other studies indicate a protective effect and reduced risk. Boyce et al. reported that only 7% of absenteeism could be explained by age, sex, and physical fitness among 514 police officers 35 years or older. Cady et al., on the other hand, found that physical capacity was related to musculoskeletal fitness. Cady defined fitness for most physical activities as combinations of strength, endurance, flexibility, musculoskeletal timing and coordination. Cady et al. evaluated male fire fighters and concluded that physical fitness and conditioning had significant preventive effects on back injuries (least fit 7.1% injured, moderately fit 3.2% injured and most fit 0.8% injured). However, the most fit group had the most severe back injuries. Low cardiovascular fitness level was a risk factor for disabling back pain in a prospective longitudinal study among aerospace manufacturing workers by Battie et al. Good endurance of back muscles was found to be associated with low occurrence of low back pain.

Few occupational epidemiologic studies have looked at non-work-related physical activity in the upper extremities. However, many of the

234

risk factors that are important in occupational studies occur in sports activities — forceful, repetitive movements with awkward postures.

A combination of high exposure to load lifting and high exposure to sports activities that engage the arm was a risk factor for shoulder tendinitis, as well as osteoarthritis of the acromioclavicular joint. Epicondylitis in professional athletes has been well documented, and many of the biomechanical and physiological studies of epicondylitis have been conducted in professional tennis players and baseball pitchers. It is important to note that professional sports activities usually provide players (i.e., workers) with more substantial breaks for recovery and shorter durations for intense tasks as compared with more traditional work settings in which workers are required to perform repetitive, forceful work for 8 hours per day, 5 days per week.

Some epidemiologic support exists for the relationship between back injury and a mismatch of physical strength and job tasks. Chaffin and Park found a sharp increase in back injury rates in subjects performing jobs requiring strength that was greater or equal to their isometric strength-test values. The risk was three times greater in the weaker subjects. In a second longitudinal study, Chaffin et al. evaluated the risk of back injuries and strength and found the risk to be three times greater in the weaker subjects. Keyserling et al. strength-tested subjects, biomechanically analyzed jobs, and assigned subjects to either stressed or non-stressed jobs. Following medical records for a year, they found that job matching based on strength criteria appeared to be beneficial. In another prospective study, Troup et al. found that reduced strength of back flexor muscles was a consistent predictor of recurrent or persistent back pain, but this association was not found for first time occurrence of back pain.

Dupuytren's contracture (also known as **Morbus Dupuytren** or **Dupuytren's disease**, and sometimes misspelled as Dupuytren's constricture) is a fixed flexion contracture of the hand where the fingers bend towards the palm and cannot be fully extended (straightened). It is named after Baron Guillaume Dupuytren, the surgeon who described an operation to correct the affliction.The ring finger and little finger are the fingers most commonly affected. The middle finger may be affected in advanced cases, but the index finger and the thumb are nearly always spared. Dupuytren's contracture progresses slowly and is usually painless. In patients with this condition, the tissues under the skin on the palm of the hand thicken and shorten so that the tendons connected to the fingers cannot move freely. The palmar aponeurosis becomes hyperplastic and undergoes contracture.

Incidence increases after the age of 40; at this age men are affected more often than women. After the age of 80 the distribution is about even.

In Dupuytren's disease, the tough connective tissue within one's hand becomes abnormally thick which can cause the fingers to curl and can result in impaired function of the fingers, especially the small and ring fingers. It usually has a gradual onset, often beginning as a tender lump in the palm. Over time, pain associated with the condition tends to go away, but tough bands of tissue may develop. These bands, which are the source of the reduced mobility commonly associated with the condition, are visible on the surface of the palm and may appear similar to a small callus. It commonly develops in both hands and has no connection to dominant or non-dominant hands, nor any correlation with right- or left-handedness.

Dupuytren's disease is a very specific affliction, and primarily affects:

— people of Scandinavian or Northern European ancestry; it has been called the "Viking disease", though it is also widespread in some Mediterranean countries (e.g. Spain and Bosnia) and in Japan;

— men rather than women (men are ten times as likely to develop the condition);

— people over the age of 40;

— people with a family history (60 to 70% of those afflicted have a genetic predisposition to Dupuytren's contracture)

Some suspected, but unproven causes of Dupuytren's contracture include trauma, diabetes, alcoholism, epilepsy and liver disease. There is no proven evidence that hand injuries or specific occupational exposures lead to a higher risk of developing Dupuytren's disease although there is some speculation that Dupuytren's may be caused or at least the onset may be triggered by physical trauma, such as manual labor or other overexertion of the hands.

De Quervain syndrome (also known as washerwoman's sprain, Radial styloid tenosynovitis, de Quervain disease, de Quervain's tenosynovitis, de Quervain's stenosing tenosynovitis or mother's wrist), is an inflammation or a tendinosis of the sheath or tunnel that surrounds two tendons that control movement of the thumb. These two tendons concerned are the tendons of the extensor pollicis brevis and abductor pollicis longus muscles. These two muscles, which run side by side, have almost the same function: the movement of the thumb away from the hand in the plane of the hand — so called radial abduction (as opposed to movement of the thumb away from the hand, out of the plane of the hand (palmar abduction)). The tendons run, as do all of the tendons passing the wrist, in syno-

vial sheaths, which contain them and allow them to exercise their function whatever the position of the wrist. While de Quervain syndrome is commonly believed to be an inflammatory condition or tendosynovitis, evaluation of histological specimens shows no inflammatory changes — rather a thickening and myxoid degeneration consistent with a chronic degenerative process are seen. De Quervain seen in new mothers.de Quervain syndrome is more common in women. A speculative rationale for this is that women have a greater styloid process angle of the radius, but scientific support for this theory is lacking.

The cause of de Quervain is not known. In medical terms, it remains idiopathic. However, some authors claim that this diagnosis should be included among overuse injuries and that repetitive movements of the thumb are a contributing factor. More specifically, repetitive eccentric lowering of the wrist into ulnar deviation especially with a load in the hand such as a child or even a stack of dishes.

The clinical manifestations are presented by pain, tenderness, and swelling over the thumb side of the wrist, and difficulty gripping.

Finkelstein's test is used to diagnose de Quervain syndrome in people who have wrist pain. To perform the test, the thumb is placed in the closed fist and the hand is tilted towards the little finger — ulna deviation in order to test for pain at the wrist below the thumb. Pain can occur in the normal individual, but if severe, de Quervain's syndrome is likely. Pain will be located on the thumb side of the forearm about an inch below the wrist.

The natural history of de Quervain's syndrome is not well documented. Nonetheless, there is enough observational experience to be fairly certain that it is a self-limited illness with no long-term consequence. Once resolved it rarely recurs. The illness tends to last about 1 year on average. There are no treatments that have been scientifically demonstrated to shorten the duration of symptoms, principally because there are no controlled scientific studies. Things that are tried, without support, and with inconsistent results include immobilization, round the clock anti-inflammatory medications, ionophoresis, and corticosteroid injections. Case series of patients receiving one of the most popular treatments (corticosteroid injection) have claimed effectiveness even when the illness did not resolve for months — clearly more study is needed. Operative release is the only known way for predictably shortening the duration of symptoms, but is elective. Surgery consists of opening the tunnels, or sheaths, that the tendons pass through. The pain usually resolves in the time it takes the wound to heal.

While patients await disease resolution, the symptoms of de Quervain's syndrome can be managed with a spica splint that immobilises the wrist and thumb, anti-inflammatory pain medications (or other non-narcotic pain medications), and ice. While avoiding activities that cause pain will certainly decrease the overall amount of pain experienced, there is no evidence that this will speed recovery, or that continuing to engage in these activities will lead to any harm — the illness is in general a harmless nuisance. Therefore, patients can safely choose their activity and pain level. It is not dangerous or neglectful to remain active in spite of the pain. The splint can be used as desired to improve function and quality of life during the illness.

Specialized hand therapists (both physical therapists and occupational therapists) provide treatment in the form of splinting to immobilise and rest the wrist and thumb. Therapists may recommend activity modification to avoid repetitive eccentric lowering of the wrist into ulnar deviation, but this is done in spite of the debate regarding the role of hand use in etiology and risks "blaming the patient." Some therapists also advocate that, once pain free, therapeutic exercise (focusing on eccentric control) are encouraged to strengthen muscles and progressively overload the tendons so that future episodes are avoided. This is also a highly debatable theory. Recurrence of de Quervain's syndrome is very uncommon. Once it runs its course it rarely returns.

While splinting and activity modification are clearly palliative, there is little scientific support for the efficacy of these treatments in shortening the duration of the illness.

In 1850 dr. A. Notta, an "interne" in Paris, described four adult patients between the ages of 20 and 60 who had a nodule on a flexor tendon of a finger, thereby inhibiting its normal movement. In adult men and women, the most common age for the triggering of digits is between 50 and 60 years. This condition took his name and is known as Notta's syndrome.

Repeated minor trauma is probably the most likely cause of trigger digit, but heavy manual labor with the direct palmar pressure of power grasp may precipitate the symptoms at any adult age. Even ordinary use of the hand is associated with a higher incidence of trigger digit in the dominant right hand. The ring finger is most commonly affected; next in involvement is the long finger, then the small finger, while the index finger is rarely involved. For some inexplicable reason, trigger thumb is far more common in women.

Tension myositis syndrome (**TMS**) is a name given by Dr. J. E. Sarno to a condition he describes as characterized by psychosomatic musculoskeletal and nerve symptoms, most notably back pain. Sarno, a Professor of Clinical Rehabilitation Medicine at New York University School of Medicine and Attending Physician at the Rusk Institute of Rehabilitation Medicine at New York University Medical Center, has described TMS in several books, and has stated that the condition may be involved in other pain disorders as well. However, the TMS diagnosis and treatment protocol are not accepted by the mainstream medical community. Some authors include TMS in a list of conditions he considers to be possible causes of back pain resulting in missed work days that increase the costs of worker's compensation programs.

Myalgia usually is a result of over-stretching of a muscle or group of muscles. Myalgia without a traumatic history is often due to viral infections. Longer-term myalgias may be indicative of a metabolic myopathy, some nutritional deficiencies or chronic fatigue syndrome.

The most common causes of myalgia are overuse, injury or stress. However, myalgia can also be caused by diseases, disorders, medications, as a response to vaccination and withdrawal syndromes.

Prevention and control. There are two approaches are widely accepted for controlling workplace ergonomic hazards. Engineering control includes measures taken to modify the forcefulness, repetitiveness, awkwardness, vibration levels, physical pressures, or environmental extremes connected with a particular job. Engineering controls are the preferred approach in preventing MSDs. Examples include modifications of:

1) the workstation layout;
2) selection and use of tools;
3) work materials;
4) work methods.

Administrative controls are management-directed work practices and policies. Administrative control strategies include (1) changes in job rules and procedures such as scheduling more rest breaks, (2) rotating workers through jobs that are physically tiring, and (3) training workers to recognize ergonomic risk factors and to learn techniques for reducing stress and strain while performing their job.

Although engineering controls are preferred, administrative controls can be helpful as temporary measures until engineering controls can be implemented or when engineering controls are not technically feasible. Since administrative controls do not eliminate hazards, the necessary precautions and safeguards must be followed.

TESTS

1. A man, 40, a locksmith-polisher at the factory of radial tools. The following symptoms have appeared: pain, swelling, crepitation of the forearm. It was noted a reduction of functions of the hand and forearm, weakness. Preliminary diagnosis:
   A. De Quervain's disease.
   B. Bursitis.
   C. Arthritis of the elbow joint.
   D. Crepitative tendovaginitis of the forearm.
   E. Epicondylitis.

2. A milkwoman complains of the pain in distal part of the forearm on the part of the beam bone. The pain appears during a motion of the 1st finger. Possible diagnosis:
   A. Stenosed tendovaginitis.
   B. Bursitis.
   C. Crepitative tendovaginitis of the forearm.
   D. Aseptic osteonecroses of the bone.

3. A woman, 35 y. o., has been working at the factory for 5 years. She complains of irradiated pains in the metacarpophalangeal joints, irradiating to the bones. Around formation is found. Your diagnosis:
   A. De Quervain's disease.
   B. Notta's disease.
   C. Bursitis.
   D. Arthritis.
   E. Tendovaginitis

4. A man C., 42 y. o., an engrover, complains of a painless tumor in the elbow joint, which is not grown with the skin. On X-Ray — an oval softtissued contours by nut-size. Your diagnosis:
   A. Bursitis.
   B. Epicondylitis.
   C. De Quervain's disease.
   D. Notta's disease.
   E. Arthritis.

KEYS

Chapter 1
1. B
2. A
3. C
4. C
5. B

Chapter 2
1. C
2. B
3. C
4. B
5. E
6. E

Chapter 3
1. C
2. C
3. C

Chapter 4
1. C
2. B
3. D
4. C
5. D

Chapter 5
1. D
2. C
3. A

Chapter 6
1. B
2. D
3. B
4. B

Chapter 7
1. D
2. B
3. E
4. A

Chapter 8
1. B
2. C
3. A
4. B
5. C

Chapter 9
1. D
2. B
3. C
4. B
5. C

Chapter 10
1. E
2. E
3. A
4. B
5. B

Chapter 11
1. C
2. D
3. D
4. C
5. C

Chapter 12
1. B
2. D
3. C
4. D
5. C

Chapter 13
1. D
2. A
3. B
4. A

REFERENCES

1. *Артамонова В. Г.* Профессиональные болезни : учебник — 3-е изд., перераб. и доп. / В. Г. Артамонова, Н. Н. Шаталов. — М. : Медицина, 1996. — 432 с.

2. *Вибрация*, шум и здоровье человека / В. Г. Артамонова, Н. Н. Шаталов ; под ред. Р. С. Орлова и В. Г. Артамоновой. — Л., 1988.

3. *Гольдельман А. Г.* Силикотуберкулез как клиническая проблема / А. Г. Гольдельман, Д. М. Зислин. — Свердловск : Уральский ун-т, 1989. — 177 с.

4. *Діагностика* судинних порушень у хворих на вібраційну хворобу та їх лікування антагоністами кальцію : метод. рекомендації / упоряд. : І. Ф. Костюк, В. А. Капустник. — Харків, 1996. — 16 с.

5. *Діагностика*, лікування і профілактика структурно-функціональних змін кісткової тканини у робітників, що працюють при підвищених вібраційних та статичних навантаженнях : метод. рекомендації / упоряд. : О. М. Ігнатьєв, К. А. Ярмула ; Одес. держ. мед. ун-т. — К. , 2006. — 37 с.

6. *Пневмокониоз* : патогенез и биологическая профилактика / Б. А. Капнельсон, О. Г. Алексеева, Л. И. Привалова, Е. В. Ползик. — Екатеринбург : Ур.ОРАН, 1995. — 226 с.

7. *Костюк І. Ф.* Професійні хвороби : підручник. / І. Ф. Костюк, В. А. Капустник. — Харків : Основа, 1998. — 400 с.

8. *Постанова* Кабінету Міністрів України «Про затвердження переліку професійних захворювань» від 08.11.00. № 1662

9. *Профессиональные* заболевания / под ред. Н. Ф. Измерова. — М. : Медицина, 1996. — Т. 1. — 335 с.; Т. 2. — 480 с.

10. *Профессиональные* заболевания работников сельского хозяйства / под ред. Ю. И. Кундиева, Е. П. Краснюк. — К. : Здоров'я, 1989. — 272 с.

11. *Кундієв Ю. І.* Професійне здоров'я в Україні / Ю. І. Кундієв, А. М. Нагорна. — К. : Авіценна, 2006. — 316 с.

12. *Саакадзе В. П.* Профессиональная бронхиальная астма / В. П. Саакадзе, С. А. Степанов. — Саратов : Саратовский ун-т, 1989. — 176 с.

13. *Чернова С. Д.* Хронический профессиональный бронхит (пылевой, токсико-пылевой в сочетании с неблагоприятными метеофакторами) : учеб. пособие / С. Д. Чернова. — Харьков : Мед. академия последиплом. образования, 1999. — 13 с.

14. *Moon R. E.* The physiology of decompression illness / R. E. Moon, R. D. Vann, P. B. Bennet // Sci. — 1995. — Vol. 273. — P. 70-77.

15. *Jeyaratnam J.* Acute pesticide poisoning: a major health problem / J. Jeyaratnam // World Health State Q. — 1990. — Vol. 43. — P. 139-145.

16. *Blain P. G.* Aspects of pesticide toxicology / P. G. Blain // Adverse Drug React Acute Poisoning Rev. — 1990. — Vol. 9. — P. 37-68.

17. WHO (World Health Organization). Inorganic mercury. Environmental Health Criteria 118. — Geneva, Switzerland : World Health Organization, 1991.

18. *Biological* monitoring of environmental and occupational exposure to mercury / S. Langworth, C. G. Elinder, C. J. Gothe, O. Vesterberg // Int. Arch. Occup. Environ. Health. — 1991. — Vol. 63. — P. 161-167.

19. *Task* Force ACCP. Workshop on environmental and occupational asthma / K. Rosenman, M. Reilly, D. Kalinowsky // Chest. — 1990. — Vol. 98 (suppl). — 252 p.

20. *Rosenman K.* Silicosis in the 1990s / K. Rosenman, M. Reilly, D. Kalinowsky // Chest. — 1997. — Vol. 11. — P. 779-786.

21. *Silicosis* and Silicate Disease Committee. Diseases associated with exposure to silica and nonfibrous silicate minerals // Arch. Pathol. Lat. Med. — 1988. — Vol. 112. — P. 673-720.

22. *Tuberculosis* / O. K. Asmolov, Yu. I. Bazhora, O. A. Baburina, I. M. Smolska. — Odessa, 2005. — P. 190.

23. *Taylor W.* The vibration syndrome / W. Taylor. — L. : Academic, 1974.

24. *Goldman R. H.* Lead poisoning in automobile radiator mechanics / R. H. Goldman. // N Eng. J. Met. — 1987. — Vol. 317. — P. 214-218.

25. *Wallace L.* Environmental exposure to benzene: an update / L. Wallace // Environ. Health Perspect. — 1996. — Vol. 104 (suppl 6). — P. 1129-1136.

26. *Snyder R.* An overview of benzene metabolism / R. Snyder, C. C. Hedii // Environ. Health Perspect. — 1996. — Vol. 104 (suppl 6). — P. 1165-1171.

27. *National* Institute for Occupational Safety and Health. Criteria for a recommended standard. Occupational noise exposure. Revised criteria. — Washington : USDHHS, 1996.

28. *Hanner P.* Acute acoustic trauma. An emergency condition. — ScandAudiol. — 1988. — Vol. 17. — P. 57-63.

CONTENTS

Бібліотека студента-медика

Провідний редактор серії
В. М. Попов

Художнє оформлення серії
О. А. Шамшуріна

Навчальне видання

ІГНАТЬЄВ Олександр Михайлович
МАЦЕГОРА Ніна Анатоліївна
ЄРМОЛЕНКО Тетяна Олексіївна
ОПАРІНА Тамара Павлівна
ЯРМУЛА Костянтин Антонович
ВОРОХТА Юрій Миколайович

ПРОФЕСІЙНІ ХВОРОБИ

Навчальний посібник

Англійською мовою

У навчальному посібнику викладено етіологію, епідеміологію, патогенез професійних хвороб, класифікації, нові методи дослідження, клінічні форми та прояви, диференційну діагностику, ускладнення та лікування. Розглянуто питання профілактики, сучасного лікування згідно з рекомендаціями Всесвітньої організації охорони здоров'я, експертизи працездатності.

Викладений матеріал відповідає навчальній програмі з професійних хвороб для студентів медичних вузів IV рівня акредитації та лікарів усіх фахів.

Рис. 2. Табл 18. Бібліогр. : 10 назв.

ББК 54.1,7я73